CONCURRENT IMPACT OF VARIOUS PROSPECTIVE DRUG LIGAND MOLECULES ON DIFFERENT ILLNESS/DISEASE MECHANISMS

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ABSTRACT

In this thesis work, we have performed binding energy computation studies of various prospective drug molecules with various proteins. Our aim in performing such studies was to observe the possible concurrent effects of such several drug-like ligand molecules on different metabolic and illness mechanisms by means of computational tools. Docking was the main computational tool we have used.

Therefore, in this study docking of 26 ligands into 229 proteins from different classes was performed. For the proteins, X-ray crystal structures were taken from PDB database [1]. Meanwhile, for the ligands structures were used from a previous study of several prospective drug molecules. These ligands previously had been studied with GOLD Software for the inhibitation of carbonic anhydrases (CA) at Calgary University by Durdagi et. al. [2,3].

The major objective of this study is to show the concurrent impact of various prospective drug ligand molecules on different disease mechanisms computationally. Correspondingly, computations in this study were performed to see whether these 26 ligands successfully binds with 229 proteins or not.

As a whole, 5 classes of proteins were considered for docking. These classes were selected from six main enzyme family classes [4]. These are; 38 proteins from the lyases, 47 proteins from hydrolases, 47 proteins from transferases, 45 proteins from ligases, 52 proteins from isomerases. In this research, Autodock Docking Software was used for the computation of the determination of the optimum binding sites and energies.

As a result, for all the proteins included in this thesis study, overall 4974 different binding energies and binding poses were obtained out of the docking results. Some of the docking results obtained here were compared with the results obtained in previous studies [2,3]. Comparing the results with the previous GOLD scores we found almost equivalent values . In addition, in this study it is observed that, how these specific ligands inhibited similarly in each class. Because of the conserved regions of amino acid sequences in each class of proteins, proteins have high structural similarity. As a result of this structural similarity, some similarities within the binding energies and positions were determined among the docking results. Looking at the results' similarity expectations were hold generally. The reason of getting similar conclusions for each class is resulted from structural and physicochemical similarity of the functional groups coming from the inherited similarity.

ÇEŞİTLİ OLASI İLAÇ LİGAND MOLEKÜLLERİNİN FARKLI HASTALIK MEKANİZMALARINA EŞ ZAMANLI ETKİSİ

ÖZET

Bu tez çalışmasında bir çok değişik olası ilaç moleküllerinin çeşitli proteinlerle bağlanma enerjileri hesaplama çalışmaları gerçekleştirmiş bulunmaktayız. Bu tarz çalışmalar geçekleştirmemizdeki amaç bu gibi ilaç benzeri moleküllerin değişik metabolik ve hastalık mekanizmaları üzerindeki eş zamanlı etkilerinin hesaplamalı yöntemlerle gözlemlenmesidir. Kullandığımız ana hesaplama aracı "Docking"dir.

Dolayısıyla bu çalışmada 26 ligandın çeşitli protein sınıflarındaki 229 protein içerisindeki bağlanma docking'leri gerçekleştirilmiştir. Proteinler için X-Işını kristal yapıları PDB veritabanından alınmıştır [1]. Bununla beraber, daha önceki bir çalışmada yer alan olası ilaç moleküllerine ait ligand yapıları kullanılmıştır. Bu ligandlar daha once Calgary Üniversitesi'nde karbonik anhidrazların (CA) inhibisyonu üzerine GOLD yazılımıyla Durdagi grubu tarafından çalışılmıştır [2,3].

Bu çalışmanın ana amacı ilaç olarak kullanılabilecek çeşitli ligand moleküllerinin değişik hastalık mekanizmaları üzerindeki eş zamanlı etkilerini hesaplamalı olarak göstermektir. Buna bağlı olarak, bu çalışmadaki hesaplamalar bu 26 ligandın 229 proteinle başarılı bir şekilde bağlanıp bağlanmadığını görmek için gerçekleştirilmiştir.

Docking için toplamda 5 protein sınıfı ele alınmıştır. Bu sınıflar alti ana enzim ailesi sınıfı arasından seçilmiştir[4]. Bunlar; liyazlardan 38 protein, 47 protein hidrolazlardan, 47 protein transferaz, 45 protein ligaz, 52 protein izomerazlardandır. Bu araştırmada optimum bağlanma bölgeleri ve enerjilerini belirleme hesaplamaları için Autodock Docking Yazılımı kullanılmıştır.

Sonuç olarak, bu tez çalışmasında yer alan bütün proteinler için toplamda 4974 farklı bağlanma enerjisi ve pozu docking sonuçlarından elde edilmiştir. Burada elde edilmiş bazı docking sonuçları daha önceki çalışmada elde edilenlerle karşılaştırılmıştır [2,3]. Sonuçların daha önceki GOLD skorlarıyla karşılaştırılması sonucunda hemen hemen eşit değerler bulduk. Bunun yanında bu çalışmada bu spesifik ligandların her bir sınıfta nasıl benzer inhibisyon yaptığını özlemledik. Her protein sınıfındaki aminoasit sekanslarındaki korunan kısımlar sayesinde, proteinler yüksek yapısal benzerliğe sahipler. Bu yapısal benzerlik sonucunda, docking sonuçlarından bağlanma enerjileri ve pozisyonları arasında bazı benzerlikler belirlenmiştir. Sonuçların benzerliğine bakınca sonuçlar genel olarak

beklenenlerle tutarlılık göstermektedir. Her sınıf için benzer çıkarımlar elde edilmesinin sebebi, kalıtılsal benzerlikten kaynaklanan fonksiyonel gruplardaki yapısal ve fizikokimyasal benzerlikten kaynaklanmaktadır.

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LIST OF ABREVIATIONS

Br: Bromine

C: Carbon

Cl: Chlorine

F: Fluorine

H: Hydrogen

N: Nitrogen

O: Oxygen

CA: Carbonic anhydrases

K_i*:* Inhibitory constant

LGA: Lamarchian genetic algorithm

PDB: Protein data bank

PDB ID: Protein data bank structure identifiers

AutoDock: Automated docking of flexible ligands to receptors

GA: Genetic algorithm

LS: Local search

MC: Monte Carlo

ΔG*:* The gibbs free energy

ΔG_{vdW}**:** Van der Waals gibbs free energy

ΔG_{hbond}**:** The hydrogen bonding gibbs free energy

ΔG_{elec}**:** Electrostatic gibbs free energy

ΔG_{tor}**:** Torsional degrees of freedom upon binding gibbs free energy

ΔG_{tor}**:** The ligand desolvation gibbs free energy

PPi: Pyrophosphate

NAD^+ : Nicotinamide adenine dinucleotide

$NADP^+$: Nicotinamide adenine dinucleotide phosphate

EC: Enzyme commission number

DNA: Deoxyribonucleic acid

DS: Discovery studio

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1. INTRODUCTION

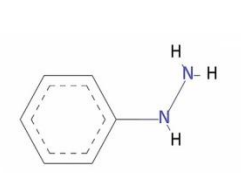
Ligands, which are molecules used in drug applications, binds to protein molecules and this binding affinity causes changes in the mechanisms where those proteins take place. Computationally it is possible to study these binding properties via a method which is called docking.

In this study, docking of 26 ligands into 229 proteins from different classes were performed in order to see whether there is a concurrent impact of these ligand molecules which may have a drug application. These concurrent impacts were aimed to be tested via docking studies. 2D structures of the docked ligand molecules were given below in Figure 1. All 26 ligands depicted were previously studied by means of kinetic and in silico analysis by Durdagi et al. [2,3]. These molecules were enumerated from 1 to 26 for this study and they are abbreviated as L, indicating the ligand property of these structures. In the figure, atoms in the 2D structures of the molecules were coloured according to atom types: H, white; C, black; N, dark blue; O, red; Cl, green; Br, reddish brown; F, light blue.

As it can be seen from the 2D plots of the structures, all the ligand molecules considered in this research consist aromatic groups in their structures. While some of these compounds include functional groups such as hydroxyl or nitrate group in their structure, a number of them include halogen atoms such as chlor (Cl) or brom (Br) in their structure. Resonance properties of the aromatic groups were also depicted in the structures shown in figure 1. These kind of electronic distributions within the molecules affects the binding characteristics of the ligands in great extent. Existence of the functionally important atoms especially like nitrogen and oxygen in the ligand molecules together with the aromaticity make these molecules functionally important in sense of binding properties. Binding affinity is one of the crucial properties considered in the drug design.

For the computational assessment of the binding energies docking studies were performed. These energy values were tabulated with color indexing throughout the thesis to show the impacts existing simultaneously in each class. As a result, the coexistence of the colors used for the labelling of the lowest best binding energy values makes the recognition of the concurrent impacts visually easier.

All dockings in this study were carried out on a workstation of multithread 12 core Linux (x86-64bit) computer. Parallel processing within the multithreads were used during the docking computations. The software used in this study was Autodock Tools [5]. Furthermore, the 2D and 3D molecular drawings, all figures of molecular structures were created with Discovery Studio 3.5(DS) [6].



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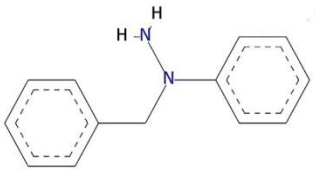

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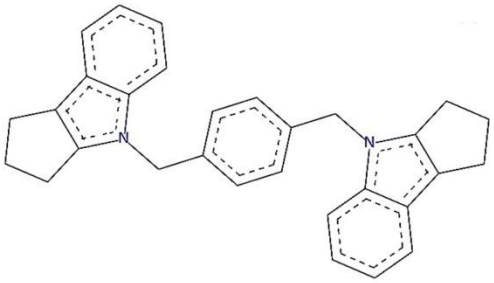

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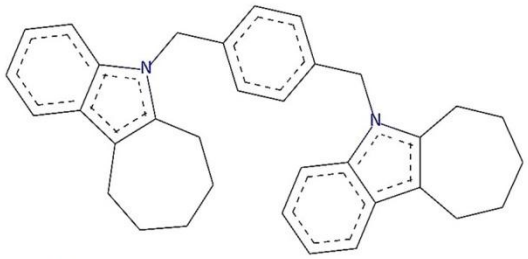

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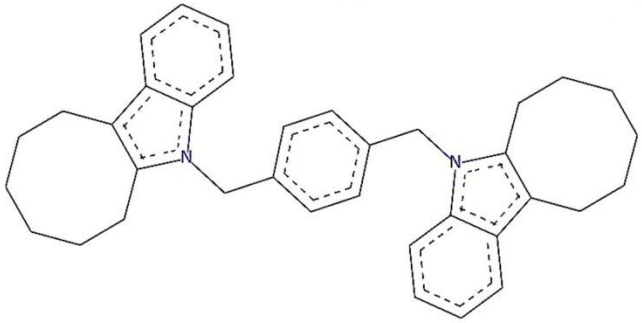

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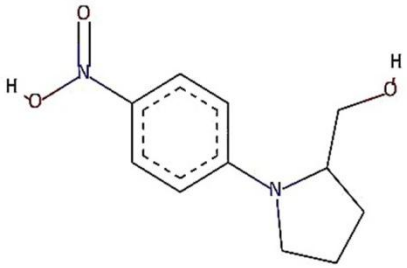

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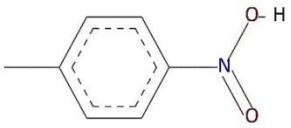

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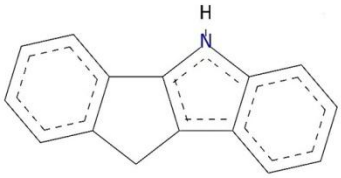

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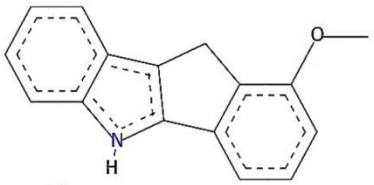

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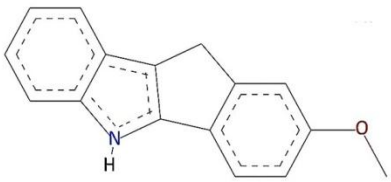

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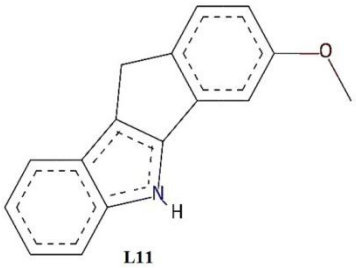

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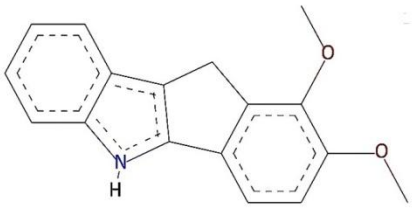

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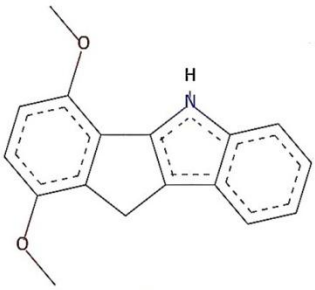

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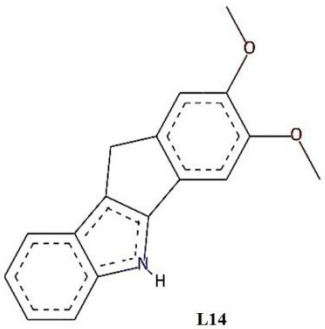

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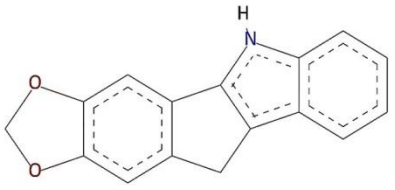

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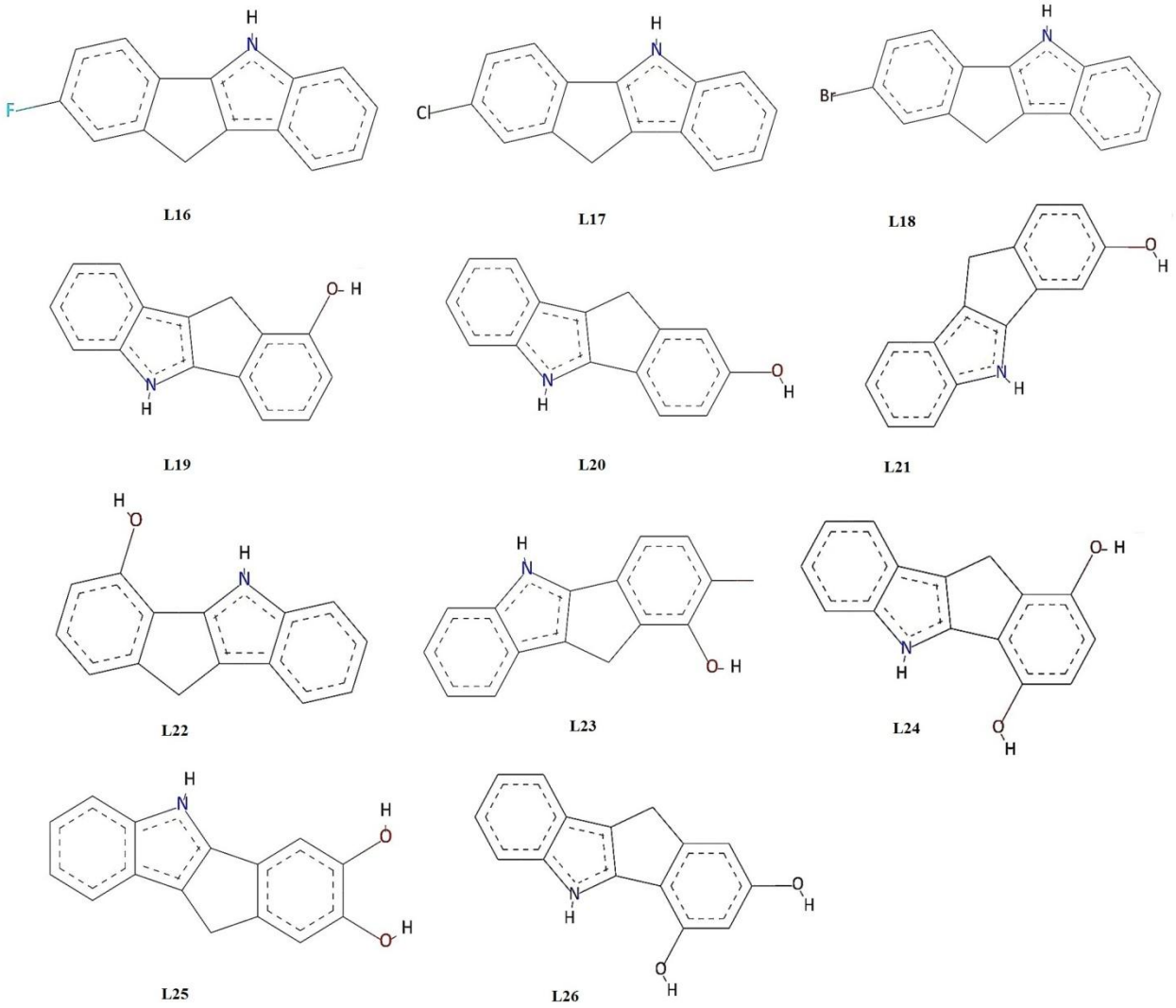


Figure 1. **Structures of the tested (docked) compounds [2,3]**

Atoms were colored according to atom types: H, white; C,black; N,dark blue; O, red; Cl; green; Br, reddish brown; F, light blue.

Enzyme Classifications

Enzymes are classified according to the reactions they catalyze. The six classes are Oxidoreductases, Transferases, Hydrolases, Lyases, Isomerases, Ligases [4].

Class 1. Oxidoreductases

Oxidoreductases catalyzes oxidoreduction reactions [7]. The oxidoreduction catalytic reaction includes transfer of electrons from the oxidant to the reductant. Oxidoreductases catalyze reactions correspond to the following,

$$A^- + B \rightarrow A + B^-$$

where A is the oxidant and B is the reductant [8]. Oxidases are enzymes implicated when molecular oxygen acts as an acceptor of hydrogen or electrons. These enzymes can be oxidases or dehydrogenases. Oxidases are enzymes involved when molecular oxygen acts as an acceptor of hydrogen or electrons. However, dehydrogenases are enzymes that oxidize a substrate by transferring hydrogen to an acceptor that is either NAD^+ / $NADP^+$ or a flavin enzyme. Oxidoreductases involves Hydroxylases, reductases, preoxidases and oxygenases. Hydroxylases supplement hydroxyl groups to its substrates. Peroxidases catalyze the reduction of hydrogen peroxide. Oxygenases contain takes place in replacement of oxygen from molecular oxygen into organic substrates. Reductases catalyze reductions can work like an oxidases [7].

Oxidoreductases enzymes have an important role in both aerobic and anaerobic metabolisms. Aerobic and anaerobic metabolisms are included in amino acid metabolism, tricarboxylic acid cycle, glycolysis, and oxidative phosphorylation.

Oxidoreductases are classified as **EC 1** in the EC number classification of enzymes. Oxidoreductases can be further classified into 22 subclasses [8]:

- EC 1.1 includes oxidoreductases that act on the CH-OH group of donors (alcohol oxidoreductases)
- EC 1.2 includes oxidoreductases that act on the aldehyde or oxo group of donors
- EC 1.3 includes oxidoreductases that act on the CH-CH group of donors (CH-CH oxidoreductases)

- EC 1.4 includes oxidoreductases that act on the CH-NH_2 group of donors (Amino acid oxidoreductases, Monoamine oxidase)
- EC 1.5 includes oxidoreductases that act on CH-NH group of donors
- EC 1.6 includes oxidoreductases that act on NADH or NADPH
- EC 1.7 includes oxidoreductases that act on other nitrogenous compounds as donors
- EC 1.8 includes oxidoreductases that act on a sulfur group of donors
- EC 1.9 includes oxidoreductases that act on a heme group of donors
- EC 1.10 includes oxidoreductases that act on diphenols and related substances as donors
- EC 1.11 includes oxidoreductases that act on peroxide as an acceptor (peroxidases)
- EC 1.12 includes oxidoreductases that act on hydrogen as donors
- EC 1.13 includes oxidoreductases that act on single donors with incorporation of molecular oxygen (oxygenases)
- EC 1.14 includes oxidoreductases that act on paired donors with incorporation of molecular oxygen
- EC 1.15 includes oxidoreductases that act on superoxide radicals as acceptors
- EC 1.16 includes oxidoreductases that oxidize metal ions
- EC 1.17 includes oxidoreductases that act on CH or CH_2 groups
- EC 1.18 includes oxidoreductases that act on iron-sulfur proteins as donors
- EC 1.19 includes oxidoreductases that act on reduced flavodoxin as a donor
- EC 1.20 includes oxidoreductases that act on phosphorus or arsenic in donors
- EC 1.21 includes oxidoreductases that act on X-H and Y-H to form an X-Y bond
- EC 1.97 includes other oxidoreductases

Class.2. Transferases

Transferases catalyze transfer (movement) of a functional group from one molecule to the other. Transferases's functional groups are different such that they can contain phosphate, glycosyl and methyl groups. The reactions correspond to the following;

$$AX + B \rightarrow A + BX$$

where A is the donor, B is the acceptor and X is functional group. Transferases got two sub-groups kinases and deaminases.

Kinases take place in catalysing the transfer of phosphate groups in phosphorylation. Therefore, they are effective on different molecules, for example nucleotides, lipids and carbohydrates. The most important kinases are kinases that are used in signal transduction and in controlling complex processes within the cell. Kinases involve more than 500 different types in the human body. Deaminases are another group of transferases. They catalyze the transfer of amino groups.

Transferases are classified as **EC 2** in the EC number classification. Transferases can be further classified into nine subclasses [8]:

- EC 2.1 includes enzymes that transfer one-carbon groups (methyltransferase)
- EC 2.2 includes enzymes that transfer aldehyde or ketone groups
- EC 2.3 includes acyltransferases
- EC 2.4 includes glycosyltransferases
- EC 2.5 includes enzymes that transfer alkyl or aryl groups, other than methyl groups
- EC 2.6 includes enzymes that transfer nitrogenous groups (transaminase)
- EC 2.7 includes enzymes that transfer phosphorus-containing groups
- EC 2.8 includes enzymes that transfer sulfur-containing groups
- EC 2.9 includes enzymes that transfer selenium-containing groups

Class 3. Hydrolases

Hydrolases catalyze hydrolysis reactions. They allocate substrates with addition of H_2O at the point of cleavage. Hydrolases catalyze reactions correspond to the following;

$$A – B + H_2O \rightarrow A – OH + B – H$$

Hydrolases involve various subclasses, such as lipases for fatty acids and glycerol for cleavage of ester bonds, nucleases for the hydrolysis of nucleic acids, proteases for proteins, etc.

Hydrolases are classified as **EC 3** in the EC number classification of enzymes. Hydrolases can be further classified into several subclasses, based upon the bonds they act upon [8]:

- EC 3.1: ester bonds (esterases: nucleases, phosphodiesterases, lipase, phosphatase)
- EC 3.2: sugars (DNA glycosylases, glycoside hydrolase)

- EC 3.3: ether bonds
- EC 3.4: peptide bonds (Proteases/peptidases)
- EC 3.5: carbon-nitrogen bonds, other than peptide bonds
- EC 3.6 acid anhydrides (acid anhydride hydrolases, including helicases and GTPase)
- EC 3.7 carbon-carbon bonds
- EC 3.8 halide bonds
- EC 3.9: phosphorus-nitrogen bonds
- EC 3.10: sulphur-nitrogen bonds
- EC 3.11: carbon-phosphorus bonds
- EC 3.12: sulfur-sulfur bonds
- EC 3.13: carbon-sulfur bonds

Class 4. Ligases

Ligases catalyse ligation. Since this catalysis requires chemical potential energy, the reaction is incorporated with the hydrolysis of a diphosphate bond in a nucleotide triphosphate such as ATP. The most important hydrolases enzyme is DNA ligase enzyme which catalyses the ligation between breaks in DNA by forming a phosphodiester bond. This enzyme involves different forms. These forms involve in catalysation of different break mechanisms.

For example DNA ligase I repairs single stranded breaks expiloiting the complementary strand as a template, like in DNA replication of the lagging strand. This reaction requires ATP too.

Ligases are classified as **EC 6** in the EC number classification of enzymes. Ligases can be further classified into six subclasses [8]:

- EC 6.1 includes ligases used to form carbon-oxygen bonds
- EC 6.2 includes ligases used to form carbon-sulfur bonds
- EC 6.3 includes ligases used to form carbon-nitrogen bonds
- EC 6.4 includes ligases used to form carbon-carbon bonds
- EC 6.5 includes ligases used to form phosphoric ester bonds
- EC 6.6 includes ligases used to form nitrogen-metal bonds

Class 5. Lyases

Lyases catalyze lysis reaction. Lysis reactions are a type of elimination reaction but are not hydrolytic or oxidative. These reactions catalyse an addition reaction, where a substrate is added to a double bond. These reactions are usually applied to as synthase enzymes.

A lyase reaction would be;

$$ATP \leftrightarrow cAMP + PPi$$

Lyases involve oxalate decarboxylase and isocitrate lyase.

Oxalate decarboxylase catalysations are chemical reactions. For example; a decarboxylase or a carboxy lyase, cleaves C-C bonds.

$$Oxalate + H^{+} \leftrightarrow formate + carbon\ dioxide$$

This reaction involved in glycoxylate and dicarboxylate metabolism.

Another group of lyases are Isocitrate lyase, which is involved in the glycoxylate cycle. This enzyme converts isocitrate to succinate.

Lyases are classified as **EC 4** in the EC number classification of enzymes. Lyases can be further classified into seven subclasses [8]:

- EC 4.1 includes lyases that cleave carbon-carbon bonds, such as decarboxylases (EC 4.1.1), aldehyde lyases (EC 4.1.2), oxo acid lyases(EC 4.1.3) and others (EC 4.1.99)
- EC 4.2 includes lyases that cleave carbon-oxygen bonds, such as dehydratases
- EC 4.3 includes lyases that cleave carbon-nitrogen bonds
- EC 4.4 includes lyases that cleave carbon-sulfur bonds
- EC 4.5 includes lyases that cleave carbon-halide bonds
- EC 4.6 includes lyases that cleave phosphorus-oxygen bonds, such as adenylate cyclase and guanylate cyclase
- EC 4.99 includes other lyases, such as ferrochelatase

Class 6. Isomerases

Isomerases enzymes catalyses structural changes within a molecule. Isomerases catalyze reactions correspond to the following,

$$A \rightarrow B$$

where B is an isomer of A.

Isomerases involved in many biochemical pathways, for example; the citric acid and the glycolitic pathway. They are included triose phosphate isomerise, photoisomerase and bisphosphoglycerate mutase. Isomerases can help in the conversion of citrate to isocitrate in the citric acid cycle. They can catalyze phosphorylation reaction pathways throughout the Krebs Cycle by preparing the molecule for oxidation states. Isomerases have the same chemical formula but diverge in their structural formula. Therefore, Isomerases splits into various classes, for example geometrically, stereoisomerically, and as enantiomers. The most important isomerases are alanine racemase and gluco-6-phosphate isomerase. Alanin racemase converts the amino acid alanine between its two optical isomers. Alanine racemase is needed in both aspartate and alanine metabolism. Glucose-6-phosphate isomerise catalyses the conversion of glucose-6-phosphate to fructose-6-phosphate in the second step of glycolysis. Fructose and glucose are 6-carbon sugars, but these show a different structural arrangement. And glucose-6-phosphate enzyme interconverts the sugar between its two forms.

Isomerases have their own EC classification of enzymes: **EC 5**. Isomerases can be further classified into six subclasses [8]:

- EC 5.1 includes enzymes that catalyze racemization (racemases) and epimerization
- EC 5.2 includes enzymes that catalyze the isomerization of geometric isomers
- EC 5.3 includes intramolecular oxidoreductases
- EC 5.4 includes intramolecular transferases (mutases)
- EC 5.5 includes intramolecular lyases
- EC 5.99 includes other isomerases (including topoisomerases)

2. METHODOLOGY

2.1. Molecular Docking

Docking provides an understanding of the molecular interactions which take place between a ligand and the corresponding receptor. Docking procedure involves three components: identification of the binding site, a search algorithm to efficiently sample the correct relative orientation and conformation of ligands, and a scoring function. Molecular docking is a well established computational technique which predicts the interaction energy between two molecules. This technique mainly incorporates algorithms like molecular dynamics, Monte Carlo stimulation, fragment based search methods. Molecular docking studies are used to determine the interaction of two molecules and to find the best orientation of ligand which would form a complex with overall minimum energy. The small molecule, known as ligand usually fits within protein's cavity which is predicted by the search algorithm. These protein cavities become active when they come in contact with any external compounds and are thus called as active sites.

2.1.1 AutoDock

AutoDock (Automated Docking of Flexible Ligands to Receptors) is the software by which docking studies carried out. AutoDock is a search tool with a grid-based method of energy evaluation. AutoDock uses Lamarckian genetic algorithm (LGA) for docking ligand and protein binding [11]. LGA is the most competent search method. The LGA combined a genetic algorithm (GA) for global searching and a local search (LS) method to render energy minimization. Mutation and crossover form in genotypic space, while phenotypic space is decided by the energy function to be optimized. Energy minimization (local sampling) is performed after genotypic changes have been made to the population (global sampling) in phenotypic space, which is conceptually similar to Monte Carlo (MC) minimization.

AutoDock program creates a grid map and compute its components by using AutoGrid program. Grid file is the imaginary box, within the range of volume where given ligand searches for best possible binding characteristics with lowest energy and high affinity.

