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(54) **HDM2-INHIBITOR COMPLEXES AND USES
THEREOF**

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(57) **ABSTRACT**

The present invention includes crystallized HDM2 peptides as well as descriptions of the X-ray diffraction patterns of the crystals. The diffraction patterns allow the three dimensional structure of HDM2 to be determined at atomic resolution so that ligand binding sites on HDM2 can be identified and the interactions of ligands with HDM2 amino acid residues can be modeled. Models prepared using such maps permit the design of ligands which can function as active agents which include, but are not limited to, those that function as inhibitors of MDM2 and HDM2 oncoproteins.

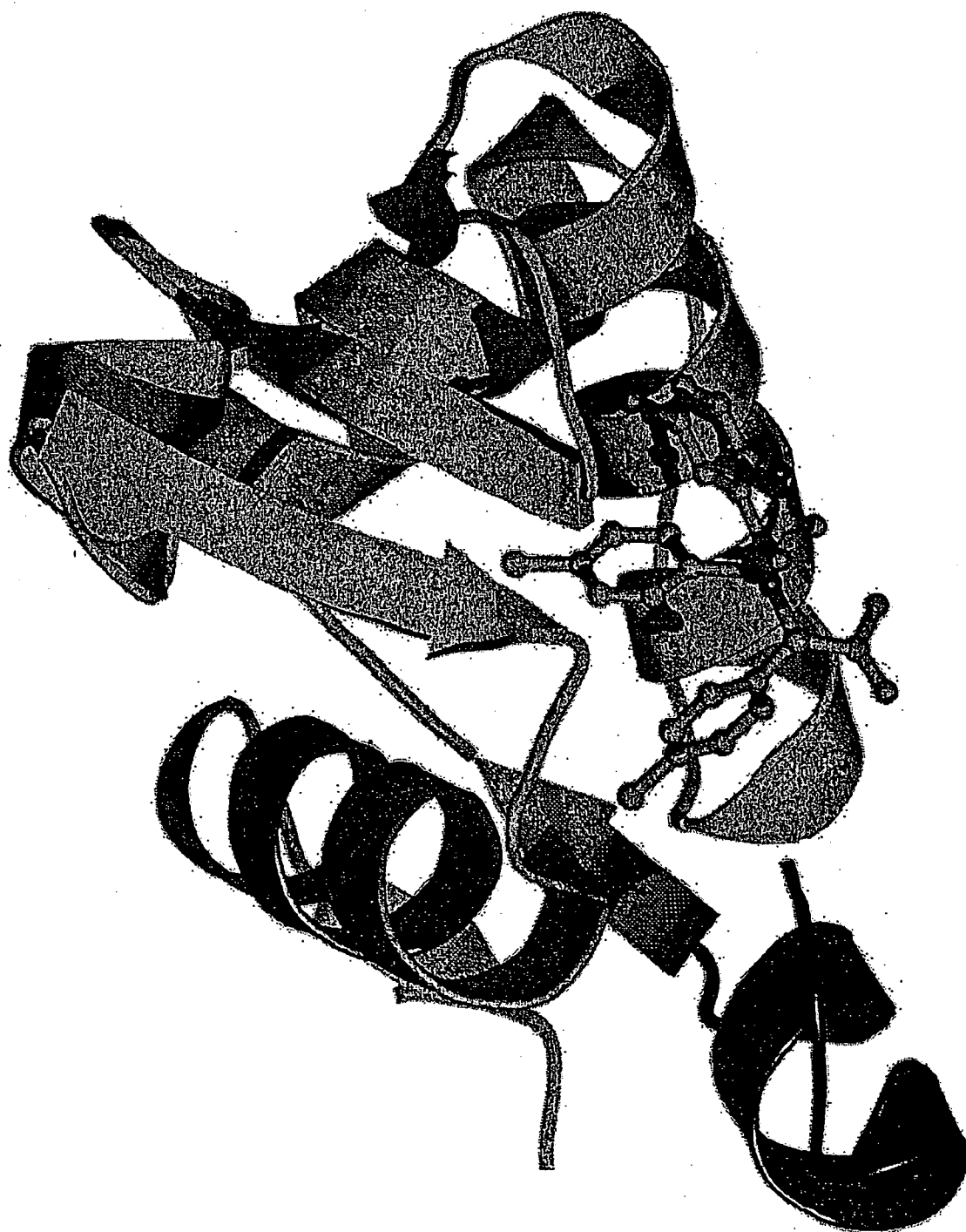


Figure 1

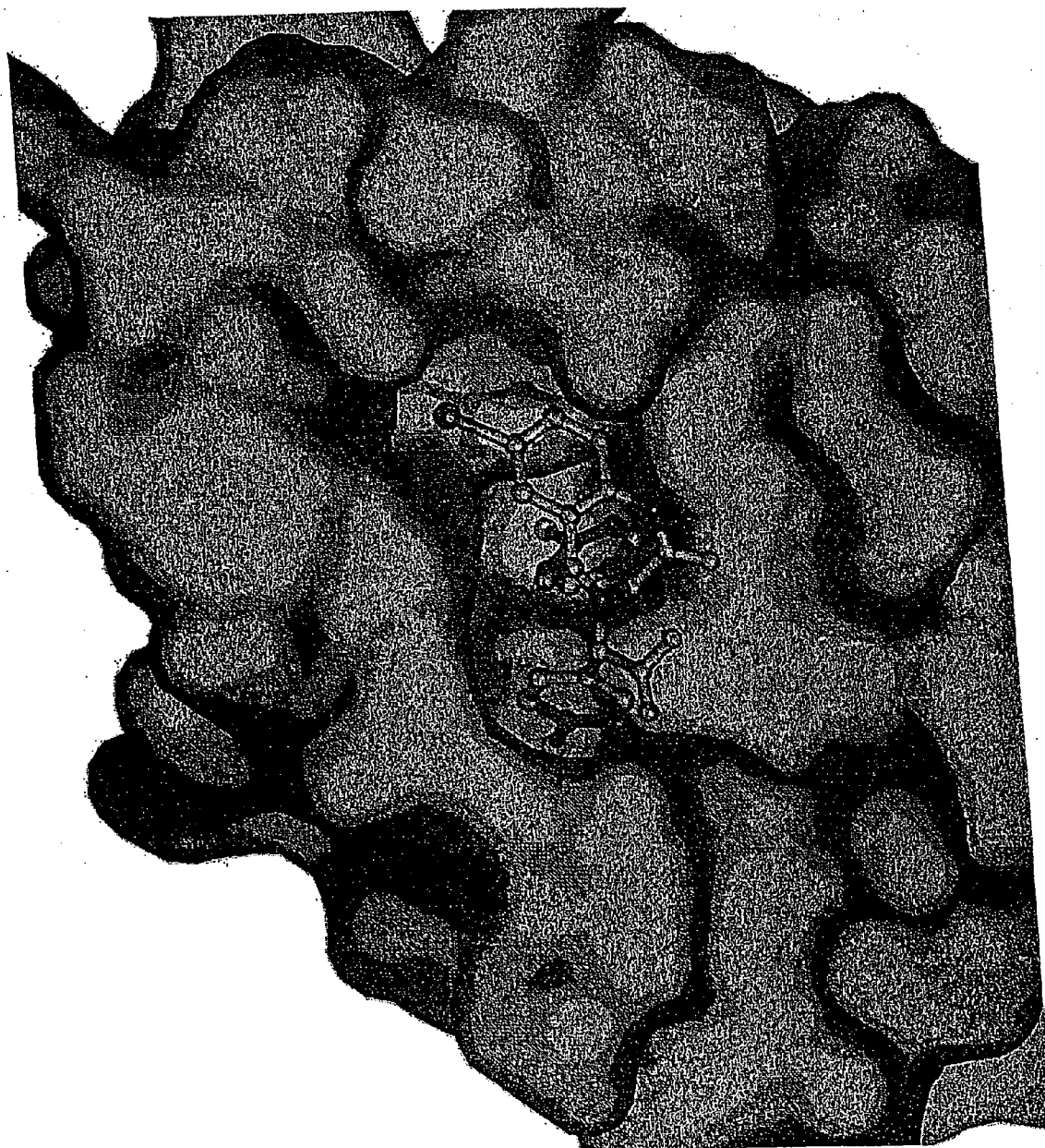


Figure 2

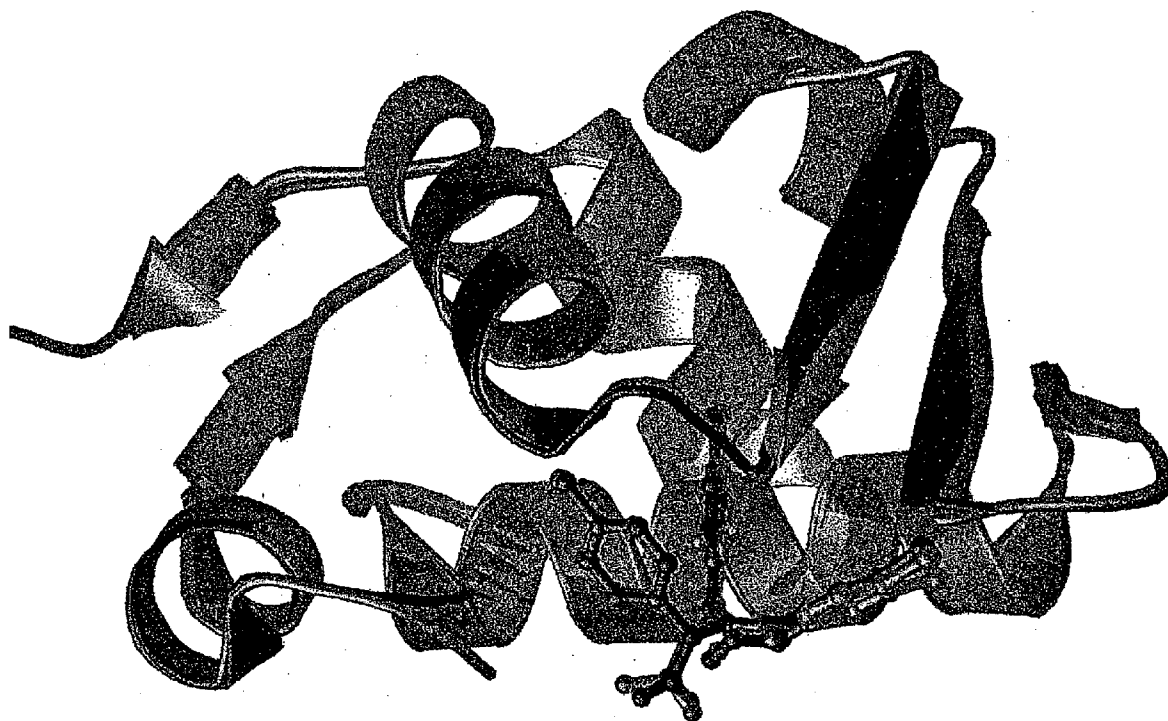


Figure 3

HDM2-INHIBITOR COMPLEXES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to Application No. 60/418,350 filed on Oct. 16, 2002.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH DEVELOPMENT

[0002] Not applicable.

FIELD OF THE INVENTION

[0003] The present invention generally pertains to the fields of molecular biology, protein crystallization, X-ray diffraction analysis, three-dimensional structural determination, molecular modeling and structure based rational drug design. The present invention provides crystallized HDM2 peptides as well as descriptions of the X-ray diffraction patterns. The X-ray diffraction patterns of the crystals in question are of sufficient resolution so that the three-dimensional structure of HDM2 can be determined at atomic resolution, ligand binding sites on HDM2 can be identified, and the interactions of ligands with HDM2 amino acid residues can be modeled.

[0004] The high resolution maps provided by the present invention and the models prepared using such maps also permit the design of ligands which can function as active agents. Thus, the present invention has applications to the design of active agents which include, but are not limited to, those that find use as inhibitors of MDM2 and HDM2 oncoproteins.

BACKGROUND OF THE INVENTION

[0005] HDM2: Structure and Function

[0006] HDM2 (human double minute 2 protein) is the expression product of hdm2, an oncogene that is overexpressed in a subset of human tumors including soft tissue sarcomas, glioblastomas and mammary carcinomas (Oliner, J. D. et al., *Nature*, 358(6381):80-83 (1992); Reifemberger, G. et al., *Cancer Res.*, 53:2736-2739 (1993); Bueso-Ramos, C. E. et al., *Breast Canc. Res. Treat.*, 37(2):179-188 (1996)).

[0007] Functional characterization of this oncogene revealed an interaction between HDM2 and p53, a tumor suppressor central to cell growth arrest and apoptosis (Momand, G. P. et al., *Cell*, 69:1237 (1992)). HDM2 is a transcriptional target of p53, and as such, HDM2 and p53 form a precisely regulated loop (Wu, X. et al., *Genes and Dev.*, 7:1126-1132 (1992)). HDM2 is further regulated by ubiquitination and by complex formation with Arf, which sequesters HDM2 to the nucleolus (Tao, W. and Levine, A. J., *Proc. Natl. Acad. Sci. USA*, 96(12):6937-6941 (1999); Weber, J. D. et al., *Nat. Cell Biol.*, 1(1):20-26 (1999)).

[0008] There are several lines of evidence that suggest that HDM2 can also function independently of p53. Splice variants of HDM2 not containing the p53-binding domain have been found in human tumors and have been shown to possess transforming ability (Sigalas, I. et al. *Nat. Med.* 2(8):912-917 (1996)). In vivo studies have also demonstrated that the spectrum of tumors that develop in transgenic mice overexpressing HDM2 is different from the

spectrum found in p53-null mice and that HDM2 can drive sarcomagenesis in p53-null animals (Jones, S. N. et al., *Proc. Natl. Acad. Sci. USA*, 95(26):15608-15612 (1998)). Lastly, other binding partners of HDM2 could assist HDM2 function along an oncogenic pathway, for example, HDM2 inhibition of MTBP-induced p53-independent G1 arrest (Boyd, M. T. et al., *J. Biol. Chem.* 275(41):31883-31890 (2000)).

[0009] Reports of enhanced tumor cell death following hdm2 inhibition by antisense nucleotides (Chen, L. et al., *Proc. Natl. Acad. Sci. USA*, 95(1):195-200 (1998); Chen, L. et al., *Mol. Med.*, 5(1):21-34 (1999); Tortora, G. et al., *Int. J. Cancer*, 88(5):804-809 (2000)) and HDM2-binding mini-proteins (Bottger, A. et al., *Curr. Biol.*, 7(11):860-869 (1997)) substantiate a prediction that inhibition of HDM2 will activate p53 and in turn trigger apoptosis. Following on this idea, a small molecule inhibitor generated against the p53 binding groove of HDM2 would be expected to prevent the interaction of the two proteins and induce p53 activity. It has been further suggested that inhibiting the interaction between p53 and HDM2 will act additively or synergistically with standard chemotherapeutic agents in the treatment of neoplasm, and this too is supported by work utilizing antisense hdm2 constructs (Wang, H. et al., *Clin. Canc. Res.* 7(11):3613-3624 (2001)).

[0010] MDM2: Structure and Function

[0011] mdm2, the murine homolog of HDM2 was originally found on mouse double minute chromosomes and was initially identified as one of three genes amplified in a tumorigenic cell line (Cahilly-Snyder, L. et al., *Somatic Cell Mol. Genet.* 13:235-244 (1987)). Its protein product was subsequently found to form a complex with p53, which was first observed in a rat fibroblast cell line (Clone 6) previously transfected with a temperature sensitive mouse p53 gene (Michalovitz, D. et al., *Cell* 62:671-680 (1990)). The rat cell line grew well at 37° C. but exhibited a G1 arrest when shifted down to 32° C., which was entirely consistent with an observed temperature dependent switch in p53 conformation and activity. However, the p53-MDM2 complex was only observed in abundance at 32° C., at which temperature p53 was predominantly in a functional or "wild-type" form (Barak, Y. et al., *EMBO J.* 11:2115-2121 (1992) and Momand, J. et al., *Cell* 69:1237-1245 (1992)). By shifting the rat cell line down to 32° C. and blocking de novo protein synthesis it was shown that only "wild-type" p53 induced expression of the mdm2 gene, thereby accounting for the differential abundance of the complex in terms of p53 transcriptional activity (Barak, Y. et al., *EMBO J.* 12:461-468 (1993)). The explanation was further developed by the identification of a DNA binding site for wild-type p53 within the first intron of the mdm2 gene (Wu, X. et al., *Genes Dev.* 7:1126-1132 (1993)). Reporter constructs employing this p53 DNA binding site revealed that they were inactivated when wild-type p53 was co-expressed with MDM2.

[0012] This inhibition of the transcriptional activity of p53 may be caused by MDM2 blocking the activation domain of p53 and/or the DNA binding site. Consequently, it was proposed that mdm2 expression is autoregulated, via the inhibitory effect of MDM2 protein on the transcriptional activity of wild-type p53. This p53-mdm2 autoregulatory feedback loop provided a novel insight as to how cell growth might be regulated by p53. Up to a third of human sarcomas

are considered to overcome p53-regulated growth control by amplification of the mdm2 gene (Oliner, J. D. et al., *Nature* 358:80-83 (1992)). Hence, the interaction between p53 and MDM2 represents a key potential therapeutic target.

[0013] p53: Interaction with HDM2 and MDM2

[0014] p53 is a transcription factor for a number of proteins that cause cell cycle arrest or cell death by apoptosis, such as p21, 14-3-3 σ , and bax. The level and transcriptional activity of p53 are increased by damage to cellular DNA. The MDM2 protein inhibits p53 function by binding to an amphipathic N-terminal helix of p53, abrogating the interaction of p53 with other proteins and its trans activation activity. The interaction with MDM2 also targets p53 for ubiquitin dependent protein degradation. MDM2 exhibits p53 independent effects on cell cycling as well, possibly by direct interaction with some of the downstream effectors such as pRB and EF2 (Reviewed in Zhang, R. and Wang, H., *Cur. Pharm. Des.* 6:393-416 (2000)).

[0015] Mutations of the p53 protein occur in 50% of all human cancers (reviewed in Agarwal, M. L. et al. *J. Biol. Chem.* 273:1-4 (1998); Levine, A. J., *Cell* 88:323-331(1997); and, references cited in Oren, M., *J. Biol. Chem.* 274:36031-36034 (1999)). Under normal circumstances, p53 is latent and a very labile protein, which turns over with a very short half-life of a few minutes (Rogel, A. et al., *Mol. Cell. Biol.* 5:2851-2855 (1985)). DNA damage or stress induces a remarkable increase in the stability of p53 (Kastan, M. B. et al., *Cancer Res.* 51:6304-6311 (1991)). Furthermore, these signals, also activate the function of p53 as a transcriptional activator of the apoptotic machinery, a function normally suppressed by autoregulatory inhibition of its transactivation domain. The amount of p53 present in the cell is tightly regulated by a negative feedback loop between p53 and the oncogene hdm2.

[0016] p53 is located in the cell nucleus and induces the expression of hdm2 through its transactivation domain. Expressed hdm2 subsequently binds to residues 19-26 of the p53 transactivation domain, inactivates it (Chen, J. et al., *Mol. Cell. Biol.* 16:2445-2452 (1996); Haupt, Y. et al., *EMBO J.* 15:1596-1606 (1996); Momand, J. et al., *Cell* 69:1237-1245 (1992)) and blocks recruitment of transcription factors necessary for gene expression (Lu, H. et al., *PNAS* 92:5154-5158 (1995); Thut, C. J. et al., *Science* 267:100-104 (1995)). Furthermore, the p53-hdm2-complex is shuttled to the cytoplasm where degradation occurs. This tight control through negative feedback is critical for the survival of the organism. Inactivation of hdm2 in hdm2-knockout mice leads to early embryonal lethality, but is completely prevented by simultaneous inactivation of p53 (Jones, S. N. et al., *Nature* 378:206-208 (1995); Montes de Oca Luna, R. et al., *Nature* 378:203-206 (1995)). On the other hand, excessive expression of hdm2 can lead to constitutive inhibition of p53 and promote cancer. Excess HDM2 also promotes cancer independently of p53 (Lundgren, K. et al., *Genes and Dev.* 11:714-725 (1997); Sun, P. et al., *Science* 282:2270-2272 (1998)).

[0017] As discussed above, inhibition of the interaction between HDM2 and p53 is an attractive target for cancer therapy (Lane, D. P., *TIBS* 22: 372-374 (1997)). It has been shown that inhibition of the complex formation between p53 and HDM2 raises the levels of p53 in the cell (Bottger, A. et al., *Current Biol.* 7:860-869 (1997)). Also, blocking

HDM2 from binding p53 would be therapeutically useful in restoring cell cycle control to cells that overexpress HDM2 as a front line cancer treatment. More generally, inhibition of HDM2 may increase the effectiveness of chemotherapy and radiation in p53 normal cancers by enhancing apoptosis and growth arrest signaling pathways. This approach may render tumor cells containing functional p53 more susceptible to chemotherapeutic agents.

[0018] One method of identifying inhibitors of the p53/HDM2 protein complex is to determine the amino acid specificities of HDM2 binding pockets by crystallography in order to establish a model for the interaction. Using this method, Kussie et al. identified p53 based peptide antagonists (Kussie, P. H. et al., *Science* 274:948-953 (1996)). A crystal structure of a truncated form of HDM2 (residues 17-125) and a 15' mer peptide derived from the N-terminal transactivation domain of p53 was published by Kussie et al. (Kussie et al., (1996)). Kussie et al. also published a crystal structure of MDM2 (Kussie et al., (1996)) derived from *Xenopus laevis* (residues 13 to 118), having a 71% sequence identity towards HDM2. Based on molecular modeling, Garcia-Echeverria et al. published a model of an 8' mer peptidomimetic, derived from the 15' mer wild-type p53 peptide, bound to the N-terminal domain of hdm2 (Garcia-Echeverria, C. et al., *J. Med. Chem.* 43:3205-3208 (2000)). No crystal structure of HDM2 with inhibitory compounds, such as small molecule inhibitors, for example, or other peptides is believed to have been disclosed.

[0019] Therefore, a need continues to exist for the development of modeling systems to design and select potent, small molecules that inhibit the interactions between HDM2 (and homologs thereof) and natural binding ligands such as p53.

SUMMARY OF THE INVENTION

[0020] The present invention includes methods of producing and using three-dimensional structure information derived from human MDM2 protein (HDM2) and inhibitory compounds which form a complex with HDM2 and prevent HDM2 from interacting with the p53 protein. The present invention also includes specific crystallization conditions to obtain crystals of the inhibitor-HDM2 complex. The crystals are subsequently used to obtain a 3-dimensional structure of the complex using X-ray crystallography (or NMR) and the obtained data is used for rational drug discovery design with the aim to improve the complex formation between HDM2 and the inhibitor, and, also to improve the inhibition of the binding of HDM2 to p53.

[0021] The present invention includes a crystal comprising HDM2, or a fragment, or target structural motif or derivative thereof, and a ligand, wherein the ligand is a small molecule inhibitor. In another embodiment, the crystal has a spacegroup selected from the group consisting of a trigonal spacegroup of P₃2₁ and a tetragonal spacegroup P4₃2₁2. The present invention also includes a crystal comprising HDM2 which comprises a peptide having at least 95% sequence identity to SEQ ID NO. 2.

[0022] In another aspect of the invention, the invention includes a computer system comprising: (a) a database containing information on the three dimensional structure of a crystal comprising HDM2, or a fragment or a target structural motif or derivative thereof, and a ligand, wherein

the ligand is a small molecule inhibitor, stored on a computer readable storage medium; and, (b) a user interface to view the information.

[0023] The present invention also includes a method of evaluating the potential of an agent to associate with HDM2 comprising: (a) exposing HDM2 to the agent; and (b) detecting the association of said agent to HDM2 amino acid residues Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷ thereby evaluating the potential.

[0024] The invention further includes a method of evaluating the potential of an agent to associate with the peptide having aa¹⁶-SEQ ID NO: 2, comprising: (a) exposing aa¹⁶-SEQ ID NO: 2 to the agent; and (b) detecting the level of association of the agent to aa¹⁶-SEQ ID NO: 2, thereby evaluating the potential.

[0025] Further included in the present invention is a method of identifying a potential agonist or antagonist against HDM2 comprising: (a) employing the three dimensional structure of HDM2 cocrystallized with a small molecule inhibitor to design or select said potential agonist or antagonist.

[0026] The instant invention comprises a method of locating the attachment site of an inhibitor to HDM2, comprising: (a) obtaining X-ray diffraction data for a crystal of HDM2; (b) obtaining X-ray diffraction data for a complex of HDM2 and an inhibitor; (c) subtracting the X-ray diffraction data obtained in step (a) from the X-ray diffraction data obtained in step (b) to obtain the difference in the X-ray diffraction data; (d) obtaining phases that correspond to X-ray diffraction data obtained in step (a); (e) utilizing the phases obtained in step (d) and the difference in the X-ray diffraction data obtained in step (c) to compute a difference Fourier image of the inhibitor; and, (f) locating the attachment site of the inhibitor to HDM2 based on the computations obtained in step (e).

[0027] The present invention further comprises a method of obtaining a modified inhibitor comprising: (a) obtaining a crystal comprising HDM2 and an inhibitor; (b) obtaining the atomic coordinates of the crystal; (c) using the atomic coordinates and one or more molecular modeling techniques to determine how to modify the interaction of the inhibitor with HDM2; and, (d) modifying the inhibitor based on the determinations obtained in step (c) to produce a modified inhibitor.

[0028] In another aspect of the invention, the invention includes an isolated protein fragment comprising a binding pocket or active site defined by structure coordinates of HDM2 amino acid residues Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷.

[0029] In another aspect of the invention, the invention includes an isolated nucleic acid molecule encoding the fragment which comprises a binding pocket or active site defined by structure coordinates of HDM2 amino acid residues Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷. In another aspect of the invention, the invention includes a method of screening for an agent that associates with HDM2, comprising: (a) exposing a protein molecule fragment to the agent; and (b) detecting the level of association of the agent to the fragment. In another aspect of the invention, the invention includes a kit comprising a protein molecule fragment.

[0030] The invention additionally comprises a method for the production of a crystal complex comprising an HDM2

polypeptide-ligand comprising: (a) contacting the HDM2 polypeptide with said ligand in a suitable solution comprising PEG and NaSCN; and, b) crystallizing said resulting complex of HDM2 polypeptide-ligand from said solution.

[0031] The invention further includes a method for the production of a crystal comprising HDM2 and a ligand wherein the ligand is a small molecule inhibitor comprising crystallizing a peptide comprising a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO:4 with a potential inhibitor.

[0032] The instant invention includes a method for identifying a potential inhibitor of HDM2 comprising: a) using a three dimensional structure of HDM2 as defined by atomic coordinates according to table 1 or table 2; b) replacing one or more HDM2 amino acids selected from Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷ in said three-dimensional structure with a different amino acid to produce a modified HDM2; c) using said three-dimensional structure to design or select said potential inhibitor; d) synthesizing said potential inhibitor; and, e) contacting said potential inhibitor with said modified HDM2 in the presence of a substrate to test the ability of said potential inhibitor to inhibit HDM2 or said modified HDM2. Also included in the invention is an inhibitor identified by the method.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] FIG. 1 Ribbon representation of HDM2 bound to compound 338437.

[0034] FIG. 2 Fit of compound 338437 into the active site of HDM2 represented as a molecular surface.

[0035] FIG. 3 Ribbon representation of a superposition between hdm2 in the trigonal crystal form and in the tetragonal form. The RMS deviation between C-alpha atom positions is 0.25 Angstroms.

DETAILED DESCRIPTION OF THE INVENTION

[0036] Definitions

[0037] As is generally the case in biotechnology and chemistry, the description of the present invention has required the use of a number of terms of art. Although it is not practical to do so exhaustively, definitions for some of these terms are provided here for ease of reference. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Definitions for other terms also appear elsewhere herein. However, the definitions provided here and elsewhere herein should always be considered in determining the intended scope and meaning of the defined terms. Although any methods and materials similar or equivalent to those described herein can be used in the practice of the present invention, the preferred methods and materials are described.

[0038] As used herein, the term "atomic coordinates" or "structure coordinates" refers to mathematical coordinates that describe the positions of atoms in crystals of HDM2 in Protein Data Bank (PDB) format, including X, Y, Z and B, for each atom. The diffraction data obtained from the crystals are used to calculate an electron density map of the

repeating unit of the crystal. The electron density maps may be used to establish the positions (i.e. coordinates X, Y and Z) of the individual atoms within the crystal. Those of skill in the art understand that a set of structure coordinates determined by X-ray crystallography is not without standard error. For the purpose of this invention, any set of structure coordinates for HDM2 from any source having a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2 are considered substantially identical or homologous. In a more preferred embodiment, any set of structure coordinates for HDM2 from any source having a root mean square deviation of non-hydrogen atoms of less than about 0.75 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2 are considered substantially identical or homologous.

[0039] The term “atom type” refers to the chemical element whose coordinates are measured. The first letter in a column in Table 1 identifies the element.

[0040] The terms “X,” “Y” and “Z” refer to the crystallographically-defined atomic position of the element measured with respect to the chosen crystallographic origin. The term “B” refers to a thermal factor that measures the mean variation of an atom’s position with respect to its average position.

[0041] As used herein, the term “crystal” refers to any three-dimensional ordered array of molecules that diffracts X-rays.

[0042] As used herein, the term “carrier” in a composition refers to a diluent, adjuvant, excipient, or vehicle with which the product is mixed.

[0043] As used herein, the term “composition” refers to the combining of distinct elements or ingredients to form a whole. A composition comprises more than one element or ingredient. For the purposes of this invention, a composition will often, but not always, comprise a carrier.

[0044] As used herein, “mdm2” is used to mean the murine double minute 2 gene, and homologous genes found in other animals.

[0045] As used herein, “MDM2” is used to mean a protein obtained as a result of expression of the mdm2 oncogene. Within the meaning of this term, it will be understood that MDM2 encompasses all proteins encoded by mdm2, mutants thereof, conservative amino acid substitutions, alternative splice proteins thereof, and phosphorylated proteins thereof. Additionally, as used herein, it will be understood that the term “MDM2” includes MDM2 homologues of other animals.

[0046] As used herein, “hdm2” is used to mean the human gene, which is homologous to the mouse mdm2 gene.

[0047] As used herein, “HDM2” is used to mean a protein obtained as a result of expression of the hdm2 oncogene. Within the meaning of this term, it will be understood that HDM2 encompasses all proteins encoded by hdm2, mutants thereof, conservative amino acid substitutions, alternative splice proteins thereof, and phosphorylated proteins thereof. As an example, HDM2 includes the protein comprising SEQ ID NO: 2 and variants thereof comprising at least about 70%

amino acid sequence identity to SEQ ID NO: 2, or preferably 80%, 85%, 90% and 95% sequence identity to SEQ ID NO: 2, or more preferably, at least about 95% or more sequence identity to SEQ ID NO: 2.

[0048] As used herein, the term “SAR,” an abbreviation for Structure-Activity Relationships, collectively refers to the structure-activity/structure property relationships pertaining to the relationship(s) between a compound’s activity/properties and its chemical structure.

[0049] As used herein, the term “molecular structure” refers to the three dimensional arrangement of molecules of a particular compound or complex of molecules (e.g., the three dimensional structure of HDM2 and ligands that interact with HDM2).

[0050] As used herein, the term “molecular modeling” refers to the use of computational methods, preferably computer assisted methods, to draw realistic models of what molecules look like and to make predictions about structure activity relationships of ligands. The methods used in molecular modeling range from molecular graphics to computational chemistry.

[0051] As used herein, the term “molecular model” refers to the three dimensional arrangement of the atoms of a molecule connected by covalent bonds or the three dimensional arrangement of the atoms of a complex comprising more than one molecule, e.g., a protein-ligand complex.

[0052] As used herein, the term “molecular graphics” refers to 3D representations of the molecules, for instance, a 3D representation produced using computer assisted computational methods.

[0053] As used herein, the term “computational chemistry” refers to calculations of the physical and chemical properties of the molecules.

[0054] As used herein, the term “molecular replacement” refers to a method that involves generating a preliminary model of a crystal of HDM2 whose coordinates are unknown, by orienting and positioning the said atomic coordinates described in the present invention so as best to account for the observed diffraction pattern of the unknown crystal. Phases can then be calculated from this model and combined with the observed amplitudes to give an approximate Fourier synthesis of the structure whose coordinates are unknown. (Rossmann, M. G., ed., “The Molecular Replacement Method”, Gordon & Breach, New York, 1972).

[0055] As used herein, the term “homolog” refers to the HDM2 protein molecule or the nucleic acid molecule which encodes the protein, or a functional domain from said protein from a first source having at least about 30%, 40% or 50% sequence identity, or at least about 60%, 70% or 75% sequence identity, or at least about 80% sequence identity, or more preferably at least about 85% sequence identity, or even more preferably at least about 90% sequence identity, and most preferably at least about 95%, 97% or 99% amino acid or nucleotide sequence identity, with the protein, encoding nucleic acid molecule or any functional domain thereof, from a second source. The second source may be a version of the molecule from the first source that has been genetically altered by any available means to change the primary amino acid or nucleotide sequence or may be from the same or a different species than that of the first source.

[0056] As used herein, the term “active site” refers to regions on HDM2 or a structural motif of HDM2 that are directly involved in the function or activity of HDM2.

[0057] As used herein, the terms “binding site” or “binding pocket” refer to a region of HDM2 or a molecular complex comprising HDM2 that, as a result of the primary amino acid sequence of HDM2 and/or its three-dimensional shape, favorably associates with another chemical entity or compound including ligands or inhibitors.

[0058] For the purpose of this invention, any active site, binding site or binding pocket defined by a set of structure coordinates for HDM2 or for a homolog of HDM2 from any source having a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2 are considered substantially identical or homologous. In a more preferred embodiment, any set of structure coordinates for HDM2 or a homolog of HDM2 from any source having a root mean square deviation of non-hydrogen atoms of less than about 0.75 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2 are considered substantially identical or homologous.

[0059] The term “root mean square deviation” means the square root of the arithmetic mean of the squares of the deviations from the mean.

[0060] As used herein, the term “amino acids” refers to the L-isomers of the naturally occurring amino acids. The naturally occurring amino acids are glycine, alanine, valine, leucine, isoleucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, γ -carboxylglutamic acid, arginine, ornithine, and lysine. Unless specifically indicated, all amino acids are referred to in this application are in the L-form.

[0061] As used herein, the term “nonnatural amino acids” refers to amino acids that are not naturally found in proteins. For example, selenomethionine.

[0062] As used herein, the term “positively charged amino acid” includes any amino acids having a positively charged side chain under normal physiological conditions. Examples of positively charged naturally occurring amino acids are arginine, lysine, and histidine.

[0063] As used herein, the term “negatively charged amino acid” includes any amino acids having a negatively charged side chains under normal physiological conditions. Examples of negatively charged naturally occurring amino acids are aspartic acid and glutamic acid.

[0064] As used herein, the term “hydrophobic amino acid” includes any amino acids having an uncharged, nonpolar side chain that is relatively insoluble in water. Examples of naturally occurring hydrophobic amino acids are alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine.

[0065] As used herein, the term “hydrophilic amino acid” refers to any amino acids having an uncharged, polar side chain that is relatively soluble in water. Examples of naturally occurring hydrophilic amino acids are serine, threonine, tyrosine, asparagine, glutamine and cysteine.

[0066] As used herein, the term “hydrogen bond” refers to two hydrophilic atoms (either O or N), which share a hydrogen that is covalently bonded to only one atom, while interacting with the other.

[0067] As used herein, the term “hydrophobic interaction” refers to interactions made by two hydrophobic residues or atoms (such as C).

[0068] As used herein, the term “conjugated system” refers to more than two double bonds are adjacent to each other, in which electrons are completely delocalized with the entire system. This also includes aromatic residues.

[0069] As used herein, the term “aromatic residue” refers to amino acids with side chains having a delocalized conjugated system. Examples of aromatic residues are phenylalanine, tryptophan, and tyrosine.

[0070] As used herein, the phrase “inhibiting the binding” refers to preventing or reducing the direct or indirect association of one or more molecules, peptides, proteins, enzymes, or receptors, or preventing or reducing the normal activity of one or more molecules, peptides, proteins, enzymes or receptors, e.g., preventing or reducing the direct or indirect association of HDM2 and p53.

[0071] As used herein, the term “competitive inhibitor” refers to inhibitors that bind to HDM2 at the same sites as its binding partner(s) (e.g., p53), thus directly competing with them. Competitive inhibition may, in some instances, be reversed completely by increasing the substrate concentration.

[0072] As used herein, the term “uncompetitive inhibitor” refers to one that inhibits the functional activity of HDM2 by binding to a different site than does its substrate(s) e.g. (p53).

[0073] As used herein, the term “non-competitive inhibitor” refers to one that can bind to either the free or p53 bound form of HDM2.

[0074] Those of skill in the art may identify inhibitors as competitive, uncompetitive, or non-competitive by computer fitting enzyme kinetic data using standard methods. See, for example, Segel, I. H., *Enzyme Kinetics*, J. Wiley & Sons, (1975).

[0075] As used herein, the term “R or S-isomer” refers to two possible stereoisomers of a chiral carbon according to the Cahn-Ingold-Prelog system adopted by International Union of Pure and Applied Chemistry (IUPAC). Each group attached to the chiral carbon is first assigned to a preference or priority a, b, c, or d on the basis of the atomic number of the atom that is directly attached to the chiral carbon. The group with the highest atomic number is given the highest preference a, the group with next highest atomic number is given the next highest preference b; and so on. The group with the lowest preference (d) is then directed away from the viewer. If the trace of a path from a to b to c is counter clockwise, the isomer is designated (S); in the opposite direction, clockwise, the isomer is designated (R).

[0076] As used herein, the term “ligand” refers to any molecule, or chemical entity which binds with or to HDM2, a subunit of HDM2, a domain of HDM2, a target structural motif of HDM2 or a fragment of HDM2. Thus, ligands include, but are not limited to, small molecule inhibitors, for example.

[0077] As used herein, the term “small molecule inhibitor” refers to compounds useful in the present invention having measurable MDM2 or HDM2 inhibiting activity. In addition to small organic molecules, peptides, antibodies, cyclic peptides and peptidomimetics are contemplated as being useful in the disclosed methods. Excluded from the invention are the p53 peptides disclosed in Kussie et al., Garcia-Echeverria et al., and the peptides derived from phage display which inhibit the binding of mdm2 to p53 (Böttger, V. A., et al., *Oncogene* 13(10): 2141-2147 (1996)). Preferred inhibitors are small molecules, preferably less than 700 Daltons, and more preferably less than 450 Daltons. Examples of classes of compounds having this property include compounds disclosed in U.S. Provisional Application No. 60/275,629; in U.S. Provisional Application No. 60/331,235; in U.S. Provisional Application No. 60/379,617; and, in U.S. application Ser. No. 10/097,249, incorporated herein in their entirety.

[0078] As used herein the terms “bind,” “binding,” “bond,” or “bonded” when used in reference to the association of atoms, molecules, or chemical groups, refer to any physical contact or association of two or more atoms, molecules, or chemical groups.

[0079] As used herein, the terms “covalent bond” or “valence bond” refer to a chemical bond between two atoms in a molecule created by the sharing of electrons, usually in pairs, by the bonded atoms.

[0080] As used herein, “noncovalent bond” refers to an interaction between atoms and/or molecules that does not involve the formation of a covalent bond between them.

[0081] As used herein, the term “native protein” refers to a protein comprising an amino acid sequence identical to that of a protein isolated from its natural source or organism.

SPECIFIC EMBODIMENTS

DETAILED EMBODIMENTS

[0082] The present invention includes a crystal comprising HDM2, or a fragment, or target structural motif or derivative thereof, and a ligand, wherein the ligand is a small molecule inhibitor. In one embodiment, the fragment or derivative thereof is a peptide selected from the group consisting of SEQ ID NO: 1 (amino acid sequence of full length HDM2), SEQ ID NO: 2 (amino acid residues 17-111 of SEQ ID NO: 1), SEQ ID NO: 3 (amino acid residues 23-114 of SEQ ID NO: 1) and SEQ ID NO: 4 (Gly¹⁶-SEQ ID NO: 2).

[0083] In another embodiment, the crystal has a space-group selected from the group consisting of a trigonal spacegroup of P3₂21 and a tetragonal spacegroup of P4₃2₁2. In a different embodiment, the crystal effectively diffracts X-rays for determination of atomic coordinates to a resolution of at least about 3.0 Å. In a preferred embodiment, the ligand is in crystalline form. In a highly preferred embodiment, the ligand is selected from the group consisting of (4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-acetic acid; [8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid, and, derivatives thereof.

[0084] The present invention also includes a crystal comprising HDM2 which comprises a peptide having at least

95% sequence identity to SEQ ID NO. 2. In a preferred embodiment, the crystal comprising SEQ ID NO: 2 comprises an atomic structure characterized by the coordinates of Table 1 or Table 2. In another preferred embodiment, the crystal comprises a unit cell selected from the group consisting of: a cell having dimensions of about 98.6 Å, 98.6 Å and 74.7 Å, and about alpha=90°, beta=90° and gamma=120°; and, a cell having dimensions of about 54.3 Å, 54.3 Å, 83.3 Å and about alpha=90°, beta=90° and gamma=90°.

[0085] In another aspect of the invention, the invention includes a computer system comprising: (a) a database containing information on the three dimensional structure of a crystal comprising HDM2, or a fragment or a target structural motif or derivative thereof, and a ligand, wherein the ligand is a small molecule inhibitor, stored on a computer readable storage medium; and, (b) a user interface to view the information. In one embodiment, the information comprises diffraction data obtained from a crystal comprising SEQ ID NO:2. In another embodiment, the information comprises an electron density map of a crystal form comprising SEQ ID NO:2. In a different embodiment, the information comprises the structure coordinates of Table 1 or Table 2 or homologous structure coordinates comprising a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2. In a preferred embodiment, the information comprises structure coordinates comprising a root mean square deviation of non-hydrogen atoms of less than about 0.75 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2. In a highly preferred embodiment, the information comprises the structure coordinates for amino acids Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷ according to Table 1 or Table 2 or similar structure coordinates for said amino acids comprising a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2. In another embodiment, the information further comprises the structure coordinates for amino acids Val⁵³, Leu⁵⁴, Phe⁵⁵, Leu⁵⁷, Gly⁵⁸, Gln⁵⁹, Ile⁶¹, Met⁶², Tyr⁶⁷, Gln⁷², His⁷³, Ile⁷⁴, Val⁷⁵, Phe⁸⁶, Phe⁹¹, Val⁹³, Lys⁹⁴, Glu⁹⁵, His⁹⁶, Ile⁹⁹, Tyr¹⁰⁰, Ile¹⁰³ according to Table 1 or Table 2 or similar structure coordinates for said amino acids comprising a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2.

