Predicting the Structure and Energetics of Protein-Ligand Interaction

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DEDICATION

This dissertation is dedicated to my parents.

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ABSTRACT

Molecular docking has been a crucial component and remains a highly active area in computer-aided drug design (CADD). In simple terms, molecular docking uses computer algorithms to identify the “best” match between two molecules, a process analogous to solving three-dimensional jigsaw puzzles. In more rigorous terms, the molecular docking problem can be defined as predicting the “correct” bound association state for the given atomic coordinates of two molecules. Docking is an important tool for structure and affinity predictions of molecular association, which would lead to the mechanistic understanding of the physicochemical interactions at the atomic level. Protein-small molecule (referred to as “ligand”) docking, in particular, has broad application to structure-based drug design, as drug compounds are usually small molecules. In this dissertation, I present my studies on protein-ligand docking. In the background introduction, I reviewed the docking methodology and the key recent developments in the field. Next, I applied an ensemble docking algorithm onto 14 protein kinases to study ligand selectivity, a major issue for the development of kinase inhibitors as anticancer drugs. In Chapter 3, I developed a web server for automated, *in silico* screening of multiple targets for a given ligand query. Finally, I integrated the new methods for protein-ligand binding mode prediction and applied the integrated method to a large-scale, blind prediction competition named Continuous Evaluation of Ligand Pose Prediction (CELPP).

Chapter 1

Introduction

Proteins are incredibly diverse macromolecules made up of amino acids as the building blocks. In a cell, proteins interact with ions, small molecules (drugs), and even macromolecules (e.g., other proteins, nucleic acids). During such interactions, shape alteration (referred to as conformational change) almost occurs at the same time. It is known that a protein structure dictates its function in living organisms.¹ Any dysfunction could lead to pathological changes. Therefore, studying protein interactions and solving the structures are crucial steps for understanding the mechanism of life, in addition to the investigation of biological systems and rational drug design.

Direct methods for the determination of three-dimensional structures of the protein-ligand complexes rely on experiments. Traditional techniques include X-ray crystallography, neutron diffraction or electrons diffraction (which depends on the source type of beams used in interacting with the specimen).^{2,3} The principle of this method is the analysis of diffraction patterns, which requires a crystalline form of the specimen. Proteins are very difficult to crystalize due to the numerous unstructured loops.

Therefore, the limitation of X-ray crystallography is the quality of the crystallization. In this circumstance, cryo-electron microscopy (cryo-EM) has the advantage that a crystalline sample is not necessary. However, cryo-EM usually has lower resolution when compared with crystallography. Nevertheless, considerable improvements have been made very recently.⁴⁻⁶ Also, magnetic resonance (NMR) spectroscopy has contributed to many structural details and dynamics of biological materials.⁷ However, NMR technology has difficulty to solve the structures of large proteins. In summary, all experimental techniques utilized to obtain protein structures have limitations. In addition, they are time consuming and costly. Ultimately, these shortcomings spur the development of computational methods.

Molecular docking is one of the examples that implement the integration of computational and experimental strategies.⁸⁻¹¹ In the past decades, molecular docking has been a powerful approach for computer-aided drug design (CADD). Generally, molecular docking is performed between two molecules (see Figure 1.2). The target (receptor) is usually a macromolecule such as a protein, DNA or RNA. The other molecule can be a protein, peptide or small molecule. Molecular docking utilizes computational algorithms to predict the bound association of the two molecules. In this work, we focus on docking of small molecules against a protein target, referred to as ligand-protein docking, because of its broad application to structure-based drug design (SBDD) (drug compounds are usually small molecules). With a protein of a known three-dimensional structure, the docking method can predict how ligands interact with their protein targets from a physical or chemical perspective. The determination of protein-ligand complex structures can be done routinely by docking algorithms. In other words, protein-ligand docking approaches allow an automatic

Figure 1.1: Protein Data Bank growth statistics.¹⁴ Number of structures deposited per year vs the number of total available structures.

way to manipulate the recognition of a drug by its protein target through capturing physical principles.

Nowadays, protein-ligand docking is widely applied to structure-activity and mutagenesis studies, virtual screening (VS), and lead optimization.¹² With the rapid growth of the protein structures in the Protein Data Bank^{13,14}), protein-ligand docking methods have become a valuable tool for mechanistic biological research and pharmaceutical drug discovery.

1.1 Physical Basis of Molecular Docking

1.1.1 Protein-ligand interaction

Protein-ligand interactions are central to the in-depth understanding of protein functions in biology because proteins accomplish molecular recognition through binding with various molecules.^{15,16} Drugs often act as inhibitors when interacting with proteins, because many diseases including cancer are attributed to the abnormally active protein-ligand interactions. In this circumstance, inhibitors can be used to prevent the abnormal interactions for specific therapy. For instance, in the treatment of chronic myelogenous leukemia (CML), STI571 (GleevecTM, imatinib mesylate) is used to inhibit Bcr-Abl target protein activation, which also exemplifies the successful development of the rational drug design.¹⁷ Therefore, insights into protein-ligand interactions are vital for the development of drugs.

Molecular docking algorithms predict protein-ligand interactions in a complex that is formed non-covalently. In biological systems, hydrogen bonds, ionic bonds, Van der Waals interactions and hydrophobic bonds are the four main types of non-covalent interactions.¹⁸ Non-covalent bonds, ranging from 1-5 kcal/mol,¹⁹ are weak in comparison with covalent bonds. Therefore, most of the time the term “non-covalent interactions” is used, rather than non-covalent bonds. However, the cumulative effect of these non-covalent interactions can be significant, which means multiple non-covalent bonds often act together at the binding interface of a complex to produce highly stable and specific associations.²⁰

Figure 1.2: Illustration of ligand-protein docking. Docking algorithms generate a variety of complex configurations. The right panel shows the surface representation of a protein binding pocket, with the ligands in different orientations.

Hydrogen bonds

Hydrogen bonds are polar electrostatic interactions that can be described in the form of $D-H \cdots A$. Here, D and A stand for an electron donor and acceptor atom, respectively. H is the hydrogen atom attached to a donor atom. Thus, the donor atom must be electronegative.²¹ Hydrogen bonds have a strength of about 5 kcal/mol, which is weaker than the covalent bond between an oxygen atom and a hydrogen atom (approximately 110 kcal/mol).¹⁹ However, biomolecules exist in solvent surroundings, in which the extensive hydrogen bonds between adjacent molecules are broken and reformed constantly, resulting in the change of system enthalpy and entropy. Both the protein and the ligand interact with the solvent before binding, so the enthalpy and entropy influence their complex formation.^{8,15} Also, hydrogen bonds contribute a stabilizing force to macromolecules (e.g., proteins and nucleic acids), which is of great importance to the structure.

Ionic bonds

Ionic interaction is the electronic attraction between oppositely charged ionic pairs. Thus, ionic bonds are highly specific electrostatic interactions. In the aqueous solution, ions are surrounded by a shell of water molecules which is caused by dissolution in water.^{20,22,23}

Van der Waals interactions

When atoms in different molecule are close enough, the transient dipoles in the electron clouds lead to an intermolecular force and form nonspecific Van der Waals interactions. Roughly, the strength of Van der Waals interaction is 1 kcal/mol, which

is even weaker than typical hydrogen bonds.

Hydrophobic interactions

Hydrophobic interactions result from the effect that nonpolar molecules tend to exclude from the solvent and aggregate in an adequate surrounding. Hydrophobic interactions are often considered as driven by the entropy gain.²³ However, the molecular mechanisms of the hydrophobic effect remain controversial. In the scaled-particle theory, the hydrophobic effect is multifaceted depending on the size of solute.^{23,24}

1.1.2 Enthalpy-Entropy Compensation

Besides the aforementioned major types of non-covalent interactions, other types of non-covalent interactions also exist in protein-ligand complexes, such as CH- π in protein-sugar complexes due to the presence of aromatic rings.²⁵ To be noted, the solvent is always considered in the system when we discuss about non-covalent interactions between the protein and the ligand. In fact, numerous solvent molecules are involved in binding and the solvent effect plays an important role in protein-ligand interactions. The contributions of various non-covalent interactions are closely related to two thermodynamic quantities, entropy and enthalpy. The enthalpic and entropic changes before and after the complex formation determine how tightly the protein and ligand bind together, which is characterized by the Gibbs binding free energy, as shown in Equation 1.1.

$$\Delta G_{bind} = \Delta H - T\Delta S \tag{1.1}$$

Here, ΔG represents the change of the free energy, and T is the absolute temperature in Kelvin. ΔH represents the types and numbers of chemical bonds and noncovalent interactions that are broken and formed, and ΔS is the change in the randomness of the system. The Gibbs binding free energy can be calculated using theoretical methods, or can be quantified experimentally by the reaction rate:²⁶

$$\Delta G_{bind} = -RT \ln K_{eq} = -RT \ln \frac{k_{on}}{k_{off}} \quad (1.2)$$

Equation 1.2 shows that complex stability can be measured through the equilibrium binding constant K_{eq} , which is determined by the two kinetic rate constants, K_{on} (for the binding reaction) and K_{off} (for the dissociation reaction). R and T is the gas constant (8.314 J/mol.K.) and the absolute temperature, respectively.

The net driving force for binding is balanced between the two factors, entropy (the tendency to achieve the highest degree of randomness) and enthalpy (the tendency to achieve the most stable bonding state). In fact, the protein-ligand binding process is driven by the decrease in the total Gibbs free energy of the system.¹⁵

1.1.3 Molecular recognition models

Noncovalent interaction-driven molecular complexes show geometrical complementarity. Three conceptual models of ligand-protein binding have been proposed to explain the mechanism for molecular recognition (Figure 1.3). Fisher’s **lock-and-key model** theorizes that the binding interface should be matched complementarily.²⁷ The protein and the ligand are rigid in this model, which means that their conformations are

identical before and after binding. Du *et al.* suggested that the lock-and-key model is an entropy-dominated binding process.¹⁵

In Koshland’s **induced-fit model**, conformational change occurs to the protein during binding in order to accommodate the ligand with the best amino acid configuration.²⁸ It should be noted that in most cases only minor conformational changes arise in proteins after ligand binding. Compared with the lock-and-key model, the induced-fit hypothesis can be linked to a “hand in glove” model, adding flexibility upon Fisher’s idea.²⁹

In the **conformational selection model**, ligands bind selectively to the most suitable conformational state among an ensemble of substates.^{30,31} In the original conformational selection model, no further conformational rearrangement occurs. However, in an extended conformational selection recognition mechanism, ligands first bind to a protein in the initial favorable protein conformational state, which induces a protein conformational change subsequently. In other words, the “induced-fit” and “conformational selection” recognition mechanisms may co-exist in ligand binding.^{32,33}

Figure 1.3: Illustration of the three conceptual protein-ligand interaction models accompanied with one extended interaction model: (a) The lock-and-key model; both protein and ligand are rigid. (b) The induced-fit model; the conformational change of the protein occurs. (c) The conformational selection model; the ligand binds to the most suitable conformation among an ensemble of protein conformations. (d) The extended conformational selection model; the ligand binds to one protein conformer first and then a subsequent conformational change occurs to the protein. To focus on protein flexibility, this figure does not show ligand flexibility.

1.2 Key Components in Ligand-Protein Docking

The basic procedure of docking can be simplified to sampling and ranking, two critical ingredients in current docking programs. Sampling refers to searching putative ligand conformations in the binding site of a receptor. Proteins are usually held rigid in most docking algorithms. Generation of 3D conformers for the ligand is required for flexible (ligand) docking. A good sampling algorithm should be able to generate a diverse ensemble of ligand structures, including the bioactive, bound ligand structure. The second component, ranking, refers to assessing the fit between a ligand conformation and the target by scoring functions. These two docking components will be discussed in detail, respectively.

1.2.1 Conformational sampling

Biomolecules are dynamic; they are either dissolved in the cytosol or associated with some other components of the cell. Besides the six translational and rotational degrees of freedom, dihedral (torsional) angles also add up extensive flexibility. For example, in sugar molecules, the diversity stems primarily from the rotatable bonds that connect monosaccharides, which are also known as glycosidic linkages (see Figure 1.4). Sugars are intricate biomolecules, as being indicated by their nomenclature, reactions, functions, and linear/branched structures. More diverse conformational sampling is required with a larger number of monosaccharides in an oligosaccharide chain.³⁴⁻³⁶

Similarly, proteins are polymers of amino acids that link together through peptide bonds. Therefore, even small variations in the conformations of protein subunits

Figure 1.4: Stick representation of sugar with the elements in different colors: C(olive), O(red), N(blue). The glycosidic torsion angles φ , ψ and ω are annotated. C and O represents carbon and oxygen, respectively. The labeled atoms define the torsion angles as φ (O5-C1-O_x-C_x), ψ (C1-O_x-C_x-C_{x-1}) and ω (O6-C6-C5-O5).

could lead to extensive flexibility in a protein. Figure 1.5 shows the dihedral angles of an amino acid in a protein. The third backbone dihedral angle ω (see Figure 1.4 for its definition) is typically close to 180° or 0° in proteins. The flexible side chain dihedral angle for each residue has various distributions.³⁷ Furthermore, the task is more complicated because proteins in solution exist as an ensemble of conformations and fluctuate over time, which make it even harder to simulate on computer. While more extensive samplings are needed to account for the induced fit and conformational selection models as we introduce in section 1.1.3. Our group has developed a docking package to consider many different conformations in an ensemble without time consuming strain. We will introduce it in section 1.2.3 and section 1.3.

1.2.2 Sampling algorithms

Computational conformational sampling has been an active realm for many years because of evolving small molecule modeling and design in pharmaceutical work.^{38,39} Sampling algorithms explore the molecules conformational space from two perspectives. One of the categories exhaustively enumerates all possible torsions, which is necessary due to our limited knowledge of pharmaceutically relevant conformational space. However, this method may cause exponential growth of the search space. To overcome high degrees of freedom, systematic search methods store the physicochemical properties in an applicate grid to prevent combinatorial explosion.⁴⁰ The typical procedures divide the ligand into fragments first and then dock into the active site sequentially. An application of automated calculating grids is incremental construction (IC) methods (anchor and grow), which are implemented in the application DOCK.⁴¹ DOCK is the first and most widely used docking program, and the newest version is DOCK 6.^{42,43} Other well known flexible ligand searching programs such as FlexX and Glide also use incremental construction methods.^{44,45}

The other perspective uses a random element to change the system degrees of freedom, which is also referred to as stochastic search. Most common stochastic methods include genetic algorithms (GAs) and Monte Carlo (MC) search.^{46,47} Also, simulation methods have been developed and widely used in molecular docking sampling procedures. Molecular dynamics (MD) is one example of simulation methods that the generated state has to be lower in energy than the initial state to move to the next step. Therefore, it may often get trapped in the local minima that cannot cross high energy barriers. An alternative strategy is to identify the conformation preliminarily, and followed by further MD simulations to implement local optimiza-

Figure 1.5: Illustration of dihedral angles in one amino acid residue of a protein: two backbone dihedral angles φ , ψ and one side chain dihedral angle χ . The elements are in different colors: C(grey), O(red), and N(blue). Hydrogen atoms are not shown. The the backbone of this amino acid is colored green.

tion. Other methods such as increasing the simulation temperature and smoothing potential energy surfaces are also introduced in previous studies.^{8,39}

1.2.3 Scoring functions

Another key aspect of molecular docking is to rank the ligand conformations that have been generated. A good scoring function should be capable of distinguishing between the true binding modes and the decoy modes. Due to the large degrees of freedom in the protein-ligand system, balancing the speed and accuracy is necessary for the scoring step. The scoring functions are mainly divided into three categories: force field-based, empirical, and knowledge-based potentials. Different scoring functions are listed in Table 1.1.

Force field-based scoring functions

Classical force field-based scoring functions calculate Coulombic (for electrostatics) and Lennard-Jones (for Van der Waals) terms for non-covalent interactions. More sophisticated forms as an extension of force field-based scoring functions also consider the terms of hydrogen bonds, solvations and entropic contributions.

Empirical scoring functions

Empirical scoring functions are often related to force field-based scoring functions because they consider similar molecular contributions such as hydrogen bonds, ionic interactions, hydrophobic effects and entropic change. Summation of all these components results in the binding free energy, which is ultimately calculated by empirical scoring functions. The empirical coefficients are trained by fitting the scoring function to the experimentally measured binding affinities. Therefore, these coefficients strongly rely on the experimental data set for fitting, which is the main drawback of empirical scoring functions.

Knowledge-based scoring functions

Knowledge-based scoring functions derive atomic pair potentials by statistical principles to extract preferred interaction geometries.⁴⁸ High efficiency is one of the major characteristics of knowledge-based scoring functions, in addition to the implicit consideration of the solvent effect, resulting in more common application of knowledge-based scoring functions than other scoring functions.^{49,50} Example knowledge-based scoring functions include DrugScore,⁴⁹ PMFScore,⁵¹ and ITScore.^{52,53}

Recent development in scoring functions

It is worth noting that there is no universal scoring function that can fit all biological systems, and it is not appropriate to do so because the existing scoring functions remain to have limitations and most of them are sensitive to the training set or have a limited scope of application. Therefore, when docking against a specific target family, training a scoring function with the particular protein family can usually improve binding mode and binding affinity prediction, which is referred to as target-specific scoring functions.⁵⁴ The consensus scoring approach is another way to overcome the deficiencies of individual scoring functions to some extent. Consensus scoring functions can mitigate the bias of a single scoring function and improve the hit rate.^{55,56} The consensus approach should not include multiple scoring functions that yield highly correlated results; otherwise the bias of these scoring functions would be amplified rather than diminished.⁵⁵ Other ongoing methodology development includes adding additional terms to the existing scoring functions to improve the scoring performance.^{57,58} Numerous comparison studies have been reported to evaluate the performance of different scoring functions.^{50,59–62}

1.3 Docking Programs

In the past two decades, more than 60 docking programs have become available,⁶³ such as SLIDE,⁶⁴ X-CSCORE⁶⁵ and ConsDock.⁶⁶ Most of the existing docking algorithms treat ligands as flexible molecules and proteins as rigid molecules, because a protein usually consists of thousands of atoms. In some programs such as GalaxyDock,⁶⁷ protein side-chains can be optimized.

Moreover, there are indirect ways to consider the protein induced fit effect in ligand binding. A common approach is to utilize ensemble protein conformations. These ensemble protein structures can be obtained either from computational analysis such as molecular dynamics (MD) simulations or from experimental measurements such as NMR or X-ray diffraction. The MDock software incorporates a method referred to as “ensemble docking” to implicitly account for protein flexibility. In this method, the protein conformational number is introduced as an additional variable during docking optimization. This ensemble docking algorithm is computationally efficient; its computational speed is comparable to that of single-protein docking.^{52,53,68} Mizutani *et al.* used an enlarged binding pocket in their docking program ADAM to allow for certain protein flexibility.⁶⁹ In this approach, the van der Waals energy curve for each atom pair is shifted to widen the protein cavity uniformly, followed by structure optimization to remove atomic clashes and to improve interaction energy. Similarly, Bottegoni *et al.* adopted the SCARE (SCan Alanines and REfine) protocol, which enlarges the binding pocket by alanine mutation within the binding pocket.⁷⁰

In order to improve the docking success, some docking programs target specific protein or ligand classes. Rather than generating a “universal scoring function”, training a system-dependent scoring function or adding additional items in energy calculations can be beneficial to the prediction accuracy. For example, Vina-carb⁷¹ integrated the Carbohydrate Intrinsic (CHI) energy terms into the AutoDock Vina scoring function (ADV), improving the docking accuracy from 55% to 74% compared with the use of the ADV score alone.

Table 1.1: Example scoring functions

Scoring function	Category	Prominent features	Ref
GOLDScore	force field-based	Default scoring function for GOLD	47
MedusaScore ^b	force field-based	Including a hydrogen-bonding model and implicit solvent model	72
DOCK6	force field-based and footprint similarity	Updated internal energy function	43
Glide	force field-based and empirical	Modifying and expanding the ChemScore function	45
AutoDock ^a	empirical	Allowing side chains to be flexible	73
AutoDockFR ^a	empirical	Considering partial receptor flexibility	74
AutoDock VinaXB	halogen bond scoring function	Adding halogen bonding parameters	75
ICM	empirical	Allowing flexible side chains which are sampled simultaneously with the ligand	76
LigScore1/LigScore2	empirical	Consisting of three terms that describe the van der Waals interaction	77
Vina	empirical	Summation of the energetic contributions from both inter- and intra-molecular interactions	78
Vinardo	empirical	Modifying the interaction terms and the atomic radii of the Vina scoring function	58
Vina-Carb	empirical	Adding a CHI-energy term to the scoring function of AutoDock Vina to improve protein-carbohydrate docking	71
SLICK	empirical	A scoring function for protein-carbohydrate docking by implementing a CH- π stacking interaction energy term in BALDock	79
DrugScore	knowledge-based	Extracting both short-range pair and solvent accessible surface potentials	49
PFM	knowledge-based	Potentials of mean force for fast calculation of atom pair interaction potentials	51
ITScore	knowledge-based	An iterative method to derive atomic pair potential energies	52
ROTA	knowledge-based	pair potentials in GalaxyDock ^a	67,80
Affiscore/N	knowledge-based	A scoring function in SLIDE for the secondary scoring step	64
X-CSCORE	consensus	Combine three empirical scoring functions	65

^aAllows certain protein flexibility in docking.

1.4 Structure-based virtual screening and inverse virtual screening

The applications of molecular docking in therapy interventions can be bidirectional depending on the purpose of docking. Conventional docking searches for a compound from a drug bank or from a compound library, a process referred to as virtual screening (VS).^{55,81} On the other hand, for a specific ligand of interest, inverse docking is useful for identification of the targets from thousands of protein candidates, a process called inverse virtual screening (IVS).^{56,82–84} Both prediction tasks are challenging and require immense calculations.

Virtual screening methods are classified into structure-based virtual screening and ligand-based virtual screening.⁸⁵ Structure-based virtual screening is explored by docking methods on a large scale. In contrast, ligand-based virtual screening methods utilize all the structural and chemical information (e.g., by searching the common features or similarity) rather than using a docking strategy. These two methods are not competitive, and can be used individually or in combination. For instance, a ligand-based prescreening step can be done for preselection in order to reduce the size of the compound database in many structure-based virtual screening applications.⁵⁵ Tan *et al.* integrated the two methods into parallel selection and postulated that structure-based and ligand-based screening could be more effective in a complementarity manner than rank fusion.⁸⁶

IVS reverse docking has been widely applied to drug development in recent years.^{82,87} Screening from a drug target database can help rapidly identify potential target candidates for a specific molecule. The molecule can be a non-drug ligand or a known drug. The major safety issues of drug candidates are possible side effects (referred

to as off-target effects) and toxicity. IVS can help investigate the interactions of the drug candidate with multiple targets in early-stage drug development. The purpose of IVS studies on known drugs is to search for alternative uses of FDA approved drugs, which reduce costs and risks in comparison with new chemical compounds. This approach is referred to as drug-repositioning (also known as drug repurposing or reprofiling).⁸⁸⁻⁹⁰ Drug development has been trending from “one gene, one drug, one disease” to polypharmacology, which means that drugs are designed to interact with multiple targets. The main challenge of IVS is the costly computational time. Recently, we have integrated our fast docking application, MDock, into a webserver platform in order to undertake the IVS tasks. The server is built-in with 3268 protein-ligand complexes (containing 3349 distinct binding sites) associated with 537 protein targets. A typical IVS run for a given ligand takes 1 to 4 hours. For the example, the IVS study on the progesterone receptor takes approximately one hour on a workstation with 24 Intel Xeon cores [Intel(R) Xeon(R) CPU E5-2650 v3 @ 2.30GHz]. In addition, the screening results from our web server provide searchable target diseases information.⁹¹

1.5 Challenges

Molecular docking methodology is rapidly evolving and improving with the exponential increase of computing power. Recently, machine learning algorithms (including neural network and deep learning)^{92,93} and hybrid approaches from high-content screening and virtual screening⁹⁴ have been proposed for docking predictions and drug discovery. A critical question in docking is how reliable the docking predic-

tions are Chen.⁹⁵ Consequently, benchmarking excises for blind docking prediction have been held, such as Community Structure-Activity Resource (CSAR),⁹⁶ Drug Design Data Resource (D3R)⁹⁷⁻⁹⁹ and Continuous Evaluation of Ligand Pose Prediction (CELPP).¹⁰⁰ Our group participate in the weekly competition (CELPP) using a fully automated systematic strategy.¹⁰¹ These large-scale protein-ligand complex structure predictions are statistically significant. Through our analysis, the current sampling (80.4%) is much better than the scoring (46.3%).¹⁰¹ The inaccuracy of current scoring functions likely arises from various sources, such as solvent effects, entropic effects, protonation or tautomer states, and so on. Development of new scoring schemes to address these issues is at large. The biggest hurdle in molecular docking stems from protein flexibility. The computational cost is immense for sampling all possible protein conformations. In conclusion, despite decades of docking algorithm development, prediction accuracy remains a major issue.

This dissertation presents my study on protein-ligand binding mode predictions and inverse virtual screening. In Chapter 2, I will present my study of virtual screening against 14 human protein kinases for ligand selectivity. Protein kinases have large population in the human body; up to 30% of all human proteins may be modified by kinase activity. Ligand selectivity is a big hurdle for the development of kinase inhibitors as anticancer drugs. We have presented an efficient ensemble docking algorithm to simultaneously address multiple target proteins. The algorithm was validated by virtual screening against 14 human protein kinases. The ensemble docking algorithm performed comparably to standard single-target docking without a significant increase in run time. We expect the algorithm to be useful for the investigation of the ligand selectivity in structure-based drug design.

In Chapter 3, I developed a ligand-protein docking server to predict potentially promising therapeutic targets for a query compound of interest. I also constructed a protein target database, which contains 537 targets, 3268 protein-ligand complex structures, and 3349 binding pockets. Our achieved success rates and computational efficiency suggest the server to be an effective tool for therapeutic intervention.

Chapter 4 describes the new methods we developed for protein-ligand binding mode prediction during the participation in the D3R Challenges. These methods were integrated, automated, and systematically tested using the large-scale data from Continuous Evaluation of Ligand Pose Prediction (CELPP) and a subset of Grand challenge 3 (GC3). The binding mode prediction results were thoroughly analyzed.

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Chapter 2

Drug Discovery against Diverse Kinases: Predicting Selectivity and Virtual Screening

Abstract

Docking against multiple target proteins is necessary for the prediction of ligand specificity and for rapid identification of inhibitors within a family of proteins. However, sequentially docking ligands into each target using conventional single-target docking methods is computationally expensive for virtual ligand screening, especially with a large number of the targets. This work introduced an efficient ensemble docking algorithm to address the issue of simultaneous docking against multiple targets. We used 14 protein kinases to study ligand selectivity and employed staurosporine and Gleevec for the representation of nonselective and selective binding. Virtual ligand screening was also performed against five protein kinases that have at least seven known inhibitors; the enrichments for ensemble docking were shown to be comparable

to those for sequentially docking the ligands to multiple targets. We demonstrated the ensemble docking algorithm to be computationally efficient, with a run time comparable to that of single-target docking. Our method will save significant amounts of computational time for studies of ligand selectivity in structure-based drug design.

2.1 Introduction

Molecular docking has become a common tool in structure-based drug design (see refs¹⁻⁶ for review). Particularly, ligand-protein docking, which addresses the likely binding modes of a ligand interacting with a protein of known 3D structure, is extensively applied to a variety of work in modern drug discovery.^{7,8} However, there are so many opportunities for promiscuity due to both similarities of cognate protein structures and flexibilities in the active binding sites when protein and ligands are cross-docked, resulting in possible side effects of drugs. An exemplary example is protein kinases.

As one of the largest families of enzymes, protein kinases are crucial in signal transduction cascades, regulating protein functions by chemically adding a negatively-charged phosphate group. Protein kinases are important targets for cancers and inflammation.⁹⁻¹¹ Consequently, numerous efforts have been devoted to developing kinase inhibitors. In the past decade alone, more than 20 drugs targeting protein kinases were approved for clinical use.¹² Despite the achieved success, the broad promiscuity causing undesirable off-target actions and side effects remains a major problem for protein kinase inhibitors. Both the presence of hundreds of protein kinases and the highly conserved residues in the active binding sites make it difficult for target

specificity. Therefore, ligand selectivity is crucial yet challenging for the development of kinase-targeted therapies.

Most current docking programs are designed for a single protein target, meaning that only one receptor can be considered in a docking process. This is a reasonable restriction in most cases, because one is often interested in a single, specific protein target at a time. However, investigating the selectivity of an inhibitor with multiple protein targets requires a more advanced method.¹⁶⁻¹⁹ Current docking programs sequentially dock ligands into each of the target proteins, a process referred to as sequential docking. The results from each single-target docking merge together via re-ranking. Despite its feasibility, this kind of sequential docking demands extensive computational investment, with the computational time being proportional to the number of the target proteins involved. In addition, sequential docking also results in added inconvenience during docking setup and the analysis of docking results. Therefore, a docking strategy that can simultaneously address multiple targets would be highly preferred.

This work presents an efficient ensemble docking algorithm that can simultaneously dock ligands into multiple target proteins without significantly increasing the computational time. The ensemble docking algorithm regards the protein structure as an additional parameter in the energy optimization process and performs docking against multiple targets like docking against a single target. After docking calculations, each ligand receives a series of energy scores corresponding to different target proteins so that one can investigate the selectivity of the ligand against different targets. The binding scores also yield multiple enrichment curves corresponding to different targets in the same virtual screening experiment. We use protein kinases as

a test case because they share similar binding pockets that provide an excellent test system and because they have important clinical applications. Our ensemble docking algorithm performs well on ligand selectivity and virtual screening of large compound database. We also employ our docking algorithm on Gleevec to identify specificity and achieve good agreement with the reference study.

2.2 Materials and Methods

2.2.1 Ensemble docking algorithm to simultaneously address multiple targets

The main purpose of our ensemble algorithm is to introduce an additional parameter in docking calculations used to describe different protein structures. In traditional single-rigid-receptor docking software such as DOCK,²⁰ the receptor is fixed and the ligand is allowed to orient in the binding site. The binding energy score between the ligand and the receptor can be expressed as

$$E^S = E(x, y, z, \theta, \phi, \psi) \tag{2.1}$$

where x , y , and z represent the coordinates of the center of mass in the ligand, and θ , ϕ , and ψ denote the three Euler angles, respectively. These six parameters define the orientation of the ligand. The binding score is only determined by the orientation of the ligand. The optimization procedure of docking involves continuous adjustment $(x, y, z, \theta, \phi, \psi)$ until the calculated score converges to the minimum, corresponding to the predicted binding mode. Therefore, if a ligand needs to be docked into an

ensemble of M target proteins by using the standard docking approach, the docking procedure needs to be performed M times. In addition, the computational time will be M times that of the CPU for docking against a single target.

In order to improve the efficiency of docking against multiple targets, our ensemble docking algorithm adds the number of protein targets as the seventh dimension for scoring. Specifically, the ensemble algorithm reconsiders the scoring procedure as

$$E^M = E(x, y, z, \theta, \phi, \psi, m) \quad (2.2)$$

where m stands for the m -th protein of the target ensemble, an integer parameter ranging from 1 to M . Namely, in our ensemble docking algorithm, the binding score depends not only on the ligand orientation (determined by $x, y, z, \theta, \phi, \psi$) but also the specific target protein (denoted by m). Thus, by adjusting the parameter set $(x, y, z, \theta, \phi, \psi, m)$, our ensemble algorithm can simultaneously dock a ligand into the ensemble of multiple target proteins.

When only one target protein exists, i.e. $M = 1$, ensemble docking by eq (2.2) reverts to standard single-target docking by eq (2.1). Similar ensemble algorithms have been used to consider protein structural variations in ligand binding.^{21,22} It has been demonstrated that the computational time of our ensemble docking is comparable to that of single-target docking.

2.2.2 Scoring function

The scoring function that used in this study is ITScore, an accurate iterative knowledge-based scoring function developed by our group.^{23,24} The energy score between protein

and ligand E_{P-L} is obtained by summing up all protein(P)-ligand(L) atom pair interactions as

$$E_{P-L} = \sum_{P-L \text{ atom pair}} u_{ij}(r) \quad (2.3)$$

where $u_{ij}(r)$ is the pair potential of ITScore between the protein atom of type i and the ligand atom of type j at the atom pair distance r . Only intermolecular interactions are considered in ITScore. In this work, the scoring function was derived via an efficient iterative method using 2897 protein-ligand complexes extracted from the Protein Data Bank (PDB).²⁵ Its efficiency and versatility were demonstrated through binding mode identification, binding affinity prediction, and virtual database screening on diverse test sets of up to 200 protein-ligand complexes. Details of the theory of ITScore and related test studies were described in our previous studies.^{23,24} In the present work, the protein is treated as a rigid body; the ligand is allowed to be flexible in docking calculations. The ligand flexibility is represented by multiple conformers, which are generated by the OMEGA software (version 2.4.6. OpenEye Scientific Software, Santa Fe, NM. <http://www.eyesopen.com>.)^{26,27}

2.2.3 Construction of the reference protein

Our docking program uses the same matching algorithm as the DOCK 4.0 package.^{20,28} Therefore, similar to DOCK 4.0, a protein structure is required to guide the generation of initial ligand orientations around the binding site. However, our ensemble docking algorithm works on multiple target proteins, and it is neither possible nor reasonable to determine which target should be used as a representative of the ensemble. Therefore, a reference protein will be automatically constructed by the

docking program for generation of initial ligand orientations.

The principle for constructing the reference protein is the same as that in the previous work.²¹ Namely, the binding pocket should be as large as possible to provide sufficient sampling space for the ligand with the least change in the overall shape of the binding site. The details are described as follows.

First, by collecting and clustering the sphere points of the ensemble, we generated a set of reference sphere points.²¹ We calculated the distances between the reference sphere points and each residue of every target protein, with the distance defined as the minimum of the distances between every atom in the residue and any of the reference sphere points. Then, we performed multiple sequence alignment for multiple target proteins by using the structure-based sequence alignment software T-Coffee,²⁹ and randomly selected one of the multiple sequences to be the reference sequence of the reference protein. Then, the conformation of a residue was chosen as a representation of the corresponding residue of the reference sequence by satisfying the following two conditions: the residue of the selected conformation was aligned with the residue of the reference sequence within at least 3 Å from the reference sphere points, and all the selected residue conformations were finally combined into the reference protein.

It should be noted that the constructed reference protein is artificial. However, this is irrelevant because the reference protein only guides the generation of initial ligand orientations. The real target proteins, rather than the reference protein, will be used for score calculations and orientation optimization.

2.2.4 Docking algorithm

We wrote a Fortran docking program to implement our ensemble docking algorithm^{21,22} by using the ligand matching method of DOCK 4.0²⁸ and the ITScore scoring function,^{23,24} named MDock (© University of Missouri-Columbia, 2007). We re-trained the scoring function using 2897 protein-ligand complexes from the Protein Data Bank. The ligand flexibility is considered by docking multiple conformers of a ligand generated by the OMEGA software under default parameters. The maximum number of output conformers per ligand, MAXCONFS, was set to the recommended values (200).

The initial ligand orientations were generated by using the exhaustive matching algorithm by Ewing et al.,³⁰ which is guided by a reference protein of multiple targets. About 50 sphere points represented the binding site. The tolerance distance between ligand atoms and sphere points was set to 0.5 Å during matching. The ligand orientation that matched the most sphere points underwent further scoring evaluation, with the maximum number of evaluated orientations set to 1000, and the maximum minimization step set to 200. Equation (2.2) calculated ligand energy scores for our ensemble docking algorithm. By employing the grid-based energy calculation algorithm of DOCK,³¹ we improved the computational speed. The grid spacing was set to 0.3 Å, and trilinear interpolation was used to calculate energy scores. SIMPLEX optimized the binding energy of each ligand orientation.³² Because SIMPLEX is essentially a local optimization method, the top 20 orientations for each ligand were re-optimized according to each target protein as a way to reduce the influence of local minima. We saved the ligand binding scores of each target protein for sequent analysis. In short, we have M sets of energy scores for each ligand corresponding to

different target proteins of the ensemble.

2.2.5 Test data sets

The protein kinases obtained from the PdbBind (2015 version) database were selected as a test set because the experimental binding affinity data of the complexes were available in this database.^{33,34} We extracted 200 kinase complexes from a collection of 2401 hits in the PdbBind database by applying guidelines as follows: (1) only human gene protein kinases; (2) pH ranges from 6.8 to 7.5; (3) not binding with ATP, ADP, ANP or peptide; (4) X-ray structures rather than NMR models. These 200 protein kinase complexes belong to 14 different protein kinases (see Table 2.1) and were used to evaluate our docking algorithm and scoring function by performing traditional single-target docking (see Supporting Information). The 200 ligands served as the active compounds in the virtual screening test.

Each of the 14 protein kinases includes a certain number of complexes. Each protein kinase was represented by one protein structure with high resolution and no missing residue in its binding site. Thus, we obtained a total of 14 target proteins representing 14 protein kinases (see Table 2.1), which will be used to evaluate our ensemble docking algorithm.

The Protein Data Bank provided coordinates for all the complexes.²⁵ The multiProt software superimposed the 14 target proteins representing 14 protein kinases according to their binding sites.³⁵ Water molecules and metal ions were removed from the protein structures. Hydrogen atoms were not considered explicitly because of the feature of the ITScore scoring function we used in this study.^{23,24} T-Coffee software²⁹ aligned the sequences of 14 target proteins for construction of the reference

protein. SYBYL software assigned atom types to the proteins and ligands(Tripos, Inc.). During docking calculations, proteins were treated as rigid bodies and ligands were allowed to be flexible.

2.2.6 Database preparation

For a small-scale virtual screening test, 1000 commercially available compounds were randomly selected from the Available Chemical Directory (ACD, distributed by Molecular Design Ltd., San Leandro, CA) with the aid of the FILTER program (OpenEye Inc.) under default parameters . These 1000 molecules served as a set of inactive compounds for virtual database screening. The CONCORD program generated coordinates for the molecules.³⁶

Table 2.1: The 14 protein kinases for testing the ensemble docking algorithm. The PDB codes of corresponding ligand-bound complexes are listed in the right column with the ligand IDs in parentheses. The protein structure with bold font represents its corresponding protein kinase in ensemble docking calculations.

Kinases	Protein-ligand Complexes
P38	1A9U(SB2), 1BL6(SB6), 1BL7(SB4), 1BMK(SB5), 1DI9(MSQ), 1KV1(BMU), 1KV2(B96), 1M7Q (DQO), 1OUK(084), 1OUY(094), 1OVE(358), 1W7H(3IP), 1WBN(L09), 1WBO(2CH), 1WBS(LI2), 1WBT(WBT), 1WBV(LI3), 1WBW(LI4), 3FC1(52P), 3GC7(B45), 3HVC(GG5), 3ITZ(P66), 3NNU(EDB), 3NNV(437), 3NNW(EDD)
TGFR	1PY5(PY1), 1RW8(580), 2X7O(ZOP), 3FAA(55F), 3KCF (JZO), 4L3P(1UH), 4L52(1UL), 4L53(1UO), 4O91(NG2)
PDK1	1OKY (STU), 1OKZ(UCN), 1UU3(LY4), 1UU7(BI2), 1UU8(BI1), 1UVR(BI8), 1Z5M(LI8), 3QC4(MP7), 3RCJ(3RC), 3RWP(ABQ), 3RWQ(3RW), 3SC1(3S1)

CDK2	1H08(BWP), 1H01(FAL), 1H07(MFP), 1H1P(CMG), 1H1Q(2A6), 1H1R(6CP), 1H1S (4SP), 1OGU(ST8), 1OI9(N20), 1OIQ(HDU), 1OIR(HDY), 1OIT(HDT), 1OIU(N76), 1OIY(N41), 1P5E(TBS), 1URW(I1P), 1V1K(3FP), 1VYW(292), 1Y91(CT9), 2BKZ(SBC), 2BPM(529), 2C4G(514), 2C68(CT6), 2C69(CT8), 2C6I(DT1), 2C6K(DT2), 2C6L(DT4), 2C6M(DT5), 2C6O(4SP), 2CLX(F18), 2G9X(NU5), 2IW6(QQ2), 2IW8(4SP), 2IW9(4SP), 2R3F(SC8), 2R3G(SC9), 2R3H(SCE), 2R3I(SCF), 2R3J(SCJ), 2R3K(SCQ), 2R3L(SCW), 2R3M(SCX), 2R3N(SCZ), 2R3O(2SC), 2R3P(3SC), 2UZB(C75), 2UZD(C85), 2UZE(C95), 2UZL(C94), 2UZN(C96), 2UZO(C62), 2VV9(IM9), 2W05(FRT), 2W06(FRV), 2W17(I19), 2XMY(CDK), 2XNB(Y8L), 3DDP(RC8), 3DDQ(RRC), 3DOG(NNN), 3LFN(A27), 3LFS(A07), 3MY5(RFZ), 3PXQ(2AN), 3PXY(JWS), 3PXZ(JWS), 3PY0(SU9), 3PY1(SU9), 3S2P(PMU), 4BCK(T3E), 4BCM(T7Z), 4BCN(T9N), 4BCO(T6Q), 4BCP(T3C), 4RJ3(3QS)
AURKA	3P9J (P9J), 4DEA(NHI), 4DEB(NHJ), 4DED(NHU), 4UZD(QMN)
CHK1	2HOG (710), 2HXL(422), 2HXQ(373), 2HY0(306), 2QHM(7CS), 2QHN(582), 2R0U(M54), 2X8D(X8D), 3TKH(07S), 3TKI(S25)
CK2	3MB6 (01I), 3MB7(14I)

JNK3	1PMN (984), 2B1P(AIZ), 2EXC(JNK), 3G90(J72), 3G9L(J67), 3G9N(j88), 3OY1(589), 3V6R(CQQ), 3V6S(0F0), 4U79(3EL), 4WHZ(3NL)
JAK2	3E62 (5B1), 3E63(5B2), 3E64(5B3), 3JY9(JZH), 3KCK(3KC), 3KRR(DQX), 3Q32(J2I), 3RVG(17P), 3ZMM(F9J), 4BBE(3O4), 4BBF(O19), 4C61(LMM), 4D0W(VVQ), 4D0X(953)
HGF	1R0P (KSA), 3CE3(1FN), 3CTH(319), 3CTJ(320), 3F82(353), 3Q6W(Q6W), 3QTI(3QT), 3R7O(M61), 4EEV(L1X), 4GG5(0J3), 4GG7(0J8), 4IWD(1JC)
ERK2	1PME (577), 2OJG(19A), 2OJI(33A), 2OJJ(82A), 3I5Z(Z48), 3I60(E86), 4O6E(2SH), 4QTA(38Z)
GSK3 β	1Q3D (STU), 1Q3W(ATU), 1Q41(679), 3GB2(G3B), 3I4B(Z48), 3L1S(Z92), 4IQ6(IQ6)
ITK	3T9T (IAQ), 4HCT(18R), 4HCU(13L), 4HCV(13J), 4M0Y(M0Y), 4M0Z(M0Z), 4M14(QWS)
PAK1	4EQC (XR1), 4O0R(X4Z), 4O0T(2OL)

Table 2.2: A ranked list of 14 protein kinases according to the computed binding energies by ensemble docking experiments for seven typical inhibitors. The true targets of each inhibitor are colored in gray.