The following figure illustrates the main features of a grid map:

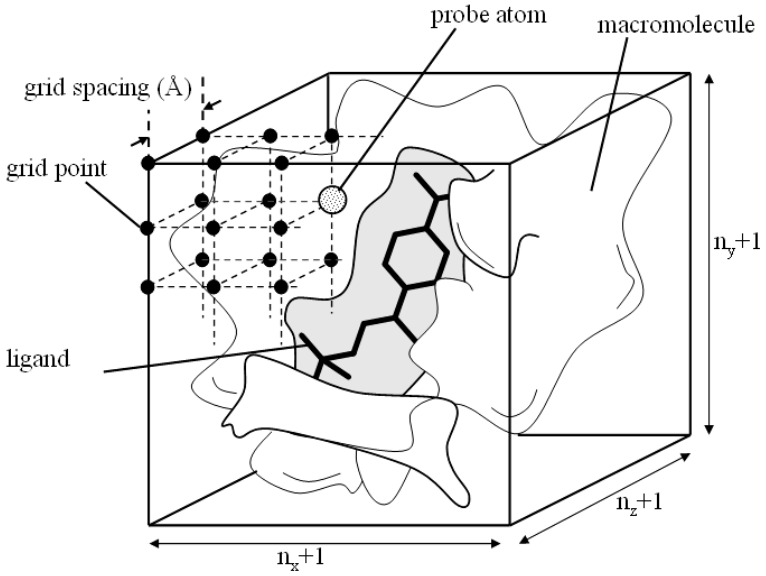


Figure 2. The main features of a grid map is illustrated.

Grid point spacing is a variable quantity from 0.2Å to 1.0Å, even though the default is 0.375Å. In the studies, the user have to define an even number of grid points in each dimension (n_x, n_y and n_z), because AutoGrid will add a central point (n_x+1, n_y+1 and n_z+1), and AutoDock requires totally an odd number of grid points. For each grid point within the grid map stores the potential energy of a 'probe' atom which is summed over all protein atoms within a nonbonded cutoff radius of 8 Å. The final grid of energies provides a lookup table for the rapid evaluation of interaction energies. Separate grids are calculated for each type of atom in the ligand, as well as a dispersion/repulsion term and added on electrostatic potential grid. These grids are read into memory at the start of the docking job, and then sampled by the ligand's atoms type using trilinear interpolation. Trilinear interpolation compute interaction energy between ligand and target [229].

The docking program AutoDock version 1.5.4 implemented a semiempirical scoring function which is rewritten by using the thermodynamic cycle on the basis of Wesson and Eisenberg.

This scoring function involves five terms, as in equation 1:

$$\Delta G = \Delta G_{vdW} \sum_{i,j} \left(\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} \right) + \Delta G_{hbond} \sum_{i,j} E(t) \left(\frac{C_{ij}}{R_{ij}^{12}} - \frac{D_{ij}}{R_{ij}^{10}} \right)$$
$$+ \Delta G_{elec} \sum_{i,j} \frac{q_i q_j}{\varepsilon(r_{ij}) r_{ij}} + \Delta G_{tor} N_{tor}$$
$$+ \Delta G_{sol} \sum_{i,j} \left(S_i V_j + S_j V_i \right) \cdot e^{(-r_{ij}^2 / 2\sigma^2)} \qquad (1)$$

The five ΔG terms on the right-hand side are coefficients empirically determined using linear regression analysis from a set of 4974 protein-ligand complexes with known binding constants.

The AutoDock force-field parameters are a subset of those of AMBER (Weiner *et al.*, 1984). For a given probe atom, i, and all protein atoms, j, within a nonbonded cut-off distance (Rcut). Van der Waals energies are calculated using a Lennard-Jones 12-6 potential:

$$E_{vdW} = \sum_{i<j, R_{ij}<R_{cut}} \left(\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} \right) \qquad (2)$$

where R_{ij} is the distance between interacting atoms. The coefficients A_{ij} and B_{ij} are calculated from well depths (ε_{xx}) and equilibrium contact distances ($r_{eqm,XX}$) between the nuclei of two like atoms, X.

Compounding rules for the Van der Waals radius, reqm, and the well depth, ε, for two different atoms X and Y, are:

$$r_{eqm,XY} = \frac{1}{2}\left(r_{eqm,XX} + r_{eqm,YY}\right) \quad (3)$$

$$\varepsilon_{XY} = \sqrt{\varepsilon_{XX}\varepsilon_{YY}} \quad (4)$$

where X and Y are different atom types. Accept that the potential is a minimum at r_{eqm} with a value of -ε, then:

$$A_{ij} = \varepsilon_{XY} r_{eqm,XY}^{12} \quad (5)$$

$$B_{ij} = 2\varepsilon_{XY} r_{eqm,XY}^{6} \quad (6)$$

Hydrogen bonds are considered with a traditional 12-10 potential:

$$E_{H-bond} = \sum_{i<j, R_{ij}<R_{cut}} \left(\frac{C_{ij}}{R_{ij}^{12}} - \frac{D_{ij}}{R_{ij}^{10}} \right) \quad (7)$$

Coefficients C_{ij} and D_{ij} may similarly be calculated for hydrogen bonds using the assumption of minimum energy,-ε, at internuclear separation, r_{eqm}.

Furthermore for the atomic affinity grid maps, AutoDock need an electrostatic-potential grid map. Partial atomic charges have to be attributed to the macromolecule. The electrostatic grid can be generated by AutoGrid tool. AutoGrid calculates electrostatic interaction energy grid maps using Coulombic interactions between the macromolecule and a probe of charge e, $+1.60219 \times 10^{-19}$ C; there is no distance cutoff used for electrostatic interactions. The latter uses a sigmoidal distance dependent dielectric function based on the work of Mehler and Solmajer.

$$\varepsilon(r) = A + \frac{B}{1 + ke^{-\lambda Br}} \quad \textbf{(8)}$$

where: B = ε_0 -A, with ε_0 = 78.4 (the dielectric constant of bulk water at 25 °C),

A = -8.5525, k = 7.7839, and λ = 0.003627 $Å^{-1}$. Electrostatic-potential grids are calculated with a probe carrying a single positive charge. The electrostatic interaction energy of each atom in the ligand is provided by multiplying the trilinearly interpolated electrostatic potential taken from this grid with the partial charge of the atom.

Furthermore, the first term in the right-hand side of equation 1 is the contribution of Van der Waals force between the ligand and the acceptor to binding free energy using a Lennard-Jones 12-6 potential. The second term is the contribution from hydrogen bond using a Lennard-Jones 12-10 potential, the hydrogen bonding term has directionality owing to the *E(t)* factor which is a function of the angle. The third term is that of electrostatic potential; the fourth is the change of binding free energy aroused by the frozen rotary free energy in ligands; and the last term accounts for desolvation effects. Autodock uses a pairwise, volume-based method to estimate the buriedness of the atom, which is multiplied by the atomic solvation parameter for that atom. This function was evaluated based on precalculated grids for the receptor contributions, and was derived based on 4974 protein-ligand complexes.

2.2. PRE-DOCKING

2.2.1. Preparation of ligand and protein structures for docking

2.2.1.1. Preparation of ligand structures

The ligand structures were taken from the research group which performs the kinetic and in silico analysis on inhibition of carbonic anhydrases (CA) at Calgary University by Durdagi et. al. [2,3]. Therefore, the coordinate files were ready to use for docking studies aimed in this thesis work. The structures of all the ligands used in this thesis study were given above in the introduction part in Figure 1. Furthermore, the results of this work and the results of Durdagi et.al. were compared in the results and discussion chapter.

2.2.1.2. Preparation of protein structures

229 protein X-ray crystal structures from the Protein Data Bank [1] were downloaded. The classes and the PDB structure identifiers (PDB ID) of the 229 protein structures used for docking are given below in Table 1. Proteins can be classified with respect to the types of organisms like, Homo Sapiens etc. In this study proteins with X-Ray Resolution less than 2Å were selected. Enzymes were classified as Lyases, Isomerases, Ligases, Hydrolases, Transferases, and the different colors applied to different columns with respect to these classification in Table 1. To get rid of the statistical bias that may occur because of the homology between proteins, similar sequences at % 90 identities were removed [1].

After selecting and downloading the protein structures from the database, several procedures were applied in order to make these structures ready for docking. Within these procedures first of all water molecules were removed. Following that bond orders were assigned and hydrogens atoms necessary for docking were added. Then, restrained minimization of hydrogen atoms was performed. After that, an optimization of hydrogen bonds was applied. Water molecules in the active site were also removed to facilitate more space for the ligand binding. The proteins converted into pqr from pdb via PDB2PQR server. As a Forcefield PARSE options selected to ensure that new atoms are not rebuilt too close to existing atoms, and then, the hydrogen bonding network were optimized. Finally, to assign protonation states at pH 7, PROPKA was used. [228]

2.2.1.2.1. PQR Format

PDB2PQR is a Python software package that automates many of the common tasks of preparing structures for continuum electrostatics calculations, providing a platform-independent utility for converting protein files in PDB format to PQR format. These tasks include adding a limited number of missing heavy atoms to biomolecular structures, determining side-chain pKas, placing missing hydrogens, optimizing the protein for favorable hydrogen bonding [228].

Table 1. The classes and the PDB structure identifier (PDB ID) of the 229 docked proteins

Ligases				Lyases		Isomerases				Transferases				Hydrolases			
PDB ID	RN	PDB ID	RN	PDB ID	RN	PDB ID	RN	PDB ID	RN	PDB ID	RN	PDB ID	RN	PDB ID	RN	PDB ID	RN
1I2T	[12]	2UVL	[39]	1ALD	[56]	1C9H	[83]	2VRE	[110]	1B4F	[135]	1KWA	162]	1A4I	[182]	1ITV	[209]
1I7K	[13]	2V40	[40]	1HCB	[57]	1EK6	[84]	2WFI	[111]	1BLX	[136]	1LS6	163]	1A6Q	[183]	1J8F	[210]
1LB6	[14]	2XEU	[41]	1IKT	[58]	1FW1	[85]	2X25	[112]	1BTK	[137]	1M9Z	[164]	1APY	[184]	1JSF	[211]
1LGP	[15]	2XOC	[42]	1JD0	[59]	1IAT	[86]	2X7K	[113]	1BX4	[138]	1MEO	[165]	1AYE	[185]	1JY1	[212]
1N3L	[16]	2XP0	[43]	1JL0	[60]	1Q1C	[87]	2XIJ	[114]	1BZY	[139]	1MFG	[166]	1B6A	[186]	1KI0	[213]
1T15	[17]	2Y1N	[44]	1JR2	[61]	1QOI	[88]	3B6H	[115]	1CB0	[140]	1MP8	[167]	1CSB	[187]	1KRN	[214]
1Y02	[18]	2YVQ	[45]	1KHB	[62]	1SG4	[89]	3EY6	[116]	1CZA	[141]	1MQ4	[168]	1DEU	[188]	1KWM	[215]
1Y6L	[19]	2YVR	[46]	1R3S	[63]	1ZKC	[90]	3I6C	[117]	1E8Y	[142]	1NB9	[169]	1DTD	[189]	1L9X	[216]
1YH2	[20]	2Z6O	[47]	1T2A	[64]	1ZXM	[91]	3ICH	[118]	1EH6	[143]	1NM8	[170]	1EDM	[190]	1LAR	[217]
1ZDN	[21]	3ASL	[48]	2AKZ	[65]	2A2N	[92]	3IDV	[119]	1EX0	[144]	1NN5	[171]	1ELV	[191]	1LCF	[218]
1ZUO	[22]	3B08	[49]	2B3Y	[66]	2CVD	[93]	3IJJ	[120]	1FGK	[145]	1NTY	[172]	1F3U	[192]	1LCY	[219]
2A4D	[23]	3B76	[50]	2B69	[67]	2DHO	[94]	3L6B	[121]	1FMK	146]	1NUU	[173]	1FH0	[193]	1LE6	[220]
2A7L	[24]	3B7Y	[51]	2J91	[68]	2ESL	[95]	3MDF	[122]	1FW1	147]	1O4R	[174]	1FIT	[194]	1LO6	[221]
2AXI	[25]	3BI7	[52]	2JIS	[69]	2F6Q	[96]	3O22	[123]	1G3M	148]	1O6L	[175]	1FJ2	[195]	1LQV	[222]
2ESK	[26]	3BUX	[53]	2O3H	[70]	2FUE	[97]	3O5E	[124]	1G55	149]	1OTH	[176]	1FO3	[196]	1M6D	[223]
2F4W	[27]	3BZH	[54]	2OO0	[71]	2G62	[98]	3O5Q	[125]	1GZ8	150]	1P4O	[177]	1FPZ	[197]	1MHW	[224]
2FAZ	[28]	3C5E	[55]	2W2J	[72]	2H8L	[99]	3OVP	[126]	1HE7	151]	1P5Z	[178]	1GQV	[198]	1NE7	[225]
2FZP	[29]			2WZ1	[73]	2HE9	[100]	3PH9	[127]	1HML	152]	1PKX	[179]	1H7S	[199]	1NNL	[226]
2I3H	[30]			2XSX	[74]	2HHJ	[101]	3RCG	[128]	1I1N	153]	1QCF	[180]	1HAZ	[200]	1NZI	[227]
2JKU	[31]			3AQI	[75]	2HQ6	[102]	3RMU	[129]	1J1B	154]	1QF8	[181]	1HDK	[201]		
2NQ3	[32]			3COG	[76]	2JK2	[103]	3TC5	[130]	1J99	155]			1HFC	[202]		
2NSQ	[33]			3D0N	[77]	2OK3	[104]	3UI4	[131]	1JDW	156]			1HKK	[203]		
2NTE	[34]			3EO4	[78]	2PBC	[105]	3UVT	[132]	1JQE	157]			1HTR	[204]		
2OOA	[35]			3EP6	[79]	2PNY	[106]	4A35	[133]	1JV1	158]			1HY7	[205]		
2PB7	[36]			3EWY	[80]	2PPN	[107]	4DIP	[134]	1K04	159]			1I71	[206]		
2PIE	[37]			3FE4	[81]	2R99	[108]			1K3Y	160]			1I76	[207]		
2POI	[38]			3FVS	[82]	2V9K	[109]			1KGD	161]			1ITU	[208]		

Table 2: Basic characteristics of selected Ligases proteins

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
1I2T	A	HYDPROTEIN	* 6.3.2.-	61	6748.95	2PIE	A	E3 ubiquitin-protein ligase RNF8	* 6.3.2.-	138	15792.1
1I7K	A	UBIQUITIN-CONJUGATING ENZYME E2 H10	* 6.3.2.19	179	19657.4	2PIE	F	phosphopeptide		7	1020.04
1I7K	B	UBIQUITIN-CONJUGATING ENZYME E2 H10	* 6.3.2.19	179	19657.4	2POI	A	Baculoviral IAP repeat-containing protein 4	* 6.3.2.-	94	10497.8
1LB6	A	TNFreceptor-associated factor 6	* 6.3.2.-	160	18676.7	2UVL	A	BACULOVIRAL IAP REPEAT-CONTAINING PROTEIN 3	* 6.3.2.-	96	11120.6
1LB6	B	CD40 antigen		9	1134.23	2UVL	B	BACULOVIRAL IAP REPEAT-CONTAINING PROTEIN 3	* 6.3.2.-	96	11120.6
1LGP	A	cell cycle checkpoint protein CHFR	* 6.3.2.-	116	13203.2	2V40	A	ADENYLOSUCCINATE SYNTHETASE ISOZYME 2	* 6.3.4.4	459	50804.4
1N3L	A	tyrosyl-tRNA synthetase	* 6.1.1.1	372	42134	2XEU	A	RING FINGER PROTEIN 4	* 6.3.2.-	64	7215.49
1T15	A	Breast cancer type 1 susceptibility protein	* 6.3.2.-	214	24531.4	2XOC	A	E3 UBIQUITIN-PROTEIN LIGASE CHFR	* 6.3.2.-	261	29268.4
1T15	B	BRCA1 interacting protein C-terminal helicase 1		8	961.94	2XOC	B	E3 UBIQUITIN-PROTEIN LIGASE CHFR	* 6.3.2.-	261	29268.4
1Y02	A	FYVE-RING finger protein SAKURA	* 6.3.2.-	120	13593.8	2XP0	A	E3 UBIQUITIN-PROTEIN LIGASE CHFR	* 6.3.2.-	274	30736.9
1Y6L	A	Ubiquitin-conjugating enzyme E2E2	* 6.3.2.19	149	16614.1	2XP0	B	E3 UBIQUITIN- PROTEIN LIGASE CHFR	* 6.3.2.-	274	30736.9
1Y6L	B	Ubiquitin-conjugating enzyme E2E2	* 6.3.2.19	149	16614.1	2Y1N	A	E3 UBIQUITIN-PROTEIN LIGASE	* 6.3.2.-	389	44929.1
1Y6L	C	Ubiquitin-conjugating enzyme E2E2	* 6.3.2.19	149	16614.1	2Y1N	B	TYROSINE-PROTEIN KINASE ZAP-70 ZAP-70,70 KDA ZETA-ASSOCIATED PROTEIN, SYK-RELATED TYROSINE KINASE	* 2.7.10.2	12	1344.29

Table 2. Basic characteristics of selected Ligases proteins continued

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
1YH2	A	HSPC150 protein similar to ubiquitin-conjugating enzyme	* 6.3.2.19	169	19345.4	2Y1N	C	E3 UBIQUITIN-PROTEIN LIGASE	* 6.3.2.-	389	44929.1
1ZDN	A	Ubiquitin-conjugating enzyme E2S	* 6.3.2.19	158	17533.2	2Y1N	D	TYROSINE-PROTEIN KINASE ZAP-70 ZAP-70,70 KDA ZETA-ASSOCIATED PROTEIN, SYK-RELATED TYROSINE KINASE	* 2.7.10.2	12	1344.29
1ZDN	B	Ubiquitin-conjugating enzyme E2S	* 6.3.2.19	158	17533.2	2YVQ	A	Carbamoyl-phosphate synthase	* 6.3.4.16	143	15608.8
1ZUO	A	Hypothetical protein LOC92912	* 6.3.2.19	186	20801.8	2YVR	A	Transcription intermediary factor 1-beta	* 6.3.2.-	50	5947.69
1ZUO	B	Hypothetical protein LOC92912	* 6.3.2.19	186	20801.8	2YVR	B	Transcription intermediary factor 1-beta	* 6.3.2.-	50	5947.69
2A4D	A	Ubiquitin-conjugating enzyme E2 variant 1	* 6.3.2.19	160	18027.7	2Z6O	A	Ufm1-conjugating enzyme 1	* 6.3.2.19	172	19898
2A7L	A	Hypothetical ubiquitin-conjugating enzyme LOC55284	* 6.3.2.19	136	15159.4	3ASL	A	E3 ubiquitin-protein ligase UHRF1	* 6.3.2.-	70	7920.99
2A7L	B	Hypothetical ubiquitin-conjugating enzyme LOC55284	* 6.3.2.19	136	15159.4	3ASL	B	Histone H3.3		11	1251.45
2AXI	A	Ubiquitin-protein ligase E3 Mdm2	* 6.3.2.-	115	13364.3	3B08	A	Polyubiquitin-C		152	17135.8
2AXI	B	cyclic 8-mer peptide		10	1399.95	3B08	B	RanBP-type and C3HC4-type zinc finger-containing protein 1	* 6.3.2.-	64	7277.2
2ESK	A	Ubiquitin-conjugating enzyme E2 D2	* 6.3.2.19	149	16883.5	3B08	D	Polyubiquitin-C		152	17135.8
2F4W	A	ubiquitin-conjugating enzyme E2, J2	* 6.3.2.19	187	21332.7	3B08	E	RanBP-type and C3HC4-type zinc finger-containing protein 1	* 6.3.2.-	64	7277.2
2F4W	B	ubiquitin-conjugating enzyme E2, J2	* 6.3.2.19	187	21332.7	3B08	G	Polyubiquitin-C		152	17135.8
2FAZ	A	Ubiquitin-like containing PHD and RING finger domains protein 1	* 6.3.2.-	78	9346.75	3B08	H	RanBP-type and C3HC4-type zinc finger-containing protein 1	* 6.3.2.-	64	7277.2
2FAZ	B	Ubiquitin-like containing PHD and RING finger domains protein 1	* 6.3.2.-	78	9346.75	3B08	J	Polyubiquitin-C		152	17135.80

Table 2. Basic characteristics of selected Ligases proteins continued

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
2FZP	A	ring finger protein 41 isoform 1	* 6.3.2.-	144	16172.5	3B08	K	RanBP-type and C3HC4-type zinc	* 6.3.2.-	64	7277.2
2I3H	A	Baculoviral IAP repeat-containing protein 7	* 6.3.2.-	133	14977.7	3B76	A	E3 ubiquitin-protein ligase LNX	* 6.3.2.-	118	12824.6
2I3H	B	Baculoviral IAP repeat-containing protein 7	* 6.3.2.-	133	14977.7	3B76	B	E3 ubiquitin-protein ligase LNX	* 6.3.2.-	118	12824.6
2I3H	C	AVPW peptide		4	471.55	3B7Y	A	E3 ubiquitin-protein ligase NEDD4	* 6.3.2.-	153	17750.7
2I3H	D	AVPW peptide		4	471.55	3B7Y	B	E3 ubiquitin-protein ligase NEDD4	* 6.3.2.-	153	17750.7
2JKU	A	PROPIONYL-COA CARBOXYLASE ALPHA CHAIN, MITOCHONDRIAL	* 6.4.1.3	94	9940.31	3BI7	A	E3 ubiquitin-protein ligase UHRF1	* 6.3.2.-	212	23910.5
2NQ3	A	Itchy homolog E3 ubiquitin protein ligase	* 6.3.2.-	173	19201.9	3BUX	A	13-meric peptide from Hepatocyte growth factor receptor	* 2.7.10.1	13	1595.55
2NSQ	A	E3 ubiquitin-protein ligase NEDD4-like protein	* 6.3.2.-	155	17935.7	3BUX	B	E3 ubiquitin-protein ligase CBL	* 6.3.2.-	329	38192.5
2NTE	A	BRCA1-associated RING domain protein 1	* 6.3.2.-	210	24103.1	3BUX	C	13-meric peptide from Hepatocyte growth factor receptor	* 2.7.10.1	13	1595.55
2NTE	B	BRCA1-associated RING domain protein 1	* 6.3.2.-	210	24103.1	3BUX	D	E3 ubiquitin-protein ligase CBL	* 6.3.2.-	329	38192.5
2OOA	A	E3 ubiquitin-protein ligase CBL-B	* 6.3.2.-	52	5703.34	3BZH	A	Ubiquitin-conjugating enzyme E2 E1	* 6.3.2.19	194	21487.4
2OOA	B	E3 ubiquitin-protein ligase CBL-B	* 6.3.2.-	52	5703.34	3C5E	A	Acyl-coenzyme A synthetase ACSM2A, mitochondrial precursor	* 6.2.1.2	570	63335.2
2PB7	A	E3 ubiquitin-protein ligase UHRF1	* 6.3.2.-	239	26792						

Table 3. Basic characteristics of selected Lyases proteins

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
1ALD	A	ALDOLASE A	* 4.1.2.13	363	39339.10	3D0N	A	Carbonic anhydrase 13	* 4.2.1.1	264	29626.50
1HCB	A	CARBONIC ANHYDRASE I	* 4.2.1.1	260	28775.20	3D0N	B	Carbonic anhydrase 13	* 4.2.1.1	264	29626.50
1IKT	A	ESTRADIOL 17 BETA-DEHYDROGENASE 4	* 4.2.1.107 * 4.2.1.119	120	13264.60	3EO4	A	Uncharacterized protein MJ1062		164	19684.70
1JD0	A	CARBONIC ANHYDRASE XII	* 4.2.1.1	263	29857.40	3EO4	B	Uncharacterized protein MJ1062		164	19684.70
1JD0	B	CARBONIC ANHYDRASE XII	* 4.2.1.1	263	29857.40	3EO4	C	Uncharacterized protein MJ1062		164	19684.70
1JL0	A	S-DENOSYLMETHIONINE DECARBOXYLASE PROENZYME	* 4.1.1.50	334	38298.80	3EO4	D	Uncharacterized protein MJ1062		164	19684.70
1JL0	B	S-DENOSYLMETHIONINE DECARBOXYLASE PROENZYME	* 4.1.1.50	334	38298.80	3EP6	A	S-adenosylmethionine decarboxylase alpha chain	* 4.1.1.50	260	29887.40
1JR2	A	UROPORPHYRINOGEN-III SYNTHASE	* 4.2.1.75	286	31189.60	3EP6	B	S-adenosylmethionine decarboxylase beta chain	* 4.1.1.50	67	7694.65
1JR2	B	UROPORPHYRINOGEN-III SYNTHASE	* 4.2.1.75	286	31189.60	3EWY	A	Orotidine-5'-phosphate decarboxylase	* 4.1.1.23	260	28317.90
1KHB	A	Phosphoenolpyruvate carboxykinase, cytosolic (GTP)	* 4.1.1.32	625	69530.20	3FE4	A	Carbonic anhydrase 6	* 4.2.1.1	278	31950.80
1R3S	A	Uroporphyrinogen Decarboxylase	* 4.1.1.37	367	40774.10	3FE4	B	Carbonic anhydrase 6	* 4.2.1.1	278	31950.80
1T2A	A	GDP-mannose 4,6 dehydratase	* 4.2.1.47	375	42699.70	3FVS	A	Kynurenine--oxoglutarate transaminase 1	* 2.6.1.64 * 2.6.1.7 * 4.4.1.13	422	48158.50
1T2A	B	GDP-mannose 4,6 dehydratase	* 4.2.1.47	375	42699.70	3FVS	B	Kynurenine--oxoglutarate transaminase 1	* 2.6.1.64 * 2.6.1.7 * 4.4.1.13	422	48158.50
1T2A	C	GDP-mannose 4,6 dehydratase	* 4.2.1.47	375	42699.70	3FW3	A	Carbonic anhydrase 4	* 4.2.1.1	266	30364.70
1T2A	D	GDP-mannose 4,6 dehydratase	* 4.2.1.47	375	42699.70	3FW3	B	Carbonic anhydrase 4	* 4.2.1.1	266	30364.70
2AKZ	A	Gamma enolase	* 4.2.1.11	439	48018.60	3IR3	A	3-hydroxyacyl-thioester dehydratase 2	* 4.2.1.-	148	16192.10

Table 3. Basic characteristics of selected Lyases proteins continued

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
2AKZ	B	Gamma enolase	* 4.2.1.11	439	48018.60	3IR3	B	3-hydroxyacyl-thioester dehydratase 2	* 4.2.1.-	148	16192.10
2B3Y	A	Iron-responsive element binding protein 1	* 4.2.1.3	888	98375.20	3KAN	A	D-dopachrome tautomerase	* 4.1.1.84	117	12593.60
2B3Y	B	Iron-responsive element binding protein 1	* 4.2.1.3	888	98375.20	3KAN	B	D-dopachrome tautomerase	* 4.1.1.84	117	12593.60
2B69	A	UDP-glucuronate decarboxylase 1	* 4.1.1.35	343	39208.80	3KAN	C	D-dopachrome tautomerase	* 4.1.1.84	117	12593.60
2J91	A	ADENYLOSUCCINATE LYASE	* 4.3.2.2	503	57221.10	3KS3	A	Carbonic anhydrase 2	* 4.2.1.1	260	29289.30
2J91	B	ADENYLOSUCCINATE LYASE	* 4.3.2.2	503	57221.10	3L6B	A	Serine racemase	* 4.3.1.17 * 4.3.1.18 * 5.1.1.18	346	37456.20
2J91	C	ADENYLOSUCCINATE LYASE	* 4.3.2.2	503	57221.10	3PCV	A	Leukotriene C4 synthase	* 4.4.1.20	156	17411.70
2J91	D	ADENYLOSUCCINATE LYASE	* 4.3.2.2	503	57221.10	3S5O	A	4-hydroxy-2-oxoglutarate aldolase, mitochondrial	* 4.1.3.16	307	32980.00
2JIS	A	CYSTEINE SULFINIC ACID DECARBOXYLASE	* 4.1.1.29	515	57649.40	3UYQ	A	Carbonic anhydrase 3	* 4.2.1.1	260	29590.50
2JIS	B	CYSTEINE SULFINIC ACID DECARBOXYLASE	* 4.1.1.29	515	57649.40	3VW9	A	Lactoylglutathione lyase	* 4.4.1.5	187	21086.10
2O3H	A	DNA-(apurinic or apyrimidinic site) lyase	* 3.1.-.- * 4.2.99.18	285	32011.70	3VW9	B	Lactoylglutathione lyase	* 4.4.1.5	187	21086.10
2OO0	A	Ornithine decarboxylase	* 4.1.1.17	471	52326.70	4E1O	A	Histidine decarboxylase	* 4.1.1.22	481	54314.80
2OO0	B	Ornithine decarboxylase	* 4.1.1.17	471	52326.70	4E1O	B	Histidine decarboxylase	* 4.1.1.22	481	54314.80
2W2J	A	CARBONIC ANHYDRASE-RELATED PROTEIN	* 4.2.1.1	291	33095.40	4E1O	C	Histidine decarboxylase	* 4.1.1.22	481	54314.80
2WZ1	A	GUANYLATE CYCLASE SOLUBLE SUBUNIT BETA-1	* 4.6.1.2	219	24657.20	4E1O	D	Histidine decarboxylase	* 4.1.1.22	481	54314.80
2WZ1	B	GUANYLATE CYCLASE SOLUBLE SUBUNIT BETA-1	* 4.6.1.2	219	24657.20	4E1O	E	Histidine decarboxylase	* 4.1.1.22	481	54314.80

Table 3. Basic characteristics of selected Lyases proteins continued

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
2XSX	A	BETA-ENOLASE	* 4.2.1.11	435	47080.20	4E1O	F	Histidine decarboxylase	* 4.1.1.22	481	54314.80
2XSX	B	BETA-ENOLASE	* 4.2.1.11	435	47080.20	4H27	A	L-serine dehydratase/L-threonine deaminase	* 4.3.1.17 * 4.3.1.19	364	38710.00
3AQI	A	Ferrochelatase	* 4.99.1.1	359	41067.70						
3AQI	B	Ferrochelatase	* 4.99.1.1	359	41067.70						
3COG	A	Cystathionine gamma-lyase	* 4.4.1.1	403	44336.10						
3COG	B	Cystathionine gamma-lyase	* 4.4.1.1	403	44336.10						
3COG	C	Cystathionine gamma-lyase	* 4.4.1.1	403	44336.10						
3COG	D	Cystathionine gamma-lyase	* 4.4.1.1	403	44336.10						