[0086] The present invention also includes a method of evaluating the potential of an agent to associate with HDM2 comprising: (a) exposing HDM2 to the agent; and (b) detecting the association of said agent to HDM2 amino acid residues Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷ thereby evaluating the potential. In one embodiment of the invention, the agent is a virtual compound. In another embodiment of the invention, step (a) comprises comparing the atomic structure of the compound to the three dimensional structure of HDM2. In a different embodiment, the comparing comprises employing a computational means to perform a fitting operation between the compound and at least one binding site of HDM2. In a preferred embodiment, the binding site is defined by structure coordinates for amino acids Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷ according to Table 1 or Table 2 similar structure coordinates for said amino acids comprising a root

mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2. In another different embodiment, the binding site is further defined by structure coordinates for amino acids Val⁵³, Leu⁵⁴, Phe⁵⁵, Leu⁵⁷, Gly⁵⁸, Gln⁵⁹, Ile⁶¹, Met⁶², Tyr⁶⁷, Gln⁷², His⁷³, Ile⁷⁴, Val⁷⁵, Phe⁸⁶, Phe⁹¹, Val⁹³, Lys⁹⁴, Glu⁹⁵, His⁹⁶, Ile⁹⁹, Tyr¹⁰⁰, Ile¹⁰³ according to Table 1 or Table 2 or similar structure coordinates for said amino acids comprising a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2. In a highly preferred embodiment, the agent is exposed to crystalline SEQ ID NO:2 and the detecting of step (b) comprises determining the three dimensional structure of the agent-SEQ ID NO: 2 complex.

[0087] The invention further includes a method of evaluating the potential of an agent to associate with the peptide having aa¹⁶-SEQ ID NO: 2, comprising: (a) exposing aa¹⁶-SEQ ID NO: 2 to the agent; and (b) detecting the level of association of the agent to aa¹⁶-SEQ ID NO: 2, thereby evaluating the potential. In one embodiment, the agent is a virtual compound.

[0088] The present invention includes a method of identifying a potential agonist or antagonist against HDM2 comprising: (a) employing the three dimensional structure of HDM2 cocrystallized with a small molecule inhibitor to design or select said potential agonist or antagonist. In one embodiment, the three dimensional structure corresponds to the atomic structure characterized by the coordinates of Table 1 or similar structure coordinates comprising a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2. In a different embodiment, the method further comprises the steps of: (b) synthesizing the potential agonist or antagonist; and (c) contacting the potential agonist or antagonist with HDM2.

[0089] The instant invention comprises a method of locating the attachment site of an inhibitor to HDM2, comprising: (a) obtaining X-ray diffraction data for a crystal of HDM2; (b) obtaining X-ray diffraction data for a complex of HDM2 and an inhibitor; (c) subtracting the X-ray diffraction data obtained in step (a) from the X-ray diffraction data obtained in step (b) to obtain the difference in the X-ray diffraction data; (d) obtaining phases that correspond to X-ray diffraction data obtained in step (a); (e) utilizing the phases obtained in step (d) and the difference in the X-ray diffraction data obtained in step (c) to compute a difference Fourier image of the inhibitor; and, (f) locating the attachment site of the inhibitor to HDM2 based on the computations obtained in step (e).

[0090] The present invention further comprises a method of obtaining a modified inhibitor comprising: (a) obtaining a crystal comprising HDM2 and an inhibitor; (b) obtaining the atomic coordinates of the crystal; (c) using the atomic coordinates and one or more molecular modeling techniques to determine how to modify the interaction of the inhibitor with HDM2; and, (d) modifying the inhibitor based on the determinations obtained in step (c) to produce a modified inhibitor. In one embodiment, the crystal comprises a pep-

tide selected from the group consisting of: a peptide having SEQ ID NO: 2; a peptide having SEQ ID NO: 3 and a peptide having SEQ ID NO:4. In a different embodiment, the one or more molecular modeling techniques are selected from the group consisting of graphic molecular modeling and computational chemistry. In a preferred embodiment, step (a) comprises detecting the interaction of the inhibitor to HDM2 amino acid residues Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷. In another embodiment of the invention, the invention includes an HDM2 inhibitor identified by this method.

[0091] In another aspect of the invention, the invention includes an isolated protein fragment comprising a binding pocket or active site defined by structure coordinates of HDM2 amino acid residues Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷. In one embodiment, the isolated fragment is linked to a solid support.

[0092] In another aspect of the invention, the invention includes an isolated nucleic acid molecule encoding the fragment which comprises a binding pocket or active site defined by structure coordinates of HDM2 amino acid residues Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷. In one embodiment, a vector comprises the nucleic acid molecule. In another embodiment, a host cell comprises the vector. In yet another aspect of the invention, the invention includes a method of producing a protein fragment, comprising culturing the host cell under conditions in which the fragment is expressed. In another aspect of the invention, the invention includes a method of screening for an agent that associates with HDM2, comprising: (a) exposing a protein molecule fragment to the agent; and (b) detecting the level of association of the agent to the fragment. In another aspect of the invention, the invention includes a kit comprising a protein molecule fragment.

[0093] In another aspect of the invention, the invention includes a method for the production of a crystal complex comprising an HDM2 polypeptide-ligand comprising: (a) contacting the HDM2 polypeptide with said ligand in a suitable solution comprising PEG and NaSCN; and, b) crystallizing said resulting complex of HDM2 polypeptide-ligand from said solution. In one embodiment, the HDM2 polypeptide is a polypeptide having SEQ ID NO: 2. In another embodiment, PEG has an average molecular weight range from 100 to 1000, wherein said PEG is present in solution at a range from about 0.5% w/v to about 10% w/v and said NaSCN is present in solution at a range of from about 50 mM to about 150 mM. In a preferred embodiment, PEG has an average molecular weight of about 400 and is present in solution at about 2% w/v and said NaSCN is present in solution at about 100 mM. In a highly preferred embodiment, the solution further comprises about 1.8-2.4 M (NH₄)₂SO₄ and about 100 mM buffer.

[0094] The invention further includes a method for the production of a crystal comprising HDM2 and a ligand wherein the ligand is a small molecule inhibitor comprising crystallizing a peptide comprising a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO:4 with a potential inhibitor.

[0095] The invention includes a method for identifying a potential inhibitor of HDM2 comprising: a) using a three dimensional structure of HDM2 as defined by atomic coordinates according to table 1; b) replacing one or more HDM2 amino acids selected from Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷ in

said three-dimensional structure with a different amino acid to produce a modified HDM2; c) using said three-dimensional structure to design or select said potential inhibitor; d) synthesizing said potential inhibitor; and, e) contacting said potential inhibitor with said modified HDM2 in the presence of a substrate to test the ability of said potential inhibitor to inhibit HDM2 or said modified HDM2. In one embodiment, replacing one or more amino acid residues further comprises replacing SEQ ID NO: 2 amino acids selected from the group consisting of Val⁵³, Leu⁵⁴, Phe⁵⁵, Leu⁵⁷, Gly⁵⁸, Gln⁵⁹, Ile⁶¹, Met⁶², Tyr⁶⁷, Gln⁷², His⁷³, Ile⁷⁴, Val⁷⁵, Phe⁸⁶, Phe⁹¹, Val⁹³, Lys⁹⁴, Glu⁹⁵, His⁹⁶, Ile⁹⁹, Tyr¹⁰⁰, and Ile¹⁰³. In another embodiment, the potential inhibitor is selected from a database. In a preferred embodiment, the potential inhibitor is designed de novo. In another preferred embodiment, the potential inhibitor is designed from a known inhibitor. In a highly preferred embodiment, the step of employing said three-dimensional structure to design or select said potential inhibitor comprises the steps of: a) identifying chemical entities or fragments capable of associating with modified HDM2; and b) assembling the identified chemical entities or fragments into a single molecule to provide the structure of said potential inhibitor. In one embodiment, the potential inhibitor is a competitive inhibitor of SEQ ID NO:4 (Gly¹⁶-SEQ ID NO: 2). In a different embodiment, the potential inhibitor is a non-competitive or uncompetitive inhibitor of SEQ ID NO:4 (Gly¹⁶-SEQ ID NO: 2). In yet another embodiment, an inhibitor is identified by the method.

[0096] A. Modeling the Three-Dimensional Structure of HDM2

[0097] The atomic coordinate data provided in Table 1, Table 2 or the coordinate data derived from homologous proteins may be used to build a three-dimensional model of HDM2. Any available computational methods may be used to build the three dimensional model. As a starting point, the X-ray diffraction pattern obtained from the assemblage of the molecules or atoms in a crystalline version of HDM2 or an HDM2 homolog can be used to build an electron density map using tools well known to those skilled in the art of crystallography and X-ray diffraction techniques. Additional phase information extracted either from the diffraction data and available in the published literature and/or from supplementing experiments may then be used to complete the reconstruction.

[0098] For basic concepts and procedures of collecting, analyzing, and utilizing X-ray diffraction data for the construction of electron densities see, for example, Campbell et al., 1984, *Biological Spectroscopy*, The Benjamin/Cummings Publishing Co., Inc., Menlo Park, Calif.; Cantor et al., 1980, *Biophysical Chemistry, Part II: Techniques for the study of biological structure and function*, W. H. Freeman and Co., San Francisco, Calif.; A. T. Brunger, 1993, *X-Flor Version 3.1: A system for X-ray crystallography and NMR*, Yale Univ. Pr., New Haven, Conn.; M. M. Woolfson, 1997, *An Introduction to X-ray Crystallography*, Cambridge Univ. Pr., Cambridge, UK; J. Drenth, 1999, *Principles of Protein X-ray Crystallography* (Springer Advanced Texts in Chemistry), Springer Verlag; Berlin; Tsirelson et al., 1996, *Electron Density and Bonding in Crystals: Principles, Theory and X-ray Diffraction Experiments in Solid State Physics and Chemistry*, Inst. of Physics Pub.; U.S. Pat. No. 5,942,428; U.S. Pat. No. 6,037,117; U.S. Pat. No. 5,200,910 and U.S. Pat. No. 5,365,456 ("Method for Modeling the Electron

Density of a Crystal"), each of which is herein specifically incorporated by reference in their entirety.

[0099] For basic information on molecular modeling, see, for example, M. Schlecht, *Molecular Modeling on the PC*, 1998, John Wiley & Sons; Gans et al., *Fundamental Principles of Molecular Modeling*, 1996, Plenum Pub. Corp.; N. C. Cohen (editor), *Guidebook on Molecular Modeling in Drug Design*, 1996, Academic Press; and W. B. Smith, *Introduction to Theoretical Organic Chemistry and Molecular Modeling*, 1996. U.S. Patents which provide detailed information on molecular modeling include U.S. Pat. Nos. 6,093,573; 6,080,576; 6,075,014; 6,075,123; 6,071,700; 5,994,503; 5,612,894; 5,583,973; 5,030,103; 4,906,122; and 4,812,12, each of which are incorporated by reference herein in their entirety.

[0100] B. Methods of Using the Atomic Coordinates to Identify and Design Ligands of Interest

[0101] The atomic coordinates of the invention, such as those described in Table 1, Table 2, Table 3 or coordinates substantially identical to or homologous to those of Table 1, Table 2, or Table 3 may be used with any available methods to prepare three dimensional models of HDM2 as well as to identify and design HDM2 ligands, inhibitors or antagonists or agonist molecules.

[0102] For instance, three-dimensional modeling may be performed using the experimentally determined coordinates derived from X-ray diffraction patterns, such as those in Table 1 or Table 2, for example, wherein such modeling includes, but is not limited to, drawing pictures of the actual structures, building physical models of the actual structures, and determining the structures of related subunits and HDM2/ligand and HDM2 subunit/ligand complexes using the coordinates. Such molecular modeling can utilize known X-ray diffraction molecular modeling algorithms or molecular modeling software to generate atomic coordinates corresponding to the three-dimensional structure of HDM2.

[0103] As described above, molecular modeling involves the use of computational methods, preferably computer assisted methods, to build realistic models of molecules that are identifiably related in sequence to the known crystal structure. It also involves modeling new small molecule inhibitors bound to HDM2 starting with the structures of HDM2 and or HDM2 complexed with known ligands or inhibitors. The methods utilized in ligand modeling range from molecular graphics (i.e., 3D representations) to computational chemistry (i.e., calculations of the physical and chemical properties) to make predictions about the binding of ligands or activities of ligands; to design new ligands; and to predict novel molecules, including ligands such as drugs, for chemical synthesis, collectively referred to as rational drug design.

[0104] One approach to rational drug design is to search for known molecular structures that might bind to an active site. Using molecular modeling, rational drug design programs can look at a range of different molecular structures of drugs that may fit into the active site of an enzyme, and by moving them in a three-dimensional environment it can be decided which structures actually fit the site well. See, for example, U.S. Appl. Nos. 60/275,629; 60/331,235; 60/379,617; and, 10/097,249. See, also, for example, data in Tables 1, 2 and 3.

[0105] An alternative but related rational drug design approach starts with the known structure of a complex with a small molecule ligand and models modifications of that small molecule in an effort to make additional favorable interactions with HDM2.

[0106] The present invention include the use of molecular and computer modeling techniques to design and select and design ligands, such as small molecule agonists or antagonists or other therapeutic agents that interact with HDM2. Such agents include, but are not limited to 1,4 benzodiazepines and derivatives thereof. For example, the invention as herein described includes the design of ligands that act as competitive inhibitors of at least one HDM2 function by binding to all, or a portion of, the active sites or other regions of HDM2.

[0107] This invention also includes the design of compounds that act as uncompetitive inhibitors of at least one function of HDM2. These inhibitors may bind to all, or a portion of, the active sites or other regions of HDM2 already bound to its substrate and may be more potent and less non-specific than competitive inhibitors that compete for HDM2 active sites. Similarly, non-competitive inhibitors that bind to and inhibit at least one function of HDM2 whether or not it is bound to another chemical entity may be designed using the atomic coordinates of HDM2 or complexes comprising HDM2 of this invention.

[0108] The atomic coordinates of the present invention also provide the needed information to probe a crystal of HDM2 with molecules composed of a variety of different chemical features to determine optimal sites for interaction between candidate inhibitors and/or activators and HDM2. For example, high resolution X-ray diffraction data collected from crystals saturated with solvent allows the determination of where each type of solvent molecule sticks. Small molecules that bind to those sites can then be designed and synthesized and tested for their inhibitory activity (Travis, J., *Science* 262:1374(1993)).

[0109] The present invention also includes methods for computationally screening small molecule databases and libraries for chemical entities, agents, ligands, or compounds that can bind in whole, or in part, to HDM2. In this screening, the quality of fit of such entities or compounds to the binding site or sites may be judged either by shape complementarity or by estimated interaction energy (Meng, E. C. et al., *J. Comp. Chem.* 13:505-524 (1992)).

[0110] The design of compounds that bind to promote or inhibit the functional activity of HDM2 according to this invention generally involves consideration of two factors. First, the compound must be capable of physically and structurally associating with HDM2. Non-covalent molecular interactions important in the association of HDM2 with the compound, include hydrogen bonding, van der Waals and hydrophobic interactions. Second, the compound must be able to assume a conformation that allows it to associate with HDM2. Although certain portions of the compound may not directly participate in the association with HDM2, those portions may still influence the overall conformation of the molecule. This, in turn, may have a significant impact on binding affinities, therapeutic efficacy, drug-like qualities and potency. Such conformational requirements include the overall three-dimensional structure and orientation of the chemical entity or compound in relation to all or a portion

of the active site or other region of HDM2, or the spacing between functional groups of a compound comprising several chemical entities that directly interact with HDM2.

[0111] The potential, predicted, inhibitory agonist, antagonist or binding effect of a ligand or other compound on HDM2 may be analyzed prior to its actual synthesis and testing by the use of computer modeling techniques. If the theoretical structure of the given compound suggests insufficient interaction and association between it and HDM2, synthesis and testing of the compound may be obviated. However, if computer modeling indicates a strong interaction, the molecule may then be synthesized and tested for its ability to interact with HDM2. In this manner, synthesis of inoperative compounds may be avoided. In some cases, inactive compounds are synthesized predicted on modeling and then tested to develop a SAR (structure-activity relationship) for compounds interacting with a specific region of HDM2.

[0112] One skilled in the art may use one of several methods to screen chemical entities fragments, compounds, or agents for their ability to associate with HDM2 and more particularly with the individual binding pockets or active sites of HDM2. This process may begin by visual inspection of, for example, the active site on the computer screen based on the atomic coordinates of HDM2 or HDM2 complexed with a ligand. Selected chemical entities, compounds, or agents may then be positioned in a variety of orientations, or docked within an individual binding pocket of HDM2. Docking may be accomplished using software such as Quanta and Sybyl, followed by energy minimization and molecular dynamics with standard molecular mechanics forcefields, such as CHARMM and AMBER.

[0113] Specialized computer programs may also assist in the process of selecting chemical entities. These include but are not limited to: GRID (Goodford, P. J., "A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules," *J. Med. Chem.* 28:849-857 (1985), available from Oxford University, Oxford, UK); MCSS (Miranker, A. and M. Karplus, "Functionality Maps of Binding Sites: A Multiple Copy Simultaneous Search Method." *Proteins: Structure, Function and Genetics* 11: 29-34 (1991), available from Molecular Simulations, Burlington, Mass.); AUTODOCK (Goodsell, D. S. and A. J. Olsen, "Automated Docking of Substrates to Proteins by Simulated Annealing" *Proteins: Structure, Function, and Genetics* 8:195-202 (1990), available from Scripps Research Institute, La Jolla, Calif.); and DOCK (Kuntz, I. D. et al., "A Geometric Approach to Macromolecule-Ligand Interactions," *J.-Mol. Biol.* 161:269-288 (1982), available from University of California, San Francisco, Calif.).

[0114] The use of software such as GRID, a program that determines probable interaction sites between probes with various functional group characteristics and the macromolecular surface, is used to analyze the surface sites to determine structures of similar inhibiting proteins or compounds. The GRID calculations, with suitable inhibiting groups on molecules (e.g., protonated primary amines) as the probe, are used to identify potential hotspots around accessible positions at suitable energy contour levels. The program DOCK may be used to analyze an active site or ligand binding site and suggest ligands with complementary steric properties.

[0115] Once suitable chemical entities, compounds, or agents have been selected, they can be assembled into a single ligand or compound or inhibitor or activator. Assembly may proceed by visual inspection of the relationship of the fragments to each other on the three-dimensional image. This may be followed by manual model building using software such as Quanta or Sybyl.

[0116] Useful programs to aid in connecting the individual chemical entities, compounds, or agents include but are not limited to: CAVEAT (Bartlett, P. A. et al., "CAVEAT: A Program to Facilitate the Structure-Derived Design of Biologically Active Molecules." In *Molecular Recognition in Chemical and Biological Problems*, Special Pub., Royal Chem. Soc., 78, pp. 82-196 (1989)); 3D Database systems such as MACCS-3D (MDL Information Systems, San Leandro, Calif. and Martin, Y.C., "3D Database Searching in Drug Design", *J. Med. Chem.* 35: 2145-2154 (1992); and HOOK (available from Molecular Simulations, Burlington, Mass.).

[0117] Several methodologies for searching three-dimensional databases to test pharmacophore hypotheses and select compounds for screening are available. These include the program CAVEAT (Bacon et al., *J. Mol. Biol.* 225:849-858 (1992)). For instance, CAVEAT uses databases of cyclic compounds which can act as "spacers" to connect any number of chemical fragments already positioned in the active site. This allows one skilled in the art to quickly generate hundreds of possible ways to connect the fragments already known or suspected to be necessary for tight binding.

[0118] Instead of proceeding to build an inhibitor activator, agonist or antagonist of HDM2 in a step-wise fashion one chemical entity at a time as described above, such compounds may be designed as a whole or "de novo" using either an empty active site or optionally including some portion(s) of a known molecules. These methods include: LUDI (Bohm, H.-J., "The Computer Program LUDI: A New Method for the De Novo Design of Enzyme Inhibitors", *J. Comput. Mol. Design*, 6, pp. 61-78 (1992), available from Biosym Technologies, San Diego, Calif.); LEGEND (Nishibata, Y. and A. Itai, *Tetrahedron* 47:8985 (1991), available from Molecular Simulations, Burlington, Mass.); and LeapFrog (available from Tripos Associates, St. Louis, Mo.).

[0119] For instance, the program LUDI can determine a list of interaction sites into which to place both hydrogen bonding and hydrophobic fragments. LUDI then uses a library of linkers to connect up to four different interaction sites into fragments. Then smaller "bridging" groups such as —CH₂— and —COO— are used to connect these fragments. For example, for the enzyme DHFR, the placements of key functional groups in the well-known inhibitor methotrexate were reproduced by LUDI. See also, Rotstein and Murcko, *J. Med. Chem.* 36: 1700-1710 (1992).

[0120] Other molecular modeling techniques may also be employed in accordance with this invention. See, e.g., Cohen, N. C. et al., "Molecular Modeling Software and Methods for Medicinal Chemistry, *J. Med. Chem.* 33:883-894 (1990). See also, Navia, M. A. and M. A. Murcko, "The Use of Structural Information in Drug Design," *Current Opinions in Structural Biology*, 2, pp. 202-210 (1992).

[0121] Once a compound has been designed or selected by the above methods, the affinity with which that compound

may bind or associate with HDM2 may be tested and optimized by computational evaluation and/or by testing biological activity after synthesizing the compound. Inhibitors or compounds may interact with the HDM2 in more than one conformation that is similar in overall binding energy. In those cases, the deformation energy of binding is taken to be the difference between the energy of the free compound and the average energy of the conformations observed when the compound binds to HDM2.

[0122] A compound designed or selected as binding or associating with HDM2 may be further computationally optimized so that in its bound state it would preferably lack repulsive electrostatic interaction with HDM2. Such non-complementary (e.g., electrostatic) interactions include repulsive charge-charge, dipole-dipole and charge-dipole interactions. Specifically, the sum of all electrostatic interactions between the inhibitor and HDM2 when the inhibitor is bound, preferably make a neutral or favorable contribution to the enthalpy of binding. Weak binding compounds will also be designed by these methods so as to determine SAR. See, for example, U.S. Appl. Nos. 60/275,629; 60/331,235; 60/379,617; and, 10/097,249.

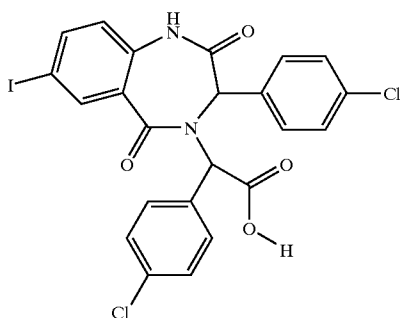
[0123] Specific computer software is available in the art to evaluate compound deformation energy and electrostatic interaction. Examples of programs designed for such uses include: Gaussian 92, revision C (M. J. Frisch, Gaussian, Inc., Pittsburgh, Pa., COPYRGT 1992); AMBER, version 4.0 (P. A. Kollman, University of California at San Francisco, COPYRGT 1994); QUANTA/CHARMM (Molecular Simulations, Inc., Burlington, Mass. COPYRGT 1994); and Insight II/Discover (Biosym Technologies Inc., San Diego, Calif. COPYRGT 1994). Other hardware systems and software packages will be known to those skilled in the art.

[0124] Once a compound that associates with HDM2 has been optimally selected or designed, as described above, substitutions may then be made in some of its atoms or side groups in order to improve or modify its binding properties. Generally, initial substitutions are conservative, i.e., the replacement group will have approximately the same size, shape, hydrophobicity and charge as the original group. It should, of course, be understood that components known in the art to alter conformation may be avoided. Such substituted chemical compounds may then be analyzed for efficiency of fit to HDM2 by the same computer methods described in detail, above.

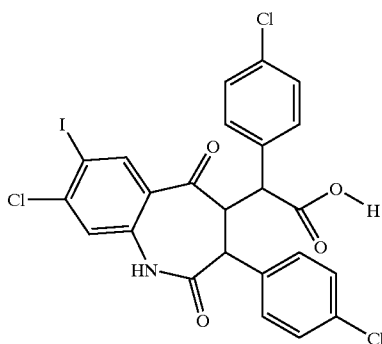
[0125] C. Use of Homology Structure Modeling to Design Ligands with Modulated Binding or Activity to HDM2

[0126] The present invention includes the use of the atomic coordinates and structures of HDM2 and/or HDM2 complexed with an inhibitor to design modifications to starting compounds, such as (4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-acetic acid; [8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid; and derivatives thereof that will bind more tightly or interact more specifically to the target enzyme. See, U.S. Appl. Nos. 60/275,629; 60/331,235; 60/379,617; and, 10/097,249, disclosing compounds 1 and 2 and derivatives thereof, all of which are incorporated herein in their entirety.

[0127] Compound 1 (338437): (4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-acetic acid



[0128] Compound 2 (876273): [8-Chloro-3-(4-chlorophenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chlorophenyl)-acetic acid



[0129] The structure of a complex between the HDM2 and the starting compound can be used to guide the modification of that compound to produce new compounds that have other desirable properties for applicable industrial and other uses (e.g., as pharmaceuticals), such as chemical stability, solubility or membrane permeability. (Lipinski et al., *Adv. Drug Deliv. Rev.* 23:3 (1997)).

[0130] Binding compounds, agonists, antagonists and such that are known in the art include but are not limited to p53 peptides and small molecule antagonists. See, for example, U.S. Appl. Nos. 60/275,629; 60/331,235; 60/379,617; and, 10/097,249 incorporated by reference herein in their entirety. Such compounds can be diffused into or soaked with the stabilized crystals of HDM2 to form a complex for collecting X-ray diffraction data. Alternatively, the compounds, known and unknown in the art, can be cocrystallized with HDM2 by mixing the compound with HDM2 before precipitation.

[0131] To produce custom high affinity and very specific compounds, the structure of HDM2 can be compared to the structure of a selected non-targeted molecule and a hybrid constructed by changing the structure of residues at the binding site for a ligand for the residues at the same positions of the non-target molecule. The process whereby this modeling is achieved is referred to as homology structure modeling. This is done computationally by removing the side chains from the molecule or target of known

structure and replacing them with the side chains of the unknown structure put in sterically plausible positions. In this way it can be understood how the shapes of the active site cavities of the targeted and non-targeted molecules differ. This process, therefore, provides information concerning how a bound ligand can be chemically altered in order to produce compounds that will bind tightly and specifically to the desired target but will simultaneously be sterically prevented from binding to the non-targeted molecule. Likewise, knowledge of portions of the bound ligands that are facing to the solvent would allow introduction of other functional groups for additional pharmaceutical purposes. The use of homology structure modeling to design molecules (ligands) that bind more tightly to the target enzyme than to the non-target enzyme has wide spread applicability.

[0132] D. High Throughput Assays

[0133] Any high throughput screening may be utilized to test new compounds which are identified or designed for their ability to interact with HDM2. For general information on high-throughput screening see, for example, Devlin, 1998, *High Throughput Screening*, Marcel Dekker; and U.S. Pat. No. 5,763,263. High throughput assays utilize one or more different assay techniques including, but not limited to, those described below.

[0134] Immunodiagnostics and Immunoassays. These are a group of techniques used for the measurement of specific biochemical substances, commonly at low concentrations in complex mixtures such as biological fluids, that depend upon the specificity and high affinity shown by suitably prepared and selected antibodies for their complementary antigens. A substance to be measured must, of necessity, be antigenic—either an immunogenic macromolecule or a haptenic small molecule. To each sample a known, limited amount of specific antibody is added and the fraction of the antigen combining with it, often expressed as the bound:free ratio, is estimated, using as indicator a form of the antigen labeled with radioisotope (radioimmunoassay), fluorescent molecule (fluoroimmunoassay), stable free radical (spin immunoassay), enzyme (enzyme immunoassay), or other readily distinguishable label.

[0135] Antibodies can be labeled in various ways, including: enzyme-linked immunosorbent assay (ELISA); radioimmuno assay (RIA); fluorescent immunoassay (FIA); chemiluminescent immunoassay (CLIA); and labeling the antibody with colloidal gold particles (immunogold).

[0136] Common assay formats include the sandwich assay, competitive or competition assay, latex agglutination assay, homogeneous assay, microtitre plate format and the microparticle-based assay.

[0137] Enzyme-linked immunosorbent assay (ELISA). ELISA is an immunochemical technique that avoids the hazards of radiochemicals and the expense of fluorescence detection systems. Instead, the assay uses enzymes as indicators. ELISA is a form of quantitative immunoassay based on the use of antibodies (or antigens) that are linked to an insoluble carrier surface, which is then used to "capture" the relevant antigen (or antibody) in the test solution. The antigen-antibody complex is then detected by measuring the activity of an appropriate enzyme that had previously been covalently attached to the antigen (or antibody).

[0138] For information on ELISA techniques, see, for example, Crowther, (1995) *ELISA—Theory and Practice* (Methods in Molecular Biology), Humana Press; Challacombe & Kemeny, (1998) *ELISA and Other Solid Phase Immunoassays—Theoretical and Practical Aspects*, John Wiley; Kemeny, (1991) *A Practical Guide to ELISA*, Pergamon Press; Ishikawa, (1991) *Ultrasensitive and Rapid Enzyme Immunoassay* (Laboratory Techniques in Biochemistry and Molecular Biology) Elsevier.

[0139] Colorimetric Assays for Enzymes. Colorimetry is any method of quantitative chemical analysis in which the concentration or amount of a compound is determined by comparing the color produced by the reaction of a reagent with both standard and test amounts of the compound, often using a colorimeter. A colorimeter is a device for measuring color intensity or differences in color intensity, either visually or photoelectrically.

[0140] Standard colorimetric assays of beta-galactosidase enzymatic activity are well known to those skilled in the art (see, for example, Norton et al., *Mol. Cell. Biol.* 5:281-290 (1985)). A colorimetric assay can be performed on whole cell lysates using O-nitrophenyl-beta-D-galactopyranoside (ONPG, Sigma) as the substrate in a standard colorimetric beta-galactosidase assay (Sambrook et al., (1989) *Molecular Cloning—A Laboratory Manual*, Cold Spring Harbor Laboratory Press). Automated colorimetric assays are also available for the detection of beta-galactosidase activity, as described in U.S. Pat. No. 5,733,720.

[0141] Immunofluorescence Assays. Immunofluorescence or immunofluorescence microscopy is a technique in which an antigen or antibody is made fluorescent by conjugation to a fluorescent dye and then allowed to react with the complementary antibody or antigen in a tissue section or smear. The location of the antigen or antibody can then be determined by observing the fluorescence by microscopy under ultra-violet light.

[0142] For general information on immunofluorescent techniques, see, for example, Knapp et al., (1978) *Immunofluorescence and Related Staining Techniques*, Elsevier; Allan, (1999) *Protein Localization by Fluorescent Microscopy—A Practical Approach* (The Practical Approach Series) Oxford University Press; Caul, (1993) *Immunofluorescence Antigen Detection Techniques in Diagnostic Microbiology*, Cambridge University Press. For detailed explanations of immunofluorescent techniques applicable to the present invention, see U.S. Pat. No. 5,912,176; U.S. Pat. No. 5,869,264; U.S. Pat. No. 5,866,319; and U.S. Pat. No. 5,861,259.

[0143] E. Databases and Computer Systems

[0144] An amino acid sequence or nucleotide sequence of HDM2 and/or X-ray diffraction data, useful for computer molecular modeling of HDM2 or a portion thereof, can be “provided” in a variety of mediums to facilitate use thereof. As used herein, “provided” refers to a manufacture, which contains, for example, an amino acid sequence or nucleotide sequence and/or atomic coordinates derived from X-ray diffraction data of the present invention, e.g., an amino acid or nucleotide sequence of HDM2, a representative fragment thereof, or a homologue thereof. Such a method provides the amino acid sequence and/or X-ray diffraction data in a form which allows a skilled artisan to analyze and molecular

model the three-dimensional structure of HDM2 or related molecules, including a subdomain thereof.

[0145] In one application of this embodiment, databases comprising data pertaining to HDM2, or at least one subdomain thereof, amino acid and nucleic acid sequence and/or X-ray diffraction data of the present invention is recorded on computer readable medium. As used herein, “computer readable medium” refers to any medium which can be read and accessed directly by a computer. Such media include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage media, and magnetic tape; optical storage media such as optical discs or CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media. A skilled artisan can readily appreciate how any of the presently known computer readable media can be used to create a manufacture comprising computer readable medium having recorded thereon an amino acid sequence and/or X-ray diffraction data of the present invention.

[0146] As used herein, “recorded” refers to a process for storing information on computer readable media. A skilled artisan can readily adopt any of the presently known methods for recording information on computer readable media to generate manufactures comprising an amino acid sequence and/or atomic coordinate/X-ray diffraction data information of the present invention.

[0147] A variety of data storage structures are available to a skilled artisan for creating a computer readable medium having recorded thereon an amino acid sequence and/or atomic coordinate/X-ray diffraction data of the present invention. The choice of the data storage structure will generally be based on the means chosen to access the stored information. In addition, a variety of data processor programs and formats can be used to store the sequence and X-ray data information of the present invention on computer readable media. The sequence information can be represented in a word processing text file, formatted in commercially-available software such as WordPerfect and MICROSOFT Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like. A skilled artisan can readily adapt any number of dataprocessor structuring formats (e.g. text file or database) in order to obtain computer readable media having recorded thereon the information of the present invention.

[0148] By providing computer readable media having sequence and/or atomic coordinates based on X-ray diffraction data, a skilled artisan can routinely access the sequence and atomic coordinate or X-ray diffraction data to model a related molecule, a subdomain, mimetic, or a ligand thereof. Computer algorithms are publicly and commercially available which allow a skilled artisan to access this data provided in a computer readable medium and analyze it for molecular modeling and/or RDD (rational drug design). See, e.g., *Biotechnology Software Directory*, MaryAnn Liebert Publ., New York (1995).

[0149] The present invention further provides systems, particularly computer-based systems, which contain the sequence and/or diffraction data described herein. Such systems are designed to do structure determination and RDD for HDM2 or at least one subdomain thereof. Non-limiting examples are microcomputer workstations available from

Silicon Graphics Incorporated and Sun Microsystems running UNIX based, Windows NT or IBM OS/2 operating systems.

[0150] As used herein, “a computer-based system” refers to the hardware means, software means, and data storage means used to analyze the sequence and/or X-ray diffraction data of the present invention. The minimum hardware means of the computer-based systems of the present invention comprises a central processing unit (CPU), input means, output means, and data storage means. A skilled artisan can readily appreciate which of the currently available computer-based systems are suitable for use in the present invention. A visualization device, such as a monitor, is optionally provided to visualize structure data.

[0151] As stated above, the computer-based systems of the present invention comprise a data storage means having stored therein sequence and/or atomic coordinate/X-ray diffraction data of the present invention and the necessary hardware means and software means for supporting and implementing an analysis means. As used herein, “data storage means” refers to memory which can store sequence or atomic coordinate/X-ray diffraction data of the present invention, or a memory access means which can access manufactures having recorded thereon the sequence or X-ray data of the present invention.

[0152] As used herein, “search means” or “analysis means” refers to one or more programs which are implemented on the computer-based system to compare a target sequence or target structural motif with the sequence or X-ray data stored within the data storage means. Search means are used to identify fragments or regions of a protein which match a particular target sequence or target motif. A variety of known algorithms are disclosed publicly and a variety of commercially available software for conducting search means are and can be used in the computer-based systems of the present invention. A skilled artisan can readily recognize that any one of the available algorithms or implementing software packages for conducting computer analyses can be adapted for use in the present computer-based systems.

[0153] As used herein, “a target structural motif,” or “target motif,” refers to any rationally selected sequence or combination of sequences in which the sequence(s) are chosen based on a three-dimensional configuration or electron density map which is formed upon the folding of the target motif. There are a variety of target motifs known in the art. Protein target motifs include, but are not limited to, enzymatic active sites, inhibitor binding sites, structural subdomains, epitopes, functional domains and signal sequences. Similar motifs are known for RNA. A variety of structural formats for the input and output means can be used to input and output the information in the computer-based systems of the present invention.

[0154] A variety of comparing means can be used to compare a target sequence or target motif with the data storage means to identify structural motifs or electron density maps derived in part from the atomic coordinate/X-ray diffraction data. A skilled artisan can readily recognize that any one of the publicly available computer modeling programs can be used as the search means for the computer-based systems of the present invention.

[0155] F. Target Molecule Fragments and Portions

[0156] Fragments of HDM2, for instance fragments comprising active sites defined by two or more amino acids selected from the group consisting of: Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷, may be prepared by any available means including synthetic or recombinant means. Such fragments may then be used in the assays as described above, for instance, high through-put assays to detect interactions between prospective agents and the active site within the fragment.

[0157] For recombinant expression or production of the fragments of the invention, nucleic acid molecules encoding the fragment may be prepared. As used herein, “nucleic acid” is defined as RNA or DNA that encodes a protein or peptide as defined above, or is complementary to nucleic acid sequence encoding such peptides, or hybridizes to such nucleic acid and remains stably bound to it under appropriate stringency conditions.

[0158] Nucleic acid molecules encoding fragments of the invention may differ in sequence because of the degeneracy in the genetic code or may differ in sequence as they encode proteins or protein fragments that differ in amino acid sequence. Homology or sequence identity between two or more such nucleic acid molecules is determined by BLAST (Basic Local Alignment Search Tool) analysis using the algorithm employed by the programs blastp, blastn, blastx, tblastn and tblastx (Karlin et al., *Proc. Natl. Acad. Sci. USA* 87:2264-2268 (1990) and Altschul, et al., *J. Mol. Evol.* 36:290-300 (1993), fully incorporated by reference) which are tailored for sequence similarity searching.

[0159] The approach used by the BLAST program is to first consider similar segments between a query sequence and a database sequence, then to evaluate the statistical significance of all matches that are identified and finally to summarize only those matches which satisfy a preselected threshold of significance. For a discussion of basic issues in similarity searching of sequence databases, see Altschul et al. (*Nat. Genet.* 6, 119-129 (1994)) which is fully incorporated by reference. The search parameters for histogram, descriptions, alignments, expect (i.e., the statistical significance threshold for reporting matches against database sequences), cutoff, matrix and filter are at the default settings. The default scoring matrix used by blastp, blastx, tblastn, and tblastx is the BLOSUM62 matrix (Henikoff et al., *Proc. Natl. Acad. Sci. USA* 89:10915-10919 (1992), fully incorporated by reference). Four blastn parameters were adjusted as follows: Q=10 (gap creation penalty); R=10 (gap extension penalty); wink=1 (generates word hits at every winkth position along the query); and gapw=16 (sets the window width within which gapped alignments are generated). The equivalent Blastp parameter settings were Q=9; R=2; wink=1; and gapw=32. A Bestfit comparison between sequences, available in the GCG package version 10.0, uses DNA parameters GAP=50 (gap creation penalty) and LEN=3 (gap extension penalty) and the equivalent settings in protein comparisons are GAP=8 and LEN=2.

[0160] “Stringent conditions” are those that (1) employ low ionic strength and high temperature for washing, for example, 0.015 M NaCl/0.0015 M sodium citrate/0.1% SDS at 50° C. or (2) employ during hybridization a denaturing agent such as formamide, for example, 50% formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5

with 750 mM NaCl, 75 mM sodium citrate at 42° C. Another example is use of 50% formamide, 5×SSC, 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5× Denhardt's solution, sonicated salmon sperm DNA (50 mg/ml), 0.1% SDS and 10% dextran sulfate at 42° C., with washes at 42° C. in 0.2×SSC and 0.1% SDS. A skilled artisan can readily determine and vary the stringency conditions appropriately to obtain a clear and detectable hybridization signal.

[0161] As used herein, a nucleic acid molecule is said to be "isolated" when the nucleic acid molecule is substantially separated from contaminant nucleic acid encoding other polypeptides from the source of nucleic acid.

[0162] The encoding nucleic acid molecules of the present invention (i.e., synthetic oligonucleotides) and those that are used as probes or specific primers for polymerase chain reaction (PCR) or to synthesize gene sequences encoding proteins of the invention can easily be synthesized by chemical techniques, for example, the phosphotriester method of Matteucci et al. (*J. Am. Chem. Soc.* 103: 185-3191 (1981)) or using automated synthesis methods. In addition, larger DNA segments can readily be prepared by well known methods, such as synthesis of a group of oligonucleotides that define various modular segments of the gene, followed by ligation of oligonucleotides to build the complete modified gene.

[0163] The encoding nucleic acid molecules of the present invention may further be modified so as to contain a detectable label for diagnostic and probe purposes. A variety of such labels are known in the art and can readily be employed with the encoding molecules herein described. Suitable labels include, but are not limited to, biotin, radiolabeled nucleotides and the like. A skilled artisan can employ any of the art-known labels to obtain a labeled encoding nucleic acid molecule.

[0164] The present invention further provides recombinant DNA molecules (rDNA) that contain a coding sequence for a protein fragment as described above. As used herein, a rDNA molecule is a DNA molecule that has been subjected to molecular manipulation. Methods for generating rDNA molecules are well known in the art, for example, see Sambrook et al. *Molecular Cloning—A Laboratory Manual*, Cold Spring Harbor Laboratory Press (1989). In the preferred rDNA molecules, a coding DNA sequence is operably linked to expression control sequences and/or vector sequences.

[0165] The choice of vector and expression control sequences to which one of the protein encoding sequences of the present invention is operably linked depends directly, as is well known in the art, on the functional properties desired (e.g., protein expression, and the host cell to be transformed). A vector of the present invention may be capable of directing the replication or insertion into the host chromosome, and preferably also expression, of the structural gene included in the rDNA molecule.

[0166] Expression control elements that are used for regulating the expression of an operably linked protein encoding sequence are known in the art and include, but are not limited to, inducible promoters, constitutive promoters, secretion signals, and other regulatory elements. Preferably, the inducible promoter is readily controlled, such as being responsive to a nutrient in the host cell's medium.

[0167] The present invention further provides host cells transformed with a nucleic acid molecule that encodes a protein fragment of the present invention. The host cell can be either prokaryotic or eukaryotic. Eukaryotic cells useful for expression of a protein of the invention are not limited, so long as the cell line is compatible with cell culture methods and compatible with the propagation of the expression vector and expression of the gene product. Preferred eukaryotic host cells include, but are not limited to, yeast, insect and mammalian cells, preferably vertebrate cells such as those from a mouse, rat, monkey or human cell line. Preferred eukaryotic host cells include Chinese hamster ovary (CHO) cells available from the ATCC as CCL61, NIH Swiss mouse embryo cells NIH-3T3 available from the ATCC as CRL1658, baby hamster kidney cells (BHK), and the like eukaryotic tissue culture cell lines.