I17		MNY		KSA		TBS		STU		084		460	
Kinase	Score	Kinase	Score	Kinase	Score	Kinase	Score	Kinase	Score	Kinase	Score	Kinase	Score
CDK2	-51.6	CK2	-45.3	HGF	-66.8	CK2	-49.2	PDK1	-52.7	P38	-51.4	TGFR	-47.1
HGF	-49.9	JAK2	-43.5	PDK1	-51.5	CDK2	-49.0	CDK2	-48.5	JNK3	-47.3	JNK3	-46.0
CHK1	-47.2	CDK2	-41.9	CK2	-51.3	ERK2	-47.4	CHK1	-45.4	ERK2	-43.2	HGF	-43.7
JNK3	-45.6	HGF	-41.4	CHK1	-46.8	HGF	-45.6	GSK3 β	-45.0	AURKA	-43.2	CK2	-41.7
ERK2	-45.2	CHK1	-41.2	TGFR	-44.6	JNK3	-44.9	JNK3	-41.5	TGFR	-41.9	ERK2	-41.5
CK2	-43.9	JNK3	-40.3	JNK3	-44.5	JAK2	-44.2	HGF	40.8	CK2	-40.4	PDK1	-38.4
AURKA	-40.6	AURKA	-38.8	AURKA	-42.4	PDK1	-43.4	ERK2	-40.7	PAK1	-40.1	AURKA	-38.2
ITK	-39.6	PDK1	-37.7	GSK3 β	-41.5	AURKA	-42.7	CK2	-40.1	GSK3 β	-40.1	ITK	-38.2
JAK2	-39.1	TGFR	-37.7	ERK2	-40.6	CHK1	-42.2	AURKA	-38.8	PDK1	-40.0	CHK1	-37.0
PDK1	-39.1	ERK2	-36.3	ITK	-38.3	ITK	-41.9	P38	-34.4	CDK2	-40.0	GSK3 β	-34.3
P38	-39.1	ITK	-35.8	JAK2	-35.4	P38	-41.6	ITK	-30.7	CHK1	-40.0	P38	-33.4
GSK3 β	-39.0	P38	-35.2	PAK1	-35.3	PAK1	-41.6	PAK1	-30.3	HGF	-38.9	CDK2	-33.2
TGFR	-38.1	PAK1	-35.2	P38	-35.2	TGFR	-41.5	TGFR	-29.5	ITK	-38.1	PAK1	-32.5
PAK1	-35.9	GSK3 β	-35.2	CDK2	-35.1	GSK3 β	-41.1	JAK2	-28.9	JAK2	-34.2	JAK2	-32.5

2.3 Results

One major limitation of standard single-target docking against multiple targets is its lack of efficiency in a large database screening, especially for a large number of the targets. We have performed virtual database screening against multiple target proteins to evaluate our ensemble docking algorithm. The test was performed on an ensemble of 14 protein kinases (see Materials and Method). The results will be compared with those of standard single-target docking.

2.3.1 Evaluation of the dock algorithm and scoring function

Before docking against the ensemble of multiple target proteins, we first re-docked the 200 ligands into their bound protein structures (Table 1), referred as native docking, which served as validation of our docking algorithm and scoring function.

In the present work, the docking accuracy was evaluated by calculating the root-mean-square deviation (rmsd) between the docked ligand and the ligand in the crystal complex structure. The ligand binding mode was considered to be successfully predicted if the $\text{rmsd} < 2.0 \text{ \AA}$ for the top orientation.³⁷ This represents the default criterion unless otherwise specified. Figure 2.1 shows the success rates of our docking algorithm for 200 ligands with different criteria ranging from $\text{rmsd} < 1.0 \text{ \AA}$ to $\text{rmsd} < 3.0 \text{ \AA}$. From this figure, we can see that our docking algorithm yields high success rates at different rmsd criteria. Under the strictest criterion, $\text{rmsd} < 1.0 \text{ \AA}$, the lowest success rate achieves 74% . Under looser restrictions the success rate increases. The highest success rate, 83%, resulted from $\text{rmsd} < 3.0$. The default criterion of $\text{rmsd} < 2.0 \text{ \AA}$, yielded a success rate of 79%. The high success rates validated our docking algorithm and scoring function.

Figure 2.1: The success rates in binding mode predictions for 200 complexes at different criteria when the top conformation was considered: $\text{rmsd} < 1.0, 1.5, 2.0, 2.5$ and $3.0 \text{ \AA}$, respectively.

2.3.2 The ligand selectivity

Another task of the ensemble docking algorithm is to investigate the ligand selectivity against different target proteins. Ideally, a docking algorithm would give the same energy scores as experimental binding affinity for those targets of an inhibitor and worse scores for those non-targets. However, our scoring function was not scaled to

Figure 2.2: The 2D structures of selected protein kinase inhibitors for ligand selectivity analysis. The ligand IDs with their corresponding PDB codes are shown in the lower-left corner of each cell. This figure is drawn with MarvinSketch, ChemAxon Ltd., <http://www.chemaxon.com/>.

reproduce experimental binding affinities, even though it obtain a good correlation between the calculated energy scores and experimental binding affinities.^{23,24} Therefore, we used an alternative ranking method to investigate the selectivity of the ligands against different protein kinases.

The principle of the ranking method is that the true targets for an inhibitor should have a more favorable ranking than those non-targets in terms of calculated binding scores. For an inhibitor, the proteins were only divided into two simple classes of targets and non-targets according to the available experimental data. Table 2.2 shows the ranked list of different protein kinases according to their binding scores for seven typical inhibitors (Figure 2.2 and Figure 2.3A). From the table we can see that the true targets of the inhibitors indeed obtain better rankings than those of the non-targets. It is also notable that our ensemble docking algorithm identifies the targets of some inhibitors such as I17, MNY, 460 etc., even though the protein kinase ensemble did not include the bound protein structures of these inhibitors.

To further discuss our ensemble algorithm in ligand selectivity which is applicable for both non-specific and specific targets, we take an example of staurosporine (STU) and Gleevec (STI) to illustrate. For non-specific binding, staurosporine represent a well-studied class which has been used as a universal kinase inhibitor.^{38,39} The consistent conformations of protein kinases as well as the almost rigid structure with few rotatable bonds of staurosporine contribute to the similar binding sites conformations when staurosporine docking against protein kinase, including two important motifs (the GXGXXG motif and the DFG motif, see Figure 2.3A, 3C). Table 2.2 shows that STU inhibit at least 4 sub-families of protein kinases, and we obtained better rankings for these 4 targets from the 14 kinases in our ensemble docking.

Comparing with promiscuity of staurosporine, a potent and effective drug Gleevec (also known as Imatinib or STI-571, Figure 2.3D), has been utilized as a primary clinical drug for treating certain cancers, such as chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GISTs).^{40,41} Gleevec exhibits an effective auto-inhibitory function specifically against c-Kit and Abl protein tyrosine kinase. In the tumor cell, tyrosine kinases are constitutively active, thus Gleevec is used to block kinase in an inactive conformation to preventing the phosphorylation that would benefit the cancerous cell. However, the reason why Gleevec is a specific and potent inhibitor has been controversial.⁴²⁻⁴⁴ Recently, Agafonov et al.⁴⁵ experimentally identified that Gleevec specifically inhibitor of Abl rather than Src because of the induced-fit conformational change. They used NMR and fluorescence to directly detect Gleevec binding and gave a convinced explanation in their paper. In Figure 2.3D, we made an alignment of the 4 tyrosine kinase complexes (PDB ID as shown in Table 2.3) and noted by different color to focus on the conformational change after Gleevec binding to kinases. In the Figure 2.3D, Gleevec bind between α C-helix and the activation loop (A-loop) with Asp-Phe-Gly (DFG) motif, as the phosphate-binding loop (P-loop) which is responsible for stabilizing Gleevec binding.⁴³ Although these 4 tyrosine kinases are homologous, they exhibit distinct conformations of the binding sites, which result in the binding specificity of Gleevec.

Our ensemble docking results on binding score of Gleevec with protein kinase yielding -76.8 and -72.8 for c-Kit and Abl, respectively. However, the energy scores are only -65.7 and -64.9 for Lck and c-Src, respectively (see Table 2.3). The energy scores exhibit sensitivity when Gleevec binding to Abl and c-Kit kinases, even including Lck and c-Src which are closely homologous tyrosine kinases of target proteins. Thus, the

present results support the conclusions about effectiveness of our ensemble docking algorithm.

To quantitatively evaluate the efficiency of our ensemble docking algorithm in discriminating targets from non-targets, we employed a similar measure to that included in previous work done by our group:²¹

$$EF = 100\% \times \frac{\langle \text{Rank}(\text{nontarget}) \rangle - \langle \text{Rank}(\text{target}) \rangle + N_{\text{proteins}}/2}{N_{\text{proteins}}} \quad (2.4)$$

where N_{proteins} ($= 14$, here) is the number of the proteins in the ensemble including both non-targets and targets, and $\langle \text{Rank}(\text{nontarget}) \rangle$ and $\langle \text{Rank}(\text{target}) \rangle$ denote the average ranking of the non-target and target proteins, respectively. The value of the efficiency factor EF can vary from 0% to 100%. If all the targets rank better than the non-targets, the efficiency factor EF will be 100%, indicating the complete agreement between the predictions and the experimental findings. In contrast, if all the non-targets rank better than the targets, the efficiency factor EF will be 0%. An equal distribution of the targets in the ranked list of proteins gives an efficiency factor of 50%, representing random selection. The higher the EF value, the better the efficiency of recovering known targets. Figure 2.4 gives the efficiency factors for all the ligands in identifying the true protein target by the ensemble docking algorithm. It can be seen from the figure that most of the ligands resulted in an efficiency factor of $> 50\%$ with an average efficiency of 74%, indicating favorable rank for the true target over the nontargets. The overall good results demonstrate effectiveness of our ensemble algorithm in investigating the selectivity of inhibitors against multiple target proteins.

Table 2.3: The energy scores of Gleevec binding to 4 homologous tyrosine kinases and to the 14 protein kinases in our ensemble docking test set. The true targets are colored gray.

Kinase	Score	Kinase	Score
c-Kit(1T46)	-76.8	CHK1	-50.3
Abl(1IEP)	-72.8	AURKA	-50.2
Lck(2PL0)	-65.7	GSK3 β	-49.0
c-Src(2OIQ)	-64.9	TGFR	-48.9
JNK3	-53.9	ERK2	-47.7
CDK2	-52.0	JAK2	-47.6
ITK	-51.8	P38	-47.3
HGF	-51.6	PDK1	-47.3
CK2	-51.2	PAK1	-46.4

2.3.3 Virtual Database Screening

A widely-used index for success in virtual screening is the enrichment factor, defined as the accumulated rate of known inhibitors identified in a certain top percentage of the ranked database. As described in the Materials and Methods section, our ensemble docking algorithm can give the binding energy scores of a ligand for each

Figure 2.3: (A) The 2D structures of staurosporine. (B) The 2D structures of Gleevec. (C) The binding pocket conformations of PDK1 kinase (sea green) and GSK3 β (forest green) bound with staurosporine. (D) Superimposition of the conformation of Gleevec bound to the Tyrosine Kinase domains of Abl (red), c-Kit (orange), Lck (green), and c-Src (blue). Gleevec is shown in the ball & stick representation.

of the targets in a docking calculation. Namely, each target protein will have a set of binding energy scores for all the docked ligands. Therefore, we can obtain multiple enrichment curves corresponding to multiple target proteins in only one ensemble docking calculation. However, one question remains: how does the accuracy of the docking results differ from that of the ensemble docking algorithm? To answer this question, we compared the enrichment data from the ensemble docking algorithm with those from the standard single-target docking method. Figure 2.5 compares the enrichment data between ensemble docking of multiple targets and standard single-target docking on five typical target proteins with at least seven known ligands (Table 2.1). It can be seen from the figure that ensemble docking performs comparably well to standard single-target docking for all the target proteins, indicating that our ensemble docking algorithm efficiently identifies known ligands.

2.3.4 Computational efficiency

In addition to docking accuracy, another advantage of our ensemble docking algorithm is its superior computational efficiency. As demonstrated previously, the run time of ensemble docking algorithm is comparable to that of single-structure docking, though the ensemble algorithm addresses multiple protein structures.^{21,22} In the present work, the ensemble docking algorithm only needs on average 2.8 seconds to place and optimize a ligand conformer in the binding site, another result comparable to that of standard single-target docking (2.4 seconds).

Figure 2.4: The efficient factors of the ligands in discriminating the true targets from the non-targets predicted by the ensemble docking algorithm.

Figure 2.5: Comparisons of the enrichments between ensemble docking and standard sequential docking on five typical target proteins. The legend applies to all the panels.

2.4 Discussion and Conclusion

Simultaneously docking against multiple target proteins is essential because compounds often inhibit multiple proteins of the same family which results in a challenging issue of ligand specificity.^{16–18,46–50} Our present ensemble docking algorithm addresses this issue by simultaneously docking against multiple targets. The virtual screening test on 14 protein kinases demonstrates that our ensemble docking algorithm is comparable of simultaneously addressing multiple target proteins, and achieved comparable performances to the standard single-target docking method without a significant increase in the computational time.

There is a similar “in situ cross-docking” approach has been presented and tested on several ensembles of up to six targets by Sottriffer and Dramburg, in which the ligands can be simultaneously docked into one united grid consisting of all the binding sites of multiple targets.¹⁸ The work closely resembles our algorithm, however, there are major differences. In the approach by Sottriffer and Dramburg,¹⁸ the binding sites of multiple target proteins are separate from each other in the united grid. Therefore, if a ligand has fairly favorable scores against more than one target, the convergence toward to the native, global optimum will be slow. This may limit the applicability of their approach for the protein ensemble of very similar targets or different conformations of the same protein.¹⁸ Moreover, because the grids from different targets are joined one by one, the united grid will boast a much larger volume than the grid of single target. Therefore, the searching efficiency for a ligand binding mode will be considerably lower as a result of the larger docking available docking space.

Unlike the “in situ cross-docking” approach, our ensemble docking algorithm

aligns the binding sites of multiple target proteins so that the united grid has almost the same volume as that of single-target docking. Accordingly, our ensemble algorithm is computationally efficient with a run time comparable to that of single-target docking. The ensemble algorithm can also be applied to different proteins for identifying potential targets of an inhibitor and also to different conformations of the same protein for considering protein flexibility regardless of whether the protein structures are similar or not. In addition, our ensemble docking also assigns ligand binding energy scores for each of the targets so that one can investigate the selectivity of a ligand.

Despite the present success, our ensemble docking algorithm contains limitations, Such as the energy optimization method mentioned in the previous work.²¹ In principle, our ensemble algorithm can simultaneously address unlimited target proteins. However, the energy landscape of the target ensemble will be more rugged with the more proteins, which will, in turn, lower the searching efficiency of an energy optimization method. In this work, we used the same optimization method, SIMPLEX³² as the DOCK 4.0 software.^{20,28} Thus, the ligand may sometimes be trapped in a local minimum because SIMPLEX is essentially a local minimization method.³² As a result, occasional wrong predictions often originate from the optimization method rather than from the ensemble algorithm itself. One solution is to use a global minimization method, which would not be affected by local minima. However, the global minimization method achieves its efficiency at the cost of consumed time. Therefore, despite the fast and accurate results obtained by the present work, it is necessary to develop an appropriate optimization method with a good balance between speed and efficiency when the number of proteins increased.

In summary, we have presented an efficient ensemble docking algorithm to simultaneously address multiple target proteins. The algorithm was validated by virtual screening against 14 human protein kinases. The ensemble docking algorithm performed comparably to standard single-target docking without a significant increase in run time. We expect the algorithm to be useful for the investigation of the ligand selectivity in structure-based drug design.

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Chapter 3

EDockMS: An Efficient Docking Platform for Multiple Target Screening

Abstract

Predicting the most likely protein target(s) for a given ligand from thousands of protein candidates is challenging yet important for finding novel targets to combat diseases such as cancer and bacterial infections. Recently, we have built a web server for Efficient Docking-based Multiple target Screening (EDockMS). EDockMS is a user-friendly ligand-protein docking server for predicting potential therapeutic targets for a query compound of interest. We have also constructed a protein database of 537 targets comprising 3268 protein-ligand complex structures with 3349 binding pockets, providing each target with searchable disease-related information. Our achieved success rates and computational efficiency showed that the server is capable of efficiently predicting the protein target(s), their structures complexed with the

query ligand, and searchable disease information about the targets. EDockMS has potentially valuable application for therapeutic intervention.

3.1 Introduction

Drug molecules often produce not only valuable therapeutic effects but also side effects (i.e. off-target effects) due to their interactions with multiple targets. Although off-target effects are predominantly undesirable, some of them can have potential applications in the treatment of complex diseases such as cancers.¹ It is now well-known that the clinical effects of a drug molecule are often the result of its interactions with multiple targets rather than with one target, which has led to a shift in the focus of the multi-target paradigm in both experimental and computational approaches.^{2,3} For example, in the emerging field of polypharmacology, the off-target binding property of an FDA-approved drug is utilized for drug repositioning, which lowers the development costs and reduces the risks of reusing this drug on new purposes.⁴⁻⁶ Consequently, it is highly desired to develop methods for discovering multiple targets.

Docking-based Inverse Virtual Screening (IVS) utilizes a molecular docking algorithm to virtually screen large libraries of protein targets to discover possible side effects and toxicities of new drugs or drug candidates.^{7,8} In contrast to the costly and time-consuming biological experiments, IVS allows for a more efficient framework in identifying potential receptor targets for a compound. The current major challenge in computational target prediction lies in the accuracy and efficiency of the scoring functions in the docking-based methods, which need to be substantially improved

Recently, we developed a web server, referred to as EDockMS, based on the latest version of our MDock package (<http://zoulab.dalton.missouri.edu/mdock.htm>) for efficient multiple target screening. The web server uses a statistical potential-based scoring function, ITScore,^{9,10} which was derived based on an statistical mechanics-based iterative method. ITScore is computationally efficient for large-scale docking.^{7,11,12} Moreover, we constructed a protein target database, referred to as MDTD, as part of the EDockMS server. Specifically, we built MDTD based on two databases, sc-PDB^{13,14} and Therapeutic Target Database (TTD).¹⁵ The sc-PDB database provides structure files (e.g., separated protein and ligand files and the binding site information) suitable for docking-based computational drug design, and TTD allows therapeutic information to be trackable. However, there is no connection between these two databases. MDTD integrates these two databases, resulting in a comprehensive and accurate database which contains both the structural and disease-relevant information for each protein target.

3.2 Implementation

The server construction includes three major components: interface, MDTD preparation, and docking/analysis.

Interface

The front-end web interface is written in HTML and python. The server hardware consists of shared resources with 24 Intel Xeon cores [Intel(R) Xeon(R) CPU E5-2650 v3 @ 2.30GHz].

MDTD preparation

We extracted PDB codes¹⁶ using the UniProt IDs¹⁷ of the targets annotated in TTD, then mapped the PDB codes to those in sc-PDB so that MDTD are finalized with the target structures and disease-relevant details. In the current version, we included 3268 protein-ligand complexes (with 3349 distinct binding sites) associated with 537 target entries which can be tracked with annotated TTD IDs for biochemical information (see Supplementary material).

Figure 3.1: Schematic representation that highlights the back-end procedures in EDockMS.

Docking and results analyzation

EDockMS uses a back-end docking protocol MDock for IVS, via a ligand-protein inverse docking strategy.^{7,8,12} Figure 3.1 illustrates the operation of EDockMS. Specif-

ically, for each submitted query ligand, we use OMEGA (Version 2.5.1. OpenEye Scientific Software, Santa Fe, NM. <http://www.eyesopen.com>.) to generate conformations for flexible-ligand docking with the default parameter for maxconfs (i.e., 200).¹⁸ Each conformer will be docked onto all the protein structures in MDTD using our in-house docking protocol MDock. MDock then ranks the generated protein-ligand structures with its scoring function, ITScore, keeping only the structure with the best (i.e., most negative) score for each target. The output of each job includes a list of the top 50 protein targets (with disease-related information), and the binding modes for the top 10 targets.

3.3 Discussion and perspectives

The docking approach implemented in EDockMS was applied to several studies.^{7,11,12} Importantly, oxidosqualene cyclase was identified as the targets of PRIMA-1 in our previous work.⁷ We further analyzed the performance of EDockMS using an IVS benchmark.¹⁹ For the 72 drugs in the benchmark, we removed the drugs whose protein targets were absent in the MDTD database. For the remaining drugs with similar structures, we selected the first one in each cluster listed in Table 3 of ref. 19. The final set contained 47 drug ligands (see Supplementary Information). The results showed that EDockMS was able to predict the first true target in 38 out of 47 cases (81%) among the top 10% of the dataset consisting of 537 targets. Moreover, the novelty of EDockMS is summarized as follows.

First, EDockMS is user-friendly. Many docking algorithms require users to set up the parameters before docking, which is tedious especially for novices. For job

submission in EDockMS, only a mol2 file of a ligand structure is required. Once a job is submitted successfully, the status can be checked from the Queue page. Meanwhile, a user has the option to provide an e-mail address, which can be used for notifications when jobs are completed. The results are compressed in a tar file, which can be downloaded directly.

Second, EDockMS is highly efficient, which is a significant feature because docking-based IVS is computationally costly. In our server, typical runs take 1-4 hours. For example, running IVS for progesterone takes about one hour.

Last, the existing docking web-servers do not provide disease-associated information. With the construction of MDTD, EDockMS provides trackable disease-relevant information for the predicted protein targets, a valuable feature for the further lead optimization.

In conclusion, we have presented the EDockMS server for docking-based IVS with disease-relevant information. The predictions of the top 50 protein targets and the top 10 binding modes are provided via a user-friendly web interface. The benchmarking evaluation results have shown that EDockMS can rapidly identify targets for a query ligand with a high success rate. Future developments include 1) adding the ensemble docking mode to account for protein flexibility, and 2) further classifying the MDTD database for users to focus on a subset of protein targets of interest.

3.4 ACKNOWLEDGEMENT

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Chapter 4

Predicting Protein Ligand Binding Modes for CELPP and GC3: Workflows and Insight

The work in this chapter has been published in Methods in J Comput Aided Mol Des.¹

Abstract

Drug Design Data Resource (D3R) continues to release valuable benchmarking datasets to promote improvement and development of computational methods for new drug discovery. We have developed several methods for protein-ligand binding mode prediction during the participation in the D3R challenges. In the present study, these methods were integrated, automated, and systematically tested using the large-scale data from Continuous Evaluation of Ligand Pose Prediction (CELPP) and a subset of Grand challenge 3 (GC3). The results show that current molecular docking methods

¹X. Xu[†], Z. Ma[†], R. Duan[†], X. Zou. Predicting proteinligand binding modes for CELPP and GC3: workflows and insight, Scoring and in Silico Screening. J Comput Aided Mol Des, 2019 ([†] Equally contributed).

benefit from the increasing number of protein-ligand complex structures deposited in Protein Data Bank. Using an appropriate protein structure for docking significantly improves the success rate of the binding mode prediction. The results of our template-based method and docking method are compared and discussed. Our future direction include the combination of these two methods for binding mode prediction.

4.1 Introduction

In silico methods for protein-ligand complex structure prediction (e.g. molecular docking) play an increasingly important role in modern drug discovery and development.¹⁻³ Although great successes have been achieved, current methods are facing several challenges such as the protein flexibility problem and the scoring function problem.^{4,5} To promote the improvement of the existing methods and the development of new approaches, Drug Design Data Resource (D3R, (<https://www.drugdesigndata.org>), starting from 2015) continues to release valuable benchmarking datasets containing experimentally determined binding structures and affinity data.⁶⁻⁸ Recently, the D3R Team has developed Continuous Evaluation of Ligand Pose Prediction (CELPP), an automated workflow to process and evaluate the challenge of protein-ligand binding mode prediction. CELPP is held weekly, in which the targets are prepared based on pre-released data from the Protein Data Bank (PDB)⁹ (including the ligands and the sequence of their target proteins). In addition to CELPP, D3R organizes one or two rounds of Grand Challenge (GC) every year for both binding mode and binding affinity predictions. In the latest Grand Challenge 3, D3R released a subset of 24 compounds targeting the human Cathepsin S (CatS) for binding mode

prediction.

Through the participation in the D3R and its previous predecessor, Community Structure-Activity Resource (CSAR, (<http://www.csardock.org>), 2010-2014),¹⁰⁻¹³ we developed several novel strategies for predicting protein-ligand complex structures.¹⁴⁻²⁰ During the CSAR challenges, we improved our in-house scoring function, ITScore2, an efficient statistical potential-based scoring function derived by using a statistical mechanics-based iterative method based on a training set of experimentally determined proteinligand complex structures [15]. During the GC 2015, we improved both binding mode and binding affinity predictions of molecular docking by using the protein structures that contain the co-bound ligands sharing high molecular similarities with the query ligands.¹⁴ A system-specific scoring function was also introduced in this round of GC. Then, in GC2, we developed a template-based approach using known protein-ligand complex structures as templates.¹⁵ These methods use known protein-ligand complex structures in different ways to improve the performance of binding mode prediction, and benefit from the increasing number of experimentally determined protein-ligand complex structures deposited in the PDB.

In this study, we thoroughly analyzed the binding mode prediction results from our recent participation in the D3R challenges, CELPP and GC3. For CELPP, we predicted more than one thousand targets in 42 CELPP weeks (from week22_2017 to week11_2018). For each target, a molecular docking approach was performed using up to 6 protein structures. Five of these protein structures were provided by CELPP. The 6th protein structure was selected from all the known experimental structures of the same protein by using a 3D molecular similarity calculation method. The docking results showed that using a proper protein structure (e.g., containing a co-bound

ligand that shares a high molecular similarity with the query ligand) significantly improved the performance of binding mode prediction for the docking method. In addition to molecular docking, a template-based method was also used and the results were compared with the docking results. The analysis showed that the performance of the template-based method highly depends on the molecular similarities between the co-bound ligands in the templates and the query ligands. Similar results were observed for the GC3 targets (CatS subset). Through systematic validation on the large-scale data from D3R (CELPP and GC), we continue to improve our protein-ligand complex structure prediction methods (both docking-based and template-based), which would become a useful, user-friendly tool for computer-aided drug design (CADD) and for biologists’ use.

4.2 Materials and Methods

4.2.1 The query protein-ligand complexes

The CELPP targets

CELPP releases 20-100 upcoming protein-ligand complex targets every Saturday (12:01 am), and the participants are required to submit predicted binding modes by the following Tuesday (2:59 pm). Experimental structures will be released in the Protein Data Bank on Wednesday (i.e., the day after the submission deadline). For each target, one query ligand and up to five candidate protein structures are provided. These five protein structures are named as LMCSS, SMCSS, hiResHolo, hiResApo, and hiTanimoto. LMCSS stands for the structure that contains the ligand with the

largest maximum common substructure to the query ligand. In contrast, SMCSS represents the structure that contains the ligand with the smallest maximum common substructure to the query ligand. hiResHolo denotes the highest-resolution, ligand-bound protein structure, and hiResApo marks the highest-resolution, apo protein structure. Similar to LMCSS, hiTanimoto corresponds to the structure that contains a ligand sharing the highest similarity (calculated by Tanimoto coefficient) with the query ligand. In addition, the participants are allowed to submit predictions based on other protein structures. For each protein structure, participants are asked to submit only one predicted binding mode. More details regarding the CELPP targets are available at the website <https://drugdesigndata.org/about/celpp>.

In this study, we analyzed our predictions based on the 1472 targets that we submitted from week22_2017 to week11_2018. A total of 1636 targets were released during these 42 weeks. Failed submissions were mainly due to the uncommon atoms (such as As) in the query ligands. In addition, for 295 cases out of these 1636 targets, their LMCSS or hiTanimoto protein structures contain co-bound ligands that were identical to the query ligands. These 295 targets were therefore discarded in the analysis of this study.

The GC3 targets

Grand Challenge 3 released a subset for proteinligand binding mode prediction. This subset contains 24 query ligands targeting the human Cathepsin S (CatS). The organizers provided the SMILES strings of the query ligands, and the participants were free to use any structures of CatS. For each query ligand, the participants were allowed to submit up to 5 predicted binding modes.

4.2.2 Overview of our binding mode prediction methods

For CELPP

For the protein structures provided by CELPP, we used a docking strategy that was developed during previous D3R challenges. Briefly, a modified version of AutoDock Vina^{16,21} was used to generate up to 500 ligand binding modes on a target protein. Then, these putative binding modes were re-ranked using our in-house scoring function, ITScore2.¹⁶ Finally, the top binding mode based on each protein structure was submitted for each target.

ITScore2 was a statistical-potential-based scoring function. It was derived using an iterative method that circumvents the reference state problem by improving atom-pair potentials iteratively through the comparison of the calculated ($g_{ij}^k(r)$) and the experimental pair distribution functions ($g_{ij}^*(r)$) until the native complex structures in the training database can be correctly discriminated from decoy structures. A detailed description of the ITScore2 method is available in the references.^{16,22,23}

Moreover, in addition to the predictions based on the protein structures provided by CELPP, we also submitted a prediction based on our own selected protein structure for each target. This protein structure was selected based on our calculated 3D molecular similarity between the co-bound ligand and the query ligand. Namely, the protein structure that contains a co-bound ligand sharing the highest 3D molecular similarity with the query ligand according to our calculation was used for binding mode prediction.

For GC3

Two approaches were used in binding mode prediction for GC3. The first approach was the docking approach that was used for CELPP. The protein structure that contains a co-bound ligand sharing the highest 3D molecular similarity with the query ligand according to our calculation was used for docking. The second approach was a template-based method. Briefly, the query ligand was superimposed onto the ligands in the known protein-ligand complexes, and the protein-query ligand complexes were ranked using the scoring function ITScore2. The top 5 models were further refined by the minimization step in molecular dynamics (MD) simulation.

4.2.3 Protein preparation

For CELPP

In addition to the protein structures provided by CELPP, we also selected a protein structure from the PDB for each target, referred to as the user-specified protein structure. Specifically, the program Protein-Protein BLAST (v2.6.0+) ^{24,25} was employed to search protein structures deposited in the PDB using the protein sequence provided by CELPP. The cutoff was set to 90% for both the sequence identity and the sequence coverage. The apo structures (i.e., the structures without co-bound ligands) were discarded. If there were more than one PDB structure that contain the same ligand, the structure with the lowest R-free value was kept. Then, 3D molecular similarities between the co-bound ligands and the query ligand were calculated by the program SHAFTS. ²⁶ The PDB structure that contained the ligand sharing the highest similarity with the query ligand was selected for docking. The whole process

was automatically performed for a given target.

For GC3

For the Grand Challenge, we manually checked the CatS structures in PDB, and found 12 PDB entries of human CatS containing different co-bound ligands. These PDB entries (2F1G, 2G7Y, 2H7J, 2R9M, 2R9O, 3IEJ, 3KWN, 3MPE, 3MPF, 3N3G, 4P6E, and 4P6G) were used for both docking method and template-based method.

4.2.4 Ligand preparation and similarity calculation

Up to 500 3D conformers were generated for each query ligand, using the program OMEGA (version 2.5.1.4, OpenEye Scientific Software, Santa Fe, NM. <http://www.eyesopen.com>)^{27,28} based on the SMILES string provided by CELPP or GC3. Only one conformer for each query ligand was necessary for molecular docking, because the ligand was treated as a flexible molecule in docking. The multiple ligand conformers were for the calculation of the 3D molecular similarities between a query ligand and the co-bound ligands in the known proteinligand complex structures, using the program SHAFTS.²⁶ The similarity score calculated by SHAFTS consists of a ShapeScore (i.e., shape-densities overlap) and a FeatureScore (i.e., pharmacophore feature fit values); both scores are normalized to a range of [0, 1], and the resulting HybridScore (i.e., the sum of ShapeScore and FeatureScore) is scaled to [0, 2], with 0 representing no similarity and 2 corresponding to the same ligand.

4.2.5 Binding mode prediction

The docking approach

AutoDock Vina²¹ was employed for sampling putative binding modes of a query ligand on a target protein. For the CELPP targets, we used the binding site center provided by CELPP as the center of the search box. The size of the cubic search box depended on the size of the query ligand. Specifically, the edge length of the cubic box was set to $\max[2 \times \text{maxL}, 22.5 \text{ \AA}]$, in which maxL was the maximum length of the query ligand structure in all dimensions. For the GC3 targets, the geometric center of the co-bound ligand was used as the center of the search box. The size of the search box was set to 30 Å. For both CELPP targets and GC3 targets, the protein structures were treated as rigid bodies and single bonds of the ligands were considered to be flexible. The exhaustiveness value was increased to 30 (default=8) to ensure exhaustive sampling. The original Vina source code was modified to set the maximum of output modes to 500 (default=20). The output modes were then re-ranked using an in-house scoring function ITScore2. ITScore2 is a knowledge-based atomic pairwise scoring function that was derived based on the known proteinligand complex structures (a refined set of PDBbind 2012 containing 2897 proteinligand complexes^{29,30}) and the statistical mechanics-based iterative method^{16,22,23}. Finally, the top mode was submitted for each CELPP target protein structure, and the top 5 modes were submitted for each GC3 target.

The template-based approach

During Grand Challenge 2, we developed a template-based approach for protein-ligand complex structure prediction. The details of the approach are described in Reference.¹⁵ Briefly, molecular similarities of a query ligand with the co-bound ligands in the known complex structures were calculated using the program SHAFTS. Then, the top 5 PDB entries that had the best similarity scores with the query ligand were chosen as the templates. For each template, the query ligand was superimposed onto the ligand using the program SHAFTS. Finally, the protein-query ligand complex was refined using the minimization step of the MD simulation.

A drawback of this template-based approach is that severe clashes/overlaps between protein atoms and ligand atoms were found in the superimposition step (i.e., before minimization) in some cases, particularly in the cases in which only low-quality templates were available. Even MD minimization were unable to remove the clashes. To avoid or reduce these clashes/overlaps, we introduced a re-scoring step after the superimposition step in GC3. Specifically, instead of using the top 5 best PDB entries as the templates, we superimposed each conformer of the query ligand onto all the co-bound ligands in the known complex structures. Then, all the generated protein-query ligand complex structures were ranked using their scores calculated by the scoring function ITScore2. If the ligand RMSD of the two models was less than 2.0 Å, the model with a more negative score was kept. Finally, the top 5 models were refined using the minimization step of the MD simulation.

4.3 Results and Discussion

To evaluate the quality of predicted binding modes, we calculated root-mean-square deviations (RMSDs) between the predicted ligand binding modes and the modes in the released experimental complex structures. Specifically, the protein structures were matched using the MatchMaker tool of UCSF Chimera,³¹ and the RMSDs of the heavy atoms in the ligands were calculated using the maximum common substructure (MCS) functionality of the OEChem Python toolkit (version 2.5.1.4, OpenEye Scientific Software, Santa Fe, NM. <http://www.eyesopen.com>).^{27,28} The MCS functionality can handle ligand atom renumbering and account for compound symmetries that are often involved in ligand superimposition.

4.3.1 CELPP

For each target, CELPP provided up to 5 protein structures, which were named as candidate protein structures. In addition to the predictions based on these candidate protein structures, we also submitted a prediction based on our own selected protein structure (referred to as the user-specified protein structure) for each target. The prediction results for using the CELPP-provided protein structures and the user-specified protein structures are reported as follows.

The CELPP-provided protein structures

CELPP provided the binding site location for each target. However, for a number of cases, the provided binding site locations were far from those in the released experimental complex structures. Here, we analyzed only the cases in which the binding

site information was correctly provided. Namely, the targets were discarded if the distance between the geometry centers of the CELPP binding site and the real binding site were larger than 10 Å. The number of the targets that were kept for each type of protein structures are reported in Table 4.1.

Table 4.1: The results of binding mode prediction for the CELPP targets

Protein Structure	Number of Targets	Top 1	Best in Top 5		Best in All		
		Median RMSD (Å)	Median RMSD (Å)	Median RMSD (Å)	Median RMSD (Å)	Median RMSD (Å)	Median RMSD (Å)
Bound	969	4.3 (0.3)	4.9 (0.1)	2.3 (0.1)	3.3 (0.1)	1.2 (0.0)	1.5 (0.0)
LMCSS	969	4.6 (0.2)	5.1 (0.1)	2.6 (0.1)	3.5 (0.1)	1.5 (0.0)	1.9 (0.0)
SMCSS	969	5.7 (0.2)	6.0 (0.1)	3.5 (0.1)	4.2 (0.1)	1.9 (0.1)	2.4 (0.1)
hiResApo	608	6.4 (0.2)	6.5 (0.1)	4.4 (0.2)	4.8 (0.1)	2.2 (0.1)	2.8 (0.1)
hiResHolo	969	5.6 (0.2)	5.8 (0.1)	3.5 (0.1)	4.2 (0.1)	1.8 (0.1)	2.4 (0.1)
hiTanimoto	969	4.9 (0.2)	5.2 (0.1)	2.6 (0.1)	3.5 (0.1)	1.5 (0.0)	1.9 (0.0)
hiSHAFTS	875	4.7 (0.2)	5.3 (0.1)	2.7 (0.1)	3.6 (0.1)	1.6 (0.1)	1.9 (0.0)

The first row (“Bound”) lists the results of using the bound protein structures for docking. The last row (hiSHAFTS) gives the results from the use of the user-specified protein structures (i.e., the protein structure that contains the ligand with the largest HybridScore to the query ligand) for docking, and the other five rows show the results from the use of the candidate protein structures provided by CELPP. The error of each value was estimated using the bootstrap method in which 1000 replicates were used, and was reported in parentheses.^{32,33}

Figure 4.1 shows the results of binding mode prediction using different RMSD values as the thresholds to define successful predictions. The vertical dashed black lines correspond to a commonly-used threshold value of 2.0 . In addition to the docking results using CELPP-provided protein structures, we also present the results of docking using bound protein structures (i.e. the protein structures extracted from the experimental complex structures) for reference. In bound dockings, ligand structures were generated from the SMILES strings. Figure 1a shows the results when the top model was considered for each protein structure. Using the threshold of 2.0 as an example, bound docking yielded the highest success rate 30.5%, as expected. The LMCSS protein structures (which contain similar ligands with the query ligands) resulted in a significantly higher success rate (23.2%) than the SMCSS protein structures (which contain dissimilar ligands with the query ligands) for which the success rate was 13.6%. The highest resolution ligand-bound candidate protein structures (hiResHolo) yielded slightly better docking performance (a success rate of 14.8%) than SMCSS, but resulted in significantly worse performance than LMCSS. When the hiResApo protein structures (i.e., the highest-resolution unbound protein structures) were used, the success rate was 8.1%, which was lower than all the other cases. Similar to LMCSS, the hiTanimoto protein structures contained similar ligands with the query ligands and achieved comparable performances with LMCSS. The same conclusion can be obtained using different threshold values (see Fig. 4.1).

Figure 4.1: The results of binding mode prediction for CELPP using the bound protein structures and the candidate protein structures provided by CELPP for docking. Different RMSD values were used as the thresholds that defined successful predictions. (A) The success rate when only the top predicted model was considered for each protein structure. (B) The success rate when top 5 models were considered for each protein structure. (C) The success rate when all the models were considered for each protein structure.

Figure 4.1B presents the results when top 5 models were considered for each protein structure. Dramatically higher success rates were observed for all types of protein structures, in comparison with those when only the top model was considered. Specifically, when 2.0 Å was used as the threshold, the success rates of dockings with the bound, LMCSS, SMCSS, hiResHolo, hiResApo, and hiTanimoto protein structures increased to 46.3%, 40.4%, 28.5%, 30.4%, 17.7%, and 40.6%, respectively. Lower success rates observed in Fig. 4.1a (considering only the top model) were mainly due to the inaccuracy of the current scoring function (ITScore2).

In addition to using the in-house scoring function, ITScore2, we also analyzed the performance of the Vina Score. The results are presented in the Supplementary Materials (Fig. S2). Vina Score achieved similar success rates as ITScore2 for each type of protein structures when the top model was considered. However, ITScore2

yielded significantly better performance than Vina Score when top 5 models were considered. In addition, similar to what was observed for ITScore2, the bound docking yielded the highest success rate. Dockings with the protein structures containing similar ligands with the query ligands (LMCSS or hiTanimoto) achieved significantly higher success rates than dockings with other types of protein structures (SMCSS, hiResHolo, or hiResApo).

Figure 4.1C shows the sampling results for the use of each type of protein structures for docking. Using 2.0 Å as the threshold, bound docking yielded the highest success rate (80.4%), similar to the results in Fig. 1a, b. Possible reasons for the failures of sampling in some targets could be the non-exhaustive sampling strategy used in Vina and the ignorance of the effects of crystal waters or co-factors during docking. For the cases using the CELPP-provided protein structures for docking, LMCSS or hiTanimoto protein structures resulted in significantly higher success rates than other CELPP-provided protein structures. Specifically, when 2.0 Å was used as the threshold, the success rates of dockings with the LMCSS, SMCSS, hiResHolo, hiResApo, and hiTanimoto protein structures were 71.0%, 53.0%, 57.7%, 45.3%, and 69.8%, respectively.