Table 4. Basic characteristics of selected Isomerases proteins

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
1C9H	A	FKBP12.6	* 5.2.1.8	107	11667.40	2PNY	A	Isopentenyl-diphosphate Delta-isomerase 2	* 5.3.3.2	246	28826.00
1EK6	A	UDP-GALACTOSE 4-EPIMERASE	* 5.1.3.2	348	38324.90	2PPN	A	FK506-binding protein 1A	* 5.2.1.8	107	11836.60
1EK6	B	UDP-GALACTOSE 4-EPIMERASE	* 5.1.3.2	348	38324.90	2R99	A	Peptidyl-prolyl cis-trans isomerase E	* 5.2.1.8	173	18985.80
1FW1	A	GLUTATHIONE TRANSFERASE ZETA	* 2.5.1.18 * 5.2.1.2	216	24108.10	2V9K	A	UNCHARACTERIZED PROTEIN FLJ32312	* 5.4.99.-	530	60385.70
1IAT	A	PHOSPHOGLUCOSE ISOMERASE	* 5.3.1.9	557	63099.40	2VRE	A	DELTA(3,5)-DELTA(2,4)-DIENOYL-COA ISOMERASE	* 5.3.3.-	296	32781.70
1Q1C	A	FK506-binding protein 4	* 5.2.1.8	280	31365.70	2VRE	B	DELTA(3,5)-DELTA(2,4)-DIENOYL-COA ISOMERASE	* 5.3.3.-	296	32781.70
1QOI	A	SNUCYP-20	* 5.2.1.8	177	19230.20	2VRE	C	DELTA(3,5)-DELTA(2,4)-DIENOYL-COA ISOMERASE	* 5.3.3.-	296	32781.70
1SG4	A	3,2-trans-enoyl-CoA isomerase, mitochondrial	* 5.3.3.8	260	28618.10	2WFI	A	PEPTIDYL-PROLYL CIS-TRANS ISOMERASE G	* 5.2.1.8	179	19891.60
1SG4	B	3,2-trans-enoyl-CoA isomerase, mitochondrial	* 5.3.3.8	260	28618.10	2X25	B	PEPTIDYL-PROLYL CIS-TRANS ISOMERASE A	* 5.2.1.8	169	18637.30
1SG4	C	3,2-trans-enoyl-CoA isomerase, mitochondrial	* 5.3.3.8	260	28618.10	2X7K	A	PEPTIDYL-PROLYL CIS-TRANS ISOMERASE-LIKE 1	* 5.2.1.8	166	18257.90
1ZKC	A	Peptidyl-prolyl cis-trans isomerase like 2	* 5.2.1.8	197	22169.00	2X7K	B	CYCLOSPORIN A		11	1220.64
1ZKC	B	Peptidyl-prolyl cis-trans isomerase like 2	* 5.2.1.8	197	22169.00	2XIJ	A	METHYLMALONYL-COA MUTASE, MITOCHONDRIAL	* 5.4.99.2	762	84836.50

Table 4. Basic characteristics of selected Isomerases proteins continued

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
1ZXM	A	DNA topoisomerase II, alpha isozyme	* 5.99.1.3	400	45661.00	3B6H	A	Prostacyclin synthase	* 5.3.99.4	498	57272.30
1ZXM	B	DNA topoisomerase II, alpha isozyme	* 5.99.1.3	400	45661.00	3B6H	B	Prostacyclin synthase	* 5.3.99.4	498	57272.30
2A2N	A	peptidylprolyl isomerase domain and WD repeat containing 1	* 5.2.1.8	176	19498.10	3EY6	A	FK506-binding protein 8	* 5.2.1.8	121	13068.10
2A2N	B	peptidylprolyl isomerase domain and WD repeat containing 1	* 5.2.1.8	176	19498.10	3I6C	A	Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1	* 5.2.1.8	123	13662.30
2A2N	C	peptidylprolyl isomerase domain and WD repeat containing 1	* 5.2.1.8	176	19498.10	3I6C	B	Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1	* 5.2.1.8	123	13662.30
2CVD	A	Glutathione-requiring prostaglandin D synthase	* 2.5.1.18 * 5.3.99.2	198	23256.90	3ICH	A	Peptidyl-prolyl cis-trans isomerase B	* 5.2.1.8	188	20736.00
2CVD	B	Glutathione-requiring prostaglandin D synthase	* 2.5.1.18 * 5.3.99.2	198	23256.90	3IDV	A	Protein disulfide-isomerase A4	* 5.3.4.1	241	26837.50
2CVD	C	Glutathione-requiring prostaglandin D synthase	* 2.5.1.18 * 5.3.99.2	198	23256.90	3IJJ	A	Macrophage migration inhibitory factor	* 5.3.2.1 * 5.3.3.12	114	12355.20
2CVD	D	Glutathione-requiring prostaglandin D synthase	* 2.5.1.18 * 5.3.99.2	198	23256.90	3IJJ	B	Macrophage migration inhibitory factor	* 5.3.2.1 * 5.3.3.12	114	12355.20
2DHO	A	Isopentenyl-diphosphate delta-isomerase 1	* 5.3.3.2	235	27374.50	3IJJ	C	Macrophage migration inhibitory factor	* 5.3.2.1 * 5.3.3.12	114	12355.20
2ESL	A	PEPTIDYL-PROLYL CIS-TRANS ISOMERASE C	* 5.2.1.8	190	20542.50	3L6B	A	Serine racemase	* 4.3.1.17 * 4.3.1.18 * 5.1.1.18	346	37456.20
2ESL	B	PEPTIDYL-PROLYL CIS-TRANS ISOMERASE C	* 5.2.1.8	190	20542.50	3MDF	A	Peptidyl-prolyl cis-trans isomerase E	* 5.2.1.8	85	9413.66
2ESL	C	PEPTIDYL-PROLYL CIS-TRANS ISOMERASE C	* 5.2.1.8	190	20542.50	3MDF	B	Peptidyl-prolyl cis-trans isomerase E	* 5.2.1.8	85	9413.66
2ESL	D	PEPTIDYL-PROLYL CIS-TRANS ISOMERASE C	* 5.2.1.8	190	20542.50	3O22	A	Prostaglandin-H2 D-isomerase	* 5.3.99.2	162	18089.40
2ESL	E	PEPTIDYL-PROLYL CIS-TRANS ISOMERASE C	* 5.2.1.8	190	20542.50	3O5E	A	Peptidyl-prolyl cis-trans isomerase FKBP5	* 5.2.1.8	144	15708.00

Table 4. Basic characteristics of selected Isomerases proteins continued

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
2ESL	F	PEPTIDYL-PROLYL CIS-TRANS ISOMERASE C	* 5.2.1.8	190	20542.50	3O5Q	A	Peptidyl-prolyl cis-trans isomerase FKBP5	* 5.2.1.8	128	14026.20
2ESL	I	CYCLOSPORIN A		11	1220.64	3OVP	A	Ribulose-phosphate 3-epimerase	* 5.1.3.1	228	24954.80
2ESL	J	CYCLOSPORIN A		11	1220.64	3OVP	B	Ribulose-phosphate 3-epimerase	* 5.1.3.1	228	24954.80
2ESL	K	CYCLOSPORIN A		11	1220.64	3PH9	A	Anterior gradient protein 3 homolog	* 5.3.4.1	151	17932.80
2ESL	L	CYCLOSPORIN A		11	1220.64	3PH9	B	Anterior gradient protein 3 homolog	* 5.3.4.1	151	17932.80
2ESL	M	CYCLOSPORIN A		11	1220.64	3RCG	A	Peptidyl-prolyl cis-trans isomerase F, mitochondrial	* 5.2.1.8	166	17870.50
2ESL	N	CYCLOSPORIN A		11	1220.64	3RMU	A	Methylmalonyl-CoA epimerase, mitochondrial	* 5.1.99.1	134	14382.00
2F6Q	A	Peroxisomal 3,2-trans-enoyl-CoA isomerase	* 5.3.3.8	280	31352.00	3RMU	B	Methylmalonyl-CoA epimerase, mitochondrial	* 5.1.99.1	134	14382.00
2F6Q	B	Peroxisomal 3,2-trans-enoyl-CoA isomerase	* 5.3.3.8	280	31352.00	3RMU	C	Methylmalonyl-CoA epimerase, mitochondrial	* 5.1.99.1	134	14382.00
2F6Q	C	Peroxisomal 3,2-trans-enoyl-CoA isomerase	* 5.3.3.8	280	31352.00	3RMU	D	Methylmalonyl-CoA epimerase, mitochondrial	* 5.1.99.1	134	14382.00
2FUE	A	Phosphomannomutase 1	* 5.4.2.8	262	29974.60	3TC5	A	Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1	* 5.2.1.8	166	18467.60
2G62	A	protein phosphatase 2A, regulatory subunit B' (PR 53)	* 5.2.1.8	325	37328.10	3UI4	A	Peptidyl-prolyl cis-trans isomerase NIMA-interacting 4	* 5.2.1.8	101	11161.10
2H8L	A	Protein disulfide-isomerase A3	* 5.3.4.1	252	28818.70	3UVT	A	Thioredoxin domain-containing protein 5	* 5.3.4.1	111	12194.00
2H8L	B	Protein disulfide-isomerase A3	* 5.3.4.1	252	28818.70	3UVT	B	Thioredoxin domain-containing protein 5	* 5.3.4.1	111	12194.00

Table 4. Basic characteristics of selected Isomerases proteins continued

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
2H8L	C	Protein disulfide-isomerase A3	* 5.3.4.1	252	28818.70	3UVT	C	Thioredoxin domain-containing protein 5	* 5.3.4.1	111	12194.00
2HE9	A	NK-tumor recognition protein	* 5.2.1.8	192	21219.40	3UVT	D	Thioredoxin domain-containing protein 5	* 5.3.4.1	111	12194.00
2HE9	B	NK-tumor recognition protein	* 5.2.1.8	192	21219.40	3UVT	E	Thioredoxin domain-containing protein 5	* 5.3.4.1	111	12194.00
2HHJ	A	Bisphosphoglycerate mutase	* 3.1.3.13 * 5.4.2.1 * 5.4.2.4	267	31197.60	4A35	A	MITOCHONDRIAL ENOLASE SUPERFAMILY MEMBER 1	* 5.-.-.-	441	49567.60
2HHJ	B	Bisphosphoglycerate mutase	* 3.1.3.13 * 5.4.2.1 * 5.4.2.4	267	31197.60	4DIP	A	Peptidyl-prolyl cis-trans isomerase FKBP14	* 5.2.1.8	125	14032.50
2HQ6	A	Serologically defined colon cancer antigen 10	* 5.2.1.8	185	20579.10	4DIP	B	Peptidyl-prolyl cis-trans isomerase FKBP14	* 5.2.1.8	125	14032.50
2JK2	A	TRIOSEPHOSPHATE ISOMERASE	* 5.3.1.1	250	26714.60	4DIP	C	Peptidyl-prolyl cis-trans isomerase FKBP14	* 5.2.1.8	125	14032.50
2JK2	B	TRIOSEPHOSPHATE ISOMERASE	* 5.3.1.1	250	26714.60	4DIP	D	Peptidyl-prolyl cis-trans isomerase FKBP14	* 5.2.1.8	125	14032.50
2OK3	A	Peptidyl-prolyl cis-trans isomerase-like 3	* 5.2.1.8	161	18177.70	4DIP	E	Peptidyl-prolyl cis-trans isomerase FKBP14	* 5.2.1.8	125	14032.50
2PBC	A	FK506-binding protein 2	* 5.2.1.8	102	11182.90	4DIP	F	Peptidyl-prolyl cis-trans isomerase FKBP14	* 5.2.1.8	125	14032.50
2PBC	B	FK506-binding protein 2	* 5.2.1.8	102	11182.90	4DIP	G	Peptidyl-prolyl cis-trans isomerase FKBP14	* 5.2.1.8	125	14032.50
2PBC	C	FK506-binding protein 2	* 5.2.1.8	102	11182.90	4DIP	H	Peptidyl-prolyl cis-trans isomerase FKBP14	* 5.2.1.8	125	14032.50
2PBC	D	FK506-binding protein 2	* 5.2.1.8	102	11182.90	4DIP	I	Peptidyl-prolyl cis-trans isomerase FKBP14	* 5.2.1.8	125	14032.50
						4DIP	J	Peptidyl-prolyl cis-trans isomerase FKBP14	* 5.2.1.8	125	14032.50

Table 5. Basic characteristics of selected Transferases proteins

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
1B4F	A	EPHB2	* 2.7.10.1	82	9401.84	1JDW	A	L-ARGININE\:GLYCINE AMIDINOTRANSFERASE	* 2.1.4.1	423	48521.90
1B4F	B	EPHB2	* 2.7.10.1	82	9401.84	1JQE	A	Histamine N-Methyltransferase	* 2.1.1.8	292	33345.30
1B4F	C	EPHB2	* 2.7.10.1	82	9401.84	1JQE	B	Histamine N-Methyltransferase	* 2.1.1.8	292	33345.30
1B4F	D	EPHB2	* 2.7.10.1	82	9401.84	1JV1	A	GlcNAc1P uridyltransferase isoform 1: AGX1	* 2.7.7.-	505	57096.70
1B4F	E	EPHB2	* 2.7.10.1	82	9401.84	1JV1	B	GlcNAc1P uridyltransferase isoform 1: AGX1	* 2.7.7.-	505	57096.70
1B4F	F	EPHB2	* 2.7.10.1	82	9401.84	1K04	A	FOCAL ADHESION KINASE 1	* 2.7.10.2	162	17949.80
1B4F	G	EPHB2	* 2.7.10.1	82	9401.84	1K3Y	A	GLUTATHIONE S-TRANSFERASE A1	* 2.5.1.18	221	25539.10
1B4F	H	EPHB2	* 2.7.10.1	82	9401.84	1K3Y	B	GLUTATHIONE S-TRANSFERASE A1	* 2.5.1.18	221	25539.10
1BLX	A	CYCLIN-DEPENDENT KINASE 6	* 2.7.11.22	326	36987.70	1KGD	A	PERIPHERAL PLASMA MEMBRANE CASK	* 2.7.11.1	180	20754.70
1BLX	B	P19INK4D		166	17832.50	1KWA	A	HCASK/LIN-2 PROTEIN	* 2.7.11.1	88	10194.90
1BTK	A	BRUTON'S TYROSINE KINASE	* 2.7.10.2	169	19929.10	1KWA	B	HCASK/LIN-2 PROTEIN	* 2.7.11.1	88	10194.90
1BTK	B	BRUTON'S TYROSINE KINASE	* 2.7.10.2	169	19929.10	1LS6	A	aryl sulfotransferase	* 2.8.2.1	295	34220.60
1BX4	A	PROTEIN (ADENOSINE KINASE)	* 2.7.1.20	345	38755.60	1M9Z	A	TGF-BETA RECEPTOR TYPE II	* 2.7.11.30	111	12624.30
1BZY	A	HYPOXANTHINE-GUANINE PHOSPHORIBOSYLTRANSFERASE	* 2.4.2.8	217	24481.40	1MEO	A	Phosphoribosylglycinamide formyltransferase	* 2.1.2.2	209	22679.10
1BZY	B	HYPOXANTHINE-GUANINE PHOSPHORIBOSYLTRANSFERASE	* 2.4.2.8	217	24481.40	1MFG	A	Erb-B2 INTERACTING PROTEIN		95	10292.70

Table 5. Basic characteristics of selected Transferases proteins continued

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
1BZY	C	HYPOXANTHINE-GUANINE PHOSPHORIBOSYLTRANSFERASE	* 2.4.2.8	217	24481.40	1MFG	B	Erb-B2 carboxyl-terminal fragment	* 2.7.10.1	9	1004.15
1BZY	D	HYPOXANTHINE-GUANINE PHOSPHORIBOSYLTRANSFERASE	* 2.4.2.8	217	24481.40	1MP8	A	focal adhesion kinase 1	* 2.7.10.2	281	32120.30
1CB0	A	PROTEIN (5'-DEOXY-5'-METHYLTHIOADENOSINE PHOSPHORYLASE)	* 2.4.2.28	283	31277.30	1MQ4	A	AURORA-RELATED KINASE 1	* 2.7.11.1	272	31440.40
1CZA	N	HEXOKINASE TYPE I	* 2.7.1.1	917	102588.00	1NB9	A	hypothetical protein FLJ11149	* 2.7.1.26	147	16772.20
1E8Y	A	PHOSPHATIDYLINOSITOL 3-KINASE CATALYTIC SUBUNIT	* 2.7.1.153 * 2.7.11.1	966	110757.00	1NM8	A	Carnitine O-acetyltransferase	* 2.3.1.7	616	69903.50
1EH6	A	O6-ALKYLGUANINE-DNA ALKYLTRANSFERASE	* 2.1.1.63	207	21672.10	1NN5	A	Similar to deoxythymidylate kinase (thymidylate kinase)	* 2.7.4.9	215	24052.70
1EX0	A	COAGULATION FACTOR XIII A CHAIN	* 2.3.2.13	731	83313.70	1NTY	A	Triple functional domain protein	* 2.7.11.1	311	36432.10
1EX0	B	COAGULATION FACTOR XIII A CHAIN	* 2.3.2.13	731	83313.70	1NUU	A	FKSG76	* 2.7.7.1 * 2.7.7.18	252	28397.00
1FGK	A	FGF RECEPTOR 1	* 2.7.10.1	310	35308.90	1NUU	B	FKSG76	* 2.7.7.1 * 2.7.7.18	252	28397.00
1FGK	B	FGF RECEPTOR 1	* 2.7.10.1	310	35308.90	1O4R	A	PROTO-ONCOGENE TYROSINE-PROTEIN KINASE SRC	* 2.7.10.2	108	12375.10
1FMK	A	TYROSINE-PROTEIN KINASE SRC	* 2.7.10.2	452	51710.10	1O6L	A	RAC-BETA SERINE/THREONINE PROTEIN KINASE	* 2.7.11.1	337	39389.20

Table 5. Basic characteristics of selected Transferases proteins continued

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
1FW1	A	GLUTATHIONE TRANSFERASE ZETA	* 2.5.1.18 * 5.2.1.2	216	24108.10	1O6L	C	GLYCOGEN SYNTHASE KINASE-3 BETA	* 2.7.1.37	10	1123.23
1G3M	A	ESTROGEN SULFOTRANSFERASE	* 2.8.2.4	294	35176.70	1OTH	A	PROTEIN (ORNITHINE TRANSCARBAMOYLASE)	* 2.1.3.3	321	36106.90
1G3M	B	ESTROGEN SULFOTRANSFERASE	* 2.8.2.4	294	35176.70	1P4O	A	Insulin-like growth factor I receptor protein	* 2.7.10.1	322	36657.20
1G55	A	DNA CYTOSINE METHYLTRANSFERASE DNMT2	* 2.1.1.204	343	39276.80	1P4O	B	Insulin-like growth factor I receptor protein	* 2.7.10.1	322	36657.20
1GZ8	A	CELL DIVISION PROTEIN KINASE 2	* 2.7.11.22	299	34034.80	1P5Z	B	Deoxycytidine kinase	* 2.7.1.74	263	30835.00
1HE7	A	HIGH AFFINITY NERVE GROWTH FACTOR RECEPTOR	* 2.7.10.1	126	13922.50	1PKX	A	Bifunctional purine biosynthesis protein PURH	* 2.1.2.3 * 3.5.4.10	592	64694.30
1HML	A	ALPHA-LACTALBUMIN	* 2.4.1.22	142	16241.00	1PKX	B	Bifunctional purine biosynthesis protein PURH	* 2.1.2.3 * 3.5.4.10	592	64694.30
1I1N	A	PROTEIN-L-ISOASPARTATE O-METHYLTRANSFERASE	* 2.1.1.77	226	24537.40	1PKX	C	Bifunctional purine biosynthesis protein PURH	* 2.1.2.3 * 3.5.4.10	592	64694.30
1J1B	A	Glycogen synthase kinase-3 beta	* 2.7.11.1 * 2.7.11.26	420	46801.70	1PKX	D	Bifunctional purine biosynthesis protein PURH	* 2.1.2.3 * 3.5.4.10	592	64694.30
1J1B	B	Glycogen synthase kinase-3 beta	* 2.7.11.1 * 2.7.11.26	420	46801.70	1QCF	A	HAEMATOPOETIC CELL KINASE (HCK)	* 2.7.10.2	454	52000.80
1J99	A	ALCOHOL SULFOTRANSFERASE	* 2.8.2.14	293	34717.00	1QF8	A	CASEIN KINASE II	* 2.7.1.37	182	21553.10
						1QF8	B	CASEIN KINASE II	* 2.7.1.37	182	21553.10

Table 6. Basic characteristics of selected Hydrolases proteins

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
1A4I	A	METHYLENETETRAHYDROFOLATE DEHYDROGENASE / METHENYLTETRAHYDROFOLATE CYCLOHYDROLASE	* 1.5.1.5 * 3.5.4.9	301	32650.80	1J8F	A	SIRTUIN 2, ISOFORM 1	* 3.5.1.-	323	36532.30
1A4I	B	METHYLENETETRAHYDROFOLATE DEHYDROGENASE / METHENYLTETRAHYDROFOLATE CYCLOHYDROLASE	* 1.5.1.5 * 3.5.4.9	301	32650.80	1J8F	B	SIRTUIN 2, ISOFORM 1	* 3.5.1.-	323	36532.30
1A6Q	A	PHOSPHATASE 2C	* 3.1.3.16	382	42503.10	1J8F	C	SIRTUIN 2, ISOFORM 1	* 3.5.1.-	323	36532.30
1APY	A	ASPARTYLGLUCOSAMINIDASE	* 3.5.1.26	162	17293.40	1JSF	A	LYSOZYME	* 3.2.1.17	130	14720.80
1APY	B	ASPARTYLGLUCOSAMINIDASE	* 3.5.1.26	141	15085.20	1JY1	A	TYROSYL-DNA PHOSPHODIESTERASE	* 3.1.4.-	464	52898.20
1APY	C	ASPARTYLGLUCOSAMINIDASE	* 3.5.1.26	162	17293.40	1KI0	A	ANGIOSTATIN	* 3.4.21.7	253	29084.40
1APY	D	ASPARTYLGLUCOSAMINIDASE	* 3.5.1.26	141	15085.20	1KRN	A	PLASMINOGEN	* 3.4.21.7	88	9899.93
1AYE	A	PROCARBOXYPEPTIDASE A2	* 3.4.17.15	401	45007.10	1KWM	A	Procarboxypeptidase B	* 3.4.17.2	402	45956.00
1B6A	A	METHIONINE AMINOPEPTIDASE	* 3.4.11.18	478	52972.10	1KWM	B	Procarboxypeptidase B	* 3.4.17.2	402	45956.00
1CS8	A	HUMAN PROCATHEPSIN L	* 3.4.22.15	316	35921.20	1L9X	A	gamma-glutamyl hydrolase	* 3.4.19.9	315	35989.30
1CSB	A	CATHEPSIN B light chain	* 3.4.22.1	47	5213.87	1L9X	B	gamma-glutamyl hydrolase	* 3.4.19.9	315	35989.30
1CSB	B	CATHEPSIN B heavy chain	* 3.4.22.1	205	22438.00	1L9X	C	gamma-glutamyl hydrolase	* 3.4.19.9	315	35989.30
1CSB	D	CATHEPSIN B light chain	* 3.4.22.1	47	5213.87	1L9X	D	gamma-glutamyl hydrolase	* 3.4.19.9	315	35989.30
1CSB	E	CATHEPSIN B heavy chain	* 3.4.22.1	205	22438.00	1LAR	A	PROTEIN (LAR)	* 3.1.3.48	575	66092.70
1DEU	A	PROCATHEPSIN X	* 3.4.18.1	277	31184.80	1LAR	B	PROTEIN (LAR)	* 3.1.3.48	575	66092.70
1DEU	B	PROCATHEPSIN X	* 3.4.18.1	277	31184.80	1LCF	A	LACTOFERRIN	* 3.4.21.-	691	76221.80

Table 6. Basic characteristics of selected Hydrolases proteins continued

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
1DTD	A	CARBOXYPEPTIDASE A2	* 3.4.17.15	303	33661.20	1LCY	A	HtrA2 serine protease	* 3.4.21.108	325	35002.10
1DTD	B	METALLOCARBOXYPEPTIDASE INHIBITOR		61	6787.68	1LE6	A	Group X Secretory Phospholipase A2	* 3.1.1.4	123	13644.60
1EDM	B	FACTOR IX	* 3.4.21.22	39	4279.65	1LE6	B	Group X Secretory Phospholipase A2	* 3.1.1.4	123	13644.60
1EDM	C	FACTOR IX	* 3.4.21.22	39	4279.65	1LE6	C	Group X Secretory Phospholipase A2	* 3.1.1.4	123	13644.60
1ELV	A	COMPLEMENT C1S COMPONENT	* 3.4.21.42	333	36687.70	1LO6	A	Kallikrein 6	* 3.4.21.-	223	24533.00
1F3U	A	TRANSCRIPTION INITIATION FACTOR IIF, BETA SUBUNIT	* 3.6.4.12	118	12718.50	1LQV	A	Endothelial protein C receptor		193	22046.80
1F3U	B	TRANSCRIPTION INITIATION FACTOR IIF, ALPHA SUBUNIT		171	19942.60	1LQV	B	Endothelial protein C receptor		193	22046.80
1F3U	C	TRANSCRIPTION INITIATION FACTOR IIF, BETA SUBUNIT	* 3.6.4.12	118	12718.50	1LQV	C	Vitamin-K dependent protein C	* 3.4.21.69	33	4359.44
1F3U	D	TRANSCRIPTION INITIATION FACTOR IIF, ALPHA SUBUNIT		171	19942.60	1LQV	D	Vitamin-K dependent protein C	* 3.4.21.69	33	4359.44
1F3U	E	TRANSCRIPTION INITIATION FACTOR IIF, BETA SUBUNIT	* 3.6.4.12	118	12718.50	1M6D	A	Cathepsin F	* 3.4.22.41	214	23657.80
1F3U	F	TRANSCRIPTION INITIATION FACTOR IIF, ALPHA SUBUNIT		171	19942.60	1M6D	B	Cathepsin F	* 3.4.22.41	214	23657.80
1F3U	G	TRANSCRIPTION INITIATION FACTOR IIF, BETA SUBUNIT	* 3.6.4.12	118	12718.50	1MHW	A	Cathepsin L	* 3.4.22.15	175	19127.10
1F3U	H	TRANSCRIPTION INITIATION FACTOR IIF, ALPHA SUBUNIT		171	19942.60	1MHW	B	Cathepsin L	* 3.4.22.15	175	19127.10
1FH0	A	CATHEPSIN V	* 3.4.22.43	221	24041.10	1MHW	C	Cathepsin L	* 3.4.22.15	42	4783.44

Table 6. Basic characteristics of selected Hydrolases proteins continued

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
1FH0	B	CATHEPSIN V	* 3.4.22.43	221	24041.10	1MHW	D	Cathepsin L	* 3.4.22.15	42	4783.44
1FIT	A	FRAGILE HISTIDINE PROTEIN	* 3.6.1.29	147	16980.20	1MHW	E	4-biphenylacetyl-Cys-(D)Arg-Tyr-N-(2-phenylethyl) amide		5	739.93
1FJ2	A	PROTEIN (ACYL PROTEIN THIOESTERASE 1)	* 3.1.2.-	232	24920.90	1MHW	F	4-biphenylacetyl-Cys-(D)Arg-Tyr-N-(2-phenylethyl) amide		5	739.93
1FJ2	B	PROTEIN (ACYL PROTEIN THIOESTERASE 1)	* 3.1.2.-	232	24920.90	1MHW	G	4-biphenylacetyl-Cys-(D)Arg-Tyr-N-(2-phenylethyl) amide		5	739.93
1FO3	A	ALPHA1,2-MANNOSIDASE	* 3.2.1.113	460	52782.50	1MHW	H	4-biphenylacetyl-Cys-(D)Arg-Tyr-N-(2-phenylethyl) amide		5	739.93
1FPZ	A	CYCLIN-DEPENDENT KINASE INHIBITOR 3	* 3.1.3.16 * 3.1.3.48	212	23819.20	1NE7	A	Glucosamine-6-phosphate isomerase	* 3.5.99.6	289	32712.80
1FPZ	B	CYCLIN-DEPENDENT KINASE INHIBITOR 3	* 3.1.3.16 * 3.1.3.48	212	23819.20	1NE7	B	Glucosamine-6-phosphate isomerase	* 3.5.99.6	289	32712.80
1FPZ	C	CYCLIN-DEPENDENT KINASE INHIBITOR 3	* 3.1.3.16 * 3.1.3.48	212	23819.20	1NE7	C	Glucosamine-6-phosphate isomerase	* 3.5.99.6	289	32712.80
1FPZ	D	CYCLIN-DEPENDENT KINASE INHIBITOR 3	* 3.1.3.16 * 3.1.3.48	212	23819.20	1NE7	D	Glucosamine-6-phosphate isomerase	* 3.5.99.6	289	32712.80
1FPZ	E	CYCLIN-DEPENDENT KINASE INHIBITOR 3	* 3.1.3.16 * 3.1.3.48	212	23819.20	1NE7	E	Glucosamine-6-phosphate isomerase	* 3.5.99.6	289	32712.80
1FPZ	F	CYCLIN-DEPENDENT KINASE INHIBITOR 3	* 3.1.3.16 * 3.1.3.48	212	23819.20	1NE7	F	Glucosamine-6-phosphate isomerase	* 3.5.99.6	289	32712.80
1GQV	A	EOSINOPHIL-DERIVED NEUROTOXIN	* 3.1.27.5	135	15611.80	1NNL	A	L-3-phosphoserine phosphatase	* 3.1.3.3	225	25052.90
1H7S	A	PMS1 PROTEIN HOMOLOG 2	* 3.1.-.-	365	40748.10	1NNL	B	L-3-phosphoserine phosphatase	* 3.1.3.3	225	25052.90
1H7S	B	PMS1 PROTEIN HOMOLOG 2	* 3.1.-.-	365	40748.10	1NZI	A	Complement C1s component	* 3.4.21.42	159	18145.00
1HAZ	A	BETA-CASOMORPHIN-7		4	458.55	1NZI	B	Complement C1s component	* 3.4.21.42	159	18145.00

Table 6. Basic characteristics of selected Hydrolases proteins continued

PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight	PDB ID	Chain ID	Macromolecule Name	EC No	Chain Length	Molecular Weight
1HAZ	B	ELASTASE 1	* 3.4.21.36	240	25928.20	1I71	A	APOLIPOPROTEIN(A)	* 3.4.21.-	83	9778.80
1HDK	A	EOSINOPHIL LYSOPHOSPHOLIPASE	* 3.1.1.5	141	16368.80	1I76	A	NEUTROPHIL COLLAGENASE	* 3.4.24.34	163	18111.90
1HFC	A	FIBROBLAST COLLAGENASE	* 3.4.24.7	169	18865.70	1ITU	A	RENAL DIPEPTIDASE	* 3.4.13.19	369	41108.60
1HKK	A	CHITOTRIOSIDASE-1	* 3.2.1.14	364	40697.00	1ITU	B	RENAL DIPEPTIDASE	* 3.4.13.19	369	41108.60
1HTR	B	GASTRICSIN	* 3.4.23.3	329	35465.20	1ITV	A	MMP9	* 3.4.24.35	195	22450.70
1HTR	P	PROGASTRICSIN (PRO SEGMENT)	* 3.4.23.3	43	5137.19	1ITV	B	MMP9	* 3.4.24.35	195	22450.70
1HY7	A	STROMELYSIN-1	* 3.4.24.17	173	19416.70						
1HY7	B	STROMELYSIN-1	* 3.4.24.17	173	19416.70						

2.3. DOCKING

2.3.1. Protein-ligand docking

2.3.1.1. Grid-box generation

The grid parameter file of each protein was generated using AutoDockTool. During the parameter file preparation process, a grid-box was generated that was large enough to cover the entire protein binding site and accommodate all ligands to move freely.