[0168] Transformed host cells of the invention may be cultured under conditions that allow the production of the recombinant protein. Optionally the recombinant protein is isolated from the medium or from the cells; recovery and purification of the protein may not be necessary in some instances where some impurities may be tolerated.

[0169] Kits may also be prepared with any of the above described nucleic acid molecules, protein fragments, vector and/or host cells optionally packaged with the reagents needed for a specific assay, such as those described above. In such kits, the protein fragments or other reagents may be attached to a solid support, such as glass or plastic beads.

[0170] G. Integrated Procedures Which Utilize the Present Invention

[0171] Molecular modeling is provided by the present invention for rational drug design (RDD) of mimetics and ligands of HDM2. As described above, the drug design paradigm uses computer modeling programs to determine potential mimetics and ligands which are expected to interact with sites on the protein. The potential mimetics or ligands are then screened for activity and/or binding and/or interaction. For HDM2-related mimetics or ligands, screening methods can be selected from assays for at least one biological activity of HDM2, e.g., such as blocking p53 binding, according to known method steps. See, for example, Kussie et al., *Science* 274:948-953 (1996); Bottger et al., *J. Mol. Biol.* 269:744-756 (1997).

[0172] Thus, the tools and methodologies provided by the present invention may be used in procedures for identifying and designing ligands which bind in desirable ways with the target. Such procedures utilize an iterative process whereby ligands are synthesized, tested and characterized. New ligands can be designed based on the information gained in the testing and characterization of the initial ligands and then such newly identified ligands can themselves be tested and characterized. This series of processes may be repeated as many times as necessary to obtain ligands with the desirable binding properties.

[0173] The following steps serve as an example of the overall procedure:

[0174] 1. A biological activity of a target is selected (e.g., binding to p53).

[0175] 2. A ligand is identified that appears to be in some way associated with the chosen biological activity (e.g., the

ligand may be an inhibitor of a known activity). The activity of the ligand may be tested by in vivo and/or in vitro methods.

[0176] A ligand of the present invention can be, but is not limited to, at least one selected from a lipid, a nucleic acid, a compound, a protein, an element, an antibody, a saccharide, an isotope, a carbohydrate, an imaging agent, a lipoprotein, a glycoprotein, an enzyme, a detectable probe, and antibody or fragment thereof, or any combination thereof, which can be detectably labeled as for labeling antibodies. Such labels include, but are not limited to, enzymatic labels, radioisotope or radioactive compounds or elements, fluorescent compounds or metals, chemiluminescent compounds and bioluminescent compounds. Alternatively, any other known diagnostic or therapeutic agent can be used in a method of the invention. Suitable compounds are then tested for activities in relationship to the target.

[0177] Complexes between HDM2 and ligands are made either by co-crystallization or more commonly by diffusing the small molecule ligand into the crystal. X-ray diffraction data from the complex crystal are measured and a difference electron density map is calculated. This process provides the precise location of the bound ligand on the target molecule. The difference Fourier is calculated using measure diffraction amplitudes and the phases of these reflections calculated from the coordinates.

[0178] 3. Using the methods of the present invention, X-ray crystallography is utilized to create electron density maps and/or molecular models of the interaction of the ligand with the target molecule.

[0179] The entry of the coordinates of the target into the computer programs discussed above results in the calculation of most probable structure of the macromolecule. These structures are combined and refined by additional calculations using such programs to determine the probable or actual three-dimensional structure of the target including potential or actual active or binding sites of ligands. Such molecular modeling (and related) programs useful for rational drug design of ligands or mimetics, are also provided by the present invention.

[0180] 4. The electron density maps and/or molecular models obtained in Step 3 are compared to the electron density maps and/or molecular models of a non-ligand containing target and the observed/calculated differences are used to specifically locate the binding of the ligand on the target or subunit.

[0181] 5. Modeling tools, such as computational chemistry and computer modeling, are used to adjust or modify the structure of the ligand so that it can make additional or different interactions with the target.

[0182] The ligand design uses computer modeling programs which calculate how different molecules interact with the various sites of a target. This procedure determines potential ligands or mimetics of the ligand(s).

[0183] The ligand design uses computer modeling programs which calculate how different molecules interact with the various sites of the target, subunit, or a fragment thereof. Thus, this procedure determines potential ligands or ligand mimetics.

[0184] 6. The newly designed ligand from Step 5 can be tested for its biological activity using appropriate in vivo or in vitro tests, including the high throughput screening methods discussed above.

[0185] The potential ligands or mimetics are then screened for activity relating to HDM2, or at least a fragment thereof. Such screening methods are selected from assays for at least one biological activity of the native target.

[0186] The resulting ligands or mimetics, provided by methods of the present invention, are useful for treating, screening or preventing diseases in animals, such as mammals (including humans) and birds.

[0187] 7. Of course, each of the above steps can be modified as desired by those of skill in the art so as to refine the procedure for the particular goal in mind. Also, additional X-ray diffraction data may be collected on HDM2, HDM2/ligand complexes, HDM2 structural target motifs and HDM2 subunit/ligand complexes at any step or phase of the procedure. Such additional diffraction data can be used to reconstruct electron density maps and molecular models which may further assist in the design and selection of ligands with the desirable binding attributes.

[0188] It is to be understood that the present invention is considered to include stereoisomers as well as optical isomers, e.g., mixtures of enantiomers as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in selected compounds, ligands or mimetics of the present series.

[0189] Some of the compounds or agents disclosed or discovered by the methods herein may contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present invention is also meant to encompass all such possible forms as well as their racemic and resolved forms and mixtures thereof. When the compounds described or discovered herein contain olefinic double bonds or other centers of geometric asymmetry, and unless otherwise specified, it is intended to include both E and Z geometric isomers. All tautomers are intended to be encompassed by the present invention as well.

[0190] As used herein, the term "stereoisomers" is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

[0191] As used herein, the term "chiral center" refers to a carbon atom to which four different groups are attached.

[0192] As used herein, the term "enantiomer" or "enantiomeric" refers to a molecule that is nonsuperimposable on its mirror image and hence optically active wherein the enantiomer rotates the plane of polarized light in one direction and its mirror image rotates the plane of polarized light in the opposite direction.

[0193] As used herein, the term "racemic" refers to a mixture of equal parts of enantiomers and which is optically active.

[0194] As used herein, the term "resolution" refers to the separation or concentration or depletion of one of the two

enantiomeric forms of a molecule. In the context of this application, the term "resolution" also refers to the amount of detail which can be resolved by the diffraction experiment. Or in other terms, since the inherent disorder of a protein crystal diffraction pattern fades away at some diffraction angle $\theta_{\max}$, the corresponding distance $d_{\min}$ of the reciprocal lattices is determined by Bragg's law.

$$d_{\min} = \frac{\lambda}{2\sin\theta_{\max}}$$

[0195] In practice in protein crystallography it is usual to quote the nominal resolution of a protein electron density in terms of $d_{\min}$, the minimum lattice distance to which data is included in the calculation of the map.

[0196] The compounds of the present invention are also useful at inhibiting the interaction between p53 and MDMX. MDMX, also known as MDM4, is a cellular protein involved in the regulation of the cell cycle. For example, see Riemenschneider et al., *Cancer Res.* 59(24):6091-6096 (1999).

[0197] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. The following working examples therefore, specifically point out preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

EXAMPLES

Example 1

[0198]

[0199] GST HDM2 Fusion Protein Construction and Expression

[0200] cDNA encoding residues 17-125 of HDM2 were cloned and expressed as follows: PCR was performed using ATCC item number 384988 containing partial human MDM2 sequence as template and the following primers:

Forward:
5'-CTCTCTCGGATCCAGATTCAGCTTCGGAACAAGAG

Reverse:
5'-TATATATCTCGAGTCAGTTCTCACTCACAGATGTACCTGAG.

[0201] The PCR product was then digested with BamHI and XhoI (sequence recognition sites underlined in primers), gel purified, and ligated into pGEX4t-3 which had also been digested with BamHI and XhoI. The purified plasmid was transformed into *E. coli* strain BL21. Protein was produced at 37° C. in 2 L shake flasks containing 800 ml LB (Laura Bertani medium)+100 μ g/ml ampicillin and supplemented with 0.2% glycerol. Briefly media was inoculated with 16 ml of overnight culture and induced with 1 mM IPTG when the absorbance at 600 reached 0.6-0.8 OD. Cells were harvested 5 hr post induction.

[0202] For HDM2 23-114, the primers used were as follows:

5'-CGACGATTGGATCCGAACAAGACCCTG
3'-GGCTACTACTCCGAGTCATTCCTGCTGATTGACTAC

[0203] For HDM2 17-111, the primers used were

5'-CTCTCTCGGATCCAGATTCAGCTTCGGAACAAGAG
3'-TTCAGCAGCTCGAGTCAATTGACTACTACCAAGTTC

[0204] The PCR fragments were cloned and expressed as above with a few exceptions. *E. coli* strain BL21 RIL was used for expression. Cells were grown at 37° C. until A_{600} of 0.2, then transferred to room temperature and induced at A_{600} of 0.6-0.8 with 0.1 mM IPTG. Cells were harvested 5 hours post induction, centrifuged, and resuspended in PBS to 10 ml/g cell paste.

[0205] Protein Production

[0206] Cells were lysed in an Avestin microfluidizer, centrifuged, and the supernatant bound to a glutathione sepharose 4B resin (Pharmacia). The resin was washed with PBS and the HDM2 construct of interest was cleaved from the GST-resin by the addition of 2 μ g/ml thrombin (Enzyme Research Labs). The cleaved HDM2 was loaded onto a Sepharose SP Fast Flow resin (Pharmacia), and eluted with a 20 mM HEPES pH. 7.5, 150 mM NaCl. Glutathione was added to 5 mM, and the protein stored at -70° C. The resulting protein has an N-terminal Glycine before amino acid 17 (Serine).

[0207] Protein Preparation for Crystallography

[0208] HDM2 17-111 was complexed with the compound of interest by dialysis at a concentration of 0.7 mg/ml, the buffer brought to 20 mM HEPES pH. 7.4, 100 mM NaCl, 5 mM DTT, filtered through a 0.02 μ m filter, and concentrated to 10 mg/ml.

Example 2

[0209] Crystallization and Data Collection

[0210] In a typical crystallization experiment, 1-2 μ l of HDM2 protein, complexed with a compound and concentrated to ca. 10 mg/ml, was mixed in a 1:1 ratio with well solution (1.8-2.4M $(\text{NH}_4)_2\text{SO}_4$, 100 mM buffer pH. 6.5-9.0, 2% PEG 400, 100 mM NaSCN) and placed on a glass cover slip. The cover slip was inverted and sealed over a reservoir of 500-1000 μ l of well solution and incubated at 4° C. Crystals usually appeared over night and were ready to harvest after 3-7 days. Crystals were harvested with a nylon loop, placed for less than 30 seconds in cryo-solution (2.2M $(\text{NH}_4)_2\text{SO}_4$, 100 mM bis-tris-propane pH. 7.5, 2% PEG 400, 100 mM NaSCN, 15% glycerol) and frozen by immersion in liquid nitrogen or liquid propane. Data were collected at 120K on a Bruker AXS MO6XCE rotating anode and a SMART 6000 CCD detector. The diffraction data was processed with the Proteum suite (Bruker AXS).

Example 3

[0211] Assay Methods: Peptide Binding Assay

[0212] The inhibition of MDM2 binding to p53 was measured using a p53 peptide analog binding to MDM2

residues 17-125. The published crystal structure of this complex (Kussie, P. H., et al., *Science* 274:948-953 (1996)) validates this fragment as containing the p53 binding site, and we have solved the X-ray structure of the p53 peptide analog MPRFMDYWEGLN, described to be a peptide inhibitor of the MDM2 p53 interaction (Böttger, A., et al., *J Mol Biol* 269:744-756 (1997)). The assay uses N terminal fluorescein RFMDYWEGL peptide (F1 9 mer). Compound was incubated for 15 minutes with 30 nM fluorescein peptide F1 9 mer and 120 nM HDM2 17-125 in 50 mM HEPES pH. 7.5, 150 mM NaCl, 3 mM octyl glucoside. The polarization of the fluorescein label was measured by excitation at 485 nm and emission at 530 nm. Polarization was expressed as a percent of a no compound control, using no MDM2 with F1 9 mer as background.

Example 4

[0213] HDM2 Atomic Coordinates: Table 1 (Compound 1)

[0214] Table 1 describes the 3-dimensional atomic coordinates of HDM2 complexed with compound 1 (338437) ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-acetic acid and bound waters in standard pdb-format. The relevant crystallographic data are contained in the REMARK section of Table 1. Two molecules of HDM2, related by non-crystallographic symmetry, are present in the asymmetric unit and are identified by the CHAINID of A for the first molecule and B for the second molecule. The compound (compound 1) is present under the residue name DCB. Compound 1 and HDM2 molecule sharing the same CHAINID are forming a complex.

Example 5

[0215] HDM2 Atomic Coordinates: Table 2 (Compound 2)

[0216] Compound 2 [8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-[3-(4-chloro-phenyl)-acetic acid (876273) and HDM2 protein were cocrystallized as described above in Example 2. Table 2 describes the 3-dimensional atomic coordinates of HDM2 complexed with compound 2 (876273) ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-[3-(4-chloro-phenyl)-acetic acid). The relevant crystallographic data are contained in the REMARK section of Table 2. Data were collected as described above. Different crystal forms can be observed under the same crystallization conditions used to obtain the trigonal crystal form.

Example 6

[0217] HDM2 Atomic Coordinates: Table 3

[0218] Table 3 describes the 3-dimensional atomic coordinates of HDM2 cocrystallized with compound 2 (compound 876273: [8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-[3-(4-chloro-phenyl)-acetic acid) in tetragonal spacegroup aligned to the structure of HDM2 complexed with compound 1 (compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-acetic acid). The relevant crystallographic data are contained in the REMARK section of Table 3. Data were collected as described above.

[0219] The pdb-format is described on various sites on the web. Depending on the program crystallographic application minor modifications to this format may be found. A good primer is provided by this link at CCP4 "www.ccp4.ac.uk/html/pdbformat.html". A more extended description can be found at the RCSB home page.

Example 7

[0220] Phasing: Model Building and Refinement

[0221] Phases were obtained by molecular replacement using the published HDM2-structure as a search model in CNX (Brunger, A. T., et al., P. D. *Acta Cryst D*54:905-921 (1998); Accelrys Inc.). Alternating cycles of structure refinement and model building were carried out according to standard protocols using CNX and O (Jones, T. A., et al., *Acta Cryst A*47: 110-119 (1991)).

Example 8

[0222] Structural Features of HDM2

[0223] FIG. 1. Ribbon representation of HDM2 bound to compound 1 (compound 338437: ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-acetic acid).

[0224] FIG. 2. Fit of compound 1 (compound 338437: ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-acetic acid into the active site of HDM2 presented as a molecular surface.

[0225] Although the present invention has been described in detail with reference to examples above, it is understood that various modifications can be made without departing from the spirit of the invention. All cited patents, patent applications and publications and other documents cited in this application are herein incorporated by reference in their entirety.

TABLE 1

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-acetic acid
REMARK coordinates from restrained individual B-factor refinement
REMARK refinement resolution: 500.0-2.6 Å
REMARK starting r = 0.2398 free_r = 0.2763
REMARK final r = 0.2390 free_r = 0.2765
REMARK B rmsd for bonded mainchain atoms = 1.358 target = 1.5
REMARK B rmsd for bonded sidechain atoms = 1.887 target = 2.0
REMARK B rmsd for angle mainchain atoms = 2.371 target = 2.0