In addition to the success rates shown in Fig. 4.1, the median and mean RMSD values for the use of each type of protein structures for docking are reported in Table 4.1. Similar to the results presented in Fig. 4.1, docking with the LMCSS and hiTanimoto protein structures achieved similar performances, and their median/mean RMSD values were significantly lower than dockings with the other three types of CELPP-provided protein structures. For instance, as shown in Columns 3 and 4, when the top predicted model was considered for each protein structure, the

LMCSS protein structures resulted in significantly lower median/mean RMSD values ($4.6\pm0.2/5.1\pm0.1$ Å) than the SMCSS protein structures ($5.7\pm0.2/6.0\pm0.1$ Å). The highest resolution ligand-bound candidate protein structures (hiResHolo) yielded slightly better docking performance ($5.6\pm0.2/5.8\pm0.1$ Å) than SMCSS, but resulted in significantly worse performance than LMCSS. When the hiResApo protein structures were used, the median/mean RMSD values were $6.4\pm0.2/6.5\pm0.1$ Å, which were larger than all the other cases. Similar to LMCSS, the hiTanimoto protein structures, which contained similar ligands with the query ligands, achieved comparable performances with LMCSS. The results based on the Vina Score are also reported in Table S1.

In summary, dockings using the LMCSS or hiTanimoto protein structures achieved significantly better performances than dockings using other CELPP-provided protein structures. Similar conclusions were also obtained in the previous Grand Challenges (GC1 and GC2), in which we found that using protein structures containing a co-bound ligand sharing a high molecular similarity with the query ligand would significantly improve the binding mode prediction.^{14,15} The above findings are consistent with the assumption that similar protein conformations, particularly similar conformations of the binding pockets, would be induced by binding of similar ligands, and that similar ligands tend to manifest similar binding modes. Next, we will present the results of prediction based on our own selected protein structures (i.e., user-specified protein structures), which were chosen with a 3D molecular similarity calculation method.

The user-specified protein structures

Fig. 4.2A shows the performances using different RMSD values as the thresholds for predictions based on our own selected protein structures (referred to as hiSHAFTS). For each target, docking was performed on the protein structure that contains a co-bound ligand sharing the highest 3D molecular similarity with the query ligand. The molecular similarity was calculated using the program SHAFTS with the default cutoff of 0.8. Based on the 875 evaluated targets, using 2.0 Å as the threshold for a correct prediction, the success rates were 22.6%, 39.0%, and 67.7% for the top model, the best in top 5 models, and the best in all sampled models, respectively. The median and mean RMSD values of binding mode prediction using hiSHAFTS are also reported in Table 4.1. The performances were similar to the performances using the best candidate protein structures (i.e., LMCSS or hiTanimoto structures provided by CELPP).

Figure 4.2: A The results of binding mode prediction for CELPP using the user-specified protein structures (i.e. hiSHAFTS structures in this study) for both docking-based and template-based methods. Different RMSD values were used as the thresholds for the definition of successful predictions. B The correlation between the RMSD values of the binding modes predicted by the template-based method and the corresponding similarity scores between the query ligands and the corresponding template ligands

Figure 4.2A also shows the results of the template-based method. Here, the hiSHAFTS complex structure was used as the template for each target. The query ligand was superimposed onto the co-bound ligand in the hiSHAFTS complex structure. It should be noted that the MD-based refinement step for the generated protein-query ligand complexes was not performed in the CELPP study, mainly due to the large number and complexity of the CELPP targets. It is surprising that a simple superimposition of the query ligand onto the template achieved a much better performance than the docking-based method. When 2.0 Å was used as the threshold, the success rate of the template-based method was 40.0%, about twice of the success rate

achieved by the docking method (considering only the top model).

Furthermore, we analyzed the correlation between the performance of the template-based method and the quality of the templates used for prediction. Figure 4.2B plots the RMSD values of each target vs the corresponding similarity scores between the query ligands and the corresponding ligands in the templates, showing that targets with higher similarity values tend to have lower RMSD values ($R = 0.44$). The value of 1.2 is the default cutoff of SHAFTS for a distinction of similar and dissimilar ligands. In this study, at least one good-quality template (SHAFTS score $\geq$ 1.2) were found for about 63.4% of the 875 evaluated cases. If only the cases in which SHAFTS score $\geq$ 1.2 were considered, the success rate increased to 53.1% using 2.0 Å as the threshold. The success rate increased to as high as 71.2% if the SHAFTS score cutoff was set to 1.5.

Although the template-based method achieved higher success rate than the docking method for binding mode prediction, the performance of the template-based method was highly dependent on the quality of the templates. The method usually failed if no good-quality template (e.g. SHAFTS score $\geq$ 1.2) was found. Furthermore, sometimes large RMSD values were also observed even if high-quality templates (e.g. SHAFTS score $\geq$ 1.5) were (see Fig. 4.2B). The failures suggest the need for the improvement of our current template-based method, in which the query ligands were simply superimposed onto the template ligands and the protein induced-fit effects were ignored.

GC3

The template-based method also achieved good performance for the CatS subset, which contains 24 compounds targeting the human Cathepsin S. The median/mean RMSD values are 3.5/4.3 (2.4/3.4) Å when the top model (top 5 models) was (were) considered for each case. Unfortunately, poor performance was observed with the docking method. The median/mean RMSD values were as high as 8.3/9.9 (5.9/6.5) Å when the top model (top 5 models) was (were) considered for each case. The predictions did not improve when the bound protein structures were used for docking. Analyzing the targets in this subset showed that the targets contain large-size flexible compounds and large-size binding pocket and that relatively few interactions were found in the released crystal structures (see Fig. 4.3 for an example), indicating that entropy may play an important role in binding for this subset. The failure of the current docking method is probably due to the inaccuracy of the scoring function for the entropy calculation for large-size ligand molecules.

Figure 4.3: The top predicted binding mode (colored red) of CatS_1 in comparison with the binding mode given by the crystal structure (colored green) released by D3R. The protein is shown in surface representation. The ligand (Cast_1) is plotted in stick representation. The predicted binding mode was obtained from the docking method using the bound protein structure

4.4 Conclusion

In this study, we thoroughly analyzed our prediction results on recent D3R challenges, CELPP and GC3. Our binding mode prediction methods have been systematically tested using the large-scale benchmark (more than one thousand targets) provided by CELPP. The results show that current molecular docking methods can benefit from the rapid increase of the number of proteinligand complex structures in the PDB. The use of an appropriate protein structure for docking will significantly improve the success rate of the binding mode prediction. In addition to the docking method, the results of a template-based approach have been assessed. The template-based method achieved better performance than the docking method. However, a drawback of the template-based method is its reliance on the templates, and its performance was poor when there was no good-quality template available. On the other hand, the docking-based method does not have this issue. Future combination of these two different methods is on the way to improve the binding mode prediction.

4.5 ACKNOWLEDGEMENT

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Supplementary

.1 EDockMS Implementation Details Related to Chapter 3.

In the development of EDockMS, we aimed to set up a user-friendly docking-based multiple target screening platform as the initial leading step in therapeutic applications.

EDockMS is a docking-based IVS web-server. The platform construction includes four major components, the interface, target database preparation, docking calculations and IVS results analysis.

.1.1 Server interface

Input

The user only needs to upload a mol2 file of the ligand structure. Users also have the options to specify such as job name and e-mail address for their convenience.

Output

The Queue page is used for checking the job status. Once a job is submitted successfully, a result page is generated at the same time, users will receive a notification through email after the job is completed. The results are compressed in a tar file which can be downloaded directly. The most promising targets are predicted and ranked by ITScore. The output of each job includes a list of the top 50 protein targets (with disease-related information), and the top 10 binding modes.

.1.2 Database preparation

The server built-in database MDTD is for storing data that EDockMS needs for multiple target screening. Moreover, MDTD crosslinks to TTD to provide the clinical trial information about the drugs, targets and pathways for therapeutically perspective analysis. First, we used Uniprot IDs¹ to extract TTD target relevant PDBs² because TTD crosslinked UniprotKB and PDB.³ Then, we mapped those PDBs to sc-PDB so that the finalized structures in MDTD are the targets that can be tracked with TTD IDs for disease associated details. Last, we used Sphgencpp to generate spheres around the whole surface of each protein in MDTD, and getsph to choose spheres in the vicinity of the protein binding site. Here, we utilized the binding site definitions in sc-PDBs, which are based on the set of amino acid residues that are within 6.5 Å to any ligand heavy atom. In the current version, we include 3268 protein ligand complexes (3349 distinguish binding sites) associate with 537 target entries. All the PDBs deposited in MDTD corresponding with TTD IDs and correlated information are listed in TableS2.

.1.3 Docking Protocol

All of the docking calculations are performed backstage using MDock software (<http://zoulab.dalton.missouri.edu/mdock.htm>), details of local installation and usage are introduced in our previous study.⁴ OMEGA is used to generate sets of query ligand conformations (up to 200 conformers as the default setting) for flexible docking (Version 2.5.1. OpenEye Scientific Software, Santa Fe, NM. (<http://www.eyesopen.com>)).

ITScore is a knowledge-based scoring function (also referred to as statistical potential-based scoring function) which has been implemented in MDock. The basic idea of the knowledge-based scoring function is to apply Boltzmann distribution principles to extract interaction potentials from the known structural information. Specifically, the pairwise interaction potentials can be expressed as:

$$u_{ij}(r) = -k_B T \ln(\rho(r)/\rho^*(r)) \quad (1)$$

i and j represent types of atom pairs, $\rho(r)$ is the atom pair density of a protein ligand atom at distance of r . r is the distance between the two atoms. k_B and T are the Boltzmann constant and absolute temperature, respectively. Yet, $\rho^*(r)$ remains the reference-state hurdle.⁵ The idea of ITScore is utilizing an iterative way to circumvent the reference state problem.^{5,6} Then, the pairwise Energy interaction potentials are generated by the following equations:

$$u_{ij}^{k+1}(r) = u_{ij}^k(r) + \Delta u_{ij}^k(r), \quad \Delta u_{ij}^k(r) = \frac{1}{2} K_B T [g_{ij}^k(r) - g_{ij}^{obs}(r)] \quad (2)$$

$g_{ij}^k(r)$ is the k -th iterative step of pair distribution functions.

.1.4 Clustering procedure

The server automatically removes redundancies of same family targets. However, for each protein target, it may contain several PDB structures. In order to do the flexible docking, we used all of the structures in the docking procedure. After docking, all of the structures are ranked according to their scores while only the structure with the highest score is kept.

.1.5 Example and validation of the approach

In terms of accuracy, we have re-docked all of the structures deposited in the database to test the ability of ITScore to predict the binding mode. ITScore achieved a success rate of 84% on identifying native-like binding modes under the criterion of $\text{rmsd} \geq 2 \text{ \AA}$. Table S1 presents the top 5 predicted targets for Progesterone as one of the examples from 47 cases (See in supplementary materials, S3).

Table S1 related to Chapter3. EDockMS results of Progesterone.

Rank	Predicted target	ITScore	PDB ID	TTD ID
1	Mineralocorticoid receptor	-58.25	2aax	T72168
2	Progesterone receptor	-55.77	1a28	T22939
3	Corticosteroid-binding globulin	-53.73	4bb2	T88452
4	Acetylcholinesterase	-53.26	4m0f	T30082
5	Androgen receptor	-52.47	1gs4	T11211

The true targets of Progesterone are colored in gray

Figure S1, related to Chapter3. ROC curves of three benchmark ligands.

Table S2: related to Chapter3. Target entries in MDTD

Target ClassTTD IDs	NameBioChemical	PDB IDs
Insulin receptor/ Kinase/ T85435		1gag 1i44 1ir3 1irk 1p14 1rqq 2auh 2b4s 2hr7 2mfr 2z8c 3bu3 3bu5 3bu6 3ekk 3ekn 3eta 3w11 3w12 3w13 4ibm 4oga 4xlv 4xss 4xst 4zxb 5e1s 5hhw 5j3h 5kqv 5u1m
Epidermal growth factor receptor/ Kinase/ T59328		1dnq 1dnr 1ivo 1m14 1m17 1mox 1nql 1xkk 1yy9 1z9i 2eb2 2eb3 2exp 2exq 2gs2 2gs6 2gs7 2itn 2ito 2itp 2itq 2itt 2itu 2itv 2itw 2itx 2ity 2itz 2j5e 2j5f 2j6m 2jit 2jiu 2jiv 2ks1 2m0b 2m20 2n5s 2rf9 2rfd 2rfe 2rgp 3b2u 3b2v 3bel 3buo 3c09 3g5v 3g5y 3gop 3gt8 3ika 3lzb 3njp 3ob2 3op0 3p0y 3pfv 3poz 3qwq 3ug1 3ug2 3vjn 3vjo 3vrp 3vrr 3w2o 3w2p 3w2q 3w2r 3w2s 3w32 3w33 4g5j 4g5p 4hjo 4ilz 4i20 4i21 4i22 4i23 4i24 4jq7 4jq8 4jr3 4jrv 4krl 4krm 4kro 4krp 4li5 4ll0 4lqm 4lrm 4r3p 4r3r 4r5s 4riw 4rix 4riy 4rj4 4rj5 4rj6 4rj7 4rj8 4tks 4uip 4uv7 4wd5 4wkq 4wrg 4zau 4zjv 4zse 5c8k 5c8m 5c8n 5cal 5can 5cao 5cap 5caq 5cas 5cau 5cav 5cnn 5cno 5czh 5czi 5d41 5edp 5edq 5edr 5em5 5em6 5em7 5em8 5fed 5fee 5feq 5gmp 5gnk 5gty 5gtz 5hcx 5hcy 5hcz 5hg5 5hg7 5hg8 5hg9 5hib 5hic 5j9y 5j9z 5jeb 5lv6 5sx4 5sx5 5u8l 5ug8 5ug9 5uga 5ugb 5ugc 5uwd 5wb7 5wb8 5xgm 5xgn
Vitamin D receptor/ Nuclear hor- mone receptor/ T34234		1db1 1ie8 1ie9 1kb2 1kb4 1kb6 1s0z 1s19 1txi 1ynw 2ham 2har 2has 2hb7 2hb8 3a2i 3a2j 3a3z 3a40 3a78 3auq 3aur 3ax8 3az1 3az2 3az3 3b0t 3cs4 3cs6 3kpz 3m7r 3ogt 3p8x 3tkc 3vhw 3w0a 3w0c 3w0y 3wgp 3wwr 3x31 3x36 4g2i 4ite 4itf 5gt4
Receptor protein-tyrosine kinase erbB-2/ Kinase/ T14597		1mfq 1mfl 1mw4 1n8z 1ovc 1qr1 1s78 2a91 2jwa 2ks1 2l4k 2n2a 3be1 3h3b 3mzw 3n85 3pp0 3rcd 3wlw 3wsq 4gfu 4hrl 4hrm 4hrn 5k33 5kwg 5my6 5tqs
C-X-C chemokine receptor 4/ GPCR rhodopsin/ T96079		2k03 2k04 2k05 2n55 3odu 3oe0 3oe6 3oe8 3oe9 4rws
Estrogen receptor/ Zinc-finger/ T89534		1a52 1akf 1ere 1err 1g50 1gwq 1gwr 1hcp 1hcq 1l2i 1pcg 1qkt 1qku 1r5k 1sj0 1uom 1x7e 1x7r 1xp1 1xp6 1xp9 1xpc 1xqc 1yim 1yin 1zky 2ayr 2b1v 2b1z 2b23 2bj4 2fai 2g44 2g5o 2i0j 2iog 2iok 2jf9 2jfa 2llo 2llq 2ocf 2ouz 2p15 2pog 2q6j 2q70 2qa6 2qa8 2qab 2qe4 2qgt 2qgw 2qh6 2qr9 2qse 2qxm 2qxs 2qzo 2r6w 2r6y 2yat 2yja 3cbm 3cbo 3cbp 3dt3 3erd 3ert 3hlv 3hml 3l03 3os8 3os9 3osa 3q95 3uu7 3uua 3uuc 3uud 4aa6 4dma 4iu7 4iui 4iv2 4iv4 4ivw 4ivy 4iw6 4iw8 4iwc 4iwf 4jc3 4jdd 4mg5 4mg6 4mg7 4mg8 4mg9 4mga 4mgb 4mgc 4mgd 4o6f 4pp6 4ppp 4pps 4pxm 4q13 4q50 4tuz 4tv1 4xi3 4zn7 4zn9 4znh 4zns 4znt 4znu 4znv 4znw 5aau 5aav 5acc 5ak2 5di7 5did 5die 5dig 5dk9 5dkb 5dke 5dkg 5dks 5dl4 5dlr 5dmc 5dmf 5dp0 5drj 5drn 5dtv 5du5 5due 5dug 5duh 5dvs 5dvv 5dwe 5dwg 5dwi 5dwj 5dx3 5dxb 5dxe 5dxg 5dxk 5dxm 5dyp 5dxq 5dxr 5dy8 5dyb 5dyd 5dz0 5dz1 5dz3 5dzh 5dzi 5e0w 5e0x 5e14 5e15 5e19 5e1c 5egv 5ehj 5ei1 5eit 5fqp 5fqr 5fqs 5fmt 5fqv 5gs4 5gtr 5hyr 5jmm 5kcc 5kcd 5kce 5kcf 5kct 5kcu 5kcw 5kd9 5kr9 5kra 5krc 5krf 5krh 5kri 5krj 5krk 5krl 5krm 5kro 5n10 5t0x 5t1z 5t92 5t97 5tld 5tlf 5tlg 5tll 5tlm 5tlo 5tlp 5tlt 5tlu 5tlv 5tlx 5tly 5tml 5tm2 5tm3 5tm4 5tm5 5tm6 5tm7 5tm8 5tm9 5tml 5tmm 5tmo 5tmq 5tmr 5tms 5tmt 5tmu 5tmv 5tmw 5tmz 5tn1 5tn3 5tn4 5tn5 5tn6 5tn7 5tn8 5tn9 5tnb 5u2b 5u2d 5w9d

Coagulation factor Xa/ Peptidase/ T84631	1c5m 1ezq 1f0r 1f0s 1fax 1fjs 1fxy 1g2l 1g2m 1hcg 1ioe 1iqe 1iqf 1iqg 1iqh 1iqi 1iqj 1iqk 1iql 1iqm 1iqn 1ksn 1lpg 1lpk 1lpz 1lqd 1mq5 1mq6 1msx 1nfu 1nfw 1nfx 1nfy 1nl8 1p0s 1v3x 1wu1 1xka 1xkb 1z6e 2bmg 2boh 2bok 2bq6 2bq7 2bqw 2cji 2dlj 2ei6 2ei7 2ei8 2fzz 2g00 2gd4 2h9e 2j2u 2j34 2j38 2j4i 2j94 2j95 2jkh 2p16 2p3f 2p3t 2p3u 2p93 2p94 2p95 2phb 2pr3 2qlj 2ra0 2uwl 2uwo 2uwp 2vh0 2vh6 2vvc 2vuu 2vvv 2vwl 2vwm 2vwn 2vwo 2w26 2w3i 2w3k 2wyg 2wyj 2xbv 2xbw 2xbx 2xby 2xc0 2xc4 2xc5 2y5f 2y5g 2y5h 2y7x 2y7z 2y80 2y81 2y82 3cen 3cs7 3ens 3ffg 3hpt 3iit 3k9x 3kl6 3kqb 3kqc 3kqd 3kqe 3liw 3m36 3m37 3q3k 3sw2 3tk5 3tk6 4a7i 4bti 4btt 4btu 4y6d 4y71 4y76 4y79 4y7a 4y7b 4zh8 4zha 5jqy 5jtc 5jz8 5jzu 5jzz 5k0h
Vascular endothelial growth factor receptor 2/ Kinase/ T80975	1vr2 1y6a 1y6b 1ywn 2m59 2met 2meu 2oh4 2p2h 2p2i 2qu5 2qu6 2rl5 2x1w 2x1x 2xir 3b8q 3b8r 3be2 3c7q 3cjf 3cjj 3cp9 3cpb 3cpc 3dtw 3eff 3ewh 3kvq 3s35 3s36 3s37 3u6j 3v2a 3v6b 3vhe 3vhk 3vid 3vnt 3vo3 3wzd 3wze 4ag8 4agc 4agd 4asd 4ase 5ew3
Fibroblast growth factor receptor 2/ Kinase/ T58454	1djs 1e0o 1ev2 1gjo 1ii4 1iil 1nun 1oec 1wvz 2fdb 2psq 2pvf 2pvy 2pwl 2py3 2pz5 2pzp 2pzz 2q0b 3b2t 3caf 3cly 3cul 3dar 3eui 3oj2 3ojm 3ril 4j23 4j95 4j96 4j97 4j98 4j99 4wv1 5eg3 5ugl 5ugx 5uhn 5ui0
Androgen receptor/ Zinc-finger/ T11211	1e3g 1gs4 1t5z 1t63 1t65 1xj7 1xow 1xq3 1z95 2am9 2ama 2amb 2ao6 2ax6 2ax7 2ax8 2ax9 2axa 2hvc 2oz7 2pio 2pip 2piq 2pir 2pit 2piu 2piv 2piw 2pix 2pkl 2pnu 2q7i 2q7j 2q7k 2q7l 2yhd 2ylo 2yly 2ylq 2z4j 3b5r 3b65 3b66 3b67 3b68 3btr 3l3x 3l3z 3rlj 3rll 3v49 3v4a 3zqt 4hlw 4k7a 4oea 4oed 4oey 4oez 4ofr 4ofu 4ogh 4oh5 4oh6 4oha 4oil 4oiu 4oj9 4ojb 4ok1 4okb 4okt 4okw 4okx 4olm 4ql8 5cj6 5jjm 5t8e 5t8j 5v8q
Nitric-oxide synthase, endothelial/ Oxidoreductases acting on paired donors/ T06046	1m9j 1m9k 1m9m 1m9q 1m9r 1niw 2ll7 2mg5 2n8j 3eah 3nos 4dl0 4dlp 5uo8 5uo9 5uoa 5uob 5uoc 5vvb 5vvc 5vvd 5xof
B-Raf proto-oncogene serine/ threonine-protein kinase/ T99089	1uwH 1uwj 2fb8 2l05 3c4c 3d4q 3idp 3ii5 3ny5 3og7 3ppj 3ppk 3prf 3pri 3psb 3psd 3qc4 3q96 3skc 3tv4 3tv6 4cqe 4dbn 4e26 4e4x 4ehe 4ehg 4fc0 4fk3 4g9c 4g9r 4h58 4jvg 4ksp 4ksq 4mbj 4mne 4mnf 4pp7 4r5y 4rzv 4rzw 4wo5 4xv1 4xv2 4xv3 4xv9 4yht 5c9c 5csw 5csx 5ct7 5fd2 5hi2 5hid 5hie 5ita 5j17 5j18 5j2r 5jrj 5jsm 5jt2 5val 5vam

Coagulation factor IIa/ Peptidase/ T94033	1a2c 1a3b 1a3e 1a46 1a4w 1a5g 1a61 1abi 1abj 1ad8 1ae8 1afe 1aht 1ai8 1aix 1awf 1awh 1ay6 1b5g 1b7x 1ba8 1bb0 1bcu 1bhx 1bmm 1bmn 1bth 1c1u 1c1v 1c1w 1c4u 1c4v 1c4y 1c5l 1c5n 1c5o 1ca8 1d3d 1d3p 1d3q 1d3t 1d4p 1d6w 1d9i 1de7 1dit 1dm4 1doj 1dwb 1dwc 1dwd 1dwe 1dx5 1e0f 1eb1 1eoj 1eol 1fpc 1fph 1g30 1g32 1g37 1ghv 1ghw 1ghx 1ghy 1gj4 1gj5 1h8d 1h8i 1hag 1hah 1hai 1hao 1hap 1hbt 1hdt 1hgt 1hlt 1hut 1hxe 1hxf 1ihs 1iht 1jmo 1jou 1jwt 1k21 1k22 1kts 1ktt 1lhc 1lhd 1lhe 1lhf 1lhg 1mh0 1mu6 1mu8 1mue 1nm6 1no9 1nrn 1nro 1nrp 1nrq 1nrr 1nrs 1nt1 1nu7 1nu9 1ny2 1nzq 1o0d 1o2g 1o5g 1ook 1oyt 1p8v 1ppb 1qbv 1qhr 1qj1 1qj6 1qj7 1qur 1rd3 1riw 1sb1 1sfq 1sg8 1sgi 1shh 1sl3 1sr5 1t4u 1t4v 1ta2 1ta6 1tb6 1tbz 1thp 1thr 1ths 1tmb 1tmt 1tmu 1tom 1tq0 1tq7 1twx 1uma 1uvs 1vr1 1vzq 1w7g 1way 1wbx 1xml 1xmn 1ype 1ypg 1ypj 1ypk 1ypl 1ypm 1z7l 1z8i 1z8j 1zgi 1zgv 1zrb 2a0q 2a2x 2a45 2afq 2ank 2anm 2b5t 2bdy 2bvr 2bvs 2bvx 2bxt 2bxu 2c8w 2c8x 2c8y 2c8z 2c90 2c93 2cf8 2cf9 2cn0 2feq 2fes 2gde 2gp9 2h9t 2hgt 2hnt 2hpp 2hpq 2hwl 2jh0 2jh5 2jh6 2od3 2pgb 2pgq 2pks 2pw8 2r2m 2thf 2uuf 2uu 2uuk 2v3h 2v3o 2zc9 2zda 2zdv 2zf0 2zff 2zfp 2zfq 2zfr 2zg0 2zgb 2zgx 2zhe 2zhf 2zhq 2zhw 2zi2 2ziq 2znk 2zo3 3b23 3b9f 3bef 3bei 3bf6 3biu 3biv 3bv9 3c1k 3c27 3d49 3da9 3dd2 3dhk 3dt0 3dux 3e6p 3ee0 3egk 3eq0 3f68 3gic 3gis 3hat 3hkj 3hte 3jz1 3jz2 3k65 3ldx 3lu9 3npx 3p17 3p6z 3p70 3pmh 3po1 3qdz 3qgn 3qlp 3qto 3qtv 3qwc 3qx5 3r3g 3rlw 3rly 3rm0 3rm2 3rml 3rmm 3rmn 3rmo 3s7h 3s7k 3sha 3shc 3si3 3si4 3sqe 3sqh 3sv2 3t5f 3tu7 3u69 3u8o 3u8r 3u8t 3u98 3u9a 3utu 3uwj 3vxe 3vxf 4ax9 4ayv 4ayy 4az2 4bah 4bak 4bam 4ban 4bao 4baq 4boh 4ch2 4ch8 4dih 4dii 4dt7 4dy7 4e05 4e06 4e7r 4h6s 4h6t 4hfp 4hte 4hzh 4i7y 4loy 4lxb 4lz1 4lz4 4mlf 4n3l 4nze 4nzq 4o03 4rkj 4rko 4rn6 4thn 4ud9 4udw 4ue7 4ueh 4ufd 4ufe 4uff 4ufg 4yes 5a2m 5af9 5afy 5afz 5ahg 5cmx 5do4 5e8e 5edk 5edm 5ew1 5ew2 5gds 5gim 5jdu 5jfd 5jzy 5l6n 5nhu 5to3 6eo6 6eo7 7kme 8kme
RAC serine/ threonine-protein ki- nase/ T67619	1h10 1unp 1unq 1unr 2uvm 2uzr 2uzs 3cqu 3cqw 3mv5 3mvh 3o96 3ocb 3ow4 3qkk 3ql 3qkm 4ejn 4ekk 4ekl 4gv1 5kcv
mRNA of RAF proto-oncogene serine/ threonine-protein kinase/ T60405	1c1y 1faq 1far 1gua 1rfa 3cu8 3iqj 3iqu 3iqv 3kuc 3kud 3nkx 3o8i 3omv 4fj3 4g0n 4g3x 4iea 4ihl
Peroxisome proliferator activated receptor gamma/ Nuclear hormone receptor/ T58921	1fm6 1fm9 1i7i 1k74 1knu 1nyx 1prg 1rdt 1wm0 1zeo 1zgy 2ath 2f4b 2fvj 2g0g 2g0h 2gtk 2hfp 2hwq 2hwr 2i4j 2i4p 2i4z 2om9 2p4y 2pob 2prg 2q59 2q5p 2q5s 2q61 2q6r 2q6s 2q8s 2qmv 2vsr 2vst 2vv0 2vv1 2vv2 2vv3 2vv4 2xkw 2yfe 2zk0 2zk1 2zk2 2zk3 2zk4 2zk5 2zk6 2zno 2zvt 3ads 3adt 3adu 3adv 3adw 3adx 3an3 3an4 3b0q 3b0r 3b1m 3b3k 3bc5 3cdp 3cds 3cs8 3cwd 3d6d 3dzu 3dzy 3e00 3et0 3et3 3fej 3fur 3g9e 3gbk 3h0a 3ho0 3hod 3ia6 3k8s 3kmg 3lmp 3noa 3osi 3osw 3pba 3po9 3prg 3qt0 3r5n 3r8a 3r8i 3s9s 3sz1 3t03 3ty0 3u9q 3v9t 3v9v 3v9y 3vjh 3vji 3vn2 3vso 3vsp 3wj4 3wj5 3wmh 3x1h 3x1i 4a4v 4a4w 4ci5 4e4k 4e4q 4em9 4ema 4f9m 4fgy 4hee 4jaz 4jl4 4l96 4l98 4o8f 4oj4 4prg 4pvu 4pwl 4r06 4r2u 4r6s 4xld 4xta 4xuh 4xum 4y29 4yt1 5azv 5dsh 5dv3 5dv6 5dv8 5dvc 5dwl 5f9b 5gtn 5gto 5gtp 5hzc 5ji0 5lsg 5tto 5two 5u5l
MMP-9/ Peptidase/ T54156	1gkc 1gkd 1itv 1l6j 1lk6 2ovx 2ovz 2ow0 2ow1 2ow2 4h1q 4h2e 4h3x 4h82 4hma 4jij 4jqg 4wzv 4xct 5cuh 5i12 5th6 5th9 5ue3 5ue4
3-hydroxy-3-methylglutaryl- coenzyme A reductase/ Short-chain dehydrogenases reductases/ T53585	1dq8 1dq9 1dqa 1hw8 1hw9 1hwi 1hwj 1hwk 1hw1 2q11 2q6b 2q6c 2r4f 3bgl 3cct 3ccw 3ccz 3cd0 3cd5 3cd7 3cda 3cdb

Basic fibroblast growth factor receptor 1/ Kinase/ T47101	1agw 1cvs 1evt 1fgi 1fgk 1fq9 1xr0 2cr3 2fgi 3c4f 3dpk 3gqi 3gql 3js2 3krj 3krl 3kxx 3ky2 3ojv 3rhx 3tt0 4f63 4f64 4f65 4nk9 4nka 4nks 4rwi 4rwj 4rwk 4rwl 4uwb 4uwc 4uwy 4v01 4v04 4v05 4wun 4zsa 5a46 5a4c 5am6 5am7 5b7v 5ew8 5ff 5uq0 5ur1 5vnd 5w59
Estradiol 17 beta-dehydrogenase 1/ Short-chain dehydrogenases reductases/ T44011	1a27 1bhs 1dht 1equ 1fds 1fdt 1fdu 1fdv 1fdw 1i5r 1iol 1jtv 1qyv 1qyw 1qyx 3dey 3dhe 3hb4 3hb5 3klm 3klp 3km0
Glucocorticoid receptor/ Zinc-finger/ T40016	1m2z 1nhz 1p93 3bqd 3cld 3e7c 3h52 3k22 3k23 4csj 4hn5 4hn6 4lsj 4mdd 4p6w 4p6x 4udc 4udd 5cbx 5cby 5cbz 5cc1 5e69 5e6a 5e6b 5e6c 5e6d 5emc 5emp 5emq 5g3j 5g5w 5nfp 5nft 5va0 5va7
Apoptosis regulator Bcl-2/ Bcl-2 family/ T31309	1g5m 1gjh 1ysw 2o21 2o22 2o2f 2w3l 2xa0 4aq3 4ieh 4lvt 4lxd 4man 5agw 5agx 5fcg 5jsn
Cytochrome P450 19/ Oxidoreductases acting on paired donors/ T13260	1tqa 3eqm 3s79 3s7s 4gl5 4gl7 4kq8 5jkv 5jkw 5jl6 5jl7 5jl9
C-C chemokine receptor type 5/ GPCR rhodopsin/ T09960	1nd8 1ne0 1opn 1opt 1opw 2l87 2mzx 2rll 2rrs 4mbs
Adenosine deaminase/ Carbon-nitrogen hydrolase/ T03661	1m7m 3iar
mRNA of HER2/ Kinase/ T96788	1mfg 1mfl 1mw4 1n8z 1ovc 1qr1 1s78 2a91 2jwa 2ks1 2l4k 2n2a 3be1 3h3b 3mzw 3n85 3pp0 3rcd 3wlv 3wsq 4gfu 4hrl 4hrm 4hrn 5k33 5kwg 5my6 5tqs
Angiopoietin 1 receptor/ Kinase/ T92144	1fvr 2gy5 2gy7 2oo8 2osc 2p4i 2wqb 3bea 3l8p 4k0v 4x3j 5mya 5myb 5utk
mRNA of Protein tyrosine phosphatase-1B/ Target of antisense drug/ T89529	1a5y 1aax 1bzc 1bzh 1bzj 1c83 1c84 1c85 1c86 1c87 1c88 1ecv 1een 1eeo 1glf 1glg 1glh 1g7f 1g7g 1gfy 1i57 1jf7 1kak 1kav 1l8g 1lqf 1nl9 1nny 1no6 1nwe 1nwl 1nz7 1oem 1oeo 1oes 1oet 1oeu 1oew 1ony 1onz 1pa1 1ph0 1ptt 1ptu 1ptv 1pty 1pxh 1pyn 1qlm 1q6j 1q6m 1q6n 1q6p 1q6s 1q6t 1qxx 1sug 1t48 1t49 1t4j 1wax 1xbo 2azr 2b07 2b4s 2bgd 2bge 2cm2 2cm3 2cm7 2cm8 2cma 2cmb 2cmc 2cne 2cnf 2cng 2cnh 2cni 2f6f 2f6t 2f6v 2f6w 2f6y 2f6z 2f70 2f71 2fjm 2fjn 2h4g 2h4k 2hb1 2hnp 2hnq 2nt7 2nta 2qbp 2qbw 2qbr 2qbs 2veu 2vev 2vew 2vex 2vey 2zmm 2zn7 3a5j 3a5k 3cwe 3d9c 3eas 3eb1 3eu0 3i7z 3i80 3qkp 3qkq 3sme 3zmp 3zmq 3zv2 4bjo 4i8n 4qah 4qap 4qbe 4qbw 4y14 4zrt 5k9v 5k9w 5ka0 5ka1 5ka2 5ka3 5ka4 5ka7 5ka8 5ka9 5kaa 5kab 5kac 5kad 5t19
Glucokinase/ Kinase/ T87166	1glk 1v4s 1v4t 3a0i 3f9m 3fgu 3fr0 3goi 3h1v 3id8 3idh 3imx 3qic 3s41 3vev 3vey 3vf6 4dch 4dhy 4ise 4isf 4isg 4iww 4ixc 4l3q 4lc9 4mle 4mlh 4no7 4rch 5v4w 5v4x
Stromelysin-1/ Peptidase/ T86702	1b3d 1b8y 1biw 1bm6 1bqo 1c3i 1c8t 1caq 1ciz 1cqr 1d5j 1d7x 1d8f 1d8m 1g05 1g49 1g4k 1hfs 1hy7 1mlw 1oo9 1qia 1qic 1slm 1sln 1uea 1ums 1umt 1usn 2d1o 2jnp 2jt5 2jt6 2srt 2usn 3ohl 3oho 3usn 4dpe 4g9l 4ja1

Proto-oncogene tyrosine-protein kinase SRC/ Kinase/ T85943	1a07 1a08 1a09 1a1a 1a1b 1a1c 1a1e 1fmk 1hcs 1hct 1ksw 1o41 1o42 1o43 1o44 1o45 1o46 1o47 1o48 1o49 1o4a 1o4b 1o4c 1o4d 1o4e 1o4f 1o4g 1o4h 1o4i 1o4j 1o4k 1o4l 1o4m 1o4n 1o4o 1o4p 1o4q 1o4r 1shd 1y57 1yi6 1yoj 1yol 1yom 2bdf 2bdj 2h8h 2src 3vro 3zmp 3zmq 4f59 4f5a 4f5b 4hxj 4k11 4mxo 4mxx 4mxy 4mxz
Purine nucleoside phosphorylase/ Pentosyltransferase/ T78198	1m73 1pf7 1pwy 1rct 1rfg 1rr6 1rsz 1rt9 1ula 1ulb 1v2h 1v3q 1v41 1v45 1yry 2a0w 2a0x 2a0y 2oc4 2oc9 2on6 2q7o 3bgs 3d1v 3gb9 3ggs 3iny 3k8o 3k8q 3phb 4ear 4eb8 4ece 4gka 5etj 5ugf
Adenosine A2a receptor/ GPCR rhodopsin/ T77365	1mmh 1upe 2ydo 2ydv 3eml 3pwh 3qak 3rey 3rfm 3uza 3uzc 3vg9 3vga 4eiy 4ug2 4uhr 5g53 5iu4 5iu7 5iu8 5iua 5iub 5jtb 5k2a 5k2b 5k2c 5k2d 5mzj 5mzp 5n2r 5nlx 5nm2 5nm4 5uig 5uvi
Mitogen-activated protein kinase 14/ Kinase/ T65864	1a9u 1bl6 1bl7 1bmk 1di9 1ian 1kv1 1kv2 1m7q 1ouk 1ouy 1ove 1oz1 1r39 1r3c 1w7h 1w82 1w83 1w84 1wbn 1wbo 1wbs 1wbt 1wbv 1wbw 1wfc 1yqj 1zyj 1zz2 1zzl 2baj 2bak 2bal 2baq 2fsl 2fsm 2fso 2fst 2gfs 2i0h 2lgc 2npq 2okr 2onl 2qd9 2rg5 2rg6 2y8o 2yis 2yiw 2yix 2zaz 2zb0 2zb1 3bv2 3bv3 3bx5 3c5u 3ctq 3d7z 3d83 3ds6 3dt1 3e92 3e93 3fc1 3fi4 3fkl 3fkn 3fko 3fl4 3fn 3flq 3fls 3flw 3fly 3flz 3fmh 3fmj 3fmk 3fml 3fmm 3fmn 3fsf 3fsk 3gc7 3gcp 3gcq 3gcs 3gcu 3gcv 3gfe 3gi3 3ha8 3hec 3heg 3hl7 3hl1 3hp2 3hp5 3hrb 3hub 3huc 3hv3 3hv4 3hv5 3hv6 3hv7 3hvc 3iph 3itz 3iw5 3iw6 3iw7 3iw8 3k3i 3k3j 3kf7 3kq7 3l8s 3l8x 3lfa 3lfb 3lfc 3lfd 3lfe 3lff 3lhj 3mgy 3mh0 3mh1 3mh2 3mh3 3mpa 3mpt 3mvl 3mvm 3mw1 3new 3nnu 3nnv 3nnw 3nnx 3nww 3o8p 3o8t 3o8u 3obg 3obj 3oc1 3ocg 3od6 3ody 3odz 3oef 3pg3 3qud 3que 3rin 3roc 3s3i 3s4q 3u8w 3uvp 3uvq 3uvr 3zs5 3zsg 3zsh 3zsi 3zya 4a9y 4aa0 4aa4 4aa5 4aac 4dli 4dlj 4e5a 4e5b 4e6a 4e6c 4e8a 4eh2 4eh3 4eh4 4eh5 4eh6 4eh7 4eh8 4eh9 4ehv 4ewq 4f9w 4f9y 4fa2 4geo 4kin 4kip 4kiq 4l8m 4r3c 4zth 5eta 5etc 5etf 5eti 5ml5 5mtx 5mty 5n63 5n64 5n65 5n66 5n67 5n68 5o8u 5o8v 5tbe 5tco
Aldo-keto reductase family 1 member C3/ Short-chain dehydrogenases reductases/ T60857	1ry0 1ry8 1slp 1slr 1s2a 1s2c 1xf0 1zq5 2f38 2fgb 3r43 3r58 3r6i 3r7m 3r8g 3r8h 3r94 3ufy 3ug8 3ugr 3uwe 4dbs 4dbu 4dbw 4dz5 4fa3 4fal 4fam 4h7c 4hmn 4wdt 4wdu 4wdw 4wdx 4wrh 4xvd 4xve 4yvv 4yvx 4zfc 5hnt 5hnu 5jm5
Mitogen-activated protein kinase 1/ Kinase/ T58970	1pme 1tvo 1wzy 2ojg 2oji 2ojj 2y9q 3d42 3d44 3i5z 3i60 3sa0 3tei 3w55 4fmq 4fux 4fuy 4fv0 4fv1 4fv2 4fv3 4fv4 4fv5 4fv6 4fv7 4fv8 4fv9 4g6n 4g6o 4h3p 4h3q 4iz5 4iz7 4iza 4n0s 4nif 4o6e 4qp1 4qp2 4qp3 4qp4 4qp6 4qp7 4qp8 4qp9 4qpa 4qta 4qte 4xj0 4zxt 4zzm 4zzn 4zzo 5ax3 5bue 5bui 5buj 5bvd 5bve 5bvf 5k4i 5lcj 5lck 5ngu 5nhf 5nhh 5nhj 5nhl 5nho 5nhp 5nhv 5v60 5v61 5v62
Apopain/ Peptidase/ T57943	1cp3 1gfw 1i3o 1nme 1nmq 1nms 1pau 1qx3 1re1 1rhj 1rhk 1rhm 1rhq 1rhr 1rhu 2c1e 2c2k 2c2m 2c2o 2cdr 2cjj 2cjk 2cny 2cnk 2cnl 2cnn 2cno 2dko 2h5i 2h5j 2h65 2j30 2j31 2j32 2j33 2xyg 2xyh 2xyp 2xzd 2xzt 2y0b 3deh 3dei 3dej 3dek 3edq 3gjq 3gjr 3gjs 3gjt 3h0e 3itn 3kjf 3pcx 3pd0 3pd1 4dcj 4dco 4dcp 4eha 4ehd 4ehf 4ehh 4ehk 4ehl 4ehn 4ije 4jqy 4jqz 4jr0 4pry 4ps0 4qtx 4qty 4qu0 4qu5 4qu8 4qu9 4qua 4qub 4qud 4que 4qug 4quh 4qui 4quj 4qul 5i9b 5i9t 5iab 5iae 5iag 5iaj 5iak 5ian 5iar 5ias 5ibc 5ibp 5ibr 5ic4
Beta-2 adrenergic receptor/ GPCR rhodopsin/ T52522	1gq4 2r4r 2r4s 2rh1 3d4s 3kj6 3ny8 3ny9 3nya 3p0g 3pds 3sn6 4gbr 4lde 4ldl 4ldo 4qkx 5d5a 5d5b 5d6l 5jqh 5x7d