The size of grid box in x, y, and z directions were all taken as 126 Å×126 Å ×126 Å. In addition to this, the distance between two connecting grid points was 0.375 Å. The center of the receptor in the X-ray crystal structure was placed as the center of the grid-box.

Normally, for protein structures that have the binding site information for any ligand molecule, the center of the binding site was estimated from the structure however in our case since there is no information blind docking was performed having a large grid box that covers the whole protein as much as possible.

2.3.1.2. Ligand docking

AutoDock4 and a LGA [9] were used for protein-fixed ligand-flexible docking calculations. Twenty search attempts (ga_run parameter) were performed for each ligand. The maximum number of energy evaluations before the termination of LGA run was 2500000 and the maximum number of generations of the LGA run before termination was 27000. Other docking parameters were set to the software's default values. After docking, the ligands were ranked according to their protein-ligand affinity.

Finally from the output files of docking analysis, different file conversions were applied for further analysis, such as visual inspections.

3. RESULTS AND DISCUSSION

Concurrent impacts, which are literally the coexistence of the effects, of the ligand molecules on certain group of proteins were searched throughout this thesis via docking analysis. Binding affinities of the ligand molecules showing similar behaviour within and among various classes of proteins was saught. For this purpose, binding energy of each 26 different ligand molecules with 296 proteins in different classes was docked. To sum up, this research reveals results of totally 4974 Dockings. These results consist of calculated binding energy values for all proteins in each class tabulated here and their corresponding binding coordinates.

Estimated Binding Energy Values of each ligand-protein pair were tabulated in five different tables; Table2, Table 3, Table 4, Tale 5 and Table 6. In these tables, values smaller than -9 were indicated with red color, values between -7 and -8 were colored with orange, values between -5 and -6 were given in yellow color and finally values greater than -5 were colored with gray. These colourings were applied in order to visualize the groupings of the ligands with different binding affinities. Especially, the grouping of the values shown by red color is important since they refer to the best binding properties. Consequently, same colourings indicated similar binding affinities, and the red colored ones performs best.

Respectively, molecular docking binding energy scores of the 15 compounds within Lyases Class were given in Table 2, binding scores of the 25 compounds within Hydrolases Class were given in Table 3, and the scores of the 24 compounds within Isomerases Class were given in Table 4. Besides these, docking binding scores of the 20 compounds within Ligases Class were given in table 5 and docking binding scores of the 23 compounds within Transferases Class were given in Table 6.

Considering the results that are tabulated, the Ligands number 3 and 5 have the lowest energy in Lyases Class, the Ligands number 4 and 5 have the lowest energy in Hydrolases Class, the Ligands number 4 and 5 have the lowest energy in Isomerases Class. Furthermore, the Ligands number 4 and 5 have the lowest energy in Ligases Class, and the Ligands number 3, 4 and 26 have the lowest energy in Transferases Class.

In this study, the Gibbs free energy (ΔG) results show that for all the classes of proteins that are considered in this thesis work, the best interactions occur with the ones with ligands number 3, 4, 5, 26.

The best binding energies, which are smaller than -9 kcal mol^{-1}, were calculated and shown with red color in the tables. These are the ones; for Lyases Class, L3 with IR3S, 3DON, 3FVS was found to be -9, -9.28, -10.6 kcal mol^{-1} respectively, and L10 with 3AQI was found to be -9.21 kcal mol^{-1} (Table 2). Additionaly, other best binding energies for Lyases Class, L5 with 1ALD, 1HCB, 1IKT, 1JD0, 1R3S, 1T2A, 2AKZ, 2B3Y, 2B69, 2J91, 2JIS, 2O3H, 2OO0, 2W2J, 2WZ1, 3AQI, 3D0N, 3EP6, 3FE4, 3FVS, 3FW3, 3IR3, 3KAN, 3KS3, 3S5O, 3VW9, 4E1O, 4H27 was found to be -9.48, -9.13, -9.86, -11.36, -11.16, -10.51, -9.3, -10.86, -10.94, -9.62, -9.68, -9.17, -10.35, -10.28, -10.22, -10.44, -10.43, -10.67, -10.24, -11.65, -9.38, -9.91, -10.09, -9.29, -9.49, -9.41, -10.19, -9.87 kcal mol^{-1} respectively (Table2). L5 successfully docked with 3FVS by forming hydrogen bonds at Lys74, Pro90, Pro70, Thr73, Leu91, Lys65, Gly68, Phe67, Thr66, Val22, Val19, Lys23 (Figure 7/B).

3FVS - Human kynurenine aminotransferase I (hKAT I) catalyzes the formation of kynurenic acid, a neuroactive compound. General functions of 3FVS are Amino acid transport and metabolism. Molecular functions of 3FVS are L-glutamine: pyruvate aminotransferase activity, L-phenylalanine-oxaloacetate-transaminaseactivity, L-phenylalanine: pyruvate aminotransferase activity, cysteine-S-conjugate beta-lyase activity, glutamine-phenylpyruvate transaminase activity, kynurenine-oxoglutarate transaminase activity and pyridoxal phosphate binding. This enzyme previously had been studied for structural insight into the Inhibition of Human Kynurenine Aminotransferase I/Glutamine transaminase K by Qian Han et. al. [82]. In this study, active sites Gly36, Arg398, Tyr101, Asn185, Tyr216, Trp18, and Tyr63 [82].

The best binding energies for Hydrolases Class of L3 with 1LE6, 1M6D was found to be -9.12, -9.07 kcal mol^{-1} , L4 with 1AYE, 1B6A, 1F3U, 1FIT, 1HKK, 1HTR, 1HY7, 1I76, 1ITU, 1ITV, 1JY1, 1LCF, 1LE6, 1NE7 was found to be -9.09, -10.29, -9.01, -10.45, -10.19, -9.75, -9.61, -9.58, -9, -9.23, -9.77, -9.68, -10.09, -9.89 kcal mol^{-1} respectively. Correspondingly, the best binding energies of L5 with 1A4I, 1AYE, 1B6A, 1CSB, 1FIT, 1H7S, 1HAZ, 1HKK, 1HTR, 1HY7, 1I76, 1ITV, 1JY1, 1LAR, 1LCF, 1LCY, 1LE6, 1LO6, 1M6D, 1MHW, 1NE7, 1NZI was found to be -9.15, -9.49, -10.82, -10.38, -10.21, -9.01, -9.21, -10.6, -9.98, -9.28, -9.34, -9.81, -9.27, -9.00, -9.28, -9.93, -10.7, -9.33, -9.00, -9.38, -9.35, -9 kcal mol^{-1} respectively.(Table 3)

L5 successfully docked with 1B6A by forming interactions at Met384, Ala414, Phe219, Ile338, His339, His331, Glu364, Asn329, Leu328, Asn327, His382, Pro443, Tyr444, His231, Pro445, Asp376, Leu447 (Figure 4/B).

1B6A-Methionine aminopeptidase 2 takes place in translation, ribosomal structure and biogenesis. General functions of 1B6A are metal ion binding, metalloexopeptidase activity, aminopeptidase activity [230]. This enzyme previously had been studied for Structure of human methionine aminopeptidase-2 complexed with fumagillin [186].

Considering the functions of the protein,1B6A, which comes out as best binding with the ligand may have drug application for protein synthesis related illnesses.

The best binding energies for Isomerases Class of L3 with 2ESL was found to be -9 kcal mol^{-1} , L11 with 2HHJ was found to be -9.14 kcal mol^{-1}, L15 with 3IJJ was found to be -9.14 kcal mol^{-1}, L22 with 2HHJ was found to be -9.04 kcal mol^{-1}, L4 with 4DIP, 2PBC, 2CVD, 2XIJ, 2ESL, 2H8L, 3B6H, 3O5Q, 3IJJ, 1C9H, 3O22, 3RMU, 1ZXM, 2DHO, 1SG4, 1Q1C, 1EK6, 2F6Q, 2WFI, 2VRE, 3UI4 was found to be -11.17, -10.22, -10.19, -10.18, -10.15, -9.83, -9.8, -9.74, -9.69, -9.41, -9.37, -9.32, -9.31, -9.24, -9.17, -9.15, -9.13, -9.13, -9.11, -9.04, -9.01 kcal mol^{-1} respectively. Correspondingly, the best binding energies of L5 with 2PBC, 4DIP, 3O5Q, 2XIJ, 1EK6, 2VRE, 3B6H, 2F6Q, 1ZXM, 2A2N, 2CVD, 2H8L, 1C9H, 3RMU, 1SG4, 1Q1C, 2PPN, 3O5E, 1FW1, 3RCG, 2X7K, 2HHJ, 3IJJ, 3IDV, 3O22, 2HQ6 was found to be -11.21, -11.16, -10.99, -10.83, -10.42, -10.42, -10.38, -10.05, -9.95, -9.94, -9.94, -9.93, -9.92, -9.9, -9.84, -9.83, -9.72, -9.51, -9.48, -9.44, -9.33, -9.32, -9.25, -9.21, -9.14, -9.04 kcal mol^{-1} respectively (Table 4).

L5 successfully docked with 2PBC by forming hydrogen bonds at Tyr112, Phe129, Tyr56, Phe76, Ile86, Trp89, Val85, Gln84, Gln84, Val85, Ile86, Tyr112, Trp89, Phe76, Tyr56, Asp67, Phe129 (Figure 6/B).

Function of 2PBC- FK506 - binding protein 2 PPlases accelerate the folding of proteins. It catalyzes the cis-trans isomerization of proline imidic peptide bonds inoligopeptides. General functions of 2PBC are FK506 binding and peptidyl-prolyl cis-trans isomerise activity [229].

Looking at the results the ligand L5 also binds well with 2PBC as well as 1B6A. Since this means that L5 may have an effect on protein folding mechanism too, in case of its use as a drug it may affect different illnesses, concurrently.

The best binding energies for Ligases Class of L4 with 2OOA, 1ZUO, 3C5E, 3B76, 2UVL, 1N3L, 1LGP, 2Z6O, 2A7L, 2F4W, 2Y1N, 3B7Y, 1T15, 2NSQ, 1I7K were found to be -11.64, -11.16, -10.68, -10.64, -10.63, -10.41, -10.3, -10.25, -9.95, -9.39, -9.38, -9.26, -9.12, -9.09, -9.01 kcal mol^{-1} respectively. Correspondingly, the best binding energies of L5 with

1LGP, 2Z6O, 1ZUO, 3B76, 2V40, 3C5E, 2A7L, 1N3L, 3B7Y, 2I3H, 2F4W, 2YVQ, 2OOA, 1T15, 2NTE, 2Y1N, 2NQ3, 1I7K, 2NSQ, 1ZDN was found to -11.28, -10.59, -10.37, -10.14, -10.1, -9.9, -9.81, -9.79, -9.67, -9.63, -9.51, -9.43, -9.41, -9.28, -9.26, -9.2, -9.19, -9.11, -9.08, -9.05 kcal mol^{-1} respectively. (Table 4)

L4 successfully docked with 2OOA by forming hydrogen bonds at Leu939, Tyr944, Val949, Ala945, Phe946, Glu947, Gly941, Ile936, Ala937, Gly941, Gly943, Glu942, Ala945, Ala937, Tyr944, Phe946, Leu939, Ile936, Asp933, Val949, Lys950 (Figure 4/B).

2OOA, E3 ubiquitin-protein ligase or ubiquitin ligase which combines with specific E2 ubiquitin-conjugating enzymes. E3 ubiquitin-protein ligase which accepts ubiquitin from specific E2 ubiquitin-conjugating enzymes, and transfers it to substrates, generally promoting their degradation by the proteasome. Tissue specificities of 2OOA are expressed in placenta, heart, lung, kidney, spleen, ovary and testis, as well as fetal brain and liver and hematopoietic cell lines, but not in adult brain, liver, pancreas, salivary gland, or skeletal muscle. This enzyme previously had been studied in Structural basis for ubiquitin mediated dimerization and activation of the ubiquitin protein ligase Cbl-b study [35].

The best binding energies for Transferases Class of L15 with 1LS6, 1G3M was found to be -9.61, -9.69 kcal mol^{-1} , L23 with 10TH, 1J99 was found to be -11.73, -10.58 kcal mol^{-1}, L26 with 1P4O, 1CB0 was found to be -13.81, -12.54 kcal mol^{-1}, L4 with 1LS6, 1K3Y, 1NB9, 1EX0, 1NN5, 1G55, 1FGK, 1JQE was found to be -11.78, -9.74, -9.69, -9.65, -9.55, -9.1, -9.04, -9 kcal mol^{-1} respectively. Correspondingly, the best binding energies of L5 with 1K3Y, 1JQE, 1EX0, 1NB9, 1NUU, 1NM8, 1FGK, 1JV1, 1J99, 1O6L, 1QF8, 1EH6, 1LS6, 1E8Y, 1BLX, 1FMK, 1G55, 1BX4, 1J1B, 1GZ8, 1MQ4, 1P5Z, 1CZA was found to -11.31, -11.27, -11.21, -10.77, -10.55, -10.46, -10.38, -10.21, -10.14, -10.09, -10.03, -9.85, -9.85, -9.83, -9.8, -9.69, -9.68, -9.47, -9.33, -9.25, -9.12, -9.11, -9.08 kcal mol^{-1} respectively(Table5)

L26 successfully docked with 1P4O by forming hydrogen bonds at Lys968, Glu961, Leu1036, Arg1034, Gly990, Val991, Trp962, Glu963, Val964, Ala965 (Figure 8/B).

Functions of 1P4O-Insulin-like growth factor 1 receptor are ATP binding, insulin binding, insulin receptor binding, insulin-like growth factor binding, insulin-like growth factor-activated receptor activity. This enzyme previously had been studied for Structure of apo, unactivated insulin-like growth factor-1 receptor kinase at 1.5 A resolution [177].

By looking at the functions of protein, 1P4O, which the ligand L26 binds with one of the highest affinities, we can conclude that in cases were L26 ligand molecule is used as a drug, then it will be also expected to have an effect on sugar metabolism. Therefore, it may have an effect on insulin dependent patients which should be considered carefully. Of course prior to its drug application, the phases of drug development in pharmaceutical-chemistry should be applied.

Table 7. Binding energy results from docking for the 15 compounds within Lyases Class

	L1	L3	L5	L7	L9	L10	L11	L12	L15	L19	L22	L23	L24	L25	L26
1ALD	-4.62	-7.85	-9.48	-5.01	-6.04	-6	-6.32	-6.05	-6.7	-6.04	-5.7	-6.31	-5.45	-6.41	-5.67
1HCB	-3.84	-6.62	-9.13	-4.33	-6.17	-6.1	-6.43	-5.96	-6.68	-5.8	-5.55	-6.43	-5.46	-6.26	-5.93
1IKT	-4.41	-8.67	-9.86	-4.4	-6.74	-7.21	-7.23	-7	-7.84	-6.17	-6.35	-6.48	-5.67	-7.26	-5.75
1JD0	-4.51	-8.62	-11.4	-4.66	-6.92	-7.32	-7.15	-7.21		-6.7	-6.86	-7.52	-6.7	-7.42	-6.6
1JL0	-4.37	-6.58	-8.49	-4.66	-5.67	-5.28	-5.87	-5.28		-5.58	-5.33	-6.09	-5.17	-6.48	-5.19
1JR2	-4.27	-6.89	-8.96	-4.68	-5.41	-5.82	-5.79	-6.34		-5.28	-5.44	-6.18	-5.37	-6.53	-5.5
1KHB	-4.7	-8.76	-8.32	-5.45	-7	-6.78	-7.12	-7.19		-7.02	-7.05	-7.12	-6.88	-6.87	-6.06
1R3S	-4.5	-9	-11.2	-4.52	-7.3	-7.49	-7.44	-7.69	-8.3	-6.63	-6.88	-7.05	-6.56	-6.82	-6.73
1T2A	-3.93	-8.93	-10.5	-5.05	-6.35	-6.31				-6.36	-6.49	-6.85	-6.68	-6.49	-6.09
2AKZ	-3.78	-7.05	-9.3	-5.16	-5.59	-5.99				-5.31	-5.63	-6.43	-5.21	-6.08	-5.38
2B3Y	-3.8	-8.96	-10.9	-4.32	-6.21	-6.95				-5.75	-5.92	-6.25	-5.7	-6.86	-5.91
2B69	-4.55	-8.55	-10.9	-5.38	-6.69	-6.79	-6.45	-7.23	-7.21	-6.46	-6.42	-6.44	-5.97	-7.28	-6.03
2J91	-4.39	-8.38	-9.62	-5.46	-6.56	-6.94				-6.61	-6.77	-6.76	-6.28	-6.68	-6.57
2JIS	-4.25	-7.35	-9.68	-4.63	-5.92	-6.12				-6	-5.7	-6.32	-5.41	-6.81	-5.6
2O3H	-4.18	-7.68	-9.17	-4.82	-6.16	-6	-6.1	-5.92	-6.19	-5.89	-5.5	-6.54	-5.81	-6.21	-5.81
2OO0	-4.36	-8.75	-10.4	-4.89	-7.35	-6.75				-6.63	-6.76	-7.67	-6.63	-6.91	-6.95
2W2J	-4.95	-8.12	-10.3	-4.96	-6.61	-6.51	-6.25	-7.05	-5.97	-5.8	-5.94	-6.72	-5.56	-6.49	-6.09
2WZ1	-5.42	-7.99	-10.2	-5.4	-6.54	-6.82	-7.22	-7.05	-7.44	-6.66	-6.44	-7.55	-6.13	-8.02	-6.56
2XSX	-3.92	-6.61	-8.5	-4.4	-6.03	-6.54				-5.92	-5.92	-6.45	-5.92	-6.64	-6.04
3AQI	-4.97	-8.72	-10.4	-4.98	-7.78	-9.21				-8.14	-7.55	-8.92	-6.39	-8.78	-7.86
3COG	-5.37	-8.25	-8.71	-5.47	-6.11	-5.54				-5.24	-5.77	-6.22	-5.27	-6.38	-5.69
3D0N	-5.62	-9.28	-10.4	-5.62	-6.54	-6.27	-6.56	-6.7		-6.16	-5.74	-6.73	-6.01	-6.48	-6.09
3EO4	-4.9	-7.88	-5.93	-4.9	-6.29	-6.2				-5.81	-5.89	-7.24	-5.92	-6.78	-5.76
3EP6	-4.79	-8.84	-10.7	-4.8	-7.01	-7.11	-7.01	-7.34	-6.56	-6.68	-6.72	-6.8	-6.22	-7.38	-6.45
3EWY	-4.69	-6.76	-7.55	-4.69	-5.62	-6.32	-5.65	-5.99	-6.47	-5.72	-5.8	-6.56	-5.55	-6.89	-5.79
3FE4	-4.86	-7.85	-10.2	-4.86	-6.63	-6.84	-6.81	-7.01		-6.06	-6.33	-6.45	-6.1	-6.65	-6.38
3FVS	-4.74	-10.6	-11.7	-4.74	-6.92	-7.15				-6.39	-6.39	-7.47	-6.01	-7.12	-6.3
3FW3	-4.57	-8.56	-9.38	-4.64	-6.61	-6.69	-6.57	-7.24		-6.34	-6.31	-6.84	-6.42	-6.69	-6.26
3IR3	-4.8	-8.8	-9.91	-4.79	-7.06	-6.67	-6.81	-6.84	-7.4	-6.44	-6.79	-7.12	-6.04	-6.88	-5.95
3KAN	-4.65	-7.9	-10.1	-4.65	-6.61	-6.67	-6.37	-6.23	-7.8	-6.29	-6.22	-6.5	-6.03	-6.27	-5.47
3KS3	-4.97	-7.37	-9.29	-4.97	-5.92	-6.27	-6.12	-6.56	-6.81	-5.87	-5.86	-6.83	-5.67	-6.64	-5.31
3L6B	-3.9	-7.85	-8.53	-5.31	-5.92	-6.32	-6.44	-6.23	-5.99	-5.92	-6.24	-6.35	-5.81	-6.73	-5.74
3PCV	-3.21	-7.11	-8.18	-3.9	-5.51	-5.77	-5.78	-5.78	-6.34	-5.1	-4.85	-5.46	-4.62	-5.68	-4.93
3S5O	-3.98	-7.28	-9.49	-4.84	-5.99	-6.2	-6.57	-6.33	-6.16	-6.25	-6.33	-6	-5.89	-6.29	-6.24
3UYQ	-4.46	-7.57	-8.82	-4.38	-6.12	-5.94	-5.95	-6.06	-6.36	-6.11	-6.14	-6.27	-6.04	-6.29	-6.33
3VW9	-4.39	-8.53	-9.41	-4.8	-6.59	-6.61	-6.67	-7.14	-6.9	-7.09	-6.75	-7.67	-6.14	-7.22	-6.12
4E1O	-3.39	-8.07	-10.2		-6.3	-6.52				-5.7	-6.08	-6.53	-5.76	-6.62	-6.05
4H27	-3.79	-8.45	-9.87	-4.87	-6.82	-6.62	-7.18	-7.16	-7.9	-5.97	-5.78	-6.37	-5.65	-6.25	-5.61

Table8. Binding energy results from docking for the 25 compounds within Hydrolases Class

	L1	L2	L3	L4	L5	L7	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17	L18	L19	L20	L21	L22	L23	L24	L26
1A4I	-4.3	-6.3	-8	-9	-9.2	-4.8	-5	-6.2	-6	-6.5	-5.7	-6.5	-6.2	-5.8	-5.5	-5.6	-5.7	-5.9	-5.5	-5.7	-5.9	-5.9	-5.5	-5.2
1A6Q	-3.8	-5.7	-6.6	-7.2	-7.9	-4.5	-5.6	-6.1	-6.3	-6.2	-6.9	-6.2	-6.8	-6.5	-6.5	-6	-6.3	-6.4	-6.1	-6.1	-5.9	-6.6	-5.5	-6.2
1APY	-3.9	-5.9	-6.7	-8.3	-8.3	-4.6	-4.6	-6.1	-6	-5.9	-5.8	-6.7	-6.3	-5.7	-5.5	-5.6	-5.7	-5.3	-5.3	-5.5	-5.4	-5.9	-5	-4.9
1AYE	-4.6	-5.9	-8.2	-9.1	-9.5	-5.5	-5.4	-6.6	-6.7	-6.6	-7.1	-6.7	-7.1	-6.4	-6.4	-6.6	-6.7	-6.3	-6.9	-6.4	-6.9	-7.6	-6.2	-6.5
1B6A	-4.3	-7.2	-8.4	-10	-11	-4.9	-4.7	-6.3	-6.4	-6.3	-6.6	-6.9	-6.6	-5.7	-6.4	-6.6	-6.6	-6.2	-6.4	-6.2	-6.7	-6.3	-6	-6.7
1CS8	-4.5	-5.1	-7.7	-8.4	-7.9	-5.2	-5.3	-6.4	-6.1	-6.4	-6.1	-6.4	-6.4	-6.1	-6.1	-6.3	-6.3	-5.9	-5.6	-5.8	-5.7	-6.2	-5.4	-5.6
1CSB	-3.7	-5.3	-7.7	-8.8	-10	-4.8	-5.8	-6.7	-6.2	-6.2	-6.8	-6.5	-6.2	-5.8	-5.9	-6.1	-6.2	-6.3	-6	-6.3	-5.8	-6.5	-6	-5.7
1DEU	-2.2	-2.7	-4.7	-5.4	-5.7	-2.5	-2.8	-3.6	-3.9	-4.1	-3.8	-4	-3.7	-3.5	-3.8	-4	-4.1	-3.8	-3.5	-3.6	-4.2	-3.9	-3.6	-3.3
1DTD	-4.1	-5.3	-7	-8.6	-8.2	-4.6	-5.2	-6.3	-6.4	-6.4	-6.8	-6.4	-6.3	-6.4	-6.3	-6.5	-6.6	-6	-6.7	-6	-6	-7.1	-5.9	-6
1EDM	-3.3	-4.8	-7.1	-8	-8.4	-4.2	-3.9	-5.5	-5.6	-5.8	-5.7	-6.3	-5.8	-4.8	-5.3	-5.6	-5.8	-5.2	-5.2	-5.6	-5.6	-5.6	-5.6	-5.2
1ELV	-4.6	-6.2	-8.1	-8.3	-8.8	-5.6	-5.9	-6.6	-7.6	-7.1	-6.8	-6.9	-6.1	-7.3	-6.3	-7	-7.1	-5.9	-6.7	-6	-6.5	-6.3	-6	-6.1
1F3U	-3.6	-4.8	-7	-7.9	-8.2	-4.4	-4.7	-5.5	-5.6	-5.8	-5.9	-6	-5.8	-5.7	-5.2	-5.3	-5.4	-5.5	-6	-5.4	-5.9	-6.6	-6	-6
1FH0	-2.7	-2.8	-4.4	-5.5	-4.9	-2.4	-4.2	-3.7	-3.5	-3.8	-3.5	-3.5	-3.8	-5	-3.6	-3.7	-3.7	-3.9	-3.5	-3.8	-3.6	-4.2	-3.5	-3.6
1FIT	-3.9	-5.5	-8.6	-10	-10	-4	-6.2	-6.5	-6.4	-6.6	-6.1	-6	-6.3	-6.9	-6	-6.2	-6.2	-5.9	-5.9	-6.2	-5.5	-6.1	-5.4	-5.6
1FJ2	-4.9	-7.2	-7.5	-8.7	-8.9	-5.6	-5.1	-6.7	-7.2	-7.4	-6.8	-6.6	-7.2	-6	-6.4	-6.6	-6.7	-6.2	-6.5	-6.7	-6.4	-6.6	-5.7	-6.4
1FO3	-3.6	-4.8	-7	-7.9	-8.2	-4.4	-4.7	-5.5	-5.6	-5.8	-5.9	-6	-5.8	-5.7	-5.2	-5.3	-5.4	-5.5	-6	-5.4	-5.9	-6.6	-6	-6
1FPZ	-3.2	-4.3	-6.5	-7.6	-8.1	-3.7	-5.6	-5.4	-5.1	-5.3	-5.3	-5.6	-5.6	-6	-5	-5.1	-5.1	-5.1	-4.7	-5.1	-4.6	-5.3	-4.4	-4.2
1GQV	-3.7	-4.5	-7.2	-8.2	-8.2	-4.6	-5.9	-5.9	-5.7	-5.2	-5.8	-5.7	-5.6	-7.4	-5.2	-5.3	-5.3	-5.3	-5.2	-5	-5.3	-5.5	-5.6	-5
1H7S	-4.1	-5.1	-7	-8.6	-9	-4.8	-5.5	-6	-6.1	-5.8	-6	-5.8	-5.9	-7.1	-5.9	-6.2	-6.4	-5.8	-5.9	-5.9	-6	-6.4	-5.7	-6
1HAZ	-4.5	-4.9	-7	-8.4	-9.2	-5.7	-5.6	-6	-5.6	-5.5	-5.7	-5.9	-5.4	-6.6	-5.3	-5.3	-5.4	-5.6	-5.7	-5.7	-5.8	-6.3	-5.4	-5.9
1HDK	-3.6	-4.3	-6.1	-7.1	-7.5	-4	-4.5	-5.3	-5.3	-5	-5	-5.8	-5.4	-5.3	-4.7	-5	-5	-4.8	-5	-5.6	-5.3	-5.7	-5.4	-5.2
1HFC	-4.7	-6.3	-7.2	-8.3	-8.4	-5.5	-5.3	-6.5	-6.3	-6.3	-6.3	-6.3	-6.5	-5.5	-6.5	-6.4	-6.4	-6.3	-6.2	-6.3	-6.3	-6.4	-5.9	-5.6
1HKK	-4.2	-5.6	-8.6	-10	-11	-5.1	-4.9	-6.2	-6.4	-6.5	-6.7	-6.3	-6.6	-5.6	-5.8	-6.1	-6.2	-6	-6.4	-6.4	-6.2	-7	-5.7	-5.7
1HTR	-4.4	-6.2	-7.6	-9.8	-10	-4.6	-4.8	-6.5	-6.9	-7	-7.1	-6.7	-7	-6.3	-6.3	-6.4	-6.5	-6	-6.3	-6.7	-6.5	-6.7	-5.8	-6.5
1HY7	-4.4	-6.3	-8.9	-9.6	-9.3	-4.8	-5.5	-7.9	-8.3	-7.9	-8.2	-7.5	-8.2	-6.7	-7.7	-8.1	-8.2	-7.6	-8.2	-7.5	-7.6	-8.3	-7.2	-8
1I71	-3.3	-4.3	-6.6	-7.6	-7.7	-4.2	-4.5	-5	-5.1	-5.3	-5.2	-5.4	-5.3	-5.7	-4.9	-5	-5	-5	-5.1	-4.8	-4.8	-5.7	-4.7	-4.8

Table 8. Binding energy results from docking for the 25 compounds within Hydrolases Class continued