ATOM C	1	C	GLY	A	16	47.235	17.293	23.953	1.00	68.07	A
ATOM O	2	O	GLY	A	16	48.284	16.646	23.907	1.00	68.13	A
ATOM N	3	N	GLY	A	16	44.698	17.056	23.726	1.00	66.75	A
ATOM C	4	CA	GLY	A	16	46.042	16.904	23.083	1.00	67.77	A
ATOM N	5	N	SER	A	17	47.083	18.352	24.744	1.00	67.81	A
ATOM C	6	CA	SER	A	17	48.154	18.831	25.618	1.00	66.82	A
ATOM C	7	CB	SER	A	17	48.407	17.831	26.743	1.00	67.50	A
ATOM O	8	OG	SER	A	17	47.247	17.658	27.540	1.00	67.94	A
ATOM C	9	C	SER	A	17	49.456	19.118	24.864	1.00	65.58	A
ATOM O	10	O	SER	A	17	49.699	20.265	24.476	1.00	66.26	A
ATOM N	11	N	GLN	A	18	50.304	18.108	24.657	1.00	63.21	A
ATOM C	12	CA	GLN	A	18	51.543	18.367	23.921	1.00	60.51	A
ATOM C	13	CB	GLN	A	18	52.778	17.995	24.735	1.00	60.31	A
ATOM C	14	CG	GLN	A	18	53.833	19.070	24.574	1.00	59.93	A
ATOM C	15	CD	GLN	A	18	53.200	20.457	24.506	1.00	59.70	A
ATOM O	16	OE1	GLN	A	18	52.584	20.919	25.464	1.00	59.78	A
ATOM N	17	NE2	GLN	A	18	53.333	21.112	23.362	1.00	59.29	A
ATOM C	18	C	GLN	A	18	51.619	17.752	22.529	1.00	58.18	A
ATOM O	19	O	GLN	A	18	52.569	17.049	22.158	1.00	57.08	A
ATOM N	20	N	ILE	A	19	50.573	18.064	21.776	1.00	54.61	A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM C	21	CA	ILE	A	19	50.380	17.673	20.399	1.00	49.59 A
ATOM C	22	CB	ILE	A	19	49.130	16.771	20.256	1.00	47.27 A
ATOM C	23	CG2	ILE	A	19	48.730	16.643	18.802	1.00	46.21 A
ATOM C	24	CG1	ILE	A	19	49.407	15.403	20.880	1.00	44.27 A
ATOM C	25	CD1	ILE	A	19	50.565	14.675	20.263	1.00	40.62 A
ATOM C	26	C	ILE	A	19	50.112	19.056	19.806	1.00	48.49 A
ATOM O	27	O	ILE	A	19	49.344	19.838	20.374	1.00	46.95 A
ATOM N	28	N	PRO	A	20	50.765	19.396	18.686	1.00	47.71 A
ATOM C	29	CD	PRO	A	20	51.681	18.610	17.840	1.00	46.47 A
ATOM C	30	CA	PRO	A	20	50.521	20.721	18.107	1.00	46.58 A
ATOM C	31	CB	PRO	A	20	51.072	20.574	16.695	1.00	46.92 A
ATOM C	32	CG	PRO	A	20	52.256	19.667	16.919	1.00	46.74 A
ATOM C	33	C	PRO	A	20	49.041	21.112	18.134	1.00	45.69 A
ATOM O	34	O	PRO	A	20	48.181	20.376	17.636	1.00	45.19 A
ATOM N	35	N	ALA	A	21	48.751	22.264	18.738	1.00	43.36 A
ATOM C	36	CA	ALA	A	21	47.379	22.755	18.832	1.00	40.68 A
ATOM C	37	CB	ALA	A	21	47.371	24.193	19.350	1.00	39.15 A
ATOM C	38	C	ALA	A	21	46.710	22.676	17.460	1.00	39.20 A
ATOM O	39	O	ALA	A	21	45.518	22.379	17.351	1.00	38.64 A
ATOM N	40	N	SER	A	22	47.490	22.937	16.414	1.00	37.13 A
ATOM C	41	CA	SER	A	22	46.996	22.881	15.042	1.00	34.91 A
ATOM C	42	CB	SER	A	22	48.140	23.167	14.077	1.00	36.91 A
ATOM O	43	OG	SER	A	22	49.177	22.202	14.208	1.00	39.98 A
ATOM C	44	C	SER	A	22	46.428	21.494	14.755	1.00	32.16 A
ATOM O	45	O	SER	A	22	45.349	21.356	14.179	1.00	32.41 A
ATOM N	46	N	GLU	A	23	47.179	20.474	15.159	1.00	28.39 A
ATOM C	47	CA	GLU	A	23	46.785	19.084	14.981	1.00	25.53 A
ATOM C	48	CB	GLU	A	23	47.986	18.167	15.280	1.00	24.74 A
ATOM C	49	CG	GLU	A	23	47.650	16.698	15.507	1.00	22.09 A
ATOM C	50	CD	GLU	A	23	48.881	15.805	15.524	1.00	21.23 A
ATOM O	51	OE1	GLU	A	23	49.956	16.270	15.952	1.00	22.29 A
ATOM O	52	OE2	GLU	A	23	48.775	14.631	15.120	1.00	19.31 A
ATOM C	53	C	GLU	A	23	45.597	18.733	15.879	1.00	23.76 A
ATOM O	54	O	GLU	A	23	44.756	17.928	15.501	1.00	21.78 A
ATOM N	55	N	GLN	A	24	45.524	19.345	17.059	1.00	22.33 A
ATOM C	56	CA	GLN	A	24	44.423	19.086	17.985	1.00	21.86 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM C	57	CB	GLN	A	24	44.628	19.838	19.294	1.00	22.56 A
ATOM C	58	CG	GLN	A	24	45.721	19.267	20.157	1.00	26.35 A
ATOM C	59	CD	GLN	A	24	45.896	20.017	21.458	1.00	27.27 A
ATOM O	60	OE1	GLN	A	24	44.964	20.131	22.262	1.00	27.74 A
ATOM N	61	NE2	GLN	A	24	47.101	20.533	21.676	1.00	29.00 A
ATOM C	62	C	GLN	A	24	43.063	19.464	17.423	1.00	21.99 A
ATOM O	63	O	GLN	A	24	42.047	18.871	17.786	1.00	21.50 A
ATOM N	64	N	GLU	A	25	43.045	20.456	16.542	1.00	22.95 A
ATOM C	65	CA	GLU	A	25	41.800	20.921	15.939	1.00	24.26 A
ATOM C	66	CB	GLU	A	25	41.874	22.432	15.665	1.00	25.71 A
ATOM C	67	CG	GLU	A	25	42.226	23.265	16.884	1.00	27.74 A
ATOM C	68	CD	GLU	A	25	41.218	23.107	18.006	1.00	30.63 A
ATOM O	69	OE1	GLU	A	25	41.640	23.112	19.187	1.00	32.01 A
ATOM O	70	OE2	GLU	A	25	40.005	22.987	17.705	1.00	30.20 A
ATOM C	71	C	GLU	A	25	41.479	20.179	14.644	1.00	23.62 A
ATOM O	72	O	GLU	A	25	40.472	20.461	13.995	1.00	24.16 A
ATOM N	73	N	THR	A	26	42.337	19.237	14.267	1.00	22.53 A
ATOM C	74	CA	THR	A	26	42.123	18.462	13.052	1.00	21.97 A
ATOM C	75	CB	THR	A	26	43.138	17.299	12.955	1.00	23.07 A
ATOM O	76	OG1	THR	A	26	44.472	17.828	12.972	1.00	22.96 A
ATOM C	77	CG2	THR	A	26	42.920	16.499	11.675	1.00	21.12 A
ATOM C	78	C	THR	A	26	40.705	17.894	13.031	1.00	21.66 A
ATOM O	79	O	THR	A	26	40.281	17.217	13.962	1.00	19.94 A
ATOM N	80	N	LEU	A	27	39.974	18.187	11.963	1.00	23.11 A
ATOM C	81	CA	LEU	A	27	38.602	17.713	11.805	1.00	25.25 A
ATOM C	82	CB	LEU	A	27	37.888	18.593	10.775	1.00	26.19 A
ATOM C	83	CG	LEU	A	27	36.362	18.646	10.828	1.00	28.80 A
ATOM C	84	CD1	LEU	A	27	35.918	19.212	12.183	1.00	26.94 A
ATOM C	85	CD2	LEU	A	27	35.840	19.512	9.677	1.00	28.47 A
ATOM C	86	C	LEU	A	27	38.620	16.240	11.350	1.00	24.95 A
ATOM O	87	O	LEU	A	27	39.275	15.901	10.359	1.00	26.23 A
ATOM N	88	N	VAL	A	28	37.898	15.373	12.064	1.00	22.99 A
ATOM C	89	CA	VAL	A	28	37.882	13.938	11.749	1.00	20.72 A
ATOM C	90	CB	VAL	A	28	38.810	13.143	12.719	1.00	18.95 A
ATOM C	91	CG1	VAL	A	28	40.213	13.729	12.734	1.00	17.23 A
ATOM C	92	CG2	VAL	A	28	38.230	13.164	14.118	1.00	16.75 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM C	93	C	VAL	A	28	36.500	13.284	11.833	1.00	21.21 A
ATOM O	94	O	VAL	A	28	35.593	13.805	12.486	1.00	19.81 A
ATOM N	95	N	ARG	A	29	36.365	12.131	11.174	1.00	22.25 A
ATOM C	96	CA	ARG	A	29	35.126	11.340	11.159	1.00	23.75 A
ATOM C	97	CB	ARG	A	29	34.559	11.229	9.742	1.00	25.97 A
ATOM C	98	CG	ARG	A	29	33.678	12.388	9.308	1.00	32.69 A
ATOM C	99	CD	ARG	A	29	33.206	12.199	7.866	1.00	38.68 A
ATOM N	100	NE	ARG	A	29	32.256	13.231	7.455	1.00	45.71 A
ATOM C	101	CZ	ARG	A	29	31.002	13.322	7.901	1.00	50.53 A
ATOM N	102	NH1	ARG	A	29	30.534	12.439	8.777	1.00	52.47 A
ATOM N	103	NH2	ARG	A	29	30.208	14.299	7.472	1.00	52.60 A
ATOM C	104	C	ARG	A	29	35.402	9.931	11.680	1.00	22.61 A
ATOM O	105	O	ARG	A	29	35.891	9.076	10.944	1.00	23.74 A
ATOM N	106	N	PRO	A	30	35.094	9.669	12.959	1.00	20.77 A
ATOM C	107	CD	PRO	A	30	34.654	10.607	14.006	1.00	19.85 A
ATOM C	108	CA	PRO	A	30	35.334	8.340	13.523	1.00	19.49 A
ATOM C	109	CB	PRO	A	30	34.798	8.471	14.951	1.00	18.27 A
ATOM C	110	CG	PRO	A	30	35.081	9.895	15.276	1.00	18.94 A
ATOM C	111	C	PRO	A	30	34.655	7.206	12.757	1.00	19.01 A
ATOM O	112	O	PRO	A	30	33.552	7.367	12.236	1.00	18.19 A
ATOM N	113	N	LYS	A	31	35.332	6.063	12.689	1.00	19.05 A
ATOM C	114	CA	LYS	A	31	34.790	4.880	12.033	1.00	19.18 A
ATOM C	115	CB	LYS	A	31	35.919	3.891	11.703	1.00	18.74 A
ATOM C	116	CG	LYS	A	31	36.881	4.392	10.630	1.00	18.49 A
ATOM C	117	CD	LYS	A	31	38.048	3.442	10.409	1.00	16.87 A
ATOM C	118	CE	LYS	A	31	39.007	3.982	9.359	1.00	16.16 A
ATOM N	119	NZ	LYS	A	31	40.238	3.161	9.254	1.00	17.03 A
ATOM C	120	C	LYS	A	31	33.777	4.260	13.009	1.00	19.76 A
ATOM O	121	O	LYS	A	31	33.862	4.465	14.221	1.00	19.24 A
ATOM N	122	N	PRO	A	32	32.816	3.480	12.492	1.00	20.78 A
ATOM C	123	CD	PRO	A	32	32.772	2.971	11.106	1.00	20.08 A
ATOM C	124	CA	PRO	A	32	31.778	2.840	13.311	1.00	20.65 A
ATOM C	125	CB	PRO	A	32	31.376	1.640	12.465	1.00	18.59 A
ATOM C	126	CG	PRO	A	32	31.460	2.197	11.079	1.00	19.84 A
ATOM C	127	C	PRO	A	32	32.108	2.460	14.761	1.00	21.61 A
ATOM O	128	O	PRO	A	32	31.412	2.877	15.695	1.00	20.03 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM N	129	N	LEU	A	33	33.164	1.679	14.955	1.00	22.55 A
ATOM C	130	CA	LEU	A	33	33.522	1.237	16.296	1.00	23.06 A
ATOM C	131	CB	LEU	A	33	34.677	0.236	16.223	1.00	23.79 A
ATOM C	132	CG	LEU	A	33	34.537	-0.992	17.135	1.00	24.29 A
ATOM C	133	CD1	LEU	A	33	33.136	-1.597	17.020	1.00	22.52 A
ATOM C	134	CD2	LEU	A	33	35.597	-2.015	16.747	1.00	23.61 A
ATOM C	135	C	LEU	A	33	33.850	2.370	17.260	1.00	23.64 A
ATOM O	136	O	LEU	A	33	33.348	2.385	18.382	1.00	25.22 A
ATOM N	137	N	LEU	A	34	34.684	3.319	16.838	1.00	23.73 A
ATOM C	138	CA	LEU	A	34	35.033	4.445	17.707	1.00	23.80 A
ATOM C	139	CB	LEU	A	34	36.173	5.281	17.108	1.00	22.45 A
ATOM C	140	CG	LEU	A	34	36.459	6.603	17.842	1.00	21.72 A
ATOM C	141	CD1	LEU	A	34	36.722	6.324	19.310	1.00	20.49 A
ATOM C	142	CD2	LEU	A	34	37.647	7.324	17.209	1.00	20.12 A
ATOM C	143	C	LEU	A	34	33.829	5.351	17.949	1.00	24.92 A
ATOM O	144	O	LEU	A	34	33.641	5.867	19.058	1.00	25.03 A
ATOM N	145	N	LEU	A	35	33.019	5.549	16.911	1.00	24.02 A
ATOM C	146	CA	LEU	A	35	31.841	6.394	17.027	1.00	24.15 A
ATOM C	147	CB	LEU	A	35	31.113	6.470	15.690	1.00	21.76 A
ATOM C	148	CG	LEU	A	35	30.415	7.787	15.341	1.00	20.69 A
ATOM C	149	CD1	LEU	A	35	29.176	7.489	14.522	1.00	17.66 A
ATOM C	150	CD2	LEU	A	35	30.026	8.526	16.589	1.00	20.82 A
ATOM C	151	C	LEU	A	35	30.889	5.849	18.101	1.00	26.94 A
ATOM O	152	O	LEU	A	35	30.302	6.617	18.870	1.00	27.88 A
ATOM N	153	N	LYS	A	36	30.735	4.527	18.152	1.00	27.77 A
ATOM C	154	CA	LYS	A	36	29.859	3.913	19.140	1.00	28.78 A
ATOM C	155	CB	LYS	A	36	29.778	2.398	18.939	1.00	31.12 A
ATOM C	156	CG	LYS	A	36	29.062	1.687	20.081	1.00	35.08 A
ATOM C	157	CD	LYS	A	36	29.472	0.220	20.223	1.00	38.33 A
ATOM C	158	CE	LYS	A	36	28.711	-0.681	19.268	1.00	41.52 A
ATOM N	159	NZ	LYS	A	36	29.044	-2.120	19.487	1.00	43.62 A
ATOM C	160	C	LYS	A	36	30.397	4.200	20.530	1.00	28.98 A
ATOM O	161	O	LYS	A	36	29.632	4.463	21.459	1.00	29.52 A
ATOM N	162	N	LEU	A	37	31.719	4.137	20.664	1.00	28.82 A
ATOM C	163	CA	LEU	A	37	32.396	4.395	21.936	1.00	28.09 A
ATOM C	164	CB	LEU	A	37	33.908	4.244	21.751	1.00	28.11 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM C	165	CG	LEU	A	37	34.888	4.330	22.929	1.00	27.55 A
ATOM C	166	CD1	LEU	A	37	34.655	5.592	23.736	1.00	27.78 A
ATOM C	167	CD2	LEU	A	37	34.730	3.109	23.788	1.00	27.77 A
ATOM C	168	C	LEU	A	37	32.079	5.814	22.402	1.00	28.36 A
ATOM O	169	O	LEU	A	37	31.730	6.034	23.559	1.00	27.57 A
ATOM N	170	N	LEU	A	38	32.209	6.772	21.486	1.00	28.83 A
ATOM C	171	CA	LEU	A	38	31.951	8.175	21.785	1.00	27.42 A
ATOM C	172	CB	LEU	A	38	32.324	9.045	20.581	1.00	25.41 A
ATOM C	173	CG	LEU	A	38	33.787	8.973	20.141	1.00	25.18 A
ATOM C	174	CD1	LEU	A	38	34.015	9.980	19.042	1.00	24.55 A
ATOM C	175	CD2	LEU	A	38	34.715	9.251	21.315	1.00	25.40 A
ATOM C	176	C	LEU	A	38	30.504	8.449	22.186	1.00	27.27 A
ATOM O	177	O	LEU	A	38	30.239	8.989	23.259	1.00	27.56 A
ATOM N	178	N	LYS	A	39	29.562	8.083	21.327	1.00	26.08 A
ATOM C	179	CA	LYS	A	39	28.163	8.325	21.638	1.00	24.78 A
ATOM C	180	CB	LYS	A	39	27.294	7.885	20.461	1.00	23.77 A
ATOM C	181	CG	LYS	A	39	27.593	8.696	19.215	1.00	25.97 A
ATOM C	182	CD	LYS	A	39	26.657	8.409	18.051	1.00	26.72 A
ATOM C	183	CE	LYS	A	39	26.943	9.401	16.916	1.00	29.24 A
ATOM N	184	NZ	LYS	A	39	26.169	9.183	15.657	1.00	31.08 A
ATOM C	185	C	LYS	A	39	27.708	7.655	22.940	1.00	23.69 A
ATOM O	186	O	LYS	A	39	26.812	8.156	23.623	1.00	24.40 A
ATOM N	187	N	SER	A	40	28.338	6.545	23.305	1.00	21.60 A
ATOM C	188	CA	SER	A	40	27.946	5.850	24.522	1.00	18.78 A
ATOM C	189	CB	SER	A	40	28.602	4.465	24.593	1.00	16.27 A
ATOM O	190	OG	SER	A	40	29.947	4.538	25.020	1.00	13.26 A
ATOM C	191	C	SER	A	40	28.299	6.663	25.766	1.00	18.97 A
ATOM O	192	O	SER	A	40	27.808	6.376	26.854	1.00	18.43 A
ATOM N	193	N	VAL	A	41	29.157	7.667	25.616	1.00	18.55 A
ATOM C	194	CA	VAL	A	41	29.515	8.496	26.758	1.00	19.39 A
ATOM C	195	CB	VAL	A	41	31.057	8.645	26.940	1.00	20.54 A
ATOM C	196	CG1	VAL	A	41	31.630	7.402	27.607	1.00	18.57 A
ATOM C	197	CG2	VAL	A	41	31.733	8.891	25.600	1.00	21.46 A
ATOM C	198	C	VAL	A	41	28.887	9.881	26.662	1.00	20.20 A
ATOM O	199	O	VAL	A	41	29.218	10.771	27.444	1.00	19.90 A
ATOM N	200	N	GLY	A	42	27.975	10.062	25.707	1.00	20.98 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM C	201	CA	GLY	A	42	27.306	11.345	25.571	1.00	21.00 A
ATOM C	202	C	GLY	A	42	27.542	12.155	24.309	1.00	22.06 A
ATOM O	203	O	GLY	A	42	26.809	13.107	24.060	1.00	23.06 A
ATOM N	204	N	ALA	A	43	28.557	11.807	23.522	1.00	23.02 A
ATOM C	205	CA	ALA	A	43	28.841	12.530	22.280	1.00	23.42 A
ATOM C	206	CB	ALA	A	43	30.075	11.940	21.593	1.00	20.28 A
ATOM C	207	C	ALA	A	43	27.632	12.427	21.354	1.00	23.40 A
ATOM O	208	O	ALA	A	43	26.816	11.517	21.495	1.00	21.98 A
ATOM N	209	N	GLN	A	44	27.505	13.352	20.407	1.00	25.42 A
ATOM C	210	CA	GLN	A	44	26.369	13.279	19.502	1.00	27.06 A
ATOM C	211	CB	GLN	A	44	25.130	13.872	20.165	1.00	27.82 A
ATOM C	212	CG	GLN	A	44	25.315	15.232	20.763	1.00	28.96 A
ATOM C	213	CD	GLN	A	44	24.576	15.357	22.085	1.00	32.56 A
ATOM O	214	OE1	GLN	A	44	24.357	16.462	22.585	1.00	34.47 A
ATOM N	215	NE2	GLN	A	44	24.200	14.215	22.668	1.00	31.28 A
ATOM C	216	C	GLN	A	44	26.520	13.854	18.106	1.00	26.84 A
ATOM O	217	O	GLN	A	44	25.532	14.268	17.500	1.00	26.83 A
ATOM N	218	N	LYS	A	45	27.745	13.881	17.592	1.00	25.93 A
ATOM C	219	CA	LYS	A	45	27.980	14.363	16.230	1.00	25.65 A
ATOM C	220	CB	LYS	A	45	28.960	15.544	16.198	1.00	25.47 A
ATOM C	221	CG	LYS	A	45	28.546	16.767	16.992	1.00	24.64 A
ATOM C	222	CD	LYS	A	45	29.614	17.860	16.948	1.00	21.21 A
ATOM C	223	CE	LYS	A	45	30.907	17.410	17.615	1.00	19.16 A
ATOM N	224	NZ	LYS	A	45	31.849	18.543	17.785	1.00	16.01 A
ATOM C	225	C	LYS	A	45	28.627	13.199	15.508	1.00	24.50 A
ATOM O	226	O	LYS	A	45	28.904	12.162	16.112	1.00	24.58 A
ATOM N	227	N	ASP	A	46	28.861	13.359	14.219	1.00	22.87 A
ATOM C	228	CA	ASP	A	46	29.539	12.314	13.483	1.00	23.75 A
ATOM C	229	CB	ASP	A	46	28.765	11.931	12.219	1.00	26.21 A
ATOM C	230	CG	ASP	A	46	27.451	11.222	12.525	1.00	28.44 A
ATOM O	231	OD1	ASP	A	46	27.379	10.480	13.530	1.00	28.33 A
ATOM O	232	OD2	ASP	A	46	26.489	11.396	11.746	1.00	30.59 A
ATOM C	233	C	ASP	A	46	30.913	12.872	13.125	1.00	23.42 A
ATOM O	234	O	ASP	A	46	31.820	12.134	12.759	1.00	24.56 A
ATOM N	235	N	THR	A	47	31.062	14.188	13.245	1.00	22.36 A
ATOM C	236	CA	THR	A	47	32.326	14.847	12.939	1.00	20.77 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM C	237	CB	THR	A	47	32.151	15.896	11.831	1.00	21.07 A
ATOM O	238	OG1	THR	A	47	31.573	15.276	10.676	1.00	22.41 A
ATOM C	239	CG2	THR	A	47	33.496	16.498	11.458	1.00	19.56 A
ATOM C	240	C	THR	A	47	32.859	15.536	14.187	1.00	19.61 A
ATOM O	241	O	THR	A	47	32.114	16.213	14.893	1.00	19.20 A
ATOM N	242	N	TYR	A	48	34.147	15.364	14.461	1.00	17.90 A
ATOM C	243	CA	TYR	A	48	34.744	15.966	15.646	1.00	17.29 A
ATOM C	244	CB	TYR	A	48	34.904	14.924	16.763	1.00	17.51 A
ATOM C	245	CG	TYR	A	48	33.645	14.195	17.178	1.00	18.47 A
ATOM C	246	CD1	TYR	A	48	33.094	13.199	16.376	1.00	17.60 A
ATOM C	247	CE1	TYR	A	48	31.926	12.549	16.743	1.00	19.18 A
ATOM C	248	CD2	TYR	A	48	32.993	14.518	18.368	1.00	18.07 A
ATOM C	249	CE2	TYR	A	48	31.826	13.877	18.746	1.00	18.21 A
ATOM C	250	CZ	TYR	A	48	31.291	12.893	17.930	1.00	19.97 A
ATOM O	251	OH	TYR	A	48	30.112	12.264	18.294	1.00	20.10 A
ATOM C	252	C	TYR	A	48	36.123	16.528	15.356	1.00	17.64 A
ATOM O	253	O	TYR	A	48	36.650	16.401	14.245	1.00	19.08 A
ATOM N	254	N	THR	A	49	36.695	17.172	16.364	1.00	16.11 A
ATOM C	255	CA	THR	A	49	38.057	17.677	16.267	1.00	16.21 A
ATOM C	256	CB	THR	A	49	38.219	19.061	16.891	1.00	15.01 A
ATOM O	257	OG1	THR	A	49	38.028	18.969	18.309	1.00	14.67 A
ATOM C	258	CG2	THR	A	49	37.212	20.006	16.316	1.00	14.41 A
ATOM C	259	C	THR	A	49	38.766	16.672	17.164	1.00	16.33 A
ATOM O	260	O	THR	A	49	38.142	16.091	18.057	1.00	16.33 A
ATOM N	261	N	MET	A	50	40.050	16.448	16.937	1.00	16.12 A
ATOM C	262	CA	MET	A	50	40.770	15.500	17.765	1.00	16.31 A
ATOM C	263	CB	MET	A	50	42.253	15.515	17.411	1.00	16.08 A
ATOM C	264	CG	MET	A	50	42.550	14.804	16.100	1.00	15.76 A
ATOM S	265	SD	MET	A	50	42.007	13.088	16.174	1.00	15.40 A
ATOM C	266	CE	MET	A	50	43.383	12.364	17.108	1.00	12.28 A
ATOM C	267	C	MET	A	50	40.570	15.820	19.236	1.00	17.20 A
ATOM O	268	O	MET	A	50	40.300	14.931	20.034	1.00	18.81 A
ATOM N	269	N	LYS	A	51	40.679	17.099	19.581	1.00	16.94 A
ATOM C	270	CA	LYS	A	51	40.515	17.551	20.952	1.00	16.59 A
ATOM C	271	CB	LYS	A	51	40.588	19.083	20.993	1.00	19.46 A
ATOM C	272	CG	LYS	A	51	40.773	19.662	22.382	1.00	24.41 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM C	273	CD	LYS	A	51	41.177	21.132	22.333	1.00	29.49 A
ATOM C	274	CE	LYS	A	51	41.633	21.623	23.711	1.00	30.87 A
ATOM N	275	NZ	LYS	A	51	42.111	23.039	23.693	1.00	32.84 A
ATOM C	276	C	LYS	A	51	39.195	17.059	21.555	1.00	15.64 A
ATOM O	277	O	LYS	A	51	39.133	16.677	22.729	1.00	14.01 A
ATOM N	278	N	GLU	A	52	38.139	17.062	20.750	1.00	15.07 A
ATOM C	279	CA	GLU	A	52	36.837	16.613	21.234	1.00	15.62 A
ATOM C	280	CB	GLU	A	52	35.738	17.017	20.254	1.00	16.29 A
ATOM C	281	CG	GLU	A	52	35.586	18.520	20.127	1.00	18.24 A
ATOM C	282	CD	GLU	A	52	34.649	18.921	19.018	1.00	19.03 A
ATOM O	283	OE1	GLU	A	52	34.764	18.341	17.918	1.00	22.90 A
ATOM O	284	OE2	GLU	A	52	33.812	19.821	19.236	1.00	19.46 A
ATOM C	285	C	GLU	A	52	36.808	15.110	21.454	1.00	15.03 A
ATOM O	286	O	GLU	A	52	36.232	14.638	22.435	1.00	16.38 A
ATOM N	287	N	VAL	A	53	37.432	14.361	20.546	1.00	14.02 A
ATOM C	288	CA	VAL	A	53	37.475	12.908	20.661	1.00	12.12 A
ATOM C	289	CB	VAL	A	53	38.216	12.274	19.478	1.00	11.38 A
ATOM C	290	CG1	VAL	A	53	38.129	10.769	19.566	1.00	10.68 A
ATOM C	291	CG2	VAL	A	53	37.612	12.750	18.171	1.00	12.22 A
ATOM C	292	C	VAL	A	53	38.191	12.540	21.955	1.00	12.50 A
ATOM O	293	O	VAL	A	53	37.691	11.744	22.761	1.00	12.84 A
ATOM N	294	N	LEU	A	54	39.362	13.129	22.158	1.00	9.57 A
ATOM C	295	CA	LEU	A	54	40.109	12.871	23.365	1.00	10.63 A
ATOM C	296	CB	LEU	A	54	41.365	13.726	23.405	1.00	11.63 A
ATOM C	297	CG	LEU	A	54	42.520	13.131	22.609	1.00	11.73 A
ATOM C	298	CD1	LEU	A	54	43.563	14.192	22.418	1.00	14.32 A
ATOM C	299	CD2	LEU	A	54	43.095	11.922	23.344	1.00	12.23 A
ATOM C	300	C	LEU	A	54	39.260	13.159	24.581	1.00	12.08 A
ATOM O	301	O	LEU	A	54	39.280	12.398	25.541	1.00	13.29 A
ATOM N	302	N	PHE	A	55	38.508	14.256	24.545	1.00	13.96 A
ATOM C	303	CA	PHE	A	55	37.653	14.612	25.675	1.00	14.56 A
ATOM C	304	CB	PHE	A	55	36.874	15.901	25.391	1.00	15.14 A
ATOM C	305	CG	PHE	A	55	35.984	16.330	26.530	1.00	12.59 A
ATOM C	306	CD1	PHE	A	55	36.478	17.135	27.551	1.00	12.50 A
ATOM C	307	CD2	PHE	A	55	34.674	15.870	26.614	1.00	11.59 A
ATOM C	308	CE1	PHE	A	55	35.679	17.473	28.643	1.00	12.57 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM C	309	CE2	PHE	A	55	33.869	16.198	27.696	1.00	10.75 A
ATOM C	310	CZ	PHE	A	55	34.373	17.001	28.714	1.00	12.37 A
ATOM C	311	C	PHE	A	55	36.654	13.503	25.998	1.00	15.87 A
ATOM O	312	O	PHE	A	55	36.537	13.073	27.149	1.00	14.84 A
ATOM N	313	N	TYR	A	56	35.916	13.059	24.985	1.00	15.22 A
ATOM C	314	CA	TYR	A	56	34.928	12.013	25.201	1.00	16.95 A
ATOM C	315	CB	TYR	A	56	34.070	11.832	23.952	1.00	14.70 A
ATOM C	316	CG	TYR	A	56	33.084	12.953	23.737	1.00	14.95 A
ATOM C	317	CD1	TYR	A	56	32.015	13.148	24.615	1.00	15.85 A
ATOM C	318	CE1	TYR	A	56	31.086	14.169	24.406	1.00	17.59 A
ATOM C	319	CD2	TYR	A	56	33.205	13.810	22.645	1.00	15.37 A
ATOM C	320	CE2	TYR	A	56	32.290	14.833	22.423	1.00	16.46 A
ATOM C	321	CZ	TYR	A	56	31.231	15.007	23.303	1.00	18.11 A
ATOM O	322	OH	TYR	A	56	30.311	16.001	23.059	1.00	18.28 A
ATOM C	323	C	TYR	A	56	35.598	10.698	25.580	1.00	17.45 A
ATOM O	324	O	TYR	A	56	35.117	9.958	26.440	1.00	16.40 A
ATOM N	325	N	LEU	A	57	36.717	10.411	24.931	1.00	18.36 A
ATOM C	326	CA	LEU	A	57	37.449	9.194	25.217	1.00	17.30 A
ATOM C	327	CB	LEU	A	57	38.621	9.081	24.245	1.00	15.20 A
ATOM C	328	CG	LEU	A	57	38.903	7.706	23.644	1.00	16.42 A
ATOM C	329	CD1	LEU	A	57	37.637	7.037	23.166	1.00	16.54 A
ATOM C	330	CD2	LEU	A	57	39.860	7.885	22.499	1.00	18.63 A
ATOM C	331	C	LEU	A	57	37.915	9.332	26.675	1.00	17.78 A
ATOM O	332	O	LEU	A	57	38.074	8.350	27.398	1.00	17.21 A
ATOM N	333	N	GLY	A	58	38.099	10.576	27.103	1.00	17.15 A
ATOM C	334	CA	GLY	A	58	38.515	10.832	28.464	1.00	16.26 A
ATOM C	335	C	GLY	A	58	37.406	10.511	29.438	1.00	17.52 A
ATOM O	336	O	GLY	A	58	37.656	9.909	30.482	1.00	18.49 A
ATOM N	337	N	GLN	A	59	36.179	10.906	29.114	1.00	15.94 A
ATOM C	338	CA	GLN	A	59	35.071	10.617	30.010	1.00	17.18 A
ATOM C	339	CB	GLN	A	59	33.761	11.199	29.481	1.00	17.70 A
ATOM C	340	CG	GLN	A	59	33.713	12.720	29.500	1.00	18.77 A
ATOM C	341	CD	GLN	A	59	34.064	13.281	30.859	1.00	19.30 A
ATOM O	342	OE1	GLN	A	59	33.435	12.939	31.856	1.00	20.86 A
ATOM N	343	NE2	GLN	A	59	35.078	14.145	30.909	1.00	18.39 A
ATOM C	344	C	GLN	A	59	34.966	9.115	30.109	1.00	17.93 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM O	345	O	GLN	A	59	34.903	8.552	31.199	1.00	17.50 A
ATOM N	346	N	TYR	A	60	34.984	8.473	28.949	1.00	19.35 A
ATOM C	347	CA	TYR	A	60	34.906	7.023	28.854	1.00	19.97 A
ATOM C	348	CB	TYR	A	60	35.270	6.580	27.450	1.00	18.67 A
ATOM C	349	CG	TYR	A	60	35.061	5.121	27.258	1.00	18.93 A
ATOM C	350	CD1	TYR	A	60	33.783	4.608	27.114	1.00	19.95 A
ATOM C	351	CE1	TYR	A	60	33.573	3.256	26.945	1.00	22.90 A
ATOM C	352	CD2	TYR	A	60	36.139	4.243	27.235	1.00	21.13 A
ATOM C	353	CE2	TYR	A	60	35.946	2.880	27.068	1.00	22.87 A
ATOM C	354	CZ	TYR	A	60	34.656	2.393	26.920	1.00	24.39 A
ATOM O	355	OH	TYR	A	60	34.439	1.051	26.722	1.00	26.24 A
ATOM C	356	C	TYR	A	60	35.833	6.309	29.837	1.00	20.15 A
ATOM O	357	O	TYR	A	60	35.384	5.527	30.682	1.00	19.42 A
ATOM N	358	N	ILE	A	61	37.130	6.564	29.701	1.00	20.01 A
ATOM C	359	CA	ILE	A	61	38.116	5.949	30.574	1.00	21.24 A
ATOM C	360	CB	ILE	A	61	39.508	6.556	30.346	1.00	19.34 A
ATOM C	361	CG2	ILE	A	61	40.449	6.169	31.481	1.00	17.74 A
ATOM C	362	CG1	ILE	A	61	40.050	6.096	28.993	1.00	18.22 A
ATOM C	363	CD1	ILE	A	61	41.343	6.774	28.602	1.00	17.99 A
ATOM C	364	C	ILE	A	61	37.717	6.175	32.020	1.00	22.76 A
ATOM O	365	O	ILE	A	61	37.731	5.261	32.837	1.00	19.91 A
ATOM N	366	N	MET	A	62	37.342	7.414	32.309	1.00	26.52 A
ATOM C	367	CA	MET	A	62	36.951	7.827	33.645	1.00	28.53 A
ATOM C	368	CB	MET	A	62	36.735	9.338	33.661	1.00	28.55 A
ATOM C	369	CG	MET	A	62	37.153	9.971	34.948	1.00	29.96 A
ATOM S	370	SD	MET	A	62	38.843	9.527	35.301	1.00	32.30 A
ATOM C	371	CE	MET	A	62	39.644	11.112	35.168	1.00	34.41 A
ATOM C	372	C	MET	A	62	35.709	7.120	34.180	1.00	29.87 A
ATOM O	373	O	MET	A	62	35.689	6.691	35.336	1.00	31.34 A
ATOM N	374	N	THR	A	63	34.677	6.992	33.350	1.00	30.81 A
ATOM C	375	CA	THR	A	63	33.450	6.342	33.792	1.00	31.38 A
ATOM C	376	CB	THR	A	63	32.265	6.625	32.834	1.00	31.49 A
ATOM O	377	OG1	THR	A	63	31.505	5.427	32.649	1.00	33.06 A
ATOM C	378	CG2	THR	A	63	32.747	7.120	31.501	1.00	32.85 A
ATOM C	379	C	THR	A	63	33.588	4.836	34.002	1.00	31.82 A
ATOM O	380	O	THR	A	63	33.045	4.301	34.975	1.00	32.68 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM N	381	N	LYS	A	64	34.305	4.149	33.115	1.00	31.19 A
ATOM C	382	CA	LYS	A	64	34.491	2.706	33.279	1.00	30.89 A
ATOM C	383	CB	LYS	A	64	34.719	2.032	31.922	1.00	29.02 A
ATOM C	384	CG	LYS	A	64	33.600	2.295	30.931	1.00	29.54 A
ATOM C	385	CD	LYS	A	64	33.657	1.380	29.723	1.00	28.26 A
ATOM C	386	CE	LYS	A	64	33.117	0.005	30.046	1.00	29.17 A
ATOM N	387	NZ	LYS	A	64	32.990	-0.829	28.825	1.00	27.96 A
ATOM C	388	C	LYS	A	64	35.661	2.408	34.221	1.00	31.59 A
ATOM O	389	O	LYS	A	64	35.926	1.256	34.559	1.00	31.45 A
ATOM N	390	N	ARG	A	65	36.345	3.463	34.653	1.00	33.27 A
ATOM C	391	CA	ARG	A	65	37.493	3.352	35.551	1.00	34.34 A
ATOM C	392	CB	ARG	A	65	37.043	2.891	36.935	1.00	37.67 A
ATOM C	393	CG	ARG	A	65	36.016	3.800	37.560	1.00	43.08 A
ATOM C	394	CD	ARG	A	65	35.585	3.283	38.909	1.00	46.77 A
ATOM N	395	NE	ARG	A	65	34.434	4.025	39.407	1.00	51.51 A
ATOM C	396	CZ	ARG	A	65	33.927	3.888	40.628	1.00	53.49 A
ATOM N	397	NH1	ARG	A	65	34.474	3.032	41.484	1.00	54.10 A
ATOM N	398	NH2	ARG	A	65	32.872	4.608	40.993	1.00	54.47 A
ATOM C	399	C	ARG	A	65	38.557	2.398	35.021	1.00	33.22 A
ATOM O	400	O	ARG	A	65	39.086	1.576	35.770	1.00	32.38 A
ATOM N	401	N	LEU	A	66	38.863	2.518	33.731	1.00	31.04 A
ATOM C	402	CA	LEU	A	66	39.868	1.687	33.089	1.00	29.81 A
ATOM C	403	CB	LEU	A	66	39.821	1.870	31.564	1.00	28.29 A
ATOM C	404	CG	LEU	A	66	38.557	1.471	30.795	1.00	27.60 A
ATOM C	405	CD1	LEU	A	66	38.809	1.611	29.301	1.00	25.14 A
ATOM C	406	CD2	LEU	A	66	38.170	0.035	31.121	1.00	26.60 A
ATOM C	407	C	LEU	A	66	41.272	2.020	33.597	1.00	30.22 A
ATOM O	408	O	LEU	A	66	42.251	1.416	33.162	1.00	30.64 A
ATOM N	409	N	TYR	A	67	41.375	2.980	34.514	1.00	30.84 A
ATOM C	410	CA	TYR	A	67	42.677	3.365	35.055	1.00	32.60 A
ATOM C	411	CB	TYR	A	67	42.688	4.846	35.438	1.00	33.43 A
ATOM C	412	CG	TYR	A	67	41.642	5.226	36.463	1.00	36.96 A
ATOM C	413	CD1	TYR	A	67	41.809	4.922	37.810	1.00	37.60 A
ATOM C	414	CE1	TYR	A	67	40.833	5.254	38.745	1.00	39.51 A
ATOM C	415	CD2	TYR	A	67	40.468	5.875	36.077	1.00	38.20 A
ATOM C	416	CE2	TYR	A	67	39.488	6.211	37.004	1.00	38.78 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM C	417	CZ	TYR	A	67	39.675	5.898	38.334	1.00	39.55 A
ATOM O	418	OH	TYR	A	67	38.703	6.227	39.254	1.00	42.02 A
ATOM C	419	C	TYR	A	67	43.037	2.534	36.270	1.00	33.52 A
ATOM O	420	O	TYR	A	67	42.167	1.968	36.929	1.00	33.03 A
ATOM N	421	N	ASP	A	68	44.327	2.459	36.567	1.00	35.06 A
ATOM C	422	CA	ASP	A	68	44.765	1.699	37.721	1.00	36.88 A
ATOM C	423	CB	ASP	A	68	46.146	1.100	37.476	1.00	37.88 A
ATOM C	424	CG	ASP	A	68	46.658	0.340	38.674	1.00	38.95 A
ATOM O	425	OD1	ASP	A	68	45.863	-0.408	39.281	1.00	39.74 A
ATOM O	426	OD2	ASP	A	68	47.850	0.486	39.006	1.00	39.12 A
ATOM C	427	C	ASP	A	68	44.795	2.593	38.952	1.00	38.61 A
ATOM O	428	O	ASP	A	68	45.391	3.671	38.939	1.00	36.17 A
ATOM N	429	N	GLU	A	69	44.138	2.138	40.013	1.00	41.45 A
ATOM C	430	CA	GLU	A	69	44.068	2.889	41.261	1.00	44.18 A
ATOM C	431	CB	GLU	A	69	43.392	2.042	42.345	1.00	47.21 A
ATOM C	432	CG	GLU	A	69	41.883	1.953	42.222	1.00	50.20 A
ATOM C	433	CD	GLU	A	69	41.238	3.322	42.249	1.00	52.69 A
ATOM O	434	OE1	GLU	A	69	41.619	4.132	43.126	1.00	53.29 A
ATOM O	435	OE2	GLU	A	69	40.352	3.586	41.403	1.00	54.11 A
ATOM C	436	C	GLU	A	69	45.421	3.366	41.774	1.00	44.17 A
ATOM O	437	O	GLU	A	69	45.615	4.553	42.023	1.00	43.71 A
ATOM N	438	N	LYS	A	70	46.349	2.430	41.933	1.00	44.88 A
ATOM C	439	CA	LYS	A	70	47.679	2.733	42.441	1.00	45.87 A
ATOM C	440	CB	LYS	A	70	48.260	1.482	43.113	1.00	47.39 A
ATOM C	441	CG	LYS	A	70	48.001	0.194	42.326	1.00	50.82 A
ATOM C	442	CD	LYS	A	70	48.491	-1.060	43.052	1.00	52.70 A
ATOM C	443	CE	LYS	A	70	48.068	-2.333	42.307	1.00	53.19 A
ATOM N	444	NZ	LYS	A	70	48.468	-3.586	43.022	1.00	53.35 A
ATOM C	445	C	LYS	A	70	48.639	3.255	41.376	1.00	45.61 A
ATOM O	446	O	LYS	A	70	49.687	3.803	41.703	1.00	46.82 A
ATOM N	447	N	GLN	A	71	48.284	3.079	40.107	1.00	45.07 A
ATOM C	448	CA	GLN	A	71	49.123	3.539	38.995	1.00	44.59 A
ATOM C	449	CB	GLN	A	71	49.852	2.352	38.357	1.00	45.81 A
ATOM C	450	CG	GLN	A	71	51.048	2.754	37.525	1.00	48.21 A
ATOM C	451	CD	GLN	A	71	52.085	3.500	38.343	1.00	49.07 A
ATOM O	452	OE1	GLN	A	71	53.008	4.103	37.795	1.00	49.90 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM N	453	NE2	GLN	A	71	51.940	3.458	39.665	1.00	49.28 A
ATOM C	454	C	GLN	A	71	48.199	4.207	37.977	1.00	42.82 A
ATOM O	455	O	GLN	A	71	48.023	3.733	36.851	1.00	41.55 A
ATOM N	456	N	GLN	A	72	47.628	5.327	38.406	1.00	40.92 A
ATOM C	457	CA	GLN	A	72	46.658	6.096	37.639	1.00	38.61 A
ATOM C	458	CB	GLN	A	72	46.144	7.232	38.519	1.00	39.65 A
ATOM C	459	CG	GLN	A	72	45.172	6.741	39.576	1.00	41.28 A
ATOM C	460	CD	GLN	A	72	44.819	7.799	40.590	1.00	41.51 A
ATOM O	461	OE1	GLN	A	72	44.671	8.976	40.253	1.00	42.50 A
ATOM N	462	NE2	GLN	A	72	44.666	7.385	41.842	1.00	41.01 A
ATOM C	463	C	GLN	A	72	46.948	6.631	36.247	1.00	35.53 A
ATOM O	464	O	GLN	A	72	46.015	6.973	35.532	1.00	34.95 A
ATOM N	465	N	HIS	A	73	48.210	6.712	35.847	1.00	33.43 A
ATOM C	466	CA	HIS	A	73	48.508	7.216	34.512	1.00	31.21 A
ATOM C	467	CB	HIS	A	73	49.841	7.975	34.514	1.00	32.43 A
ATOM C	468	CG	HIS	A	73	51.039	7.111	34.753	1.00	35.52 A
ATOM C	469	CD2	HIS	A	73	51.615	6.683	35.901	1.00	36.10 A
ATOM N	470	ND1	HIS	A	73	51.796	6.588	33.725	1.00	36.24 A
ATOM C	471	CE1	HIS	A	73	52.788	5.876	34.230	1.00	36.90 A
ATOM N	472	NE2	HIS	A	73	52.701	5.918	35.548	1.00	37.46 A
ATOM C	473	C	HIS	A	73	48.518	6.076	33.487	1.00	29.68 A
ATOM O	474	O	HIS	A	73	48.681	6.297	32.278	1.00	28.72 A
ATOM N	475	N	ILE	A	74	48.315	4.859	33.987	1.00	26.57 A
ATOM C	476	CA	ILE	A	74	48.281	3.663	33.152	1.00	25.03 A
ATOM C	477	CB	ILE	A	74	49.167	2.538	33.745	1.00	23.93 A
ATOM C	478	CG2	ILE	A	74	48.928	1.244	33.010	1.00	23.04 A
ATOM C	479	CG1	ILE	A	74	50.643	2.933	33.669	1.00	22.73 A
ATOM C	480	CD1	ILE	A	74	51.140	3.210	32.279	1.00	21.40 A
ATOM C	481	C	ILE	A	74	46.856	3.135	33.017	1.00	24.39 A
ATOM O	482	O	ILE	A	74	46.199	2.833	34.010	1.00	25.39 A
ATOM N	483	N	VAL	A	75	46.387	3.025	31.782	1.00	23.12 A
ATOM C	484	CA	VAL	A	75	45.048	2.527	31.506	1.00	22.39 A
ATOM C	485	CB	VAL	A	75	44.413	3.306	30.319	1.00	21.87 A
ATOM C	486	CG1	VAL	A	75	43.016	2.784	30.024	1.00	19.40 A
ATOM C	487	CG2	VAL	A	75	44.376	4.777	30.629	1.00	21.46 A
ATOM C	488	C	VAL	A	75	45.121	1.044	31.120	1.00	23.43 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM O	489	O	VAL	A	75	46.031	0.631	30.396	1.00	24.66 A
ATOM N	490	N	TYR	A	76	44.174	0.246	31.604	1.00	22.50 A
ATOM C	491	CA	TYR	A	76	44.115	-1.173	31.256	1.00	22.83 A
ATOM C	492	CB	TYR	A	76	44.106	-2.063	32.508	1.00	22.60 A
ATOM C	493	CG	TYR	A	76	45.435	-2.130	33.237	1.00	23.26 A
ATOM C	494	CD1	TYR	A	76	45.728	-1.257	34.284	1.00	23.34 A
ATOM C	495	CE1	TYR	A	76	46.964	-1.291	34.928	1.00	24.06 A
ATOM C	496	CD2	TYR	A	76	46.414	-3.041	32.855	1.00	22.74 A
ATOM C	497	CE2	TYR	A	76	47.654	-3.083	33.493	1.00	23.63 A
ATOM C	498	CZ	TYR	A	76	47.926	-2.207	34.526	1.00	23.89 A
ATOM O	499	OH	TYR	A	76	49.159	-2.234	35.150	1.00	23.35 A
ATOM C	500	C	TYR	A	76	42.825	-1.367	30.465	1.00	23.68 A
ATOM O	501	O	TYR	A	76	41.727	-1.245	31.003	1.00	24.33 A
ATOM N	502	N	CYS	A	77	42.953	-1.663	29.181	1.00	24.40 A
ATOM C	503	CA	CYS	A	77	41.780	-1.826	28.342	1.00	26.23 A
ATOM C	504	CB	CYS	A	77	41.778	-0.744	27.258	1.00	24.90 A
ATOM S	505	SG	CYS	A	77	43.313	-0.601	26.325	1.00	17.76 A
ATOM C	506	C	CYS	A	77	41.681	-3.193	27.692	1.00	29.22 A
ATOM O	507	O	CYS	A	77	41.001	-3.354	26.676	1.00	29.98 A
ATOM N	508	N	SER	A	78	42.337	-4.176	28.300	1.00	32.27 A
ATOM C	509	CA	SER	A	78	42.366	-5.538	27.775	1.00	35.19 A
ATOM C	510	CB	SER	A	78	43.016	-6.469	28.798	1.00	36.60 A
ATOM O	511	OG	SER	A	78	43.133	-7.782	28.279	1.00	38.65 A
ATOM C	512	C	SER	A	78	41.020	-6.119	27.340	1.00	36.61 A
ATOM O	513	O	SER	A	78	40.777	-6.309	26.144	1.00	38.66 A
ATOM N	514	N	ASN	A	79	40.145	-6.402	28.297	1.00	36.16 A
ATOM C	515	CA	ASN	A	79	38.849	-6.982	27.961	1.00	37.19 A
ATOM C	516	CB	ASN	A	79	38.340	-7.871	29.109	1.00	40.14 A
ATOM C	517	CG	ASN	A	79	39.448	-8.682	29.769	1.00	42.98 A
ATOM O	518	OD1	ASN	A	79	40.255	-8.146	30.538	1.00	44.77 A
ATOM N	519	ND2	ASN	A	79	39.495	-9.978	29.471	1.00	42.57 A
ATOM C	520	C	ASN	A	79	37.805	-5.909	27.669	1.00	36.10 A
ATOM O	521	O	ASN	A	79	36.619	-6.105	27.936	1.00	36.61 A
ATOM N	522	N	ASP	A	80	38.227	-4.787	27.101	1.00	33.75 A
ATOM C	523	CA	ASP	A	80	37.283	-3.716	26.836	1.00	31.35 A
ATOM C	524	CB	ASP	A	80	37.630	-2.513	27.708	1.00	33.87 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM C	525	CG	ASP	A	80	36.563	-1.448	27.672	1.00	34.54 A
ATOM O	526	OD1	ASP	A	80	35.832	-1.315	28.679	1.00	35.54 A
ATOM O	527	OD2	ASP	A	80	36.453	-0.758	26.631	1.00	33.13 A
ATOM C	528	C	ASP	A	80	37.229	-3.280	25.383	1.00	29.65 A
ATOM O	529	O	ASP	A	80	38.182	-3.474	24.634	1.00	30.16 A
ATOM N	530	N	LEU	A	81	36.109	-2.675	24.995	1.00	27.43 A
ATOM C	531	CA	LEU	A	81	35.932	-2.200	23.629	1.00	26.30 A
ATOM C	532	CB	LEU	A	81	34.605	-1.461	23.475	1.00	25.12 A
ATOM C	533	CG	LEU	A	81	34.437	-0.778	22.111	1.00	23.81 A
ATOM C	534	CD1	LEU	A	81	34.714	-1.778	21.013	1.00	23.42 A
ATOM C	535	CD2	LEU	A	81	33.040	-0.213	21.971	1.00	23.74 A
ATOM C	536	C	LEU	A	81	37.064	-1.278	23.194	1.00	26.69 A
ATOM O	537	O	LEU	A	81	37.416	-1.235	22.010	1.00	27.34 A
ATOM N	538	N	LEU	A	82	37.621	-0.529	24.144	1.00	25.53 A
ATOM C	539	CA	LEU	A	82	38.717	0.375	23.827	1.00	24.07 A
ATOM C	540	CB	LEU	A	82	39.087	1.217	25.047	1.00	20.46 A
ATOM C	541	CG	LEU	A	82	40.236	2.202	24.829	1.00	18.75 A
ATOM C	542	CD1	LEU	A	82	39.913	3.166	23.689	1.00	17.60 A
ATOM C	543	CD2	LEU	A	82	40.488	2.955	26.112	1.00	18.82 A
ATOM C	544	C	LEU	A	82	39.908	-0.468	23.376	1.00	25.11 A
ATOM O	545	O	LEU	A	82	40.569	-0.149	22.381	1.00	26.18 A
ATOM N	546	N	GLY	A	83	40.162	-1.553	24.105	1.00	24.69 A
ATOM C	547	CA	GLY	A	83	41.249	-2.451	23.760	1.00	24.41 A
ATOM C	548	C	GLY	A	83	41.170	-2.920	22.318	1.00	24.29 A
ATOM O	549	O	GLY	A	83	42.196	-3.139	21.681	1.00	23.83 A
ATOM N	550	N	ASP	A	84	39.958	-3.076	21.796	1.00	24.91 A
ATOM C	551	CA	ASP	A	84	39.803	-3.503	20.410	1.00	27.77 A
ATOM C	552	CB	ASP	A	84	38.386	-3.996	20.149	1.00	28.89 A
ATOM C	553	CG	ASP	A	84	38.093	-5.295	20.837	1.00	31.01 A
ATOM O	554	OD1	ASP	A	84	39.042	-6.085	21.039	1.00	32.12 A
ATOM O	555	OD2	ASP	A	84	36.913	-5.532	21.160	1.00	31.66 A
ATOM C	556	C	ASP	A	84	40.119	-2.392	19.410	1.00	28.99 A
ATOM O	557	O	ASP	A	84	40.587	-2.664	18.297	1.00	29.29 A
ATOM N	558	N	LEU	A	85	39.849	-1.146	19.799	1.00	28.12 A
ATOM C	559	CA	LEU	A	85	40.104	-0.009	18.926	1.00	26.68 A
ATOM C	560	CB	LEU	A	85	39.385	1.241	19.441	1.00	27.62 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-acetic acid										
ATOM C	561	CG	LEU	A	85	37.866	1.155	19.582	1.00	29.80 A
ATOM C	562	CD1	LEU	A	85	37.325	2.478	20.104	1.00	28.93 A
ATOM C	563	CD2	LEU	A	85	37.245	0.807	18.234	1.00	30.79 A
ATOM C	564	C	LEU	A	85	41.592	0.268	18.866	1.00	25.94 A
ATOM O	565	O	LEU	A	85	42.169	0.400	17.783	1.00	25.60 A
ATOM N	566	N	PHE	A	86	42.208	0.354	20.042	1.00	24.28 A
ATOM C	567	CA	PHE	A	86	43.636	0.633	20.143	1.00	23.89 A
ATOM C	568	CB	PHE	A	86	43.980	1.113	21.563	1.00	23.07 A
ATOM C	569	CG	PHE	A	86	43.601	2.548	21.837	1.00	21.05 A
ATOM C	570	CD1	PHE	A	86	42.858	3.284	20.914	1.00	19.37 A
ATOM C	571	CD2	PHE	A	86	43.992	3.165	23.021	1.00	20.29 A
ATOM C	572	CE1	PHE	A	86	42.509	4.612	21.167	1.00	18.94 A
ATOM C	573	CE2	PHE	A	86	43.649	4.496	23.285	1.00	20.32 A
ATOM C	574	CZ	PHE	A	86	42.903	5.220	22.352	1.00	19.94 A
ATOM C	575	C	PHE	A	86	44.498	-0.575	19.781	1.00	22.94 A
ATOM O	576	O	PHE	A	86	45.550	-0.430	19.156	1.00	22.42 A
ATOM N	577	N	GLY	A	87	44.049	-1.762	20.178	1.00	21.80 A
ATOM C	578	CA	GLY	A	87	44.800	-2.969	19.881	1.00	20.71 A
ATOM C	579	C	GLY	A	87	45.882	-3.270	20.904	1.00	18.88 A
ATOM O	580	O	GLY	A	87	46.874	-3.940	20.604	1.00	17.62 A
ATOM N	581	N	VAL	A	88	45.703	-2.769	22.119	1.00	17.60 A
ATOM C	582	CA	VAL	A	88	46.685	-3.014	23.158	1.00	17.15 A
ATOM C	583	CB	VAL	A	88	47.642	-1.815	23.356	1.00	16.00 A
ATOM C	584	CG1	VAL	A	88	48.277	-1.430	22.032	1.00	13.25 A
ATOM C	585	CG2	VAL	A	88	46.901	-0.652	23.975	1.00	15.16 A
ATOM C	586	C	VAL	A	88	45.997	-3.290	24.472	1.00	17.59 A
ATOM O	587	O	VAL	A	88	44.841	-2.922	24.667	1.00	18.43 A
ATOM N	588	N	PRO	A	89	46.699	-3.966	25.390	1.00	18.50 A
ATOM C	589	CD	PRO	A	89	47.976	-4.673	25.177	1.00	17.26 A
ATOM C	590	CA	PRO	A	89	46.138	-4.287	26.705	1.00	17.37 A
ATOM C	591	CB	PRO	A	89	46.958	-5.496	27.137	1.00	16.69 A
ATOM C	592	CG	PRO	A	89	48.310	-5.170	26.575	1.00	17.70 A
ATOM C	593	C	PRO	A	89	46.271	-3.115	27.677	1.00	17.13 A
ATOM O	594	O	PRO	A	89	45.549	-3.042	28.669	1.00	18.98 A
ATOM N	595	N	SER	A	90	47.196	-2.200	27.397	1.00	16.91 A
ATOM C	596	CA	SER	A	90	47.394	-1.044	28.273	1.00	16.57 A

TABLE 1-continued

compound 338437 ((4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-acetic acid										
ATOM C	597	CB	SER	A	90	48.002	-1.485	29.612	1.00	15.12 A
ATOM O	598	OG	SER	A	90	49.329	-1.956	29.439	1.00	13.05 A
ATOM C	599	C	SER	A	90	48.291	0.023	27.653	1.00	16.15 A
ATOM O	600	O	SER	A	90	49.090	-0.261	26.764	1.00	17.41 A

[0226]

TABLE 2

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
REMARK coordinates from restrained individual B-factor refinement										
REMARK refinement resolution: 25 - 2.6 A										
REMARK starting r = 0.2563 free_r = 0.2787										
REMARK final r = 0.2553 free_r = 0.2761										
REMARK B rmsd for bonded mainchain atoms = 1.483 target = 1.5										
REMARK B rmsd for bonded sidechain atoms = 1.740 target = 2.0										
REMARK B rmsd for angle mainchain atoms = 2.593 target = 2.0										
REMARK B rmsd for angle sidechain atoms = 2.780 target = 2.5										
REMARK rweight = 0.1000 (with wa = 3.71696)										
REMARK target = mlf steps = 30										
REMARK sg = P4(3)2(1)2 a = 54.3 b = 54.3 c = 83.3 alpha = 90 beta = 90 gamma = 90										
REMARK parameter file 1: MSI_CNX_TOPPAR:protein_rep.param										
REMARK parameter file 2: ./cid.par										
REMARK molecular structure file: recycle.psf										
REMARK input coordinates: anneal_9.pdb										
REMARK reflection file = ../M876273_2_P43212.cv										
REMARK ncs = none										
REMARK B-correction resolution: 6.0 - 2.6										
REMARK initial B-factor correction applied to fobs:										
REMARK B11 = -1.189 B22 = -1.189 B33 = 2.379										
REMARK B12 = 0.000 B13 = 0.000 B23 = 0.000										
REMARK B-factor correction applied to coordinate array B: -0.119										
REMARK bulk solvent: (Mask) density level = 0.341945 e/A ³ , B-factor = 22.3925 A ²										
REMARK reflections with Fobs /sigma_F < 0.0 rejected										
REMARK reflections with Fobs > 10000 * rms (Fobs) rejected										
REMARK theoretical total number of refl. in resol. range: 4173 (100.0%)										
REMARK number of unobserved reflections (no entry or F = 0): 9 (0.2%)										
REMARK number of reflections rejected: 0 (0.0%)										
REMARK total number of reflections used: 4164 (99.8%)										
REMARK number of reflections in working set: 3737 (89.6%)										
REMARK number of reflections in test set: 427 (10.2%)										
CRYST1 54.300 54.300 83.300 90.00 90.00 90.00 P 43 21 2										
REMARK FILENAME = "bindividual.pdb"										
REMARK Written by CNX VERSION: 2000.12										
ATOM C	1	C	GLY	A	16	50.842	45.566	39.472	1.00	68.15 A
ATOM O	2	O	GLY	A	16	49.884	45.429	40.244	1.00	68.22 A
ATOM N	3	N	GLY	A	16	51.272	44.956	37.085	1.00	67.11 A
ATOM C	4	CA	GLY	A	16	51.225	44.463	38.498	1.00	67.90 A
ATOM N	5	N	SER	A	17	51.601	46.662	39.435	1.00	67.05 A
ATOM C	6	CA	SER	A	17	51.358	47.819	40.296	1.00	64.73 A
ATOM C	7	CB	SER	A	17	52.359	47.851	41.458	1.00	65.01 A
ATOM O	8	OG	SER	A	17	52.175	46.743	42.330	1.00	63.84 A
ATOM C	9	C	SER	A	17	51.495	49.080	39.449	1.00	62.82 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM O	10	O	SER	A	17	51.039	50.157	39.837	1.00	62.75 A
ATOM N	11	N	GLN	A	18	52.130	48.925	38.289	1.00	60.52 A
ATOM C	12	CA	GLN	A	18	52.323	50.023	37.346	1.00	57.89 A
ATOM C	13	CB	GLN	A	18	53.377	49.652	36.306	1.00	57.50 A
ATOM C	14	CG	GLN	A	18	54.800	49.725	36.791	1.00	57.38 A
ATOM C	15	CD	GLN	A	18	55.786	49.390	35.687	1.00	58.16 A
ATOM O	16	OE1	GLN	A	18	55.675	49.892	34.565	1.00	56.84 A
ATOM N	17	NE2	GLN	A	18	56.761	48.543	36.002	1.00	58.44 A
ATOM C	18	C	GLN	A	18	51.013	50.299	36.620	1.00	55.87 A
ATOM O	19	O	GLN	A	18	50.763	51.414	36.157	1.00	55.83 A
ATOM N	20	N	ILE	A	19	50.187	49.261	36.524	1.00	52.87 A
ATOM C	21	CA	ILE	A	19	48.898	49.337	35.850	1.00	50.05 A
ATOM C	22	CB	ILE	A	19	48.721	48.131	34.883	1.00	48.06 A
ATOM C	23	CG2	ILE	A	19	47.404	48.239	34.138	1.00	48.17 A
ATOM C	24	CG1	ILE	A	19	49.885	48.069	33.889	1.00	45.44 A
ATOM C	25	CD1	ILE	A	19	49.939	49.218	32.921	1.00	43.26 A
ATOM C	26	C	ILE	A	19	47.769	49.319	36.884	1.00	49.72 A
ATOM O	27	O	ILE	A	19	47.863	48.631	37.902	1.00	49.03 A
ATOM N	28	N	PRO	A	20	46.694	50.095	36.643	1.00	49.57 A
ATOM C	29	CD	PRO	A	20	46.609	51.167	35.636	1.00	49.58 A
ATOM C	30	CA	PRO	A	20	45.546	50.162	37.553	1.00	49.39 A
ATOM C	31	CB	PRO	A	20	44.693	51.271	36.949	1.00	48.67 A
ATOM C	32	CG	PRO	A	20	45.704	52.159	36.318	1.00	48.94 A
ATOM C	33	C	PRO	A	20	44.784	48.836	37.628	1.00	49.97 A
ATOM O	34	O	PRO	A	20	44.551	48.184	36.606	1.00	50.18 A
ATOM N	35	N	ALA	A	21	44.399	48.446	38.840	1.00	49.45 A
ATOM C	36	CA	ALA	A	21	43.660	47.207	39.057	1.00	49.81 A
ATOM C	37	CB	ALA	A	21	43.252	47.094	40.528	1.00	49.85 A
ATOM C	38	C	ALA	A	21	42.419	47.133	38.160	1.00	49.65 A
ATOM O	39	O	ALA	A	21	42.160	46.112	37.517	1.00	49.33 A
ATOM N	40	N	SER	A	22	41.650	48.217	38.125	1.00	48.76 A
ATOM C	41	CA	SER	A	22	40.451	48.260	37.302	1.00	47.75 A
ATOM C	42	CB	SER	A	22	39.873	49.678	37.296	1.00	47.15 A
ATOM O	43	OG	SER	A	22	40.857	50.625	36.915	1.00	48.43 A
ATOM C	44	C	SER	A	22	40.792	47.816	35.877	1.00	46.34 A
ATOM O	45	O	SER	A	22	40.029	47.083	35.242	1.00	45.89 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM N	46	N	GLU	A	23	41.947	48.251	35.384	1.00	44.68 A
ATOM C	47	CA	GLU	A	23	42.375	47.887	34.040	1.00	43.25 A
ATOM C	48	CB	GLU	A	23	43.526	48.771	33.588	1.00	42.16 A
ATOM C	49	CG	GLU	A	23	43.939	48.525	32.164	1.00	40.86 A
ATOM C	50	CD	GLU	A	23	44.747	49.671	31.612	1.00	40.82 A
ATOM O	51	OE1	GLU	A	23	45.613	50.189	32.344	1.00	41.52 A
ATOM O	52	OE2	GLU	A	23	44.523	50.054	30.448	1.00	41.56 A
ATOM C	53	C	GLU	A	23	42.790	46.428	33.991	1.00	42.01 A
ATOM O	54	O	GLU	A	23	42.419	45.701	33.076	1.00	42.32 A
ATOM N	55	N	GLN	A	24	43.561	45.998	34.977	1.00	41.29 A
ATOM C	56	CA	GLN	A	24	43.973	44.610	35.027	1.00	42.07 A
ATOM C	57	CB	GLN	A	24	44.762	44.334	36.314	1.00	41.13 A
ATOM C	58	CG	GLN	A	24	46.206	44.813	36.250	1.00	42.57 A
ATOM C	59	CD	GLN	A	24	46.978	44.602	37.546	1.00	43.91 A
ATOM O	60	OE1	GLN	A	24	46.823	43.580	38.225	1.00	44.84 A
ATOM N	61	NE2	GLN	A	24	47.831	45.564	37.884	1.00	43.17 A
ATOM C	62	C	GLN	A	24	42.714	43.747	34.984	1.00	43.32 A
ATOM O	63	O	GLN	A	24	42.750	42.596	34.541	1.00	43.40 A
ATOM N	64	N	GLU	A	25	41.596	44.326	35.423	1.00	44.62 A
ATOM C	65	CA	GLU	A	25	40.314	43.618	35.464	1.00	44.92 A
ATOM C	66	CB	GLU	A	25	39.471	44.123	36.642	1.00	48.33 A
ATOM C	67	CG	GLU	A	25	40.216	44.254	37.972	1.00	53.04 A
ATOM C	68	CD	GLU	A	25	40.899	42.969	38.423	1.00	55.79 A
ATOM O	69	OE1	GLU	A	25	41.474	42.972	39.533	1.00	57.11 A
ATOM O	70	OE2	GLU	A	25	40.869	41.961	37.681	1.00	57.84 A
ATOM C	71	C	GLU	A	25	39.472	43.697	34.184	1.00	42.75 A
ATOM O	72	O	GLU	A	25	38.563	42.887	33.992	1.00	42.62 A
ATOM N	73	N	THR	A	26	39.760	44.666	33.319	1.00	40.18 A
ATOM C	74	CA	THR	A	26	39.013	44.813	32.067	1.00	38.13 A
ATOM C	75	CB	THR	A	26	39.714	45.803	31.100	1.00	37.92 A
ATOM O	76	OG1	THR	A	26	40.061	47.002	31.803	1.00	37.02 A
ATOM C	77	CG2	THR	A	26	38.798	46.161	29.945	1.00	36.76 A
ATOM C	78	C	THR	A	26	38.897	43.456	31.367	1.00	36.79 A
ATOM O	79	O	THR	A	26	39.859	42.693	31.321	1.00	36.47 A
ATOM N	80	N	LEU	A	27	37.715	43.152	30.841	1.00	36.63 A
ATOM C	81	CA	LEU	A	27	37.490	41.887	30.138	1.00	35.77 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM C	82	CB	LEU	A	27	36.035	41.429	30.291	1.00	36.16 A
ATOM C	83	CG	LEU	A	27	35.799	39.909	30.293	1.00	38.05 A
ATOM C	84	CD1	LEU	A	27	36.293	39.313	31.617	1.00	36.12 A
ATOM C	85	CD2	LEU	A	27	34.305	39.610	30.112	1.00	38.41 A
ATOM C	86	C	LEU	A	27	37.808	42.130	28.665	1.00	34.52 A
ATOM O	87	O	LEU	A	27	37.395	43.139	28.090	1.00	33.72 A
ATOM N	88	N	VAL	A	28	38.540	41.204	28.054	1.00	33.53 A
ATOM C	89	CA	VAL	A	28	38.941	41.364	26.662	1.00	32.88 A
ATOM C	90	CB	VAL	A	28	40.420	41.848	26.589	1.00	32.86 A
ATOM C	91	CG1	VAL	A	28	40.570	43.182	27.302	1.00	31.21 A
ATOM C	92	CG2	VAL	A	28	41.340	40.821	27.242	1.00	33.40 A
ATOM C	93	C	VAL	A	28	38.792	40.107	25.802	1.00	31.29 A
ATOM O	94	O	VAL	A	28	38.708	38.992	26.314	1.00	30.99 A
ATOM N	95	N	ARG	A	29	38.754	40.312	24.489	1.00	29.80 A
ATOM C	96	CA	ARG	A	29	38.641	39.224	23.528	1.00	28.94 A
ATOM C	97	CB	ARG	A	29	37.379	39.371	22.685	1.00	33.14 A
ATOM C	98	CG	ARG	A	29	36.132	38.818	23.326	1.00	38.54 A
ATOM C	99	CD	ARG	A	29	34.905	39.188	22.511	1.00	43.39 A
ATOM N	100	NE	ARG	A	29	33.712	38.549	23.051	1.00	47.28 A
ATOM C	101	CZ	ARG	A	29	33.397	37.276	22.843	1.00	49.30 A
ATOM N	102	NH1	ARG	A	29	34.185	36.511	22.093	1.00	49.75 A
ATOM N	103	nh2	ARG	A	29	32.309	36.763	23.405	1.00	50.29 A
ATOM C	104	C	ARG	A	29	39.842	39.254	22.602	1.00	26.43 A
ATOM O	105	O	ARG	A	29	39.935	40.121	21.727	1.00	25.41 A
ATOM N	106	N	PRO	A	30	40.785	38.315	22.789	1.00	24.69 A
ATOM C	107	CD	PRO	A	30	40.798	37.274	23.830	1.00	23.43 A
ATOM C	108	CA	PRO	A	30	41.995	38.234	21.958	1.00	23.00 A
ATOM C	109	CB	PRO	A	30	42.826	37.151	22.643	1.00	21.72 A
ATOM C	110	CG	PRO	A	30	42.261	37.064	24.025	1.00	22.48 A
ATOM C	111	C	PRO	A	30	41.620	37.801	20.544	1.00	22.20 A
ATOM O	112	O	PRO	A	30	40.663	37.050	20.360	1.00	22.27 A
ATOM N	113	N	LYS	A	31	42.365	38.273	19.551	1.00	21.65 A
ATOM C	114	CA	LYS	A	31	42.118	37.880	18.166	1.00	19.51 A
ATOM C	115	CB	LYS	A	31	42.825	38.839	17.210	1.00	19.68 A
ATOM C	116	CG	LYS	A	31	42.364	40.279	17.348	1.00	20.82 A
ATOM C	117	CD	LYS	A	31	43.115	41.174	16.376	1.00	22.74 A