Interstitial collagenase/ Peptidase/ T52450	1ayk 1cge 1cgf 1cgl 1hfc 1su3 2ayk 2clt 2j0t 2tcl 3ayk 3shi 4auo 4ayk 966c
Bile acid receptor/ Nuclear hormone receptor/ T51426	1osh 1osk 3bej 3dct 3dcu 3fli 3fxv 3gd2 3hc5 3hc6 3l1b 3okh 3oki 3olf 3omk 3omm 3oof 3ook 3p88 3p89 3rut 3ruu 3rvf 4oiv 4qe6 4qe8 4wvd 5iaw 5ick 5q0i 5q0j 5q0k 5q0l 5q0m 5q0n 5q0o 5q0p 5q0q 5q0r 5q0s 5q0t 5q0u 5q0v 5q0w 5q0x 5q0y 5q0z 5q10 5q11 5q12 5q13 5q14 5q15 5q16 5q17 5q18 5q19 5q1a 5q1b 5q1c 5q1d 5q1e 5q1f 5q1g 5q1h 5q1i
Muscarinic acetylcholine receptor M2/ GPCR rhodopsin/ T46185	1lub 3uon 4mq5 4mqt
Xanthine dehydrogenase/ oxidase/ T40954	2ckj 2elq
Glyceraldehyde 3-phosphate dehydrogenase, muscle/ Glyceraldehyde-3-phosphate/ T39321	1u8f 1znq 2feh 3gpd 4wnc 4wni
Acetylcholinesterase/ Carboxylic ester hydrolase/ T30082	1b4l 1f8u 1puv 1puw 1vzj 2clj 2x8b 3lii 4bdt 4ey4 4ey5 4ey6 4ey7 4ey8 4m0e 4m0f 4pqe 5foq 5fpq 5hf5 5hf6 5hf8 5hf9 5hfa
Progesterone receptor/ Zinc-finger/ T22939	1a28 1e3k 1sqn 1sr7 1zuc 2c7a 2ovh 2ovm 2w8y 3d90 3g8o 3hq5 3kba 3zr7 3zra 3zrb 4a2j 4apu 4oar 5cc0
Tumor necrosis factor/ Cytokine: tumor necrosis factor/ T20178	1a8m 1tnf 2az5 2e7a 2tun 2zjc 2zpx 3alq 3it8 3l9j 3wd5 4g3y 4tsv 4tw7 4y6o 5m2i 5m2j 5m2m 5mu8 5tsw 5uui 5wux
Urokinase-type plasminogen activa- tor/ Peptidase/ T17758	1c5w 1c5x 1c5y 1c5z 1ejn 1f5k 1f5l 1f92 1fv9 1gi7 1gi8 1gi9 1gj7 1gj8 1gj9 1gja 1gjb 1gjc 1gjd 1kdu 1lmw 1o3p 1o5a 1o5b 1o5c 1owd 1owe 1owh 1owi 1owj 1owk 1sc8 1sqa 1sqo 1sqt 1u6q 1urk 1vj9 1vja 1w0z 1w10 1w11 1w12 1w13 1w14 2fd6 2i9a 2i9b 2nwn 2o8t 2o8u 2o8w 2r2w 2vin 2vio 2vip 2viq 2viv 2viw 2vnt 3bt1 3bt2 3ig6 3kgp 3khv 3kid 3m6l 3mhw 3mwi 3ox7 3oy5 3oy6 3pb1 3qn7 3u73 4dva 4dw2 4fu7 4fu8 4fu9 4fub 4fuc 4fud 4fue 4fuf 4fug 4fuh 4fui 4fuj 4gly 4h42 4jk5 4jk6 4jni 4jnl 4k24 4mnv 4mnw 4mnx 4mny 4osl 4os2 4os4 4os5 4os6 4os7 4x0w 4x1n 4x1p 4x1q 4x1r 4x1s 4xsk 4zhl 4zhm 4zkn 4zko 4zkr 4zks 5hgg 5xg4
Cellular tumor antigenp53/ T15739	1a1u 1aie 1c26 1dt7 1gzh 1h26 1hs5 1jsp 1kzy 1ma3 1olg 1olh 1pes 1pet 1sae 1saf 1sak 1sal 1tsr 1tup 1uol 1xqh 1yc5 1ycq 1ycr 1yos 2ac0 2ady 2ahi 2ata 2b3g 2bim 2bin 2bio 2bip 2biq 2flx 2fej 2foj 2foo 2gs0 2h1l 2h2d 2h2f 2h4f 2h4h 2h4j 2h59 2j0z 2j10 2j11 2j1w 2j1x 2j1y 2j1z 2j20 2j21 2k8f 2l14 2ly4 2mej 2mwo 2mwp 2mwy 2mzd 2ocj 2pcx 2ruk 2vuk 2wgx 2x0u 2x0v 2x0w 2xwr 2ybg 2ydr 2z5s 2z5t 3d05 3d06 3d07 3d08 3d09 3d0a 3dab 3dac 3igk 3igl 3kmd 3kz8 3lw1 3oq5 3pdh 3q01 3q05 3q06 3sak 3tg5 3ts8 3zme 4agl 4agm 4agn 4ago 4agp 4agq 4buz 4bv2 4hfv 4hje 4ibq 4ibs 4ibt 4ibu 4ibv 4ibw 4iby 4ibz 4ijt 4kvp 4lo9 4loe 4lof 4mzi 4mzr 4qo1 4rp6 4rp7 4x34 4xr8 4zzj 5a7b 5ab9 5aba 5aoi 5aoj 5aok 5aol 5aom 5bua 5ecg 5g4m 5g4n 5g4o 5hou 5hp0 5hpd 5lap 5lgy 5mhc 5moc 5un8

Protein kinase C, alpha type/ Kinase/ T12808	2eli 3iw4 4dnl 4ra4
Lck tyrosine kinase/ Kinase/ T12499	1bhf 1bhh 1cwd 1cwe 1fbz 1h92 1ijr 1kik 1lcj 1lck 1lkk 1lkl 1q68 1q69 1qpc 1qpd 1qpe 1qpj 1x27 2iim 2of2 2of4 2ofu 2ofv 2og8 2pl0 2zm1 2zm4 2zyb 3ac1 3ac2 3ac3 3ac4 3ac5 3ac8 3acj 3ack 3ad4 3ad5 3ad6 3b2w 3brh 3bym 3byo 3bys 3byu 3kmm 3kxz 3lck 3mpm 4c3f 4d8k 5mtm 5mtn
Glutamate carboxypeptidase II/ Peptidase/ T97071	1z8l 2c6c 2c6g 2c6p 2cij 2bjj 2jbk 2oot 2or4 2pvv 2pvw 2xef 2xeg 2xei 2xej 3bhx 3bi0 3bi1 3bxm 3d7d 3d7f 3d7g 3d7h 3iww 3rbu 3sje 3sjf 3sjg 3sjx 4jyw 4jz0 4lqg 4mcp 4mcq 4mcr 4mcs 4ngm 4ngn 4ngp 4ngq 4ngr 4ngs 4ngt 4oc0 4oc1 4oc2 4oc3 4oc4 4oc5 4ome 4p44 4p45 4p4b 4p4d 4p4e 4p4f 4p4i 4p4j 4w9y 4x3r 5d29 5ely 5f09
Cell division protein kinase 6/ Kinase/ T89361	1bi7 1bi8 1blx 1g3n 1jow 1xo2 2euf 2f2c 3nup 3nux 4aua 4ez5 4tth 5l2i 5l2s 5l2t
Peroxisome proliferator activated receptor alpha/ Zinc-finger/ T86591	1i7g 1k7l 1kkq 2npa 2p54 2rew 2znn 3et1 3fei 3g8i 3kdt 3kdu 3sp6 3vi8 4bcr 4ci4 5azt 5hyk
Sphingosine kinase/ Kinase/ T86014	3vzb 3vzc 3vzd 4l02 4v24
Inhibitor of apoptosis protein 2/ Carbon-nitrogen ligase/ T84780	1qbh 2l9m 3d9t 3d9u 3mld 3mup 3oz1 3t6p 3uw4 4eb9 4hy4 4hy5 4kmn 4lge 4lgu 4mti 4mu7 5m6n
Amine oxidase [flavin-containing] B/ Oxidoreductases acting on CH-NH2 group of donors/ T83011	1gos 1h8r 1oj9 1oja 1ojc 1ojd 1s2q 1s2y 1s3b 1s3e 2bk3 2bk4 2bk5 2byb 2c64 2c65 2c66 2c67 2c70 2c72 2c73 2c75 2c76 2v5z 2v60 2v61 2vrl 2vrm 2vz2 2xcg 2xfn 2xfo 2xfp 2xfq 2xfu 3po7 3zyx 4a79 4a7a 4crt 5mrl
ADAM 17/ Peptidase/ T82393	1bkc 1zxc 2a8h 2ddf 2fv5 2fv9 2i47 2m2f 2oi0 3b92 3cki 3e8r 3edz 3ewj 3g42 3kmc 3kme 3l0t 3l0v 3le9 3lea 3lgp 3o64
Estrogen receptor beta/ Nuclear hormone receptor/ T80896	1l2j 1nde 1qkm 1u3q 1u3r 1u3s 1u9e 1x76 1x78 1x7b 1x7j 1yy4 1yye 1zaf 2fsz 2giu 2i0g 2jj3 2nv7 2qtu 2yjd 2yly 2z4b 3oll 3ols 3omo 3omp 3omq 4j24 4j26 4zi1 5toa
PI3K alpha/ Kinase/ T80276	2enq 2rd0 3hhm 3hiz 3zim 4jps 4l1b 4l23 4l2y 4ovu 4ovv 4tuu 4tv3 4waf 4ykn 4zop 5dxh 5dxt 5fi4 5itd 5sw8 5swg 5swo 5swp 5swr 5swt 5sx8 5sx9 5sxa 5sxb 5sxc 5sxd 5sxe 5sxf 5sxi 5sxj 5sxk 5ubr 5uk8 5ukj 5ul1
Glycogen synthase kinase-3 beta/ Kinase/ T70977	1gng 1h8f 1i09 1j1b 1j1c 1o6k 1o6l 1o9u 1pyx 1q3d 1q3w 1q41 1q4l 1q5k 1r0e 1uv5 2jdo 2jdr 2jld 2o5k 2ow3 2uw9 2x39 2xh5 3cqu 3cqW 3du8 3e87 3e88 3e8d 3f7z 3f88 3gb2 3i4b 3l1s 3m1s 3mv5 3ow4 3pup 3q3b 3qkk 3say 3sd0 3zdi 3zrk 3zrl 3zrm 4acc 4acd 4acg 4ach 4afj 4b7t 4dit 4ekk 4iq6 4j1r 4j71 4nm0 4nm3 4nm5 4nm7 4ptc 4pte 4ptg 5f94 5f95 5hln 5hlp 5k5n 5oy4 6b8j

Lanosterol synthase/ Intramolecular transferases/ T56175	1w6j 1w6k
TGF-beta receptor type I/ Kinase/ T53389	1b6c 1ias 1py5 1rw8 1tbi 1vjy 2l5s 2pjy 2wot 2wou 2x7o 3faa 3gxl 3hmm 3kcf 3kfd 3tzm 4x0m 4x2f 4x2g 4x2j 4x2k 4x2n 5e8s 5e8t 5e8u 5e8w 5e8x 5e8z 5e90 5fri 5usq
Nociceptin receptor/ GPCR rhodopsin/ T52921	4ea3 5dhg 5dhh
Insulin-like growth factor I receptor/ Kinase/ T48069	ligr 1jqh 1k3a 1m7n 1p4o 2oj9 2zm3 3d94 3f5p 3i81 3lvp 3lw0 3nw5 3nw6 3nw7 3o23 3qqu 4d2r 4xss 5fxq 5fxr 5fxs 5hzn
Hepatocyte growth factor receptor/ Kinase/ T40474	1fyr 1r0p 1r1w 1shy 1ssl 1ux3 2g15 2rfn 2rfs 2uzx 2uzy 2wd1 2wgj 2wkm 3a4p 3bux 3c1x 3ccn 3cd8 3ce3 3cth 3ctj 3dkc 3dkf 3dkg 3efj 3efk 3f66 3f82 3i5n 3l8v 3lq8 3q6u 3q6w 3qti 3r7o 3rhk 3u6h 3u6i 3vw8 3zbx 3zc5 3zcl 3zzx 3zze 4aoi 4ap7 4deg 4deh 4dei 4eev 4gg5 4gg7 4iwd 4k3j 4knb 4mxc 4o3t 4o3u 4r1v 4r1y 4xmo 4xyf 5dg5 5eob 5eyc 5eyd 5hlw 5hni 5ho6 5hoa 5hor 5hti 5lsp 5t3q 5uab 5uad 5uaf
Protein kinase C, beta type/ Kinase/ T40276	2i0e
Mitogen-activated protein kinase 8/ Kinase/ T40097	1ukh 1uki 2g01 2gmX 2h96 2no3 2xrw 2xs0 3elj 3o17 3o2m 3pze 3v3v 3vud 3vug 3vuh 3vui 3vuk 3vul 3vum 4awi 4e73 4g1w 4hys 4hyu 4izy 4l7f 4qtd 4ux9 4yr8 5len
Calmodulin/ Calmodulin-dependent secretion/ T39610	3o77 3o78 5coc 5vms 5wsu 5wsv 1aji 1cdl 1cll 1ctr 1iwq 1j7o 1j7p 1k90 1k93 1l7z 1lvc 1nkf 1pk0 1s26 1sk6 1sw8 1up5 1wrz 1xfu 1xfv 1xfw 1xfx 1xfy 1xfz 1y6w 1yr5 1yrt 1yru 1zot 1zuz 2be6 2f3y 2f3z 2hf5 2i08 2jzi 2k0e 2k0f 2k0j 2k61 2kne 2kug 2kuh 2l53 2l7l 2lqf 2ll6 2ll7 2lqc 2lqp 2lv6 2m0j 2m0k 2m55 2mg5 2n27 2n6a 2n77 2n8j 2r28 2v01 2v02 2vay 2w73 2wel 2x0g 2y4v 3bya 3dve 3dvj 3dvk 3dvm 3ewt 3ewv 3g43 3hr4 3j41 3o77 3o78 3oxq 3sui 3uct 3ucw 3ucy 4bw7 4bw8 4byf 4dck 4djc 4gow 4j pz 4jq0 4l79 4lzx 4m1l 4ovn 4q57 4q5u 4umo 4upu 4v0c 5coc 5dbr 5dow 5dsu 5ggm 5i0i 5j03 5j8h 5jqa 5jth 5k7l 5k8q 5tp5 5tp6
Peroxisomeproliferator activated receptor delta/ Zinc-finger/ T36557	1gwx 1y0s 2awh 2b50 2baw 2env 2gwx 2j14 2q5g 2xyj 2xyw 2xyx 2znp 2znq 3d5f 3dy6 3et2 3gwx 3gz9 3oz0 3peq 3sp9 3tkm 5u3q 5u3r 5u3s 5u3t 5u3u 5u3v 5u3w 5u3x 5u3y 5u3z 5u40 5u41 5u42 5u43 5u44 5u45 5u46
Thrombin receptor/ GPCR rhodopsin/ T36483	1nrn 1nro 1nrp 1nrq 1nrr 3bef 3hki 3hkj 3lu9 3vw7
Dual specificity mitogen-activated protein kinase kinase 1/ Kinase/ T35940	1s9j 2p55 3dv3 3dy7 3e8n 3eqb 3eqc 3eqd 3eqf 3eqg 3eqh 3eqi 3mbl 3orn 3os3 3pp1 3sls 3v01 3v04 3vvh 3w8q 3wig 3zls 3zlw 3zlx 3zly 3zm4 4an2 4an3 4an9 4anb 4ark 4lmm 4mne 4u7z 4u80 4u81 5bx0 5eym 5hze
Lymphocyte function-associated antigen 1/ T35640	1cqp 1dgq 1ij4 1lfa 1mjn 1mq8 1mq9 1mqa 1rd4 1t0p 1xdd 1xdg 1xuo 1zon 1zoo 1zop 2ica 2k8o 2m3e 2o7n 3bn3 3bqm 3bqn 3e2m 3eoa 3eob 3f74 3f78 3hi6 3m6f 3tcx 4ixd 5e6r 5e6s 5e6u

Collagenase 3/ Peptidase/ T34296	1eub 1fls 1fm1 1pex 1ucl 1xuc 1xud 1xur 1you 1ztq 2d1n 2e2d 2ow9 2ozr 2pjt 2yig 3elm 3i7g 3i7i 3kek 3kej 3kek 3kry 3ljz 3o2x 3tvc 3wv1 3wv2 3wv3 3zxh 456c 4a7b 4fu4 4fvl 4g0d 4jp4 4jpa 4l19 5b5o 5b5p 5bot 5boy 5bpa 5uwk 5uwl 5uwm 5uwn 830c
Integrin alpha-5/ Integrin/ T29879	3vi3 3vi4 4wjk 4wk0 4wk2 4wk4
Histone Deacetylase 8/ Carbon-nitrogen hydrolase/ T28887	1t64 1t67 1t69 1vkg 1w22 2v5w 2v5x 3ew8 3ewf 3ezp 3ezt 3f06 3f07 3f0r 3mz3 3mz4 3mz6 3mz7 3rqd 3sff 3sfh 4qa0 4qa1 4qa2 4qa3 4qa4 4qa5 4qa6 4qa7 4rn0 4rn1 4rn2 5bwz 5dlb 5dlc 5d1d 5dc5 5dc6 5dc7 5dc8 5fcw 5ths 5tht 5thu 5thv 5vi6
Metabotropicglutamate receptor 1/ GPCR glutamate/ T27137	3ks9 4or2
Aldose reductase/ Short-chain de- hydrogenases reductases/ T26623	1abn 1ads 1az1 1az2 1ef3 1el3 1iei 1mar 1pwl 1pwm 1t40 1t41 1us0 1x96 1x97 1x98 1xgd 1z3n 1z89 1z8a 2acq 2acr 2acs 2acu 2agt 2dux 2duz 2dv0 2f2k 2fz8 2fz9 2fzb 2fzd 2hv5 2hvn 2hvo 2i16 2i17 2ikg 2ikh 2iki 2ikj 2ine 2inz 2ipw 2iq0 2iqd 2is7 2isf 2j8t 2nvc 2nvd 2pd5 2pd9 2pdb 2pdc 2pdf 2pdg 2pdh 2pdi 2pdj 2pdk 2pdl 2pdm 2pdn 2pdp 2pdq 2pdu 2pdw 2pdx 2pdy 2pev 2pf8 2pfh 2pzn 2qxx 2r24 3bcj 3dn5 3g5e 3ghr 3ghs 3ght 3ghu 3lbo 3ld5 3len 3lep 3lqg 3lql 3lz3 3lz5 3m0i 3m4h 3m64 3mb9 3mc5 3onb 3onc 3p2v 3q65 3q67 3rx2 3rx3 3rx4 3s3g 3t42 3u2c 3v35 3v36 4gca 4gq0 4igs 4jir 4lau 4laz 4lb3 4lb4 4lbr 4lbs 4nkc 4pr4 4prp 4prt 4puu 4puw 4q7b 4qbx 4qr6 4qx4 4qxi 4rpq 4xzh 4xzi 4ys1 4yu1 5ha7
Tyrosine-protein kinase BTK/ Ki- nase/ T25005	1aww 1awx 1b55 1btk 1bwn 1k2p 1qly 2ge9 2z0p 3gen 3k54 3ocs 3oct 3p08 3pix 3piy 3piz 3pj1 3pj2 3pj3 4nwm 4ot5 4ot6 4otf 4otq 4otr 4rfy 4rfz 4rg0 4rx5 4yhf 4z3v 4zly 4zly 5bpy 5bq0 5fbn 5fbo 5j87 5jrs 5kup 5p9f 5p9g 5p9h 5p9i 5p9j 5p9k 5p9l 5p9m 5t18 5u9d 5vgo
Tyrosine-protein kinase JAK3/ Ki- nase/ T23172	1yvj 3lxx 3lxl 3pjc 3zc6 3zep 4hvd 4hvg 4hvh 4hvi 4i6q 4qps 4qt1 4rio 4v0g 4z16 5lwm 5lwn 5toz 5tts 5ttu 5ttv 5vo6 5w86 5wfj
NAD-dependent deacetylase sirtuin-1/ Carbon-nitrogen hy- drolase/ T14731	4i5i 4if6 4ig9 4kxq 4zzh 4zzi 4zzj 5btr
Sphingosine 1-phosphate receptor 1/ GPCR rhodopsin/ T13852	3v2w 3v2y
Retinoic acid receptor RXR-alpha/ Zinc-finger/ T13726	1by4 1dsz 1fby 1fm6 1fm9 1glu 1g5y 1k74 1lbd 1mv9 1mvc 1mzn 1r0n 1rdt 1rxr 1xls 1xv9 1xvp 1ynw 2acl 2nll 2p1t 2p1u 2p1v 2zxz 2zy0 3dzu 3dzy 3e00 3e94 3fal 3fc6 3fug 3h0a 3kwy 3nsp 3nsq 3oap 3ozj 3pcu 3r29 3r2a 3r5m 3uvv 4cn2 4cn3 4cn5 4cn7 4j5w 4j5x 4k4j 4k6i 4m8e 4m8h 4n5g 4n8r 4nqa 4oc7 4poh 4poj 4pp3 4pp5 4rfw 4rmc 4rmd 4rme 4zo1 4zsh 5ec9 5gym 5ji0 5lyq 5mj5 5mk4 5mkj 5mku 5mmw 5tbp 5uan
Carbonic anhydrase I/ Carbon- oxygen lyases/ T13201	1azm 1bzm 1crm 1czm 1hcb 1hug 1huh 1j9w 1jv0 2cab 2foy 2fw4 2it4 2nmx 2nn1 2nn7 3lxe 3w6h 3w6i 4wr7 4wup 4wuq 5e2m 5gmm

Acetyl-CoA carboxylase 2/ Ligases forming carbon-carbon bonds/ T08922	2dn8 2hjl 2kcc 3ff6 3gid 3glk 3jrw 3jrx 3tdc 4hq6 5kkn
mRNA of PDK-1/ Kinase/ T08074	1h1w 1oky 1okz 1uu3 1uu7 1uu8 1uu9 1uvr 1w1d 1w1g 1w1h 1z5m 2biy 2pe0 2pe1 2pe2 2r7b 2vki 2xch 2xck 3h9o 3hrc 3hrf 3ion 3iop 3nax 3nay 3nun 3nus 3nuu 3nuy 3orx 3orz 3otu 3pwy 3qc4 3qcq 3qcs 3qcx 3qcy 3qd0 3qd3 3qd4 3rcj 3rwp 3rwq 3sc1 4a06 4a07 4aw0 4aw1 4ct1 4ct2 4rqk 4rqv 4rrv 4xx9 5ack 5hkm 5hng 5ho7 5ho8 5lv1 5lvm 5lvn 5lvo 5lvp 5mrd
CGMP-specific 3',5'-cyclic phosphodiesterase/ Phosphoric diester hydrolases/ T07663	1rkp 1t9r 1t9s 1tbf 1udt 1udu 1uho 1xoz 1xp0 2chm 2h40 2h42 2h44 2xss 3b2r 3bjc 3hc8 3hdz 3jwq 3jwr 3lfv 3mf0 3shy 3shz 3sie 3tge 3tgg 4g2w 4g2y 4i9z 4ia0 4md6 4oew 4oex 5jo3
Neurotrophic tyrosine kinase receptor 1/ Kinase/ T07173	1he7 1shc 1wwa 1www 2ifg 2n90 4aoj 4crp 4f0i 4gt5 4pmm 4pmp 4pms 4pmt 4yne 4yps 5h3q 5i8a 5jfs 5jfv 5jfw 5jfx 5kmi 5kmj 5kmk 5kml 5kmm 5kmn 5kmo
Poly [ADP-ribose] polymerase-1/ Pentosyltransferase/ T06273	1uk0 1uk1 1wok 2cok 2cr9 2cs2 2dmj 2jvn 2l30 2l31 2n8a 2rcw 2rd6 2riq 3gjw 3gn7 3l3l 3l3m 3od8 3oda 3odc 3ode 4av1 4dqy 4gv7 4hhy 4hhz 4l6s 4opx 4oqa 4oqb 4pjt 4r5w 4r6e 4rv6 4und 4uxb 4xhu 4zzz 5a00 5ds3 5ha9 5kpn 5kpo 5kpp 5kpq 5wrq 5wry 5wrz 5ws0 5ws1 5wtc
Nitric oxide synthase, inducible/ Oxidoreductases acting on paired donors/ T02703	1nsi 2ll6 2nsi 3e7g 3ej8 3hr4 4cx7 4nos 5tp6 5xn3
D(3) dopamine receptor/ GPCR rhodopsin/ T02551	3pbl
Phosphoinositide 3 kinase/ Kinase/ T95913	1e8y 1e8z 1he8 2a4z 2a5u 2chw 2chx 2chz 2v4l 3apc 3apd 3apf 3csf 3cst 3dbs 3dpd 3ene 3ibe 3l08 3l13 3l16 3l17 3l54 3lj3 3mjw 3ml8 3ml9 3nzs 3nzu 3oaw 3p2b 3pre 3prz 3ps6 3qaq 3qar 3qjz 3qk0 3r7q 3r7r 3s2a 3sd5 3t8m 3tjp 3tl5 3zvv 3zw3 4anu 4anv 4anw 4anx 4aof 4dk5 4ezj 4ezk 4ezl 4fls 4fa6 4fad 4fhj 4fhk 4fjy 4fjz 4flh 4ful 4g11 4gb9 4hle 4hvb 4j6i 4kz0 4kzc 4ps3 4ps7 4ps8 4urk 4wwn 4ww0 4wwp 4xx5 4xz4 5eds 5g2n 5g55 5jha 5jhb 5kae 5oq4 5t23
Ribosomal protein S6 kinase/ Kinase/ T94479	3a60 3a61 3a62 3we4 3wf5 3wf6 3wf7 3wf8 3wf9 4l3j 4l3l 4l42 4l43 4l44 4l45 4l46 4rlo 4rlp
Receptor protein-tyrosine kinase erbB-4/ Kinase/ T92057	2ahx 2l2t 2lcx 2r4b 3bbt 3bbw 3bce 3u2p 3u7u 3u9u
mRNA of B-Raf/ Kinase/ T90648	1uwH 1uwj 2fb8 2l05 3c4c 3d4q 3idp 3ii5 3ny5 3og7 3ppj 3ppk 3prf 3pri 3psb 3psd 3q4c 3q96 3skc 3tv4 3tv6 4cqe 4dbn 4e26 4e4x 4ehe 4ehg 4fc0 4fk3 4g9c 4g9r 4h58 4jvg 4ksp 4ksq 4mbj 4mne 4mnf 4pp7 4r5y 4rzv 4rzw 4wo5 4xv1 4xv2 4xv3 4xv9 4yht 5c9c 5csw 5csx 5ct7 5fd2 5hi2 5hid 5hie 5ita 5j17 5j18 5j2r 5jrq 5jsm 5jt2 5val 5vam

Glycinamide ribonucleotide formyl-transferase/ Carbon-nitrogen ligase/ T89918	1mej 1men 1meo 1njs 1rbm 1rbq 1rby 1rbz 1rc0 1rc1 1zlx 1zly 2qk4 2v9y 4ew1 4ew2 4ew3 4zyt 4zyu 4zyv 4zyw 4zyx 4zyy 4zyz 4zz0 4zz1 4zz2 4zz3 5j9f
17 alpha-hydroxylase-C17, 20-lyase/ Oxidoreductases acting on paired donors/ T89041	2c17 3ruk 3swz 4nkv 4nkw 4nkx 4nky 4nkz 5irq 5irv
Protein farnesyltransferase beta subunit/ Alkyl aryl transferase/ T86428	1jcc 1ld7 1ld8 1mzc 1s63 1sa4 1tn6 2f0y 2h6f 2h6g 2h6h 2h6i 2iej 3e37
Coagulation factor IX/ Peptidase/ T83369	1cfh 1cfi 1edm 1ixa 1mgx 1nl0 1rfn 2wph 2wpi 2wpj 2wpk 2wpl 2wpm 3keg 3lc3 3lc5 4wm0 4wma 4wmb 4wmi 4wmk 4wn2 4wnh 4yzu 4z0k 4zae 5egm 5f84 5f85 5f86 5jb8 5jb9 5jba 5jbb 5jbc 5tno 5tnt 5vyg
Angiotensin-converting enzyme/ Glycosylases/ T82577	1o86 1o8a 1uze 1uzf 2c6f 2c6n 2iul 2iux 2oc2 2xy9 2xyd 2ydm 3bkk 3bkl 3l3n 3nxq 4aph 4apj 4bxx 4bzz 4bzs 4c2n 4c2o 4c2p 4c2q 4c2r 4ca5 4ca6 4ufa 4ufb 5am8 5am9 5ama 5amb 5amc
Retinoic acid receptor gamma/ Nuclear hormone receptor/ T82146	1exa 1exx 1fcx 1fcy 1fcz 1fd0 2lbd 3lbd 4lbd 5m24
mRNA of Inhibitor of apoptosis protein/ Target of antisense drug/ T81892	1c9q 1f9x 1g3f 1g73 1i3o 1i4o 1i5l 1kmc 1nw9 1tfq 1tft 2ecg 2jk7 2kna 2opy 2opz 2poi 2pop 2qra 2vsl 3clx 3cm2 3cm7 3eyl 3g76 3hl5 3uw4 3uw5 4ec4 4hy0 4ic2 4ic3 4j3y 4j44 4j45 4j46 4j47 4j48 4kju 4kjj 4kmp 4mtz 4oxc 4wvs 4wvt 4wvu 5c0k 5c0l 5c3h 5c3k 5c7a 5c7b 5c7c 5c7d 5c83 5c84 5m6e 5m6f 5m6h 5m6l 5m6m 5o6t
Squalene synthetase/ Alkyl aryl transferase/ T81850	1ezf 3asx 3lee 3q2z 3q30 3v66 3vj8 3vj9 3vja 3vjb 3vjc 3wc9 3wcd 3wcf 3wch 3wci 3wcj 3wcl 3wcm 3wef 3weg 3weh 3wei 3wej 3wek 3wsa
MAP kinase p38/ Kinase/ T79798	1cm8 4qum
Thyroid hormone receptor alpha/ Nuclear hormone receptor/ T79591	1nav 2h77 2h79 3hzf 3ilz 3jzb 4lnw 4lnx
Catechol-O-methyl-transferase/ Methyltransferase superfamily/ T76904	3a7e 3bwm 3bwy 4pyi 4pyj 4pyk 4xuc 4xud 4xue 5lsa
Antithrombin-III/ Serpin family/ T73476	1ant 1ath 1azx 1br8 1dzg 1dzh 1e03 1e04 1e05 1jvq 1lk6 1nq9 1oyh 1r1l 1sr5 1t1f 1tb6 2ant 2b4x 2b5t 2beh 2gd4 2hij 2znh 3evj 3kcg 4eb1
Tissue factor/ Transmembrane protein/ T72702	1ahw 1boy 1dan 1fak 1j9c 1jps 1nl8 1o5d 1tfh 1uj3 1w0y 1w2k 1wqv 1wss 1wtg 1wun 1wv7 1z6j 2a2q 2aei 2aer 2b7d 2b8o 2c4f 2cef 2ceh 2cez 2cfj 2ec9 2f9b 2fir 2flb 2fir 2hft 2puq 2zp0 2zwl 2zzu 3ela 3th2 3th3 3th4 4ibl 4m7l 4ylq 4z6a 4zma 5w06

Mineralocorticoid receptor/ Zinc-finger/ T72168	1y9r 1ya3 2a3i 2aa2 2aa5 2aa6 2aa7 2aax 2ab2 2abi 2oax 3vhu 3vhv 3wff 3wfg 4pf3 4tnt 4uda 4udb 5hcv 5l7e 5l7g 5l7h
Corticosteroid 11-beta-dehydrogenase, isozyme 1/ Short-chain dehydrogenases reductases/ T65200	1xu7 1xu9 2bel 2ilt 2irw 2rbe 3byz 3bzu 3ch6 3czr 3d3e 3d4n 3d5q 3ey4 3feo 3frj 3h6k 3hfg 3oq1 3pdj 3qqp 3tfq 4bb5 4bb6 4c7j 4c7k 4hfr 4hx5 4iju 4ijv 4ijw 4k1l 4p38 4yyz 5pgu 5pgv 5pgw 5pgx 5pgy
JAK1/ Kinase/ T62460	3eyg 3eyh 4e4l 4e4n 4e5w 4ehz 4ei4 4fk6 4gs0 4i5c 4ivb 4ivc 4ivd 4k6z 4k77 4l00 4l01 5e1e 5hx8 5ixd 5ixi 5khw 5kxh 5l04
Interleukin-2/ Cytokine: interleukin/ T61698	1ilm 1iln 1irl 1m47 1m48 1m49 1m4a 1m4b 1m4c 1nbp 1pw6 1py2 1qvn 1z92 2b5i 2erj 3ink 3qaz 3qb1 4nej 4nem 5lqb 5m5e
Kappa-type opioid receptor/ GPCR rhodopsin/ T60693	2a0d 2iqn 4djh
Mast/ stem cell growth factor receptor/ T57700	1pkg 1qzj 1qzk 1r0l 1t45 1t46 2e9w 2ec8 2iuh 2vif 3g0e 3g0f 4hvs 4k94 4k9e 4pgz 4u0i
S-adenosylmethioninedecarboxylase proenzyme/ Carbon-carbon lyase/ T55922	1i72 1i79 1i7b 1i7c 1i7m 1jen 1jl0 1msv 3dz2 3dz3 3dz4 3dz5 3dz6 3dz7 3ep3 3ep4 3ep5 3ep6 3ep7 3ep8 3ep9 3epa 3epb 3h0v 3h0w
Mitogen-activated protein kinase 11/ Kinase/ T55729	3gc8 3gc9 3gp0
cystic fibrosis transmembrane conductance regulator/ Acid anhydrides hydrolase/ T55654	1nbd 1xmi 1xmj 2bbo 2bbs 2bbt 2lob 2pze 2pzf 2pzg 3gd7 3isw 4wz6 5d2d 5d3e 5d3f 5uak
Nicotinamide phosphoribosyl-transferase/ Pentosyltransferase/ T54582	2e5b 2e5c 2e5d 2gvg 2gvj 3dgr 3dhd 3dhf 3dkj 3dkl 4jnm 4jr5 4kfn 4kfo 4kfp 4l4l 4l4m 4lts 4lv9 4lva 4lvb 4lvd 4lvf 4lvg 4lww 4m6p 4m6q 4n9b 4n9c 4n9d 4n9e 4o0z 4o10 4o12 4o13 4o14 4o15 4o16 4o17 4o18 4o19 4o1a 4o1b 4o1c 4o1d 4o28 4wq6 5kit 5lx3 5lx5 5u2m 5u2n 5upe 5upf
Carbonic anhydrase IV/ Carbon-oxygen lyases/ T53378	1znc 3f7b 3f7u 3fw3 5ipz 5jn8 5jn9 5jna 5jnc 5ku6
NAD(P)H dehydrogenase [quinone] 1/ Oxidoreductases acting on NADH or NADPH/ T52389	1d4a 1dxo 1gg5 1h66 1h69 1kbo 1kbq 1qbg 2f1o 3jsx 4cet 4cf6 5a4k 5ea2 5eai 5fuq

Casein kinase II, alpha chain/ Kinase/ T51565	1jwh 1na7 1pjk 2pvr 2zjw 3amy 3at2 3at3 3at4 3axw 3bqc 3c13 3fwq 3h30 3juh 3mb6 3mb7 3nga 3nsz 3owj 3owk 3owl 3pe1 3pe2 3pe4 3q04 3q9w 3q9x 3q9y 3q9z 3qa0 3r0t 3rps 3tax 3u4u 3u87 3u9c 3w8l 3war 3wik 3wil 3wow 4dgl 4fbx 4grb 4gub 4gyw 4gyy 4gz3 4ib5 4kwp 4md7 4md8 4md9 4nh1 4rll 4ub7 4uba 5b0x 5clp 5cqu 5cqW 5cs6 5csh 5csp 5csv 5ct0 5ctp 5cu0 5cu2 5cu3 5cu4 5cu5 5cvf 5cvg 5cvh 5cx9 5h8b 5h8e 5h8g 5hgv 5ku8 5kwh 5m44 5m4c 5m4f 5m4i 5mmf 5mmr 5mo5 5mo6 5mo7 5mo8 5mod 5moe 5moh 5mot 5mov 5mow 5mp8 5mpj 5n1v 5nqc 5vie 5vif
Toll-like receptor 8/ Toll-like receptor family/ T48703	3w3g 3w3j 3w3k 3w3l 3w3m 3w3n 3wn4 4qbz 4qc0 4r07 4r08 4r09 4r0a 4r6a 5awa 5awb 5awc 5awd 5az5 5hdh
mRNA of androgen receptor/ Target of antisense drug/ T46521	1e3g 1gs4 1t5z 1t63 1t65 1xj7 1xow 1xq3 1z95 2am9 2ama 2amb 2ao6 2ax6 2ax7 2ax8 2ax9 2axa 2hvc 2oz7 2pio 2pip 2piq 2pir 2pit 2piu 2piv 2piw 2pix 2pkl 2pnu 2q7i 2q7j 2q7k 2q7l 2yhd 2ylo 2ylp 2ylq 2z4j 3b5r 3b65 3b66 3b67 3b68 3btr 3l3x 3l3z 3rlj 3rll 3v49 3v4a 3zqt 4hlw 4k7a 4oea 4oed 4oey 4oez 4ofr 4ofu 4ogh 4oh5 4oh6 4oha 4oil 4oiu 4oj9 4ojb 4ok1 4okb 4okt 4okw 4okx 4olm 4ql8 5cj6 5jjm 5t8e 5t8j 5v8q
Coagulation factor VII/ Peptidase/ T43332	1bf9 1cvw 1dan 1dva 1f7e 1f7m 1fak 1ff7 1ffm 1j9c 1jbu 1kli 1klj 1n18 1o5d 1qfk 1w0y 1w2k 1w7x 1w8b 1wqv 1wss 1wtg 1wun 1wv7 1ygc 1z6j 2a2q 2aei 2aer 2b7d 2b8o 2bz6 2c4f 2ec9 2f9b 2fir 2flb 2flr 2puq 2zp0 2zwl 2zzu 3ela 3th2 3th3 3th4 4ibl 4ish 4isi 4jyu 4jyv 4jzd 4jze 4jzf 4na9 4ng9 4nga 4x8s 4x8t 4x8u 4x8v 4ylq 4yt6 4yt7 4z6a 4zma 4zxx 4zxy 5i46 5l0s 5l2y 5l2z 5l30 5pa8 5pa9 5paa 5pab 5pac 5pae 5paf 5pag 5pai 5paj 5pak 5pam 5pan 5pao 5paq 5par 5pas 5pat 5pau 5pav 5paw 5pax 5pay 5pb0 5pb1 5pb2 5pb3 5pb4 5pb5 5pb6 5tqe 5tqf 5tqg 5u6j
Ferrochelatase/ Ferrochelatase/ T42822	1hrk 2hrc 2hre 2pnj 2po5 2po7 2qd1 2qd2 2qd3 2qd4 2qd5 3aqi 3hcn 3hco 3hcp 3hcr 3w1w 4f4d 4kla 4klc 4klr 4kmm 4mk4
Gamma-aminobutyric acid B receptor/ GPCR glutamate/ T42446	4f11 4f12 4mqe 4mqf 4mr7 4mr8 4mr9 4mrm 4ms1 4ms3 4ms4 4pas
5-hydroxytryptamine 2B receptor/ GPCR rhodopsin/ T31204	4ib4 4nc3 5tud 5tvn
Protein kinase C, theta type/ Kinase/ T23995	1xjd 2enj 2enn 2enz 2jed 4q9z 4ra5 5f9e
Mitogen-activated protein kinase 3/ Kinase/ T23276	2zoq 4qtb
3-phosphoinositide dependent protein kinase-1/ Kinase/ T20891	1hlw 1oky 1okz 1uu3 1uu7 1uu8 1uu9 1uvr 1w1d 1w1g 1w1h 1z5m 2biy 2pe0 2pe1 2pe2 2r7b 2vki 2xch 2xck 3h9o 3hrc 3hrf 3ion 3iop 3nax 3nay 3nun 3nus 3nuu 3nuy 3orx 3orz 3otu 3pwy 3qc4 3qcq 3qcs 3qcx 3qcy 3qd0 3qd3 3qd4 3rcj 3rwp 3rwq 3sc1 4a06 4a07 4aw0 4aw1 4ct1 4ct2 4rqk 4rqv 4rrv 4xx9 5ack 5hkm 5hng 5ho7 5ho8 5l1v 5lvm 5lvn 5lvo 5lvp 5mrd