	L1	L2	L3	L4	L5	L7	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17	L18	L19	L20	L21	L22	L23	L24	L26
1I76	-4.8	-6.7	-7.6	-9.6	-9.3	-4.8	-6	-7.7	-8.4	-8.1	-8	-7.1	-8.4	-7.3	-7.7	-7.9	-7.9	-7.6	-8.3	-7.6	-7.5	-8.4	-7.3	-8.1
1ITU	-4.4	-5.5	-7.7	-9	-9	-5.3	-5.9	-6.6	-6.5	-6.4	-6.9	-7.1	-6.6	-6.8	-6.1	-6.3	-6.4	-6.1	-6.3	-6.2	-6.6	-6.8	-6.2	-6.6
1ITV	-5	-6.4	-7.5	-9.2	-9.8	-4.9	-6.2	-7.1	-7.9	-7.2	-8.1	-6.5	-7.5	-8	-7	-7.3	-7.4	-6.7	-7.1	-7.3	-7.1	-7.5	-6.9	-7
1J8F	-3.6	-5.3	-6.6	-8.2	-8.1	-5	-4	-5.7	-6.3	-6.7	-5.4	-5.7	-5.9	-6.2	-5.5	-5.5	-5.6	-5.6	-6	-5.5	-5.5	-6.4	-5.4	-5.6
1JSF	-3.7	-5.8	-7.4	-7.9	-8.7	-4.4	-5.1	-5.8	-5.8	-6.2	-5.9	-5.9	-6.8	-6	-5.6	-5.7	-5.7	-5.6	-5.2	-5.9	-5.8	-5.7	-5.8	-5.3
1JY1	-4.2	-6.7	-8	-9.8	-9.3	-4.7	-6.6	-6	-7.7	-7.3	-6.9	-6	-7.3	-8	-6.8	-7.3	-7.5	-6.8	-7	-6.2	-6.6	-7.5	-6.5	-6.7
1KI0	-4.3	-6	-7.2	-8.8	-9	-4.9	-5.6	-6.2	-6.5	-6.5	-6.3	-6.4	-5.8	-6.6	-5.8	-5.9	-6	-6.1	-5.9	-6.2	-5.9	-6.3	-5.9	-5.5
1KRN	-4.2	-5.3	-6.6	-8.5	-8.5	-4.3	-5.8	-5.5	-5.2	-5.7	-5.2	-6.1	-5.9	-6.3	-5.1	-5.2	-5	-5.1	-4.9	-5.1	-5.1	-5.7	-5	-5
1KWM	-3.8	-4.9	-6.4	-7.8	-7.7	-4.4	-5.3	-5.5	-5.4	-5.6	-5.6	-5.3	-5.5	-5.8	-5	-5.5	-5.7	-5.4	-5.1	-5	-5.1	-5.6	-5.1	-5.4
1L9X	-4.1	-6	-7.1	-7.8	-8.5	-4.7	-6.2	-5.9	-6.8	-5.9	-6.2	-6.2	-6.7	-6.8	-6.1	-6.5	-6.4	-6.3	-6.6	-7.1	-6.5	-6.3	-5.5	-5.6
1LAR	-3.9	-4.7	-7.1	-8.1	-9	-4.7	-5.1	-5.7	-5.9	-5.6	-6.5	-5.8	-6	-6.7	-5.2	-5.4	-5.7	-5.4	-5.8	-5.2	-5.4	-6	-5.2	-5.6
1LCF	-4.2	-6	-7.7	-9.7	-9.3	-5.2	-5.9	-6.7	-6.9	-6.4	-6.9	-7.1	-6.8	-7.5	-5.8	-6.4	-6.5	-6.5	-6.6	-6.5	-5.9	-7.1	-6.3	-5.9
1LCY	-4.4	-6	-7.6	-8.9	-9.9	-4.7	-5.8	-6.9	-7.2	-7.3	-7.2	-7.4	-7.5	-7	-6.8	-6.9	-7	-7.2	-6.9	-6.8	-6.9	-7.1	-6.3	-6.3
1LE6	-4	-5.5	-9.1	-10	-11	-4.4	-5.4	-6.8	-7	-7.3	-7.3	-7.2	-7	-6.8	-6.4	-6.7	-6.8	-6.2	-6.3	-6.9	-6.3	-7.3	-5.5	-5.8
1LO6	-4	-5.3	-7.5	-8.8	-9.3	-4.7	-5.7	-7	-6.6	-6.5	-6.4	-6.7	-6.2	-7	-6	-6.2	-6.1	-6.1	-6	-6.2	-6.2	-6.6	-5.8	-5.8
1LQV	-3.6	-6.2	-7.5	-8.4	-8.9	-4.1	-6.6	-6.9	-7.4	-7.1	-7.5	-7.1	-7.2	-7.8	-6.8	-7.4	-7.6	-6.6	-6.5	-6.5	-6.4	-6.9	-5.8	-5.8
1M6D	-4.7	-5.6	-9.1	-8.8	-9	-4.6	-5.1	-6.7	-7.1	-6.8	-7	-6.9	-7.5	-6.6	-6.3	-6.8	-6.7	-6.1	-6.5	-5.9	-6	-6.9	-5.7	-6.1
1MHW	-5.6	-5.2	-8.3	-8.9	-9.4	-4.6	-5	-6.1	-5.8	-6.2	-6.2	-6.4	-5.9	-5.5	-5.4	-5.5	-5.9	-5.8	-5.7	-5.7	-5.9	-6.3	-6	-6
1NE7	-4.1	-5.7	-8.1	-9.9	-9.4	-5.3	-6.3	-6.4	-6.9	-6.3	-6.6	-6	-6.6	-7.4	-5.9	-5.8	-6.5	-5.7	-6.4	-5.6	-5.7	-6.5	-5.7	-5.9
1NNL	-3.6	-4.9	-6.6	-7.8	-8.3	-4.5	-6.2	-5.9	-5.9	-5.9	-6	-6.1	-6.1	-7.3	-5.5	-5.6	-5.7	-6	-5.6	-5.8	-5.7	-6.5	-5.8	-5.3
1NZI	-4.2	-5.8	-7.6	-8.7	-9	-4.5	-3.8	-6	-6.4	-6.1	-6.1	-5.9	-6.3	-4.9	-6	-6.3	-6.1	-5.6	-6	-5.7	-5.7	-6.2	-5.3	-5.4

Table 9. Binding energy results from docking for the 24 compounds within Isomerases Class

	L1	L3	L4	L5	L6	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17	L18	L19	L20	L21	L22	L23	L24	L25	L26
1C9H	-4	-6.5	-9.4	-9.9	-5.2	-5.9	-6.6	-6.5	-6.5	-5.9	-6.1	-5.5	-5.8	-6.4	-6.2	-6.3	-6.6	-5.9	-6	-6.3	-6.2	-5.7	-5.8	-5.4
1EK6	-3.9	-8.9	-9.1	-10	-6.6	-6.2	-7	-6.8	-7	-7	-7.2	-7.4	-7.5	-6.3	-6.7	-6.8	-6.7	-6.7	-6.4	-6.6	-7.7	-6.4	-7.4	-6.3
1FW1	-3.9	-7.4	-9	-9.5	-6.2	-6.2	-5.9	-5.9	-5.9	-5.7	-6.3	-5.8	-7	-5.2	-5.5	-5.6	-5.3	-5.6	-5.5	-5.7	-6.6	-5.6	-6	-5.5
1IAT	-4.2	-7.6	-8.8	-8.9	-5.7	-5.5	-6	-6.2	-6.3	-6	-6.4	-6.2	-7.1	-5.7	-5.8	-6.1	-5.7	-5.6	-5.6	-5.9	-6.1	-5.6	-6.3	-5.9
1Q1C	-4	-7.5	-9.2	-9.8	-5.2	-5.3	-6.3	-6.3	-6.5	-6.1	-5.9	-6.7	-5.9	-6	-6.2	-6.3	-6.7	-6.2	-6.3	-5.9	-6.9	-6	-7.1	-6.3
1QOI	-3.6	-7	-7.9	-8	-5.1	-4.8	-5.1	-5.3	-5.5	-5.5	-5.4	-5.2	-6	-5	-5.4	-5.6	-5.1	-5.4	-5.2	-5.2	-5.6	-5	-5.7	-5.1
1SG4	-4.2	-8.2	-9.2	-9.8	-6.7	-6	-7.3	-8.1	-7.5	-8.5	-7.3	-7.8	-8.2	-6.9	-7.3	-7.4	-7	-7	-7.2	-6.7	-7.3	-6.3	-8.1	-6.5
1ZKC	-3.8	-7.1	-7.9	-8.3	-5.4	-6.6	-5.9	-6.8	-6.8	-5.6	-6	-6.4	-7.7	-5.7	-5.8	-5.9	-5.7	-6.2	-6.4	-5.7	-6.4	-5.3	-6.6	-5.4
1ZXM	-4.4	-7.4	-9.3	-10	-7.1	-6.5	-6.9	-7.1	-7.1	-6.8	-7.6	-6.8	-7.5	-6.4	-6.8	-6.5	-6.5	-6.4	-5.7	-6.6	-6.4	-6.1	-6.3	-6.3
2A2N	-4.1	-7.6	-8.8	-9.9	-5.2	-5.1	-6	-6	-6.2	-6.2	-6.1	-6.3	-6.6	-5.6	-6.1	-6.2	-5.3	-5.9	-5.6	-5.8	-6.4	-5.7	-7.1	-5.9
2CVD	-4	-7.8	-10	-9.9	-5.6	-5.2	-6.4	-6.6	-6.7	-6.5	-6.5	-6.5	-6.2	-6.1	-6.5	-6.6	-6.1	-6.2	-6.4	-5.9	-6.4	-6.1	-6.8	-5.8
2DHO	-4	-7.8	-9.2	-8.9	-4.8	-5.2	-5.8	-5.6	-5.7	-5.8	-5.8	-5.9	-6.7	-5.2	-5.5	-5.5	-5.3	-5.3	-5.6	-5.1	-5.6	-5.1	-6.2	-5.1
2ESL	-4.6	-9	-10	-8.8	-5.9	-5.9	-7.1	-7.3	-6.8	-7.4	-7.1	-7.3	-6.8	-6.7	-7.2	-7.3	-7	-6.9	-7.2	-7.2	-6.8	-6.7	-7.8	-7.1
2F6Q	-4.3	-7.3	-9.1	-10	-6.4	-6.8	-7.7	-7.9	-8.1	-7.7	-8.1	-6.3	-7.3	-7.2	-7.2	-7	-7.1	-7.8	-7.7	-7.1	-8.2	-6.7	-8.6	-7.5
2FUE	-4.1	-6.7	-7.8	-8.3	-4.9	-5.9	-5.9	-5.7	-5.4	-5.6	-6	-5.4	-6.2	-5.6	-5.5	-5.5	-5.8	-5.7	-5.7	-5.4	-6.1	-5.1	-6.1	-5.9
2G62	-3.8	-6.9	-8.1	-8.7	-5.1	-5.2	-5.3	-5.6	-5.6	-5.5	-6.1	-6.3	-6.4	-5.1	-5.2	-5.5	-5.6	-5.8	-5.8	-5.3	-6.4	-5.5	-6.5	-5.6
2H8L	-4.4	-9	-9.8	-9.9	-5.4	-6	-7.5	-7.8	-6.8	-7.3	-7.2	-7.3	-7	-7.1	-7.5	-7.4	-6.4	-7.2	-6.7	-7.1	-7.1	-6.7	-7.3	-7.1
2HE9	-4.4	-6.4	-8.1	-7.7	-5.6	-6.3	-6.3	-6.8	-6.2	-6.1	-6.3	-6.3	-7.3	-6.1	-6.3	-6.2	-6	-6.5	-6.4	-6.4	-6.3	-6	-7	-6.2
2HHJ	-4.2	-8	-8.9	-9.3	-5.3	-6.9	-7.8	-7.5	-9.1	-7.2	-7.5	-7.3	-7.3	-8.2	-7.3	-7.4	-8.1	-8	-8.6	-9	-8.7	-8.7	-8.9	-8.5
2HQ6	-3.9	-6.7	-8.1	-9	-4.9	-4.8	-5.6	-5.4	-5.6	-5.6	-5.5	-5.5	-5.6	-5.2	-5.3	-5.4	-5.4	-5.4	-5.1	-5.2	-6.1	-5.6	-6.3	-5.3
2JK2	-3.7	-7.2	-8.1	-8	-5.9	-5.3	-6.1	-6.2	-6	-5.9	-6.5	-6	-6.1	-5.8	-6	-6.1	-6.5	-6.9	-6.5	-6.2	-8	-6	-7.6	-6.3
2OK3	-4.2	-6.8	-7.7	-8.1	-5	-4.9	-5.4	-5.9	-6.3	-5.7	-5.4	-5.4	-5.9	-5.3	-5.7	-5.9	-5.3	-5.2	-5.8	-5.7	-5.6	-5.6	-6.5	-5.1
2PBC	-4.3	-8.4	-10	-11	-5.3	-5.6	-6.5	-6.1	-5.9	-6.4	-6.8	-6.1	-7	-5.9	-6	-6	-6	-5.8	-5.6	-5.7	-6.3	-5.7	-6.8	-5.5
2PNY	-4.5	-7	-8.4	-8.8	-4.4	-4.8	-5.4	-5.8	-5.3	-5.6	-5.8	-5.6	-5.6	-5.4	-5.7	-5.8	-5.1	-5.2	-5.2	-5.5	-6.3	-5.3	-6.3	-5.1
2PPN	-4.1	-7.1	-8.7	-9.7	-4.8	-5	-5.8	-5.2	-5.6	-5.6	-5.9	-5.5	-6	-5.4	-5.3	-5.4	-5.6	-5.2	-5.7	-5.7	-5.8	-5.3	-5.9	-5.2
2R99	-4.1	-6.9	-7.9	-8.8	-5.5	-6	-6	-5.7	-5.8	-6.1	-6.3	-6.2	-7.1	-5.3	-5.7	-5.8	-5.6	-5.3	-5.6	-5.6	-6	-5.7	-6	-5.2
2V9K	-3.6	-7.2	-8.7	-8.1	-5.2	-5.5	-5.6	-6.2	-5.7	-7	-5.9	-6.9	-6.5	-5.1	-5.5	-5.6	-5.6	-5.7	-5.5	-5.5	-6.6	-5.6	-6.8	-5.3

Table 9. Binding energy results from docking for the 24 compounds within Isomerases Class continued

	L1	L3	L4	L5	L6	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17	L18	L19	L20	L21	L22	L23	L24	L25	L26
2VRE	-4	-8	-9	-10	-5.3	-6.2	-7.1	-7.2	-7.3	-7.5	-7.2	-7.9	-7.5	-6.5	-7.1	-7.3	-6.3	-6.6	-6.5	-6.1	-7	-5.7	-7.6	-5.9
2WFI	-4.2	-7.6	-9.1	-8.5	-5.8	-5.2	-6.2	-6.7	-6.7	-7	-6.4	-7	-6.8	-6.1	-6.4	-6.4	-6.2	-6.6	-6.3	-5.8	-6.3	-5.7	-6.7	-6.1
2X25	-3.8	-6.8	-8.2	-8.8	-5.3	-5.6	-5.3	-5.7	-5.4	-5.8	-5.8	-5.8	-6.6	-5.1	-5.5	-5.6	-5.3	-5.5	-5.5	-5.4	-6.4	-5	-6.6	-5.1
2X7K	-4.1	-6.8	-8.6	-9.3	-5.3	-5.4	-5.9	-6	-6	-6.4	-5.9	-6.1	-7.1	-5.4	-5.8	-5.8	-5.5	-5.8	-5.7	-5.5	-5.9	-5.3	-6.9	-5.5
2XIJ	-4.2	-8.9	-10	-11	-5.7	-5.8	-7.3	-7.3	-6.9	-7.6	-7.1	-7.3	-7.5	-6.8	-7.2	-7.4	-6.6	-6.4	-6.5	-6.5	-6.9	-6.3	-7.1	-6.2
3B6H	-3.8	-8.3	-9.8	-10	-5.6	-5.5	-6.3	-6.2	-6.6	-7.6	-6.4	-6.2	-6.8	-5.8	-6.3	-6.4	-5.7	-5.7	-5.5	-5.6	-5.9	-5.7	-6.3	-5.9
3EY6	-3.9	-7.6	-8.5	-8.9	-4.5	-4.8	-5.6	-5.2	-5.2	-5.4	-5.7	-5.1	-6	-4.9	-5.2	-5.4	-5.3	-5.1	-5	-5.6	-6.2	-5.2	-5.9	-5.2
3I6C	-3.4	-7	-8.3	-8.8	-4.6	-5.2	-5.6	-5.5	-6.1	-5.6	-5.6	-5.8	-6.6	-5.4	-5.5	-5.6	-5.8	-5.6	-5.5	-5.6	-6.3	-5.2	-6.6	-5.1
3ICH	-3.6	-6.4	-7.5	-8.1	-5.3	-5.8	-5.5	-6	-5.7	-6	-5.6	-5.6	-7.2	-5.5	-5.8	-5.9	-5.5	-5.6	-5.6	-5.2	-6.2	-5.4	-6	-5.5
3IDV	-3.8	-7.7	-8.6	-9.2	-5.5	-5.3	-6.7	-6.4	-6.1	-6	-6.8	-6.2	-7.2	-6	-6.1	-5.9	-6.6	-6.1	-6.3	-5.9	-7.5	-6.6	-6.8	-6.2
3IJJ	-4.5	-7.9	-9.7	-9.3	-5.6	-7.9	-6.1	-6.7	-6.6	-6.2	-6.1	-6.6	-9.1	-6.3	-6.7	-6.8	-5.9	-5.9	-6.1	-5.6	-6.1	-5.6	-6.5	-5.6
3L6B	-4	-7.8	-8.1	-8.4	-6.1	-6.2	-5.9	-6.4	-6.4	-6.2	-6.1	-6.3	-6	-6	-6.5	-6.6	-5.9	-6.2	-6.3	-6.2	-6.4	-5.8	-6.7	-5.8
3MDF	-3.9	-7.3	-8.2	-8.3	-4.7	-4.4	-5.5	-5.6	-5.3	-5.8	-5.4	-5.4	-5.1	-4.9	-5.2	-5.2	-5.2	-5.5	-5.2	-5.3	-6.1	-5.1	-6.3	-5
3O22	-4	-7.8	-9.4	-9.1	-5.5	-7.1	-6.6	-6.8	-7.1	-6.7	-6.8	-7.2	-8	-6.6	-6.9	-7	-6.5	-6.5	-6.7	-6.6	-6.8	-6.2	-7.1	-6.3
3O5E	-4.1	-7.4	-8.9	-9.5	-5.1	-5.9	-6.1	-6	-5.8	-5.6	-5.8	-5.8	-6.9	-5.7	-5.8	-5.9	-5.7	-5.6	-5.5	-6.1	-6	-5.7	-6.2	-5.7
3O5Q	-4.5	-7.9	-9.7	-11	-4.9	-5.9	-6.2	-5.5	-5.5	-5.7	-6.3	-5.8	-6.6	-5.4	-5.3	-5.4	-5.7	-5.2	-5.4	-5.7	-5.8	-5.6	-6.3	-5.1
3OVP	-3.6	-7.7	-8.8	-8.8	-5	-4.2	-6.4	-6.4	-6	-6.5	-6.2	-6.4	-4.8	-5.5	-5.9	-6.1	-5.8	-6	-5.8	-6	-6.4	-5.6	-6.7	-6.4
3PH9	-4.1	-8	-8.7	-8.9	-4.7	-4.7	-5.3	-5.6	-5.7	-5.6	-5.7	-5.5	-6.2	-5	-5.1	-5.3	-5.1	-5.4	-5.3	-5	-5.8	-5.3	-6.4	-5.5
3RCG	-3.8	-6.7	-8.4	-9.4	-5.4	-5.3	-5.3	-5.4	-5.6	-5.4	-5.3	-5.2	-6.1	-5.1	-5.5	-5.6	-5	-5.6	-5.7	-5.4	-5.5	-5	-5.8	-5
3RMU	-4.1	-8	-9.3	-9.9	-5.4	-5.3	-7	-6.7	-6.3	-7.2	-6.9	-6.1	-6.2	-6.2	-6.5	-6.4	-6.7	-6.1	-6.1	-6.2	-6.8	-6.3	-6.5	-5.8
3TC5	-3.5	-6.6	-7.9	-8.5	-5.5	-5.5	-5.7	-5.6	-5.8	-5.7	-5.8	-5.8	-6.6	-5.1	-5.4	-5.5	-5.5	-5.3	-5.3	-5.5	-6.2	-5.4	-6.5	-5.5
3UI4	-4.1	-7.3	-9	-8.2	-4.8	-5	-5.7	-5.8	-5.5	-5.9	-5.8	-5.7	-6.3	-5.1	-5.3	-5.4	-5.2	-5.5	-5.3	-5.6	-6.1	-5.1	-6.2	-5.1
3UVT	-4.2	-8	-8.7	-8.6	-5.4	-5.4	-6	-6.3	-6.1	-6.2	-6.1	-6.1	-6.6	-5.8	-6.1	-6.2	-5.7	-6	-5.6	-6.4	-6.2	-5.7	-6.3	-5.9
4A35	-4.7	-7.7	-8.1	-8.4	-5.4	-5	-6.2	-6	-6.2	-6.2	-6.2	-6	-5.7	-5.6	-5.7	-5.7	-6.1	-5.5	-6.1	-5.9	-6.4	-5.4	-6.1	-5.7

Table 10. Binding energy results from docking for the 20 compounds within Ligases Class

	L1	L2	L4	L5	L7	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17	L18	L19	L22	L23	L24
1I2T	-3.09	-3.71	-7.57	-7.82	-3.59	-4.71	-4.49	-4.37	-5.15	-4.5	-4.48	-5.28	-5.29	-4.34	-4.51	-4.56	-4.48	-4.42	-5.64	-4.41
1I7K	-4.13	-5.62	-9.01	-9.11	-4.12	-5.6	-6.3	-6.54	-6.13	-6.14	-6.18	-6.14	-6.36	-5.6	-5.76	-5.87	-5.87	-5.49	-6.92	-5.4
1LB6	-3.78	-5.1	-8.38	-8.38	-4.14	-4.66	-5.22	-5.41	-5.21	-5.41	-5.78	-5.62	-5.76	-4.95	-5.08	-5.19	-5.29	-5.18	-5.61	-5.18
1LGP	-3.58	-5.4	-10.3	-11.3	-4.03	-5.86	-6.55	-6.7	-6.47	-6.91	-6.74	-6.89	-7.34	-5.87	-6.31	-6.45	-6.05	-6.33	-6.62	-5.84
1N3L	-4.03	-5.41	-10.4	-9.79	-4.59	-5.92	-6.62	-6.64	-6.56	-6.9	-5.85	-6.44	-7.36	-6.29	-6.69	-6.79	-6.08	-6.69	-6.61	-5.72
1T15	-3.66	-5.16	-9.12	-9.28	-4.53	-6.24	-5.49	-6.06	-5.76	-5.77	-5.74	-5.79	-7.58	-5.31	-5.63	-5.75	-5.68	-5.7	-6.18	-6.01
1Y02	-3.18	-4.52	-7.75	-7.78	-4.19	-5.28	-5.95	-5.67	-5.36	-5.76	-6.2	-6.03	-6.17	-5.1	-5.09	-5.12	-4.92	-5.35	-5.74	-5
1Y6L	-4.09	-5.38	-8.21	-8.69	-4.51	-5.99	-6.29	-5.85	-6.02	-6.02	-5.77	-6.1	-7.26	-5.94	-5.77	-6.31	-5.74	-5.64	-6.41	-5.68
1YH2	-3.18	-4.52	-7.75	-7.78	-4.19	-5.28	-5.95	-5.67	-5.36	-5.76	-6.2	-6.03	-6.17	-5.1	-5.09	-5.12	-4.92	-5.35	-5.74	-5
1ZDN	-4.09	-5.38	-8.21	-8.69	-4.51	-5.99	-6.29	-5.85	-6.02	-6.02	-5.77	-6.1	-7.26	-5.94	-5.77	-6.31	-5.74	-5.64	-6.41	-5.68
1ZUO	-4.25	-6.12	-11.2	-10.4	-4.51	-6.71	-7.6	-7.19	-6.98	-7.94	-7.74	-7.53	-7.94	-6.49	-7.06	-7.3	-7.1	-6.99	-7.63	-6.97
2A4D	-4.13	-5.09	-8.57	-8.31	-5.25	-5.01	-5.6	-5.19	-6.05	-5.63	-5.7	-5.53	-6.11	-4.91	-4.96	-5.03	-5.27	-5.22	-5.85	-4.86
2A7L	-4.13	-5.15	-9.95	-9.81	-4.23	-4.03	-5.54	-5.96	-5.88	-5.87	-5.39	-5.85	-5.15	-5.3	-5.42	-5.48	-5.7	-5.3	-5.92	-5.29
2AXI	-3.79	-6.3	-7.05	-6.92	-4.57	-7.09	-4.88	-6.64	-7.44	-5.74	-5.32	-5.5	-6.12	-6.96	-5.54	-5.14	-5.6	-7.2	-5.34	-4.8
2ESK	-3.85	-5.45	-8.1	-8.51	-4.52	-6.36	-6.53	-6.46	-6.59	-5.89	-5.62	-6.15	-7.02	-6.06	-6.07	-5.83	-5.68	-6.12	-6.18	-6.1
2F4W	-3.81	-5.28	-9.39	-9.51	-4.21	-5.77	-5.9	-6.17	-6.13	-5.88	-6.17	-6.1	-6.92	-5.71	-6.14	-6.3	-5.78	-6.04	-6.43	-5.94
2FAZ	-3.87	-4.34	-7.68	-7.82	-4.31	-5.24	-5.31	-5.42	-5.8	-5.79	-5.04	-5.48	-6.67	-5.06	-5.15	-5.23	-5.3	-5.18	-6.05	-5.22
2FZP	-4.31	-5.19	-8.62	-8.46	-4.46	-5.25	-6.08	-6.8	-6.22	-6.38	-6.62	-6.23	-6.51	-5.77	-5.95	-5.88	-6.51	-5.73	-6.84	-5.61
2I3H	-3.72	-5.81	-8.79	-9.63	-4.07	-5.18	-6.74	-6.16	-6.29	-6.78	-6.9	-6.41	-5.65	-6.06	-6.03	-6.17	-5.96	-5.77	-7.28	-5.73
2JKU	-3.04	-4.42	-8.07	-8.64	-3.67	-4.37	-5.16	-5.11	-5.06	-5.39	-5.9	-5.11	-4.88	-4.95	-5.16	-5.22	-4.97	-5.63	-5.73	-5.52
2NQ3	-3.48	-5.08	-8.35	-9.19	-4.09	-5.23	-6.2	-5.76	-6.13	-5.88	-6.37	-5.97	-6.01	-5.43	-5.5	-5.53	-5.67	-6.01	-6.31	-5.78
2NSQ	-4.04	-4.94	-9.09	-9.08	-4.77	-5.93	-6	-5.97	-6.9	-5.9	-5.46	-5.6	-6.67	-6.46	-6.2	-5.61	-6.87	-6.41	-6.89	-5.73
2NTE	-3.82	-5.71	-8.54	-9.26	-4.62	-5.72	-5.91	-6.32	-6.09	-7.14	-6.12	-6.98	-6.96	-5.51	-5.94	-6.03	-5.86	-5.8	-7.01	-5.74
2OOA	-3.89	-5.92	-11.6	-9.41	-4.25	-5.52	-6.52	-6.53	-6.58	-6.57	-6.81	-6.66	-6.39	-6.34	-6.3	-6.54	-6.28	-6.45	-6.91	-5.76
2PB7	-4.2	-5.66	-8.35	-8.37	-4.83	-5.76	-6.91	-6.62	-6.64	-6.64	-6.1	-6.7	-7.13	-6.08	-6.67	-6.9	-5.63	-6.91	-6.44	-5.97
2PIE	-4.53	-5.45	-7.96	-8.24	-4.74	-5.32	-5.54	-5.99	-5.76	-5.71	-5.93	-6.31	-7.05	-5.38	-5.47	-5.53	-5.73	-5.55	-5.88	-5.62
2POI	-3.25	-4.63	-7.29	-8.06	-3.98	-5.23	-5.32	-5.6	-5.33	-5.6	-5.33	-5.35	-5.91	-5.28	-5.53	-5.61	-5.04	-5.18	-5.78	-4.79
2UVL	-3.9	-5.82	-10.6	-8.32	-4.68	-6.3	-6.29	-6.1	-6.23	-6.36	-6.8	-6.09	-7.35	-5.74	-5.91	-6.04	-6.07	-5.83	-6.83	-5.73

Table10. Binding energy results from docking for the 20 compounds within Ligases Class continued