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM C	118	CE	LYS	A	31	42.641	42.630	16.435	1.00	20.68 Å
ATOM N	119	NZ	LYS	A	31	43.356	43.433	15.396	1.00	21.75 Å
ATOM C	120	C	LYS	A	31	42.666	36.454	18.011	1.00	18.36 Å
ATOM O	121	O	LYS	A	31	43.441	35.983	18.847	1.00	17.38 Å
ATOM N	122	N	PRO	A	32	42.291	35.760	16.930	1.00	17.15 Å
ATOM C	123	CD	PRO	A	32	41.612	36.293	15.736	1.00	16.30 Å
ATOM C	124	CA	PRO	A	32	42.737	34.387	16.684	1.00	16.70 Å
ATOM C	125	CB	PRO	A	32	42.392	34.182	15.213	1.00	16.53 Å
ATOM C	126	CG	PRO	A	32	41.180	35.032	15.044	1.00	16.35 Å
ATOM C	127	C	PRO	A	32	44.198	34.043	16.997	1.00	16.73 Å
ATOM O	128	O	PRO	A	32	44.470	33.062	17.695	1.00	17.12 Å
ATOM N	129	N	LEU	A	33	45.137	34.830	16.483	1.00	14.62 Å
ATOM C	130	CA	LEU	A	33	46.540	34.538	16.724	1.00	13.59 Å
ATOM C	131	CB	LEU	A	33	47.425	35.427	15.843	1.00	15.36 Å
ATOM C	132	CG	LEU	A	33	48.097	34.759	14.626	1.00	13.91 Å
ATOM C	133	CD1	LEU	A	33	47.597	33.319	14.406	1.00	13.51 Å
ATOM C	134	CD2	LEU	A	33	47.838	35.609	13.411	1.00	8.87 Å
ATOM C	135	C	LEU	A	33	46.936	34.641	18.189	1.00	13.14 Å
ATOM O	136	O	LEU	A	33	47.545	33.724	18.715	1.00	12.37 Å
ATOM N	137	N	LEU	A	34	46.610	35.744	18.856	1.00	14.58 Å
ATOM C	138	CA	LEU	A	34	46.930	35.859	20.279	1.00	13.84 Å
ATOM C	139	CB	LEU	A	34	46.540	37.236	20.826	1.00	13.73 Å
ATOM C	140	CG	LEU	A	34	46.613	37.449	22.347	1.00	10.65 Å
ATOM C	141	CD1	LEU	A	34	48.041	37.367	22.818	1.00	9.38 Å
ATOM C	142	CD2	LEU	A	34	46.029	38.795	22.701	1.00	11.47 Å
ATOM C	143	C	LEU	A	34	46.158	34.771	21.039	1.00	15.75 Å
ATOM O	144	O	LEU	A	34	46.678	34.176	21.975	1.00	16.50 Å
ATOM N	145	N	LEU	A	35	44.917	34.506	20.635	1.00	17.07 Å
ATOM C	146	CA	LEU	A	35	44.125	33.469	21.295	1.00	18.94 Å
ATOM C	147	CB	LEU	A	35	42.720	33.381	20.686	1.00	16.70 Å
ATOM C	148	CG	LEU	A	35	41.753	32.424	21.391	1.00	14.51 Å
ATOM C	149	CD1	LEU	A	35	41.542	32.888	22.825	1.00	13.73 Å
ATOM C	150	CD2	LEU	A	35	40.425	32.379	20.653	1.00	13.01 Å
ATOM C	151	C	LEU	A	35	44.815	32.094	21.218	1.00	20.66 Å
ATOM O	152	O	LEU	A	35	44.668	31.276	22.133	1.00	21.36 Å
ATOM N	153	N	LYS	A	36	45.563	31.845	20.140	1.00	20.77 Å

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM C	154	CA	LYS	A	36	46.279	30.581	19.979	1.00	22.28 A
ATOM C	155	CB	LYS	A	36	46.792	30.398	18.547	1.00	23.62 A
ATOM C	156	CG	LYS	A	36	45.782	29.781	17.586	1.00	28.23 A
ATOM C	157	CD	LYS	A	36	46.444	28.754	16.647	1.00	30.56 A
ATOM C	158	CE	LYS	A	36	47.556	29.366	15.789	1.00	32.43 A
ATOM N	159	NZ	LYS	A	36	48.108	28.414	14.778	1.00	31.16 A
ATOM C	160	C	LYS	A	36	47.461	30.504	20.937	1.00	23.86 A
ATOM O	161	O	LYS	A	36	47.716	29.451	21.537	1.00	26.24 A
ATOM N	162	N	LEU	A	37	48.196	31.603	21.076	1.00	23.16 A
ATOM C	163	CA	LEU	A	37	49.332	31.612	21.994	1.00	24.32 A
ATOM C	164	CB	LEU	A	37	49.920	33.019	22.134	1.00	25.18 A
ATOM C	165	CG	LEU	A	37	50.647	33.606	20.934	1.00	27.89 A
ATOM C	166	CD1	LEU	A	37	51.343	34.901	21.343	1.00	28.24 A
ATOM C	167	CD2	LEU	A	37	51.659	32.597	20.431	1.00	28.07 A
ATOM C	168	C	LEU	A	37	48.884	31.144	23.377	1.00	23.05 A
ATOM O	169	O	LEU	A	37	49.526	30.304	24.003	1.00	20.34 A
ATOM N	170	N	LEU	A	38	47.770	31.706	23.834	1.00	23.36 A
ATOM C	171	CA	LEU	A	38	47.218	31.399	25.139	1.00	24.58 A
ATOM C	172	CB	LEU	A	38	46.036	32.322	25.447	1.00	21.20 A
ATOM C	173	CG	LEU	A	38	46.216	33.821	25.189	1.00	19.16 A
ATOM C	174	CD1	LEU	A	38	44.954	34.538	25.619	1.00	16.77 A
ATOM C	175	CD2	LEU	A	38	47.420	34.370	25.950	1.00	18.04 A
ATOM C	176	C	LEU	A	38	46.772	29.950	25.241	1.00	27.20 A
ATOM O	177	O	LEU	A	38	46.970	29.309	26.273	1.00	29.33 A
ATOM N	178	N	LYS	A	39	46.175	29.419	24.182	1.00	28.13 A
ATOM C	179	CA	LYS	A	39	45.720	28.041	24.241	1.00	29.30 A
ATOM C	180	CB	LYS	A	39	44.782	27.741	23.071	1.00	28.63 A
ATOM C	181	CG	LYS	A	39	43.532	28.596	23.123	1.00	28.78 A
ATOM C	182	CD	LYS	A	39	42.451	28.113	22.184	1.00	27.98 A
ATOM C	183	CE	LYS	A	39	41.239	29.021	22.270	1.00	26.89 A
ATOM N	184	NZ	LYS	A	39	40.089	28.444	21.537	1.00	27.11 A
ATOM C	185	C	LYS	A	39	46.884	27.062	24.270	1.00	30.33 A
ATOM O	186	O	LYS	A	39	46.787	25.998	24.883	1.00	31.74 A
ATOM N	187	N	SER	A	40	47.993	27.428	23.633	1.00	30.27 A
ATOM C	188	CA	SER	A	40	49.169	26.559	23.607	1.00	29.62 A
ATOM C	189	CB	SER	A	40	50.280	27.175	22.735	1.00	28.81 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM O	190	OG	SER	A	40	50.904	28.292	23.357	1.00	26.68 A
ATOM C	191	C	SER	A	40	49.701	26.301	25.020	1.00	29.48 A
ATOM O	192	O	SER	A	40	50.396	25.316	25.254	1.00	29.59 A
ATOM N	193	N	VAL	A	41	49.374	27.186	25.958	1.00	30.35 A
ATOM C	194	CA	VAL	A	41	49.827	27.044	27.345	1.00	30.76 A
ATOM C	195	CB	VAL	A	41	50.717	28.252	27.799	1.00	30.64 A
ATOM C	196	CG1	VAL	A	41	52.087	28.184	27.125	1.00	29.00 A
ATOM C	197	CG2	VAL	A	41	50.030	29.574	27.470	1.00	28.32 A
ATOM C	198	C	VAL	A	41	48.678	26.891	28.345	1.00	32.02 A
ATOM O	199	O	VAL	A	41	48.691	27.500	29.419	1.00	31.05 A
ATOM N	200	N	GLY	A	42	47.675	26.092	27.983	1.00	33.77 A
ATOM C	201	CA	GLY	A	42	46.563	25.862	28.889	1.00	36.14 A
ATOM C	202	C	GLY	A	42	45.260	26.597	28.641	1.00	38.10 A
ATOM O	203	O	GLY	A	42	44.201	25.971	28.653	1.00	40.02 A
ATOM N	204	N	ALA	A	43	45.317	27.912	28.432	1.00	38.97 A
ATOM C	205	CA	ALA	A	43	44.107	28.703	28.203	1.00	39.16 A
ATOM C	206	CB	ALA	A	43	44.459	30.022	27.518	1.00	38.86 A
ATOM C	207	C	ALA	A	43	43.080	27.938	27.375	1.00	39.94 A
ATOM O	208	O	ALA	A	43	43.437	27.164	26.485	1.00	40.04 A
ATOM N	209	N	GLN	A	44	41.802	28.155	27.675	1.00	41.54 A
ATOM C	210	CA	GLN	A	44	40.733	27.475	26.955	1.00	42.78 A
ATOM C	211	CB	GLN	A	44	40.609	26.037	27.466	1.00	45.11 A
ATOM C	212	CG	GLN	A	44	40.573	25.913	28.984	1.00	47.61 A
ATOM C	213	CD	GLN	A	44	40.868	24.493	29.456	1.00	49.56 A
ATOM O	214	OE1	GLN	A	44	40.913	24.221	30.662	1.00	49.35 A
ATOM N	215	NE2	GLN	A	44	41.075	23.581	28.506	1.00	49.08 A
ATOM C	216	C	GLN	A	44	39.379	28.183	27.030	1.00	42.23 A
ATOM O	217	O	GLN	A	44	38.355	27.557	27.322	1.00	42.70 A
ATOM N	218	N	LYS	A	45	39.391	29.488	26.763	1.00	40.15 A
ATOM C	219	CA	LYS	A	45	38.184	30.307	26.765	1.00	37.90 A
ATOM C	220	CB	LYS	A	45	38.085	31.150	28.034	1.00	39.62 A
ATOM C	221	CG	LYS	A	45	38.193	30.392	29.341	1.00	41.18 A
ATOM C	222	CD	LYS	A	45	37.768	31.288	30.502	1.00	42.96 A
ATOM C	223	CE	LYS	A	45	38.491	32.629	30.473	1.00	45.64 A
ATOM N	224	NZ	LYS	A	45	38.045	33.556	31.559	1.00	48.08 A
ATOM C	225	C	LYS	A	45	38.296	31.254	25.585	1.00	36.61 A
ATOM O	226	O	LYS	A	45	39.258	31.183	24.822	1.00	36.82 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM N	227	N	ASP	A	46	37.323	32.149	25.448	1.00	34.69 A
ATOM C	228	CA	ASP	A	46	37.332	33.128	24.368	1.00	33.64 A
ATOM C	229	CB	ASP	A	46	36.015	33.106	23.577	1.00	35.21 A
ATOM C	230	CG	ASP	A	46	35.826	31.828	22.778	1.00	36.60 A
ATOM O	231	OD1	ASP	A	46	36.819	31.326	22.204	1.00	35.63 A
ATOM O	232	OD2	ASP	A	46	34.677	31.337	22.712	1.00	36.79 A
ATOM C	233	C	ASP	A	46	37.529	34.526	24.935	1.00	32.32 A
ATOM O	234	O	ASP	A	46	38.032	35.419	24.249	1.00	33.06 A
ATOM N	235	N	THR	A	47	37.118	34.715	26.186	1.00	30.30 A
ATOM C	236	CA	THR	A	47	37.233	36.012	26.850	1.00	27.52 A
ATOM C	237	CB	THR	A	47	35.849	36.568	27.265	1.00	28.37 A
ATOM O	238	OG1	THR	A	47	35.055	35.513	27.822	1.00	28.12 A
ATOM C	239	CG2	THR	A	47	35.130	37.169	26.071	1.00	28.11 A
ATOM C	240	C	THR	A	47	38.097	35.897	28.088	1.00	25.47 A
ATOM O	241	O	THR	A	47	38.111	34.862	28.759	1.00	24.25 A
ATOM N	242	N	TYR	A	48	38.820	36.973	28.382	1.00	24.41 A
ATOM C	243	CA	TYR	A	48	39.716	37.010	29.526	1.00	24.02 A
ATOM C	244	CB	TYR	A	48	41.142	36.566	29.126	1.00	23.01 A
ATOM C	245	CG	TYR	A	48	41.265	35.192	28.492	1.00	22.29 A
ATOM C	246	CD1	TYR	A	48	40.966	34.992	27.143	1.00	21.16 A
ATOM C	247	CE1	TYR	A	48	41.035	33.713	26.568	1.00	20.20 A
ATOM C	248	CD2	TYR	A	48	41.647	34.079	29.254	1.00	21.34 A
ATOM C	249	CE2	TYR	A	48	41.721	32.806	28.688	1.00	20.29 A
ATOM C	250	CZ	TYR	A	48	41.409	32.633	27.348	1.00	19.58 A
ATOM O	251	OH	TYR	A	48	41.436	31.378	26.795	1.00	20.11 A
ATOM C	252	C	TYR	A	48	39.829	38.419	30.085	1.00	24.38 A
ATOM O	253	O	TYR	A	48	39.512	39.403	29.409	1.00	22.46 A
ATOM N	254	N	THR	A	49	40.288	38.497	31.329	1.00	24.50 A
ATOM C	255	CA	THR	A	49	40.554	39.774	31.974	1.00	25.25 A
ATOM C	256	CB	THR	A	49	40.510	39.647	33.515	1.00	26.57 A
ATOM O	257	OG1	THR	A	49	41.215	38.459	33.914	1.00	26.24 A
ATOM C	258	CG2	THR	A	49	39.056	39.580	34.017	1.00	24.91 A
ATOM C	259	C	THR	A	49	42.000	40.027	31.524	1.00	25.63 A
ATOM O	260	O	THR	A	49	42.738	39.079	31.248	1.00	24.71 A
ATOM N	261	N	MET	A	50	42.414	41.281	31.424	1.00	26.39 A
ATOM C	262	CA	MET	A	50	43.776	41.545	30.986	1.00	26.62 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM C	263	CB	MET	A	50	44.053	43.040	30.977	1.00	25.74 A
ATOM C	264	CG	MET	A	50	43.446	43.740	29.780	1.00	25.74 A
ATOM S	265	SD	MET	A	50	44.280	43.286	28.239	1.00	24.59 A
ATOM C	266	CE	MET	A	50	45.652	44.433	28.225	1.00	22.52 A
ATOM C	267	C	MET	A	50	44.797	40.832	31.855	1.00	28.23 A
ATOM O	268	O	MET	A	50	45.890	40.518	31.396	1.00	29.67 A
ATOM N	269	N	LYS	A	51	44.442	40.554	33.105	1.00	28.66 A
ATOM C	270	CA	LYS	A	51	45.370	39.872	33.993	1.00	29.11 A
ATOM C	271	CB	LYS	A	51	44.878	39.943	35.439	1.00	32.66 A
ATOM C	272	CG	LYS	A	51	45.919	39.458	36.443	1.00	37.67 A
ATOM C	273	CD	LYS	A	51	45.462	39.604	37.889	1.00	41.07 A
ATOM C	274	CE	LYS	A	51	46.527	39.071	38.855	1.00	42.73 A
ATOM N	275	NZ	LYS	A	51	46.109	39.129	40.295	1.00	45.66 A
ATOM C	276	C	LYS	A	51	45.597	38.411	33.586	1.00	28.29 A
ATOM O	277	O	LYS	A	51	46.723	37.908	33.669	1.00	28.36 A
ATOM N	278	N	GLU	A	52	44.537	37.729	33.152	1.00	25.71 A
ATOM C	279	CA	GLU	A	52	44.662	36.334	32.732	1.00	23.60 A
ATOM C	280	CB	GLU	A	52	43.278	35.702	32.522	1.00	24.83 A
ATOM C	281	CG	GLU	A	52	42.420	35.589	33.777	1.00	27.15 A
ATOM C	282	CD	GLU	A	52	40.989	35.116	33.479	1.00	29.01 A
ATOM O	283	OE1	GLU	A	52	40.281	35.785	32.691	1.00	29.80 A
ATOM O	284	OE2	GLU	A	52	40.568	34.078	34.032	1.00	29.19 A
ATOM C	285	C	GLU	A	52	45.476	36.230	31.432	1.00	21.67 A
ATOM O	286	O	GLU	A	52	46.128	35.214	31.183	1.00	20.99 A
ATOM N	287	N	VAL	A	53	45.425	37.266	30.598	1.00	18.55 A
ATOM C	288	CA	VAL	A	53	46.181	37.255	29.351	1.00	16.46 A
ATOM C	289	CB	VAL	A	53	45.807	38.454	28.423	1.00	17.02 A
ATOM C	290	CG1	VAL	A	53	46.806	38.553	27.264	1.00	15.92 A
ATOM C	291	CG2	VAL	A	53	44.402	38.261	27.853	1.00	14.61 A
ATOM C	292	C	VAL	A	53	47.650	37.331	29.742	1.00	15.15 A
ATOM O	293	O	VAL	A	53	48.436	36.443	29.403	1.00	13.10 A
ATOM N	294	N	LEU	A	54	48.010	38.394	30.463	1.00	15.42 A
ATOM C	295	CA	LEU	A	54	49.375	38.570	30.952	1.00	14.74 A
ATOM C	296	CB	LEU	A	54	49.454	39.698	31.982	1.00	12.86 A
ATOM C	297	CG	LEU	A	54	49.718	41.124	31.497	1.00	13.00 A
ATOM C	298	CD1	LEU	A	54	50.874	41.100	30.500	1.00	14.60 A
ATOM C	299	CD2	LEU	A	54	48.494	41.706	30.859	1.00	11.73 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM C	300	C	LEU	A	54	49.846	37.281	31.619	1.00	15.13 A
ATOM O	301	O	LEU	A	54	51.009	36.897	31.502	1.00	16.88 A
ATOM N	302	N	PHE	A	55	48.942	36.605	32.312	1.00	14.69 A
ATOM C	303	CA	PHE	A	55	49.305	35.371	32.991	1.00	16.41 A
ATOM C	304	CB	PHE	A	55	48.137	34.831	33.819	1.00	18.34 A
ATOM C	305	CG	PHE	A	55	48.428	33.500	34.429	1.00	20.72 A
ATOM C	306	CD1	PHE	A	55	49.136	33.411	35.626	1.00	20.24 A
ATOM C	307	CD2	PHE	A	55	48.101	32.324	33.749	1.00	20.52 A
ATOM C	308	CE1	PHE	A	55	49.524	32.170	36.135	1.00	20.60 A
ATOM C	309	CE2	PHE	A	55	48.485	31.079	34.248	1.00	21.73 A
ATOM C	310	CZ	PHE	A	55	49.199	31.001	35.444	1.00	20.59 A
ATOM C	311	C	PHE	A	55	49.779	34.268	32.058	1.00	16.04 A
ATOM O	312	O	PHE	A	55	50.853	33.698	32.259	1.00	17.31 A
ATOM N	313	N	TYR	A	56	48.960	33.949	31.060	1.00	16.71 A
ATOM C	314	CA	TYR	A	56	49.283	32.904	30.087	1.00	17.61 A
ATOM C	315	CB	TYR	A	56	48.079	32.620	29.189	1.00	18.45 A
ATOM C	316	CG	TYR	A	56	46.996	31.859	29.902	1.00	21.48 A
ATOM C	317	CD1	TYR	A	56	47.213	30.541	30.318	1.00	23.38 A
ATOM C	318	CE1	TYR	A	56	46.237	29.832	31.013	1.00	25.16 A
ATOM C	319	CD2	TYR	A	56	45.766	32.459	30.198	1.00	22.53 A
ATOM C	320	CE2	TYR	A	56	44.773	31.761	30.898	1.00	23.90 A
ATOM C	321	CZ	TYR	A	56	45.019	30.445	31.303	1.00	26.15 A
ATOM O	322	OH	TYR	A	56	44.065	29.738	32.003	1.00	26.91 A
ATOM C	323	C	TYR	A	56	50.450	33.345	29.243	1.00	16.78 A
ATOM O	324	O	TYR	A	56	51.235	32.530	28.754	1.00	18.53 A
ATOM N	325	N	LEU	A	57	50.543	34.656	29.065	1.00	15.78 A
ATOM C	326	CA	LEU	A	57	51.619	35.252	28.300	1.00	13.13 A
ATOM C	327	CB	LEU	A	57	51.348	36.749	28.171	1.00	11.95 A
ATOM C	328	CG	LEU	A	57	51.232	37.364	26.771	1.00	13.21 A
ATOM C	329	CD1	LEU	A	57	50.535	36.422	25.805	1.00	10.11 A
ATOM C	330	CD2	LEU	A	57	50.491	38.694	26.888	1.00	10.01 A
ATOM C	331	C	LEU	A	57	52.922	34.973	29.074	1.00	12.23 A
ATOM O	332	O	LEU	A	57	53.974	34.734	28.477	1.00	9.19 A
ATOM N	333	N	GLY	A	58	52.824	34.984	30.404	1.00	11.88 A
ATOM C	334	CA	GLY	A	58	53.969	34.719	31.249	1.00	14.46 A
ATOM C	335	C	GLY	A	58	54.403	33.278	31.089	1.00	17.50 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM O	336	O	GLY	A	58	55.594	32.988	30.928	1.00	18.69 A
ATOM N	337	N	GLN	A	59	53.435	32.368	31.132	1.00	18.46 A
ATOM C	338	CA	GLN	A	59	53.728	30.958	30.975	1.00	19.45 A
ATOM C	339	CB	GLN	A	59	52.463	30.128	31.161	1.00	22.28 A
ATOM C	340	CG	GLN	A	59	51.877	30.260	32.549	1.00	24.82 A
ATOM C	341	CD	GLN	A	59	52.956	30.214	33.619	1.00	25.90 A
ATOM O	342	OE1	GLN	A	59	53.655	29.212	33.768	1.00	26.11 A
ATOM N	343	NE2	GLN	A	59	53.104	31.312	34.361	1.00	26.90 A
ATOM C	344	C	GLN	A	59	54.299	30.729	29.592	1.00	19.50 A
ATOM O	345	O	GLN	A	59	55.218	29.927	29.410	1.00	20.93 A
ATOM N	346	N	TYR	A	60	53.765	31.450	28.616	1.00	17.52 A
ATOM C	347	CA	TYR	A	60	54.239	31.315	27.252	1.00	18.33 A
ATOM C	348	CB	TYR	A	60	53.432	32.220	26.317	1.00	14.85 A
ATOM C	349	CG	TYR	A	60	53.776	32.069	24.845	1.00	15.47 A
ATOM C	350	CD1	TYR	A	60	53.279	31.001	24.089	1.00	14.63 A
ATOM C	351	CE1	TYR	A	60	53.581	30.873	22.716	1.00	11.14 A
ATOM C	352	CD2	TYR	A	60	54.594	33.007	24.196	1.00	15.88 A
ATOM C	353	CE2	TYR	A	60	54.902	32.886	22.826	1.00	13.26 A
ATOM C	354	CZ	TYR	A	60	54.391	31.818	22.096	1.00	12.81 A
ATOM O	355	OH	TYR	A	60	54.678	31.716	20.748	1.00	10.53 A
ATOM C	356	C	TYR	A	60	55.728	31.664	27.158	1.00	20.42 A
ATOM O	357	O	TYR	A	60	56.557	30.793	26.871	1.00	19.39 A
ATOM N	358	N	ILE	A	61	56.069	32.928	27.418	1.00	21.45 A
ATOM C	359	CA	ILE	A	61	57.458	33.361	27.319	1.00	23.11 A
ATOM C	360	CB	ILE	A	61	57.624	34.874	27.588	1.00	22.76 A
ATOM C	361	CG2	ILE	A	61	56.939	35.682	26.499	1.00	23.31 A
ATOM C	362	CG1	ILE	A	61	57.085	35.230	28.965	1.00	22.24 A
ATOM C	363	CD1	ILE	A	61	57.384	36.655	29.349	1.00	23.32 A
ATOM C	364	C	ILE	A	61	58.410	32.604	28.235	1.00	25.11 A
ATOM O	365	O	ILE	A	61	59.573	32.396	27.899	1.00	25.25 A
ATOM N	366	N	MET	A	62	57.931	32.186	29.393	1.00	27.56 A
ATOM C	367	CA	MET	A	62	58.797	31.452	30.293	1.00	30.23 A
ATOM C	368	CB	MET	A	62	58.158	31.371	31.680	1.00	32.88 A
ATOM C	369	CG	MET	A	62	59.042	30.734	32.738	1.00	34.56 A
ATOM S	370	SD	MET	A	62	58.113	29.481	33.637	1.00	39.80 A
ATOM C	371	CE	MET	A	62	58.272	28.115	32.471	1.00	35.55 A
ATOM C	372	C	MET	A	62	59.064	30.043	29.737	1.00	31.22 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM O	373	O	MET	A	62	60.218	29.656	29.513	1.00	30.54 A
ATOM N	374	N	THR	A	63	57.997	29.291	29.483	1.00	31.07 A
ATOM C	375	CA	THR	A	63	58.150	27.931	28.976	1.00	31.77 A
ATOM C	376	CB	THR	A	63	56.775	27.264	28.687	1.00	30.74 A
ATOM O	377	OG1	THR	A	63	56.009	28.092	27.808	1.00	31.02 A
ATOM C	378	CG2	THR	A	63	56.004	27.044	29.982	1.00	31.19 A
ATOM C	379	C	THR	A	63	59.023	27.823	27.724	1.00	32.00 A
ATOM O	380	O	THR	A	63	59.890	26.947	27.645	1.00	33.74 A
ATOM N	381	N	LYS	A	64	58.797	28.697	26.747	1.00	30.45 A
ATOM C	382	CA	LYS	A	64	59.578	28.655	25.522	1.00	29.14 A
ATOM C	383	CB	LYS	A	64	58.783	29.262	24.363	1.00	28.22 A
ATOM C	384	CG	LYS	A	64	57.581	28.437	23.947	1.00	26.54 A
ATOM C	385	CD	LYS	A	64	56.870	29.029	22.738	1.00	26.08 A
ATOM C	386	CE	LYS	A	64	57.757	29.029	21.514	1.00	26.73 A
ATOM N	387	NZ	LYS	A	64	57.043	29.526	20.308	1.00	26.87 A
ATOM C	388	C	LYS	A	64	60.926	29.358	25.674	1.00	29.64 A
ATOM O	389	O	LYS	A	64	61.640	29.574	24.695	1.00	28.68 A
ATOM N	390	N	ARG	A	65	61.264	29.716	26.909	1.00	31.08 A
ATOM C	391	CA	ARG	A	65	62.541	30.359	27.206	1.00	31.77 A
ATOM C	392	CB	ARG	A	65	63.624	29.278	27.281	1.00	32.61 A
ATOM C	393	CG	ARG	A	65	63.422	28.319	28.456	1.00	36.27 A
ATOM C	394	CD	ARG	A	65	64.128	26.980	28.268	1.00	38.75 A
ATOM N	395	NE	ARG	A	65	63.951	26.108	29.433	1.00	41.50 A
ATOM C	396	CZ	ARG	A	65	64.107	24.782	29.425	1.00	43.14 A
ATOM N	397	NH1	ARG	A	65	64.444	24.144	28.308	1.00	43.25 A
ATOM N	398	NH2	ARG	A	65	63.923	24.087	30.540	1.00	41.34 A
ATOM C	399	C	ARG	A	65	62.931	31.442	26.193	1.00	30.62 A
ATOM O	400	O	ARG	A	65	63.990	31.365	25.562	1.00	31.11 A
ATOM N	401	N	LEU	A	66	62.069	32.447	26.043	1.00	27.85 A
ATOM C	402	CA	LEU	A	66	62.315	33.554	25.117	1.00	24.57 A
ATOM C	403	CB	LEU	A	66	60.996	34.080	24.535	1.00	21.73 A
ATOM C	404	CG	LEU	A	66	60.195	33.192	23.588	1.00	18.58 A
ATOM C	405	CD1	LEU	A	66	58.917	33.893	23.171	1.00	16.38 A
ATOM C	406	CD2	LEU	A	66	61.039	32.882	22.373	1.00	16.78 A
ATOM C	407	C	LEU	A	66	63.023	34.696	25.829	1.00	24.06 A
ATOM O	408	O	LEU	A	66	63.334	35.715	25.221	1.00	22.74 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM N	409	N	TYR	A	67	63.255	34.535	27.127	1.00	25.28 A
ATOM C	410	CA	TYR	A	67	63.931	35.569	27.900	1.00	26.02 A
ATOM C	411	CB	TYR	A	67	63.406	35.580	29.344	1.00	26.69 A
ATOM C	412	CG	TYR	A	67	63.546	34.267	30.069	1.00	26.95 A
ATOM C	413	CD1	TYR	A	67	64.668	34.000	30.850	1.00	27.52 A
ATOM C	414	CE1	TYR	A	67	64.836	32.770	31.469	1.00	27.15 A
ATOM C	415	CD2	TYR	A	67	62.587	33.269	29.928	1.00	26.57 A
ATOM C	416	CE2	TYR	A	67	62.742	32.031	30.544	1.00	27.84 A
ATOM C	417	CZ	TYR	A	67	63.875	31.787	31.312	1.00	27.23 A
ATOM O	418	OH	TYR	A	67	64.068	30.554	31.888	1.00	24.32 A
ATOM C	419	C	TYR	A	67	65.443	35.347	27.857	1.00	26.40 A
ATOM O	420	O	TYR	A	67	65.917	34.216	27.828	1.00	25.07 A
ATOM N	421	N	ASP	A	68	66.194	36.440	27.837	1.00	28.69 A
ATOM C	422	CA	ASP	A	68	67.645	36.365	27.764	1.00	31.43 A
ATOM C	423	CB	ASP	A	68	68.222	37.737	27.411	1.00	31.86 A
ATOM C	424	CG	ASP	A	68	69.688	37.666	27.043	1.00	31.50 A
ATOM O	425	OD1	ASP	A	68	69.997	37.105	25.972	1.00	29.47 A
ATOM O	426	OD2	ASP	A	68	70.526	38.154	27.833	1.00	33.11 A
ATOM C	427	C	ASP	A	68	68.313	35.848	29.035	1.00	33.44 A
ATOM O	428	O	ASP	A	68	67.871	36.128	30.152	1.00	33.12 A
ATOM N	429	N	GLU	A	69	69.399	35.105	28.845	1.00	36.37 A
ATOM C	430	CA	GLU	A	69	70.152	34.529	29.950	1.00	39.07 A
ATOM C	431	CB	GLU	A	69	71.214	33.558	29.420	1.00	42.56 A
ATOM C	432	CG	GLU	A	69	70.627	32.277	28.851	1.00	48.37 A
ATOM C	433	CD	GLU	A	69	69.565	31.677	29.766	1.00	51.95 A
ATOM O	434	OE1	GLU	A	69	69.848	31.514	30.974	1.00	54.24 A
ATOM O	435	OE2	GLU	A	69	68.449	31.370	29.281	1.00	54.25 A
ATOM C	436	C	GLU	A	69	70.810	35.566	30.837	1.00	38.35 A
ATOM O	437	O	GLU	A	69	70.695	35.506	32.057	1.00	38.84 A
ATOM N	438	N	LYS	A	70	71.504	36.519	30.235	1.00	38.42 A
ATOM C	439	CA	LYS	A	70	72.162	37.542	31.030	1.00	38.82 A
ATOM C	440	CB	LYS	A	70	73.285	38.187	30.210	1.00	41.21 A
ATOM C	441	CG	LYS	A	70	74.320	37.148	29.776	1.00	43.81 A
ATOM C	442	CD	LYS	A	70	75.539	37.743	29.092	1.00	46.99 A
ATOM C	443	CE	LYS	A	70	76.504	36.632	28.674	1.00	47.44 A
ATOM N	444	NZ	LYS	A	70	77.794	37.156	28.143	1.00	48.71 A
ATOM C	445	C	LYS	A	70	71.121	38.554	31.494	1.00	37.27 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM O	446	O	LYS	A	70	70.854	38.673	32.690	1.00	36.92 A
ATOM N	447	N	GLN	A	71	70.512	39.262	30.551	1.00	35.72 A
ATOM C	448	CA	GLN	A	71	69.476	40.228	30.893	1.00	33.41 A
ATOM C	449	CB	GLN	A	71	69.478	41.365	29.878	1.00	34.05 A
ATOM C	450	CG	GLN	A	71	70.781	42.116	29.818	1.00	35.15 A
ATOM C	451	CD	GLN	A	71	70.728	43.264	28.839	1.00	36.85 A
ATOM O	452	OE1	GLN	A	71	70.697	43.062	27.621	1.00	37.63 A
ATOM N	453	NE2	GLN	A	71	70.701	44.482	29.364	1.00	38.20 A
ATOM C	454	C	GLN	A	71	68.115	39.512	30.898	1.00	31.00 A
ATOM O	455	O	GLN	A	71	67.412	39.466	29.883	1.00	31.06 A
ATOM N	456	N	GLN	A	72	67.754	38.957	32.051	1.00	27.04 A
ATOM C	457	CA	GLN	A	72	66.505	38.216	32.200	1.00	23.77 A
ATOM C	458	CB	GLN	A	72	66.437	37.583	33.592	1.00	21.94 A
ATOM C	459	CG	GLN	A	72	65.172	36.783	33.877	1.00	19.04 A
ATOM C	460	CD	GLN	A	72	65.343	35.849	35.066	1.00	18.27 A
ATOM O	461	OE1	GLN	A	72	66.141	34.917	35.018	1.00	16.43 A
ATOM N	462	NE2	GLN	A	72	64.600	36.098	36.137	1.00	19.03 A
ATOM C	463	C	GLN	A	72	65.231	39.003	31.936	1.00	21.79 A
ATOM O	464	O	GLN	A	72	64.255	38.438	31.464	1.00	20.39 A
ATOM N	465	N	HIS	A	73	65.234	40.300	32.226	1.00	21.17 A
ATOM C	466	CA	HIS	A	73	64.039	41.103	32.004	1.00	19.46 A
ATOM C	467	CB	HIS	A	73	64.143	42.440	32.738	1.00	19.40 A
ATOM C	468	CG	HIS	A	73	65.242	43.328	32.244	1.00	21.41 A
ATOM C	469	CD2	HIS	A	73	66.560	43.376	32.556	1.00	21.24 A
ATOM N	470	ND1	HIS	A	73	65.029	44.339	31.331	1.00	22.42 A
ATOM C	471	CE1	HIS	A	73	66.167	44.972	31.104	1.00	21.05 A
ATOM N	472	NE2	HIS	A	73	67.111	44.406	31.836	1.00	21.25 A
ATOM C	473	C	HIS	A	73	63.772	41.338	30.526	1.00	20.37 A
ATOM O	474	O	HIS	A	73	62.667	41.747	30.156	1.00	19.89 A
ATOM N	475	N	ILE	A	74	64.774	41.083	29.681	1.00	19.94 A
ATOM C	476	CA	ILE	A	74	64.607	41.259	28.239	1.00	19.76 A
ATOM C	477	CB	ILE	A	74	65.942	41.605	27.523	1.00	20.27 A
ATOM C	478	CG2	ILE	A	74	65.699	41.745	26.022	1.00	18.27 A
ATOM C	479	CG1	ILE	A	74	66.536	42.906	28.072	1.00	22.09 A
ATOM C	480	CD1	ILE	A	74	65.704	44.127	27.810	1.00	22.98 A
ATOM C	481	C	ILE	A	74	64.060	39.970	27.611	1.00	19.56 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM O	482	O	ILE	A	74	64.555	38.875	27.885	1.00	19.09 A
ATOM N	483	N	VAL	A	75	63.045	40.115	26.764	1.00	17.84 A
ATOM C	484	CA	VAL	A	75	62.429	38.982	26.087	1.00	16.49 A
ATOM C	485	CB	VAL	A	75	60.918	38.928	26.388	1.00	14.74 A
ATOM C	486	CG1	VAL	A	75	60.245	37.892	25.529	1.00	13.12 A
ATOM C	487	CG2	VAL	A	75	60.707	38.602	27.852	1.00	15.39 A
ATOM C	488	C	VAL	A	75	62.650	39.136	24.588	1.00	17.78 A
ATOM O	489	O	VAL	A	75	62.249	40.140	23.995	1.00	17.51 A
ATOM N	490	N	TYR	A	76	63.302	38.150	23.977	1.00	17.97 A
ATOM C	491	CA	TYR	A	76	63.570	38.201	22.544	1.00	18.96 A
ATOM C	492	CB	TYR	A	76	64.958	37.622	22.229	1.00	20.36 A
ATOM C	493	CG	TYR	A	76	66.085	38.507	22.713	1.00	22.91 A
ATOM C	494	CD1	TYR	A	76	66.677	38.306	23.966	1.00	22.46 A
ATOM C	495	CE1	TYR	A	76	67.685	39.168	24.438	1.00	24.23 A
ATOM C	496	CD2	TYR	A	76	66.525	39.587	21.942	1.00	23.56 A
ATOM C	497	CE2	TYR	A	76	67.532	40.457	22.408	1.00	23.98 A
ATOM C	498	CZ	TYR	A	76	68.102	40.242	23.653	1.00	23.95 A
ATOM O	499	OH	TYR	A	76	69.065	41.112	24.120	1.00	24.89 A
ATOM C	500	C	TYR	A	76	62.499	37.438	21.801	1.00	17.43 A
ATOM O	501	O	TYR	A	76	62.277	36.273	22.074	1.00	18.57 A
ATOM N	502	N	CYS	A	77	61.841	38.094	20.850	1.00	19.17 A
ATOM C	503	CA	CYS	A	77	60.755	37.458	20.100	1.00	20.17 A
ATOM C	504	CB	CYS	A	77	59.410	37.978	20.628	1.00	18.05 A
ATOM S	505	SG	CYS	A	77	59.288	39.802	20.678	1.00	17.89 A
ATOM C	506	C	CYS	A	77	60.792	37.612	18.575	1.00	20.92 A
ATOM O	507	O	CYS	A	77	59.817	37.293	17.902	1.00	22.93 A
ATOM N	508	N	SER	A	78	61.904	38.083	18.027	1.00	21.73 A
ATOM C	509	CA	SER	A	78	62.002	38.261	16.582	1.00	23.67 A
ATOM C	510	CB	SER	A	78	63.369	38.828	16.209	1.00	23.31 A
ATOM O	511	OG	SER	A	78	64.394	38.058	16.804	1.00	24.57 A
ATOM C	512	C	SER	A	78	61.754	36.978	15.791	1.00	24.32 A
ATOM O	513	O	SER	A	78	61.341	37.039	14.632	1.00	24.57 A
ATOM N	514	N	ASN	A	79	62.003	35.824	16.403	1.00	23.65 A
ATOM C	515	CA	ASN	A	79	61.794	34.553	15.709	1.00	24.00 A
ATOM C	516	CB	ASN	A	79	63.081	33.709	15.694	1.00	24.75 A
ATOM C	517	CG	ASN	A	79	64.160	34.293	14.792	1.00	25.05 A
ATOM O	518	OD1	ASN	A	79	65.059	34.994	15.254	1.00	25.04 A