DHFR/ Oxidoreductases acting on CH-NH group of donors/ T17345	1boz 1dhf 1dlr 1dls 1drf 1hfp 1hfq 1hfr 1kms 1kmv 1mvs 1mvt 1ohj 1ohk 1pd8 1pd9 1pdb 1s3u 1s3v 1s3w 1u7l 1u72 1yho 2c2s 2c2t 2dhf 2w3a 2w3b 2w3m 3eig 3f8y 3f8z 3f9l 3fs6 3ghc 3ghv 3ghw 3gi2 3gyf 3l3r 3n0h 3ntz 3nu0 3nxx 3nxx 3nxt 3nxv 3nxx 3nxy 3nzd 3oaf 3s3v 3s7a 4ddr 4g95 4kak 4kbn 4kd7 4keb 4kfj 4m6j 4m6k 4m6l 4qhv 4qjc 5hpb 5hqy 5hqz 5hsr 5hsu 5ht4 5ht5 5hui 5hvb 5hve
X-linked inhibitor of apoptosis protein/ Carbon-nitrogen ligase/ T16769	1c9q 1f9x 1g3f 1g73 1i3o 1i4o 1i5l 1kmc 1nw9 1tfq 1tft 2ecg 2jk7 2kna 2opy 2opz 2poi 2pop 2qra 2vsl 3clx 3cm2 3cm7 3eyl 3g76 3hl5 3uw4 3uw5 4ec4 4hy0 4ic2 4ic3 4j3y 4j44 4j45 4j46 4j47 4j48 4kju 4kju 4kmp 4mtz 4oxc 4wvs 4wvt 4wvu 5c0k 5c0l 5c3h 5c3k 5c7a 5c7b 5c7c 5c7d 5c83 5c84 5m6e 5m6f 5m6h 5m6l 5m6m 5o6t
Caspase-8/ Peptidase/ T15700	1f9e 1i4e 1qdu 1qtn 2c2z 2fun 2k7z 2y1l 3h1l 3kjm 3kjq 4jj7 4prz 4psl 4zbw 5h3l 5h33 5jqe 5l08
Methylmalonyl-CoA mutase/ Intramolecular transferases/ T15569	2xij 2xiq 3bic
Focal adhesion kinase/ Kinase/ T15068	1k04 1k05 1mp8 1ow6 1ow7 1ow8 2etm 2ijm 3b7l 3bz3 3pxk 3s9o 4ebv 4ebw 4gu6 4gu9 4i4e 4i4f 4k8a 4k9y 4kab 4kao 4ny0 4q9s
Succinate semialdehyde dehydrogenase, mitochondrial/ Oxidoreductases acting on aldehyde or oxo group of donors/ T13259	2w8n 2w8o 2w8p 2w8q 2w8r
Tyrosine-protein kinase JAK2/ Kinase/ T08391	2b7a 2w1i 2xa4 3e62 3e63 3e64 3fup 3io7 3io8 3jy9 3kck 3krr 3lpb 3q32 3rvq 3tjc 3tjd 3ugc 3zmm 4aqc 4bbe 4bbf 4c6l 4c62 4d0w 4d0x 4d1s 4e4m 4e6d 4e6q 4f08 4f09 4fvp 4fvq 4fvr 4gfm 4gmy 4hge 4iva 4ji9 4jia 4p7e 4ytc 4ytf 4yth 4yti 4z32 4zim 5aep 5cf4 5cf5 5cf6 5cf8 5hez 5i4n 5l3a 5tq3 5tq4 5tq5 5tq6 5tq7 5tq8 5usy 5usz 5ut0 5ut1 5ut2 5ut3 5ut4 5ut5 5ut6 5wev
5-hydroxytryptamine 1B receptor/ GPCR rhodopsin/ T07806	2g1x 4iaq 4iar
Rho-associated protein kinase 1/ Kinase/ T07102	1s1c 2esm 2etk 2etr 2v55 3d9v 3ncz 3ndm 3o0z 3tv7 3twj 3v8s 4l2w 4w7p 4yvc 4yve 5bml 5f5p 5hvu 5kks 5kkt
CBP/ Acyltransferase/ T03634	1jsp 1liq 1rtd 1wo3 1wo4 1wo5 1wo6 1wo7 1zoq 2d82 2kje 2kwf 2l84 2l85 2lxs 2lxt 2n1a 2rny 3dwy 3p1c 3p1d 3p1e 3p1f 3svh 4a9k 4n3w 4n4f 4nr4 4nr5 4nr6 4nr7 4nyv 4nyw 4nyx 4ouf 4tqn 4ts8 4whu 4yk0 5cgp 5dbm 5eic 5eng 5ep7 5gh9 5h85 5i83 5i86 5i89 5i8b 5i8g 5j0d 5jem 5ktu 5ktw 5ktx 5lpj 5lpl 5mpz 5mqe 5mqg 5mqk 5nrw 5nu3 5tb6
Integrin beta-1/ Integrin/ T01851	1k1l 1lha 3g9w 3t9k 3vi3 3vi4 4dx9 4wj 4wk0 4wk2 4wk4

Dihydroorotate dehydrogenase, mitochondrial/ Oxidoreductases acting on CH-CH group of donors/ T01318	1tv5 3i65 3i68 3i6r 3o8a 3sfk 4cq8 4cq9 4cqa 4orm 4rx0 5boo 5del 5fi8 5tbo
Mitogen-activated protein kinase 10/ Kinase/ T00663	1jnk 1pmn 1pmu 1pmv 2b1p 2exc 2o0u 2o2u 2ok1 2p33 2r9s 2waj 2zdt 2zdu 3cgf 3cgo 3da6 3fi2 3fi3 3fv8 3g90 3g9l 3g9n 3kvx 3oxi 3oy1 3ptg 3rtp 3tti 3ttj 3v6r 3v6s 4h36 4h39 4h3b 4kke 4kkg 4kkh 4u79 4w4v 4w4w 4w4x 4w4y 4whz 4x21 4y46 4y5h 4z9l
Ubiquitin-protein ligase E3 Mdm2/ Carbon-nitrogen ligase/ T00176	1rv1 1t4e 1t4f 1ycr 1z1m 2axi 2c6a 2c6b 2fly 2fop 2gv2 2hdp 2lzg 2m86 2mps 2ruh 2vje 2vjf 3eqs 3g03 3iux 3iwy 3jzk 3jzr 3jzs 3lbk 3lbl 3lnj 3lnz 3mqs 3tj2 3tpx 3tu1 3v3b 3vbg 3vzv 3w69 4dij 4ere 4erf 4hbm 4hfb 4hg7 4jv7 4jv9 4jve 4jvr 4jwr 4mdn 4mdq 4oas 4oba 4occ 4ode 4odf 4ogn 4ogt 4ogv 4oq3 4qo4 4qoc 4ud7 4uel 4umn 4wt2 4xxb 4zfi 4zgz 4zyc 4zyf 4zyi 5afg 5c5a 5hmf 5hmi 5hmk 5j7f 5j7g 5lav 5law 5lay 5laz 5ln2 5mnj 5swk 5trf
Thyroid hormone receptor beta-1/ Nuclear hormone receptor/ T98933	1bsx 1n46 1nax 1nq0 1nq1 1nq2 1nuo 1q4x 1r6g 1xzx 1y0x 2j4a 2nll 2pin 3d57 3gws 3imy 3jzc 4zo1
Mitogen-activated protein kinase kinase 5/ Kinase/ T97589	2clq 3vw6 4bf2 4bhn 4bib 4bic 4bid 4bie 5ulm 5uor 5uox 5up3 5v19 5v24 6ejl
UDP-glucose 4-epimerase/ Racemases and epimerases/ T96014	1ek5 1ek6 1hzj 1i3k 1i3l 1i3m 1i3n
Retinoic acid receptor alpha/ Nuclear hormone receptor/ T94085	1dkf 1dsz 3a9e 3kmr 3kmz 4dqm 5k13
FGF-3 receptor/ Kinase/ T91331	1ry7 2lzl 4k33
DNMT1/ Methyltransferase superfamily/ T88304	3epz 3pta 3swr 4wxw 4yoc 4z96 4z97
Aurora kinase A/ Kinase/ T87675	1mq4 1muo 1ol5 1ol6 1ol7 2bmc 2c6d 2c6e 2dwb 2j4z 2j50 2np8 2w1c 2w1d 2w1e 2w1f 2w1g 2wqe 2wtv 2wtw 2x6d 2x6e 2x81 2xne 2xng 2xru 3coh 3e5a 3efw 3fdn 3h0y 3h0z 3h10 3ha6 3k5u 3lau 3m11 3myg 3nrm 3o50 3o51 3p9j 3qbn 3r21 3r22 3unz 3uo4 3uo5 3uo6 3uod 3uoh 3uoj 3uok 3uol 3up2 3up7 3vap 3w10 3w16 3w18 3w2c 4b0g 4bn1 4byi 4byj 4c3p 4c3r 4ceg 4dea 4deb 4ded 4dee 4dhf 4j8m 4j8n 4jai 4jaj 4jbo 4jbp 4jbq 4o0s 4o0u 4o0w 4prj 4utd 4uyn 4uzd 4uzh 4zs0 4ztq 4ztr 4zts 5aad 5aae 5aaf 5aag 5dn3 5dnr 5dos 5dpv 5dr2 5dr6 5dr9 5drd 5dt0 5dt3 5dt4 5ew9 5glx 5l8j 5l8k 5l8l 5lxm 5obj 5obr 5one 5orl 5orn 5oro 5orp 5orr 5ors 5ort 5orv 5orw 5orx 5ory 5orz 5os0 5os1 5os2 5os3 5os4 5os5 5os6 5osd 5ose 5osf
Receptor protein-tyrosine kinase erbB-3/ Kinase/ T86350	1m6b 2l9u 3kex 3lmg 3p11 4leo 4otw 4p59 4riw 4rix 4riy 5cus

Thioredoxin/ Thioredoxin/ T85616	1aiu 1auc 1cqq 1cqh 1ert 1eru 1erv 1erw 1m7t 1mdi 1mdj 1mdk 1trs 1tru 1trv 1trw 1w1c 1w1e 2hsh 2hsk 2ifq 2iyy 3e3e 3kd0 3m9j 3m9k 3qfa 3qfb 3trx 4ll1 4ll4 4oo4 4oo5 4pok 4pol 4pom 4puf 4trx 5dqy
Glutamate receptor, ionotropic kainate 1/ Glutamate-gated ion channel/ T73495	2zns 2znt 2znu 3fuz 3fv1 3fv2 3fvg 3fvk 3fvn 3fvo 4mf3
Steroid hormone receptor ERR1/ Nuclear hormone receptor/ T72841	1xb7 2pjl 3d24 3k6p
mRNA of Protein kinase C-theta/ Kinase/ T72295	1xjd 2enj 2enn 2enz 2jed 4q9z 4ra5 5f9e
Wee1-like protein kinase/ Kinase/ T69991	1x8b 2in6 2io6 2z2w 3bi6 3biz 3cqe 3cr0 5v5y 5vc3 5vc4 5vc5 5vc6 5vd2
Cathepsin S/ Peptidase/ T68290	1bxf 1glo 1ms6 1npz 1nqc 2c0y 2f1g 2fq9 2fra 2frq 2ft2 2fud 2fye 2g6d 2g7y 2h7j 2hh5 2hhn 2hxx 2op3 2r9m 2r9n 2r9o 3iej 3kwn 3mpe 3mpf 3n3g 3n4c 3ovx 4p6e 4p6g
5'-Nucleotidase/ Phosphoric monoester hydrolases/ T65116	4h1s 4h1y 4h2b 4h2f 4h2g 4h2i
Serine/ threonine-protein kinase Sgk1/ T64682	2r5t 3hdm 3hdm
Serine/ threonine-protein kinase Chk1/ T62449	1ia8 1nvq 1nvr 1nvs 1zlt 1zys 2ayp 2br1 2brb 2brg 2brh 2brm 2brn 2bro 2c3j 2c3k 2c3l 2cgu 2cgv 2cgw 2cgx 2e9n 2e9o 2e9p 2e9u 2e9v 2gdo 2ghg 2hog 2hxl 2hxx 2hy0 2qhm 2qhn 2r0u 2wmq 2wmr 2wms 2wmt 2wmu 2wmv 2wmw 2wmx 2x8d 2x8e 2x8i 2xey 2xez 2xf0 2ydi 2ydj 2ydk 2yer 2yex 2ym3 2ym4 2ym5 2ym6 2ym7 2ym8 2ywp 3f9n 3jvr 3jvs 3nlb 3ot3 3ot8 3pa3 3pa4 3pa5 3tkh 3tki 3u9n 4fsm 4fsn 4fsq 4fsr 4fst 4fsu 4fsw 4fsy 4fsz 4ft0 4ft3 4ft5 4ft7 4ft9 4fta 4ftc 4fti 4ftj 4ftk 4ftl 4ftm 4ftn 4fto 4ftq 4ftr 4ftt 4ftu 4gh2 4hyh 4hyi 4jik 4qye 4qyf 4qyg 4qyh 4rvk 4rvl 4rvm 5dls 5f4n 5oop 5oor 5oot 5op2 5op4 5op5 5op7 5opb 5opr 5ops 5opu 5opv 5opq 5oq5 5oq6 5oq7 5oq8
Dihydroorotate dehydrogenase/ Oxidoreductases acting on CH-CH group of donors/ T61400	1d3g 1d3h 2b0m 2bxv 2fpt 2fpv 2fpy 2fqj 2prh 2prl 2prm 2wv8 3f1q 3fj6 3fjl 3g0u 3g0x 3kvj 3kvk 3kvl 3kvm 3u2o 3w7r 3zws 3zwt 4igh 4jgd 4js3 4jts 4jtt 4jtu 4ls0 4ls1 4ls2 4oqv 4rk8 4rka 4rli 4rr4 4ylw 4zl1 4zmg 5h2z 5h73 5hin 5hqe 5k9c 5k9d 5mut 5mvc 5mvd 5tce
Proto-oncogene tyrosine-protein kinase receptor ret/ Kinase/ T60631	1xpd 2ivs 2ivt 2ivu 2ivv 2x2k 2x2l 2x2m 2x2u 4cki 4ckj 4ux8 5amn 5fm2 5fm3
Cell division protein kinase 7/ Kinase/ T58449	1lg3 1pa8 1ua2 2hic

Ephrin type-A receptor 2/ Kinase/ T57278	1mqb 2e8n 2k9y 2kso 2x10 2x11 3c8x 3czu 3fl7 3hei 3hpn 3kka 3mbw 3mx0 3skj 4p2k 4pdo 4trl 5ek7 5i9u 5i9v 5i9w 5i9x 5i9y 5i9z 5ia0 5ia1 5ia2 5ia3 5ia4 5ia5 5njz 5nk0 5nk1 5nk2 5nk3 5nk4 5nk5 5nk6 5nk7 5nk8 5nk9 5nka 5nkb 5nkc 5nkd 5nke 5nkf 5nkg 5nkh 5nki
Choline kinase/ Kinase/ T55709	2cko 2ckp 2ckq 2i7q 3f2r 3gl5 3zm9 4br3 4cg8 4cg9 4cga 4da5 5afv 5eqe 5eqp 5eqy 5ftg 5fut
ATP-citrate synthase/ Acyltrans- ferase/ T52189	3mwd 3mwe 3pff 5tde 5tdf 5tdm 5tdz 5tel 5teq 5tes 5tet
Ephrin type-B receptor 4/ Kinase/ T49507	2bba 2e7h 2hle 2qkq 2vwu 2vww 2vwx 2vwy 2vwz 2vx0 2vx1 2x9f 2xvd 2yn8 3zew 4aw5 4bb4
Aurora kinase B/ Kinase/ T46781	4af3
Corticotropin releasing factor re- ceptor 1/ GPCR secretin/ T45262	2l27 3ehs 3eht 3ehu 4k5y 4z9g
Cell division protein kinase 9/ Ki- nase/ T44458	1pf6 3blh 3blq 3blr 3lq5 3mi9 3mia 3my1 3tn8 3tnh 3tni 4bcf 4bcg 4bch 4bci 4bcj 4ec8 4ec9 4imy 4ogr 4or5 5llz
Serine/ threonine-protein kinase PLK1/ T40694	1q4k 1q4o 1umw 2ogq 2ojx 2ou7 2owb 2rku 2v5q 2yac 3bzi 3c5l 3fc2 3fvh 3hih 3hik 3kb7 3p2w 3p2z 3p34 3p35 3p36 3p37 3q1i 3rq7 3thb 4a4l 4a4o 4dfw 4e67 4e9c 4e9d 4h5x 4h7l 4hab 4hco 4hy2 4j52 4j53 4lkl 4lkm 4o56 4o6w 4o9w 4rcp 4whh 4whk 4whl 4x9r 4x9v 4x9w 5j19 5ta6 5ta8
mRNA of human PKC-eta/ Kinase/ T40149	2fk9 3txo
Cytochrome P450 3A4/ Oxidore- ductases acting on paired donors/ T37848	1tqn 1w0e 1w0f 1w0g 2j0d 2v0m 3nxu 3tjs 3ua1 4d6z 4d75 4d78 4d7d 4i3q 4i4g 4i4h 4k9t 4k9u 4k9v 4k9w 4k9x 4ny4 5a1p 5a1r 5g5j 5te8 5vc0 5vcc 5vcd 5vce 5vcg
mRNA of KRAS/ Ras family/ T35474	1d8d 1d8e 1kzo 1kzp 1n4p 1n4q 1n4r 1n4s 3gft 4dsn 4dso 4epr 4ept 4epv 4epw 4epx 4epy 4l8g 4ldj 4lpk 4lrw 4luc 4lv6 4lyf 4lyh 4lyj 4m1o 4m1s 4m1t 4m1w 4m1y 4m21 4m22 4nmm 4obe 4pzy 4pzz 4q01 4q02 4q03 4ql3 4tq9 4tqa 4wa7 5f2e 5kyk 5o2s 5o2t 5tar 5tb5 5ufe 5ufq 5uqw 5us4 5usj 5v6s 5v6v 5v71 5v9l 5v9o 5vbm 5xco
Calcitonine-related peptide type 1 receptor/ GPCR secretin/ T32262	3aqf 3n7p 3n7r 3n7s 4rwf 4rwg
mRNA of glucocorticoid receptor/ Zinc-finger/ T30687	1m2z 1nhz 1p93 3bqd 3cld 3e7c 3h52 3k22 3k23 4csj 4hn5 4hn6 4lsj 4mdd 4p6w 4p6x 4udc 4udd 5cbx 5cby 5cbz 5cc1 5e69 5e6a 5e6b 5e6c 5e6d 5emc 5emp 5emq 5g3j 5g5w 5nfp 5nft 5va0 5va7

mRNA of human caspase 6/ Peptidase/ T25927	1mi9 2wdp 3k7e 3nkf 3nr2 3od5 3p45 3p4u 3qnw 3s70 3s8e 3v6l 3v6m 4ejf 4fxo 4hva 4iyr 4n5d 4n6g 4n7j 4n7m 4nbk 4nbl 4nbn
PFKFB3 kinase/ Kinase/ T23787	2axn 2dwo 2dwp 2ilv 3qpu 3qp v 3qp w 4d4j 4d4k 4d4l 4d4m 4ma4 5ajv 5ajw 5ajx 5ajy 5ajz 5ak0
Cytochrome P450 11A1, mitochondrial/ Oxidoreductases acting on paired donors/ T23145	3n9y 3n9z 3na0 3na1
MAPKAP kinase 2/ Kinase/ T21307	1kwp 1nxk 1ny3 2jbo 2jbp 2okr 2onl 2oza 2p3g 2pzy 3a2c 3fpm 3fyj 3fyk 3gok 3ka0 3kc3 3kga 3m2w 3m42 3r2b 3r2y 3r30 3wi6 4tyh
Cell division protein kinase 5/ Kinase/ T20973	1h4l 1lfr 1lung 1unh 1unl 3o0g 4au8
mRNA of PKA Catalytic Subunit C-alpha/ Kinase/ T20669	2gu8 3agl 3agm 3ama 3amb 3l9l 3l9m 3l9n 3mvj 3nx8 3oog 3ovv 3owp 3oxt 3p0m 3poo 3vqh 4ae6 4ae9 4uj1 4uj2 4uj9 4uja 4ujb 4wb5 4wb6 4wb7 4wb8 5bx6 5bx7 5izf 5izj 5j5x

Carbonic anhydrase II/ Carbon-oxygen lyases/ T20401	12ca 1a42 1am6 1avn 1bcd 1bic 1bn1 1bn3 1bn4 1bnm 1bnn 1bnq 1bnt 1bnu 1bnv 1bnw 1bv3 1ca2 1ca3 1cah 1cai 1caj 1cak 1cal 1cam 1can 1cao 1cay 1caz 1ccs 1cct 1ccu 1cil 1cim 1cin 1cnb 1cnc 1cng 1cnh 1cni 1cnj 1cnk 1cnw 1cnx 1cny 1cra 1cva 1cvb 1cvc 1cvd 1cve 1cvf 1cvh 1dca 1dcb 1eou 1f2w 1fq1 1fqm 1fqn 1fqr 1fr4 1fr7 1fsn 1fsq 1fsr 1g0e 1g0f 1g1d 1g3z 1g45 1g46 1g48 1g4j 1g4o 1g52 1g53 1g54 1h4n 1h9n 1h9q 1hca 1hea 1heb 1hec 1hed 1hva 1i8z 1i90 1i91 1i9l 1i9m 1i9n 1i9o 1i9p 1i9q 1if4 1if5 1if6 1if7 1if8 1if9 1kwq 1kwr 1lg5 1lg6 1lgd 1lug 1lzw 1moo 1mua 1okl 1okm 1okn 1oq5 1ray 1raz 1rza 1rzb 1rzc 1rzd 1rze 1t9n 1tb0 1tb1 1te3 1teq 1teu 1tg3 1tg9 1th9 1thk 1ttm 1uga 1ugb 1ugc 1ugd 1uge 1ugf 1ugg 1xeg 1xev 1xpz 1xq0 1yda 1ydb 1ydc 1ydd 1yo0 1yo1 1yo2 1z9y 1ze8 1zfk 1zfq 1zge 1zgf 1zh9 1zsa 1zsb 1zsc 2abe 2aw1 2ax2 2ca2 2cba 2cbb 2cbc 2cbd 2cbe 2eu2 2eu3 2ez7 2f14 2fmg 2fmz 2fnk 2fnm 2fnn 2foq 2fos 2fou 2fov 2gd8 2geh 2h15 2h4n 2hd6 2hkk 2hl4 2hnc 2hoc 2ili 2nng 2nno 2nns 2nnv 2nwo 2nwp 2nwy 2nwz 2nxx 2nxt 2o4z 2osf 2osm 2pou 2pow 2q1b 2q1q 2q38 2qo8 2qoa 2qp6 2vva 2vvb 2wd2 2wd3 2weg 2weh 2wej 2weo 2x7s 2x7t 2x7u 3b4f 3bet 3bl0 3bl1 3c7p 3ca2 3caj 3cyu 3d8w 3d92 3d93 3d9z 3daz 3dbu 3dc3 3dc9 3dcc 3dcs 3dcw 3dd0 3dd8 3dv7 3dvv 3dvc 3dvd 3efi 3eft 3f4x 3f8e 3ffp 3gz0 3hfp 3hkn 3hkq 3hkt 3hku 3hlj 3hs4 3ibi 3ibl 3ibn 3ibu 3ieo 3igp 3k2f 3k34 3k7k 3kig 3kkx 3kne 3koi 3kok 3kon 3ks3 3kwa 3l14 3m04 3m14 3m1j 3m1k 3m1q 3m1w 3m2n 3m2x 3m2y 3m2z 3m3x 3m40 3m5e 3m5s 3m5t 3m67 3m96 3m98 3mhc 3mhi 3mhl 3mhm 3mho 3ml2 3mmf 3mna 3mnh 3mni 3mnj 3mnk 3mnu 3mwo 3myq 3mzc 3n0n 3n2p 3n3j 3n4b 3nb5 3ni5 3nj9 3oik 3oil 3oim 3oku 3okv 3oy0 3oyq 3oys 3p3h 3p3j 3p44 3p4v 3p55 3p58 3p5a 3p5l 3pjj 3po6 3pyk 3qyk 3r16 3r17 3rg3 3rg4 3rge 3rj7 3rld 3ryj 3ryv 3ryx 3ryy 3ryz 3rz0 3rz1 3rz5 3rz7 3rz8 3s71 3s72 3s73 3s74 3s75 3s76 3s77 3s78 3s8x 3s9t 3sap 3sax 3sbh 3sbi 3t5u 3t5z 3t82 3t83 3t84 3t85 3tmj 3tvn 3tvo 3u3a 3u45 3u47 3u7c 3v2j 3v2m 3v3f 3v3g 3v3h 3v3i 3v3j 3v5g 3v7x 3vbd 3zp9 4bcw 4bfl 4bf6 4ca2 4cac 4cq0 4dz7 4dz9 4e3d 4e3f 4e3g 4e3h 4e49 4e4a 4e5q 4fik 4fl7 4fpt 4frc 4fu5 4fvn 4fvo 4g0c 4gl1 4hba 4hew 4hey 4hez 4hf3 4ht0 4idr 4ilx 4ito 4itp 4iww 4js6 4jsa 4jss 4jsw 4jsz 4k0s 4k0t 4k0z 4k13 4k1q 4kap 4kni 4knj 4kuv 4kuw 4kuy 4kv0 4l5u 4l5v 4l5w 4lhi 4lp6 4m2r 4m2u 4m2v 4m2w 4mdg 4mdl 4mdm 4mlt 4mlx 4mo8 4mtu 4n0x 4n16 4pq7 4pxx 4pyx 4pyy 4pzh 4q06 4q07 4q08 4q09 4q49 4q6d 4q6e 4q78 4q7p 4q7s 4q7v 4q7w 4q81 4q83 4q87 4q8x 4q8y 4q8z 4q90 4q99 4q9y 4qef 4qiy 4qjm 4qk1 4qk2 4qk3 4qsa 4qsb 4qsi 4qtl 4qy3 4r59 4r5a 4r5b 4rfc 4rfd 4rh2 4riu 4riv 4rn4 4rux 4rui 4ruz 4wl4 4ww6 4xel 4y0j 4ygj 4yvk 4ygl 4ygn 4yvy 4ywp 4yx4 4yxi 4yxo 4yxu 4yyt 4z0q 4z1e 4z1j 4z1k 4z1n 4zao 4zwi 4zwx 4zwy 4zww 4zx0 4zx1 5a6h 5amd 5amg 5aml 5bnl 5bru 5brv 5brw 5byi 5c8i 5ca2 5cac 5cjl 5clu 5dog 5doh 5drs 5dsi 5dsj 5dsk 5dsl 5dsm 5dsn 5dso 5dsp 5dsq 5dsr 5e28 5e2k 5e2r 5e2s 5eh5 5eh7 5eh8 5ehe 5ehv 5ehw 5eij 5ekh 5ekj 5ekm 5eoi 5fdc 5fdi 5flo 5flp 5flq 5flr 5fls 5flt 5fng 5fnh 5fni 5fnj 5fnk 5fnl 5fnn 5g01 5g03 5g0b 5g0c 5gmn 5j8z 5jdv 5je7 5jeg 5jeh 5jep 5jes 5jg3 5jg5 5jgs 5jgt 5jnz 5jn1 5jn3 5jn7 5jq0 5jqt 5l3o 5l6k 5l6t 5l70 5l9e 5ljq 5ljt 5ll4 5ll8 5llc 5lle 5llg 5llh 5lmd 5lvs 5n0d 5n0e 5o07 5sz0 5sz1 5sz2 5sz3 5sz4 5sz5 5sz6 5sz7 5t71 5t72 5t74 5t75 5tfx 5th4 5thi 5thj 5thn 5ti0 5txy 5ty1 5ty8 5ty9 5tya 5u0d 5u0e 5u0f 5u0g 5uln 5vgu 5wex 6ca2 7ca2 8ca2 9ca2
Glutathione S-transferase/ Intra-molecular oxidoreductases/ T19433	1iyh 1iyi 1v40 2cvd 2vcq 2vcw 2vcx 2vcz 2vd0 2vd1 3ee2 3kxo 3vi5 3vi7 4ec0 4edy 4edz 4ee0 5ais 5aiv 5aix
Phospholipase A2, membrane associated/ Carboxylic ester hydrolase/ T19160	1ayp 1bbc 1db4 1db5 1dcy 1j1a 1kqu 1kvo 1n28 1n29 1pod 1poe 2gny 3u8b 3u8d 3u8h 3u8i 5g3n

Histamine N-methyltransferase/ Methyltransferase superfamily/ T17448	licz 1jqd 1jqe 2aot 2aou 2aov 2aow 2aox
Protein tyrosine phosphatase-1B/ Phosphoric monoester hydrolases/ T16347	1a5y 1aax 1bzc 1bzh 1bzj 1c83 1c84 1c85 1c86 1c87 1c88 1ecv 1een 1eeo 1g1f 1g1g 1g1h 1g7f 1g7g 1gfy 1i57 1jf7 1kak 1kav 1l8g 1lqf 1nl9 1nny 1no6 1nwe 1nwl 1nz7 1oem 1oeo 1oes 1oet 1oeu 1oev 1ony 1onz 1pa1 1ph0 1ptt 1ptu 1ptv 1pty 1pxh 1pyn 1qlm 1q6j 1q6m 1q6n 1q6p 1q6s 1q6t 1qxx 1sug 1t48 1t49 1t4j 1wax 1xbo 2azr 2b07 2b4s 2bgd 2bge 2cm2 2cm3 2cm7 2cm8 2cma 2cmb 2cmc 2cne 2cnf 2cng 2cnh 2cni 2f6f 2f6t 2f6v 2f6w 2f6y 2f6z 2f70 2f71 2fjm 2fjn 2h4g 2h4k 2hb1 2hnp 2hnq 2nt7 2nta 2qbp 2qbw 2qbr 2qbs 2veu 2vev 2vew 2vex 2vey 2zmm 2zn7 3a5j 3a5k 3cwe 3d9c 3eax 3eb1 3eu0 3i7z 3i80 3qkp 3qkq 3sme 3zmp 3zmq 3zv2 4bjo 4i8n 4qah 4qap 4qbe 4qbw 4y14 4zrt 5k9v 5k9w 5ka0 5ka1 5ka2 5ka3 5ka4 5ka7 5ka8 5ka9 5kaa 5kab 5kac 5kad 5t19
Integrin-linked protein kinase 1/ Kinase/ T13616	2kbx 3f6q 3ixe 3kmu 3kmw 3rep 4hi8 4hi9
CAMP-specific 3',5'-cyclic phos- phodiesterase 4B/ Phosphoric di- ester hydrolases/ T10265	1f0j 1jp1 1jp2 1ro6 1ro9 1ror 1tb5 1xlx 1xlz 1xm4 1xm6 1xmu 1xmy 1xn0 1xos 1xot 1y2h 1y2j 2chm 2qyl 3d3p 3frg 3g45 3gwt 3hc8 3hdz 3hmv 3kkt 3ly2 3o0j 3o56 3o57 3w5e 3wd9 4kp6 4myq 4nw7 4wzi 4x0f 5k6j
Neutrophil collagenase/ Peptidase/ T08856	1a85 1a86 1bzs 1i73 1i76 1jan 1jao 1jap 1jaq 1jh1 1jj9 1kbc 1mmb 1mnc 1zp5 1zs0 1zvx 2oy2 2oy4 3dng 3dpe 3dpf 3tt4 4qkz 5h8x
Granzyme B/ Peptidase/ T08298	1fq3 1iau
Focal adhesion kinase-2/ Kinase/ T07087	2fo6 2lk4 3cc6 3et7 3fzo 3fzp 3fzr 3fzs 3fzt 3gml 3gm2 3gm3 3h3c 3u3f 4eku 4hlj 4h1m 4r32 4xef 4xek 4xev 5to8
Neutral endopeptidase/ Peptidase/ T05409	1dl9 1dmt 1qvd 1rlh 1rli 1rlj 1y8j 2qpj 2yb9 4cth 5jmy
Mitogen-activated protein kinase kinase kinase 7/ Kinase/ T04361	2eva 2yiy 4gs6 4l3p 4l52 4l53 4o91 5e7r 5gjd 5gjf 5gjj 5j7s 5j8i 5j9l 5jga 5jgb 5jgd 5jh6 5jk3 5v5n
mRNA of H-ras/ Ras family/ T03871	121p 1aa9 1agp 1bkd 1clu 1crp 1crq 1crr 1ctq 1gnp 1gnq 1gnr 1he8 1iaq 1ioz 1jah 1jai 1k8r 1lf0 1lf5 1lfd 1nvu 1nvv 1nvw 1nvx 1p2s 1p2t 1p2u 1p2v 1plj 1plk 1pll 1q21 1qra 1rvd 1wq1 1xcm 1xd2 1xj0 1zvq 1zw6 221p 2c5l 2ce2 2cl0 2cl6 2cl7 2clc 2cld 2evw 2gdp 2lcf 2lwi 2n42 2n46 2q21 2quz 2rga 2rgb 2rgc 2rgd 2rge 2rgg 2uzi 2vh5 2x1v 3ddc 3i3s 3k8y 3k9l 3k9n 3kkm 3kkn 3kud 3l8y 3l8z 3lbi 3lbn 3lo5 3oiu 3oiv 3oiw 3rry 3rrz 3rs0 3rs2 3rs3 3rs4 3rs5 3rs7 3rsl 3rso 3tgp 421p 4dlr 4dls 4dlt 4dlu 4dlv 4dlw 4dlx 4dly 4dlz 4dst 4dsu 4efl 4efm 4efn 4g0n 4g3x 4k81 4l9s 4l9w 4nyi 4nyj 4nym 4q21 4rsg 4uru 4urv 4urw 4urx 4ury 4urz 4us0 4us1 4us2 4xvq 4xvr 521p 5b2z 5b30 5e95 5p21 5vbe 5vbx 5wdo 5wdp 5wdq 5x9s 621p 6amb 6axg 6q21 721p 821p

mRNA of PPAR-gamma/ Nuclear hormone receptor/ T03818	1fm6 1fm9 1i7i 1k74 1knu 1nyx 1prg 1rdt 1wm0 1zeo 1zgy 2ath 2f4b 2fvj 2g0g 2g0h 2gtk 2hfp 2hwq 2hwr 2i4j 2i4p 2i4z 2om9 2p4y 2pob 2prg 2q59 2q5p 2q5s 2q61 2q6r 2q6s 2q8s 2qmv 2vsr 2vst 2vv0 2vv1 2vv2 2vv3 2vv4 2xkw 2yfe 2zk0 2zk1 2zk2 2zk3 2zk4 2zk5 2zk6 2zno 2zvt 3ads 3adt 3adu 3adv 3adw 3adx 3an3 3an4 3b0q 3b0r 3b1m 3b3k 3bc5 3cdp 3cds 3cs8 3cwd 3d6d 3dzu 3dzy 3e00 3et0 3et3 3fej 3fur 3g9e 3gbk 3h0a 3ho0 3hod 3ia6 3k8s 3kmg 3lmp 3noa 3osi 3osw 3pba 3po9 3prg 3qt0 3r5n 3r8a 3r8i 3s9s 3sz1 3t03 3ty0 3u9q 3v9t 3v9v 3v9y 3vjh 3vji 3vn2 3vso 3vsp 3wj4 3wj5 3wmh 3x1h 3x1i 4a4v 4a4w 4ci5 4e4k 4e4q 4em9 4ema 4f9m 4fgy 4hee 4jaz 4jl4 4l96 4l98 4o8f 4oj4 4prg 4pvu 4pwl 4r06 4r2u 4r6s 4xld 4xta 4xuh 4xum 4y29 4yt1 5azv 5dsh 5dv3 5dv6 5dv8 5dvc 5dwl 5f9b 5gtn 5gto 5gtp 5hzc 5ji0 5lsg 5tto 5two 5u5l
Type IV phosphodiesterase/ Phosphoric diester hydrolases/ T02001	1e9k 1mkd 1oyn 1ptw 1q9m 1tb7 1tbb 1xom 1xon 1xoq 1xor 1y2b 1y2c 1y2d 1y2e 1y2k 1zkn 2fm0 2fm5 2pw3 2qyn 3g4g 3g4i 3g4k 3g4l 3g58 3iad 3iak 3k4s 3sl3 3sl4 3sl5 3sl6 3sl8 3v9b 4ogb 4w1o 4wcu 5k1i 5k32 5tkb 5wqa
Catalase/ Peroxidases/ T01597	1dgb 1dgi 1dgg 1dgh 1f4j 1qqw
Glycogen phosphorylase, muscle form/ Hexosyltransferase/ T98062	1z8d
Cytochrome P450 1B1/ Oxidoreductases acting on paired donors/ T92521	3pm0
mRNA of human RIP2/ Kinase/ T92463	2n7z 2n83 4c8b 5ar2 5ar3 5ar4 5ar5 5ar7 5ar8 5j79 5j7b 5ng0 5ng2 5ng3 5w5j 5w5o
Tyrosine-protein kinase itk/ tsf/ T91761	1sm2 1snu 1snx 2e6i 2lmj 2yuq 3miy 3mj1 3mj2 3qgw 3qgy 3t9t 3v5j 3v5l 3v8t 3v8w 4hct 4hcu 4hcv 4kio 4l7s 4m0y 4m0z 4m12 4m13 4m14 4m15 4mf0 4mf1 4pp9 4ppa 4ppb 4ppc 4pqn 4qd6 4rfm
Adenosine kinase/ Kinase/ T91661	1bx4 2i6a 2i6b 4o1l
mRNA of Abl/ Kinase/ T89747	1ab2 1abl 1awo 1bbz 1ju5 1opl 1zzp 2abl 2e2b 2f4j 2fo0 2g1t 2g2f 2g2h 2g2i 2gqg 2hiw 2hyy 2hz0 2hz4 2hzi 2o88 2v7a 3cs9 3eg0 3eg1 3eg2 3eg3 3egu 3k2m 3ppy 3qri 3qrj 3qrk 3t04 3ue4 3uyo 4j9b 4j9c 4j9d 4j9e 4j9f 4j9g 4j9h 4j9i 4j9j 4j9k 4j9l 4j9m 4j9n 4j9o 4j9p 4j9q 4j9r 4j9s 4j9t 4j9u 4j9v 4j9w 4j9x 4j9y 4j9z 4k0a 4k0b 4k0c 4k0d 4k0e 4k0f 4k0g 4k0h 4k0i 4k0j 4k0k 4k0l 4k0m 4k0n 4k0o 4k0p 4k0q 4k0r 4k0s 4k0t 4k0u 4k0v 4k0w 4k0x 4k0y 4k0z 4l1a 4l1b 4l1c 4l1d 4l1e 4l1f 4l1g 4l1h 4l1i 4l1j 4l1k 4l1l 4l1m 4l1n 4l1o 4l1p 4l1q 4l1r 4l1s 4l1t 4l1u 4l1v 4l1w 4l1x 4l1y 4l1z 4m2a 4m2b 4m2c 4m2d 4m2e 4m2f 4m2g 4m2h 4m2i 4m2j 4m2k 4m2l 4m2m 4m2n 4m2o 4m2p 4m2q 4m2r 4m2s 4m2t 4m2u 4m2v 4m2w 4m2x 4m2y 4m2z 4n3a 4n3b 4n3c 4n3d 4n3e 4n3f 4n3g 4n3h 4n3i 4n3j 4n3k 4n3l 4n3m 4n3n 4n3o 4n3p 4n3q 4n3r 4n3s 4n3t 4n3u 4n3v 4n3w 4n3x 4n3y 4n3z 4o4a 4o4b 4o4c 4o4d 4o4e 4o4f 4o4g 4o4h 4o4i 4o4j 4o4k 4o4l 4o4m 4o4n 4o4o 4o4p 4o4q 4o4r 4o4s 4o4t 4o4u 4o4v 4o4w 4o4x 4o4y 4o4z 4p5a 4p5b 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4z4i 4z4j 4z4k 4z4l 4z4m 4z4n 4z4o 4z4p 4z4q 4z4r 4z4s 4z4t 4z4u 4z4v 4z4w 4z4x 4z4y 4z4z 4z5a 4z5b 4z5c 4z5d 4z5e 4z5f 4z5g 4z5h 4z5i 4z5j 4z5k 4z5l 4z5m 4z5n 4z5o 4z5p 4z5q 4z5r 4z5s 4z5t 4z5u 4z5v 4z5w 4z5x 4z5y 4z5z 4z6a 4z6b 4z6c 4z6d 4z6e 4z6f 4z6g 4z6h 4z6i 4z6j 4z6k 4z6l 4z6m 4z6n 4z6o 4z6p 4z6q 4z6r 4z6s 4z6t 4z6u 4z6v 4z6w 4z6x 4z6y 4z6z 4z7a 4z7b 4z7c 4z7d 4z7e 4z7f 4z7g 4z7h 4z7i 4z7j 4z7k 4z7l 4z7m 4z7n 4z7o 4z7p 4z7q 4z7r 4z7s 4z7t 4z7u 4z7v 4z7w 4z7x 4z7y 4z7z 4z8a 4z8b 4z8c 4z8d 4z8e 4z8f 4z8g 4z8h 4z8i 4z8j 4z8k 4z8l 4z8m 4z8n 4z8o 4z8p 4z8q 4z8r 4z8s 4z8t 4z8u 4z8v 4z8w 4z8x 4z8y 4z8z 4z9a 4z9b 4z9c 4z9d 4z9e 4z9f 4z9g 4z9h 4z9i 4z9j 4z9k 4z9l 4z9m 4z9n 4z9o 4z9p 4z9q 4z9r 4z9s 4z9t 4z9u 4z9v 4z9w 4z9x 4z9y 4z9z 4z0a 4z0b 4z0c 4z0d 4z0e 4z0f 4z0g 4z0h 4z0i 4z0j 4z0k 4z0l 4z0m 4z0n 4z0o 4z0p 4z0q 4z0r 4z0s 4z0t 4z0u 4z0v 4z0w 4z0x 4z0y 4z0z 4z1a 4z1b 4z1c 4z1d 4z1e 4z1f 4z1g 4z1h 4z1i 4z1j 4z1k 4z1l 4z1m 4z1n 4z1o 4z1p 4z1q 4z1r 4z1s 4z1t 4z1u 4z1v 4z1w 4z1x 4