	L1	L2	L4	L5	L7	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17	L18	L19	L22	L23	L24
2V40	-4.38	-5.42	-8.98	-10.1	-4.7	-5.72	-6.56	-6.51	-6.19	-6.1	-6.49	-6.7	-6.47	-5.95	-6.02	-6.09	-5.75	-5.81	-6.14	-5.67
2XEU	-3.7	-4.68	-7.47	-7.65	-4.07	-5.21	-5.31	-5.64	-5.74	-5.5	-5.29	-5.91	-6.45	-4.88	-5.28	-5.35	-5.28	-5.06	-6.25	-4.95
2XOC	-3.93	-5.21	-8.85	-8.67	-4.78	-6.95	-7.13	-7.11	-6.92	-7.03	-7.39	-6.84	-7.76	-6.6	-6.99	-7.11	-6.22	-6.61	-6.83	-6.31
2XP0	-3.87	-5.48	-8.22	-8.78	-4.91	-6.7	-6.52	-6.99	-6.61	-6.95	-7.15	-6.14	-7.57	-6.39	-6.77	-6.9	-6.04	-6.28	-6.96	-6.07
2Y1N	-4.78	-6.19	-9.38	-9.2	-5.57	-6.36	-7.19	-6.96	-6.83	-6.44	-6.13	-6.63	-7.31	-6.59	-6.5	-5.92	-6.01	-6.47	-6.26	-6.61
2YVQ	-3.66	-5.08	-8.93	-9.43	-4.77	-5.76	-5.76	-6.44	-6.2	-5.93	-5.99	-6.27	-7.19	-5.61	-5.89	-5.97	-5.75	-5.76	-6.48	-5.02
2YVR	-3.85	-6.17	-8.51	-8.49	-5.46	-4.77	-6.47	-6.91	-6.8	-6.82	-6.29	-6.76	-6.54	-6.57	-6.48	-6.53	-7.1	-6.6	-7.06	-6.34
2Z6O	-4.55	-7.32	-10.3	-10.6	-4.97	-6.07	-7.34	-6.57	-6.44	-6.62	-6.66	-6.64	-7.17	-6	-6.31	-6.53	-6.52	-5.97	-7.11	-6.23
3ASL	-3.26	-3.8	-6.79	-7.08	-4.07	-4.37	-5.07	-5.04	-4.97	-4.99	-5.03	-5.17	-5.55	-4.72	-5.03	-5.21	-4.68	-5.1	-5.52	-4.8
3B08	-3.61	-5.11	-8.36	-8.37	-4.47	-5.28	-5.96	-5.95	-6.11	-6.02	-5.44	-5.65	-6.48	-5.27	-5.37	-5.43	-5.6	-5.39	-6.47	-5.03
3B76	-4.16	-5.72	-10.6	-10.1	-4.46	-5.29	-6.84	-6.52	-6.54	-6.62	-6.65	-6.45	-6.16	-6.13	-6.36	-6.44	-6.41	-6.25	-7.85	-6.38
3B7Y	-3.93	-5.19	-9.26	-9.67	-4.24	-6.29	-5.89	-5.87	-5.97	-6.49	-6.23	-6.14	-7.34	-5.65	-5.94	-5.9	-5.63	-6.11	-6.24	-5.99
3BI7	-3.88	-5.32	-8.41	-8.59	-4.89	-5.53	-6.48	-6.27	-6.33	-6.58	-6.63	-6.5	-6.69	-6.02	-6.4	-6.55	-6.01	-6.06	-6.41	-5.97
3BUX	-4.32	-5	-7.56	-8.37	-4.22	-6.19	-5.72	-5.56	-5.68	-5.66	-5.85	-5.7	-7.23	-5.61	-5.77	-5.83	-5.15	-5.36	-5.71	-5.37
3BZH	-4.21	-6.05	-7.89	-8.54	-4.63	-6.81	-7.08	-7.06	-6.73	-6.96	-7.06	-6.37	-7.42	-6.72	-6.99	-7.08	-6.47	-7.1	-6.76	-6.75
3C5E	-4.34	-5.77	-10.7	-9.9	-4.92	-5.83	-6.72	-6.7	-6.47	-6.84	-6.57	-7.23	-7.74	-5.9	-6.37	-6.49	-6.21	-6.78	-6.78	-6.83

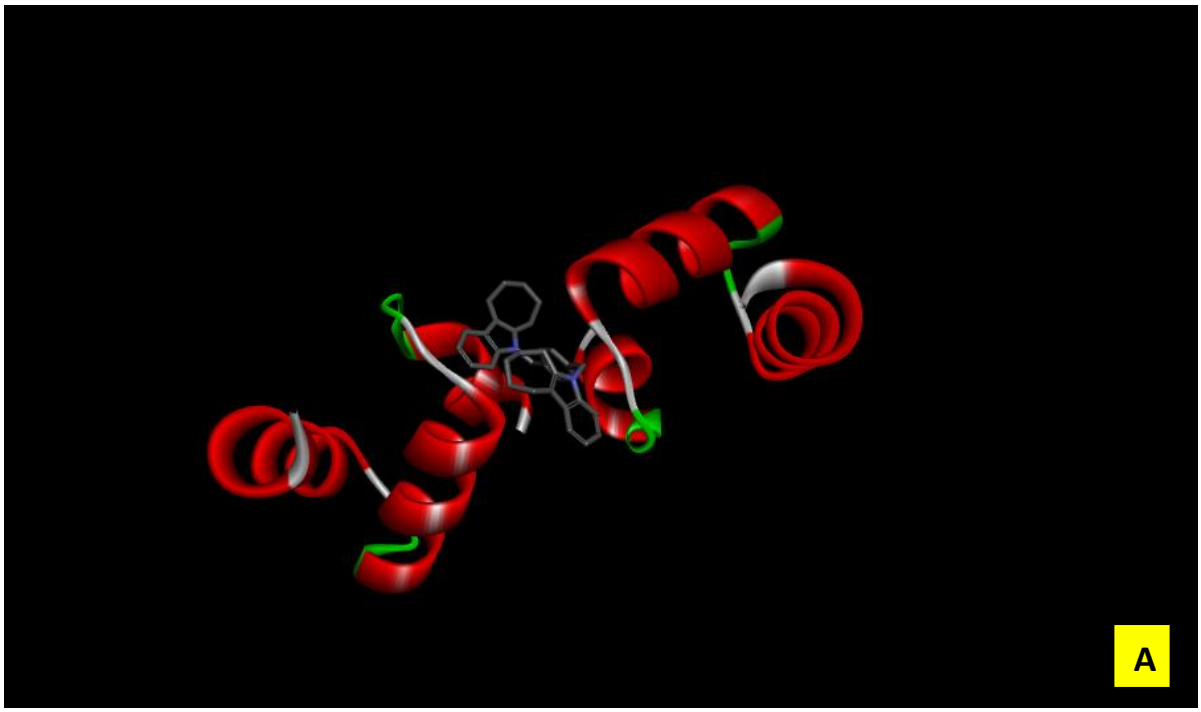
Table 11. Binding energy results from docking for the 23 compounds within Transferases Class

	L1	L2	L3	L4	L7	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17	L18	L19	L20	L21	L22	L23	L25	L26
1B4F	-4.12	-5.9	-7.12	-8.7	-4.95	-5.26	-6.02	-6.05	-6.4	-6.09	-5.75	-5.7	-5.92	-5.37	-5.87	-5.74	-5.52	-5.4	-5.69	-5.28	-6.13	-6.37	-5.39
1BLX	-4.36	-5.52	-8.24	-9.8	-5.15	-5.12	-5.97	-6.84	-6.02	-6.47	-6.62	-6.65	-6.78	-5.59	-5.97	-6	-5.75	-6.02	-5.55	-5.85	-6.29	-6.06	-5.45
1BTK	-4.08	-5.54	-7.01	-8.18	-4.42	-6.18	-5.71	-5.94	-5.86	-5.75	-6.2	-5.86	-6.98	-5.34	-5.49	-5.67	-5.26	-5.8	-6.03	-6.09	-5.83	-6.2	-6.09
1BX4	-4.25	-5.8	-8.38	-9.47	-4.9	-5.78	-5.92	-6.22	-6.02	-6.31	-6.64	-6.22	-6.63	-5.88	-6.32	-6.38	-6.04	-5.99	-6.02	-6.06	-6.42	-6.93	6.3
1BZY	-4.29	-5.99	-7.18	-7.78	-5.41	-5.25	-6.22	-7.14	-5.98	-5.39	-5.62	-6.47	-6.22	-6.19	-6.82	-6.97	-6.33	-6.18	-6.62	-6.29	-7.05	-7.07	-6.82
1CB0	-4.27	-5.08	-7.89	-8.7	-4.5	-6.17	-6.19	-7.19	-6.11	-6.28	-5.93	-5.87	-7.62	-6.34	-6.38	-6.57	-6.64	-6.38	-6	-6.43	-6.57	-6.16	-12.5
1CZA	-4.13	-5.78	-8.61	-9.08	-4.71	-5.7	-6.15	-6.54	-6.68	-6.64	-6.5	-6.92	-6.83	-6.47	-6.47	-6.63	-7.35	-6.38	-4.88	-4.7	-5.08	-5.03	-4.07
1E8Y	-4.38	-6.67	-8.48	-9.83	-5.45	-6.26	-7.79	-6.77	-6.81	-6.75	-7.84	-6.67	-6.5	-6.16	-6.56	-6.69	-7.21	-6.07	-5.37	-5.05	-5.65	-6.04	-8.06
1EH6	-4.58	-5.98	-7.75	-9.85	-5.29	-6.82	-6.33	-6.21	-6.24	-6.73	-6.28	-6.83	-7.58	-6.02	-6.19	-6.22	-6.43	-6.13	-6.01	-6.64	-6.53	-6.71	-6.74
1EX0	-4.73	-6.14	-9.65	-11.2	-4.74	-4.72	-7.07	-8.01	-7.47	-7.13	-7.37	-8.29	-6.53	-7.08	-7.57	-7.5	-6.49	-7.25	-5.05	-5.95	-5.95	-6.15	-5.34
1FGK	-4.29	-6.4	-9.04	-10.4	-5.46	-5.42	-6.57	-6.66	-6.43	-6.84	-6.77	-6.51	-7.17	-6.08	-6.28	-6.41	-6.11	-6.26	-5.47	-5.42	-5.47	-5.62	-5.16
1FMK	-4.2	-5.97	-8.32	-9.69	-4.58	-5.68	-6.95	-7.05	-6.9	-6.95	-7.55	-7.14	-6.65	-6.45	-6.92	-7.04	-6.27	-6.41	-6.32	-6.71	-6.67	-6.81	-5.88
1FW1	-3.89	-5.44	-7.3	-8.92	-5.11	-6.24	-5.92	-5.85	-5.98	-5.74	-6.25	-5.77	-6.97	-5.22	-5.49	-5.61	-5.3	-5.61	-5.44	-5.68	-6.14	-6.17	-5.21
1G3M	-4.54	-6.06	-6.69	-7.68	-5.06	-7.56	-8.02	-8.31	-8.24	-8.1	-8.23	-8.59	-9.69	-7.47	-7.97	-8.13	-7.57	-7.19	-7.39	-7.12	-7.72	-7.9	-6.88
1G55	-4.13	-5.78	-9.1	-9.68	-4.51	-5.18	-6.1	-6.52	-6.38	-6.39	-6.44	-6.47	-6.64	-6.11	-6.43	-6.47	-6.44	-6.24	-6.43	-5.85	-6.63	-5.4	-5.9
1GZ8	-4.67	-5.55	-8.31	-9.25	-5.08	-6.09	-6.43	-6.53	-6.72	-6.12	-6.78	-6.41	-7.11	-6.26	-6.54	-6.61	-6.48	-6.67	-5.57	-6.34	-6.33	-6.6	-6.06
1HE7	-4.01	-5.92	-7.27	-8.8	-4.59	-5.62	-6.02	-6.5	-6.79	-6.28	-6.49	-6.99	-6.54	-6.2	-6.53	-6.68	-6.09	-6.24	-6.82	-5.74	-6.84	-6.8	-5.8
1HML	-3.85	-5.14	-7.4	-8.38	-3.93	-4.34	-5.69	-5.68	-5.24	-5.78	-5.54	-5.39	-5.08	-5.46	-5.34	-5.29	-5.79	-5.96	-6.2	-5.07	-6.42	-6.46	-5.09
1I1N	-4.6	-6.07	-7.34	-8.64	-4.66	-5.49	-7.88	-6.82	-6.7	-6.86	-6.78	-7.2	-5.95	-6.29	-6.66	-6.66	-7.21	-6.5	-6.76	-6.12	-6.88	-6.73	-6.03
1J1B	-4.72	-6.19	-8.72	-9.33	-5.18	-6.8	-6.57	-7.15	-6.75	-7.53	-6.25	-7.09	-8.43	-6.16	-6.56	-6.71	-6.16	-6.16	-6.71	-7.62	-6.61	-6.42	-6.19
1J99	-3.9	-6.13	-8.74	-10.1	-4.91	-6.24	-6.89	-6.93	-7.28	-7.08	-6.57	-7.2	-7.42	-6.53	-6.85	-7.01	-6.13	-6.07	-6.22	-6.16	-10.6	-7.01	-5.2
1JDW	-3.94	-5.57	-7.51	-8.24	-5.03	-5.52	-5.74	-6.18	-5.81	-6.14	-5.72	-5.89	-6.16	-5.52	-5.83	-5.7	-5.63	-5.73	-5.05	-5.47	-6.78	-6.32	-5.29
1JQE	-4.15	-5.89	-9	-11.3	-5.01	-4.77	-6.99	-7.28	-7.15	-7.63	-7.38	-7.69	-6.72	-6.55	-7.08	-7.24	-6.65	-7.07	-6.04	-6.79	-7.93	-6.2	-4.2
1JV1	-4.15	-6.45	-8.79	-10.2	-5.23	-6.63	-7.53	-6.98	-6.95	-6.78	-6.73	-7.33	-8.25	-6.69	-6.64	-6.82	-7.02	-6.58	-5.85	-7.3	-7.14	-6.44	-4.2
1K04	-3.04	-4.36	-7.24	-8.65	-3.96	-4.82	-5.28	-5.17	-5.42	-5.5	-5.49	-5.81	-5.73	-5.12	-5.3	-5.34	-4.92	-4.9	-5.78	-4.95	-5.79	-5.7	-4.67
1K3Y	-4.3	-5.65	-9.74	-11.3	-5.26	-5.74	-6.5	-6.68	-6.63	-7.03	-6.61	-7.17	-7.28	-6.09	-6.57	-6.81	-6.17	-5.87	-7.28	-6.08	-6.52	-5.3	-5.65
1KGD	-4.06	-4.94	-7.14	-8.22	-4.68	-5.62	-5.8	-5.67	-5.77	-5.69	-5.83	-5.72	-6.36	-5.18	-5.44	-5.62	-5.62	-5.43	-5.74	-5.64	-6.11	-6.55	-5.54

Table 11. Binding energy results from docking for the 23 compounds within Transferases Class continued

	L1	L2	L3	L4	L7	L8	L9	L10	L11	L12	L13	L14	L15	L16	L17	L18	L19	L20	L21	L22	L23	L25	L26
1KWA	-3.94	-5.03	-6.94	-8.37	-4.18	-6.21	-5.8	-5.99	-6.12	-6.21	-6.03	-6.02	-7.49	-5.43	-5.58	-5.69	-5.49	-5.87	-5.78	-5.64	-6.47	-6.69	-5.35
1LS6	-4.4	-7	-11.8	-9.85	-4.97	-7.69	-7.86	-8.15	-7.88	-7.07	-8.1	-8.83	-9.61	-7.25	-7.88	-8.05	-7.32	-7.52	-5.69	-7.31	-7.49	-8.33	-7.34
1M9Z	-3.73	-4.78	-7.21	-8.64	-4.91	-4.86	-5.8	-5.52	-6.37	-5.8	-6.17	-6.28	-5.61	-5.49	-5.28	-5.2	-5.59	-5.74	-6.11	-5.62	-6.77	-6.88	-5.44
1MEO	-3.63	-4.54	-7.43	-8.15	-4.19	-5.17	-5.47	-5.67	-5.98	-5.75	-5.36	-5.97	-6.68	-5.29	-5.35	-5.6	-5.16	-5.38	-6.37	-5.73	-5.72	-5.97	-5.5
1MFG	-3.49	-5.73	-6.68	-7.75	-4.9	-5.75	-6.11	-6.64	-6.21	-5.94	-6.08	-6.55	-7.32	-5.82	-6.32	-6.48	-5.63	-5.72	-7.23	-5.64	-6.16	-6.15	-5.5
1MP8	-4.65	-5.21	-8.09	-8.24	-4.37	-5.43	-5.95	-5.9	-6.18	-5.81	-6.3	-6.03	-6.84	-5.4	-5.89	-6.01	-5.52	-5.88	-5.4	-5.79	-6.76	-5.93	-4.49
1MQ4	-4.47	-5.58	-8	-9.12	-4.76	-6.54	-6.54	-6.35	-6.56	-6.61	-6.62	-6.67	-8.04	-5.99	-6.21	-6.29	-6.33	-6.12	-6.2	-6.6	-6.1	-6.37	-5.96
1NB9	-4.16	-6.63	-9.69	-10.8	-5.56	-6.11	-7.38	-7.44	-7.43	-7.69	-8.66	-7.54	-7.38	-6.82	-6.81	-6.68	-6.92	-7.21	-5.29	-6.96	-7.86	-7.7	-6.92
1NM8	-5.07	-5.68	-8.48	-10.5	-4.49	-6.66	-7.67	-7.24	-7.18	-7.31	-6.73	-7.09	-7.69	-6.97	-7.1	-7.19	-7.09	-6.68	-6.74	-5.29	-5.96	-5.22	-4.47
1NN5	-3.64	-5.55	-9.55	-7.68	-4.88	-5.91	-6.63	-6.58	-6.88	-6.32	-7	-6.72	-6.71	-6.03	-6.19	-6.19	-6.19	-6.12	-5.24	-5.6	-7.19	-5.2	-5.77
1NTY	-4.13	-5.1	-6.8	-7.88	-3.9	-4.87	-5.47	-5.31	-5.6	-5.49	-5.38	-5.45	-5.77	-5.3	-5.44	-5.47	-5.57	-5.35	-6.12	-5.98	-8.86	-6.36	-6.1
1NUU	-4.42	-6.4	-8.62	-10.6	-5.3	-6.14	-6.85	-6.99	-6.89	-7.04	-7.31	-6.93	-7.63	-6.46	-6.61	-6.68	-6.6	-6.47	-6.26	-7.11	-6.7	-7.01	-7.32
1O4R	-3.67	-4.78	-6.38	-7.01	-4.65	-5.15	-5.07	-5.26	-5.19	-5.56	-5.44	-5.41	-6.6	-4.68	-4.97	-4.94	-4.98	-4.83	-6.4	-5.18	-5.68	-5.99	-5.16
1O6L	-4.89	-5.69	-8.36	-10.1	-5.06	-5.9	-6.08	-6.03	-6.18	-6.17	-6.17	-6.06	-6.63	-5.79	-5.92	-6	-6	-5.94	-6.31	-6.27	-6.5	-6.71	-5.46
1OTH	-3.67	-4.77	-6.43	-8.25	-5.69	-6.69	-6.51	-6.85	-6.47	-7.28	-7.03	-6.77	-8.06	-5.76	-5.44	-5.83	-6.02	-6.18	-5.02	-5.72	-11.7	-6.92	-5.33
1P4O	-4.71	-4.97	-7.51	-7.94	-4.81	-5.33	-6.59	-5.94	-6.03	-5.39	-6.11	-6.03	-6.39	-6.2	-6.04	-6.07	-6.59	-5.91	-5.87	-6.76	-6.67	-6.48	-13.8
1P5Z	-4.11	-5.48	-7.62	-9.11	-4.82	-5.41	-6.52	-6.25	-5.97	-6.37	-6.67	-6.32	-6.59	-5.94	-6.27	-6.4	-6.39	-5.64	-6.7	-6.1	-6.61	-6.42	-5.46
1PKX	-4.23	-5.63	-6.99	-8.63	-4.65	-6.12	-6.74	-6.78	-6.63	-6.16	-6.9	-5.79	-7.72	-5.94	-6.26	-6.38	-5.84	-6.52	-5.02	-5.45	-4.98	-6.82	-3.24
1QCF	-4.18	-6.14	-8.36	-8.94	-5.1	-5.77	-7.17	-7.45	-7.04	-6.6	-7.32	-7.02	-6.77	-6.41	-6.66	-6.74	-6.5	-6.04	-5.87	-6.2	-6.37	-6.2	-5.48
1QF8	-4.33	-6.88	-8.29	-10	-5.15	-6.47	-7.15	-7.03	-6.93	-7.47	-7.53	-7.29	-7.29	-6.78	-7.03	-7.19	-6.82	-6.49	-6.7	-6.16	-7.03	-6.1	-6.13

For each class of proteins the best binding poses with the lowest binding energy values were shown in figures 4, 5, 6, 7 and 8. These figures were created by using the visualization tool Discovery Studio software. In all figures there are two parts; in the upper part protein-ligand complexes at the best binding positions were depicted and in the lower part only the aminoacids of the protein that involved in binding interactions were depicted. In the upper part of the figures helices were shown with red color, turns are colored in green, beta-sheets are depicted in blue color whereas the ligands were shown with gray color. Moreover, in the upper part secondary structure graphical representation was applied for the proteins whereas for the ligands line representation was applied. In addition to these, in the lower part of the figures line representation of the atoms were used for the parts of the protein that are in interaction with the ligand, and there the atoms were colored according to their atomic numbers such that carbons are gray, oxygens are red, nitrogens are blue, hydrogens are shown in white color generally. Furthermore, different colors are used for halogens, Br and Cl. Besides these, ligands were depicted by green color as a whole in the lower part of the figures.



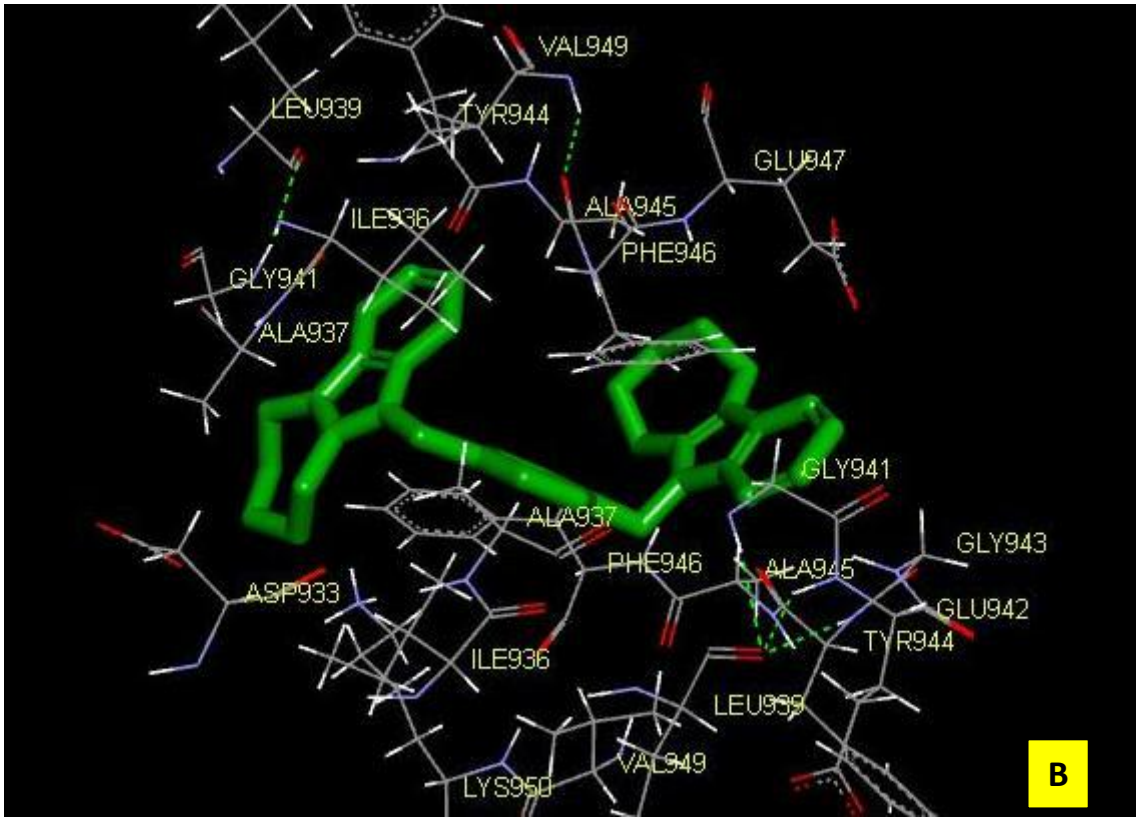


Figure 4. Binding interactions for top docking poses of L4 within 2OOA, (A: secondary structure represantation, B: in detail)

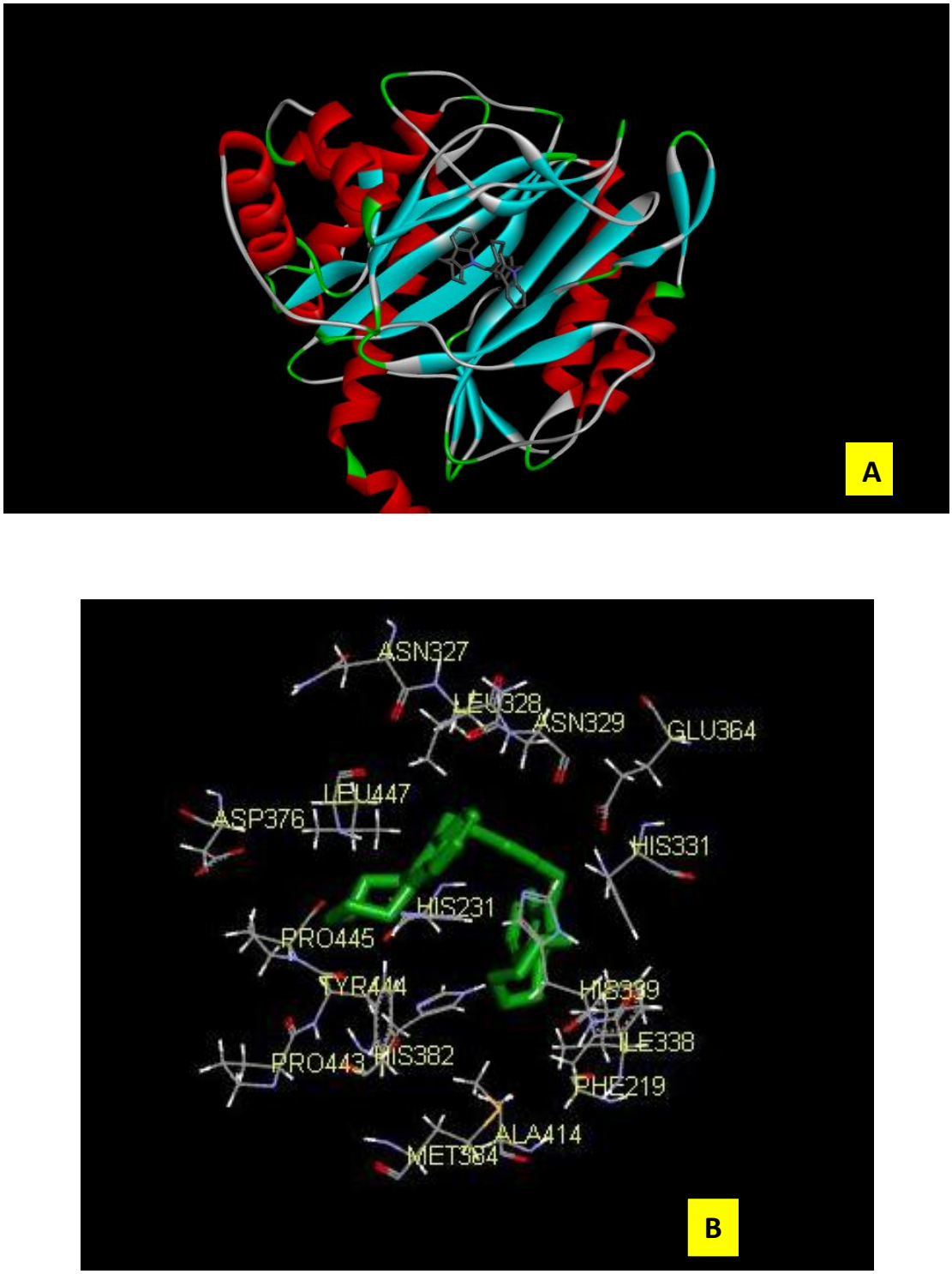


Figure 5. Binding interactions for top docking poses of L5 within1B6A, (A: secondary structure represantation, B: in detail)

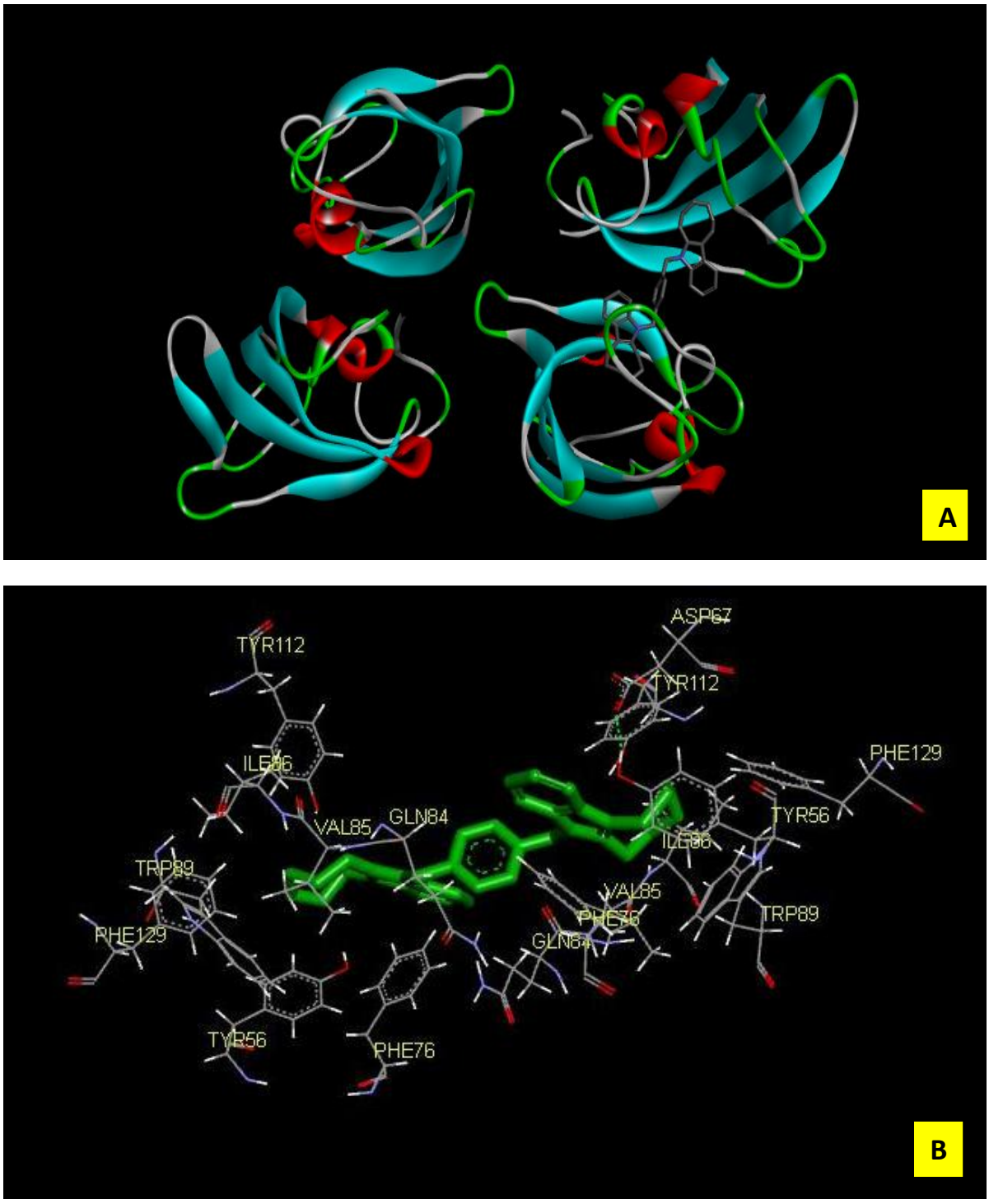


Figure 6. Binding interactions for top docking poses of L5 within 2PBC, (A: secondary structure represantation, B: in detail)