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)											
ATOM N	519	ND2	ASN	A	79	64.064	34.015	13.495	1.00	25.70	A
ATOM C	520	C	ASN	A	79	60.668	33.742	16.343	1.00	23.53	A
ATOM O	521	O	ASN	A	79	60.753	32.512	16.451	1.00	23.89	A
ATOM N	522	N	ASP	A	80	59.612	34.437	16.747	1.00	21.43	A
ATOM C	523	CA	ASP	A	80	58.472	33.797	17.381	1.00	20.47	A
ATOM C	524	CB	ASP	A	80	58.658	33.789	18.907	1.00	20.36	A
ATOM C	525	CG	ASP	A	80	57.567	33.022	19.626	1.00	20.02	A
ATOM O	526	OD1	ASP	A	80	57.870	31.966	20.215	1.00	20.17	A
ATOM O	527	OD2	ASP	A	80	56.404	33.469	19.597	1.00	20.97	A
ATOM C	528	C	ASP	A	80	57.193	34.542	17.024	1.00	20.46	A
ATOM O	529	O	ASP	A	80	57.218	35.752	16.742	1.00	20.32	A
ATOM N	530	N	LEU	A	81	56.078	33.812	17.034	1.00	19.74	A
ATOM C	531	CA	LEU	A	81	54.766	34.379	16.725	1.00	19.05	A
ATOM C	532	CB	LEU	A	81	53.685	33.351	17.047	1.00	20.17	A
ATOM C	533	CG	LEU	A	81	52.228	33.802	17.023	1.00	23.86	A
ATOM C	534	CD1	LEU	A	81	51.870	34.357	15.650	1.00	24.25	A
ATOM C	535	CD2	LEU	A	81	51.339	32.608	17.378	1.00	24.57	A
ATOM C	536	C	LEU	A	81	54.537	35.657	17.539	1.00	17.50	A
ATOM O	537	O	LEU	A	81	54.022	36.656	17.027	1.00	15.88	A
ATOM N	538	N	LEU	A	82	54.948	35.604	18.805	1.00	14.87	A
ATOM C	539	CA	LEU	A	82	54.821	36.718	19.734	1.00	12.91	A
ATOM C	540	CB	LEU	A	82	55.545	36.376	21.049	1.00	11.35	A
ATOM C	541	CG	LEU	A	82	55.603	37.457	22.138	1.00	10.75	A
ATOM C	542	CD1	LEU	A	82	54.187	37.899	22.505	1.00	10.31	A
ATOM C	543	CD2	LEU	A	82	56.344	36.922	23.354	1.00	9.38	A
ATOM C	544	C	LEU	A	82	55.374	38.023	19.157	1.00	12.97	A
ATOM O	545	O	LEU	A	82	54.738	39.083	19.263	1.00	9.83	A
ATOM N	546	N	GLY	A	83	56.561	37.944	18.557	1.00	12.95	A
ATOM C	547	CA	GLY	A	83	57.163	39.129	17.980	1.00	15.06	A
ATOM C	548	C	GLY	A	83	56.238	39.761	16.951	1.00	16.77	A
ATOM O	549	O	GLY	A	83	56.060	40.980	16.919	1.00	15.55	A
ATOM N	550	N	ASP	A	84	55.635	38.924	16.112	1.00	18.65	A
ATOM C	551	CA	ASP	A	84	54.742	39.412	15.078	1.00	21.41	A
ATOM C	552	CB	ASP	A	84	54.347	38.272	14.141	1.00	25.41	A
ATOM C	553	CG	ASP	A	84	55.547	37.604	13.507	1.00	28.55	A
ATOM O	554	OD1	ASP	A	84	56.489	38.335	13.100	1.00	27.94	A

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-(4-chloro-phenyl)-acetic acid)										
ATOM N	519	ND2	ASN	A	79	64.064	34.015	13.495	1.00	25.70
ATOM C	520	C	ASN	A	79	60.668	33.742	16.343	1.00	23.53
ATOM O	521	O	ASN	A	79	60.753	32.512	16.451	1.00	23.89
ATOM N	522	N	ASP	A	80	59.612	34.437	16.747	1.00	21.43
ATOM C	523	CA	ASP	A	80	58.472	33.797	17.381	1.00	20.47
ATOM C	524	CB	ASP	A	80	58.658	33.789	18.907	1.00	20.36
ATOM C	525	CG	ASP	A	80	57.567	33.022	19.626	1.00	20.02
ATOM O	526	OD1	ASP	A	80	57.870	31.966	20.215	1.00	20.17
ATOM O	527	OD2	ASP	A	80	56.404	33.469	19.597	1.00	20.97
ATOM C	528	C	ASP	A	80	57.193	34.542	17.024	1.00	20.46
ATOM O	529	O	ASP	A	80	57.218	35.752	16.742	1.00	20.32
ATOM N	530	N	LEU	A	81	56.078	33.812	17.034	1.00	19.74
ATOM C	531	CA	LEU	A	81	54.766	34.379	16.725	1.00	19.05
ATOM C	532	CB	LEU	A	81	53.685	33.351	17.047	1.00	20.17
ATOM C	533	CG	LEU	A	81	52.228	33.802	17.023	1.00	23.86
ATOM C	534	CD1	LEU	A	81	51.870	34.357	15.650	1.00	24.25
ATOM C	535	CD2	LEU	A	81	51.339	32.608	17.378	1.00	24.57
ATOM C	536	C	LEU	A	81	54.537	35.657	17.539	1.00	17.50
ATOM O	537	O	LEU	A	81	54.022	36.656	17.027	1.00	15.88
ATOM N	538	N	LEU	A	82	54.948	35.604	18.805	1.00	14.87
ATOM C	539	CA	LEU	A	82	54.821	36.718	19.734	1.00	12.91
ATOM C	540	CB	LEU	A	82	55.545	36.376	21.049	1.00	11.35
ATOM C	541	CG	LEU	A	82	55.603	37.457	22.138	1.00	10.75
ATOM C	542	CD1	LEU	A	82	54.187	37.899	22.505	1.00	10.31
ATOM C	543	CD2	LEU	A	82	56.344	36.922	23.354	1.00	9.38
ATOM C	544	C	LEU	A	82	55.374	38.023	19.157	1.00	12.97
ATOM O	545	O	LEU	A	82	54.738	39.083	19.263	1.00	9.83
ATOM N	546	N	GLY	A	83	56.561	37.944	18.557	1.00	12.95
ATOM C	547	CA	GLY	A	83	57.163	39.129	17.980	1.00	15.06
ATOM C	548	C	GLY	A	83	56.238	39.761	16.951	1.00	16.77
ATOM O	549	O	GLY	A	83	56.060	40.980	16.919	1.00	15.55
ATOM N	550	N	ASP	A	84	55.635	38.924	16.112	1.00	18.65
ATOM C	551	CA	ASP	A	84	54.742	39.412	15.078	1.00	21.41
ATOM C	552	CB	ASP	A	84	54.347	38.272	14.141	1.00	25.41
ATOM C	553	CG	ASP	A	84	55.547	37.604	13.507	1.00	28.55
ATOM O	554	OD1	ASP	A	84	56.489	38.335	13.100	1.00	27.94

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM O	555	OD2	ASP	A	84	55.539	36.354	13.412	1.00	30.30 Å
ATOM C	556	C	ASP	A	84	53.491	40.055	15.650	1.00	21.92 Å
ATOM O	557	O	ASP	A	84	53.065	41.104	15.173	1.00	22.99 Å
ATOM N	558	N	LEU	A	85	52.906	39.428	16.666	1.00	21.04 Å
ATOM C	559	CA	LEU	A	85	51.697	39.955	17.288	1.00	22.00 Å
ATOM C	560	CB	LEU	A	85	51.092	38.915	18.240	1.00	21.98 Å
ATOM C	561	CG	LEU	A	85	50.821	37.544	17.609	1.00	23.19 Å
ATOM C	562	CD1	LEU	A	85	50.177	36.593	18.628	1.00	20.96 Å
ATOM C	563	CD2	LEU	A	85	49.923	37.734	16.390	1.00	22.60 Å
ATOM C	564	C	LEU	A	85	51.979	41.258	18.039	1.00	21.67 Å
ATOM O	565	O	LEU	A	85	51.122	42.143	18.102	1.00	20.70 Å
ATOM N	566	N	PHE	A	86	53.182	41.376	18.597	1.00	21.86 Å
ATOM C	567	CA	PHE	A	86	53.565	42.579	19.338	1.00	20.91 Å
ATOM C	568	CB	PHE	A	86	54.531	42.224	20.470	1.00	19.44 Å
ATOM C	569	CG	PHE	A	86	53.852	41.763	21.741	1.00	16.86 Å
ATOM C	570	CD1	PHE	A	86	52.508	41.381	21.742	1.00	15.83 Å
ATOM C	571	CD2	PHE	A	86	54.564	41.710	22.936	1.00	14.83 Å
ATOM C	572	CE1	PHE	A	86	51.878	40.952	22.914	1.00	14.04 Å
ATOM C	573	CE2	PHE	A	86	53.949	41.281	24.119	1.00	18.00 Å
ATOM C	574	CZ	PHE	A	86	52.596	40.902	24.105	1.00	16.08 Å
ATOM O	575	C	PHE	A	86	54.211	43.604	18.416	1.00	22.21 Å
ATOM O	576	O	PHE	A	86	54.233	44.797	18.714	1.00	23.98 Å
ATOM N	577	N	GLY	A	87	54.728	43.140	17.284	1.00	22.25 Å
ATOM C	578	CA	GLY	A	87	55.360	44.055	16.356	1.00	20.93 Å
ATOM C	579	C	GLY	A	87	56.711	44.578	16.820	1.00	20.93 Å
ATOM O	580	O	GLY	A	87	57.055	45.731	16.534	1.00	22.00 Å
ATOM N	581	N	VAL	A	88	57.471	43.752	17.542	1.00	18.42 Å
ATOM C	582	CA	VAL	A	88	58.802	44.136	18.014	1.00	16.75 Å
ATOM C	583	CB	VAL	A	88	58.791	44.793	19.420	1.00	16.55 Å
ATOM C	584	CG1	VAL	A	88	57.951	46.054	19.405	1.00	15.93 Å
ATOM C	585	CG2	VAL	A	88	58.312	43.795	20.462	1.00	13.35 Å
ATOM C	586	C	VAL	A	88	59.695	42.911	18.100	1.00	16.74 Å
ATOM O	587	O	VAL	A	88	59.215	41.792	18.273	1.00	16.22 Å
ATOM N	588	N	PRO	A	89	61.013	43.114	17.978	1.00	16.36 Å
ATOM C	589	CD	PRO	A	89	61.636	44.398	17.606	1.00	17.10 Å
ATOM C	590	CA	PRO	A	89	62.013	42.042	18.040	1.00	16.05 Å
ATOM C	591	CB	PRO	A	89	63.221	42.659	17.344	1.00	15.83 Å

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM C	592	CG	PRO	A	89	63.124	44.096	17.747	1.00	18.07 A
ATOM C	593	C	PRO	A	89	62.322	41.623	19.476	1.00	16.21 A
ATOM O	594	O	PRO	A	89	62.832	40.522	19.715	1.00	15.73 A
ATOM N	595	N	SER	A	90	62.009	42.505	20.425	1.00	15.13 A
ATOM C	596	CA	SER	A	90	62.243	42.232	21.843	1.00	14.02 A
ATOM C	597	CB	SER	A	90	63.738	42.128	22.130	1.00	12.56 A
ATOM O	598	OG	SER	A	90	64.336	43.403	21.986	1.00	13.74 A
ATOM C	599	C	SER	A	90	61.652	43.350	22.702	1.00	12.89 A
ATOM O	600	O	SER	A	90	61.331	44.422	22.192	1.00	12.05 A
ATOM N	601	N	PHE	A	91	61.517	43.091	24.001	1.00	11.19 A
ATOM C	602	CA	PHE	A	91	60.972	44.069	24.926	1.00	11.45 A
ATOM C	603	CB	PHE	A	91	59.439	44.173	24.759	1.00	10.33 A
ATOM C	604	CG	PHE	A	91	58.705	42.895	25.039	1.00	8.05 A
ATOM C	605	CD1	PHE	A	91	58.263	42.598	26.325	1.00	7.52 A
ATOM C	606	CD2	PHE	A	91	58.496	41.961	24.024	1.00	7.09 A
ATOM C	607	CE1	PHE	A	91	57.620	41.373	26.605	1.00	7.90 A
ATOM C	608	CE2	PHE	A	91	57.859	40.739	24.287	1.00	7.31 A
ATOM C	609	CZ	PHE	A	91	57.419	40.445	25.588	1.00	7.15 A
ATOM C	610	C	PHE	A	91	61.327	43.737	26.373	1.00	13.35 A
ATOM O	611	O	PHE	A	91	61.795	42.632	26.685	1.00	12.34 A
ATOM N	612	N	SER	A	92	61.102	44.708	27.254	1.00	14.78 A
ATOM C	613	CA	SER	A	92	61.398	44.547	28.667	1.00	16.74 A
ATOM C	614	CB	SER	A	92	62.086	45.809	29.203	1.00	15.00 A
ATOM O	615	OG	SER	A	92	62.293	45.719	30.607	1.00	15.51 A
ATOM C	616	C	SER	A	92	60.148	44.254	29.499	1.00	18.09 A
ATOM O	617	O	SER	A	92	59.156	44.978	29.422	1.00	17.05 A
ATOM N	618	N	VAL	A	93	60.206	43.189	30.295	1.00	19.76 A
ATOM C	619	CA	VAL	A	93	59.094	42.822	31.163	1.00	21.70 A
ATOM C	620	CB	VAL	A	93	59.322	41.442	31.866	1.00	22.34 A
ATOM C	621	CG1	VAL	A	93	59.380	40.329	30.828	1.00	22.82 A
ATOM C	622	CG2	VAL	A	93	60.606	41.462	32.683	1.00	20.47 A
ATOM C	623	C	VAL	A	93	58.891	43.884	32.239	1.00	22.48 A
ATOM O	624	O	VAL	A	93	58.089	43.702	33.140	1.00	24.56 A
ATOM N	625	N	LYS	A	94	59.618	44.991	32.146	1.00	24.37 A
ATOM C	626	CA	LYS	A	94	59.494	46.078	33.121	1.00	26.51 A
ATOM C	627	CB	LYS	A	94	60.873	46.623	33.515	1.00	27.71 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM C	628	CG	LYS	A	94	61.581	45.888	34.659	1.00	30.96 Å
ATOM C	629	CD	LYS	A	94	62.965	46.516	34.914	1.00	33.87 Å
ATOM C	630	CE	LYS	A	94	63.695	45.915	36.127	1.00	35.49 Å
ATOM N	631	NZ	LYS	A	94	65.052	46.534	36.343	1.00	35.43 Å
ATOM C	632	C	LYS	A	94	58.655	47.232	32.579	1.00	26.44 Å
ATOM O	633	O	LYS	A	94	58.156	48.054	33.342	1.00	27.30 Å
ATOM N	634	N	GLU	A	95	58.522	47.305	31.259	1.00	25.84 Å
ATOM C	635	CA	GLU	A	95	57.747	48.361	30.620	1.00	25.31 Å
ATOM C	636	CB	GLU	A	95	58.317	48.651	29.231	1.00	26.45 Å
ATOM C	637	CG	GLU	A	95	59.798	49.016	29.200	1.00	28.64 Å
ATOM C	638	CD	GLU	A	95	60.081	50.452	29.615	1.00	30.17 Å
ATOM O	639	OE1	GLU	A	95	59.138	51.277	29.622	1.00	31.51 Å
ATOM O	640	OE2	GLU	A	95	61.257	50.759	29.917	1.00	28.42 Å
ATOM C	641	C	GLU	A	95	56.286	47.904	30.500	1.00	24.66 Å
ATOM O	642	O	GLU	A	95	55.776	47.667	29.398	1.00	22.08 Å
ATOM N	643	N	HIS	A	96	55.619	47.799	31.647	1.00	24.62 Å
ATOM C	644	CA	HIS	A	96	54.234	47.348	31.702	1.00	26.26 Å
ATOM C	645	CB	HIS	A	96	53.694	47.452	33.132	1.00	27.90 Å
ATOM C	646	CG	HIS	A	96	54.457	46.635	34.128	1.00	30.90 Å
ATOM C	647	CD2	HIS	A	96	55.784	46.395	34.257	1.00	31.52 Å
ATOM N	648	ND1	HIS	A	96	53.844	45.963	35.164	1.00	32.30 Å
ATOM C	649	CE1	HIS	A	96	54.761	45.345	35.887	1.00	32.43 Å
ATOM N	650	NE2	HIS	A	96	55.947	45.591	35.358	1.00	32.16 Å
ATOM C	651	C	HIS	A	96	53.279	48.052	30.747	1.00	26.13 Å
ATOM O	652	O	HIS	A	96	52.436	47.400	30.136	1.00	26.36 Å
ATOM N	653	N	ARG	A	97	53.403	49.370	30.618	1.00	25.66 Å
ATOM C	654	CA	ARG	A	97	52.522	50.123	29.728	1.00	25.19 Å
ATOM C	655	CB	ARG	A	97	52.708	51.639	29.953	1.00	25.74 Å
ATOM C	656	CG	ARG	A	97	51.909	52.562	29.031	1.00	24.90 Å
ATOM C	657	CD	ARG	A	97	50.440	52.148	28.919	1.00	27.96 Å
ATOM N	658	NE	ARG	A	97	49.677	52.294	30.157	1.00	29.51 Å
ATOM C	659	CZ	ARG	A	97	48.450	51.804	30.337	1.00	29.81 Å
ATOM N	660	NH1	ARG	A	97	47.849	51.133	29.359	1.00	31.04 Å
ATOM N	661	NH2	ARG	A	97	47.817	51.986	31.489	1.00	27.76 Å
ATOM C	662	C	ARG	A	97	52.758	49.745	28.262	1.00	24.39 Å
ATOM O	663	O	ARG	A	97	51.805	49.623	27.497	1.00	25.23 Å
ATOM N	664	N	LYS	A	98	54.010	49.547	27.865	1.00	23.55 Å

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM C	665	CA	LYS	A	98	54.288	49.166	26.480	1.00	23.84 A
ATOM C	666	CB	LYS	A	98	55.800	49.167	26.195	1.00	25.86 A
ATOM C	667	CG	LYS	A	98	56.406	50.558	26.039	1.00	29.53 A
ATOM C	668	CD	LYS	A	98	57.892	50.512	25.693	1.00	31.47 A
ATOM C	669	CE	LYS	A	98	58.519	51.909	25.794	1.00	33.99 A
ATOM N	670	NZ	LYS	A	98	59.989	51.918	25.509	1.00	34.37 A
ATOM C	671	C	LYS	A	98	53.708	47.779	26.170	1.00	23.22 A
ATOM O	672	O	LYS	A	98	53.150	47.563	25.091	1.00	21.35 A
ATOM N	673	N	ILE	A	99	53.844	46.846	27.115	1.00	21.20 A
ATOM C	674	CA	ILE	A	99	53.323	45.496	26.938	1.00	20.16 A
ATOM C	675	CB	ILE	A	99	53.723	44.584	28.130	1.00	18.26 A
ATOM C	676	CG2	ILE	A	99	52.911	43.290	28.108	1.00	16.58 A
ATOM C	677	CG1	ILE	A	99	55.227	44.283	28.063	1.00	16.19 A
ATOM C	678	CD1	ILE	A	99	55.764	43.539	29.255	1.00	12.79 A
ATOM C	679	C	ILE	A	99	51.799	45.545	26.802	1.00	21.79 A
ATOM O	.680	O	ILE	A	99	51.217	44.909	25.919	1.00	21.34 A
ATOM N	681	N	TYR	A	100	51.156	46.316	27.672	1.00	23.34 A
ATOM C	682	CA	TYR	A	100	49.706	46.457	27.639	1.00	24.14 A
ATOM C	683	CB	TYR	A	100	49.243	47.387	28.763	1.00	25.12 A
ATOM C	684	CG	TYR	A	100	48.602	46.651	29.911	1.00	28.22 A
ATOM C	685	CD1	TYR	A	100	49.336	45.739	30.681	1.00	28.65 A
ATOM C	686	CE1	TYR	A	100	48.734	45.008	31.700	1.00	28.51 A
ATOM C	687	CD2	TYR	A	100	47.248	46.817	30.196	1.00	28.65 A
ATOM C	688	CE2	TYR	A	100	46.632	46.088	31.215	1.00	29.38 A
ATOM C	689	CZ	TYR	A	100	47.380	45.187	31.957	1.00	29.62 A
ATOM O	690	OH	TYR	A	100	46.766	44.450	32.938	1.00	31.04 A
ATOM C	691	C	TYR	A	100	49.154	46.960	26.299	1.00	25.10 A
ATOM O	692	O	TYR	A	100	48.138	46.446	25.812	1.00	25.32 A
ATOM N	693	N	THR	A	101	49.798	47.956	25.693	1.00	23.58 A
ATOM C	694	CA	THR	A	101	49.269	48.447	24.434	1.00	24.54 A
ATOM C	695	CB	THR	A	101	49.683	49.926	24.162	1.00	25.48 A
ATOM O	696	OG1	THR	A	101	51.085	50.021	23.920	1.00	26.87 A
ATOM C	697	CG2	THR	A	101	49.330	50.786	25.361	1.00	27.33 A
ATOM C	698	C	THR	A	101	49.627	47.539	23.259	1.00	23.52 A
ATOM O	699	O	THR	A	101	49.034	47.642	22.188	1.00	24.28 A
ATOM N	700	N	MET	A	102	50.585	46.636	23.450	1.00	22.80 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM C	701	CA	MET	A	102	50.921	45.697	22.377	1.00	20.40 A
ATOM C	702	CB	MET	A	102	52.321	45.109	22.567	1.00	15.37 A
ATOM C	703	CG	MET	A	102	53.403	46.131	22.321	1.00	14.03 A
ATOM S	704	SD	MET	A	102	55.075	45.483	22.349	1.00	11.93 A
ATOM C	705	CE	MET	A	102	55.294	45.184	24.125	1.00	10.87 A
ATOM C	706	C	MET	A	102	49.863	44.592	22.392	1.00	19.65 A
ATOM O	707	O	MET	A	102	49.528	44.017	21.356	1.00	19.47 A
ATOM N	708	N	ILE	A	103	49.338	44.319	23.580	1.00	18.90 A
ATOM C	709	CA	ILE	A	103	48.300	43.321	23.764	1.00	21.34 A
ATOM C	710	CB	ILE	A	103	48.131	42.966	25.273	1.00	20.40 A
ATOM C	711	CG2	ILE	A	103	46.835	42.185	25.497	1.00	19.03 A
ATOM C	712	CG1	ILE	A	103	49.339	42.156	25.750	1.00	19.84 A
ATOM C	713	CD1	ILE	A	103	49.457	42.046	27.259	1.00	18.82 A
ATOM C	714	C	ILE	A	103	46.985	43.896	23.228	1.00	24.13 A
ATOM O	715	O	ILE	A	103	46.189	43.185	22.612	1.00	24.18 A
ATOM N	716	N	TYR	A	104	46.775	45.192	23.461	1.00	27.06 A
ATOM C	717	CA	TYR	A	104	45.566	45.886	23.016	1.00	29.10 A
ATOM C	718	CB	TYR	A	104	45.608	47.344	23.491	1.00	30.33 A
ATOM C	719	CG	TYR	A	104	45.205	47.494	24.940	1.00	30.58 A
ATOM C	720	CD1	TYR	A	104	45.775	48.469	25.754	1.00	29.56 A
ATOM C	721	CE1	TYR	A	104	45.415	48.584	27.095	1.00	29.30 A
ATOM C	722	CD2	TYR	A	104	44.259	46.638	25.502	1.00	31.51 A
ATOM C	723	CE2	TYR	A	104	43.894	46.746	26.836	1.00	31.90 A
ATOM C	724	CZ	TYR	A	104	44.476	47.718	27.625	1.00	30.22 A
ATOM O	725	OH	TYR	A	104	44.113	47.801	28.947	1.00	32.03 A
ATOM C	726	C	TYR	A	104	45.321	45.824	21.510	1.00	29.49 A
ATOM O	727	O	TYR	A	104	44.173	45.769	21.067	1.00	30.07 A
ATOM N	728	N	ARG	A	105	46.397	45.831	20.731	1.00	30.44 A
ATOM C	729	CA	ARG	A	105	46.291	45.757	19.281	1.00	31.09 A
ATOM C	730	CB	ARG	A	105	47.561	46.288	18.614	1.00	32.59 A
ATOM C	731	CG	ARG	A	105	47.624	47.803	18.491	1.00	35.48 A
ATOM C	732	CD	ARG	A	105	48.761	48.212	17.567	1.00	38.68 A
ATOM N	733	NE	ARG	A	105	50.069	47.877	18.129	1.00	41.14 A
ATOM C	734	CZ	ARG	A	105	50.806	48.712	18.859	1.00	42.11 A
ATOM N	735	NH1	ARG	A	105	50.368	49.942	19.117	1.00	41.27 A
ATOM N	736	NH2	ARG	A	105	51.984	48.317	19.333	1.00	42.61 A
ATOM C	737	C	ARG	A	105	46.059	44.317	18.845	1.00	31.15 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM O	738	O	ARG	A	105	45.919	44.040	17.649	1.00	30.58 A
ATOM N	739	N	ASN	A	106	46.029	43.403	19.814	1.00	30.35 A
ATOM C	740	CA	ASN	A	106	45.797	41.992	19.523	1.00	31.38 A
ATOM C	741	CB	ASN	A	106	46.927	41.120	20.069	1.00	30.13 A
ATOM C	742	CG	ASN	A	106	48.164	41.186	19.219	1.00	30.74 A
ATOM O	743	OD1	ASN	A	106	48.957	42.126	19.327	1.00	30.89 A
ATOM N	744	ND2	ASN	A	106	48.335	40.193	18.346	1.00	30.12 A
ATOM C	745	C	ASN	A	106	44.480	41.497	20.087	1.00	32.04 A
ATOM O	746	O	ASN	A	106	44.309	40.303	20.324	1.00	30.99 A
ATOM N	747	N	LEU	A	107	43.543	42.409	20.297	1.00	34.74 A
ATOM C	748	CA	LEU	A	107	42.257	42.009	20.834	1.00	39.45 A
ATOM C	749	CB	LEU	A	107	42.392	41.716	22.335	1.00	39.46 A
ATOM C	750	CG	LEU	A	107	43.091	42.738	23.238	1.00	38.61 A
ATOM C	751	CD1	LEU	A	107	42.333	44.055	23.242	1.00	38.52 A
ATOM C	752	CD2	LEU	A	107	43.181	42.176	24.647	1.00	37.16 A
ATOM C	753	C	LEU	A	107	41.157	43.025	20.604	1.00	42.25 A
ATOM O	754	O	LEU	A	107	41.327	43.993	19.859	1.00	42.75 A
ATOM N	755	N	VAL	A	108	40.021	42.778	21.245	1.00	46.00 A
ATOM C	756	CA	VAL	A	108	38.859	43.653	21.163	1.00	49.43 A
ATOM C	757	CB	VAL	A	108	37.823	43.129	20.149	1.00	48.08 A
ATOM C	758	CG1	VAL	A	108	37.030	44.290	19.594	1.00	48.02 A
ATOM C	759	CG2	VAL	A	108	38.509	42.343	19.040	1.00	46.78 A
ATOM C	760	C	VAL	A	108	38.216	43.671	22.555	1.00	53.19 A
ATOM O	761	O	VAL	A	108	37.589	42.690	22.966	1.00	52.78 A
ATOM N	762	N	VAL	A	109	38.386	44.778	23.280	1.00	57.34 A
ATOM C	763	CA	VAL	A	109	37.829	44.921	24.630	1.00	61.10 A
ATOM C	764	CB	VAL	A	109	38.035	46.351	25.191	1.00	61.46 A
ATOM C	765	CG	VAL	A	109	37.715	46.367	26.683	1.00	61.63 A
ATOM C	766	CG2	VAL	A	109	39.458	46.830	24.928	1.00	62.28 A
ATOM C	767	C	VAL	A	109	36.326	44.631	24.662	1.00	63.47 A
ATOM O	768	O	VAL	A	109	35.527	45.410	24.131	1.00	63.73 A
ATOM N	769	N	VAL	A	110	35.947	43.518	25.293	1.00	65.46 A
ATOM C	770	CA	VAL	A	110	34.542	43.127	25.392	1.00	67.21 A
ATOM C	771	CB	VAL	A	110	34.366	41.919	26.365	1.00	66.97 A
ATOM C	772	CG1	VAL	A	110	32.939	41.374	26.283	1.00	67.04 A
ATOM C	773	CG2	VAL	A	110	35.371	40.825	26.033	1.00	66.24 A

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)										
ATOM C	774	C	VAL	A	110	33.697	44.309	25.898	1.00	69.20 A
ATOM O	775	O	VAL	A	110	34.287	45.249	26.488	1.00	69.94 A
ATOM O	776	OXT	VAL	A	110	32.456	44.284	25.705	1.00	70.58 A
ATOM INH1 C	777	C1	CID	A	1	55.200	42.184	33.980	1.00	21.13
ATOM INH1 C	778	C2	CID	A	1	54.610	43.160	33.125	1.00	21.31
ATOM INH1 C	779	C3	CID	A	1	53.194	43.197	32.974	1.00	21.72
ATOM INH1 C	780	C4	CID	A	1	52.372	42.284	33.667	1.00	21.74
ATOM INH1 C	781	C5	CID	A	1	52.953	41.311	34.515	1.00	21.42
ATOM INH1 C	782	C6	CID	A	1	54.387	41.238	34.692	1.00	22.49
ATOM INH1 C	783	C7	CID	A	1	55.092	40.168	35.590	1.00	23.66
ATOM INH1 C	784	C8	CID	A	1	54.267	39.594	36.800	1.00	25.69
ATOM INH1 O	785	O1	CID	A	1	54.677	38.706	37.544	1.00	29.01
ATOM INH1 O	786	O2	CID	A	1	53.229	40.347	37.224	1.00	30.64
ATOM INH1 N	787	N1	CID	A	1	55.591	39.038	34.674	1.00	19.99
ATOM INH1 C	788	C9	CID	A	1	54.593	38.352	33.801	1.00	18.95
ATOM INH1 C	789	C10	CID	A	1	54.631	38.684	32.289	1.00	18.04
ATOM INH1 C	790	C11	CID	A	1	55.647	39.488	31.665	1.00	17.01
ATOM INH1 C	791	C12	CID	A	1	55.614	39.775	30.286	1.00	16.97
ATOM INH1 C	792	C13	CID	A	1	54.563	39.261	29.507	1.00	17.64
ATOM INH1CL	793	CL1	CID	A	1	54.498	39.606	27.865	1.00	14.96
ATOM INH1 C	794	C14	CID	A	1	53.550	38.464	30.083	1.00	18.96
ATOM INH1 C	795	C15	CID	A	1	53.586	38.180	31.458	1.00	17.55
ATOM INH1 C	796	C16	CID	A	1	54.559	36.817	34.087	1.00	18.08
ATOM INH1 O	797	O3	CID	A	1	53.499	36.278	34.423	1.00	18.82
ATOM INH1 N	798	N2	CID	A	1	55.695	36.036	33.977	1.00	16.78
ATOM INH1 C	799	C17	CID	A	1	57.002	36.408	33.618	1.00	17.03
ATOM INH1 C	800	C18	CID	A	1	57.616	37.644	33.943	1.00	16.70
ATOM INH1 C	801	C19	CID	A	1	56.972	38.734	34.754	1.00	19.45
ATOM INH1 O	802	O4	CID	A	1	57.728	39.367	35.532	1.00	18.52
ATOM INH1 C	803	C20	CID	A	1	58.948	37.897	33.495	1.00	17.26
ATOM INH1 C	804	C21	CID	A	1	59.660	36.940	32.750	1.00	18.91
ATOM INH1 I	805	I1	CID	A	1	61.599	37.431	32.161	1.00	19.64
ATOM INH1 C	806	C22	CID	A	1	59.069	35.711	32.436	1.00	17.86
ATOM INH1 C	807	C23	CID	A	1	57.742	35.435	32.859	1.00	17.23
ATOM INH1CL	808	CL2	CID	A	1	52.462	44.354	31.946	1.00	20.99
ATOM	809	CL3	CID	A	1	59.915	34.517	31.548	1.00	20.31

TABLE 2-continued

compound 876273 ([8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid)
INH1CL
END

[0227]

TABLE 3

Superimposed: trigonal and tetragonal crystal forms									
REMARK Superimposed on /xray1/hmdm2/PDB/M338437.pdb									
REMARK The 19 atoms have an RMS distance of 0.249 A									
REMARK RMS delta B = 6.724 A2									
REMARK Estimated RMSD for 2 random proteins = 5.398 A									
REMARK Relative RMSD = 0.04621									
REMARK Normalised RMSD (100) = 1.471 A									
REMARK coordinates from restrained individual B-factor refinement									
REMARK refinement resolution: 25 - 2.6 A									
REMARK starting r = 0.2563 free_r = 0.2787									
REMARK final r = 0.2553 free_r = 0.2761									
REMARK B rmsd for bonded mainchain atoms = 1.483 target = 1.5									
REMARK B rmsd for bonded sidechain atoms = 1.740 target = 2.0									
REMARK B rmsd for angle mainchain atoms = 2.593 target = 2.0									
REMARK B rmsd for angle sidechain atoms = 2.780 target = 2.5									
REMARK rweight = 0.1000 (with wa = 3.71696)									
REMARK target = mlf steps = 30									
REMARK sg = P4(3)2(1)2 a = 54.3 b = 54.3 c = 83.3 alpha = 90 beta = 90 gamma = 90									
REMARK parameter file 1: MSI_CNX_TOPPAR: protein_rep.param									
REMARK parameter file 2: ../cid.par									
REMARK molecular structure file: recycle.psf									
REMARK input coordinates: anneal_9.pdb									
REMARK reflection file = ../M876273_2_P43212.cv									
REMARK ncs = none									
REMARK B-correction resolution: 6.0 - 2.6									
REMARK initial B-factor correction applied to fobs:									
REMARK B11 = -1.189 B22 = -1.189 B33 = 2.379									
REMARK B12 = 0.000 B13 = 0.000 B23 = 0.000									
REMARK B-factor correction applied to coordinate array B: -0.119									
REMARK bulk solvent: (Mask) density level = 0.341945 e/A ³ , B-factor = 22.3925 A ²									
REMARK reflections with Fobs /sigma_F < 0.0 rejected									
REMARK reflections with Fobs > 10000 * rms(Fobs) rejected									
REMARK theoretical total number of refl.in resol.range: 4173 (100.0%)									
REMARK number of unobserved reflections (no entry or F = 0): 9 (0.2%)									
REMARK number of reflections rejected: 0 (0.0%)									
REMARK total number of reflections used: 4164 (99.8%)									
REMARK number of reflections in working set: 3737 (89.6%)									
REMARK number of reflections in test set: 427 (10.2%)									
REMARK FILENAME = "bindividual.pdb"									
REMARK Written by CNX VERSION: 2000.12									
ATOM	1	C	GLY	A	16	48.607	19.990	25.187	1.00 68.15 A
ATOM	2	O	GLY	A	16	48.239	21.106	24.797	1.00 68.22 A
ATOM	3	N	GLY	A	16	47.838	17.646	24.774	1.00 67.11 A
ATOM	4	CA	GLY	A	16	47.594	18.911	25.537	1.00 67.90 A
ATOM	5	N	SER	A	17	49.889	19.652	25.332	1.00 67.05 A
ATOM	6	CA	SER	A	17	50.986	20.568	25.025	1.00 64.73 A
ATOM	7	CB	SER	A	17	51.581	21.155	26.312	1.00 65.01 A
ATOM	8	OG	SER	A	17	50.639	21.978	26.989	1.00 63.84 A
ATOM	9	C	SER	A	17	52.053	19.794	24.258	1.00 62.82 A
ATOM	10	O	SER	A	17	52.921	20.382	23.611	1.00 62.75 A
ATOM	11	N	GLN	A	18	51.970	18.468	24.343	1.00 60.52 A
ATOM	12	CA	GLN	A	18	52.895	17.577	23.647	1.00 57.89 A
ATOM	13	CB	GLN	A	18	52.794	16.161	24.210	1.00 57.50 A
ATOM	14	CG	GLN	A	18	53.480	15.955	25.534	1.00 57.38 A
ATOM	15	CD	GLN	A	18	53.377	14.514	25.999	1.00 58.16 A
ATOM	16	OE1	GLN	A	18	53.614	13.581	25.228	1.00 56.84 A
ATOM	17	NE2	GLN	A	18	53.027	14.327	27.268	1.00 58.44 A
ATOM	18	C	GLN	A	18	52.532	17.529	22.169	1.00 55.87 A
ATOM	19	O	GLN	A	18	53.378	17.267	21.312	1.00 55.83 A
ATOM	20	N	ILE	A	19	51.256	17.781	21.889	1.00 52.87 A
ATOM	21	CA	ILE	A	19	50.727	17.763	20.532	1.00 50.05 A

TABLE 3-continued

Superimposed: trigonal and tetragonal crystal forms
REMARK Superimposed on /xray1/hmdm2/PDB/M338437.pdb

ATOM	22	CB	ILE	A	19	49.408	16.940	20.476	1.00	48.06	A
ATOM	23	CG2	ILE	A	19	48.886	16.873	19.053	1.00	48.17	A
ATOM	24	CG1	ILE	A	19	49.638	15.526	21.020	1.00	45.44	A
ATOM	25	CD1	ILE	A	19	50.552	14.677	20.180	1.00	43.26	A
ATOM	26	C	ILE	A	19	50.443	19.194	20.066	1.00	49.72	A
ATOM	27	O	ILE	A	19	50.014	20.036	20.856	1.00	49.03	A
ATOM	28	N	PRO	A	20	50.702	19.490	18.777	1.00	49.57	A
ATOM	29	CD	PRO	A	20	51.486	18.667	17.841	1.00	49.58	A
ATOM	30	CA	PRO	A	20	50.469	20.822	18.209	1.00	49.39	A
ATOM	31	CB	PRO	A	20	51.058	20.705	16.808	1.00	48.67	A
ATOM	32	CG	PRO	A	20	52.153	19.717	16.991	1.00	48.94	A
ATOM	33	C	PRO	A	20	48.982	21.187	18.171	1.00	49.97	A
ATOM	34	O	PRO	A	20	48.138	20.358	17.819	1.00	50.18	A
ATOM	35	N	ALA	A	21	48.672	22.429	18.534	1.00	49.45	A
ATOM	36	CA	ALA	A	21	47.296	22.913	18.540	1.00	49.81	A
ATOM	37	CB	ALA	A	21	47.270	24.405	18.880	1.00	49.85	A
ATOM	38	C	ALA	A	21	46.613	22.670	17.189	1.00	49.65	A
ATOM	39	O	ALA	A	21	45.483	22.179	17.128	1.00	49.33	A
ATOM	40	N	SER	A	22	47.302	23.022	16.107	1.00	48.76	A
ATOM	41	CA	SER	A	22	46.753	22.830	14.774	1.00	47.75	A
ATOM	42	CB	SER	A	22	47.823	23.134	13.721	1.00	47.15	A
ATOM	43	OG	SER	A	22	49.001	22.382	13.964	1.00	48.43	A
ATOM	44	C	SER	A	22	46.254	21.391	14.628	1.00	46.34	A
ATOM	45	O	SER	A	22	45.195	21.143	14.045	1.00	45.89	A
ATOM	46	N	GLU	A	23	47.012	20.445	15.172	1.00	44.68	A
ATOM	47	CA	GLU	A	23	46.632	19.041	15.098	1.00	43.25	A
ATOM	48	CB	GLU	A	23	47.804	18.149	15.472	1.00	42.16	A
ATOM	49	CG	GLU	A	23	47.513	16.684	15.303	1.00	40.86	A
ATOM	50	CD	GLU	A	23	48.777	15.866	15.250	1.00	40.82	A
ATOM	51	OE1	GLU	A	23	49.695	16.146	16.045	1.00	41.52	A
ATOM	52	OE2	GLU	A	23	48.856	14.942	14.418	1.00	41.56	A
ATOM	53	C	GLU	A	23	45.453	18.760	16.013	1.00	42.01	A
ATOM	54	O	GLU	A	23	44.505	18.087	15.625	1.00	42.32	A
ATOM	55	N	GLN	A	24	45.512	19.278	17.229	1.00	41.29	A
ATOM	56	CA	GLN	A	24	44.413	19.089	18.154	1.00	42.07	A
ATOM	57	CB	GLN	A	24	44.666	19.872	19.450	1.00	41.13	A
ATOM	58	CG	GLN	A	24	45.643	19.180	20.391	1.00	42.57	A
ATOM	59	CD	GLN	A	24	45.950	19.981	21.650	1.00	43.91	A
ATOM	60	OE1	GLN	A	24	45.068	20.622	22.233	1.00	44.84	A
ATOM	61	NE2	GLN	A	24	47.205	19.931	22.085	1.00	43.17	A
ATOM	62	C	GLN	A	24	43.140	19.589	17.475	1.00	43.32	A
ATOM	63	O	GLN	A	24	42.035	19.139	17.790	1.00	43.40	A
ATOM	64	N	GLU	A	25	43.310	20.505	16.521	1.00	44.62	A
ATOM	65	CA	GLU	A	25	42.183	21.095	15.795	1.00	44.92	A
ATOM	66	CB	GLU	A	25	42.507	22.543	15.406	1.00	48.33	A
ATOM	67	CG	GLU	A	25	43.121	23.398	16.516	1.00	53.04	A
ATOM	68	CD	GLU	A	25	42.283	23.449	17.787	1.00	55.79	A
ATOM	69	OE1	GLU	A	25	42.680	24.180	18.720	1.00	57.11	A
ATOM	70	OE2	GLU	A	25	41.236	22.766	17.864	1.00	57.84	A
ATOM	71	C	GLU	A	25	41.731	20.336	14.541	1.00	42.75	A
ATOM	72	O	GLU	A	25	40.616	20.547	14.059	1.00	42.62	A
ATOM	73	N	THR	A	26	42.587	19.467	14.008	1.00	40.18	A
ATOM	74	CA	THR	A	26	42.237	18.692	12.814	1.00	38.13	A
ATOM	75	CB	THR	A	26	43.254	17.547	12.563	1.00	37.92	A
ATOM	76	OG1	THR	A	26	44.589	18.059	12.647	1.00	37.02	A
ATOM	77	CG2	THR	A	26	43.047	16.942	11.187	1.00	36.76	A
ATOM	78	C	THR	A	26	40.847	18.074	12.983	1.00	36.79	A
ATOM	79	O	THR	A	26	40.511	17.574	14.054	1.00	36.47	A
ATOM	80	N	LEU	A	27	40.036	18.128	11.931	1.00	36.63	A
ATOM	81	CA	LEU	A	27	38.686	17.559	11.973	1.00	35.77	A
ATOM	82	CB	LEU	A	27	37.739	18.336	11.052	1.00	36.16	A
ATOM	83	CG	LEU	A	27	36.264	18.393	11.488	1.00	38.05	A
ATOM	84	CD1	LEU	A	27	36.120	19.331	12.692	1.00	36.12	A
ATOM	85	CD2	LEU	A	27	35.394	18.895	10.328	1.00	38.41	A
ATOM	86	C	LEU	A	27	38.796	16.110	11.505	1.00	34.52	A
ATOM	87	O	LEU	A	27	39.467	15.818	10.513	1.00	33.72	A
ATOM	88	N	VAL	A	28	38.135	15.204	12.218	1.00	33.53	A
ATOM	89	CA	VAL	A	28	38.214	13.787	11.886	1.00	32.88	A
ATOM	90	CB	VAL	A	28	39.207	13.071	12.850	1.00	32.86	A
ATOM	91	CG1	VAL	A	28	40.592	13.685	12.724	1.00	31.21	A
ATOM	92	CG2	VAL	A	28	38.726	13.204	14.292	1.00	33.40	A
ATOM	93	C	VAL	A	28	36.876	13.044	11.919	1.00	31.29	A
ATOM	94	O	VAL	A	28	35.910	13.501	12.527	1.00	30.99	A