Glucosylceramidase/ Glycosylases/ T84173	1ogs 1y7v 2f61 2j25 2nsx 2nt0 2nt1 2v3d 2v3e 2v3f 2vt0 2wcg 2wkl 2xwd 2xwe 3gxd 3gxf 3gxi 3gxm 3ke0 3keh 3rik 3ril 5lvx
Protein kinase C iota/ Kinase/ T83174	1vd2 1wmh 1zrz 3a8w 3a8x 3zh8 5li1 5li9 5lih
Insulin-degrading Enzyme/ Pepti- dase/ T81900	2g47 2g48 2g49 2g54 2g56 2jbu 2jg4 2wby 2wc0 2wk3 2ypu 3cww 3e4a 3e4z 3e50 3h44 3hgz 3n56 3n57 3ofi 3qz2 4dt 4dwk 4gs8 4gsc 4gsf 4ifh 4iof 4lte 4mlc 4nxo 4pes 4pf7 4pf9 4pfc 4q5z 4qia 4ral 4re9 5cjo 6b7y
mRNA of VEGFR1/ Kinase/ T80782	1ft 1qsv 1qsz 1qty 1rv6 2xac 3hng 4ckv 4cl7 5abd 5ex3 5t89
Tryptophan 5-hydroxylase-1/ Ox- idoreductases acting on paired donors/ T78915	1in9 1mlw 3hf6 3hf8 3hfb 5j6d 5l01 5tpg
78 kDa glucose-regulated protein/ Heat shock protein/ T77594	3iuc 3ldl 3ldn 3ldo 3ldp 5e84 5e85 5e86 5evz 5ex5 5exw 5ey4 5f0x 5f1x 5f2r
CGMP-dependent3',5'-cyclic phos- phodiesterase/ Phosphoric diester hydrolases/ T77400	1z1l 3ibj 3itm 3itu 4c1i 4d08 4d09 4htx 4htz 4jib 5tz3 5tza 5tzc 5tzh 5tzw 5tzx 5tzz 5u00 5u7d 5u7i 5u7j 5u7k 5u7l 5vp0 5xkm
Pyridoxal kinase/ Kinase/ T76522	2ajp 2f7k 2yxt 2yxu 3fhx 3fhy 3keu 4en4 4eoh
6-phosphogluconate dehydrogenase, decarboxylating/ Short-chain dehy- drogenases reductases/ T76497	2jkv 4gwg 4gwk
Liver carboxylesterase/ Carboxylic ester hydrolase/ T76369	1mx1 1mx5 1mx9 1ya4 1ya8 1yah 1yaj 2dqy 2dqz 2dr0 2h7c 2hrq 2hrr 3k9b 4ab1 5a7f 5a7g 5a7h
GMP synthase [glutamine- hydrolyzing]/ Carbon-nitrogen ligase/ T75517	2vpi 2vx0
mRNA of CCR5/ ddRNAi/ T72171	1nd8 1ne0 1opn 1opt 1opw 2l87 2mzx 2rl 2rrs 4mbs
Bifunctional aminoacyl tRNA synthetase/ Carbon-oxygen ligase/ T67416	1fyj 4hvc 4k86 4k87 4k88 5a1n 5a34 5a5h 5bmu 5vad
mRNA of Insulin-like growth fac- tor 1 receptor/ Target of antisense drug/ T64977	1igr 1jqh 1k3a 1m7n 1p4o 2oj9 2zm3 3d94 3f5p 3i81 3lvp 3lw0 3nw5 3nw6 3nw7 3o23 3qqu 4d2r 4xss 5fxq 5fxr 5fxs 5hzn

CAMP-specific 3',5'-cyclic phosphodiesterase 4A/ Phosphoric diester hydrolases/ T61744	2qyk 3i8v 3tvx
Retinoic acid receptor beta/ Nuclear hormone receptor/ T61657	1hra 1xap 4dm6 4dm8 4jyg 4jyh 4jyi 5uan
Aldosterone synthase/ Oxidoreductases acting on paired donors/ T59056	4dvq 4fdh 4zgx
Cytochrome P450 2D6/ Oxidoreductases acting on paired donors/ T57392	2f9q 3qm4 3tbg 3tda 4wnt 4wnu 4wnv 4wnw 4xry 4xrz 5tft 5tfu
Interleukin-1receptor-associated kinase-4/ Kinase/ T55398	2nru 2nry 2o8y 2oib 2oic 2oid 3mop 4rmz 4u97 4u9a 4xs2 4y73 4yo6 4yp8 4ztl 4ztn 4ztn 5kx7 5kx8 5t1s 5t1t 5uiq 5uir 5uis 5uit 5uiu 5w84 5w85
Oxysterols receptor LXR-alpha/ Nuclear hormone receptor/ T52297	1uhl 3ipq 3ips 3ipu 5avi 5avl 5hjs
Porphobilinogen deaminase/ Alkyl aryl transferase/ T47466	3ecr 3eq1
Aldehyde dehydrogenase, mitochondrial/ Oxidoreductases acting on aldehyde or oxo group of donors/ T44282	1cw3 1nzw 1nxz 1nzz 1o00 1o01 1o02 1o04 1o05 1zum 2onm 2onn 2ono 2onp 2vle 3inj 3inl 3n80 3n81 3n82 3n83 3sz9 4fqf 4fr8 4kwf 4kwg 5l13
mRNA of human IL-1 receptor-associated kinase-4/ Kinase/ T41766	2nru 2nry 2o8y 2oib 2oic 2oid 3mop 4rmz 4u97 4u9a 4xs2 4y73 4yo6 4yp8 4ztl 4ztn 4ztn 5kx7 5kx8 5t1s 5t1t 5uiq 5uir 5uis 5uit 5uiu 5w84 5w85
mRNA of SYK/ Target of siRNA drug/ T37952	1a81 1csy 1csz 1xba 1xbb 1xbc 3buw 3emg 3fqe 3fqh 3fqs 3srv 3tub 3tuc 3tud 3vf8 3vf9 4df1 4dfn 4f4p 4fl1 4fl2 4fl3 4fyn 4fyo 4fz6 4fz7 4gfg 4i0r 4i0s 4i0t 4puz 4pv0 4px6 4rss 4rx7 4rx8 4rx9 4wnm 4xg2 4xg3 4xg4 4xg6 4xg7 4xg8 4xg9 4yjo 4yjp 4yjq 4yjr 4yjs 4yjt 4yju 4yvv 5c26 5c27 5cxh 5cxz 5cy3 5ghv 5lma 5lmb 5t68 5tiu 5tr6 5tt7
Soluble epoxide hydrolase/ Ether-hydrolase/ T35734	1s8o 1vj5 1zd2 1zd3 1zd4 1zd5 3ans 3ant 3ily 3i28 3koo 3otq 3pdc 3wk4 3wk5 3wk6 3wk7 3wk8 3wk9 3wka 3wkb 3wkc 3wkd 3wke 4c4x 4c4y 4c4z 4hai 4j03 4jnc 4ocz 4od0 4x6x 4x6y 4y2j 4y2p 4y2q 4y2r 4y2s 4y2t 4y2u 4y2v 4y2x 4y2y 5ahx 5ai0 5ai4 5ai5 5ai6 5ai8 5ai9 5aia 5aib 5aic 5ak3 5ak4 5ak5 5ak6 5ake 5akg 5akh 5aki 5akj 5akk 5akl 5akx 5aky 5akz 5ald 5ale 5alf 5alg 5alh 5ali 5alj 5alk 5all 5alm 5aln 5alo 5alp 5alq 5alr 5als 5alt 5alu 5alv 5alw 5alx 5aly 5alz 5am0 5am1 5am2 5am3 5am4 5am5 5fp0

HIF prolyl hydroxylase-2/ Oxidoreductases acting on paired donors/ T32880	2g19 2g1m 2hbt 2hbu 2y33 2y34 3hqr 3hqu 3ouh 3oui 3ouj 4bqw 4bqx 4bqy 4jzr 4kbz 4uwd 5a3u 5l9b 5l9r 5l9v 5la9 5las 5lat 5lb6 5lbb 5lbc 5lbe 5lbf 5ox5 5ox6 5v18
Glutamyl aminopeptidase/ Peptidase/ T31956	4kx7 4kx8 4kx9 4kxa 4kxb 4kxc 4kxd
Glutathione reductase/ Oxidoreductases acting on a sulfur group of donors/ T30803	1alg 1bwc 1dnc 1gra 1grb 1gre 1grf 1grg 1grh 1grt 1gsn 1k4q 1xan 2aaq 2gh5 2grt 3djg 3djj 3dk4 3dk8 3dk9 3grs 3grt 3sqp 4grl 4grt 5grt
Serine/ threonine-protein kinase Chk2/ T28713	1gxc 2cn5 2cn8 2w0j 2w7x 2wtc 2wtd 2wti 2wtj 2xbj 2xk9 2xm8 2xm9 2ycf 2ycq 2ycr 2ycs 2yiq 2yir 2yit 3i6u 3i6w 3va4 4a9r 4a9s 4a9t 4a9u 4bda 4bdb 4bdc 4bdd 4bde 4bdf 4bdg 4bdh 4bdi 4bdj 4bdk
Recombinant human angiotensin converting enzyme 2/ Peptidase/ T27889	1r42 1r4l 1xjp 2ajf 3d0g 3d0h 3d0i 3kbh 3sci 3scj 3sck 3scl
Nuclear receptor coactivator 3/ Acyltransferase/ T26774	1kbh 3l3x 3l3z
Myeloperoxidase/ Peroxidases/ T23471	1cxp 1d2v 1d5l 1d7w 1dnu 1dnw 1mhl 1myp 3f9p 3zs0 3zs1 4c1m 4dl1 4ejx 5fiw 5mfa 5uzu
mRNA of integrin beta 3/ Integrin/ T23355	1jv2 1kup 1kuz 1l5g 1m1x 1m8o 1miz 1mk7 1mk9 1rn0 1s4x 1tye 1u8c 2ini 2k9j 2knc 2kv9 2l1c 2l91 2ljd 2lje 2ljf 2mtp 2n9y 2q6w 2rmz 2rn0 2vc2 2vdk 2vdl 2vdm 2vdn 2vdo 2vdp 2vdq 2vdr 3fcs 3fcu 3ije 3nid 3nif 3nig 3t3m 3t3p 3zdx 3zdy 3zdz 3ze0 3ze1 3ze2 4cak 4gle 4glm 4mmx 4mmy 4mmz 4o02 4z7n 4z7o 4z7q 5hdb 6avq 6avr 6avu
mRNA of Bcl-x/ Bcl-2 family/ T19923	1bxl 1g5j 1lxl 1maz 1r2d 1r2e 1r2g 1r2h 1r2i 1ysg 1ysi 1ysn 2b48 2lp8 2lpc 2m03 2m04 2me8 2me9 2mej 2o1y 2o2m 2o2n 2p1l 2pon 2yj1 2yq6 2yq7 2yxj 3cva 3fdl 3fdm 3inq 3io8 3pl7 3qkd 3r85 3sp7 3spf 3wiz 3zk6 3zln 3zlo 3zlr 4a1u 4a1w 4aq3 4bpk 4c52 4c5d 4cin 4ehr 4hnj 4ieh 4ppi 4qve 4qvf 4qvx 4tuh 4z9v 5agw 5agx 5b1z 5c3g 5fmj 5fmk 6bf2

MMP-12/ Peptidase/ T03500	1jiz 1jk3 1os2 1os9 1rmz 1ros 1utt 1utz 1y93 1ycm 1z3j 2hu6 2jxy 2k2g 2k9c 2krj 2mlr 2mls 2n8r 2oxu 2oxw 2oxz 2poj 2w0d 2wo8 2wo9 2woa 2z2d 3ba0 3ehx 3ehy 3f15 3f16 3f17 3f18 3f19 3f1a 3lik 3lil 3lir 3ljg 3lk8 3lka 3n2u 3n2v 3nx7 3rts 3rtt 3ts4 3tsk 3uvc 4efs 4gql 4gr0 4gr3 4gr8 4guy 4h30 4h49 4h76 4h84 4i03 4ijo 5cxa 5czm 5d2b 5d3c 5i0l 5i2z 5i3m 5i43 5i4o 5l79 5l7f 5lab 5n5j 5n5k
Aggrecanase/ Peptidase/ T98896	2rjq 3b8z 3hy7 3hy9 3hyg 3ljt
PAK-4 protein kinase/ Kinase/ T98293	2bva 2cdz 2j0i 2ov2 2q0n 2x4z 4app 4fie 4fif 4fig 4fih 4fi 4fj 4jdh 4jdi 4jdj 4jdk 4l67 4njd 4o0v 4o0x 4o0y 4xbr 4xbu 5bms 5i0b 5ved 5vee 5vef
Transforming protein RhoA/ Small GTPase superfamily/ T96736	1a2b 1cc0 1cxz 1dpf 1ftn 1kmq 1lb1 1ow3 1slc 1tx4 1x86 1xcg 2rgn 3kz1 3lw8 3lwn 3lxr 3msx 3t06 4d0n 4xh9 4xoi 4xsg 4xsh 5a0f 5bwm 5c2k 5c4m 5ez6 5fr1 5fr2 5hpy 5irc 5jcp 5jhg 5jhh 5m6x 5m70
Branched chain amino acid-dependent aminotransferase/ Transferases of nitrogenous groups/ T94788	1ekf 1ekp 1ekv 1kt8 1kta 2a1h 2hdk 2hg8 2hgw 2hgx 2hhf 5bwr 5bwt 5bwu 5bvw 5bww 5bwx 5cr5 5hne 5i5s 5i5t 5i5u 5i5v 5i5w 5i5x 5i5y 5i60 5mpr
DOT1L/ Methyltransferase super-family/ T87686	1nw3 2mv7 3qow 3qox 3sr4 3sx0 3uwp 4ek9 4ekg 4eki 4eqz 4er0 4er3 4er5 4er6 4er7 4hra 4wvl 5drt 5dry 5dsx 5dt2 5dtm 5dtq 5dtr 5juw 5mvs 5mw3 5mw4
Folate receptor alpha/ Folate receptor/ T83386	4km6 4km7 4kmx 4lrh 5izq
mRNA of p53/ Target of siRNA drug/ T82051	1a1u 1aie 1c26 1dt7 1gzh 1h26 1hs5 1jsp 1kzy 1ma3 1olg 1olh 1pes 1pet 1sae 1saf 1sak 1sal 1tsr 1tup 1uol 1xqh 1yc5 1ycq 1ycr 1ycs 2ac0 2ady 2ahi 2ata 2b3g 2bim 2bin 2bio 2bip 2biq 2flx 2fej 2foj 2foo 2gs0 2h1l 2h2d 2h2f 2h4f 2h4h 2h4j 2h59 2j0z 2j10 2j11 2j1w 2j1x 2j1y 2j1z 2j20 2j21 2k8f 2l14 2ly4 2mej 2mwo 2mwp 2mwy 2mzd 2ocj 2pcx 2ruk 2vuk 2wgx 2x0u 2x0v 2x0w 2xwr 2ybg 2ydr 2z5s 2z5t 3d05 3d06 3d07 3d08 3d09 3d0a 3dab 3dac 3igk 3igl 3kmd 3kz8 3lw1 3oq5 3pdh 3q01 3q05 3q06 3sak 3tg5 3ts8 3zme 4agl 4agm 4agn 4ago 4agp 4agq 4buz 4bv2 4hfh 4hje 4ibq 4ibs 4ibt 4ibu 4ibv 4ibw 4iby 4ibz 4ijt 4kvp 4lo9 4loe 4lof 4mzi 4mzr 4qo1 4rp6 4rp7 4x34 4xr8 4zzj 5a7b 5ab9 5aba 5aoi 5aoj 5aok 5aol 5aom 5bua 5ecg 5g4m 5g4n 5g4o 5hou 5hp0 5hpd 5lap 5lgy 5mhc 5moc 5un8
mRNA of Caspase-2/ Target of siRNA drug/ T81103	1pyo 2p2c 3r5j 3r6g 3r6l 3r7b 3r7n 3r7s 3rjm
Phenylalanine hydroxylase/ Oxidoreductases acting on paired donors/ T76213	1dmw 1j8t 1j8u 1kw0 1lrm 1mmk 1mmt 1pah 1tdw 1tg2 2pah 3pah 4anp 4pah 5fi 5pah 6pah
FK506-binding protein 1A/ Cis-trans-isomerases/ T76059	1a7x 1b6c 1bkf 1bl4 1d6o 1d7h 1d7i 1d7j 1eym 1f40 1fap 1fkb 1fkd 1fkf 1fkg 1fkh 1fki 1fkj 1fkr 1fks 1fkt 1j4h 1j4i 1j4r 1nsg 1qpf 1qpl 2dg3 2dg4 2dg9 2fap 2fke 2nd5 2ppn 2ppo 2ppp 2rse 3fap 3h9r 3mdy 4dh0 4fap 4ipx 4n19 4odp 4odq 4odr 5i7p 5i7q

Methionine aminopeptidase 2/ Peptidase/ T75596	1b59 1b6a 1bn5 1boa 1kq0 1kq9 1qzy 1r58 1r5g 1r5h 1yw7 1yw8 1yw9 2adu 2ea2 2ea4 2ga2 2oaz 5cls 5d6e 5d6f 5jfr 5jhu 5ji6 5lyw 5lyx
Lethal factor/ Peptidase/ T72335	1j7n 1jky 1pwp 1pwq 1pwu 1pww 1yqy 1zxx 2l0r 3kwv 4dv8 4pkq 4pkr 4pks 4pkt 4pku 4pkv 4pkw 4wf6 4xm6 4xm7 4xm8 5d1s 5d1t 5d1u
Orphan nuclear receptor NR1I3/ Nuclear hormone receptor/ T69506	1xv9 1xvp
Mitogen-activated protein kinase 9/ Kinase/ T69375	3e7o 3npc
Zap70 tyrosine kinase/ Kinase/ T64553	1fbv 1m6l 1u59 2cbl 2oq1 2ozo 2y1n 3zni 4a4b 4a4c 4k2r 4xz0 4xz1
Serum albumin/ Serum albumin family/ T63068	1ao6 1bj5 1bke 1bm0 1e78 1e7a 1e7b 1e7c 1e7e 1e7f 1e7g 1e7h 1e7i 1gni 1gnj 1h9z 1ha2 1hk1 1hk2 1hk3 1hk4 1hk5 1n5u 1o9x 1tf0 1uor 1ysx 2bx8 2bxa 2bxb 2bxc 2bxd 2bxe 2bxf 2bxg 2bxh 2bxi 2bxk 2bxl 2bxm 2bxn 2bxo 2bxp 2bxq 2esg 2i2z 2i30 2n0x 2vdb 2vue 2vuf 2xsi 2xvq 2xvu 2xvv 2xvw 2xw0 2xw1 2ydf 3a73 3b9l 3b9m 3cx9 3jqz 3jry 3lu6 3lu7 3lu8 3sqj 3tdl 3uiv 4bke 4e99 4emx 4g03 4g04 4hgk 4hgm 4iw1 4iw2 4k2c 4k71 4l8u 4l9k 4l9q 4la0 4lb2 4lb9 4n0f 4n0u 4s1y 4z69 5fuo 5gix 5giy 5id7 5ifo 5ijf 5ujb 5x52
Beta-adrenergic receptor kinase 1/ Kinase/ T62548	1bak 3cik 3krw 3krx 3v5w 4mk0 4pnk 5he1 5ukk 5ukl 5uuu 5uvc
Sorbitoldehydrogenase/ Short-chain dehydrogenases reductases/ T59445	1pl6 1pl7 1pl8
Cyclin-A2/ T58470	1e9h 1fin 1fvv 1gy3 1hl1p 1hl1q 1hl1r 1hl1s 1h24 1h25 1h26 1h27 1h28 1jst 1jsu 1ogu 1oi9 1oiu 1oiy 1okv 1okw 1ol1 1ol2 1p5e 1pkd 1q mz 1urc 1vyw 2bkz 2bpm 2c4g 2c5n 2c5o 2c5v 2c5x 2c6t 2cch 2cci 2cjm 2i40 2iw6 2iw8 2iw9 2uue 2uzb 2uzd 2uze 2uzl 2v22 2wev 2wfy 2whb 2wih 2wip 2wma 2wmb 2wpa 2wxv 2x1n 3eid 3ej1 3eoc 3f5x 4bck 4bcm 4bcn 4bcp 4cfm 4cfn 4cfu 4cfv 4cfw 4cfx 4eoi 4eoj 4eok 4eol 4eom 4eon 4eoo 4eop 4eoa 4eor 4eos 4fx3 5cyi 5if1 5lmk 5nev

HIV protease/ Peptidase/ T56915	1a9m 1ajv 1ajx 1axa 1bqm 1bqn 1d4h 1d4i 1d4j 1dlo 1dw6 1ebk 1ebw 1eby 1ebz 1ec0 1ec1 1ec2 1ec3 1eet 1g35 1gnm 1gnn 1gno 1har 1hbw 1hef 1heg 1hih 1hmv 1hni 1hny 1hos 1hps 1hpz 1hqe 1hqu 1hrh 1hte 1htf 1htg 1hvi 1hvk 1hvp 1hvu 1hys 1likv 1likw 1likx 1iky 1j5o 1kjh 1mer 1mes 1met 1meu 1n5y 1n6q 1npa 1npv 1npw 1qe1 1qmc 1r0a 1rdh 1rtd 1rvl 1rvm 1rvn 1rvo 1rvp 1rvq 1rvr 1s6p 1s6q 1s9e 1s9g 1sbg 1suq 1sv5 1t03 1t05 1t7k 1tv6 1tvr 1uwb 1w5v 1w5w 1w5x 1w5y 1yt9 1zp8 1zpa 1zsf 1zsr 2a2u 2b5j 2b6a 2ban 2bbb 2be2 2exf 2g69 2hb3 2hmi 2hnz 2hs1 2hs2 2i4d 2i4u 2i4v 2i4w 2i4x 2i5j 2iaj 2ic3 2idw 2ieo 2jzw 2l45 2l46 2l4l 2uxz 2uy0 2vg5 2vg6 2vg7 2x4u 2ykm 2ykn 2zd1 2ze2 3avi 3bgr 3dlk 3gga 3ggv 3ggx 3hvt 3ig1 3irx 3is9 3isn 3ith 3jsm 3jyt 3k2p 3k4v 3kle 3klf 3klg 3klh 3kli 3ndt 3nu3 3nu4 3nu5 3nu6 3nu9 3nuj 3nuo 3ok9 3psu 3qaa 3qlh 3qo9 3tkg 3tkw 3tl9 3tlh 3v4i 3v6d 3v8l 3zps 3zpt 3zpu 4coe 4cp7 4cpq 4cpr 4cps 4cpt 4cpu 4cpw 4cpz 4dgl 4glq 4g8g 4g8i 4g9d 4g9f 4h4m 4h4o 4i2p 4i2q 4icl 4id5 4idk 4ifv 4ify 4ig0 4ig3 4klb 4kko 4ko0 4lsl 4lsn 4mfb 4o44 4o4g 4ojr 4pqu 4puo 4pwd 4q0b 4qag 4r5p 4rw4 4rw6 4rw7 4rw8 4rw9 4u8w 4we1 4ye3 4yhq 4zip 4zls 5agz 5ah6 5ah7 5ah8 5ah9 5aha 5ahb 5ahc 5bry 5bs4 5c24 5c25 5c42 5cym 5cyq 5d3g 5fdl 5hbm 5hlf 5hp1 5hro 5i3u 5i42 5j1e 5jfp 5jfu 5jg1 5t6z 5t70 5tep 5ter 5tuq 5tw3 5txl 5txm 5txn 5txo 5txp 5ult 5uov 5upz 5uv5 5v5l 5v5m 5vqq 5vqr 5vqs 5vqt 5vqu 5vqv 5vqw 5vqx 5vqy 5vqz
ALK tyrosine kinase receptor/ Ki-nase/ T56418	2kup 2kuq 2xb7 2xba 2xp2 2yfx 2yhw 2yjr 2yjs 2ys5 2yt2 3aox 3l9p 3lcs 3lct 4anl 4anq 4ans 4ccb 4ccu 4cd0 4cli 4clj 4cmo 4cmt 4cmu 4cnh 4ctb 4ctc 4dce 4fnw 4fnx 4fny 4fnz 4fob 4foc 4fod 4joa 4mkc 4tt7 4z55 5a9u 5aa8 5aa9 5aaa 5aab 5aac 5fto 5ftq 5imx 5iug 5iuh 5iui 5j7h 5kz0
Farnesyl pyrophosphate synthase/ Alkyl aryl transferase/ T52373	1yq7 1yv5 1zw5 2f7m 2f89 2f8c 2f8z 2f92 2f94 2f9k 2opm 2opn 2qis 2rah 2vf6 3b7l 3cp6 3n1v 3n1w 3n3l 3n45 3n46 3n49 3n5h 3n5j 3n6k 3rye 3s4j 4dem 4ga3 4h5c 4h5d 4h5e 4jvj 4kfa 4kpd 4kpj 4kq5 4kqs 4kqu 4l2x 4lfv 4lpg 4lph 4n1z 4n9u 4nfi 4nfj 4nfk 4ng6 4nke 4nkf 4nua 4ogu 4p0v 4p0w 4p0x 4pvx 4pvy 4q23 4qpf 4qxs 4rxa 4xqr 4xqs 4xqt 5cg5 5cg6 5dgm 5dgn 5dgs 5diq 5djp 5djr 5djv 5ja0 5juz 5jv0 5jv1 5jv2 5ksx
Proto-oncogene pim-1/ Kinase/ T50594	1xqz 1xrl 1xws 1yhs 1yi3 1yi4 1yww 1yxs 1yxt 1yxu 1yxv 1yxx 2bik 2bil 2bzh 2bzi 2bzj 2bzk 2c3i 2j2i 2o3p 2o63 2o64 2o65 2obj 2oi4 2xix 2xiy 2xiz 2xj0 2xj1 2xj2 3a99 3bgp 3bgq 3bgz 3bwf 3c4e 3cxw 3cy2 3cy3 3dcv 3f2a 3jpv 3jxw 3jy0 3jya 3ma3 3qf9 3r00 3r01 3r02 3r04 3t9i 3uix 3umw 3umx 3vbw 3vbt 3vbw 3vbw 3vbw 3vbx 3vby 3vc4 3we8 4a7c 4alu 4alv 4alw 4as0 4bzn 4bzo 4dtk 4enx 4eny 4gw8 4i41 4iaa 4jx3 4jx7 4k0y 4k18 4k1b 4ll5 4lm5 4lmu 4mbi 4mbl 4med 4mta 4n6y 4n6z 4n70 4rbl 4rc2 4rc3 4rc4 4rpx 4ty1 4wrs 4wsy 4wt6 4xh6 4xhk 5clq 5dgz 5dhj 5dia 5dwr 5eol 5iis 5ipj 5kcx 5kgd 5keg 5kgg 5kgi 5kgk 5kzi 5o11 5o12 5o13 5tel 5tex 5toe 5tur 5v82
mRNA of Eukaryotic translation initiation factor 4E/ T48614	lipb lipc 1wkx 2gpg 2v8w 2v8x 2v8y 2w97 3am7 3tf2 3u7x 4aza 4bea 4dt6 4dum 4tpw 4tqb 4tqc 4ued 5ehc 5ei3 5eir 5ekv 5gw6 5t46
mRNA of BCL-2/ Target of anti-sense drug/ T47387	1g5m 1gjh 1ysw 2o21 2o22 2o2f 2w3l 2xa0 4aq3 4ieh 4lvt 4lxd 4man 5agw 5agx 5fcg 5jsn
Glutamate receptor 2/ Glutamate-gated ion channel/ T42392	2wjw 2wjx 2xhd 3r7x 3rn8 3rnn 3ua8 5h8s

5'-methylthioadenosine phosphorylase/ Pentosyltransferase/ T40787	1cb0 1cg6 1k27 1sd1 1sd2 3ln5 3ozc 3ozd 3oze 5eub 5tc5 5tc6 5tc7 5tc8
Biliverdin reductase A/ Oxidoreductases acting on CH-CH group of donors/ T37046	2h63
Cholesterol 24-hydroxylase/ Oxidoreductases acting on paired donors/ T33641	2q9f 2q9g 3mdm 3mdr 3mdt 3mdv 4enh 4fia 4j14
Dipeptidyl peptidase IV/ Peptidase/ T31391	1j2e 1n1m 1nu6 1nu8 1pfq 1r9m 1r9n 1rwq 1tk3 1tkr 1u8e 1w1i 1wcy 1x70 2ajl 2bgn 2bgr 2bub 2fjp 2g5p 2g5t 2g63 2hha 2i03 2i78 2iit 2iiv 2jid 2oag 2ogz 2ole 2onc 2oph 2oqi 2oqv 2p8s 2qjr 2qky 2qoe 2qt9 2qtb 2rgu 2rip 3bjm 3c43 3c45 3ccb 3ccc 3d4l 3eio 3f8s 3g0b 3g0c 3g0d 3g0g 3h0c 3hab 3hac 3kwf 3kwj 3nox 3o95 3o9v 3oc0 3opm 3q0t 3q8w 3qbj 3sww 3sx4 3vjk 3vjl 3vjm 3w2t 3wqh 4a5s 4dsa 4dsz 4dtc 4g1f 4j3j 4jh0 4kr0 4l72 4lko 4n8d 4n8e 4pnz 4pv7 4qzv 5i7u 5ism 5j3j 5kby 5t4b 5t4e 5t4f 5t4h 6b1e 6b1o
mRNA of Caspase 8/ Peptidase/ T28705	1f9e 1i4e 1qdu 1qtn 2c2z 2fun 2k7z 2y1l 3h11 3kjin 3kjq 4jj7 4prz 4ps1 4zbw 5h31 5h33 5jqe 5l08
Kinesin-like protein KIF11/ Kinesin-like protein family/ T28484	1ii6 1q0b 1x88 1yrs 2fky 2f2 2f6 2fme 2g1q 2gm1 2ieh 2pg2 2q2y 2q2z 2uyi 2uym 2wog 2x2r 2x7c 2x7d 2x7e 2xae 3cjo 3hqf 3k3b 3k5e 3ken 3l9h 3wpn 3zcw 4a1z 4a28 4a50 4a51 4a5y 4ap0 4aqv 4aqw 4as7 4b7b 4bbg 4bxn 4ck5 4ck6 4ck7 4zca 4zhi 5jv3
Epha3 tyrosine kinase receptor/ Kinase/ T28413	2gsf 2qo2 2qo7 2qo9 2qob 2qoc 2qod 2qof 2qoi 2qok 2qol 2qon 2qoo 2qoq 3dzq 3fxx 3fy2 4g2f 4gk2 4gk3 4gk4 4l0p 4p4c 4p5q 4p5z 4twn 4two
mRNA of Beta 2 adrenoceptor/ Target of siRNA drug/ T24555	1gq4 2r4r 2r4s 2rh1 3d4s 3kj6 3ny8 3ny9 3nya 3p0g 3pds 3sn6 4gbr 4lde 4ldl 4ldo 4qkx 5d5a 5d5b 5d6l 5jqh 5x7d
Monoglyceride lipase/ Carboxylic ester hydrolase/ T18664	3hju 3jw8 3jwe 3pe6 4uuq
Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1/ Cis-trans-isomerases/ T16308	1f8a 1i6c 1i8g 1i8h 1nmv 1nmw 1pin 1zcn 2f21 2itk 2kbu 2kcf 2lb3 2m8i 2m8j 2m9e 2m9f 2m9i 2m9j 2n1o 2q5a 2ruc 2rud 2ruq 2rur 2xp3 2xp4 2xp5 2xp6 2xp7 2xp8 2xp9 2xpa 2xpb 2zqs 2zqt 2zqu 2zqv 2zr4 2zr5 2zr6 3i6c 3ik8 3ikd 3ikg 3jyj 3kab 3kac 3kad 3kaf 3kag 3kah 3kai 3kce 3ntp 3odk 3oob 3tc5 3tcz 3tdb 3wh0 4gwt 4gww 4qib 4tns 4tyo 4u84 4u85 4u86 5b3w 5b3x 5b3y 5b3z 5bmy 5gph 5uy9
mRNA of Factor XI/ Target of antisense drug/ T15803	1xx9 1xxd 1xxf 1zhm 1zhp 1zhr 1zjd 1zlr 1zmj 1zml 1zmn 1zom 1zpb 1zpc 1zpz 1zrk 1zsj 1zsk 1zsl 1ztj 1ztk 1ztl 2f83 2fda 2j8j 2j8l 3bg8 3sor 3sos 4cr5 4cr9 4cra 4crb 4crc 4crd 4cre 4crf 4crg 4d76 4d7f 4d7g 4na7 4na8 4ty6 4ty7 4wxi 4x6m 4x6n 4x6o 4x6p 4y8x 4y8y 4y8z 5e2o 5e2p 5eod 5eok 5exl 5exm 5exn 5i25 5q0d 5q0e 5q0f 5q0g 5q0h 5qck 5qcl 5qcm 5qcn 5tk5 5tkl 5tku 5wb6

Induced myeloid leukemia cell differentiation protein Mcl-1/ Bcl-2 family/ T14912	2kbw 2mhs 2n19 2nla 2pqk 3d7v 3io9 3kj0 3kj1 3kj2 3kz0 3mk8 3pk1 3twu 3wix 3wiy 4bpi 4bpj 4hw2 4hw3 4hw4 4oq5 4oq6 4wgi 4wmr 4wms 4wmt 4wmu 4wmv 4wmw 4wmx 4zbf 4zbi 5c3f 5c6h 5fc4 5fdo 5fdr 5iez 5if4 5jsb 5ku9 5lof 5mes 5mev 5uum 5vkc 6b4l 6b4u
Troponin C/ Troponin/ T12966	1ap4 1ih0 1j1d 1j1e 1lxf 1mxl 1ozs 1spy 1wrk 1wrl 2jt0 2jt3 2jt8 2jtz 2jxl 2kdh 2kfx 2kgb 2krd 2l1r 2l98 2mkp 2mle 2mlf 2mzp 2n79 2n7l 3rv5 3sd6 3swb 4gje 4gjf 4gjj 4y99 5vln 5w88 5wcl
CD38/ Glycosylases/ T10877	1yh3 1zvm 2efl 2hct 2i65 2i66 2i67 2o3q 2o3r 2o3s 2o3t 2o3u 2pgj 2pgl 3dzf 3dzh 3dzi 3dzj 3dzk 3f6y 3i9m 3i9n 3ofs 3raj 3rok 3rom 3rop 3roq 3u4h 3u4i 4cmh 4f45 4f46 4ogw 4tmf 4xjs 4xjt 5flk 5flo 5f2l
Fatty acid-binding protein, adipocyte/ Calycin family/ T07217	1tou 1tow 2hnx 2nnq 3fr2 3fr4 3fr5 3p6c 3p6d 3p6e 3p6f 3p6g 3p6h 3q6l 3rzy 4nns 4nnt 5d45 5d47 5d48 5d4a 5edb 5edc 5hz6 5hz8
mRNA of CYP3A4/ Target of anti-sense drug/ T90391	1tqn 1w0e 1w0f 1w0g 2j0d 2v0m 3nxu 3tjs 3ua1 4d6z 4d75 4d78 4d7d 4i3q 4i4g 4i4h 4k9t 4k9u 4k9v 4k9w 4k9x 4ny4 5a1p 5a1r 5g5j 5te8 5vc0 5vcc 5vcd 5vce 5veg
Dihydrofolate reductase/ Oxidoreductases acting on CH-NH group of donors/ T89515	3g5k 3g5p
Ras-related C3 botulinum toxin substrate 1/ Small GTPase superfamily/ T88752	1e96 1foe 1g4u 1he1 1hh4 1i4d 1i4l 1i4t 1mh1 1ryf 1ryh 2fju 2h7v 2nz8 2p2l 2rmk 2vrw 2wkp 2wkq 2wkr 2yin 3b13 3bji 3ryt 3sbd 3sbe 3su8 3sua 3th5 4gzl 4gzm 4yon 5f0 5hzh 5o33
Bromodomain-containing protein 2/ Bromodomain/ T86399	1x0j 2dvq 2dvr 2dvs 2dvv 2e3k 2g4a 2ydw 2yek 3aqa 3oni 4a9e 4a9f 4a9h 4a9i 4a9j 4a9m 4a9n 4a9o 4akn 4alg 4alh 4j1p 4mr5 4mr6 4qeu 4qev 4qew 4uyf 4uyg 4uyh 5bt5 5dfb 5dfc 5dfd 5dw1 5ek9 5hel 5hem 5hen 5hfk 5ibn 5ig6 5u5s 5uew 5xhe 5xhk
Phosphodiesterase 10A (PDE10A)/ Phosphoric diester hydrolases/ T84133	1lrb 2oun 2oup 2ouq 2our 2ous 2ouu 2ouv 2ouy 2wey 2y0j 2zmf 3sn7 3sni 3snl 3ui7 3uuo 3wi2 3ws8 3ws9 3wyk 3wyl 3wym 4ael 4ajd 4ajf 4ajg 4ajm 4bbx 4ddl 4dff 4fcb 4fcd 4heu 4hf4 4lkq 4llj 4llk 4llp 4llx 4lm0 4lm1 4lm2 4lm3 4lm4 4mrw 4mrz 4ms0 4msa 4mse 4msh 4msn 4muw 4mvh 4p0n 4p1r 4phw 4tpm 4tpp 4wn1 4xy2 4yqh 4ys7 4zo5 5axp 5axq 5b4k 5b4l 5c1w 5c28 5c29 5c2a 5c2e 5c2h 5dh4 5dh5 5ede 5edg 5edh 5edi 5i2r 5k9r 5uwf
Wiskott-Aldrich syndrome protein/ T83585	1cee 1ej5 1t84 2a3z 2k42 2ot0
Pregnane X receptor/ Zinc-finger/ T82702	1ilg 1ilh 1m13 1nrl 1skx 2o9i 2qnv 3ctb 3hvl 3r8d 4j5w 4j5x 4ny9 4s0s 4s0t 4x1f 4x1g 4xao 4xhd 5a86 5x0r
Endoplasmic/ Heat shock protein/ T81311	4nh9

Enoyl-[acyl-carrier-protein] reductase [NADH]/ Oxidoreductases acting on CH-CH group of donors/ T79068	1bvr 1eny 1enz 1p44 1p45 1zid 2aq8 2aqh 2aqi 2aql 2b35 2b36 2b37 2h9i 2idz 2ie0 2ieb 2ied 2nsd 2ntj 2nv6 2pr2 2x22 2x23 3fne 3fnf 3fng 3fnh 3oew 3oey 3of2 4bge 4bgi 4bii 4bqp 4bqr 4cod 4d0r 4d0s 4dqu 4dre 4dti 4ohu 4oim 4oxk 4oxn 4oxy 4oyr 4qxm 4r9r 4r9s 4trj 4trm 4trn 4tro 4tzk 4tzt 4u0j 4u0k 4uvd 4uve 4uvg 4uvh 4uvi 5coq 5cp8 5cpb 5cpf 5g0s 5g0t 5g0u 5g0v 5g0w 5jfo 5mtp 5mtq 5mtr 5ugs 5ugt 5ugu
TYK2/ Kinase/ T78932	3lxn 3lxp 3nyx 3nz0 3zon 4gfo 4gih 4gii 4gj2 4gj3 4gvj 4oli 4po6 4py1 4wov 5c01 5c03 5flz 5f20 5tkd 5wal
mRNA of Aurora B/ Kinase/ T77764	4af3
Dual specificity protein kinase TTK/ Kinase/ T74977	2x9e 2zmc 2zmd 3cek 3dbq 3gfw 3h9f 3hmn 3hmo 3hmp 3vqu 3w1f 3wyx 3wyy 3wzj 3wzk 4b94 4bhz 4bi0 4bi1 4bi2 4c4e 4c4f 4c4g 4c4h 4c4i 4c4j 4cv8 4cv9 4cva 4d2s 4h7x 4h7y 4js8 4jt3 4o6l 4zeg 5ap0 5ap1 5ap2 5ap3 5ap4 5ap5 5ap6 5ap7 5eh0 5ehl 5eho 5ehy 5ei2 5ei6 5ei8 5ljj 5mrb 5n7v 5n84 5n87 5n93 5n9s 5na0 5nad 5ntt 5o9l 6b4w
Beta-ketoacyl-ACP synthase III/ Acyltransferase/ T72444	1ebl 1hn9 1hnd 1hnh 1hnj 1hnk 1mzs 2eft 2gyo 3il9 4z8d 5bnm 5bnr 5bns
Isocitrate dehydrogenase [NADP] cytoplasmic/ Short-chain dehydrogenases reductases/ T69563	1t09 1t0l 3inn 3map 3mar 3mas 4i3k 4i3l 4kzo 4l03 4l04 4l06 4umx 4umy 4xrx 4xs3 5de1 5gir 5k10 5k11 5l57 5l58 5lge 5sun 5svf 5tqh 5yfm 5yfn 6b0z
mRNA of kinesin spindle protein/ Kinesin-like protein family/ T63986	lii6 1q0b 1x88 1yrs 2fky 2fi2 2fi6 2fme 2glq 2gm1 2ieh 2pg2 2q2y 2q2z 2uyi 2uym 2wog 2x2r 2x7c 2x7d 2x7e 2xae 3cjo 3hqf 3k3b 3k5e 3ken 3l9h 3wpn 3zcw 4a1z 4a28 4a50 4a51 4a5y 4ap0 4aqv 4aqw 4as7 4b7b 4bbg 4bxn 4ck5 4ck6 4ck7 4zca 4zhi 5jv3
Activated CDC42 kinase 1/ Kinase/ T63220	1cf4 1u46 1u4d 1u54 3eqp 3eqr 4ewh 4hzz 4hzs 4id7
Deoxyhypusine synthase/ Alkyl aryl transferase/ T62265	1dhs 1rlz 1roz 1rqd
Ornithine aminotransferase, mitochondrial/ Transferases of nitrogenous groups/ T62073	1gbn 1oat 2byj 2byl 2can 2oat 5vwo
Polo-like kinase 2/ Kinase/ T59654	4i5m 4i5p 4i6b 4i6f 4i6h 4rs6 4xb0
mRNA of PLK1/ Target of siRNA drug/ T59273	1q4k 1q4o 1umw 2ogq 2ojx 2ou7 2owb 2rku 2v5q 2yac 3bzi 3c5l 3fc2 3fvh 3hih 3hik 3kb7 3p2w 3p2z 3p34 3p35 3p36 3p37 3qli 3rq7 3thb 4a4l 4a4o 4dfw 4e67 4e9c 4e9d 4h5x 4h7l 4hab 4hco 4hy2 4j52 4j53 4lkl 4lkm 4o56 4o6w 4o9w 4rcp 4whh 4whk 4whl 4x9r 4x9v 4x9w 5j19 5ta6 5ta8