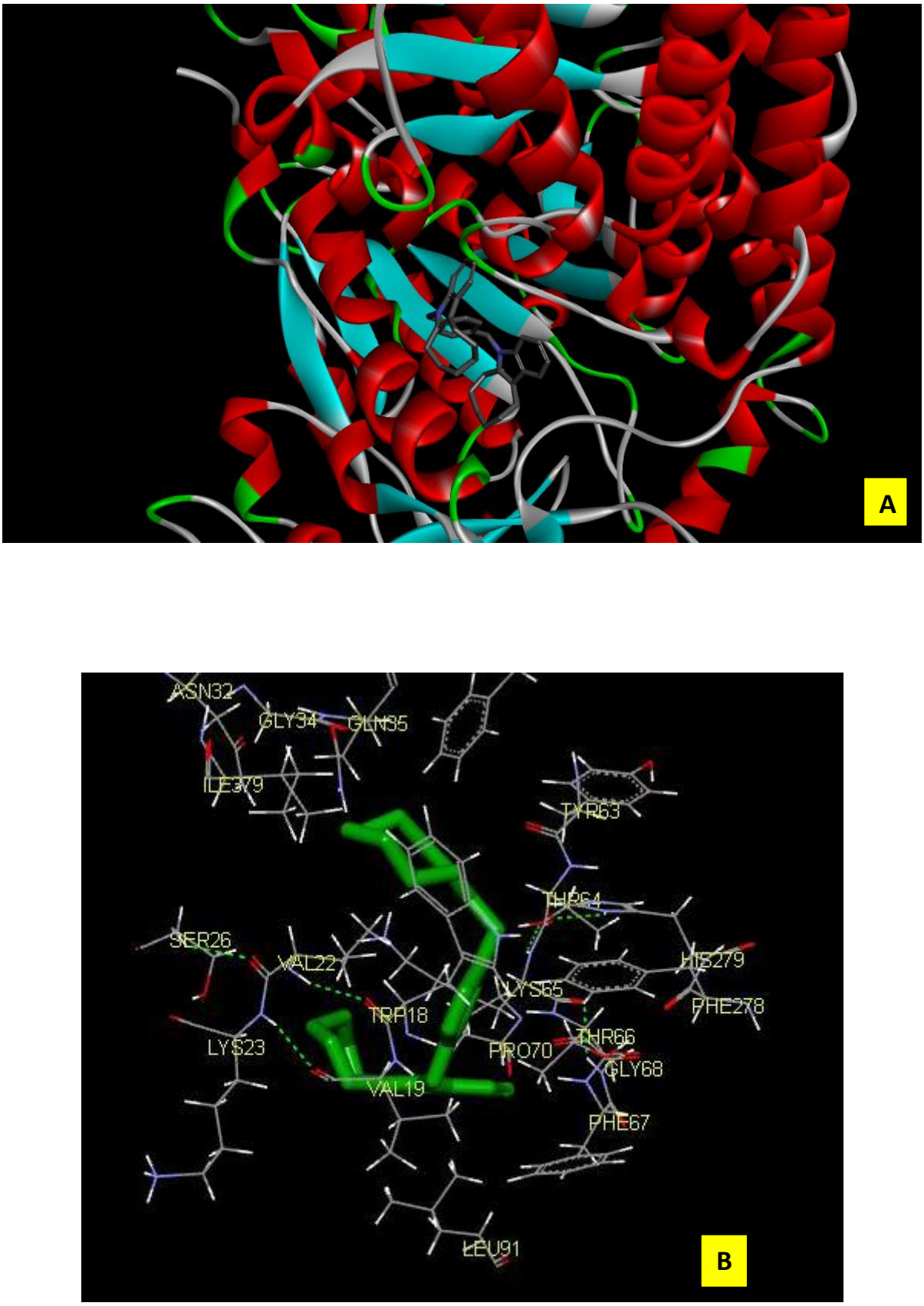
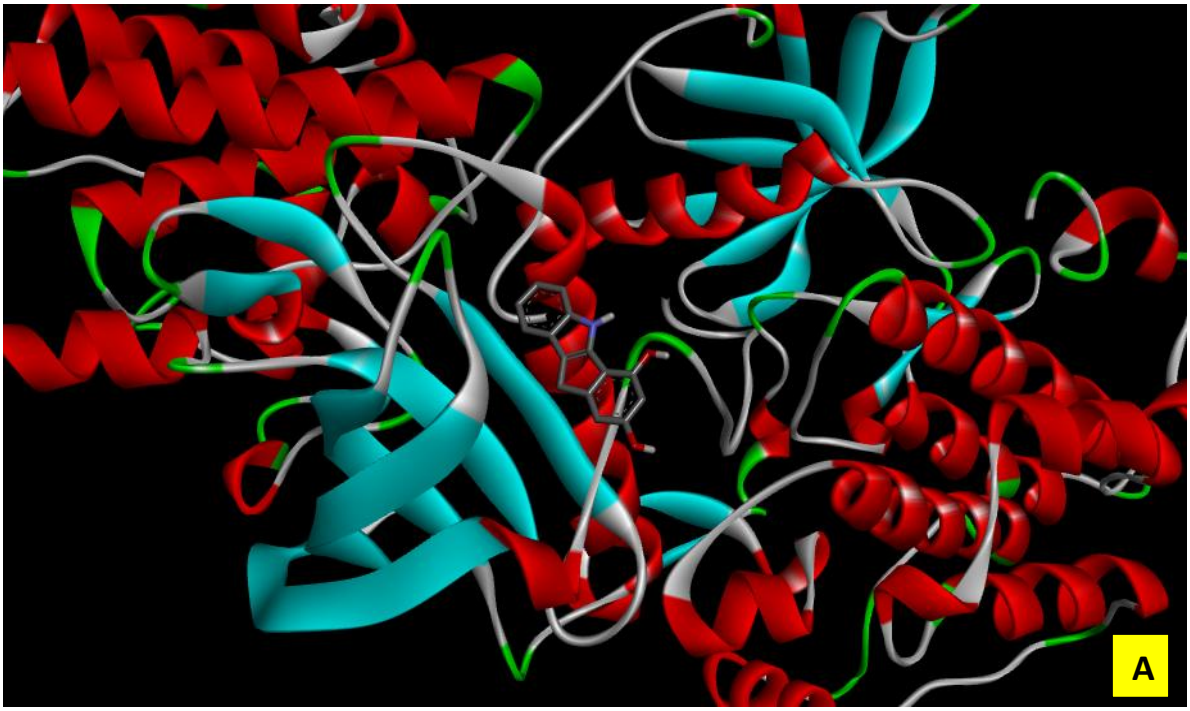


Figure 7. Binding interactions for top docking poses of L5 within 3FVS, (A: secondary structure represantation, B: in detail)



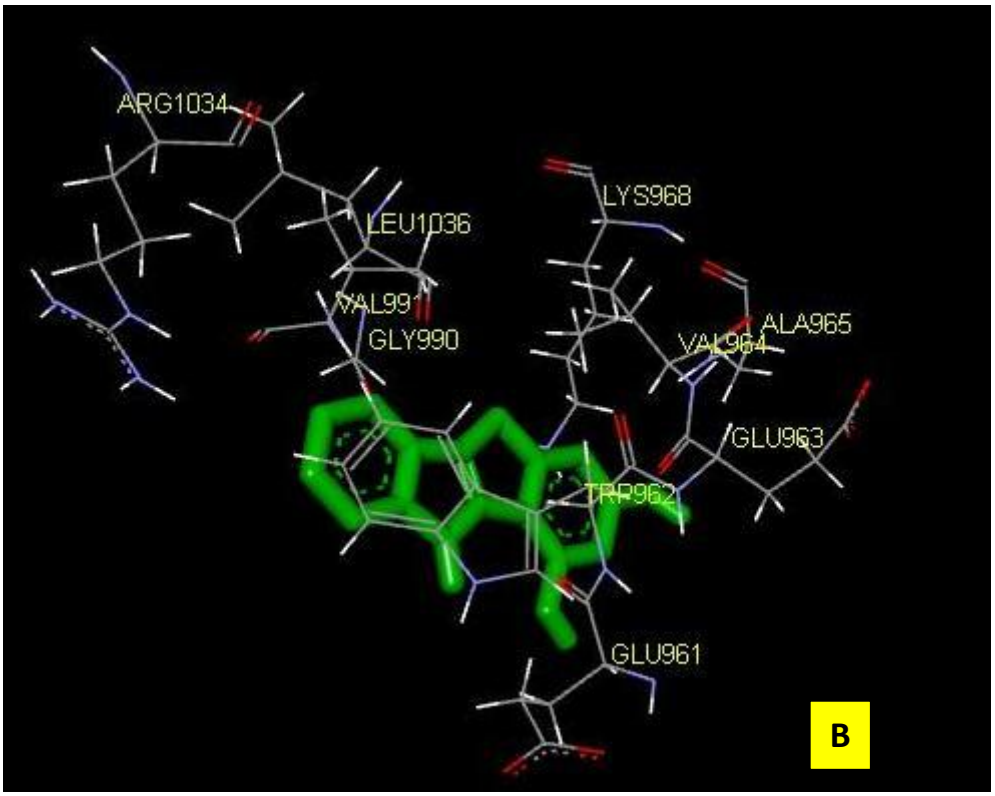


Figure 8. Binding interactions for top docking poses of L26 within 1P4O, (A: secondary structure represantation, B: in detail)

CONCLUSION

For all the proteins included in this thesis study, overall 4974 different binding energies and binding poses were obtained out of the docking results (Gibbs free energy results). Gibbs free energy results obtained from the docking analysis were tabulated for all of these 4974 protein-ligand pairs. Ligands considered here in this thesis had been studied before by Durdagi *et. al.* using GOLD [2,3] and then by us using Autodock. According to previously studies, GOLD Chemm Score of L5 with hCAI was -7.88 kcal/mol and binding sites were Ala121, Leu131, Ala135, Leu198, Trp5, Pro201, His200, Thr199, His94. In our recent study, Autodock score of L5 with hCAI is -9.13 kcal/mol and binding sites are Ala121, Leu131, Ala135, Leu198, Trp5, Pro201, His200, Thr199, His94, Ala132, Phe91, Asp72, Val143, Leu141. The result which calculated by AutoDock has shown approximately the same binding site and better binding energy score. And GOLD Chemm Score of L5 with hCAII was -11.61 kcal/mol and binding sites were Phe70, Ile91, Glu69, His119, Val135, Trp123, Gln92, Leu141, Val135, Val121, His122, Leu198, Pro202, Trp123 [2,3]. In our study, Autodock score of L5 with hCAII is -9.29 kcal/mol and binding sites are Pro247, Trp245, Asp243, Val242, Glu14, Pro13, Gly12, Tyr7, Gly16, Lys9, Gly8, Asn11, His10, Phe231, Glu239. The result which calculated by AutoDock has shown different binding sites and different but approximate binding energy scores. Another result, GOLD Chemm score of L3 with hCAI was -8.01 kcal/mol and binding sites were His94, Phe91, Leu141, Pro201, His64. The AutoDock score of L3 with hCAI is -6.62 kcal/mol and binding sites are Trp209, Thr199, Val143, His119, Leu198, His200, Ala121, His94, Pro202, Gln92, His67, Val62, Phe91, Leu131, Asn69, Ile60 [2,3]. The result which calculated by AutoDock has shown similar binding site and similar binding energy score with 1.39 kcal/mol difference. And GOLD Chemm score of L3 with hCAII was -11.62 kcal/mol and binding sites were Ln92, Phe131, Ile91, Trp123, Val121, Val135, Pro202, Ile91, Glu69, Phe70, Leu141, Leu57 [2,3]. The AutoDock score of L3 with hCAII -7.37 kcal/mol and binding sites are Gln92, His119, Val121, Val143, Trp209, Val207, Phe131, Val135, Leu198, Thr199, His94, His96, Thr200, His64, Pro201, Pro202, Trp5. The result which calculated by AutoDock has shown similar binding site and binding energy score with 4.25 kcal/mol difference**.** Corresponding to previous studies, GOLD Chemm Scores of L3, L5, L9, L10, L11 ,L12, L13, L15, L19, L22, L23, L24, L25, L26 with hCAI had been found -8.01, -7.88, -9.75, -8.54, -9.71, -8.46, -9.22, -8.7, -8.1, -8.2, -8.3, -7.9, -9.2 kcal mol^{-1} respectively [2,3]. And Autodock Scores of L3, L5, L9, L10, L11, L12, L13, L15, L19, L22, L23, L24, L25, L26 with hCAI are computed as

-6.62, -9.13, -6.17, -6.1, -6.43, -5.96, -6.68, -5.8, -5.55, -6.43, -5.46, -6.26, -5.93 kcal/mol respectively. In addition GOLD Chemm Scores of L3, L5, L9, L10, L11 ,L12, L13, L15, L19, L22, L23, L24, L25, L26 with hCAII had been found -11.62, -11.61, -10.2, -10.15, -9.98, -10.42, -10.48, -9.48, -11.45, -10.01, -8.72, -11.31, -10.5 kcal/mol respectively [2,3]. And Autodock Scores of L3, L5, L9, L10, L11 ,L12, L13, L15, L19, L22, L23, L24, L25, L26 with hCAII are calculated -7.37, -9.29, -5.92, -6.27, -6.12, -6.56, -6.81, -5.87, -5.86, -6.83, -5.67, -6.64, -5.31 kcal/mol respectively. The variations between the binding energy scores obtained from two different docking softwares, GOLD and AutoDock, might most probably be resulted from the differences in the force field parameters or from the differences in their algorithms. In any case, there is no huge difference observed between the results of these two different docking studies.

Considering our docking results, a few number of ligands are computed to have highly better binding energies within all classes. Because of the electrostatic properties of the atoms and fulfilment of the proper free volume requirement for the binding process, ligands L4, L5, L26 have the best binding affinities generally. From the results of this study, we get similar conclusions for each class. This is mainly because of the similarities on either structure or functional groups that exist in each class of proteins. They are supposed to be resulted from the aminoacid regions conserved during the evolutionary period in an inherited way.

By looking at the dominant red colored columns in the tables 7-11, a number of ligands have high binding properties with many proteins at the same time. According to these simultaneous high binding affinities of these ligands, such as L5, with high number of proteins, we may conclude such ligands may most probably have concurrent effects on different metabolic and illness mechanisms.

Following the docking analysis, cluster analysis can be performed to support the conclusions. In order to improve the results statistically, more runs and different analysis from the different Docking Programs may be used in a future work.

REFERENCES

1. http://www.rcsb.org/pdb/home/home.do
2. Durdagi,S. et. al. , European Journal of Medicinal Chemistry 49 (2012) 68-73
3. Durdagi,S. et. al., Bioorganic & Medicinal Chemistry 19 (2011) 1381–1389
4. IUBMB Nomenclature Committee Enzyme Nomenclature. Recommendations of the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology. http://www.chem.qmw.ac.uk/iubmb/enzyme/
5. http://autodock.scripps.edu/resources/adt
6. http://accelrys.com/products/discovery-studio/
7. A Medical Terminology Dictionary Published at the Dept. of Medical Oncology, University of Newcastle upon Tyne © Copyright 1997-2005 http://cancerweb.ncl.ac.uk/cgi-bin/omd
8. Prasad, N.K. 2011. Enzyme Technology-Pacemaker of Biotechnology. Asoke K. Ghosh, PHI Learning Private Limited, M-97, Connaught Circus, New Delhi-11001 and Printed by Mudrak, 30-A, Patparganj, Delhi-110091
9. E. M. Krovat, T. Steindl and T. Langer , Current Computer-Aided Drug Design 1(2005) 93-102
10. Morris, G. M., Goodsell, D. S., Halliday, R.S., Huey, R., Hart, W. E., Belew, R. K. and Olson, A. J., Automated Docking Using a Lamarckian Genetic Algorithm and and Empirical Binding Free Energy Function, J. Computational Chemistry, 19 (1998) 1639-16
11. Deo, R.C., Sonenberg, N.,Burley, S.K., Proc. Natl. Acad. Sci. USA 98(2001) 4414-4419
12. Lin, Y., Hwang, W.C., Basavappa, R.,J. Biol. Chem. 277(2002) 21913-21921
13. Ye, H., Arron, J.R., Lamothe, B., Cirilli, M., Kobayashi, T., Shevde, N.K., Segal, D., Dzivenu, O.K., Vologodskaia, M., Yim, M., Du, K., Singh, S., Pike, J.W., Darnay, B.G., Choi, Y., Wu, H., Nature 418(2002) 443-447
14. Stavridi, E.S., Huyen, Y., Loreto, I.R., Scolnick, D.M., Halazonetis, T.D., Pavletich, N.P., Jeffrey, P.D. Structure 10(2002) 891-899
15. Yang, X.-L., Skene,R.J., McRee, D.E., Schimmel, P., Proc. Natl. Acad. Sci. USA 99(2002) 15369-15374

16. Clapperton, J.A., Manke, I.A., Lowery, D.M., Ho, T., Haire, L.F., Yaffe, M.B., Smerdon, S.J., Nat. Struct. Mol. Biol. 11(2004) 512-518

17. Tibbetts, M.D., Shiozaki, E.N., Gu, L., McDonald, E.R., El-Deiry, W.S., Shi, Y., STRUCTURE 12(2004) 2257-2263

18. Sheng, Y., Hong, J.H., Doherty, R., Srikumar, T., Shloush, J., Avvakumov, G.V., Walker, J.R., Xue, S., Neculai, D., Wan, J.W., Kim, S.K., Arrowsmith, C.H., Raught, B., Dhe-Paganon, S., Mol Cell Proteomics 11(2012) 329-341

19. Sheng, Y., Hong, J.H., Doherty, R., Srikumar, T., Shloush, J., Avvakumov, G.V., Walker, J.R., Xue, S., Neculai, D., Wan, J.W., Kim, S.K., Arrowsmith, C.H., Raught, B., Dhe-Paganon, S., Mol Cell Proteomics 11(2012) 329-341

20. Sheng, Y., Hong, J.H., Doherty, R., Srikumar, T., Shloush, J., Avvakumov, G.V., Walker, J.R., Xue, S., Neculai, D., Wan, J.W., Kim, S.K., Arrowsmith, C.H., Raught, B., Dhe-Paganon, S., Mol Cell Proteomics 11(2012) 329-341

21. Sheng, Y., Hong, J.H., Doherty, R., Srikumar, T., Shloush, J., Avvakumov, G.V., Walker, J.R., Xue, S., Neculai, D., Wan, J.W., Kim, S.K., Arrowsmith, C.H., Raught, B., Dhe-Paganon, S., Mol Cell Proteomics 11(2012) 329-341

22. Sheng, Y., Hong, J.H., Doherty, R., Srikumar, T., Shloush, J., Avvakumov, G.V., Walker, J.R., Xue, S., Neculai, D., Wan, J.W., Kim, S.K., Arrowsmith, C.H., Raught, B., Dhe-Paganon, S., Mol Cell Proteomics 11(2012) 329-341

23. Sheng, Y., Hong, J.H., Doherty, R., Srikumar, T., Shloush, J., Avvakumov, G.V., Walker, J.R., Xue, S., Neculai, D., Wan, J.W., Kim, S.K., Arrowsmith, C.H., Raught, B., Dhe-Paganon, S., Mol Cell Proteomics 11(2012) 329-341

24. Fasan, R., Dias, R.L., Moehle, K., Zerbe, O., Obrecht, D., Mittl, P.R., Robinson, J.A., Chembiochem 7(2006) 515-526

25. Ozkan, E., Yu, H., Deisenhofer, J.,Proc.Natl.Acad.Sci.Usa 102(2005) 18890-18895

26. Sheng, Y., Hong, J.H., Doherty, R., Srikumar, T., Shloush, J., Avvakumov, G.V., Walker, J.R., Xue, S., Neculai, D., Wan, J.W., Kim, S.K., Arrowsmith, C.H., Raught, B., Dhe-Paganon, S.,Mol Cell Proteomics 11(2012) 329-341

27. Walker, J.R., Wybenga-Groot, L., Doherty, R.S., Finerty Jr., P.J., Newman, E., Mackenzie, F.M., Weigelt, J., Sundstrom, M., Arrowsmith, C., Edwards, A., Bochkarev, A., Dhe-Paganon, S., To be Published

28. Avvakumov, G.V., Walker, J.R., Xue, S., Finerty Jr., P.J., Mackenzie, F., Newman, E.M., Dhe-Paganon, S.,J. Biol. Chem. 281(2006) 38061-38070

29. Zobel, K., Wang, L., Varfolomeev, E., Franklin, M.C., Elliott, L.O., Wallweber, H.J., Okawa, D.C., Flygare, J.A., Vucic, D., Fairbrother, W.J., Deshayes, K.,Acs Chem.Biol. 1(2006) 525-533

30. Healy, S., Mcdonald, M.K., Wu, X., Yue, W.W., Kochan, G., Oppermann, U., Gravel, R. A., Biochemistry 49(2010) 4687-4694

31. Walker, J.R., Avvakumov, G.V., Xue, S., Butler-Cole, C., Finerty Jr., P.J., Weigelt, J., Sundstrom, M., Arrowsmith, C.H., Edwards, A.M., Bochkarev, A., Dhe-Paganon, S., To be Published

32. Walker, J.R., Avvakumov, G.V., Xue, S., Butler-Cole, C., Finerty Jr., P.J., Weigelt, J., Sundstrom, M., Arrowsmith, C.H., Edwards, A.M., Bochkarev, A., Dhe-Paganon, S., To be Published

33. Birrane, G., Varma, A.K., Soni, A., Ladias, J.A.,Biochemistry 46(2007) 7706-7712

34. Peschard, P., Kozlov, G., Lin, T., Mirza, I.A., Berghuis, A.M., Lipkowitz, S., Park, M., Gehring, K., Mol. Cell 27 (2007) 474-485

35. Delagoutte, B., Atmanene, C., Birck, C., Sanglier, S., Mantovani, R., Bonapace, I.M., Oudet, P., Van Dorsselaer, A., Moras, D., Samama, J.P., To be Published

36. Huen, M.S., Grant, R., Manke, I., Minn, K., Yu, X., Yaffe, M.B., Chen, J. Cell 131(2007) 901-914

37. Lu, M., Lin, S.C., Huang, Y., Kang, Y.J., Rich, R., Lo, Y.C., Myszka, D., Han, J., Wu, H. Mol. Cell 26(2007) 689-702

38. Herman, M.D., Moche, M., Flodin, S., Welin, M., Tresaugues, L., Johansson, I., Nilsson, M., Nordlund, P., Nyman, T., Acta Crystallogr., Sect. F 65(2009) 1091

39. Welin, M., Moche, M., Arrowsmith, C., Berglund, H., Busam, R., Collins, R., Dahlgren, L.G., Edwards, A., Flodin, S., Flores, A., Graslund, S., Hammarstrom, M., Hallberg, B.M., Holmberg-Schiavone, L., Johansson, I., Kallas, A., Karlberg, T., Kotenyova, T., Lehtio, L., Nyman, T., Ogg, D., Persson, C., Sagemark, J., Stenmark, P., Sundstrom, M., Thorsell, A.G., Van-Den-Berg, S., Weigelt, J., Nordlund, P., To be Published

40. Plechanovova, A., Jaffray, E.G., Mcmahon, S.A., Johnson, K.A., Navratilova, I., Naismith, J.H., Hay, R.T., Nat. Struct. Mol. Biol. 18(2011) 1052

41. Oberoi, J., Richards, M.W., Crumpler, S., Brown, N., Blagg, J., Bayliss, R.,J. Biol. Chem. 285 (2010) 39348

42. Oberoi, J., Richards, M.W., Crumpler, S., Brown, N., Blagg, J., Bayliss, R.,J. Biol. Chem. 285 (2010) 39348

43. Dou, H., Buetow, L., Hock, A., Sibbet, G.J., Vousden, K.H., Huang, D.T., Nat. Struct. Mol. Biol. 19 (2012) 184

44. Xie, Y., Ihsanawati, Kishishita, S., Murayama, K., Takemoto, C., Shirozu, M., Yokoyama, S., To be Published

45. Wang, H., Kishishita, S., Takemoto, C., Terada, T., Shirouzu, M., Yokoyama, S., To be Published

46. Mizushima, T., Tatsumi, K., Ozaki, Y., Kawakami, T., Suzuki, A., Ogasahara, K., Komatsu, M., Kominami, E., Tanaka, K., Yamane, T,Biochem. Biophys. Res. Commun. 362 (2007) 1079-1084

47. Arita, K., Isogai, S., Oda, T., Unoki, M., Sugita, K., Sekiyama, N., Kuwata, K., Hamamoto, R., Tochio, H., Sato, M., Ariyoshi, M., Shirakawa, M., Proc.Natl.Acad.Sci.USA 109(2012) 12950-12955

48. Sato, Y., Fujita, H., Yoshikawa, A., Yamashita, M., Yamagata, A., Kaiser, S.E., Iwai, K., Fukai, S., Proc.Natl.Acad.Sci.USA (2011)

49. Ugochukwu, E., Burgess-Brown, N., Berridge, G., Elkins, J., Bunkoczi, G., Pike, A.C.W., Sundstrom, M., Arrowsmith, C.H., Weigelt, J., Edwards, A.M., Gileadi, O., von Delft, F., Doyle, D., To be Published

50. Walker, J.R., Ruzanov, M., Butler-Cole, C., Weigelt, J., Arrowsmith, C.H., Edwards, A.M., Bochkarev, A., Dhe-Paganon, S., To be Published

51. Avvakumov, G.V., Walker, J.R., Xue, S., Li, Y., Duan, S., Bronner, C., Arrowsmith, C.H., Dhe-Paganon, S.,Nature 455(2008) 822-826

52. Ng, C., Jackson, R.A., Buschdorf, J.P., Sun, Q., Guy, G.R., Sivaraman, J. Embo J. 27 (2008) 804-816

53. Sheng, Y., Hong, J.H., Doherty, R., Srikumar, T., Shloush, J., Avvakumov, G.V., Walker, J.R., Xue, S., Neculai, D., Wan, J.W., Kim, S.K., Arrowsmith, C.H., Raught, B., Dhe-Paganon, S., Mol Cell Proteomics 11(2012) 329-341

54. Kochan, G., Pilka, E.S., von Delft, F., Oppermann, U., Yue, W.W. J. Mol. Biol. 388 (2009) 997-1008

55. Gamblin, S.J., Davies, G.J., Grimes, J.M., Jackson, R.M., Littlechild, J.A., Watson, H.C., J.Mol.Biol. 219(1991) 573-576

56. Kumar, V., Kannan, K.K. J.Mol.Biol. 241 (1994) 226- 232

57. Haapalainen, A.M., van Aalten, D.M., Merilainen, G., Jalonen, J.E., Pirila, P., Wierenga, R.K., Hiltunen, J.K., Glumoff, T., J.Mol.Biol. 313(2001) 1127-1138

58. Whittington, D.A., Waheed, A., Ulmasov, B., Shah, G.N., Grubb, J.H., Sly, W.S., Christianson, D.W., Proc.Natl.Acad.Sci.USA 98(2001) 9545-9550

59. Ekstrom, J.L., Tolbert, W.D., Xiong, H., Pegg, A.E., Ealick, S.E., Biochemistry 40(2001) 9495-9504

60. Mathews, M.A., Schubert, H.L., Whitby, F.G., Alexander, K.J., Schadick, K., Bergonia, H.A., Phillips, J.D., Hill, C.P., EMBO J. 20(2001) 5832-5839

61. Dunten, P., Belunis, C., Crowther, R., Hollfelder, K., Kammlott, U., Levin, W., Michel, H., Ramsey, G.B., Swain, A., Weber, D., Wertheimer, S.J., J.Mol.Biol. 316(2002) 257-264

62. Phillips, J.D., Whitby, F.G., Kushner, J.P., Hill, C.P., Embo J. 22(2003) 6225-6233

63. Vedadi, M., Walker, J.R., Sharma, S., Houston, S., Wasney, G., Loppnau, P., Oppermann, U., To be Published

64. Qin, J., Chai, G., Brewer, J.M., Lovelace, L.L., Lebioda, L., Biochemistry 45(2006) 793-800

65. Dupuy, J., Volbeda, A., Carpentier, P., Darnault, C., Moulis, J.M., Fontecilla-Camps, J.C., Structure 14(2006) 129-139

66. Ugochukwu, E., Dubinina, E., Kavanagh, K., Sundstrom, M., Weigelt, J., Edwards, A., Arrowsmith, C., von Delft, F., Oppermann, U., To be Published

67. Stenmark, P., Moche, M., Arrowsmith, C., Berglund, H., Busam, R., Collins, R., Edwards, A., Ericsson, U.B., Flodin, S., Flores, A., Graslund, S., Hammarstrom, M., Hallberg, B.M., Holmberg Schiavone, L., Hogbom, M., Johansson, I., Karlberg, T., Kosinska, U., Kotenyova, T., Magnusdottir, A., Nilsson, M.E., Nilsson-Ehle, P., Nyman, T., Ogg, D., Persson, C., Sagemark, J., Sundstrom, M., Uppenberg, J., Uppsten, M., Thorsell, A.G., Van Den Berg, S., Wallden, K., Weigelt, J., Nordlund, P., To be Published