TABLE 3-continued

Superimposed: trigonal and tetragonal crystal forms									
REMARK Superimposed on /xray1/hmdm2/PDB/M338437.pdb									
ATOM	95	N	ARG	A	29	36.841	11.897	11.248	1.00 29.80 A
ATOM	96	CA	ARG	A	29	35.655	11.054	11.198	1.00 28.94 A
ATOM	97	CB	ARG	A	29	35.174	10.876	9.762	1.00 33.14 A
ATOM	98	CG	ARG	A	29	34.296	11.991	9.254	1.00 38.54 A
ATOM	99	CD	ARG	A	29	34.036	11.830	7.767	1.00 43.39 A
ATOM	100	NE	ARG	A	29	33.084	12.828	7.296	1.00 47.28 A
ATOM	101	CZ	ARG	A	29	31.772	12.741	7.477	1.00 49.30 A
ATOM	102	NH1	ARG	A	29	31.257	11.691	8.110	1.00 49.75 A
ATOM	103	NH2	ARG	A	29	30.978	13.716	7.049	1.00 50.29 A
ATOM	104	C	ARG	A	29	35.994	9.688	11.762	1.00 26.43 A
ATOM	105	O	ARG	A	29	36.680	8.895	11.110	1.00 25.41 A
ATOM	106	N	PRO	A	30	35.528	9.397	12.989	1.00 24.69 A
ATOM	107	CD	PRO	A	30	34.749	10.285	13.869	1.00 23.43 A
ATOM	108	CA	PRO	A	30	35.784	8.108	13.647	1.00 23.00 A
ATOM	109	CB	PRO	A	30	35.223	8.308	15.053	1.00 21.72 A
ATOM	110	CG	PRO	A	30	35.147	9.792	15.218	1.00 22.48 A
ATOM	111	C	PRO	A	30	35.023	7.001	12.923	1.00 22.20 A
ATOM	112	O	PRO	A	30	33.945	7.243	12.382	1.00 22.27 A
ATOM	113	N	LYS	A	31	35.580	5.796	12.910	1.00 21.65 A
ATOM	114	CA	LYS	A	31	34.909	4.658	12.286	1.00 19.51 A
ATOM	115	CB	LYS	A	31	35.901	3.519	12.056	1.00 19.68 A
ATOM	116	CG	LYS	A	31	37.058	3.899	11.150	1.00 20.82 A
ATOM	117	CD	LYS	A	31	38.006	2.724	10.976	1.00 22.74 A
ATOM	118	CE	LYS	A	31	39.161	3.040	10.019	1.00 20.68 A
ATOM	119	NZ	LYS	A	31	40.000	1.818	9.826	1.00 21.75 A
ATOM	120	C	LYS	A	31	33.795	4.225	13.249	1.00 18.36 A
ATOM	121	O	LYS	A	31	33.793	4.605	14.422	1.00 17.38 A
ATOM	122	N	PRO	A	32	32.848	3.406	12.774	1.00 17.15 A
ATOM	123	CD	PRO	A	32	32.886	2.665	11.501	1.00 16.30 A
ATOM	124	CA	PRO	A	32	31.729	2.939	13.595	1.00 16.70 A
ATOM	125	CB	PRO	A	32	31.178	1.775	12.778	1.00 16.53 A
ATOM	126	CG	PRO	A	32	31.463	2.200	11.378	1.00 16.35 A
ATOM	127	C	PRO	A	32	32.023	2.548	15.048	1.00 16.73 A
ATOM	128	O	PRO	A	32	31.343	3.014	15.967	1.00 17.12 A
ATOM	129	N	LEU	A	33	33.016	1.692	15.264	1.00 14.62 A
ATOM	130	CA	LEU	A	33	33.324	1.265	16.619	1.00 13.59 A
ATOM	131	CB	LEU	A	33	34.332	0.110	16.594	1.00 15.36 A
ATOM	132	CG	LEU	A	33	33.787	-1.301	16.896	1.00 13.91 A
ATOM	133	CD1	LEU	A	33	32.250	-1.320	16.992	1.00 13.51 A
ATOM	134	CD2	LEU	A	33	34.270	-2.239	15.822	1.00 8.87 A
ATOM	135	C	LEU	A	33	33.800	2.397	17.516	1.00 13.14 A
ATOM	136	O	LEU	A	33	33.281	2.560	18.608	1.00 12.37 A
ATOM	137	N	LEU	A	34	34.786	3.176	17.082	1.00 14.58 A
ATOM	138	CA	LEU	A	34	35.238	4.305	17.895	1.00 13.84 A
ATOM	139	CB	LEU	A	34	36.430	5.015	17.246	1.00 13.73 A
ATOM	140	CG	LEU	A	34	36.892	6.346	17.861	1.00 10.65 A
ATOM	141	CD1	LEU	A	34	37.437	6.120	19.247	1.00 9.38 A
ATOM	142	CD2	LEU	A	34	37.951	6.971	16.986	1.00 11.47 A
ATOM	143	C	LEU	A	34	34.073	5.294	18.042	1.00 15.75 A
ATOM	144	O	LEU	A	34	33.877	5.874	19.103	1.00 16.50 A
ATOM	145	N	LEU	A	35	33.294	5.484	16.979	1.00 17.07 A
ATOM	146	CA	LEU	A	35	32.152	6.395	17.046	1.00 18.94 A
ATOM	147	CB	LEU	A	35	31.440	6.482	15.690	1.00 16.70 A
ATOM	148	CG	LEU	A	35	30.311	7.514	15.602	1.00 14.51 A
ATOM	149	CD1	LEU	A	35	30.880	8.904	15.849	1.00 13.73 A
ATOM	150	CD2	LEU	A	35	29.646	7.453	14.237	1.00 13.01 A
ATOM	151	C	LEU	A	35	31.151	5.968	18.136	1.00 20.66 A
ATOM	152	O	LEU	A	35	30.494	6.823	18.742	1.00 21.36 A
ATOM	153	N	LYS	A	36	31.039	4.661	18.385	1.00 20.77 A
ATOM	154	CA	LYS	A	36	30.135	4.152	19.415	1.00 22.28 A
ATOM	155	CB	LYS	A	36	29.938	2.637	19.298	1.00 23.62 A
ATOM	156	CG	LYS	A	36	28.839	2.214	18.330	1.00 28.23 A
ATOM	157	CD	LYS	A	36	28.007	1.043	18.889	1.00 30.56 A
ATOM	158	CE	LYS	A	36	28.853	-0.202	19.171	1.00 32.43 A
ATOM	159	NZ	LYS	A	36	28.037	-1.385	19.580	1.00 31.16 A
ATOM	160	C	LYS	A	36	30.668	4.471	20.807	1.00 23.86 A
ATOM	161	O	LYS	A	36	29.901	4.855	21.700	1.00 26.24 A
ATOM	162	N	LEU	A	37	31.971	4.301	21.006	1.00 23.16 A
ATOM	163	CA	LEU	A	37	32.558	4.608	22.308	1.00 24.32 A
ATOM	164	CB	LEU	A	37	34.085	4.515	22.263	1.00 25.18 A
ATOM	165	CG	LEU	A	37	34.708	3.137	22.100	1.00 27.89 A
ATOM	166	CD1	LEU	A	37	36.217	3.232	22.302	1.00 28.24 A
ATOM	167	CD2	LEU	A	37	34.095	2.198	23.119	1.00 28.07 A

TABLE 3-continued

Superimposed: trigonal and tetragonal crystal forms									
REMARK Superimposed on /xray1/hmdm2/PDB/M338437.pdb									
ATOM	168	C	LEU	A	37	32.179	6.027	22.725	1.00 23.05 A
ATOM	169	O	LEU	A	37	31.758	6.268	23.854	1.00 20.34 A
ATOM	170	N	LEU	A	38	32.338	6.956	21.788	1.00 23.36 A
ATOM	171	CA	LEU	A	38	32.055	8.359	22.022	1.00 24.58 A
ATOM	172	CB	LEU	A	38	32.493	9.198	20.819	1.00 21.20 A
ATOM	173	CG	LEU	A	38	33.886	8.937	20.238	1.00 19.16 A
ATOM	174	CD1	LEU	A	38	34.126	9.914	19.106	1.00 16.77 A
ATOM	175	CD2	LEU	A	38	34.966	9.092	21.306	1.00 18.04 A
ATOM	176	C	LEU	A	38	30.581	8.602	22.302	1.00 27.20 A
ATOM	177	O	LEU	A	38	30.236	9.411	23.162	1.00 29.33 A
ATOM	178	N	LYS	A	39	29.702	7.908	21.590	1.00 28.13 A
ATOM	179	CA	LYS	A	39	28.283	8.119	21.815	1.00 29.30 A
ATOM	180	CB	LYS	A	39	27.467	7.488	20.686	1.00 28.63 A
ATOM	181	CG	LYS	A	39	27.777	8.127	19.347	1.00 28.78 A
ATOM	182	CD	LYS	A	39	26.776	7.761	18.276	1.00 27.98 A
ATOM	183	CE	LYS	A	39	27.154	8.415	16.960	1.00 26.89 A
ATOM	184	NZ	LYS	A	39	26.074	8.260	15.959	1.00 27.11 A
ATOM	185	C	LYS	A	39	27.840	7.587	23.169	1.00 30.33 A
ATOM	186	O	LYS	A	39	26.931	8.141	23.789	1.00 31.74 A
ATOM	187	N	SER	A	40	28.495	6.531	23.644	1.00 30.27 A
ATOM	188	CA	SER	A	40	28.148	5.948	24.939	1.00 29.62 A
ATOM	189	CB	SER	A	40	28.995	4.691	25.213	1.00 28.81 A
ATOM	190	OG	SER	A	40	30.349	5.002	25.520	1.00 26.68 A
ATOM	191	C	SER	A	40	28.340	6.960	26.073	1.00 29.48 A
ATOM	192	O	SER	A	40	27.745	6.822	27.139	1.00 29.59 A
ATOM	193	N	VAL	A	41	29.170	7.974	25.843	1.00 30.35 A
ATOM	194	CA	VAL	A	41	29.432	9.002	26.854	1.00 30.76 A
ATOM	195	CB	VAL	A	41	30.944	9.047	27.267	1.00 30.64 A
ATOM	196	CG1	VAL	A	41	31.298	7.826	28.115	1.00 29.00 A
ATOM	197	CG2	VAL	A	41	31.834	9.108	26.030	1.00 28.32 A
ATOM	198	C	VAL	A	41	29.013	10.407	26.413	1.00 32.02 A
ATOM	199	O	VAL	A	41	29.742	11.380	26.628	1.00 31.05 A
ATOM	200	N	GLY	A	42	27.845	10.509	25.779	1.00 33.77 A
ATOM	201	CA	GLY	A	42	27.355	11.811	25.360	1.00 36.14 A
ATOM	202	C	GLY	A	42	27.488	12.202	23.901	1.00 38.10 A
ATOM	203	O	GLY	A	42	26.516	12.669	23.310	1.00 40.02 A
ATOM	204	N	ALA	A	43	28.675	12.035	23.318	1.00 38.97 A
ATOM	205	CA	ALA	A	43	28.897	12.403	21.919	1.00 39.16 A
ATOM	206	CB	ALA	A	43	30.124	11.678	21.370	1.00 38.86 A
ATOM	207	C	ALA	A	43	27.678	12.101	21.054	1.00 39.94 A
ATOM	208	O	ALA	A	43	26.968	11.120	21.284	1.00 40.04 A
ATOM	209	N	GLN	A	44	27.435	12.952	20.061	1.00 41.54 A
ATOM	210	CA	GLN	A	44	26.294	12.769	19.173	1.00 42.78 A
ATOM	211	CB	GLN	A	44	25.018	13.232	19.881	1.00 45.11 A
ATOM	212	CG	GLN	A	44	25.132	14.598	20.546	1.00 47.61 A
ATOM	213	CD	GLN	A	44	24.026	14.838	21.568	1.00 49.56 A
ATOM	214	OE1	GLN	A	44	23.986	15.884	22.227	1.00 49.35 A
ATOM	215	NE2	GLN	A	44	23.124	13.866	21.708	1.00 49.08 A
ATOM	216	C	GLN	A	44	26.434	13.470	17.821	1.00 42.23 A
ATOM	217	O	GLN	A	44	25.520	14.171	17.375	1.00 42.70 A
ATOM	218	N	LYS	A	45	27.585	13.271	17.180	1.00 40.15 A
ATOM	219	CA	LYS	A	45	27.871	13.845	15.870	1.00 37.90 A
ATOM	220	CB	LYS	A	45	28.802	15.050	15.980	1.00 39.62 A
ATOM	221	CG	LYS	A	45	28.359	16.141	16.933	1.00 41.18 A
ATOM	222	CD	LYS	A	45	29.197	17.399	16.713	1.00 42.96 A
ATOM	223	CE	LYS	A	45	30.690	17.093	16.732	1.00 45.64 A
ATOM	224	NZ	LYS	A	45	31.535	18.294	16.451	1.00 48.08 A
ATOM	225	C	LYS	A	45	28.590	12.774	15.071	1.00 36.61 A
ATOM	226	O	LYS	A	45	28.771	11.657	15.553	1.00 36.82 A
ATOM	227	N	ASP	A	46	29.012	13.121	13.859	1.00 34.69 A
ATOM	228	CA	ASP	A	46	29.736	12.187	13.006	1.00 33.64 A
ATOM	229	CB	ASP	A	46	29.089	12.074	11.617	1.00 35.21 A
ATOM	230	CG	ASP	A	46	27.726	11.403	11.652	1.00 36.60 A
ATOM	231	OD1	ASP	A	46	27.557	10.427	12.417	1.00 35.63 A
ATOM	232	OD2	ASP	A	46	26.830	11.846	10.899	1.00 36.79 A
ATOM	233	C	ASP	A	46	31.174	12.651	12.830	1.00 32.32 A
ATOM	234	O	ASP	A	46	32.071	11.843	12.578	1.00 33.06 A
ATOM	235	N	THR	A	47	31.388	13.959	12.950	1.00 30.30 A
ATOM	236	CA	THR	A	47	32.718	14.543	12.790	1.00 27.52 A
ATOM	237	CB	THR	A	47	32.762	15.556	11.620	1.00 28.37 A
ATOM	238	OG1	THR	A	47	31.586	16.375	11.650	1.00 28.12 A
ATOM	239	CG2	THR	A	47	32.846	14.836	10.287	1.00 28.11 A
ATOM	240	C	THR	A	47	33.138	15.254	14.059	1.00 25.47 A

TABLE 3-continued

Superimposed: trigonal and tetragonal crystal forms
REMARK Superimposed on /xray1/hmdm2/PDB/M338437.pdb

ATOM	241	O	THR	A	47	32.307	15.811	14.781	1.00	24.25	A
ATOM	242	N	TYR	A	48	34.441	15.227	14.324	1.00	24.41	A
ATOM	243	CA	TYR	A	48	34.997	15.844	15.517	1.00	24.02	A
ATOM	244	CB	TYR	A	48	35.073	14.830	16.681	1.00	23.01	A
ATOM	245	CG	TYR	A	48	33.769	14.162	17.077	1.00	22.29	A
ATOM	246	CD1	TYR	A	48	33.259	13.087	16.347	1.00	21.16	A
ATOM	247	CE1	TYR	A	48	32.030	12.499	16.685	1.00	20.20	A
ATOM	248	CD2	TYR	A	48	33.021	14.632	18.166	1.00	21.34	A
ATOM	249	CE2	TYR	A	48	31.801	14.050	18.510	1.00	20.29	A
ATOM	250	CZ	TYR	A	48	31.312	12.990	17.762	1.00	19.58	A
ATOM	251	OH	TYR	A	48	30.092	12.442	18.066	1.00	20.11	A
ATOM	252	C	TYR	A	48	36.412	16.340	15.265	1.00	24.38	A
ATOM	253	O	TYR	A	48	37.080	15.913	14.318	1.00	22.46	A
ATOM	254	N	THR	A	49	36.855	17.245	16.130	1.00	24.50	A
ATOM	255	CA	THR	A	49	38.221	17.744	16.092	1.00	25.25	A
ATOM	256	CB	THR	A	49	38.333	19.134	16.762	1.00	26.57	A
ATOM	257	OG1	THR	A	49	37.583	19.131	17.989	1.00	26.24	A
ATOM	258	CG2	THR	A	49	37.796	20.235	15.829	1.00	24.91	A
ATOM	259	C	THR	A	49	38.932	16.699	16.965	1.00	25.63	A
ATOM	260	O	THR	A	49	38.307	16.088	17.833	1.00	24.71	A
ATOM	261	N	MET	A	50	40.216	16.466	16.740	1.00	26.39	A
ATOM	262	CA	MET	A	50	40.907	15.470	17.545	1.00	26.62	A
ATOM	263	CB	MET	A	50	42.373	15.388	17.150	1.00	25.74	A
ATOM	264	CG	MET	A	50	42.589	14.617	15.865	1.00	25.74	A
ATOM	265	SD	MET	A	50	42.250	12.852	16.072	1.00	24.59	A
ATOM	266	CE	MET	A	50	43.816	12.259	16.701	1.00	22.52	A
ATOM	267	C	MET	A	50	40.785	15.760	19.031	1.00	28.23	A
ATOM	268	O	MET	A	50	40.843	14.848	19.847	1.00	29.67	A
ATOM	269	N	LYS	A	51	40.594	17.026	19.388	1.00	28.66	A
ATOM	270	CA	LYS	A	51	40.467	17.377	20.794	1.00	29.11	A
ATOM	271	CB	LYS	A	51	40.573	18.891	20.980	1.00	32.66	A
ATOM	272	CG	LYS	A	51	40.687	19.300	22.445	1.00	37.67	A
ATOM	273	CD	LYS	A	51	40.874	20.801	22.628	1.00	41.07	A
ATOM	274	CE	LYS	A	51	40.948	21.164	24.116	1.00	42.73	A
ATOM	275	NZ	LYS	A	51	41.069	22.639	24.365	1.00	45.66	A
ATOM	276	C	LYS	A	51	39.159	16.862	21.406	1.00	28.29	A
ATOM	277	O	LYS	A	51	39.143	16.411	22.557	1.00	28.36	A
ATOM	278	N	GLU	A	52	38.064	16.929	20.647	1.00	25.71	A
ATOM	279	CA	GLU	A	52	36.775	16.451	21.144	1.00	23.60	A
ATOM	280	CB	GLU	A	52	35.638	16.866	20.199	1.00	24.83	A
ATOM	281	CG	GLU	A	52	35.407	18.369	20.084	1.00	27.15	A
ATOM	282	CD	GLU	A	52	34.383	18.732	18.998	1.00	29.01	A
ATOM	283	OE1	GLU	A	52	34.598	18.371	17.818	1.00	29.80	A
ATOM	284	OE2	GLU	A	52	33.364	19.380	19.320	1.00	29.19	A
ATOM	285	C	GLU	A	52	36.785	14.921	21.293	1.00	21.67	A
ATOM	286	O	GLU	A	52	36.069	14.370	22.132	1.00	20.99	A
ATOM	287	N	VAL	A	53	37.578	14.235	20.473	1.00	18.55	A
ATOM	288	CA	VAL	A	53	37.659	12.782	20.559	1.00	16.46	A
ATOM	289	CB	VAL	A	53	38.461	12.163	19.371	1.00	17.02	A
ATOM	290	CG1	VAL	A	53	38.749	10.682	19.645	1.00	15.92	A
ATOM	291	CG2	VAL	A	53	37.659	12.282	18.075	1.00	14.61	A
ATOM	292	C	VAL	A	53	38.350	12.471	21.879	1.00	15.15	A
ATOM	293	O	VAL	A	53	37.788	11.784	22.735	1.00	13.10	A
ATOM	294	N	LEU	A	54	39.570	12.988	22.037	1.00	15.42	A
ATOM	295	CA	LEU	A	54	40.328	12.814	23.273	1.00	14.74	A
ATOM	296	CB	LEU	A	54	41.548	13.736	23.309	1.00	12.86	A
ATOM	297	CG	LEU	A	54	42.871	13.232	22.730	1.00	13.00	A
ATOM	298	CD1	LEU	A	54	43.132	11.821	23.250	1.00	14.60	A
ATOM	299	CD2	LEU	A	54	42.833	13.235	21.232	1.00	11.73	A
ATOM	300	C	LEU	A	54	39.439	13.153	24.467	1.00	15.13	A
ATOM	301	O	LEU	A	54	39.515	12.511	25.514	1.00	16.88	A
ATOM	302	N	PHE	A	55	38.588	14.156	24.309	1.00	14.69	A
ATOM	303	CA	PHE	A	55	37.710	14.556	25.397	1.00	16.41	A
ATOM	304	CB	PHE	A	55	36.904	15.803	25.028	1.00	18.34	A
ATOM	305	CG	PHE	A	55	35.899	16.171	26.069	1.00	20.72	A
ATOM	306	CD1	PHE	A	55	36.278	16.916	27.184	1.00	20.24	A
ATOM	307	CD2	PHE	A	55	34.596	15.672	26.001	1.00	20.52	A
ATOM	308	CE1	PHE	A	55	35.376	17.153	28.223	1.00	20.60	A
ATOM	309	CE2	PHE	A	55	33.687	15.901	27.034	1.00	21.73	A
ATOM	310	CZ	PHE	A	55	34.078	16.644	28.149	1.00	20.59	A
ATOM	311	C	PHE	A	55	36.739	13.473	25.838	1.00	16.04	A
ATOM	312	O	PHE	A	55	36.661	13.148	27.025	1.00	17.31	A
ATOM	313	N	TYR	A	56	35.978	12.941	24.886	1.00	16.71	A

TABLE 3-continued

Superimposed: trigonal and tetragonal crystal forms										
REMARK Superimposed on /xray1/hmdm2/PDB/M338437.pdb										
ATOM	314	CA	TYR	A	56	34.996	11.892	25.165	1.00	17.61 A
ATOM	315	CB	TYR	A	56	34.136	11.624	23.930	1.00	18.45 A
ATOM	316	CG	TYR	A	56	33.142	12.723	23.671	1.00	21.48 A
ATOM	317	CD1	TYR	A	56	32.090	12.951	24.565	1.00	23.38 A
ATOM	318	CE1	TYR	A	56	31.182	13.987	24.363	1.00	25.16 A
ATOM	319	CD2	TYR	A	56	33.266	13.562	22.557	1.00	22.53 A
ATOM	320	CE2	TYR	A	56	32.363	14.610	22.339	1.00	23.90 A
ATOM	321	CZ	TYR	A	56	31.322	14.816	23.251	1.00	26.15 A
ATOM	322	OH	TYR	A	56	30.425	15.846	23.068	1.00	26.91 A
ATOM	323	C	TYR	A	56	35.709	10.628	25.567	1.00	16.78 A
ATOM	324	O	TYR	A	56	35.189	9.810	26.329	1.00	18.53 A
ATOM	325	N	LEU	A	57	36.910	10.472	25.028	1.00	15.78 A
ATOM	326	CA	LEU	A	57	37.743	9.325	25.327	1.00	13.13 A
ATOM	327	CB	LEU	A	57	38.982	9.382	24.437	1.00	11.95 A
ATOM	328	CG	LEU	A	57	39.277	8.207	23.497	1.00	13.21 A
ATOM	329	CD1	LEU	A	57	38.000	7.628	22.913	1.00	10.11 A
ATOM	330	CD2	LEU	A	57	40.224	8.690	22.402	1.00	10.01 A
ATOM	331	C	LEU	A	57	38.108	9.418	26.821	1.00	12.23 A
ATOM	332	O	LEU	A	57	38.197	8.403	27.515	1.00	9.19 A
ATOM	333	N	GLY	A	58	38.291	10.649	27.300	1.00	11.88 A
ATOM	334	CA	GLY	A	58	38.620	10.877	28.691	1.00	14.46 A
ATOM	335	C	GLY	A	58	37.448	10.490	29.567	1.00	17.50 A
ATOM	336	O	GLY	A	58	37.613	9.800	30.579	1.00	18.69 A
ATOM	337	N	GLN	A	59	36.257	10.934	29.178	1.00	18.46 A
ATOM	338	CA	GLN	A	59	35.059	10.614	29.929	1.00	19.45 A
ATOM	339	CB	GLN	A	59	33.850	11.322	29.328	1.00	22.28 A
ATOM	340	CG	GLN	A	59	33.967	12.829	29.389	1.00	24.82 A
ATOM	341	CD	GLN	A	59	34.506	13.295	30.732	1.00	25.90 A
ATOM	342	OE1	GLN	A	59	33.883	13.079	31.771	1.00	26.11 A
ATOM	343	NE2	GLN	A	59	35.679	13.928	30.714	1.00	26.90 A
ATOM	344	C	GLN	A	59	34.850	9.115	29.898	1.00	19.50 A
ATOM	345	O	GLN	A	59	34.441	8.511	30.893	1.00	20.93 A
ATOM	346	N	TYR	A	60	35.148	8.510	28.757	1.00	17.52 A
ATOM	347	CA	TYR	A	60	34.991	7.075	28.617	1.00	18.33 A
ATOM	348	CB	TYR	A	60	35.359	6.636	27.198	1.00	14.85 A
ATOM	349	CG	TYR	A	60	35.120	5.162	26.914	1.00	15.47 A
ATOM	350	CD1	TYR	A	60	33.838	4.676	26.632	1.00	14.63 A
ATOM	351	CE1	TYR	A	60	33.620	3.311	26.347	1.00	11.14 A
ATOM	352	CD2	TYR	A	60	36.184	4.247	26.913	1.00	15.88 A
ATOM	353	CE2	TYR	A	60	35.974	2.882	26.631	1.00	13.26 A
ATOM	354	CZ	TYR	A	60	34.691	2.425	26.349	1.00	12.81 A
ATOM	355	OH	TYR	A	60	34.494	1.089	26.052	1.00	10.53 A
ATOM	356	C	TYR	A	60	35.862	6.332	29.635	1.00	20.42 A
ATOM	357	O	TYR	A	60	35.339	5.672	30.541	1.00	19.39 A
ATOM	358	N	ILE	A	61	37.184	6.453	29.501	1.00	21.45 A
ATOM	359	CA	ILE	A	61	38.092	5.753	30.401	1.00	23.11 A
ATOM	360	CB	ILE	A	61	39.576	5.969	30.026	1.00	22.76 A
ATOM	361	CG2	ILE	A	61	39.879	5.334	28.680	1.00	23.31 A
ATOM	362	CG1	ILE	A	61	39.913	7.453	30.028	1.00	22.24 A
ATOM	363	CD1	ILE	A	61	41.385	7.709	29.846	1.00	23.32 A
ATOM	364	C	ILE	A	61	37.911	6.115	31.869	1.00	25.11 A
ATOM	365	O	ILE	A	61	38.112	5.284	32.751	1.00	25.25 A
ATOM	366	N	MET	A	62	37.531	7.350	32.145	1.00	27.56 A
ATOM	367	CA	MET	A	62	37.335	7.737	33.527	1.00	30.23 A
ATOM	368	CB	MET	A	62	37.237	9.260	33.632	1.00	32.88 A
ATOM	369	CG	MET	A	62	37.161	9.783	35.056	1.00	34.56 A
ATOM	370	SD	MET	A	62	35.808	10.961	35.203	1.00	39.80 A
ATOM	371	CE	MET	A	62	34.440	9.803	35.399	1.00	35.55 A
ATOM	372	C	MET	A	62	36.066	7.073	34.087	1.00	31.22 A
ATOM	373	O	MET	A	62	36.118	6.340	35.083	1.00	30.54 A
ATOM	374	N	THR	A	63	34.934	7.302	33.428	1.00	31.07 A
ATOM	375	CA	THR	A	63	33.673	6.735	33.896	1.00	31.77 A
ATOM	376	CB	THR	A	63	32.495	7.074	32.939	1.00	30.74 A
ATOM	377	OG1	THR	A	63	32.818	6.664	31.608	1.00	31.02 A
ATOM	378	CG2	THR	A	63	32.206	8.569	32.956	1.00	31.19 A
ATOM	379	C	THR	A	63	33.710	5.221	34.115	1.00	32.00 A
ATOM	380	O	THR	A	63	33.230	4.730	35.142	1.00	33.74 A
ATOM	381	N	LYS	A	64	34.265	4.481	33.159	1.00	30.45 A
ATOM	382	CA	LYS	A	64	34.331	3.035	33.288	1.00	29.14 A
ATOM	383	CB	LYS	A	64	34.397	2.380	31.905	1.00	28.22 A
ATOM	384	CG	LYS	A	64	33.121	2.523	31.099	1.00	26.54 A
ATOM	385	CD	LYS	A	64	33.198	1.785	29.769	1.00	26.08 A
ATOM	386	CE	LYS	A	64	33.343	0.293	29.967	1.00	26.73 A

TABLE 3-continued

Superimposed: trigonal and tetragonal crystal forms									
REMARK Superimposed on /xray1/hmdm2/PDB/M338437.pdb									
ATOM	387	NZ	LYS	A	64	33.332	-0.444	28.675	1.00 26.87 A
ATOM	388	C	LYS	A	64	35.509	2.586	34.151	1.00 29.64 A
ATOM	389	O	LYS	A	64	35.824	1.398	34.223	1.00 28.68 A
ATOM	390	N	ARG	A	65	36.160	3.548	34.799	1.00 31.08 A
ATOM	391	CA	ARG	A	65	37.279	3.259	35.691	1.00 31.77 A
ATOM	392	CB	ARG	A	65	36.720	2.800	37.041	1.00 32.61 A
ATOM	393	CG	ARG	A	65	35.955	3.907	37.771	1.00 36.27 A
ATOM	394	CD	ARG	A	65	34.975	3.376	38.812	1.00 38.75 A
ATOM	395	NE	ARG	A	65	34.298	4.465	39.521	1.00 41.50 A
ATOM	396	CZ	ARG	A	65	33.149	4.343	40.190	1.00 43.14 A
ATOM	397	NH1	ARG	A	65	32.519	3.173	40.251	1.00 43.25 A
ATOM	398	NH2	ARG	A	65	32.622	5.396	40.799	1.00 41.34 A
ATOM	399	C	ARG	A	65	38.254	2.216	35.131	1.00 30.62 A
ATOM	400	O	ARG	A	65	38.488	1.173	35.750	1.00 31.11 A
ATOM	401	N	LEU	A	66	38.817	2.505	33.958	1.00 27.85 A
ATOM	402	CA	LEU	A	66	39.773	1.606	33.309	1.00 24.57 A
ATOM	403	CB	LEU	A	66	39.657	1.699	31.781	1.00 21.73 A
ATOM	404	CG	LEU	A	66	38.392	1.185	31.099	1.00 18.58 A
ATOM	405	CD1	LEU	A	66	38.477	1.413	29.603	1.00 16.38 A
ATOM	406	CD2	LEU	A	66	38.240	-0.289	31.393	1.00 16.78 A
ATOM	407	C	LEU	A	66	41.195	1.960	33.712	1.00 24.06 A
ATOM	408	O	LEU	A	66	42.146	1.312	33.286	1.00 22.74 A
ATOM	409	N	TYR	A	67	41.343	3.008	34.515	1.00 25.28 A
ATOM	410	CA	TYR	A	67	42.665	3.428	34.962	1.00 26.02 A
ATOM	411	CB	TYR	A	67	42.703	4.953	35.146	1.00 26.69 A
ATOM	412	CG	TYR	A	67	41.675	5.492	36.106	1.00 26.95 A
ATOM	413	CD1	TYR	A	67	41.983	5.673	37.452	1.00 27.52 A
ATOM	414	CE1	TYR	A	67	41.025	6.108	38.356	1.00 27.15 A
ATOM	415	CD2	TYR	A	67	40.378	5.764	35.683	1.00 26.57 A
ATOM	416	CE2	TYR	A	67	39.407	6.202	36.579	1.00 27.84 A
ATOM	417	CZ	TYR	A	67	39.738	6.368	37.919	1.00 27.23 A
ATOM	418	OH	TYR	A	67	38.780	6.753	38.826	1.00 24.32 A
ATOM	419	C	TYR	A	67	43.032	2.700	36.256	1.00 26.40 A
ATOM	420	O	TYR	A	67	42.178	2.422	37.091	1.00 25.07 A
ATOM	421	N	ASP	A	68	44.311	2.381	36.403	1.00 28.69 A
ATOM	422	CA	ASP	A	68	44.785	1.659	37.574	1.00 31.43 A
ATOM	423	CB	ASP	A	68	46.199	1.130	37.326	1.00 31.86 A
ATOM	424	CG	ASP	A	68	46.635	0.139	38.382	1.00 31.50 A
ATOM	425	OD1	ASP	A	68	46.072	-0.975	38.409	1.00 29.47 A
ATOM	426	OD2	ASP	A	68	47.524	0.482	39.192	1.00 33.11 A
ATOM	427	C	ASP	A	68	44.770	2.474	38.864	1.00 33.44 A
ATOM	428	O	ASP	A	68	45.033	3.679	38.866	1.00 33.12 A
ATOM	429	N	GLU	A	69	44.477	1.789	39.966	1.00 36.37 A
ATOM	430	CA	GLU	A	69	44.415	2.416	41.279	1.00 39.07 A
ATOM	431	CB	GLU	A	69	43.852	1.432	42.311	1.00 42.56 A
ATOM	432	CG	GLU	A	69	42.371	1.145	42.123	1.00 48.37 A
ATOM	433	CD	GLU	A	69	41.564	2.420	41.901	1.00 51.95 A
ATOM	434	OE1	GLU	A	69	41.715	3.364	42.708	1.00 54.24 A
ATOM	435	OE2	GLU	A	69	40.782	2.480	40.921	1.00 54.25 A
ATOM	436	C	GLU	A	69	45.750	2.946	41.759	1.00 38.35 A
ATOM	437	O	GLU	A	69	45.845	4.084	42.207	1.00 38.84 A
ATOM	438	N	LYS	A	70	46.788	2.128	41.672	1.00 38.42 A
ATOM	439	CA	LYS	A	70	48.096	2.575	42.118	1.00 38.82 A
ATOM	440	CB	LYS	A	70	48.982	1.360	42.412	1.00 41.21 A
ATOM	441	CG	LYS	A	70	48.362	0.471	43.491	1.00 43.81 A
ATOM	442	CD	LYS	A	70	49.261	-0.669	43.940	1.00 46.99 A
ATOM	443	CE	LYS	A	70	48.551	-1.515	44.999	1.00 47.44 A
ATOM	444	NZ	LYS	A	70	49.436	-2.552	45.599	1.00 48.71 A
ATOM	445	C	LYS	A	70	48.694	3.493	41.058	1.00 37.27 A
ATOM	446	O	LYS	A	70	48.890	4.684	41.300	1.00 36.92 A
ATOM	447	N	GLN	A	71	48.958	2.950	39.876	1.00 35.72 A
ATOM	448	CA	GLN	A	71	49.496	3.755	38.787	1.00 33.41 A
ATOM	449	CB	GLN	A	71	50.372	2.888	37.891	1.00 34.05 A
ATOM	450	CG	GLN	A	71	51.544	2.272	38.608	1.00 35.15 A
ATOM	451	CD	GLN	A	71	52.414	1.462	37.678	1.00 36.85 A
ATOM	452	OE1	GLN	A	71	52.026	0.382	37.220	1.00 37.63 A
ATOM	453	NE2	GLN	A	71	53.596	1.983	37.377	1.00 38.20 A
ATOM	454	C	GLN	A	71	48.326	4.349	37.986	1.00 31.00 A
ATOM	455	O	GLN	A	71	47.855	3.759	37.007	1.00 31.06 A
ATOM	456	N	GLN	A	72	47.865	5.521	38.411	1.00 27.04 A
ATOM	457	CA	GLN	A	72	46.737	6.192	37.771	1.00 23.77 A
ATOM	458	CB	GLN	A	72	46.355	7.443	38.567	1.00 21.94 A
ATOM	459	CG	GLN	A	72	45.189	8.240	37.996	1.00 19.04 A

TABLE 3-continued

Superimposed: trigonal and tetragonal crystal forms
REMARK Superimposed on /xray1/hmdm2/PDB/M338437.pdb

ATOM	460	CD	GLN	A	72	44.592	9.192	39.022	1.00	18.27	A
ATOM	461	OE1	GLN	A	72	44.040	8.758	40.029	1.00	16.43	A
ATOM	462	NE2	GLN	A	72	44.704	10.491	38.773	1.00	19.03	A
ATOM	463	C	GLN	A	72	46.926	6.558	36.307	1.00	21.79	A
ATOM	464	O	GLN	A	72	45.965	6.558	35.552	1.00	20.39	A
ATOM	465	N	HIS	A	73	48.155	6.859	35.899	1.00	21.17	A
ATOM	466	CA	HIS	A	73	48.395	7.227	34.510	1.00	19.46	A
ATOM	467	CB	HIS	A	73	49.768	7.880	34.355	1.00	19.40	A
ATOM	468	CG	HIS	A	73	50.918	6.974	34.667	1.00	21.41	A
ATOM	469	CD2	HIS	A	73	51.514	6.660	35.843	1.00	21.24	A
ATOM	470	ND1	HIS	A	73	51.613	6.290	33.692	1.00	22.42	A
ATOM	471	CE1	HIS	A	73	52.588	5.596	34.254	1.00	21.05	A
ATOM	472	NE2	HIS	A	73	52.548	5.804	35.559	1.00	21.25	A
ATOM	473	C	HIS	A	73	48.273	6.037	33.572	1.00	20.37	A
ATOM	474	O	HIS	A	73	48.166	6.219	32.355	1.00	19.89	A
ATOM	475	N	ILE	A	74	48.290	4.823	34.128	1.00	19.94	A
ATOM	476	CA	ILE	A	74	48.158	3.618	33.310	1.00	19.76	A
ATOM	477	CB	ILE	A	74	48.869	2.389	33.941	1.00	20.27	A
ATOM	478	CG2	ILE	A	74	48.667	1.165	33.052	1.00	18.27	A
ATOM	479	CG1	ILE	A	74	50.368	2.655	34.118	1.00	22.09	A
ATOM	480	CD1	ILE	A	74	51.121	2.838	32.833	1.00	22.98	A
ATOM	481	C	ILE	A	74	46.676	3.261	33.133	1.00	19.56	A
ATOM	482	O	ILE	A	74	45.911	3.245	34.099	1.00	19.09	A
ATOM	483	N	VAL	A	75	46.287	2.968	31.895	1.00	17.84	A
ATOM	484	CA	VAL	A	75	44.913	2.603	31.578	1.00	16.49	A
ATOM	485	CB	VAL	A	75	44.335	3.551	30.508	1.00	14.74	A
ATOM	486	CG1	VAL	A	75	42.999	3.053	30.027	1.00	13.12	A
ATOM	487	CG2	VAL	A	75	44.189	4.941	31.092	1.00	15.39	A
ATOM	488	C	VAL	A	75	44.901	1.172	31.058	1.00	17.78	A
ATOM	489	O	VAL	A	75	45.568	0.858	30.070	1.00	17.51	A
ATOM	490	N	TYR	A	76	44.155	0.300	31.731	1.00	17.97	A
ATOM	491	CA	TYR	A	76	44.077	-1.098	31.319	1.00	18.96	A
ATOM	492	CB	TYR	A	76	44.029	-2.024	32.544	1.00	20.36	A
ATOM	493	CG	TYR	A	76	45.341	-2.070	33.294	1.00	22.91	A
ATOM	494	CD1	TYR	A	76	45.582	-1.227	34.385	1.00	22.46	A
ATOM	495	CE1	TYR	A	76	46.827	-1.231	35.044	1.00	24.23	A
ATOM	496	CD2	TYR	A	76	46.371	-2.920	32.878	1.00	23.56	A
ATOM	497	CE2	TYR	A	76	47.621	-2.929	33.530	1.00	23.98	A
ATOM	498	CZ	TYR	A	76	47.840	-2.083	34.606	1.00	23.95	A
ATOM	499	OH	TYR	A	76	49.073	-2.071	35.223	1.00	24.89	A
ATOM	500	C	TYR	A	76	42.856	-1.303	30.454	1.00	17.43	A
ATOM	501	O	TYR	A	76	41.753	-0.999	30.870	1.00	18.57	A
ATOM	502	N	CYS	A	77	43.052	-1.833	29.250	1.00	19.17	A
ATOM	503	CA	CYS	A	77	41.940	-2.034	28.318	1.00	20.17	A
ATOM	504	CB	CYS	A	77	41.984	-0.939	27.242	1.00	18.05	A
ATOM	505	SG	CYS	A	77	43.606	-0.777	26.414	1.00	17.89	A
ATOM	506	C	CYS	A	77	41.853	-3.405	27.639	1.00	20.92	A
ATOM	507	O	CYS	A	77	41.084	-3.577	26.698	1.00	22.93	A
ATOM	508	N	SER	A	78	42.619	-4.379	28.110	1.00	21.73	A
ATOM	509	CA	SER	A	78	42.590	-5.706	27.504	1.00	23.67	A
ATOM	510	CB	SER	A	78	43.569	-6.636	28.216	1.00	23.31	A
ATOM	511	OG	SER	A	78	43.353	-6.594	29.612	1.00	24.57	A
ATOM	512	C	SER	A	78	41.202	-6.344	27.497	1.00	24.32	A
ATOM	513	O	SER	A	78	40.917	-7.189	26.647	1.00	24.57	A
ATOM	514	N	ASN	A	79	40.343	-5.949	28.432	1.00	23.65	A
ATOM	515	CA	ASN	A	79	38.996	-6.517	28.492	1.00	24.00	A
ATOM	516	CB	ASN	A	79	38.716	-7.139	29.872	1.00	24.75	A
ATOM	517	CG	ASN	A	79	39.516	-8.411	30.120	1.00	25.05	A
ATOM	518	OD1	ASN	A	79	40.571	-8.380	30.753	1.00	25.04	A
ATOM	519	ND2	ASN	A	79	39.021	-9.534	29.608	1.00	25.70	A
ATOM	520	C	ASN	A	79	37.928	-5.472	28.186	1.00	23.53	A
ATOM	521	O	ASN	A	79	36.857	-5.455	28.806	1.00	23.89	A
ATOM	522	N	ASP	A	80	38.222	-4.611	27.219	1.00	21.43	A
ATOM	523	CA	ASP	A	80	37.304	-3.554	26.831	1.00	20.47	A
ATOM	524	CB	ASP	A	80	37.609	-2.277	27.631	1.00	20.36	A
ATOM	525	CG	ASP	A	80	36.608	-1.170	27.370	1.00	20.02	A
ATOM	526	OD1	ASP	A	80	35.855	-0.817	28.299	1.00	20.17	A
ATOM	527	OD2	ASP	A	80	36.567	-0.656	26.236	1.00	20.97	A
ATOM	528	C	ASP	A	80	37.439	-3.270	25.341	1.00	20.46	A
ATOM	529	O	ASP	A	80	38.505	-3.492	24.744	1.00	20.32	A
ATOM	530	N	LEU	A	81	36.350	-2.783	24.746	1.00	19.74	A
ATOM	531	CA	LEU	A	81	36.317	-2.448	23.323	1.00	19.05	A
ATOM	532	CB	LEU	A	81	35.019	-1.709	23.010	1.00	20.17	A