Estradiol 17 beta-dehydrogenase 4/ Short-chain dehydrogenases reduc- tases/ T59230	likt 1s9c 1zbq
Glycoprotein IIb/ IIIa receptor/ T50688	1dpk 1dpq 1jx5 1kup 1kuz 1m8o 1rn0 1s4w 1tye 1uv9 2k1a 2k9j 2knc 2mtp 2n9y 2vc2 2vdk 2vdl 2vdm 2vdn 2vdo 2vdp 2vdq 2vdr 3fcs 3fcu 3nid 3nif 3nig 3t3m 3t3p 3zdx 3zdy 3zdz 3ze0 3ze1 3ze2 4cak 4z7n 4z7o 4z7q 5hdb
Nonstructural protein NS3/ Pepti- dase/ T40492	1rtl 2a4g 2gvf 3eyd 3hkw 3kn2 3qgh 3qgi 3rc4 3rc5 3su4
Cathepsin A/ Peptidase/ T37154	1ivy 3bp4 3bp7 3bxn 4az0 4az3 4ci9 4cia 4cib 4mws 4mwt
Activin receptor-like kinase-1/ Ki- nase/ T36959	2lcr 3my0 4fao
D-amino acid oxidase/ Oxidoreduc- tases acting on CH-NH2 group of donors/ T33124	2du8 2e48 2e49 2e4a 2e82 2gnz 3cuk 3g3e 3w4i 3w4j 3w4k 3znn 3zno 3znp 3znq 4qfc 4qfd
Thymidine kinase/ Kinase/ T30081	1w4r 1xbt 2orv 2wvj
Glutathione S-transferase P/ Alkyl aryl transferase/ T21669	10gs 11gs 12gs 13gs 14gs 16gs 17gs 18gs 19gs 1aqv 1aqw 1aqx 1eog 1eoh 1gss 1kbn 1lbk 1md3 1md4 1pgt 1px6 1px7 1zgn 20gs 22gs 2a2r 2a2s 2gss 2j9h 2pgt 3csh 3csi 3csj 3dd3 3dgq 3gss 3gus 3hjm 3hjo 3hkr 3ie3 3km6 3kmn 3kmo 3n9j 3pgt 4gss 4pgt 5dak 5dal 5dcg 5ddl 5djl 5djm 5gss 5j41 5jcw 5l6x 5x79 6gss 7gss 8gss 9gss
Isocitrate dehydrogenase (IDH2)/ Short-chain dehydrogenases reduc- tases/ T20808	4ja8 5gis 5i95 5i96 5svn 5svo
Phosphodiesterase (PDE) 9/ Phos- phoric diester hydrolases/ T17852	2hd1 2yy2 3dy8 3dyl 3dyn 3dyq 3dys 3jsi 3jsw 3k3e 3k3h 3n3z 3qi3 3qi4 4e90 4g2j 4g2l 4gh6 4y86 4y87 4y8c
P300/ CBP-associated factor/ T16902	1cm0 1jm4 1n72 1wug 1wum 1zs5 2rnw 2rnx 3gg3 4nsq 5fdz 5fe0 5fe1 5fe2 5fe3 5fe4 5fe5 5fe6 5fe7 5fe8 5fe9 5lvq 5lvr
Lysine specific histone demethy- lase 1/ Flavin monoamine oxidase/ T16739	2com 2dw4 2ejr 2h94 2hko 2iw5 2l3d 2uxn 2uxx 2v1d 2x0l 2xaf 2xag 2xah 2xaj 2xaq 2xas 2y48 2z3y 2z5u 3abt 3abu 3zms 3zmt 3zmu 3zmv 3zmz 3zn0 3zn1 4bay 4czz 4kum 4uv8 4uv9 4uva 4uvb 4uvc 4uxn 4xbf 5afw 5h6q 5h6r 5it3 5l3b 5l3c 5l3d 5l3e 5l3f 5l3g 5l3q 5lgn 5lgt 5lgu 5lhg 5lhh 5lhi 5x60
Protein arginine N- methyltransferase 4/ Methyl- transferase superfamily/ T12837	2y1w 2y1x 4ikp 5dwq 5dx0 5dx1 5dx8 5dxa 5dxj 5u4x
mRNA of HER4/ Kinase/ T06559	2ahx 2l2t 2lcx 2r4b 3bbt 3bbw 3bce 3u2p 3u7u 3u9u

Trypanothione reductase/ Oxidoreductases acting on a sulfur group of donors/ T99616	2wba
Integrin alpha-2/ beta-1/ T97353	1k11 1lha 3g9w 3t9k 3vi3 3vi4 4dx9 4wj 4wk0 4wk2 4wk4
Cytochrome P450 reductase/ Oxidoreductases acting on NADH or NADPH/ T95446	1b1c 3fjo 3qe2 3qfc 3qfr 3qfs 3qft 5emn 5fa6
Integrin alpha-5/ beta-1/ T94306	3vi3 3vi4 4wj 4wk0 4wk2 4wk4
TTR/ T86462	1bm7 1bmz 1bz8 1bzd 1bze 1dvq 1dvs 1dvt 1dvu 1dvx 1dvy 1dvz 1e3f 1e4h 1e5a 1eta 1etb 1f41 1f64 1f86 1fh2 1fhn 1g1o 1gko 1ict 1iii 1iik 1ijn 1qab 1qwh 1rlb 1sok 1soq 1tha 1thc 1tlm 1tsh 1tt6 1tta 1ttb 1ttc 1ttr 1tyr 1tz8 1u21 1x7s 1x7t 1y1d 1z7j 1zcr 1zd6 2b14 2b15 2b16 2b77 2b9a 2f7i 2f8i 2fbr 2flm 2g3x 2g3z 2g4e 2g4g 2g5u 2g9k 2gab 2h4e 2m5n 2nbo 2nbp 2noy 2pab 2qel 2qgb 2qgc 2qgd 2qge 2rox 2roy 2trh 2try 2wqa 3a4d 3a4e 3a4f 3b56 3bsz 3bt0 3cbr 3cfm 3cfn 3cfq 3cft 3cn0 3cn1 3cn2 3cn3 3cn4 3cxf 3d2t 3d7p 3dgd 3did 3djr 3djs 3djt 3djz 3dk0 3dk2 3do4 3esn 3eso 3esp 3fc8 3fcb 3glz 3gps 3grb 3grg 3gs0 3gs4 3gs7 3hj0 3i9a 3i9i 3i9p 3imr 3ims 3imt 3imu 3imv 3imw 3ipb 3ipe 3kgs 3kgt 3kgu 3m1o 3nee 3neo 3nes 3nex 3ng5 3ozk 3ozl 3p3r 3p3s 3p3t 3p3u 3ssg 3tct 3tfb 3u2i 3u2j 3w3b 4abq 4abu 4abv 4abw 4ac2 4ac4 4act 4ank 4d7b 4der 4des 4det 4deu 4dew 4fi6 4fi7 4fi8 4hiq 4his 4hjs 4hjt 4hju 4i85 4i87 4i89 4iiz 4ik6 4ik7 4iki 4ikj 4ikk 4ikl 4ky2 4lls 4llt 4mas 4mrb 4mrc 4n85 4n86 4n87 4pml 4pme 4pmf 4pvl 4pvm 4pvn 4pwe 4pwf 4pwg 4pwh 4pwi 4pwj 4pwk 4qrf 4qxv 4qya 4tkw 4tl4 4tl5 4tlk 4tls 4tlt 4tlu 4tm9 4tne 4tnf 4tng 4tq8 4tqh 4tqi 4tqp 4wnj 4wns 4wo0 4y9b 4y9c 4y9e 4y9f 4y9g 4ydm 4ydn 5a6i 5aks 5akt 5akv 5al0 5al8 5ayt 5boj 5clx 5cly 5clz 5cm1 5cn3 5cnh 5cr1 5dej 5dwp 5e23 5e4a 5e4o 5en3 5ezp 5fo2 5fw6 5fw7 5fw8 5h0v 5h0w 5h0x 5h0y 5h0z 5hjq 5ihh 5jid 5jim 5jiq 5klj 5kln 5l4f 5l4i 5l4j 5l4m 5lll 5llv 5ttr 5tzt 5u48 5u49 5u4a 5u4b 5u4c 5u4d 5u4e 5u4f 5u4g
CDC7 protein kinase/ Kinase/ T81358	4f99 4f9a 4f9b 4f9c 5uwq 5uwr
ADAMTS-4/ Peptidase/ T79570	2rjp 3b2z 4wk7 4wke 4wki
Alpha v beta 3 integrin receptor/ Integrin/ T72245	1jv2 1kup 1kuz 1l5g 1m1x 1m8o 1miz 1mk7 1mk9 1rn0 1s4x 1tye 1u8c 2ini 2k9j 2knc 2kv9 2llc 2l91 2ljd 2lje 2ljf 2mtp 2n9y 2q6w 2rmz 2rn0 2vc2 2vdk 2vdl 2vdm 2vdn 2vdo 2vdp 2vdq 2vdr 3fcs 3fcu 3ije 3nid 3nif 3nig 3t3m 3t3p 3zdx 3zdy 3zdz 3ze0 3ze1 3ze2 4cak 4gle 4glm 4mmx 4mmy 4mmz 4o02 4z7n 4z7o 4z7q 5hdb 6avq 6avr 6avu
Integrin alpha-5/ beta-3/ T67363	1jv2 1kup 1kuz 1l5g 1m1x 1m8o 1miz 1mk7 1mk9 1rn0 1s4x 1tye 1u8c 2ini 2k9j 2knc 2kv9 2llc 2l91 2ljd 2lje 2ljf 2mtp 2n9y 2q6w 2rmz 2rn0 2vc2 2vdk 2vdl 2vdm 2vdn 2vdo 2vdp 2vdq 2vdr 3fcs 3fcu 3ije 3nid 3nif 3nig 3t3m 3t3p 3zdx 3zdy 3zdz 3ze0 3ze1 3ze2 4cak 4gle 4glm 4mmx 4mmy 4mmz 4o02 4z7n 4z7o 4z7q 5hdb 6avq 6avr 6avu

Scavenger decapping enzyme DcpS/ Acid anhydrides hydrolase/ T64074	1st0 1st4 1xml 1xmm 3bl7 3bl9 3bla 4qde 4qdv 4qeb
Bone morphogenetic protein recep- tor/ Kinase/ T60213	2hlq 3g2f
mRNA of RhoA/ Ras family/ T58474	1a2b 1cc0 1cxz 1dpf 1ftn 1kmq 1lb1 1ow3 1s1c 1tx4 1x86 1xcg 2rgn 3kz1 3lw8 3lwn 3lxx 3msx 3t06 4d0n 4xh9 4xoi 4xsg 4xsh 5a0f 5bwm 5c2k 5c4m 5ez6 5fr1 5fr2 5hpy 5irc 5jcp 5jhg 5jhh 5m6x 5m70
Endothelin-converting enzyme 1/ Peptidase/ T50970	3dwb
PDE4/ Phosphoric diester hydro- lases/ T47941	2qyk 3i8v 3tvx
Nuclear receptor ROR-alpha/ Nu- clear hormone receptor/ T43206	1n83 1s0x 4s15
1-deoxy-D-xylulose-5-phosphate re- ductoisomerase/ Short-chain dehy- drogenases reductases/ T31751	3au8 3au9 3aua 3wqq 3wqr 3wqs 4gae 4kp7
Fatty acid-bindingprotein, epider- mal/ Fatty acid bindingprotein/ T21507	1b56 1jjj 4azm 4azr 4lqp 4lkt 5hz5 5ur9
Mitogen-activated protein kinase kinase kinase 9/ Kinase/ T19760	3dtc 4uy9
Dual specificity mitogen-activated protein kinase kinase 5/ Kinase/ T17143	2npt 2o2v 4ic7
SET and MYND domain-containing protein 2/ Methyltransferase super- family/ T15797	3rib 3s7b 3s7d 3s7f 3s7j 3tg4 3tg5 4o6f 4wuy 4ynd 5arf 5arg 5kjk 5kjl 5kjm 5kjm 5wgc
Tryptase/ Peptidase/ T14558	1lto 2f9n 2f9o 2f9p 2zeb 2zec 4a6l 4mpu 4mpv 4mpw 4mpx 4mq4 5f03
Valosin-containing protein p97/ Acid anhydrides hydrolase/ T12646	3ebb 3hu1 3hu2 3hu3 3qc8 3qq7 3qq8 3qwz 3tiw 4kdi 4kdl 4kln 4ko8 4kod 4p0a 5b6c 5c18 5c19 5c1a 5c1b 5dyg 5dyi 5epp 5ftj 5ftk 5ftl 5ftm 5ftn 5glf 5ifs 5ifw 5x4l
Myosin-7/ TRAFAC class myosin- kinesin ATPase/ T07507	1ik2 2fxm 2fxo 3dtp 4db1 4p7h 4pa0 4xa1 4xa3 4xa4 4xa6 5chx 5cj0 5cj1 5cj4 5tby 5wj7 5wjb 5wlq 5wlv 5wme
RON/ Kinase/ T01973	3pls 4fww 4qt8

BCAM-AKT2 fusion gene/ Kinase/ T94621	1gzk 1gzn 1gzo 1mrv 1mry 1o6k 1o6l 1p6s 2jdo 2jdr 2uw9 2x39 2xh5 3d0e 3e87 3e88 3e8d
Thymidine monophosphate kinase/ Kinase/ T94400	1g3u 1gsi 1gtv 1mrn 1mrs 1n5i 1n5j 1n5k 1n5l 1w2g 1w2h 4unn 4unp 4unq 4unr 4uns
Corticosteroid-binding globulin/ Serpin family/ T88452	2vdx 2vdy 4bb2 4c41 4c49
UDP-3-O-[3-hydroxymyristoyl] n-acetylglucosamine deacetylase/ Carbon-nitrogen hydrolase/ T85944	2ves 3p3e 3u1y 3uhm 4fw3 4fw4 4fw5 4fw6 4fw7 4j3d 4lcf 4lch 4lch 4okg 5drq 5drr 5n8c 5u39 5u3b 5upg 5vwm
3-oxoacyl-[acyl-carrier-protein] synthase II/ Acyltransferase/ T82723	1b3n 1kas 2gfv 2gfw 2gfx 2gfy 3g0y 3g11 3hnz 3ho2 3ho9 3i8p
NRH dehydrogenase [quinone] 2/ Oxidoreductases acting on diphenols as donors/ T75498	1qr2 1sg0 1xi2 1zx1 2bzs 2qmy 2qmz 2qr2 2qwx 2qx4 2qx6 2qx8 2qx9 3fw1 3g5m 3gam 3nfr 3nhf 3nhj 3nhk 3nhl 3nhp 3nhr 3nhs 3nhu 3nhw 3nhy 3o2n 3o73 3ovm 3owh 3owx 3ox1 3ox2 3ox3 3te7 3tem 3tzb 3uxe 3uxh 4fgj 4fgk 4fgl 4gqi 4gr9 4qod 4qoe 4qof 4qog 4qoh 4qoi 4qoj 4u7f 4u7g 4u7h 4xdg 4xdh 4zvk 4zvl 4zvm 4zvn 5buc 5lbt 5lbu
mRNA of Colony stimulating factor-1 receptor/ Target of anti-sense drug/ T55414	2i0v 2i0y 2i1m 2ogv 3bea 3dpk 3krj 3krl 3lcd 3lco 4dkd 4hw7 4liq 4r7h 4r7i 4wrl 4wrm
Plasmeprin 1/ Peptidase/ T50547	1lcr 1ldu 3qrv 3qsl
Cdc2-like kinase 1/ Kinase/ T46685	1z57 2vag 5j1v 5j1w 5x8i
Nicotinate-nucleotide pyrophosphorylase [carboxylating]/ Pentosyltransferase/ T44515	1qpq 1qpo 1qpq 1qpr
mRNA of HIF2-alpha/ T41003	1p97 2a24 3fln 3fl0 3flp 3h7w 3h82 4ghi 4gs9 4pky 4xt2 5kiz 5tbm 5ufp

Bromodomain-containing protein 4/ Bromodomain/ T40556	2i8n 2lsp 2mjv 2n3k 2ncz 2nd0 2nd1 2nnu 2oss 2ouo 2yel 2yem 3mxf 3p5o 3svf 3svg 3u5j 3u5k 3u5l 3uvw 3uvx 3uvy 3uw9 3zyu 4a9l 4bjx 4bw1 4bw2 4bw3 4bw4 4c66 4c67 4cfk 4cfl 4cl9 4clb 4don 4e96 4f3i 4gpj 4hbv 4hbw 4hbx 4hby 4hxx 4hxl 4hxm 4hxn 4hxo 4hxp 4hxr 4hxs 4ioo 4ioq 4ior 4j0r 4j0s 4j3i 4kv1 4kv4 4lr6 4lrg 4lyi 4lys 4lyw 4lzs 4lzs 4men 4meo 4mep 4meq 4mr3 4mr4 4nqm 4nr8 4nuc 4nud 4nue 4o70 4o71 4o72 4o74 4o75 4o76 4o77 4o78 4o7a 4o7b 4o7c 4o7e 4o7f 4ogi 4ogj 4pce 4pci 4ps5 4qb3 4qr3 4qr4 4qr5 4qzs 4uix 4uiy 4uiz 4uyd 4whw 4wiv 4x2i 4xy9 4xya 4yh3 4yh4 4z1q 4z1s 4z93 4zc9 4zw1 5a5s 5a85 5acy 5ad2 5ad3 5bt4 5cfw 5coi 5cp5 5cpe 5cqt 5crm 5crz 5cs8 5ctl 5cy9 5d0c 5d24 5d25 5d26 5d3h 5d3j 5d3l 5d3n 5d3p 5d3r 5d3s 5d3t 5dlx 5dlz 5dw2 5dx4 5e0r 5egu 5ei4 5eis 5f5z 5f60 5f61 5f62 5f63 5fbx 5h21 5hcl 5hls 5hm0 5hq5 5hq6 5hq7 5i80 5i88 5igk 5jwm 5kdh 5khm 5kj0 5ku3 5lj1 5lj2 5lrq 5luu 5m39 5m3a 5t35 5ti2 5ti3 5ti4 5ti5 5ti6 5ti7 5u28 5u2c 5u2e 5u2f 5ueo 5uep 5ueq 5uer 5ues 5uet 5ueu 5uev 5uex 5uey 5uez 5uf0 5ula 5uoo 5uvs 5uvt 5uvu 5uvv 5uvw 5uvx 5uvy 5uvz 5vom 5wuu
HIV integrase/ Integrase/ T39087	1a9m 1ajv 1ajx 1axa 1bqm 1bqn 1d4h 1d4i 1d4j 1dlo 1dw6 1ebk 1ebw 1eby 1ebz 1ec0 1ec1 1ec2 1ec3 1eet 1g35 1gnm 1gnn 1gno 1har 1hbw 1hef 1heg 1hii 1hmv 1hni 1hny 1hos 1hps 1hpz 1hqe 1hqu 1hrh 1hte 1htf 1htg 1hvi 1hvk 1hvp 1hvu 1hys 1lik 1lik 1ikx 1iky 1j5o 1kjh 1mer 1mes 1met 1meu 1n5y 1n6q 1npa 1npv 1npw 1qe1 1qmc 1r0a 1rdh 1rtd 1rvl 1rvm 1rvn 1rvo 1rvp 1rvq 1rvr 1s6p 1s6q 1s9e 1s9g 1sbz 1suq 1sv5 1t03 1t05 1t7k 1tv6 1tvr 1uwb 1w5v 1w5w 1w5x 1w5y 1yt9 1zp8 1zpa 1zsf 1zsr 2aqu 2b5j 2b6a 2ban 2bbb 2be2 2exf 2g69 2hb3 2hmi 2hnz 2hs1 2hs2 2i4d 2i4u 2i4v 2i4w 2i4x 2i5j 2iaj 2ic3 2idw 2ieo 2jzw 2l45 2l46 2l4l 2uxz 2uy0 2vg5 2vg6 2vg7 2x4u 2ykm 2ykn 2zd1 2ze2 3avi 3bgr 3dlk 3gga 3ggv 3ggx 3hvt 3ig1 3irx 3is9 3isn 3ith 3jsm 3jyt 3k2p 3k4v 3kle 3klf 3klg 3klh 3kli 3ndt 3nu3 3nu4 3nu5 3nu6 3nu9 3nuj 3nuo 3ok9 3psu 3qaa 3qlh 3qo9 3tkg 3tkw 3tl9 3tlh 3v4i 3v6d 3v8l 3zps 3zpt 3zpu 4coe 4cp7 4cpq 4cpr 4cps 4cpt 4cpu 4cpw 4cpx 4dgl 4glq 4g8g 4g8i 4g9d 4g9f 4h4m 4h4o 4i2p 4i2q 4icl 4id5 4idk 4ifv 4ify 4ig0 4ig3 4kfb 4kko 4ko0 4lsl 4lsn 4mfb 4o44 4o4g 4ojr 4pqu 4puo 4pwd 4q0b 4qag 4r5p 4rw4 4rw6 4rw7 4rw8 4rw9 4u8w 4we1 4ye3 4yfq 4zip 4zls 5agz 5ah6 5ah7 5ah8 5ah9 5aha 5ahb 5ahc 5bry 5bs4 5c24 5c25 5c42 5cym 5cyq 5d3g 5fdl 5hbm 5hlf 5hp1 5hro 5i3u 5i42 5j1e 5jfp 5jfu 5jg1 5t6z 5t70 5tep 5ter 5tuq 5tw3 5txl 5txm 5txn 5txo 5txp 5ult 5uov 5upz 5uv5 5v5l 5v5m 5vqq 5vqr 5vqs 5vqt 5vqu 5vqv 5vqw 5vqx 5vqy 5vqz
Kininogen/ T30731	1ny2 2wok 4asq 4asr 4ecb 4ecc 5i25
UDP-N-acetylglucosamine 1- carboxyvinyltransferase/ Alkyl aryl transferase/ T24634	1a2n 1uae 2z2c 3iss 3kqj 3kr6 3swd

mRNA of transthyretin/ T23389	1bm7 1bmz 1bz8 1bzd 1bze 1dvq 1dvs 1dvt 1dvy 1dvx 1dvy 1dvz 1e3f 1e4h 1e5a 1eta 1etb 1f41 1f64 1f86 1fh2 1fhn 1g1o 1gko 1ict 1iii 1iik 1ijn 1qab 1qwh 1rlb 1sok 1soq 1tha 1thc 1tlm 1tsh 1tt6 1tta 1ttb 1ttc 1ttr 1tyr 1tz8 1u21 1x7s 1x7t 1y1d 1z7j 1zcr 1zd6 2b14 2b15 2b16 2b77 2b9a 2f7i 2f8i 2fbr 2flm 2g3x 2g3z 2g4e 2g4g 2g5u 2g9k 2gab 2h4e 2m5n 2nbo 2nbp 2noy 2pab 2qel 2qgb 2qgc 2qgd 2qge 2rox 2roy 2trh 2try 2wqa 3a4d 3a4e 3a4f 3b56 3bsz 3bt0 3cbr 3cfm 3cfn 3cfq 3cft 3cn0 3cn1 3cn2 3cn3 3cn4 3cxf 3d2t 3d7p 3dgd 3did 3djr 3djs 3djt 3djz 3dk0 3dk2 3do4 3esn 3eso 3esp 3fc8 3fcb 3glz 3gps 3grb 3grg 3gs0 3gs4 3gs7 3hj0 3i9a 3i9i 3i9p 3imr 3ims 3imt 3imu 3imv 3imw 3ipb 3ipe 3kgs 3kgt 3kgu 3m1o 3nee 3neo 3nes 3nex 3ng5 3ozk 3ozl 3p3r 3p3s 3p3t 3p3u 3ssg 3tct 3tfb 3u2i 3u2j 3w3b 4abq 4abu 4abv 4abw 4ac2 4ac4 4act 4ank 4d7b 4der 4des 4det 4deu 4dew 4f6 4f7 4f8 4hiq 4his 4hjs 4hjt 4hju 4i85 4i87 4i89 4iiz 4ik6 4ik7 4iki 4ikj 4ikk 4ikl 4ky2 4lls 4llt 4mas 4mrb 4mrc 4n85 4n86 4n87 4pml 4pme 4pmf 4pvl 4pvm 4pvn 4pwe 4pwf 4pwg 4pwh 4pwi 4pwj 4pwk 4qrf 4qxv 4qya 4tkw 4tl4 4tl5 4tlk 4tls 4tlt 4tlu 4tm9 4tne 4tnf 4tng 4tq8 4tqh 4tqi 4tqp 4wnj 4wns 4wo0 4y9b 4y9c 4y9e 4y9f 4y9g 4ydm 4ydn 5a6i 5aks 5akt 5akv 5al0 5al8 5ayt 5boj 5clx 5cly 5clz 5cm1 5cn3 5cnh 5cr1 5dej 5dwp 5e23 5e4a 5e4o 5en3 5ezp 5fo2 5fw6 5fw7 5fw8 5h0v 5h0w 5h0x 5h0y 5h0z 5hjg 5ihh 5jid 5jim 5jiq 5klj 5k1n 5l4f 5l4i 5l4j 5l4m 5lll 5llv 5ttr 5tzt 5u48 5u49 5u4a 5u4b 5u4c 5u4d 5u4e 5u4f 5u4g
Pyruvate dehydrogenase kinase iso- form 2 (PDHK2)/ Kinase/ T17967	2btz 2bu2 2bu5 2bu6 2bu7 2bu8 4mp2 4mp7 4mpc 4mpe 4mpn 4v25 4v26 5j6a 5j71 5m4k 5m4m 5m4n 5m4p
Nicotinate-nucleotide adenylyl- transferase/ Kinase/ T88126	1k4k 1k4m
Pancreatic alpha-amylase/ Glyco- sylases/ T86918	1b2y 1bsi 1cpu 1hny 1kb3 1kbb 1kbb 1kgu 1kgw 1kgx 1u2y 1u30 1u33 1xcw 1xcx 1xd0 1xd1 1xgz 1xh0 1xh1 1xh2 2cpu 2qmk 2qv4 3bai 3baj 3bak 3baw 3bax 3bay 3cpu 3ij7 3ij8 3ij9 3old 3ole 3olg 3oli 4gqq 4gqr 4w93 4x9y 5e0f 5emy 5kez 5td4
Thioredoxin reductase, cytoplas- mic/ Oxidoreductases acting on a sulfur group of donors/ T84581	1w1c 2cfy 2j3n 2zz0 2zzb 2zzc 3qfa 3qfb
Pyruvate decarboxylase/ Oxidore- ductases acting on aldehyde or ox- ogroup of donors/ T71690	1l8a 1rp7 2g25 2g28 2g67 2iea 2qta 2qtc
S-nitrosoglutathione reductase/ Short-chain dehydrogenases reduc- tases/ T70518	1wma 2pfg 3bhi 3bhj 3bhm 4z3d
DNA ligase/ Ligases forming phos- phoric ester bonds/ T70310	2owo 4glx 5tt5
mRNA of DMPK/ Target of anti- sense drug/ T68766	1wt6 2vd5

Pyruvate kinase M2/ Kinase/ T65889	1t5a 1zjh 3bjf 3bjt 3g2g 3gqy 3gr4 3h6o 3me3 3srd 3srf 3srh 3u2z 4b2d 4xfx 4fxj 4g1n 4jpg 4qg6 4qg8 4qg9 4qgc 4rpp 4wj8 4yj5 5x1v 5x1w
M1-family aminopeptidase/ Peptidase/ T63159	3ebg 3ebh 3ebi 3q43 3q44 3t8v 4j3b 4k5l 4k5m 4k5n 4k5o 4k5p 4r5t 4r5v 4r5x 4x2u 4zw3 4zw5 4zw6 4zw7 4zw8 4zx3 4zx4 4zx5 4zx6
Tyrosine-protein kinase MELK/ Kinase/ T61518	4bky 4bkz 4bl1 4d2p 4d2t 4d2v 4d2w 4ixp 4ump 4umq 4umr 4umt 4umu 5ih8 5ih9 5iha 5ihc 5k00
Plasmepsin 2/ Peptidase/ T46465	1j8j 1lee 1lf2 1lf3 1lf4 1m43 1me6 1pfz 1sme 1w6h 1w6i 1xdh 1xe5 1xe6 2bjv 2bl3 2igx 2igy 2r9b 3f9q 4cku 4y6m 4ya8 4z22 5bwy
Proto-oncogene c-RAF/ Kinase/ T23673	1c1y 1faq 1far 1gua 1rfa 3cu8 3iqj 3iqu 3iqv 3kuc 3kud 3nxx 3o8i 3omv 4fj3 4g0n 4g3x 4iea 4ihl
Gelsolin/ T23000	1c0f 1c0g 1d4x 1dej 1eqy 1esv 1h1v 1kcq 1mdu 1nlv 1nm1 1nmd 1p8x 1p8z 1sol 1t44 1yag 1yvn 2ff3 2ff6 2fh1 2fh2 2fh3 2fh4 3a5l 3a5m 3a5n 3a5o 3ci5 3cip 3cjb 3cjc 3ffk 3fn 3tu5 4pkg 4pkh 4pki 4s10 4z94 5dd2 5fae 5faf 5h3m 5h3n 5o2z
Deoxyribonucleoside phosphotransferase/ Kinase/ T22976	1j90 1oe0 1ot3 1zm7 1zmx 2jcs 2jj8 2vp0 2vp2 2vp4 2vp5 2vp6 2vp9 2vpp 2vqs
Glycosyltransferase MurG/ Hexosyltransferase/ T07466	1f0k 1nlm
BMX non-receptor tyrosine kinase/ T99990	2ekx 2ys2 3sxx 3sxs
casein kinase 1, epsilon/ T99989	4hni 4hok
receptor (TNFRSF)-interacting serine-threonine kinase 1/ T99340	4ith 4iti 4itj 4neu 5hx6 5tx5
[Pyruvate dehydrogenase [lipoamide]] kinase isozyme 3, mitochondrial/ Kinase/ T99029	1y8n 1y8o 1y8p 2pnr 2q8i
histone deacetylase 7/ T98698	3c0y 3c0z 3c10 3znr 3zns
Thymidylate synthase/ Methyltransferase superfamily/ T98397	1hvy 1hw3 1hw4 1hzw 1i00 1ju6 1juj 1ypv 2onb 2rd8 2rda 3eaw 3ebu 3ed7 3edw 3ef9 3egy 3ehi 3ejl 3gg5 3gh0 3gh2 3h9k 3hb8 3n5e 3n5g 3ob7 4e28 4fgt 4g2o 4g6w 4gd7 4gyh 4h1i 4jef 4kpw 4o1u 4o1x 4up1 5hs3 5wrn 5x4w 5x4x 5x4y 5x5a 5x5d 5x5q 5x66 5x67 5x69
Peptidyl-prolyl cis-trans isomerase FKBP5/ Cis-trans-isomerases/ T98337	1kt0 3o5d 3o5e 3o5f 3o5g 3o5i 3o5j 3o5k 3o5l 3o5m 3o5o 3o5p 3o5q 3o5r 4drh 4dri 4drk 4drn 4drn 4dro 4drp 4drq 4jfi 4jfi 4jfk 4jfl 4jfm 4r0x 4tw6 4tw7 4tx0 4w9o 4w9p 4w9q 5bxj 5dit 5diu 5div 5njx 5omp

Deoxycytidine kinase/ Kinase/ T98089	1p5z 1p60 1p61 1p62 2a2z 2a30 2a7q 2no0 2no1 2no6 2no7 2no9 2noa 2qrn 2qro 2zi3 2zi4 2zi5 2zi6 2zi7 2zi9 2zia 3hpl 3ipx 3ipy 3kfx 3mjr 3qej 3qen 3qeo 4jlj 4jlk 4jlm 4jln 4kcg 4l5b 4q18 4q19 4q1a 4q1b 4q1c 4q1d 4q1e 4q1f
ADAM 8/ Peptidase/ T95761	4dd8
mitogen-activated protein kinase kinase kinase 14/ T95736	4dn5 4g3d 4idt 4idv
mRNA of MMP9/ Peptidase/ T93690	1gkc 1gkd 1itv 1l6j 1lkg 2ovx 2ovz 2ow0 2owl 2ow2 4h1q 4h2e 4h3x 4h82 4hma 4jij 4jqg 4wzv 4xct 5cuh 5i12 5th6 5th9 5ue3 5ue4
Prostatic acid phosphatase/ T93283	1cvi 1nd5 1nd6 2hpa 2l3h 2l77 2l79 2mg0 3ppd
dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A/ T92803	2vx3 2wo6 3anq 3anr 4aze 4mq1 4mq2 4nct 4ylj 4ylk 4yll 4yu2 5a3x 5a4e 5a4l 5a4q 5a4t 5a54 5aik
Replicase polyprotein 1ab/ Viral RNA helicase/ T92724	1o5s 1p76 1p9t 1pa5 1puk 1qlx 1q2w 1qz8 1sxf 1uj1 1uk2 1uk3 1uk4 1uw7 1wof 1ysy 1z1i 1z1j 2a5a 2a5i 2a5k 2acf 2ahm 2aj5 2alv 2amd 2amq 2bx3 2bx4 2c3s 2d2d 2duc 2fav 2fe8 2fyg 2g1f 2g9t 2ga6 2gdt 2gri 2gt7 2gt8 2gtb 2gx4 2gz7 2gz8 2gz9 2h2z 2h85 2hob 2hsx 2idy 2jzd 2jze 2jzf 2k87 2op9 2ozk 2pwx 2q6g 2qc2 2qcy 2qiq 2rhb 2rnk 2v6n 2vj1 2xyq 2xyr 2xyv 2z3c 2z3d 2z3e 2z94 2z9g 2z9j 2z9k 2z9l 3d62 3e9s 3ebn 3r24 4tww 4twy 4wy3 4zuh 5b6o 5c5n 5c5o 5c8s 5c8t 5c8u 5e6j 5f22
Pantothenate kinase/ Kinase/ T91895	1esm 1esn 1sq5
ADAMTS1/ T90987	2jih 2v4b 3q2g 3q2h
Adenylosuccinate synthetase/ Carbon-nitrogen ligase/ T89054	1p9b
Integrin alpha-V/ beta-1/ T88806	1k1l 1lha 3g9w 3t9k 3vi3 3vi4 4dx9 4wjK 4wk0 4wk2 4wk4
L-lactate dehydrogenase/ Short-chain dehydrogenases reductases/ T88057	1sov 1sow 3czm
casein kinase 1, delta/ T87109	3uys 3uyt 3uzp 4hgt 4hnf 4kb8 4kba 4kbc 4kbb 4tn6 4tw9 4twc 5ih4 5ih5 5ih6 5mqv 5w4w
Scytalone dehydratase/ Carbon-oxygen lyases/ T86829	1idp 1std 2std 3std 4std 5std 6std 7std

NH(3)-dependentNAD(+) syn- thetase/ Carbon-nitrogen ligase/ T86152	1wxe 1wxf 1wxg 1wxh 1wxi
mRNA of cytohesin-2/ T85056	1pbv 1r8m 1r8q 1r8s 1s9d 4jmi 4jmo 4jwl 4jxh 4l5m 4z21
Prostacyclin synthase/ Intramolec- ular oxidoreductases/ T83979	2iag 3b6h
Quinone oxidoreductase/ T83284	1yb5
ribosomal protein S6 kinase, 90kDa, polypeptide 1/ T83202	2wnt 2z7q 2z7r 2z7s 3rny 3tei 4h3p 4nif 5csf 5csi 5csj 5csn 5n7d 5n7f 5n7g 5v61 5v62
ABL proto-oncogene 2, non- receptor tyrosine kinase/ T83009	2ecd 2kk1 2xyn 3gvu 3hmi 3ulr 4eih
HCV helicase/ Acid anhydrides hy- drolase/ T82916	1rtl 2a4g 2gvf 3eyd 3hkw 3kn2 3qgh 3qgi 3rc4 3rc5 3su4
casein kinase 1, gamma 2/ T82773	2c47
Kynurenine oxoglutarate transami- nase II/ Transferases of nitrogenous groups/ T82668	2qlr 2r2n 2vgz 2xh1 3dc1 3ue8 4gdy 4ge4 4ge7 4ge9 4geb 5efs 5eun 5tf5
Folate receptor beta/ Folate recep- tor/ T82297	4kmy 4kmz 4kn0 4kn1 4kn2
Calmodulin-dependent kinase II/ T82262	2zv2 5uy6 5uyj 5vt1
death-associated protein kinase 3/ T81623	1yrp 2j90 3bhy 3bqr 5a6n 5a6o
DNA gyrase B subunit/ ATP- hydrolyzing DNA topoisomerase/ T81503	1aj6 1ei1 1kzn 3g7e 3nuh 4duh 4hyp 4kfg 4prv 4prx 4pu9 4wub 4wuc 4wud 4xtj 4zvi 5l3j 5mmn 5mmo 5mmp
casein kinase 2, alpha prime polypeptide subunit/ T80526	3e3b 3ofm 3u87 5m4u 5m56
Von Hippel-Lindau disease tumor suppressor (VHL)/ T80423	1lm8 1lqb 1vcb 3zrc 3zrf 3ztc 3ztd 3zun 4ajy 4awj 4b95 4b9k 4bks 4bkt 4w9c 4w9d 4w9e 4w9f 4w9g 4w9h 4w9i 4w9j 4w9k 4w9l 4w9o 5lli 5n4w 5nvw 5nvx 5nvz 5nvz 5nvz 5nw0 5nw1 5nw2 5t35

Dihydrolipoamide dehydrogenase, mitochondrial/ Oxidoreductases acting on a sulfur group of donors/ T80175	2qae
mRNA of VLA-4/ Target of anti-sense drug/ T79690	1k11 1lha 3g9w 3t9k 3vi3 3vi4 4dx9 4wj 4wk0 4wk2 4wk4
Ketohexokinase/ Kinase/ T79326	2hlz 2hq 2hw1 3b3l 3nbv 3nbw 3nc2 3nc9 3nca 3q92 3qa2 3qai 3ro4 5wbm 5wbo 5wbp 5wbq 5wbr 5wbz
Protein kinase G (PKG) 1/ T78543	1zxa 3nmd 3ocp 3od0 3ogj 4ku7 4ku8 4qx5 4qxx 4r4l 4r4m 4z07 5j48 5jax 5jd7 5l0n
Glycerol-3-phosphate dehydrogenase [NAD+], cytoplasmic/ Short-chain dehydrogenases reductases/ T77721	1wpq 1x0v 1x0x
WD repeat domain 5/ T77393	2cnx 2co0 2g99 2g9a 2gnq 2h13 2h14 2h68 2h6k 2h6n 2h6q 2h9l 2h9m 2h9n 2h9p 2o9k 3eg6 3emh 3mxx 3n0d 3n0e 3p4f 3psl 3smr 3ur4 3uvk 3uvl 3uvm 3uvm 3uvo 4a7j 4cy1 4cy2 4erq 4ery 4erz 4es0 4esg 4ewr 4gm3 4gm8 4gm9 4gmb 4ia9 4o45 4ql1 4y7r 5eal 5eam 5eap 5ear 5m23 5m25 5sxx 5vfc
mRNA cap guanine N7 methyltransferase/ Methyltransferase superfamily/ T77174	3bgv 3epp 5e8j 5e9j 5e9w
protein arginine methyltransferase 3/ T76723	2fyt 3smq 4hsg 4qqn 4ryl
Integrin alpha-1/ beta-3/ T74109	1jv2 1kup 1kuz 1l5g 1m1x 1m8o 1miz 1mk7 1mk9 1rn0 1s4x 1tye 1u8c 2ini 2k9j 2knc 2kv9 2l1c 2l91 2ljd 2lje 2ljf 2mtp 2n9y 2q6w 2rmz 2rn0 2vc2 2vdk 2vdl 2vdm 2vdm 2vdo 2vdp 2vdq 2vdr 3fcs 3fcu 3ije 3nid 3nif 3nig 3t3m 3t3p 3zdx 3zdy 3zdz 3ze0 3ze1 3ze2 4cak 4g1e 4g1m 4mmx 4mmy 4mmz 4o02 4z7n 4z7o 4z7q 5hdb 6avq 6avr 6avu
CDC-like kinase 2/ T73725	3nr9
SET domain containing (lysine methyltransferase) 7/ T73184	1h3i 1mt6 1muf 1n6a 1n6c 1o9s 1xqh 2f69 3cbm 3cbo 3cbp 3m53 3m54 3m55 3m56 3m57 3m58 3m59 3m5a 3os5 3vuz 3vv0 4e47 4j7f 4j7i 4j83 4j8o 4jds 4jlg 5ayf 5eg2
Adipocyte-derived leucine aminopeptidase/ Peptidase/ T72849	2yd0 3mdj 3qnf 3rjo 5j5e
TRAF2 and NCK interacting kinase/ T72534	2x7f 5ax9 5cwz 5d7a