68. Collins, R., Moche, M., Arrowsmith, C., Berglund, H., Busam, R., Dahlgren, L.G., Edwards, A., Flodin, S., Flores, A., Graslund, S., Hammarstrom, M., Hallberg, B.M., Johansson, I., Kallas, A., Karlberg, T., Kotenyova, T., Lehtio, L., Nordlund, P., Nyman, T., Ogg, D., Persson, C., Sagemark, J., Stenmark, P., Sundstrom, M., Thorsell, A.G., Tresaugues, L., Van Den Berg, S., Weigelt, J., Welin, M., Holmberg-Schiavone, L., To be Published

69. Georgiadis, M.M., Luo, M., Gaur, R.K., Delaplane, S., Li, X., Kelley, M.R., Mutat.Res. 643(2008) 54-63

70. Dufe, V.T., Ingner, D., Heby, O., Khomutov, A.R., Persson, L., Al-Karadaghi, S., Biochem.J. 405(2007) 261-268

71. Picaud, S.S., Muniz, J.R.C., Kramm, A., Pilka, E.S., Kochan, G., Oppermann, U., Yue, W.W., Proteins 76(2009) 507

72. Allerston, C.K., Von Delft, F., Gileadi, O., Plos One 8(2013) 57644

73. Vollmar, M., Krysztofinska, E., Chaikuad, A., Krojer, T., Cocking, R., Von Delft, F., Bountra, C., Arrowsmith, C.H., Weigelt, J., Edwards, A., Yue, W.W., Oppermann, U., To be Published

74. Lanzilotta, W.N., Medlock, A.E., Dailey, T.A., Dailey, H.A., To be published

75. Sun, Q., Collins, R., Huang, S., Holmberg-Schiavone, L., Anand, G.S., Tan, C.H., van-den-Berg, S., Deng, L.W., Moore, P.K., Karlberg, T., Sivaraman, J., J.Biol.Chem. 284(2009) 3076-3085

76. Di Fiore, A., Monti, S.M., Hilvo, M., Parkkila, S., Romano, V., Scaloni, A., Pedone, C., Scozzafava, A., Supuran, C.T., De Simone, G., Proteins 74(2008) 164-175

77. Tan, K., Hatzos, C., Freeman, L., Joachimiak, A., To be Published

78. Bale, S., Lopez, M.M., Makhatadze, G.I., Fang, Q., Pegg, A.E., Ealick, S.E., Biochemistry 47(2008) 13404-13417

79. Heinrich, D., Diederichsen, U., Rudolph, M.G., Chemistry 15(2009) 6619-6625

80. Pilka, E.S., Kochan, G., Krysztofinska, E., Muniz, J., Yue, W.W., Roos, A.K., von Delft, F., Arrowsmith, C.H., Weigelt, J., Edwards, A., Bountra, C., Oppermann, U., To be Published

81. Han, Q., Robinson, H., Cai, T., Tagle, D.A., Li, J., J.Med.Chem. 52(2009) 2786-2793

82. Deivanayagam, C.C., Carson, M., Thotakura, A., Narayana, S.V., Chodavarapu, R.S., Acta Crystallogr.,Sect.D, 56(2000) 266-271

83. Thoden, J.B., Wohlers, T.M., Fridovich-Keil, J.L., Holden, H.M., Biochemistry 39(2000) 5691-5701

84. Polekhina, G., Board, P.G., Blackburn, A.C., Parker, M.W., Biochemistry 40(2001) 1567-1576

85. ead, J., Pearce, J., Li, X., Muirhead, H., Chirgwin, J., Davies, C., J.Mol.Biol. 309(2001) 447-463

86. Wu, B., Li, P., Liu, Y., Lou, Z., Ding, Y., Shu, C., Ye, S., Bartlam, M., Shen, B., Rao, Z., Proc.Natl.Acad.Sci.USA 101(2004) 8348-8353

87. Reidt, U., Reuter, K., Achsel, T., Ingelfinger, D., Luehrmann, R., Ficner, R., J.Biol.Chem. 275(2000) 7439

88. Partanen, S.T., Novikov, D.K., Popov, A.N., Mursula, A.M., Hiltunen, J.K., Wierenga, R.K., J.Mol.Biol. 342(2004) 1197-1208

89. Walker, J.R., Davis, T., Newman, E.M., Mackenzie, F., Weigelt, J., Sundstrom, M., Arrowsmith, C., Edwards, A., Bochkarev, A., Dhe-Paganon, S., Structural Genomics Consortium (SGC), To be Published

90. Wei, H., Ruthenburg, A.J., Bechis, S.K., Verdine, G.L., J.Biol.Chem. 280(2005) 37041-37047

91. Davis, T.L., Walker, J.R., Ouyang, H., MacKenzie, F., Butler-Cole, C., Newman, E.M., Eisenmesser, E.Z., Dhe-Paganon, S., Febs J. 275(2008) 2283-2295

92. Aritake, K., Kado, Y., Inoue, T., Miyano, M., Urade, Y., J.Biol.Chem. 281(2006) 15277-15286

93. Zhang, C., Liu, L., Xu, H., Wei, Z., Wang, Y., Lin, Y., Gong, W., J.Mol.Biol. 366(2007) 1437-1446

94. Walker, J.R., Davis, T., Newman, E.M., Finerty Jr, P.J., Mackenzie, F., Weigelt, J., Sundstrom, M., Arrowsmith, C., Edwards, A., Bochkarev, A., Dhe-Paganon, S., To be Published

95. Turnbull, A., Lukacik, P., Shafqat, N., Smee, C., Berridge, G., Guo, K., von Delft, F., Weigelt, J., Sundstrom, M., Arrowsmith, C., Edwards, A., Gileadi, O., Oppermann, U., To be Published

96. Silvaggi, N.R., Zhang, C., Lu, Z., Dai, J., Dunaway-Mariano, D., Allen, K.N., J.Biol.Chem. 281(2006) 14918-14926

97. Magnusdottir, A., Stenmark, P., Flodin, S., Nyman, T., Hammarstrom, M., Ehn, M., Bakali H, M.A., Berglund, H., Nordlund, P., J.Biol.Chem. 281(2006) 22434-22438

98. Kozlov, G., Maattanen, P., Schrag, J.D., Pollock, S., Cygler, M., Nagar, B., Thomas, D.Y., Gehring, K., Structure 14(2006) 1331-1339

99. Davis, T., Walker, J.R., Newman, E.M., Mackenzie, F., Butler-Cole, C., Finerty Jr., P.J., Weigelt, J., Sundstrom, M., Arrowsmith, C.H., Edwards, A.M., Bochkarev, A., Dhe-Paganon, S., To be Published

100. Wang, Y., Liu, L., Wei, Z., Cheng, Z., Lin, Y., Gong, W., J.Biol.Chem. 281(2006) 39642-39648

101. Walker, J.R., Davis, T., Paramanathan, R., Newman, E.M., Finerty Jr., P.J., Mackenzie, F., Weigelt, J., Sundstrom, M., Arrowsmith, C.H., Edwards, A.M., Bochkarev, A., Dhe-Paganon, S., To be Published

102. Rodriguez-Almazan, C., Arreola, R., Rodriguez-Larrea, D., Aguirre-Lopez, B., De Gomez-Puyou, M.T., Perez-Montfort, R., Costas, M., Gomez-Puyou, A., Torres-Larios, A., J.Biol.Chem. 283(2008) 23254-23263

103. Chen, J., Chen, S., Huang, L., Zhao, X., Tan, J., Huang, C., Saiyin, H., Zhang, M., Zeng, X., Xi, J., Wan, B., Zhao, Y., Xia, Z., Jiang, H., Yi, Q., Liu, J.O., Yu, L., To be Published

104. Walker, J.R., Neculai, D., Davis, T., Butler-Cole, C., Sicheri, F., Weigelt, J., Sundstrom, M., Arrowsmith, C.H., Edwards, A.M., Bochkarev, A., Dhe-Paganon, S., To be Published

105. Walker, J.R., Davis, T., Butler-Cole, C., Weigelt, J., Sundstrom, M., Arrowsmith, C.H., Edwards, A.M., Bochkarev, A., Dhe-Paganon, S. To be Published

106. Szep, S., Park, S., Boder, E.T., Van Duyne, G.D., Saven, J.G., Proteins 74(2009) 603-611

107. Walker, J.R., Davis, T., Newman, E.M., Mackenzie, F., Sundstrom, M., Arrowsmith, C.H., Edwards, A.M., Bochkarev, A., Dhe-Paganon, S., To be Published

108. Mccleverty, C.J., Hornsby, M., Spraggon, G., Kreusch, A., J.Mol.Biol., 373(2007) 1243

109. Yue, W., Guo, K., Von Delft, F., Pilka, E., Murray, J., Roos, A., Kochan, G., Bountra, C., Arrowsmith, C., Wikstrom, M., Edwards, A., Oppermann, U., To be Published

110. Stegmann, C.M., Seeliger, D., Sheldrick, G.M., De Groot, B.L., Wahl, M.C., Angew.Chem.Int.Ed.Engl. 48(2009) 5207-5210

111. Lammers, M., Neumann, H., Chin, J.W., James, L.C., Nat.Chem.Biol. 6(2010) 331

112. Stegmann, C.M., Luehrmann, R., Wahl, M.C., Plos One 5(2010) 13

113. Froese, D.S., Kochan, G., Muniz, J., Wu, X., Gileadi, C., Ugochukwu, E., Krysztofinska, E., Gravel, R.A., Oppermann, U., Yue, W.W., J.Biol.Chem. 285(2010) 38204

114. Li, Y.-C., Chiang, C.-W., Yeh, H.-C., Hsu, P.-Y., Whitby, F.G., Wang, L.-H., Chan, N.-L., J.Biol.Chem. 283(2008) 2917-2926

115. Maestre-Martinez, M., Haupt, K., Edlich, F., Neumann, P., Parthier, C., Stubbs, M.T., Fischer, G., Luecke, C., J.Mol.Recognit. 24(2011) 23-34

116. Dong, L., Marakovits, J., Hou, X., Guo, C., Greasley, S., Dagostino, E., Ferre, R., Johnson, M.C., Kraynov, E., Thomson, J., Pathak, V., Murray, B.W., Bioorg.Med.Chem.Lett. 20(2010) 2210-2214

117. Kozlov, G., Bastos-Aristizabal, S., Maattanen, P., Rosenauer, A., Zheng, F., Killikelly, A., Trempe, J.F., Thomas, D.Y., Gehring, K., J.Biol.Chem. 285(2010) 35551-5557

118. Kozlov, G., Azeroual, S., Rosenauer, A., Maattanen, P., Denisov, A.Y., Thomas, D.Y., Gehring, K., J.Mol.Biol. 401(2010) 618-625

119. Cho, Y., Crichlow, G.V., Vermeire, J.J., Leng, L., Du, X., Hodsdon, M.E., Bucala, R., Cappello, M., Gross, M., Gaeta, F., Johnson, K., Lolis, E.J. Proc.Natl.Acad.Sci.USA 107 (2010) 11313- 11318

120. Smith, M.A., Mack, V., Ebneth, A., Moraes, I., Felicetti, B., Wood, M., Schonfeld, D., Mather, O., Cesura, A., Barker, J., J.Biol.Chem. 285(2010) 12873-12881

121. Hom, R.A., Chang, P.Y., Roy, S., Musselman, C.A., Glass, K.C., Selezneva, A.I., Gozani, O., Ismagilov, R.F., Cleary, M.L., Kutateladze, T.G., J.Mol.Biol. 400(2010) 145-154

122. Zhou, Y., Shaw, N., Li, Y., Zhao, Y., Zhang, R., Liu, Z.-J., To be Published

123. Bracher, A., Kozany, C., Thost, A.K., Hausch, F., Acta Crystallogr.,Sect.D 67(2011) 549-559

124. Bracher, A., Kozany, C., Thost, A.K., Hausch, F., Acta Crystallogr.,Sect.D 67(2011) 549-559

125. Liang, W.G., Ouyang, S.Y., Shaw, N., Joachimiak, A., Zhang, R.G., Liu, Z.J., Faseb J. 25(2011) 497-504

126. Nguyen, V.D., Ruddock, L.W., Salin, M., Wierenga, R.K., To be Published

127. Colliandre, L., Ahmed-Belkacem, H., Bessin, Y., Pawlotsky, J.M., Guichou, J.F., To be Published

128. Chaikuad, A., Krysztofinska, E., Froese, D.S., Yue, W.W., Vollmar, M., Muniz, J.R.C., von Delft, F., Weigelt, J., Arrowsmith, C.H., Edwards, A.M., Bountra, C., Oppermann, U., Structural Genomics Consortium (SGC), To be Published

129. Graber, M., Janczyk, W., Sperl, B., Elumalai, N., Kozany, C., Hausch, F., Holak, T.A., Berg, T., Acs Chem.Biol. 6(2011) 1008-1014

130. Mueller, J.W., Link, N.M., Matena, A., Hoppstock, L., Ruppel, A., Bayer, P., Blankenfeldt, W., J.Am.Chem.Soc. 133(2011) 20096-20099

131. Gulerez, I.E., Kozlov, G., Rosenauer, A., Gehring, K., Acta Crystallogr.,Sect.F 68(2012) 378-381

132. Muniz, J.R.C., Froese, D.S., Krojer, T., Vollmar, M., Canning, P., Oppermann, U., Arrowsmith, C.H., Edwards, A.M., Weigelt, J., Bountra, C., Von Delft, F., Yue, W.W., To be Published

133. Krojer, T., Kiyani, W., Goubin, S., Muniz, J.R.C., Filippakopoulos, P., Arrowsmith, C.H., Edwards, A., Bountra, C., von Delft, F., Oppermann, U., Zschocke, J., Yue, W.W., Structural Genomics Consortium (SGC), To be Published

134. Thanos, C.D., Goodwill, K.E., Bowie, J.U. Science 283(1999) 833-836

135. Brotherton, D.H., Dhanaraj, V., Wick, S., Brizuela, L., Domaille, P.J., Volyanik, E., Xu, X., Parisini, E., Smith, B.O., Archer, S.J., Serrano, M., Brenner, S.L., Blundell, T.L., Laue, E.D., Nature 395(1998) 244-250

136. Hyvonen, M., Saraste, M., EMBO J. 16(1997) 3396- 3404

137. Mathews, I.I., Erion, M.D., Ealick, S.E., Biochemistry 37(1998) 15607-15620

138. Shi, W., Li, C.M., Tyler, P.C., Furneaux, R.H., Grubmeyer, C., Schramm, V.L., Almo, S.C., Nat.Struct.Mol.Biol. 6(1999) 588-593

139. Appleby, T.C., Erion, M.D., Ealick, S.E., Structure Fold.Des. 7(1999) 629-641

140. Aleshin, A.E., Kirby, C., Liu, X., Bourenkov, G.P., Bartunik, H.D., Fromm, H.J., Honzatko, R.B., J.Mol.Biol. 296(2000) 1001-1015

141. Walker, E.H., Pacold, M.E., Perisic, O., Stephens, L., Hawkins, P.T., Whymann, M.P., Williams, R.L., Mol.Cell 6(2000) 909

142. Daniels, D.S., Mol, C.D., Arvai, A.S., Kanugula, S., Pegg, A.E., Tainer, J.A., EMBO J. 19(2000) 1719-1730

143. Garzon, R.J., Pratt, K.P., Bishop, P.D., Le Trong, I., Stenkamp, R.E., Teller, D.C., To be Published

144. Mohammadi, M., Schlessinger, J., Hubbard, S.R., Cell 86(1996) 577-587

145. Xu, W., Harrison, S.C., Eck, M.J., Nature 385(1997) 595-602

146. Polekhina, G., Board, P.G., Blackburn, A.C., Parker, M.W., Biochemistry 40(2001) 1567-1576

147. Shevtsov, S., Petrotchenko, E.V., Pedersen, L.C., Negishi, M., Environ.Health Perspect. 111(2003) 884-888

148. Dong, A., Yoder, J.A., Zhang, X., Zhou, L., Bestor, T.H., Cheng, X., Nucleic Acids Res. 29(2001) 439-448

149. Gibson, A.E., Arris, C.E., Bentley, J., Boyle, F.T., Curtin, N.J., Davies, T.G., Endicott, J.A., Golding, B.T., Grant, S., Griffin, R.J., Jewsbury, P., Johnson, L.N., Mesguiche, V., Newell, D.R., Noble, M.E., Tucker, J.A., Whitfield, H.J., J.Med.Chem. 45(2002) 3381

150. Robertson, A.G.S., Banfield, M.J., Allen, S.J., Dando, J.A., Mason, G.G.F., Tyler, S.J., Bennett, G.S., Brain, S.D., Clarke, A.R., Naylor, R.L., Wilcock, G.K., Brady, R.L., Dawbarn, D., Biochem.Biophys.Res.Commun. 282(2001) 131

151. Ren, J., Stuart, D.I., Acharya, K.R., J.Biol.Chem. 268(1993) 19292-19298

152. Smith, C.D., Carson, M., Friedman, A.M., Skinner, M.M., Delucas, L., Chantalat, L., Weise, L., Shirasawa, T., Chattopadhyay, D., Protein Sci. 11(2002) 625-635

153. Aoki, M., Yokota, T., Sugiura, I., Sasaki, C., Hasegawa, T., Okumura, C., Ishiguro, K., Kohno, T., Sugio, S., Matsuzaki, T., Acta Crystallogr.,Sect.D 60(2004) 439-446

154. Rehse, P.H., Zhou, M., Lin, S.X., Biochem.J. 364(2002) 165-171

155. Humm, A., Fritsche, E., Steinbacher, S., Huber, R., EMBO J. 16(1997) 3373-3385

156. Horton, J.R., Sawada, K., Nishibori, M., Zhang, X., Cheng, X., Structure 9(2001) 837-849

157. Peneff, C., Ferrari, P., Charrier, V., Taburet, Y., Monnier, C., Zamboni, V., Winter, J., Harnois, M., Fassy, F., Bourne, Y., EMBO J. 20(2001) 6191-6202

158. Arold, S.T., Hoellerer, M.K., Noble, M.E., Structure 10(2002) 319-327

159. Le Trong, I., Stenkamp, R.E., Ibarra, C., Atkins, W.M., Adman, E.T., Proteins 48 (2002) 618- 627

160. Li, Y., Spangenberg, O., Paarmann, I., Konrad, M., Lavie, A., J.Biol.Chem. 277(2002) 4159-4165

161. Daniels, D.L., Cohen, A.R., Anderson, J.M., Brunger, A.T., Nat.Struct.Mol.Biol. 5(1998) 317-325

162. Gamage, N.U., Duggleby, R.G., Barnett, A.C., Tresillian, M., Latham, C.F., Liyou, N.E., McManus, M.E., Martin, J.L., J.Biol.Chem. 278(2003) 7655-7662

163. Boesen, C.C., Radaev, S., Motyka, S.A., Patamawenu, A., Sun, P.D., Structure 10(2002) 913-919

164. Zhang, Y., Desharnais, J., Greasley, S.E., Beardsley, G.P., Boger, D.L., Wilson, I.A., Biochemistry 41(2002) 14206-14215

165. Birrane, G., Chung, J., Ladias, J.A., J.Biol.Chem. 278 (2003) 1399- 1402

166. Nowakowski, J., Cronin, C.N., McRee, D.E., Knuth, M.W., Nelson, C.G., Pavletich, N.P., Rodgers, J., Sang, B.-C., Scheibe, D.N., Swanson, R.V., Thompson, D.A., Structure 10(2002) 1659-1667

167. Nowakowski, J., Cronin, C.N., McRee, D.E., Knuth, M.W., Nelson, C., Pavletich, N.P., Rodgers, J., Sang, B.-C., Scheibe, D.N., Swanson, R.V., Thompson, D.A., Structure 10(2002) 1659- 1667

168. Karthikeyan, S., Zhou, Q., Mseeh, F., Grishin, N.V., Osterman, A.L., Zhang, H., Structure 11(2003) 265-273

169. Wu, D., Govindasamy, L., Lian, W., Gu, Y., Kukar, T., Agbandje-McKenna, M., McKenna, R., J.Biol.Chem. 278(2003) 13159-13165

170. Ostermann, N., Segura-Pena, D., Meier, C., Veit, T., Monnerjahn, M., Konrad, M., Lavie, A., Biochemistry 42(2003) 2568-2577

171. Skowronek, K.R., Guo, F., Zheng, Y., Nassar, N., J.Biol.Chem. 279(2004) 37895-37907

172. ZHANG, X., KURNASOV, O.V., KARTHIKEYAN, S., GRISHIN, N.V., OSTERMAN, A.L., ZHANG, H., J.Biol.Chem. 278(2003) 13503-13511

173. Lange, G., Lesuisse, D., Deprez, P., Schoot, B., Loenze, P., Benard, D., Marquette, J.P., Broto, P., Sarubbi, E., Mandine, E., J.Med.Chem. 46(2003) 5184-5195

174. Yang, J., Cron, P., Good, V.M., Thompson, V., Hemmings, B.A., Barford, D., Nat.Struct.Mol.Biol. 9(2002) 940

175. Shi, D., Morizono, H., Ha, Y., Aoyagi, M., Tuchman, M., Allewell, N.M., J.Biol.Chem. 273(1998) 34247-34254

176. Munshi, S., Hall, D.L., Kornienko, M., Darke, P.L., Kuo, L.C., Acta Crystallogr.,Sect.D 59(2003)1725-1730

177. Sabini, E., Ort, S., Monnerjahn, C., Konrad, M., Lavie, A., Nat.Struct.Mol.Biol. 10 (2003) 513-519

178. Wolan, D.W., Cheong, C.G., Greasley, S.E., Wilson, I.A., Biochemistry 43 (2004) 1171-1183

179. Schindler, T., Sicheri, F., Pico, A., Gazit, A., Levitzki, A., Kuriyan, J., Mol.Cell 3(1999) 639-648

180. Chantalat, L., Leroy, D., Filhol, O., Nueda, A., Benitez, M.J., Chambaz, E.M., Cochet, C., Dideberg, O., EMBO J. 18(1999) 2930-2940

181. Allaire, M., Li, Y., MacKenzie, R.E., Cygler, M., Structure 6(1998) 173-182

182. Das, A.K., Helps, N.R., Cohen, P.T., Barford, D., EMBO J. 15(1996) 6798-6809

183. Oinonen, C., Tikkanen, R., Rouvinen, J., Peltonen, L., Nat.Struct.Mol.Biol. 2(1995) 1102-1108

184. Garcia-Saez, I., Reverter, D., Vendrell, J., Aviles, F.X., Coll, M., EMBO J. 16(1997) 6906-6913

185. Liu, S., Widom, J., Kemp, C.W., Crews, C.M., Clardy, J., Science 282(1998) 1324-1327

186. Turk, D., Podobnik, M., Popovic, T., Katunuma, N., Bode, W., Huber, R., Turk, V., Biochemistry 34(1995) 4791-4797

187. Sivaraman, J., Nagler, D.K., Zhang, R., Menard, R., Cygler, M., J.Mol.Biol. 295(2000) 939-951

188. Reverter, D., Fernandez-Catalan, C., Baumgartner, R., Pfander, R., Huber, R., Bode, W., Vendrell, J., Holak, T.A., Aviles, F.X., Nat.Struct.Mol.Biol. 7(2000) 322-328

189. Rao, Z., Handford, P., Mayhew, M., Knott, V., Brownlee, G.G., Stuart, D., Cell 82(1995) 131-141

190. Gaboriaud, C., Rossi, V., Bally, I., Arlaud, G.J., Fontecilla-Camps, J.C., EMBO J. 19(2000) 1755-1765

191. Gaiser, F., Tan, S., Richmond, T.J., J.Mol.Biol. 302(2000) 1119-1127

192. Somoza, J.R., Zhan, H., Bowman, K.K., Yu, L., Mortara, K.D., Palmer, J.T., Clark, J.M., McGrath, M.E. Biochemistry. 39 (2000) 12543-12551

193. Lima, C.D., D'Amico, K.L., Naday, I., Rosenbaum, G., Westbrook, E.M., Hendrickson, W.A. Structure. 5(1997) 763-774

194. Devedjiev, Y., Dauter, Z., Kuznetsov, S.R., Jones, T.L., Derewenda, Z.S., Structure Fold.Des. 8 (2000) 1137-1146

195. Vallee, F., Karaveg, K., Herscovics, A., Moremen, K.W., Howell, P.L., J.Biol.Chem. 275 (2000) 41287-41298

196. Song, H., Hanlon, N., Brown, N.R., Noble, M.E., Johnson, L.N., Barford, D., Mol.Cell 7 (2001) 615-626

197. Swaminathan, G.J., Holloway, D.E., Veluraja, K., Acharya, K.R., Biochemistry 41 (2002) 3341-3352

198. Guarne, A., Junop, M.S., Yang, W., Embo J. 20 (2001) 5521

199. Wilmouth, R.C., Edman, K., Neutze, R., Wright, P.A., Clifton, I.J., Schneider, T.R., Schofield, C.J., Hajdu, J., Nat.Struct.Mol.Biol. 8 (2001) 689

200. Ackerman, S.J., Liu, L., Kwatia, M.A., Savage, M.P., Swaminathan, D.D.Leonidasg.J., Acharya, K.R., J.Biol.Chem. 277 (2002) 14859

201. Spurlino, J.C., Smallwood, A.M., Carlton, D.D., Banks, T.M., Vavra, K.J., Johnson, J.S., Cook, E.R., Falvo, J., Wahl, R.C., Pulvino, T.A., Wendoloski, J.J., Smith, D.L., Proteins 19 (1994) 98-109

202. Rao, F.V., Houston, D.R., Boot, R.G., Aerts, J.M.F.G., Sakuda, S., Van Aalten, D.M.F., J.Biol.Chem. 278 (2003) 20110

203. Moore, S.A., Sielecki, A.R., Chernaia, M.M., Tarasova, N.I., James, M.N., J.Mol.Biol. 247 (1995) 466-485

204. Natchus, M.G., Bookland, R.G., Laufersweiler, M.J., Pikul, S., Almstead, N.G., De, B., Janusz, M.J., Hsieh, L.C., Gu, F., Pokross, M.E., Patel, V.S., Garver, S.M., Peng, S.X., Branch, T.M., King, S.L., Baker, T.R., Foltz, D.J., Mieling, G.E., J.Med.Chem. 44 (2001) 1060-1071

205. Ye, Q., Rahman, M.N., Koschinsky, M.L., Jia, Z. Protein Sci. 10 (2001) 1124-1129

206. Gavuzzo, E., Pochetti, G., Mazza, F., Gallina, C., Gorini, B., D'Alessio, S., Pieper, M., Tschesche, H., Tucker, P.A., J.Med.Chem. 43 (2000) 3377-3385

207. Nitanai, Y., Satow, Y., Adachi, H., Tsujimoto, M. J.Mol.Biol. 321 (2002) 177-184

208. Cha, H., Kopetzki, E., Huber, R., Lanzendorfer, M., Brandstetter, H., J.Mol.Biol. 320 (2002) 1065-1079

209. Finnin, M.S., Donigian, J.R., Pavletich, N.P., Nat.Struct.Mol.Biol. 8(2001) 621-625

210. Harata, K., Abe, Y., Muraki, M., Proteins 30(1998) 232-243

211. Davies, D.R., Interthal, H., Champoux, J.J., Hol, W.G., Structure 10 (2002) 237-248

212. Abad, M.C., Arni, R.K., Grella, D.K., Castellino, F.J., Tulinsky, A., Geiger, J.H., J.Mol.Biol. 318 (2002) 1009-1017

213. Stec, B., Yamano, A., Whitlow, M., Teeter, M.M., Acta Crystallogr.Sect.D 53(1997) 169-178

214. Barbosa Pereira, P.J., Segura-Martin, S., Oliva, B., Ferrer-Orta, C., Aviles, F.X., Coll, M., Gomis-Ruth, F.X., Vendrell, J., J.Mol.Biol. 321 (2002) 537-547

215. Li, H., Ryan, T.J., Chave, K.J., Van Roey, P., J.Biol.Chem. 277 (2002) 24522-24529

216. Nam, H.J., Poy, F., Krueger, N.X., Saito, H., Frederick, C.A., Cell 97 (1999) 449-457

217. Smith, C.A., Anderson, B.F., Baker, H.M., Baker, E.N., Acta Crystallogr.,Sect.D 50 (1994) 302-316

218. Li, W., Srinivasula, S.M., Chai, J., Li, P., Wu, J.W., Zhang, Z., Alnemri, E.S., Shi, Y., Nat.Struct.Mol.Biol. 9 (2002) 436-441

219. Pan, Y.H., Yu, B.Z., Singer, A.G., Ghomashchi, F., Lambeau, G., Gelb, M.H., Jain, M.K., Bahnson, B.J., J.Biol.Chem. 277 (2002) 29086-29093

220. Bernett, M.J., Blaber, S.I., Scarisbrick, I.A., Dhanarajan, P., Thompson, S.M., Blaber, M., To be Published

221. Oganesyan, V., Oganesyan, N., Terzyan, S., Qu, D., Dauter, Z., Esmon, N.L., Esmon, C.T., J.Biol.Chem. 277 (2002) 24851-24854

222. Somoza, J.R., Palmer, J.T., Ho, J.D., J.Mol.Biol. 322 (2002) 559-568

223. Chowdhury, S., Sivaraman, J., Wang, J., Devanathan, G., Lachance, P., Qi, H., Menard, R., Lefebvre, J., Konishi, Y., Cygler, M., Sulea, T., Purisima, E.O., J.Med.Chem. 45(2002) 5321-5329

224. Arreola, R., Valderrama, B., Morante, M.L., Horjales, E., Febs Lett. 551 (2003) 63- 70

225. Peeraer, Y., Rabijns, A., Verboven, C., Collet, J.F., Van Schaftingen, E., De Ranter, C., Acta Crystallogr.,Sect.D 59 (2003) 971-977

226. Gregory, L.A., Thielens, N.M., Arlaud, G.J., Fontecilla-Camps, J.C., Gaboriaud, C., J.Biol.Chem. 278 (2003) 32157-32164

227. http://nbcr-222.ucsd.edu/pdb2pqr_1.8/

228. A. Doi , S. Suzuki , K. Koyamada and S. Sannakari- "Vortex Flow Visualization Using Tetrahedral Cell Subdivision - An Improved Method and Its Effectiveness -", *J. of the Institute of Image Electronics Engineers of Japan*, 26 (1997) 333-340

229. http://www.uniprot.org/uniprot/P26885

230. http://www.uniprot.org/uniprot/P50579