TABLE 3-continued

Superimposed: trigonal and tetragonal crystal forms									
REMARK Superimposed on /xray1/hmdm2/PDB/M338437.pdb									
ATOM	533	CG	LEU	A	81	34.870	-1.058	21.638	1.00 23.86 A
ATOM	534	CD1	LEU	A	81	35.022	-2.102	20.539	1.00 24.25 A
ATOM	535	CD2	LEU	A	81	33.500	-0.381	21.563	1.00 24.57 A
ATOM	536	C	LEU	A	81	37.522	-1.576	22.957	1.00 17.50 A
ATOM	537	O	LEU	A	81	38.155	-1.766	21.913	1.00 15.88 A
ATOM	538	N	LEU	A	82	37.831	-0.633	23.846	1.00 14.87 A
ATOM	539	CA	LEU	A	82	38.944	0.290	23.679	1.00 12.91 A
ATOM	540	CB	LEU	A	82	39.117	1.125	24.961	1.00 11.35 A
ATOM	541	CG	LEU	A	82	40.296	2.107	25.024	1.00 10.75 A
ATOM	542	CD1	LEU	A	82	40.216	3.088	23.855	1.00 10.31 A
ATOM	543	CD2	LEU	A	82	40.284	2.839	26.357	1.00 9.38 A
ATOM	544	C	LEU	A	82	40.252	-0.430	23.344	1.00 12.97 A
ATOM	545	O	LEU	A	82	40.992	-0.012	22.439	1.00 9.83 A
ATOM	546	N	GLY	A	83	40.538	-1.503	24.080	1.00 12.95 A
ATOM	547	CA	GLY	A	83	41.756	-2.248	23.834	1.00 15.06 A
ATOM	548	C	GLY	A	83	41.816	-2.728	22.391	1.00 16.77 A
ATOM	549	O	GLY	A	83	42.853	-2.635	21.732	1.00 15.55 A
ATOM	550	N	ASP	A	84	40.691	-3.233	21.894	1.00 18.65 A
ATOM	551	CA	ASP	A	84	40.631	-3.736	20.534	1.00 21.41 A
ATOM	552	CB	ASP	A	84	39.294	-4.432	20.288	1.00 25.41 A
ATOM	553	CG	ASP	A	84	39.043	-5.561	21.263	1.00 28.55 A
ATOM	554	OD1	ASP	A	84	40.004	-6.324	21.550	1.00 27.94 A
ATOM	555	OD2	ASP	A	84	37.887	-5.685	21.730	1.00 30.30 A
ATOM	556	C	ASP	A	84	40.830	-2.640	19.503	1.00 21.92 A
ATOM	557	O	ASP	A	84	41.547	-2.838	18.525	1.00 22.99 A
ATOM	558	N	LEU	A	85	40.197	-1.491	19.719	1.00 21.04 A
ATOM	559	CA	LEU	A	85	40.314	-0.373	18.790	1.00 22.00 A
ATOM	560	CB	LEU	A	85	39.286	0.713	19.133	1.00 21.98 A
ATOM	561	CG	LEU	A	85	37.835	0.226	19.211	1.00 23.19 A
ATOM	562	CD1	LEU	A	85	36.884	1.393	19.514	1.00 20.96 A
ATOM	563	CD2	LEU	A	85	37.472	-0.450	17.892	1.00 22.60 A
ATOM	564	C	LEU	A	85	41.727	0.214	18.799	1.00 21.67 A
ATOM	565	O	LEU	A	85	42.216	0.686	17.770	1.00 20.70 A
ATOM	566	N	PHE	A	86	42.381	0.173	19.958	1.00 21.86 A
ATOM	567	CA	PHE	A	86	43.740	0.702	20.086	1.00 20.91 A
ATOM	568	CB	PHE	A	86	43.965	1.264	21.491	1.00 19.44 A
ATOM	569	CG	PHE	A	86	43.487	2.688	21.671	1.00 16.86 A
ATOM	570	CD1	PHE	A	86	42.626	3.282	20.744	1.00 15.83 A
ATOM	571	CD2	PHE	A	86	43.899	3.431	22.773	1.00 14.83 A
ATOM	572	CE1	PHE	A	86	42.181	4.597	20.908	1.00 14.04 A
ATOM	573	CE2	PHE	A	86	43.461	4.749	22.955	1.00 18.00 A
ATOM	574	CZ	PHE	A	86	42.597	5.334	22.013	1.00 16.08 A
ATOM	575	C	PHE	A	86	44.774	-0.377	19.794	1.00 22.21 A
ATOM	576	O	PHE	A	86	45.917	-0.080	19.447	1.00 23.98 A
ATOM	577	N	GLY	A	87	44.370	-1.635	19.923	1.00 22.25 A
ATOM	578	CA	GLY	A	87	45.298	-2.717	19.664	1.00 20.93 A
ATOM	579	C	GLY	A	87	46.363	-2.894	20.735	1.00 20.93 A
ATOM	580	O	GLY	A	87	47.499	-3.266	20.417	1.00 22.00 A
ATOM	581	N	VAL	A	88	46.015	-2.621	21.994	1.00 18.42 A
ATOM	582	CA	VAL	A	88	46.947	-2.787	23.110	1.00 16.75 A
ATOM	583	CB	VAL	A	88	47.763	-1.506	23.426	1.00 16.55 A
ATOM	584	CG1	VAL	A	88	48.589	-1.098	22.223	1.00 15.93 A
ATOM	585	CG2	VAL	A	88	46.836	-0.394	23.892	1.00 13.35 A
ATOM	586	C	VAL	A	88	46.185	-3.155	24.371	1.00 16.74 A
ATOM	587	O	VAL	A	88	45.010	-2.822	24.518	1.00 16.22 A
ATOM	588	N	PRO	A	89	46.854	-3.851	25.300	1.00 16.36 A
ATOM	589	CD	PRO	A	89	48.202	-4.420	25.116	1.00 17.10 A
ATOM	590	CA	PRO	A	89	46.269	-4.283	26.574	1.00 16.05 A
ATOM	591	CB	PRO	A	89	47.181	-5.427	27.000	1.00 15.83 A
ATOM	592	CG	PRO	A	89	48.517	-4.975	26.501	1.00 18.07 A
ATOM	593	C	PRO	A	89	46.232	-3.155	27.604	1.00 16.21 A
ATOM	594	O	PRO	A	89	45.462	-3.210	28.570	1.00 15.73 A
ATOM	595	N	SER	A	90	47.066	-2.138	27.391	1.00 15.13 A
ATOM	596	CA	SER	A	90	47.131	-0.988	28.292	1.00 14.02 A
ATOM	597	CB	SER	A	90	47.652	-1.409	29.663	1.00 12.56 A
ATOM	598	OG	SER	A	90	49.018	-1.764	29.560	1.00 13.74 A
ATOM	599	C	SER	A	90	48.060	0.083	27.719	1.00 12.89 A
ATOM	600	O	SER	A	90	48.833	-0.191	26.803	1.00 12.05 A
ATOM	601	N	PHE	A	91	47.978	1.293	28.267	1.00 11.19 A
ATOM	602	CA	PHE	A	91	48.807	2.397	27.816	1.00 11.45 A
ATOM	603	CB	PHE	A	91	48.290	2.943	26.466	1.00 10.33 A
ATOM	604	CG	PHE	A	91	46.891	3.480	26.518	1.00 8.05 A
ATOM	605	CD1	PHE	A	91	46.655	4.817	26.828	1.00 7.52 A

TABLE 3-continued

Superimposed: trigonal and tetragonal crystal forms										
REMARK Superimposed on /xray1/hmdm2/PDB/M338437.pdb										
ATOM	606	CD2	PHE	A	91	45.800	2.638	26.304	1.00	7.09 A
ATOM	607	CE1	PHE	A	91	45.338	5.315	26.932	1.00	7.90 A
ATOM	608	CE2	PHE	A	91	44.485	3.118	26.404	1.00	7.31 A
ATOM	609	CZ	PHE	A	91	44.256	4.467	26.721	1.00	7.15 A
ATOM	610	C	PHE	A	91	48.869	3.517	28.852	1.00	13.35 A
ATOM	611	O	PHE	A	91	48.090	3.547	29.817	1.00	12.34 A
ATOM	612	N	SER	A	92	49.807	4.437	28.644	1.00	14.78 A
ATOM	613	CA	SER	A	92	49.996	5.558	29.548	1.00	16.74 A
ATOM	614	CB	SER	A	92	51.493	5.769	29.811	1.00	15.00 A
ATOM	615	OG	SER	A	92	51.712	6.925	30.610	1.00	15.51 A
ATOM	616	C	SER	A	92	49.384	6.854	29.012	1.00	18.09 A
ATOM	617	O	SER	A	92	49.653	7.257	27.881	1.00	17.05 A
ATOM	618	N	VAL	A	93	48.562	7.502	29.835	1.00	19.76 A
ATOM	619	CA	VAL	A	93	47.941	8.765	29.456	1.00	21.70 A
ATOM	620	CB	VAL	A	93	46.883	9.242	30.506	1.00	22.34 A
ATOM	621	CG1	VAL	A	93	45.727	8.253	30.571	1.00	22.82 A
ATOM	622	CG2	VAL	A	93	47.520	9.393	31.880	1.00	20.47 A
ATOM	623	C	VAL	A	93	49.001	9.852	29.311	1.00	22.48 A
ATOM	624	O	VAL	A	93	48.672	11.011	29.120	1.00	24.56 A
ATOM	625	N	LYS	A	94	50.272	9.479	29.402	1.00	24.37 A
ATOM	626	CA	LYS	A	94	51.369	10.441	29.268	1.00	26.51 A
ATOM	627	CB	LYS	A	94	52.454	10.190	30.323	1.00	27.71 A
ATOM	628	CG	LYS	A	94	52.235	10.866	31.682	1.00	30.96 A
ATOM	629	CD	LYS	A	94	53.375	10.491	32.648	1.00	33.87 A
ATOM	630	CE	LYS	A	94	53.298	11.223	33.998	1.00	35.49 A
ATOM	631	NZ	LYS	A	94	54.414	10.825	34.930	1.00	35.43 A
ATOM	632	C	LYS	A	94	52.014	10.375	27.886	1.00	26.44 A
ATOM	633	O	LYS	A	94	52.693	11.309	27.469	1.00	27.30 A
ATOM	634	N	GLU	A	95	51.821	9.260	27.190	1.00	25.84 A
ATOM	635	CA	GLU	A	95	52.386	9.076	25.859	1.00	25.31 A
ATOM	636	CB	GLU	A	95	52.648	7.590	25.612	1.00	26.45 A
ATOM	637	CG	GLU	A	95	53.540	6.907	26.643	1.00	28.64 A
ATOM	638	CD	GLU	A	95	55.022	7.198	26.457	1.00	30.17 A
ATOM	639	OE1	GLU	A	95	55.415	7.657	25.359	1.00	31.51 A
ATOM	640	OE2	GLU	A	95	55.798	6.948	27.407	1.00	28.42 A
ATOM	641	C	GLU	A	95	51.394	9.612	24.818	1.00	24.66 A
ATOM	642	O	GLU	A	95	50.809	8.851	24.037	1.00	22.08 A
ATOM	643	N	HIS	A	96	51.225	10.932	24.808	1.00	24.62 A
ATOM	644	CA	HIS	A	96	50.295	11.590	23.900	1.00	26.26 A
ATOM	645	CB	HIS	A	96	50.410	13.113	24.027	1.00	27.90 A
ATOM	646	CG	HIS	A	96	50.114	13.629	25.400	1.00	30.90 A
ATOM	647	CD2	HIS	A	96	50.422	13.138	26.625	1.00	31.52 A
ATOM	648	ND1	HIS	A	96	49.432	14.807	25.621	1.00	32.30 A
ATOM	649	CE1	HIS	A	96	49.333	15.018	26.922	1.00	32.43 A
ATOM	650	NE2	HIS	A	96	49.926	14.019	27.554	1.00	32.16 A
ATOM	651	C	HIS	A	96	50.420	11.193	22.435	1.00	26.13 A
ATOM	652	O	HIS	A	96	49.408	11.006	21.764	1.00	26.36 A
ATOM	653	N	ARG	A	97	51.648	11.067	21.938	1.00	25.66 A
ATOM	654	CA	ARG	A	97	51.857	10.696	20.540	1.00	25.19 A
ATOM	655	CB	ARG	A	97	53.344	10.864	20.161	1.00	25.74 A
ATOM	656	CG	ARG	A	97	53.734	10.433	18.746	1.00	24.90 A
ATOM	657	CD	ARG	A	97	52.779	10.981	17.684	1.00	27.96 A
ATOM	658	NE	ARG	A	97	52.817	12.435	17.532	1.00	29.51 A
ATOM	659	CZ	ARG	A	97	51.931	13.132	16.820	1.00	29.81 A
ATOM	660	NH1	ARG	A	97	50.936	12.508	16.197	1.00	31.04 A
ATOM	661	NH2	ARG	A	97	52.037	14.451	16.722	1.00	27.76 A
ATOM	662	C	ARG	A	97	51.371	9.269	20.265	1.00	24.39 A
ATOM	663	O	ARG	A	97	50.775	9.012	19.222	1.00	25.23 A
ATOM	664	N	LYS	A	98	51.605	8.344	21.189	1.00	23.55 A
ATOM	665	CA	LYS	A	98	51.145	6.970	20.983	1.00	23.84 A
ATOM	666	CB	LYS	A	98	51.678	6.034	22.082	1.00	25.86 A
ATOM	667	CG	LYS	A	98	53.151	5.669	21.933	1.00	29.53 A
ATOM	668	CD	LYS	A	98	53.621	4.689	23.004	1.00	31.47 A
ATOM	669	CE	LYS	A	98	55.149	4.543	22.978	1.00	33.99 A
ATOM	670	NZ	LYS	A	98	55.672	3.627	24.040	1.00	34.37 A
ATOM	671	C	LYS	A	98	49.611	6.908	20.955	1.00	23.22 A
ATOM	672	O	LYS	A	98	49.031	6.190	20.136	1.00	21.35 A
ATOM	673	N	ILE	A	99	48.963	7.658	21.849	1.00	21.20 A
ATOM	674	CA	ILE	A	99	47.507	7.689	21.909	1.00	20.16 A
ATOM	675	CB	ILE	A	99	47.017	8.541	23.112	1.00	18.26 A
ATOM	676	CG2	ILE	A	99	45.526	8.843	22.980	1.00	16.58 A
ATOM	677	CG1	ILE	A	99	47.306	7.793	24.421	1.00	16.19 A
ATOM	678	CD1	ILE	A	99	47.022	8.589	25.665	1.00	12.79 A

TABLE 3-continued

Superimposed: trigonal and tetragonal crystal forms
REMARK Superimposed on /xray1/hmdm2/PDB/M338437.pdb

ATOM	679	C	ILE	A	99	46.949	8.256	20.601	1.00	21.79	A
ATOM	680	O	ILE	A	99	46.008	7.710	20.019	1.00	21.34	A
ATOM	681	N	TYR	A	100	47.543	9.348	20.133	1.00	23.34	A
ATOM	682	CA	TYR	A	100	47.113	9.978	18.891	1.00	24.14	A
ATOM	683	CB	TYR	A	100	47.961	11.220	18.611	1.00	25.12	A
ATOM	684	CG	TYR	A	100	47.228	12.508	18.883	1.00	28.22	A
ATOM	685	CD1	TYR	A	100	46.799	12.833	20.177	1.00	28.65	A
ATOM	686	CE1	TYR	A	100	46.065	13.989	20.423	1.00	28.51	A
ATOM	687	CD2	TYR	A	100	46.908	13.379	17.843	1.00	28.65	A
ATOM	688	CE2	TYR	A	100	46.170	14.541	18.077	1.00	29.38	A
ATOM	689	CZ	TYR	A	100	45.752	14.835	19.366	1.00	29.62	A
ATOM	690	OH	TYR	A	100	45.002	15.961	19.589	1.00	31.04	A
ATOM	691	C	TYR	A	100	47.149	9.048	17.671	1.00	25.10	A
ATOM	692	O	TYR	A	100	46.216	9.055	16.857	1.00	25.32	A
ATOM	693	N	THR	A	101	48.206	8.251	17.524	1.00	23.58	A
ATOM	694	CA	THR	A	101	48.252	7.383	16.362	1.00	24.54	A
ATOM	695	CB	THR	A	101	49.714	7.004	15.972	1.00	25.48	A
ATOM	696	OG1	THR	A	101	50.297	6.160	16.962	1.00	26.87	A
ATOM	697	CG2	THR	A	101	50.552	8.262	15.841	1.00	27.33	A
ATOM	698	C	THR	A	101	47.376	6.143	16.527	1.00	23.52	A
ATOM	699	O	THR	A	101	47.074	5.459	15.553	1.00	24.28	A
ATOM	700	N	MET	A	102	46.949	5.851	17.753	1.00	22.80	A
ATOM	701	CA	MET	A	102	46.052	4.711	17.956	1.00	20.40	A
ATOM	702	CB	MET	A	102	46.081	4.229	19.408	1.00	15.37	A
ATOM	703	CG	MET	A	102	47.385	3.556	19.756	1.00	14.03	A
ATOM	704	SD	MET	A	102	47.437	2.805	21.384	1.00	11.93	A
ATOM	705	CE	MET	A	102	47.530	4.281	22.436	1.00	10.87	A
ATOM	706	C	MET	A	102	44.645	5.163	17.563	1.00	19.65	A
ATOM	707	O	MET	A	102	43.829	4.371	17.091	1.00	19.47	A
ATOM	708	N	ILE	A	103	44.384	6.451	17.755	1.00	18.90	A
ATOM	709	CA	ILE	A	103	43.108	7.049	17.406	1.00	21.34	A
ATOM	710	CB	ILE	A	103	42.959	8.459	18.055	1.00	20.40	A
ATOM	711	CG2	ILE	A	103	41.789	9.217	17.425	1.00	19.03	A
ATOM	712	CG1	ILE	A	103	42.757	8.312	19.565	1.00	19.84	A
ATOM	713	CD1	ILE	A	103	42.941	9.601	20.345	1.00	18.82	A
ATOM	714	C	ILE	A	103	43.045	7.183	15.881	1.00	24.13	A
ATOM	715	O	ILE	A	103	41.996	6.968	15.271	1.00	24.18	A
ATOM	716	N	TYR	A	104	44.182	7.530	15.277	1.00	27.06	A
ATOM	717	CA	TYR	A	104	44.283	7.701	13.827	1.00	29.10	A
ATOM	718	CB	TYR	A	104	45.702	8.155	13.462	1.00	30.33	A
ATOM	719	CG	TYR	A	104	45.914	9.635	13.689	1.00	30.58	A
ATOM	720	CD1	TYR	A	104	47.148	10.137	14.093	1.00	29.56	A
ATOM	721	CE1	TYR	A	104	47.328	11.499	14.323	1.00	29.30	A
ATOM	722	CD2	TYR	A	104	44.862	10.533	13.516	1.00	31.51	A
ATOM	723	CE2	TYR	A	104	45.032	11.892	13.742	1.00	31.90	A
ATOM	724	CZ	TYR	A	104	46.264	12.366	14.146	1.00	30.22	A
ATOM	725	OH	TYR	A	104	46.411	13.711	14.379	1.00	32.03	A
ATOM	726	C	TYR	A	104	43.895	6.466	13.017	1.00	29.49	A
ATOM	727	O	TYR	A	104	43.336	6.587	11.926	1.00	30.07	A
ATOM	728	N	ARG	A	105	44.188	5.287	13.553	1.00	30.44	A
ATOM	729	CA	ARG	A	105	43.851	4.039	12.883	1.00	31.09	A
ATOM	730	CB	ARG	A	105	44.714	2.889	13.407	1.00	32.59	A
ATOM	731	CG	ARG	A	105	46.098	2.802	12.783	1.00	35.48	A
ATOM	732	CD	ARG	A	105	46.758	1.479	13.140	1.00	38.68	A
ATOM	733	NE	ARG	A	105	47.041	1.380	14.572	1.00	41.14	A
ATOM	734	CZ	ARG	A	105	48.198	1.727	15.132	1.00	42.11	A
ATOM	735	NH1	ARG	A	105	49.192	2.196	14.382	1.00	41.27	A
ATOM	736	NH2	ARG	A	105	48.362	1.605	16.446	1.00	42.61	A
ATOM	737	C	ARG	A	105	42.382	3.705	13.104	1.00	31.15	A
ATOM	738	O	ARG	A	105	41.887	2.692	12.599	1.00	30.58	A
ATOM	739	N	ASN	A	106	41.691	4.552	13.867	1.00	30.35	A
ATOM	740	CA	ASN	A	106	40.272	4.349	14.137	1.00	31.38	A
ATOM	741	CB	ASN	A	106	39.995	4.297	15.639	1.00	30.13	A
ATOM	742	CG	ASN	A	106	40.393	2.984	16.250	1.00	30.74	A
ATOM	743	OD1	ASN	A	106	41.568	2.754	16.549	1.00	30.89	A
ATOM	744	ND2	ASN	A	106	39.415	2.094	16.427	1.00	30.12	A
ATOM	745	C	ASN	A	106	39.408	5.429	13.517	1.00	32.04	A
ATOM	746	O	ASN	A	106	38.293	5.677	13.970	1.00	30.99	A
ATOM	747	N	LEU	A	107	39.914	6.070	12.474	1.00	34.74	A
ATOM	748	CA	LEU	A	107	39.144	7.115	11.828	1.00	39.45	A
ATOM	749	CB	LEU	A	107	39.166	8.383	12.694	1.00	39.46	A
ATOM	750	CG	LEU	A	107	40.507	8.908	13.220	1.00	38.61	A
ATOM	751	CD1	LEU	A	107	41.418	9.298	12.068	1.00	38.52	A

Superimposed: trigonal and tetragonal crystal forms											
REMARK Superimposed on /xray1/hmdm2/PDB/M338437.pdb											
ATOM	752	CD2	LEU	A	107	40.252	10.105	14.120	1.00	37.16	A
ATOM	753	C	LEU	A	107	39.614	7.441	10.425	1.00	42.25	A
ATOM	754	O	LEU	A	107	40.442	6.732	9.848	1.00	42.75	A
ATOM	755	N	VAL	A	108	39.057	8.516	9.882	1.00	46.00	A
ATOM	756	CA	VAL	A	108	39.397	8.997	8.549	1.00	49.43	A
ATOM	757	CB	VAL	A	108	38.365	8.541	7.499	1.00	48.08	A
ATOM	758	CG1	VAL	A	108	39.032	8.443	6.146	1.00	48.02	A
ATOM	759	CG2	VAL	A	108	37.735	7.216	7.907	1.00	46.78	A
ATOM	760	C	VAL	A	108	39.389	10.529	8.612	1.00	53.19	A
ATOM	761	O	VAL	A	108	38.321	11.145	8.684	1.00	52.78	A
ATOM	762	N	VAL	A	109	40.576	11.136	8.601	1.00	57.34	A
ATOM	763	CA	VAL	A	109	40.708	12.596	8.664	1.00	61.10	A
ATOM	764	CB	VAL	A	109	42.177	13.052	8.480	1.00	61.46	A
ATOM	765	CG1	VAL	A	109	42.306	14.528	8.847	1.00	61.63	A
ATOM	766	CG2	VAL	A	109	43.115	12.193	9.320	1.00	62.28	A
ATOM	767	C	VAL	A	109	39.875	13.293	7.584	1.00	63.47	A
ATOM	768	O	VAL	A	109	40.196	13.206	6.394	1.00	63.73	A
ATOM	769	N	VAL	A	110	38.817	13.989	8.004	1.00	65.46	A
ATOM	770	CA	VAL	A	110	37.941	14.697	7.073	1.00	67.21	A
ATOM	771	CB	VAL	A	110	36.927	15.603	7.840	1.00	66.97	A
ATOM	772	CG1	VAL	A	110	35.873	16.155	6.878	1.00	67.04	A
ATOM	773	CG2	VAL	A	110	36.262	14.817	8.961	1.00	66.24	A
ATOM	774	C	VAL	A	110	38.775	15.570	6.119	1.00	69.20	A
ATOM	775	O	VAL	A	110	39.949	15.862	6.458	1.00	69.94	A
ATOM	776	OXT	VAL	A	110	38.248	15.956	5.046	1.00	70.58	A
ATOM	777	C1	CID	A	1	46.320	13.011	27.769	1.00	21.13	
INH1											
ATOM	778	C2	CID	A	1	46.849	12.548	26.529	1.00	21.31	
INH1											
ATOM	779	C3	CID	A	1	46.319	13.053	25.307	1.00	21.72	
INH1											
ATOM	780	C4	CID	A	1	45.283	14.011	25.313	1.00	21.74	
INH1											
ATOM	781	C5	CID	A	1	44.753	14.472	26.542	1.00	21.42	
INH1											
ATOM	782	C6	CID	A	1	45.261	13.981	27.804	1.00	22.49	
INH1											
ATOM	783	C7	CID	A	1	44.698	14.428	29.194	1.00	23.66	
INH1											
ATOM	784	C8	CID	A	1	44.052	15.860	29.277	1.00	25.69	
INH1											
ATOM	785	O1	CID	A	1	43.517	16.308	30.288	1.00	29.01	
INH1											
ATOM	786	O2	CID	A	1	44.409	16.731	28.309	1.00	30.64	
INH1											
ATOM	787	N1	CID	A	1	43.714	13.347	29.673	1.00	19.99	
INH1											
ATOM	788	C9	CID	A	1	42.570	12.996	28.781	1.00	18.95	
INH1											
ATOM	789	C10	CID	A	1	42.648	11.641	28.034	1.00	18.04	
INH1											
ATOM	790	C11	CID	A	1	43.669	10.654	28.259	1.00	17.01	
INH1											
ATOM	791	C12	CID	A	1	43.700	9.448	27.530	1.00	16.97	
INH1											
ATOM	792	C13	CID	A	1	42.708	9.210	26.564	1.00	17.64	
INH1											
ATOM	793	CL1	CID	A	1	42.737	7.786	25.674	1.00	14.96	
INH1											
ATOM	794	C14	CID	A	1	41.687	10.153	26.318	1.00	18.96	
INH1											
ATOM	795	C15	CID	A	1	41.659	11.354	27.046	1.00	17.55	
INH1											
ATOM	796	C16	CID	A	1	41.205	13.214	29.506	1.00	18.08	
INH1											
ATOM	797	O3	CID	A	1	40.363	13.973	29.015	1.00	18.82	
INH1											
ATOM	798	N2	CID	A	1	40.909	12.577	30.698	1.00	16.78	
INH1											
ATOM	799	C17	CID	A	1	41.690	11.680	31.447	1.00	17.03	
INH1											
ATOM	800	C18	CID	A	1	43.101	11.735	31.572	1.00	16.70	
INH1											

TABLE 3-continued

Superimposed: trigonal and tetragonal crystal forms REMARK Superimposed on /xray1/hmdm2/PDB/M338437.pdb										
ATOM	801	C19	CID	A	1	43.977	12.786	30.947	1.00	19.45
INH1										
ATOM	802	O4	CID	A	1	44.965	13.160	31.626	1.00	18.52
INH1										
ATOM	803	C20	CID	A	1	43.769	10.744	32.353	1.00	17.26
INH1										
ATOM	804	C21	CID	A	1	43.051	9.726	33.006	1.00	18.91
INH1										
ATOM	805	I1	CID	A	1	44.145	8.343	34.119	1.00	19.64
INH1										
ATOM	806	C22	CID	A	1	41.657	9.670	32.902	1.00	17.86
INH1										
ATOM	807	C23	CID	A	1	40.966	10.637	32.123	1.00	17.23
INH1										
ATOM	808	CL2	CID	A	1	46.930	12.505	23.805	1.00	20.99
INH1										
ATOM	809	CL3	CID	A	1	40.751	8.456	33.699	1.00	20.31
INH1										
END										

We claim:

1. A crystal comprising HDM2, or a fragment, or target structural motif or derivative thereof, and a ligand, wherein said ligand is a small molecule inhibitor.

2. The crystal of claim 1 wherein said fragment or derivative thereof is a peptide selected from the group consisting of SEQ ID NO: 1 (amino acid sequence of full length HDM2), SEQ ID NO: 2 (amino acid residues 17-111 of SEQ ID NO: 1), SEQ ID NO: 3 (amino acid residues 23-114 of SEQ ID NO: 1) and SEQ ID NO: 4 (Gly¹⁶-SEQ ID NO: 2).

3. The crystal of claim 1 wherein said crystal has a spacegroup selected from the group consisting of a trigonal spacegroup of P₃2₁ and a tetragonal spacegroup of P₄2₁2.

4. The crystal of claim 1, wherein the crystal effectively diffracts X-rays for determination of atomic coordinates to a resolution of at least about 3.0 Å.

5. The crystal of claim 1, wherein the ligand is in crystalline form.

6. The crystal of claim 1 wherein said ligand is selected from the group consisting of (4-Chloro-phenyl)-[3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-acetic acid; [8-Chloro-3-(4-chloro-phenyl)-7-iodo-2,5-dioxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl]-(4-chloro-phenyl)-acetic acid); and derivatives thereof.

7. The crystal of claim 1 wherein said HDM2 comprises a peptide having at least 95% sequence identity to SEQ ID NO: 2.

8. A crystal comprising SEQ ID NO: 2 comprising an atomic structure characterized by the coordinates of Table 1 or Table 2.

9. The crystal of claim 1 comprising a unit cell having dimensions selected from the group consisting of: dimensions of about 98.6 Å, 98.6 Å and 74.7 Å, and about alpha=90°, beta=90° and gamma=120°; and, dimensions of about 54.3 Å, 54.3 Å, 83.3 Å and about alpha=90°, beta=90° and gamma=90°.

10. A computer system comprising:

(a) a database containing information on the three dimensional structure of a crystal comprising HDM2, or a

fragment or a target structural motif or derivative thereof, and a ligand, wherein said ligand is a small molecule inhibitor, stored on a computer readable storage medium; and,

(b) a user interface to view the information.

11. A computer system of claim 10, wherein the information comprises diffraction data obtained from a crystal comprising SEQ ID NO:2.

12. A computer system of claim 10, wherein the information comprises an electron density map of a crystal form comprising SEQ ID NO:2.

13. A computer system of claim 10, wherein the information comprises the structure coordinates of Table 1 or Table 2 or homologous structure coordinates comprising a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2.

14. A computer system of claim 13, wherein the information comprises structure coordinates for amino acid residues comprising a root mean square deviation of non-hydrogen atoms of less than about 0.75 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2.

15. A computer system of claim 10, wherein the information comprises the structure coordinates for amino acids Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷ according to Table 1 or Table 2 or similar structure coordinates for said amino acids comprising a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2.

16. A computer system of claim 15, wherein the information further comprises the structure coordinates for amino acids Val⁵³, Leu⁵⁴, Phe⁵⁵, Leu⁵⁷, Gly⁵⁸, Gln⁵⁹, Ile⁶², Met⁶², Tyr⁶⁷, Gln⁷², His⁷³, Ile⁷⁴, Val⁷⁵, Phe⁸⁶, Phe⁹¹, Val⁹³, Lys⁹⁴, Glu⁹⁵, His⁹⁶, Ile⁹⁹, Tyr¹⁰⁰, Ile¹⁰³ according to Table 1 or Table 2 or similar structure coordinates for said amino acids comprising a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the

non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2.

17. A method of evaluating the potential of an agent to associate with HDM2 comprising:

- (a) exposing HDM2 to the agent; and
- (b) detecting the association of said agent to HDM2 amino acid residues Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷ thereby evaluating the potential.

18. A method of claim 17, wherein the agent is a virtual compound.

19. A method of evaluating the potential of an agent to associate with the peptide having aa¹⁶-SEQ ID NO: 2, comprising:

- (a) exposing aa¹⁶-SEQ ID NO: 2 to the agent; and
- (b) detecting the level of association of the agent to aa¹⁶-SEQ ID NO: 2, thereby evaluating the potential.

20. A method of claim 19, wherein the agent is a virtual compound.

21. A method of claim 17 wherein step (a) comprises comparing the atomic structure of the compound to the three dimensional structure of HDM2.

22. A method of claim 17, wherein the comparing comprises employing a computational means to perform a fitting operation between the compound and at least one binding site of HDM2.

23. A method of claim 22, wherein the binding site is defined by structure coordinates for amino acids Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷ according to Table 1 or Table 2 or similar structure coordinates for said amino acids comprising a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2.

24. A method of claim 23, wherein the binding site is further defined by structure coordinates for amino acids Val⁵³, Leu⁵⁴, Phe⁵⁵, Leu⁵⁷, Gly⁵⁸, Gln⁵⁹, Ile⁶¹, Met⁶², Tyr⁶⁷, Gln⁷², His⁷³, Ile⁷⁴, Val⁷⁵, Phe⁸⁶, Phe⁹¹, Val⁹³, Lys⁹⁴, Glu⁹⁵, His⁹⁶, Ile⁹⁹, Tyr¹⁰⁰, Ile¹⁰³ according to Table 1 or Table 2 or similar structure coordinates for said amino acids comprising a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2.

25. A method of claim 17, wherein the agent is exposed to crystalline SEQ ID NO:2 and the detecting of step (b) comprises determining the three dimensional structure of the agent-SEQ ID NO: 2 complex.

26. A method of identifying a potential agonist or antagonist against HDM2 comprising:

- (a) employing the three dimensional structure of HDM2 cocrystallized with a small molecule inhibitor to design or select said potential agonist or antagonist.

27. A method of claim 26, wherein the three dimensional structure corresponds to the atomic structure characterized by the coordinates of Table 1 or Table 2 or similar structure coordinates comprising a root mean square deviation of non-hydrogen atoms of less than about 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of Table 1 or Table 2.

28. A method of claim 26, further comprising the steps of: (b) synthesizing the potential agonist or antagonist; and (c) contacting the potential agonist or antagonist with HDM2.

29. A method of locating the attachment site of an inhibitor to HDM2, comprising:

- (a) obtaining X-ray diffraction data for a crystal of HDM2;
- (b) obtaining X-ray diffraction data for a complex of HDM2 and an inhibitor;
- (c) subtracting the X-ray diffraction data obtained in step (a) from the X-ray diffraction data obtained in step (b) to obtain the difference in the X-ray diffraction data;
- (d) obtaining phases that correspond to X-ray diffraction data obtained in step (a);
- (e) utilizing the phases obtained in step (d) and the difference in the X-ray diffraction data obtained in step (c) to compute a difference Fourier image of the inhibitor; and,
- (f) locating the attachment site of the inhibitor to HDM2 based on the computations obtained in step (e).

30. A method of obtaining a modified inhibitor comprising:

- (a) obtaining a crystal comprising HDM2 and an inhibitor;
- (b) obtaining the atomic coordinates of the crystal;
- (c) using the atomic coordinates and one or more molecular modeling techniques to determine how to modify the interaction of the inhibitor with HDM2; and
- (d) modifying the inhibitor based on the determinations obtained in step (c) to produce a modified inhibitor.

31. The method of claim 30 wherein said crystal comprises a peptide selected from the group consisting of: a peptide having SEQ ID NO: 2; a peptide having SEQ ID NO: 3 and a peptide having SEQ ID NO:4.

32. A method of claim 30, wherein the one or more molecular modeling techniques are selected from the group consisting of graphic molecular modeling and computational chemistry.

33. A method of claim 30, wherein step (a) comprises detecting the interaction of the inhibitor to HDM2 amino acid residues Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷.

34. An HDM2 inhibitor identified by the method of claim 30.

35. An isolated protein fragment comprising a binding pocket or active site defined by structure coordinates of HDM2 amino acid residues Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷.

36. An isolated fragment of claim 35 linked to a solid support.

37. An isolated nucleic acid molecule encoding the fragment of claim 35.

38. A vector comprising a nucleic acid molecule of claim 37.

39. A host cell comprising the vector of claim 38.

40. A method of producing a protein fragment, comprising culturing the host cell of claim 39 under conditions in which the fragment is expressed.

41. A method of screening for an agent that associates with HDM2, comprising:

- (a) exposing a protein molecule fragment of claim 35 to the agent; and

- (b) detecting the level of association of the agent to the fragment.
42. A kit comprising a protein molecule fragment of claim 35.
43. A method for the production of a crystal complex comprising an HDM2 polypeptide-ligand comprising:
- contacting the HDM2 polypeptide with said ligand in a suitable solution comprising PEG and NaSCN; and,
 - crystallizing said resulting complex of HDM2 polypeptide-ligand from said solution.
44. The method of claim 43 wherein said HDM2 polypeptide is a polypeptide having SEQ ID NO: 2.
45. The method of claim 43 wherein said PEG has an average molecular weight range from 100 to 1000, wherein said PEG is present in solution at a range from about 0.5% w/v to about 10% w/v and said NaSCN is present in solution at a range of from about 50 mM to about 150 mM.
46. The method of claim 45 wherein said PEG has an average molecular weight of about 400 and is present in solution at about 2% w/v and said NaSCN is present in solution at about 100 mM.
47. The method of claim 46 wherein said solution further comprises about 1.8-2.4 M $(\text{NH}_4)_2\text{SO}_4$ and about 100 mM buffer.
48. A method for the production of a crystal of claim 1 comprising crystallizing a peptide comprising a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO:4 with a potential inhibitor.
49. A method for identifying a potential inhibitor of HDM2 comprising:
- using a three dimensional structure of HDM2 as defined by atomic coordinates according to Table 1 or Table 2;
 - replacing one or more HDM2 amino acids selected from Ser¹⁷, Ile¹⁹, Leu⁸² and Arg⁹⁷ in said three-dimensional structure with a different amino acid to produce a modified HDM2;
 - using said three-dimensional structure to design or select said potential inhibitor;
 - synthesizing said potential inhibitor; and,
 - contacting said potential inhibitor with said modified HDM2 in the presence of a substrate to test the ability of said potential inhibitor to inhibit HDM2 or said modified HDM2.
50. The method of claim 49 wherein said replacing one or more amino acid residues further comprises replacing SEQ ID NO: 2 amino acids selected from the group consisting of Val⁵³, Leu⁵⁴, Phe⁵⁵, Leu⁵⁷, Gly⁵⁸, Gln⁵⁹, Ile⁶¹, Met⁶², Tyr⁶⁷, Gln⁷², His⁷³, Ile⁷⁴, Val⁷⁵, Phe⁸⁶, Phe⁹¹, Val⁹³, Lys⁹⁴, Glu⁹⁵, His⁹⁶, Ile⁹⁹, Tyr¹⁰⁰, and Ile¹⁰³.
51. The method of claim 49 wherein said potential inhibitor is selected from a database.
52. The method of claim 49 wherein said potential inhibitor is designed de novo.
53. The method of claim 49 wherein said potential inhibitor is designed from a known inhibitor.
54. The method of claim 49, wherein said step of employing said three-dimensional structure to design or select said potential inhibitor comprises the steps of:
- identifying chemical entities or fragments capable of associating with modified HDM2; and
 - assembling the identified chemical entities or fragments into a single molecule to provide the structure of said potential inhibitor.
55. The method of claim 49, wherein the potential inhibitor is a competitive inhibitor of SEQ ID NO:4 (Gly¹⁶-SEQ ID NO: 2).
56. The method of claim 49, wherein said potential inhibitor is a non-competitive or uncompetitive inhibitor of SEQ ID NO:4 (Gly¹⁶-SEQ ID NO: 2).
57. The inhibitor identified by the method of claim 49.

* * * * *