Caspase 7/ T72252	1flj 1gqf 1i4o 1i51 1k86 1k88 1kmc 1mia 1shj 1shl 2ql5 2ql7 2ql9 2qlb 2qlf 2qlj 3edr 3h1p 3ibc 3ibf 3r5k 4fdl 4fea 4hq0 4hqr 4jb8 4jj8 4jr1 4jr2 4lsz 4zvo 4zvp 4zvf 4zvr 4zvs 4zvt 4zvu 5ic6 5k20 5v6u
GAR transformylase/ T72042	1mej 1men 1meo 1njs 1rbm 1rbq 1rby 1rbz 1rc0 1rc1 1zlx 1zly 2qk4 2v9y 4ew1 4ew2 4ew3 4zyt 4zyu 4zyv 4zyw 4zyx 4zyy 4zyz 4zz0 4zz1 4zz2 4zz3 5j9f
Neutrophil gelatinase-associated lipocalin/ Calycin family/ T72010	1dfv 1l6m 1ngl 1qqs 1x71 1x89 1x8u 3by0 3cbc 3cmp 3dsz 3dtq 3fw4 3fw5 3hwd 3hwe 3hwf 3hwg 3i0a 3k3l 3pec 3ped 3t1d 3tf6 3tzs 3u03 3u0d 4gh7 4iaw 4iax 4k19 4mvi 4mvk 4mvl 4qae 4zfx 4zhc 4zhd 4zhf 4zhg 4zhh 5jr8 5khp 5kic 5kid 5mhh
GTPase HRas/ Ras family/ T71081	121p 1aa9 1agp 1bkd 1clu 1crp 1crq 1crr 1ctq 1gnp 1gnq 1gni 1he8 1iaq 1ioz 1jah 1jai 1k8r 1lf0 1lf5 1lfd 1nvu 1nvv 1nvw 1nvx 1p2s 1p2t 1p2u 1p2v 1plj 1plk 1pll 1q21 1qra 1rvd 1wq1 1xcm 1xd2 1xj0 1zvq 1zw6 221p 2c5l 2ce2 2cl0 2cl6 2cl7 2clc 2cld 2evw 2gdp 2lcf 2lwi 2n42 2n46 2q21 2quz 2rga 2rgb 2rgc 2rgd 2rge 2rgg 2uzi 2vh5 2x1v 3ddc 3i3s 3k8y 3k9l 3k9n 3kkm 3kkn 3kud 3l8y 3l8z 3lbh 3lbi 3lbn 3lo5 3oiu 3oiv 3oiw 3rry 3rrz 3rs0 3rs2 3rs3 3rs4 3rs5 3rs7 3rsl 3rso 3tgp 421p 4dlr 4dls 4dlt 4dlu 4dlv 4dlw 4dlx 4dly 4dlz 4dst 4dsu 4efl 4efm 4efn 4g0n 4g3x 4k81 4l9s 4l9w 4nyi 4nyj 4nym 4q21 4rsg 4uru 4urv 4urw 4urx 4ury 4urz 4us0 4us1 4us2 4xvq 4xvr 521p 5b2z 5b30 5e95 5p21 5vbe 5vbw 5wdo 5wdp 5wdq 5x9s 621p 6amb 6axg 6q21 721p 821p
mitogen-activated protein kinase 7/ T70851	2q8y 4b99 4ic7 4ic8 4zsg 4zsj 4zsl 5byy 5byz
mRNA of human zinc finger protein-217/ Zinc-finger/ T70278	2hu2 3uk3 4f2j 4is1
Nuclear receptor binding SET domain containing protein 1/ Methyltransferase superfamily/ T68777	3ooi
Poly(ADP-ribose) glycohydrolase/ Glycosylases/ T66935	4a0d 4b1g 4b1h 4bli 4blj 5a7r 5lhb
Endoplasmic reticulum aminopeptidase 2/ T65818	3se6 4e36 4jbs 5ab0 5ab2 5cu5 5j6s 5k1v
HCN2/ T65005	2mpf 3u10
Angiotensinogen/ Serpin family/ T64485	1n9u 1n9v 2jp8 2wxw 2x0b 3ck0 3woo 3wor 4aa1 4aph 4fys 5e2q
cyclin-dependent kinase-like 1 (CDC2-related kinase)/ T63851	4agu

UDP-N-acetylenolpyruvylglucosamine reductase/ Short-chain dehydrogenases reductases/ T63359	1mbb 1mbt 1uxy 2mbr 2q85
TANK-binding kinase 1/ T63024	4efo 4eut 4euu 4im0 4im2 4im3 4iw0 4iwo 4iwp 4iwq 5eoa 5eof 5ep6
Retinoid X receptor-beta/ T60077	1h9u 1uhl 5hjp 5i4v 5kya 5kyj
Estrogen-related receptor-gamma/ T59875	1kv6 1tfc 1vjb 2e2r 2ewp 2gp7 2gpo 2gpp 2gpu 2gpv 2p7a 2p7g 2p7z 2zas 2zbs 2zkc
EPH receptor A7/ T57006	2rei 3dko 3h8m 3nru
mRNA of Protein kinase C alpha/ Kinase/ T56722	2eli 3iw4 4dnl 4ra4
Phenylethanolamine N-methyltransferase/ T56496	1hnn 1n7i 1n7j 1yz3 2an3 2an4 2an5 2g70 2g71 2g72 2g8n 2obf 2ony 2onz 2opb 3hca 3hcb 3hcc 3hcd 3hce 3hcf 3kpj 3kpu 3kp v 3kpw 3kpy 3kqm 3kqo 3kqp 3kqq 3kqs 3kqt 3kqv 3kqw 3kqy 3kr0 3kr1 3kr2 4dm3 4mik 4mq4
lysine (K)-specific demethylase 6B/ T56057	2xue 2xxz 4ask 5fp3 5oy3
Plasma retinol-binding protein/ Calycin family/ T55703	1brp 1brq 1jyd 1jyj 1qab 1rbp 1rlb 2wq9 2wqa 2wr6 3bsz 3fmz 4o9s 4psq
Mycobacterium tuberculosis serine/ threonine-protein kinase PknB/ T55435	1mru 1o6y 2fum 2kud 2kue 2kuf 2kui 3f61 3f69 3ori 3oro 5e0y 5e0z 5e10 5e12
Schistosoma mansoni purine nucleoside phosphorylase/ T54519	1tcu 1tcv 1td1 3djf 3e0q 3e9r 3e9z 3f8w 3faz 3fb1 3fnq 3iex
Cyclin-dependent protein kinase PFK5/ Kinase/ T54472	1lch 1ob3 1v0b 1v0o 1v0p
euchromatic histone-lysine N-methyltransferase 2/ T53251	2o8j 3dm1 3k5k 3rjw 4nvq 5jhn 5jin 5jji 5jj0 5t0k 5t0m 5ttf 5tuy 5vsc 5vse
Acidic mammalian chitinase/ Glycosylases/ T51597	2ybt 2ybu 3fxy 3fy1 3rm4 3rm8 3rm9 3rme
Tryptophan hydroxylase/ Oxidoreductases acting on paired donors/ T51593	1in9 1mlw 3hf6 3hf8 3hfb 5j6d 5l0l 5tpg

Cytochrome p450 121/ Oxidoreductases acting on paired donors/ T49627	1n40 1n4g 2ij5 2ij7 3cxx 3cyy 3cxz 3cy0 3cy1 3g5f 3g5h 4g1x 4g2g 4g44 4g45 4g46 4g47 4g48 4ict 4ips 4ipw 4iq7 4iq9 5ibd 5ibe 5ibf 5ibg 5ibh 5ibi 5ibj 5edt
NIMA-related kinase 2/ T49102	2jav 2w5a 2w5b 2w5h 2wqo 2xk3 2xk4 2xk6 2xk7 2xk8 2xkc 2xkd 2xke 2xkf 2xnm 2xnn 2xno 2xnp 4a4x 4afe 5m51 5m53 5m55 5m57
ADP-ribosylation factor 1/ Small GTPase superfamily/ T47351	1hur 1re0 1u81 3o47 4hmy
Angiotensin converting enzyme-like protein/ Peptidase/ T46103	1r42 1r4l 1xjp 2ajf 3d0g 3d0h 3d0i 3kbh 3sci 3scj 3sck 3scl
Coagulation factor XI/ Peptidase/ T46040	1xx9 1xxd 1xxf 1zhm 1zhp 1zhr 1zjd 1zlr 1zmj 1zml 1zmn 1zom 1zpb 1zpc 1zpz 1zrk 1zsj 1zsk 1zsl 1ztj 1ztk 1ztl 2f83 2fda 2j8j 2j8l 3bg8 3sor 3sos 4cr5 4cr9 4cra 4crb 4crc 4crd 4cre 4crf 4crg 4d76 4d7f 4d7g 4na7 4na8 4ty6 4ty7 4wxi 4x6m 4x6n 4x6o 4x6p 4y8x 4y8y 4y8z 5e2o 5e2p 5eod 5eok 5exl 5exm 5exn 5i25 5q0d 5q0e 5q0f 5q0g 5q0h 5qcl 5qcm 5qcn 5tk5 5tkk 5tku 5wb6
NM23-H1/ Kinase/ T42533	1jxv 1ucn 2hvd 2hve 3l7u 4eno
Methionyl aminopeptidase 1/ T42337	2b3h 2b3k 2b3l 2g6p 2gz5 2nq6 2nq7 4fli 4flj 4flk 4fll 4hxx 4ikr 4iks 4ikt 4iku 4iue 4ulb 4u69 4u6c 4u6e 4u6j 4u6w 4u6z 4u70 4u71 4u73 4u75 4u76
casein kinase 1, gamma 1/ T41702	2cmw
mRNA of EGFR/ Target of anti-sense drug/ T41560	1dnq 1dnr 1ivo 1m14 1m17 1mox 1nql 1xkk 1yy9 1z9i 2eb2 2eb3 2exp 2exq 2gs2 2gs6 2gs7 2itn 2ito 2itp 2itq 2itt 2itu 2itv 2itw 2itx 2ity 2itz 2j5e 2j5f 2j6m 2jit 2jiu 2jiv 2ks1 2m0b 2m20 2n5s 2rf9 2rfd 2rfe 2rgp 3b2u 3b2v 3bel 3buo 3c09 3g5v 3g5y 3gop 3gt8 3ika 3lzb 3njp 3ob2 3op0 3p0y 3pfv 3poz 3qwq 3ug1 3ug2 3vjn 3vjo 3vrp 3vrr 3w2o 3w2p 3w2q 3w2r 3w2s 3w32 3w33 4g5j 4g5p 4hjo 4ilz 4i20 4i21 4i22 4i23 4i24 4jq7 4jq8 4jr3 4jrv 4krl 4krm 4kro 4krp 4li5 4ll0 4lqm 4lrm 4r3p 4r3r 4r5s 4riw 4rix 4riy 4rj4 4rj5 4rj6 4rj7 4rj8 4tk5 4uip 4uv7 4wd5 4wkq 4wrg 4zau 4zjv 4zse 5c8k 5c8m 5c8n 5cal 5can 5cao 5cap 5caq 5cas 5cau 5cav 5cnn 5cno 5czh 5czi 5d41 5edp 5edq 5edr 5em5 5em6 5em7 5em8 5fed 5fee 5feq 5gmp 5gnk 5gty 5gtz 5hcx 5hcy 5hcz 5hg5 5hg7 5hg8 5hg9 5hib 5hic 5j9y 5j9z 5jeb 5lv6 5sx4 5sx5 5u8l 5ug8 5ug9 5uga 5ugb 5ugc 5uud 5wb7 5wb8 5xgm 5xgn
Nuclear receptor subfamily 4 group A member 1/ Zinc-finger/ T41119	2qw4 3v3e 3v3q 4jgv 4kzi 4kzj 4kzm 4re8 4ree 4ref 4rze 4rzf 4rzg 4whf 4whg
MMP10/ T40488	1q3a 3v96 4ilw
euchromatic histone-lysine N-methyltransferase 1/ T39996	2igq 2rfi 3b7b 3b95 3fpd 3hna 3mo0 3mo2 3mo5 3sw9 3swc 4i51 5ttg 5tuz 5vsd 5vsf
HCV nucleoside triphosphatase/ Acid anhydrides hydrolase/ T39753	1b78 2mjp

dUTP pyrophosphatase/ Acid anhydrides hydrolase/ T39054	1q5h 1q5u 2hqu 3ara 3arn 3ehw 4mz5 4mz6 5h4j
p21 protein (Cdc42/ Rac)-activated kinase 1/ T37961	1f3m 1yhv 1yhw 1zsg 2hy8 2qme 3dvp 3fxz 3fy0 3q4z 3q52 3q53 4daw 4eqc 4o0r 4o0t 4p90 4zji 4zjj 4zlo 4zy4 4zy5 4zy6 5dew 5dey 5dfp 5ime 5kbq 5kbr 6b16
PAS domain containing serine/threoninekinase/ T37371	1ll8 3dls
mitogen-activated protein kinase-activated protein kinase 3/ T36581	3fhr 3fxw 3r1n 3she
S100 calcium binding protein A4/ T35265	1m31 2lnk 2mrd 2q91 3c1v 3cga 3ko0 3m0w 3zwh 4cfq 4cfr 4eto 4hsz 5lpu
Hepatitis C virus serine protease NS4a/ T34997	1rtl 2a4g 2gvf 3eyd 3hkw 3kn2 3qgh 3qgi 3rc4 3rc5 3su4
Undecaprenyl pyrophosphate synthetase/ Alkyl aryl transferase/ T34337	1jp3 1ueh 1v7u 1x06 1x07 1x08 1x09 2e98 2e99 2e9a 2e9c 2e9d 3qas 3sgv 3sgx 3sh0 3th8 3wyj 4h2j 4h2m 4h2o 4h38 4h3a 4h3c 5cqb 5cqj
Protoporphyrinogen oxidase/ T34239	3nks 4ivm 4ivo
Tyrosyl DNA phosphodiesterase 1/ Phosphoric diester hydrolases/ T33492	1jy1 1mu7 1mu9 1nop 1qzq 1rff 1rfi 1rg1 1rg2 1rgt 1rgu 1rh0
3-alpha-hydroxysteroid dehydrogenase/ Short-chain dehydrogenases reductases/ T32109	1afs 1lwi 1ral
HCK proto-oncogene, Src family tyrosine kinase/ T31406	1ad5 1bul 1qcf 2c0i 2c0o 2c0t 2hck 2hk5 2oi3 2oj2 3hck 3nhn 3rbb 3rea 3reb 3vry 3vrz 3vs0 3vs1 3vs2 3vs3 3vs4 3vs5 3vs6 3vs7 4hck 4lud 4lue 4orz 4u5w 5h09 5h0b 5h0e 5h0g 5h0h 5hck 5nuh
Eukaryotic translation initiation factor 4E/ T31186	1ipb 1ipc 1kwk 2gpq 2v8w 2v8x 2v8y 2w97 3am7 3tf2 3u7x 4aza 4bea 4dt6 4dum 4tpw 4tqb 4tqc 4ued 5ehc 5ei3 5eir 5ekv 5gw6 5t46
SET domain containing (lysine methyltransferase) 8/ T30420	1zkk 2bqz 3f9w 3f9x 3f9y 3f9z 4ij8 5hq2 5t5g 5teg 5th7 5w1y
HCN4/ T30286	2mng 3otf 3u11 4hbn 4kl1 4nvp
casein kinase 1, gamma 3/ T29728	2chl 2izr 2izs 2izt 2izu 4g16 4g17 4hgl 4hgs

Ketol-acid reductoisomerase/ Short-chain dehydrogenases reduc- tases/ T28153	lyrl 3ulk
Integrin beta-3/ Integrin/ T26457	1jv2 1kup 1kuz 1l5g 1m1x 1m8o 1miz 1mk7 1mk9 1rn0 1s4x 1tye 1u8c 2ini 2k9j 2knc 2kv9 2l1c 2l91 2ljd 2lje 2ljf 2mtp 2n9y 2q6w 2rmz 2rn0 2vc2 2vdk 2vdl 2vdm 2vdm 2vdo 2vdp 2vdq 2vdr 3fcs 3fcu 3ije 3nid 3nif 3nig 3t3m 3t3p 3zdx 3zdy 3zdz 3ze0 3zel 3ze2 4cak 4gle 4glm 4mmx 4mmy 4mmz 4o02 4z7n 4z7o 4z7q 5hdb 6avq 6avr 6avu
Fibrinogen/ Fibrinogen/ T26144	1dug 1fib 1fic 1fid 1fza 1fzb 1fzc 1fze 1fzf 1fzg 1lt9 1ltj 1n86 1n8e 1re3 1re4 1rf0 1rfl 2a45 2ffd 2fib 2h43 2hlo 2hod 2hpc 2hwl 2oyh 2oyi 2q9i 2vdo 2vdp 2vdq 2vdr 2vr3 2xnx 2xny 2y7l 2z4e 3bvh 3eli 3fib 3ghg 3h32 3hus 4b60
Mixed-lineage leukemia protein (MLL) complex/ Methyltransferase superfamily/ T25462	2agh 2j2s 2jyi 2kkf 2ku7 2kyu 2lxs 2lxt 2msr 2mtn 2w5y 2w5z 3eg6 3emh 3lqh 3lqi 3lqj 3p4f 3u85 3u88 4esg 4gq6 4nw3 5f5e 5f6l
RAR-related orphan receptor- gamma/ T25307	3b0w 3kyt 3l0j 3l0l 4nb6 4nie 4qm0 4s14 4wlb 4wpf 4wqp 4xt9 4ymq 4ypq 4zjr 4zjw 4zom 5aph 5apj 5apk 5ayg 5c4o 5c4s 5c4t 5c4u 5ejv 5eth 5g42 5g43 5g44 5g45 5g46 5ixk 5iz0 5k38 5k3l 5k3m 5k3n 5k6e 5k74 5lwp 5m96 5nti 5ntk 5ntn 5ntp 5ntq 5ntw 5nu1 5ufo 5ufr 5uhi 5vb3 5vb5 5vb6 5vb7 5x8q
3-Deoxy-D-manno-octulosonate 8- phosphate synthase/ Alkyl aryl transferase/ T23688	1d9e 1g7u 1g7v 1gg0 1phq 1phw 1pl9 1q3n 1x6u 1x8f
HIV p24 capsid protein/ T23343	1a9m 1ajv 1ajx 1axa 1bqm 1bqn 1d4h 1d4i 1d4j 1dlo 1dw6 1ebk 1ebw 1eby 1ebz 1ec0 1ec1 1ec2 1ec3 1eet 1g35 1gnm 1gmn 1gno 1har 1hbv 1hef 1heg 1hjh 1hmv 1hni 1hnv 1hos 1hps 1hpz 1hqe 1hqu 1hrh 1hte 1htf 1htg 1hvi 1hvk 1hvp 1hvu 1hys 1ikv 1ikw 1ikx 1iky 1j5o 1kjh 1mer 1mes 1met 1meu 1n5y 1n6q 1npa 1npv 1npw 1qe1 1qmc 1r0a 1rdh 1rtd 1rvl 1rvm 1rvn 1rvo 1rvp 1rvq 1rvr 1s6p 1s6q 1s9e 1s9g 1sbg 1suq 1sv5 1t03 1t05 1t7k 1tv6 1tvr 1uwb 1w5v 1w5w 1w5x 1w5y 1yt9 1zp8 1zpa 1zsf 1zsr 2aqu 2b5j 2b6a 2ban 2bbb 2be2 2exf 2g69 2hb3 2hmi 2hnz 2hs1 2hs2 2i4d 2i4u 2i4v 2i4w 2i4x 2i5j 2iaj 2ic3 2idw 2ieo 2jzw 2l45 2l46 2l4l 2uxz 2uy0 2vg5 2vg6 2vg7 2x4u 2ykm 2ykn 2zd1 2ze2 3avi 3bgr 3dlk 3gga 3ggv 3ggx 3hvt 3ig1 3irx 3is9 3isn 3ith 3jsm 3jyt 3k2p 3k4v 3kle 3klf 3klg 3klh 3kli 3ndt 3nu3 3nu4 3nu5 3nu6 3nu9 3nuj 3nuo 3ok9 3psu 3qaa 3qlh 3qo9 3tkg 3tkw 3tl9 3tlh 3v4i 3v6d 3v81 3zps 3zpt 3zpu 4coe 4cp7 4cpq 4cpr 4cps 4cpt 4cpu 4cpw 4cpv 4dgl 4g1q 4g8g 4g8i 4g9d 4g9f 4h4m 4h4o 4i2p 4i2q 4icl 4id5 4idk 4ifv 4ify 4ig0 4ig3 4kfb 4kko 4ko0 4lsl 4lsn 4mfb 4o44 4o4g 4ojr 4pqu 4puo 4pwd 4q0b 4qag 4r5p 4rw4 4rw6 4rw7 4rw8 4rw9 4u8w 4we1 4ye3 4yhq 4zip 4zls 5agz 5ah6 5ah7 5ah8 5ah9 5aha 5ahb 5ahc 5bry 5bs4 5c24 5c25 5c42 5cym 5cyq 5d3g 5fdl 5hbm 5hlf 5hp1 5hro 5i3u 5i42 5j1e 5jfp 5jfu 5jg1 5t6z 5t70 5tep 5ter 5tuq 5tw3 5txl 5txm 5txn 5txo 5txp 5ult 5uov 5upz 5uv5 5v5l 5v5m 5vqq 5vqr 5vqs 5vqt 5vqu 5vqv 5vqw 5vqx 5vqy 5vqz
mRNA of AKT1/ Target of anti- sense drug/ T22306	1h10 1unp 1unq 1unr 2uvm 2uzr 2uzs 3cqu 3cqw 3mv5 3mvh 3o96 3ocb 3ow4 3qkk 3qkl 3qkm 4ejn 4ekk 4ekl 4gv1 5kcv

5-methyltetrahydrofolate– homocysteine methyltransferase/ Methyltransferase superfamily/ T21661	2o2k 4ccz
Phosphodiesterase (PDE) 3B/ Phosphoric diester hydrolases/ T21357	1so2 1soj
Troponin I, cardiac muscle/ Tro- ponin/ T20186	1jld 1jle 1lxf 1mxl 1ozs 2kgb 2krd 2l1r 2mzp 2n7l 4y99 5vln 5w88 5wcl
Cytochrome P450 2C9/ T19244	1og2 1og5 1r9o 4nz2 5a5i 5a5j 5k7k 5w0c 5x23 5x24 5xxi
Ribosome-inactivating protein alpha-trichosanthin/ T18416	1gis 1giu 1j4g 1mrj 1mrk 1nli 1qd2 1tcs 2jdl 2jjr 2vs6
poly (ADP-ribose) polymerase 3/ T17228	2eoc 3c49 3c4h 3ce0 3fhh 4gv0 4gv2 4gv4 4l6z 4l70 4l7l 4l7n 4l7o 4l7p 4l7r 4l7u
mRNA of TNF alpha ligand/ Cy- tokine: tumor necrosis factor/ T16486	1a8m 1tnf 2az5 2e7a 2tun 2zjc 2zpx 3alq 3it8 3l9j 3wd5 4g3y 4tsv 4twl 4y6o 5m2i 5m2j 5m2m 5mu8 5tsw 5uui 5wux
bromodomain adjacent to zinc fin- ger domain, 2B/ T15745	2e7o 3g0l 3q2f 4cup 4cuq 4cur 4cus 4cut 4cuu 4ir3 4ir4 4ir5 4ir6 4nr9 4nra 4nrb 4nrc 4qc1 4qc3 4qf3 4rvr 4xua 4xub 5cq3 5cq4 5cq5 5cq6 5cq7 5cq8 5cqa 5cu8 5cua 5cub 5cuc 5cud 5cue 5cug 5dyu 5dyx 5e73 5e74 5e9i 5e9k 5e9l 5e9m 5e9y 5l8t 5l8u 5l96 5l97 5l98 5l99 5mge 5mgf 5mgg 5or9 5orb 5pb7 5pb8 5pb9 5pba 5pbb 5pbc 5pbd 5pbe 5pbf 5pbg 5pbh 5pbi 5pbj 5pbk 5pbl 5pbm 5pbn 5pbo 5pbp 5pbq 5pbr 5pbs 5pbt 5pbu 5pbv 5pbw 5pbx 5pby 5pbz 5pc0 5pc1 5pc2 5pc3 5pc4 5pc5 5pc6 5pc7 5pc8 5pc9 5pca 5pcb 5pcc 5pcd 5pce 5pcf 5pcg 5pch 5pci 5pcj 5pck 5pcl 5pcm 5pcn 5pco 5pcp 5pcq 5pcr 5pcs 5pct 5pcu 5pcv 5pcw 5pcx 5pcz 5pd0 5pd1 5pd2 5pd3 5pd4 5pd5 5pd6 5pd7 5pd8 5pd9 5pda 5pdb 5pdc 5pdd 5pde 5pdf 5pdg 5pdh 5pdi 5pdj 5pdk 5pdl 5pdm 5pdn 5pdo 5pdp 5pdq 5pdr 5pds 5pdt 5pdu 5pdv 5pdw 5pdx 5pdy 5pdz 5pe0 5pe1 5pe2 5pe3 5pe4 5pe5 5pe6 5pe7 5pe8 5pe9 5pea 5peb 5pec 5ped 5pee 5pef 5peg 5peh 5pei 5pej 5pek 5pel 5pem 5pen 5peo 5peq 5per 5pes 5pet 5peu 5pev 5pew 5pex 5pey 5pez 5pf0 5pf1 5pf2 5pf3 5pf4 5pf5 5pf6 5pf7 5pf8 5pf9 5pfa 5pfb 5pfc 5pfd 5pfe 5pff 5pfg 5pfh 5pfi 5pfj 5pfl 5pfm 5pfn 5pfo 5pfp 5pfq 5pfr 5pfs 5pft 5pfu 5pfv 5pfw 5pfx 5pfy 5pfz 5pg0 5pg1 5pg2 5pg3 5pg4 5pg5 5pg6 5pg7 5pg8 5pg9 5pga 5pgb 5pgc 5pgd 5pge 5pgf 5pgg 5pgh 5pgi 5pgj 5pgk 5pgl 5pgn 5pgo 5pgp 5pgq 5pgr 5pgs 5pgt

HIV reverse transcriptase/ T15352	1a9m 1ajv 1ajx laxa 1bqm 1bqn 1d4h 1d4i 1d4j 1dlo 1dw6 1ebk 1ebw 1eby 1ebz 1ec0 1ec1 1ec2 1ec3 1eet 1g35 1gnm 1gnn 1gno 1har 1hbv 1hef 1heg 1hih 1hmv 1hni 1hnv 1hos 1hps 1hpz 1hqe 1hqu 1hrh 1hte 1htf 1htg 1hvi 1hvk 1hvp 1hvu 1hys 1ikv 1ikw 1ikx 1iky 1j5o 1kjh 1mer 1mes 1met 1meu 1n5y 1n6q 1npa 1npv 1npw 1qe1 1qmc 1r0a 1rdh 1rtd 1rvl 1rvm 1rvn 1rvo 1rvp 1rvq 1rvr 1s6p 1s6q 1s9e 1s9g 1sbg 1suq 1sv5 1t03 1t05 1t7k 1tv6 1tvr 1uwb 1w5v 1w5w 1w5x 1w5y 1yt9 1zp8 1zpa 1zsf 1zsr 2aqu 2b5j 2b6a 2ban 2bbb 2be2 2exf 2g69 2hb3 2hmi 2hnz 2hs1 2hs2 2i4d 2i4u 2i4v 2i4w 2i4x 2i5j 2iaj 2ic3 2idw 2ieo 2jzw 2l45 2l46 2l4l 2uxz 2uy0 2vg5 2vg6 2vg7 2x4u 2ykm 2ykn 2zd1 2ze2 3avi 3bgr 3dlk 3gga 3ggv 3ggx 3hvt 3ig1 3irx 3is9 3isn 3ith 3jsm 3jyt 3k2p 3k4v 3kle 3klf 3klg 3klh 3kli 3ndt 3nu3 3nu4 3nu5 3nu6 3nu9 3nuj 3nuo 3ok9 3psu 3qaa 3qlh 3qo9 3tkg 3tkw 3tl9 3tlh 3v4i 3v6d 3v81 3zps 3zpt 3zpu 4coe 4cp7 4cpq 4cpr 4cps 4cpt 4cpu 4cpw 4cpx 4dgl 4g1q 4g8g 4g8i 4g9d 4g9f 4h4m 4h4o 4i2p 4i2q 4icl 4id5 4idk 4ifv 4ify 4ig0 4ig3 4kfb 4kko 4ko0 4lsl 4lsn 4mfb 4o44 4o4g 4ojr 4pqu 4puo 4pwd 4q0b 4qag 4r5p 4rw4 4rw6 4rw7 4rw8 4rw9 4u8w 4we1 4ye3 4yhq 4zip 4zls 5agz 5ah6 5ah7 5ah8 5ah9 5aha 5ahb 5ahc 5bry 5bs4 5c24 5c25 5c42 5cym 5cyq 5d3g 5fdl 5hbm 5hlf 5hp1 5hro 5i3u 5i42 5j1e 5jfp 5jfu 5jg1 5t6z 5t70 5tep 5ter 5tuq 5tw3 5txl 5txm 5txn 5txo 5txp 5ult 5uov 5upz 5uv5 5v5l 5v5m 5vqq 5vqr 5vqs 5vqt 5vqu 5vqv 5vqw 5vqx 5vqy 5vqz
Phosphoglycerate dehydrogenase/ Short-chain dehydrogenases reduc- tases/ T15139	2g76 5n53 5nzo 5nzp 5nzq 5ofm 5ofv 5ofw
HIV p7 nucleocapsid protein/ T15107	1a9m 1ajv 1ajx laxa 1bqm 1bqn 1d4h 1d4i 1d4j 1dlo 1dw6 1ebk 1ebw 1eby 1ebz 1ec0 1ec1 1ec2 1ec3 1eet 1g35 1gnm 1gnn 1gno 1har 1hbv 1hef 1heg 1hih 1hmv 1hni 1hnv 1hos 1hps 1hpz 1hqe 1hqu 1hrh 1hte 1htf 1htg 1hvi 1hvk 1hvp 1hvu 1hys 1ikv 1ikw 1ikx 1iky 1j5o 1kjh 1mer 1mes 1met 1meu 1n5y 1n6q 1npa 1npv 1npw 1qe1 1qmc 1r0a 1rdh 1rtd 1rvl 1rvm 1rvn 1rvo 1rvp 1rvq 1rvr 1s6p 1s6q 1s9e 1s9g 1sbg 1suq 1sv5 1t03 1t05 1t7k 1tv6 1tvr 1uwb 1w5v 1w5w 1w5x 1w5y 1yt9 1zp8 1zpa 1zsf 1zsr 2aqu 2b5j 2b6a 2ban 2bbb 2be2 2exf 2g69 2hb3 2hmi 2hnz 2hs1 2hs2 2i4d 2i4u 2i4v 2i4w 2i4x 2i5j 2iaj 2ic3 2idw 2ieo 2jzw 2l45 2l46 2l4l 2uxz 2uy0 2vg5 2vg6 2vg7 2x4u 2ykm 2ykn 2zd1 2ze2 3avi 3bgr 3dlk 3gga 3ggv 3ggx 3hvt 3ig1 3irx 3is9 3isn 3ith 3jsm 3jyt 3k2p 3k4v 3kle 3klf 3klg 3klh 3kli 3ndt 3nu3 3nu4 3nu5 3nu6 3nu9 3nuj 3nuo 3ok9 3psu 3qaa 3qlh 3qo9 3tkg 3tkw 3tl9 3tlh 3v4i 3v6d 3v81 3zps 3zpt 3zpu 4coe 4cp7 4cpq 4cpr 4cps 4cpt 4cpu 4cpw 4cpx 4dgl 4g1q 4g8g 4g8i 4g9d 4g9f 4h4m 4h4o 4i2p 4i2q 4icl 4id5 4idk 4ifv 4ify 4ig0 4ig3 4kfb 4kko 4ko0 4lsl 4lsn 4mfb 4o44 4o4g 4ojr 4pqu 4puo 4pwd 4q0b 4qag 4r5p 4rw4 4rw6 4rw7 4rw8 4rw9 4u8w 4we1 4ye3 4yhq 4zip 4zls 5agz 5ah6 5ah7 5ah8 5ah9 5aha 5ahb 5ahc 5bry 5bs4 5c24 5c25 5c42 5cym 5cyq 5d3g 5fdl 5hbm 5hlf 5hp1 5hro 5i3u 5i42 5j1e 5jfp 5jfu 5jg1 5t6z 5t70 5tep 5ter 5tuq 5tw3 5txl 5txm 5txn 5txo 5txp 5ult 5uov 5upz 5uv5 5v5l 5v5m 5vqq 5vqr 5vqs 5vqt 5vqu 5vqv 5vqw 5vqx 5vqy 5vqz
Lactate dehydrogenase A/ Short- chain dehydrogenases reductases/ T15053	1i10 4ajp 4jnk 4l4r 4l4s 4m49 4ojn 4okn 4qo7 4qo8 4qsm 4qt0 4r68 4r69 4rls 4zvv 5ixs 5ixy
mRNA of VEGF-1 receptor/ T14439	1ftt 1qsv 1qsZ 1qty 1rv6 2xac 3hng 4ckv 4cl7 5abd 5ex3 5t89

Ras-related protein Rab-7a/ Small GTPase superfamily/ T14030	1t9l 1yhn 3law
Liver receptor homolog-1/ Nuclear hormone receptor/ T13902	1yok 1yuc 1zdu 2a66 3plz 3tx7 4dor 4dos 4is8 4oni 4pld 4ple 4rvv 5l0m 5l1l 5syz 5unj
eukaryotic translationinitiation factor 2-alpha kinase 3/ T13176	4g3l 4g34 4m7i 4x7h 4x7j 4x7k 4x7l 4x7n 4x7o 4yzs 5sv7
Farnesyl protein transferase/ T13127	1jcc 1ld7 1ld8 1mzc 1s63 1sa4 1tn6 2f0y 2h6f 2h6g 2h6h 2h6i 2iej 3e37
activin A receptor, type I/ T12091	3h9r 3mtf 3oom 3q4u 4bgg 4c02 4dym 5oxg 5oy6 6eix
Cytochrome P450 2B6/ Oxidoreductases acting on paired donors/ T11793	3ibd 3qoa 3qu8 3ua5 4i9l 4rql 4rrt 4zv8 5uap 5uda 5uec 5ufg
mRNA of WEE1/ Kinase/ T10939	1x8b 2in6 2io6 2z2w 3bi6 3biz 3cqe 3cr0 5v5y 5vc3 5vc4 5vc5 5vc6 5vd2
mRNA of HCV core protein/ T09874	1rtl 2a4g 2gvf 3eyd 3hkw 3kn2 3qgh 3qgi 3rc4 3rc5 3su4
Retinol dehydrogenase/ Short-chain dehydrogenases reductases/ T09770	1agn 1dl1s 1dl1t
Cyclin dependent kinase 5 activator 1/ Cyclin-dependent kinase 5 activator/ T09513	1h4l 1ung 1unh 1unl 3o0g
discoidin domain receptor tyrosine kinase 1/ T09185	3zos 4ag4 4bkj 4ckr 5bvk 5bvn 5bvo 5bvw 5fdp 5fdx
Caspase-2/ Peptidase/ T09128	1pyo 2p2c 3r5j 3r6g 3r6l 3r7b 3r7n 3r7s 3rjm
DTDP-4-dehydrorhamnose 3,5-epimerase rmlC/ Racemases and epimerases/ T08218	1pm7 1upi 2ixc
oxidative stress responsive 1/ T08198	2v3s 2vwi 3dak
Integrin alpha-1/ beta-1/ T06717	1k1l 1lha 3g9w 3t9k 3vi3 3vi4 4dx9 4wjk 4wk0 4wk2 4wk4
Hepatitis C virus NS5B polymerase/ T05152	1rtl 2a4g 2gvf 3eyd 3hkw 3kn2 3qgh 3qgi 3rc4 3rc5 3su4

Hepatitis C virus protein NS4B/ Hepacivirus polyprotein/ T04911	1rtl 2a4g 2gvf 3eyd 3hkw 3kn2 3qgh 3qgi 3rc4 3rc5 3su4
Botulinum toxin B/ Peptidase/ T04233	1epw 1f3l 1f82 1g9a 1g9b 1g9c 1g9d 1ile 1s0b 1s0c 1s0d 1s0e 1s0f 1s0g 1z0h 2etf 2nm1 2np0 2xhl 3zuq 4kbb 5vid 5vmr
Hepatitis C virus serine protease NS3/ 4A/ T03896	1rtl 2a4g 2gvf 3eyd 3hkw 3kn2 3qgh 3qgi 3rc4 3rc5 3su4
ribosomal protein S6 kinase, 90kDa, polypeptide 3/ T03279	4d9t 4d9u 4jg6 4jg7 4jg8 4nus 4nw5 4nw6 5d9k 5d9l
Bacterial DHFR/ T02702	1ddr 1dds 1dhi 1dhj 1dra 1drb 1dre 1drh 1dyh 1dyi 1dyj 1jol 1jom 1ra1 1ra2 1ra3 1ra8 1ra9 1rb2 1rb3 1rc4 1rd7 1re7 1rf7 1rg7 1rh3 1rx1 1rx2 1rx3 1rx4 1rx5 1rx6 1rx7 1rx8 1rx9 1tdr 2ano 2anq 2d0k 2drc 2inq 3dau 3drc 3k74 3kfy 3och 3ql3 3qyl 3qyo 3r33 4dfr 4eig 4eiz 4ejl 4fhb 4gh8 4il3 4iln 4kjj 4kjk 4kjl 4nx6 4nx7 4pdj 4x5f 4x5g 4x5h 4x5i 4x5j 5cc9 5ccc 5dfr 5e8q 5eaj 5w3q 6dfr 7dfr
beta-site APP-cleaving enzyme 2/ T01280	2ewy 3zkg 3zki 3zkm 3zkn 3zkq 3zks 3zqx 3zl7 3zlq 4bel 4bfb
endoplasmic reticulum to nucleus signaling 1/ T01003	2hz6 3p23 4u6r 4yz9 4yzc 4yzd 4z7g 4z7h 5hgi

Table S3, related to Chapter 3. Benchmark for validation

Drug Name	number of prediction pdb ranked in top 10%	number of true positive pdb
Dorzolamide	2	3
Lovastatin	2	3
Estradiol	2	3
Efavirenz	1	1
Delavirdine	1	1
Niflumic acid	0	1
Nevirapine	1	1
Galantamine	1	1
Sitagliptin	1	1
Tadalafil	3	3
Imatinib	3	3
Succinylcholine	1	1
Apixaban	1	1
Cocaine	0	1
Dichlorphenamide	1	3
Proflavine	0	1
Minocycline	1	1
Indomethacine	3	6
Pentoxifylline	0	8
Chloramphenicol	1	9
Topiramate	2	3
Papaverine	0	7

Balsalazide	1	2
Ethoxzolamide	0	3
Gefitinib	3	20
Prazosin	1	2
Pyrimethamine	1	2
Ethacrynic acid	1	1
Abacavir	0	1
Captopril	2	3
Celecoxib	2	2
Levonorgestrel	4	5
Zonisamide	1	4
Ampicillin	0	1
Progesterone	4	5
Diazepam	0	1
Diclofenac	1	2
Methotrexate	2	2
Clomipramine	1	2
Trimethoprim	2	2
Dexamethasone	1	2
Hydrocortisone	2	2
Fludrocortisone	3	3
Trifluoperazine	1	4
Hydrochlorothiazide	1	3
Sildenafil	3	3
Ursodeoxycholic	2	2

Figure S2, related to Figure 4.1. The results of the binding mode prediction based on the Vina Score. (A) The success rate when only the top predicted model was considered for each protein structure. When 2.0 Å was used as the threshold, the success rates of dockings with the bound, LMCSS, SMCSS, hiResHolo, hiResApo, and hiTanimoto protein structures are 32.8%, 22.9%, 14.5%, 13.8%, 7.1%, 22.1%, respectively. (B) The success rate when top 5 models were considered for each protein structure. When 2.0 Å was used as the threshold, the success rates of dockings with the bound, LMCSS, SMCSS, hiResHolo, hiResApo, and hiTanimoto protein structures were 44.2%, 31.3%, 21.3%, 21.7%, 11.1%, and 30.6%, respectively.

Table S4, related to Table 4.1. The results of binding mode prediction for the CELPP targets based on the Vina Score. The first row (Bound) lists the results of docking with the bound protein structures. The last row (hiSHAFTS) gives the results of docking with the user-specified protein structures, and the other five rows show the results of docking using the candidate protein structures provided by CELPP. The error of each value was estimated with the bootstrap method, in which 1000 replicates were used, and was reported in the parentheses.

Protein Structure	Number of Targets	Top 1		Best in Top 5		Best in All	
		Median RMSD (Å)	Median RMSD (Å)	Median RMSD (Å)	Median RMSD (Å)	Median RMSD (Å)	Median RMSD (Å)
Bound	969	3.9 (0.3)	4.8 (0.1)	2.5 (0.2)	3.7 (0.1)	1.2 (0.0)	1.5 (0.0)
LMCSS	969	5.0 (0.2)	5.3 (0.1)	3.8 (0.2)	4.3 (0.1)	1.5 (0.0)	1.9 (0.0)
SMCSS	969	6.0 (0.1)	5.9 (0.1)	4.8 (0.2)	5.1 (0.1)	1.9 (0.1)	2.4 (0.1)
hiResApo	608	6.5 (0.1)	6.7 (0.1)	5.6 (0.2)	5.7 (0.1)	2.2 (0.1)	2.8 (0.1)
hiResHolo	969	5.8 (0.2)	6.0 (0.1)	4.8 (0.2)	5.0 (0.1)	1.8 (0.1)	2.4 (0.1)
hiTanimoto	969	5.2 (0.1)	5.4 (0.1)	4.0 (0.2)	4.0 (0.1)	1.5 (0.0)	1.9 (0.0)
hiSHAFTS	875	5.2 (0.2)	5.5 (0.1)	4.0 (0.2)	4.5 (0.1)	1.6 (0.1)	1.9 (0.0)

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VITA

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After graduation, she was admitted into Department of Physics and Astronomy at University of Missouri as a Ph.D student under Dr. Xiaoqin Zou's supervision, and also joined the Zou Lab as a research assistant in 2014. During the PhD period, she conducted research in the field of computational structure biology. She focused on developing the large scale molecular docking methods to predict protein-ligand interactions. With the completion of her PhD study, she will join the Dr. Tzyh-Chang Hwang's lab for her postdoctoral research.