Sudan University of Science and Technology
College of Post Graduate Studies

Design and Molecular modeling of some phthalazinone derivatives as PARP2 Inhibitors

التصميم والنمذجه الجزيئيه لبعض مشتقات الفثالازينونات كمثبطات ل (PARP2)

A Thesis Submitted in partial fulfillment of the Requirements for the Degree of M. Sc. Chemistry

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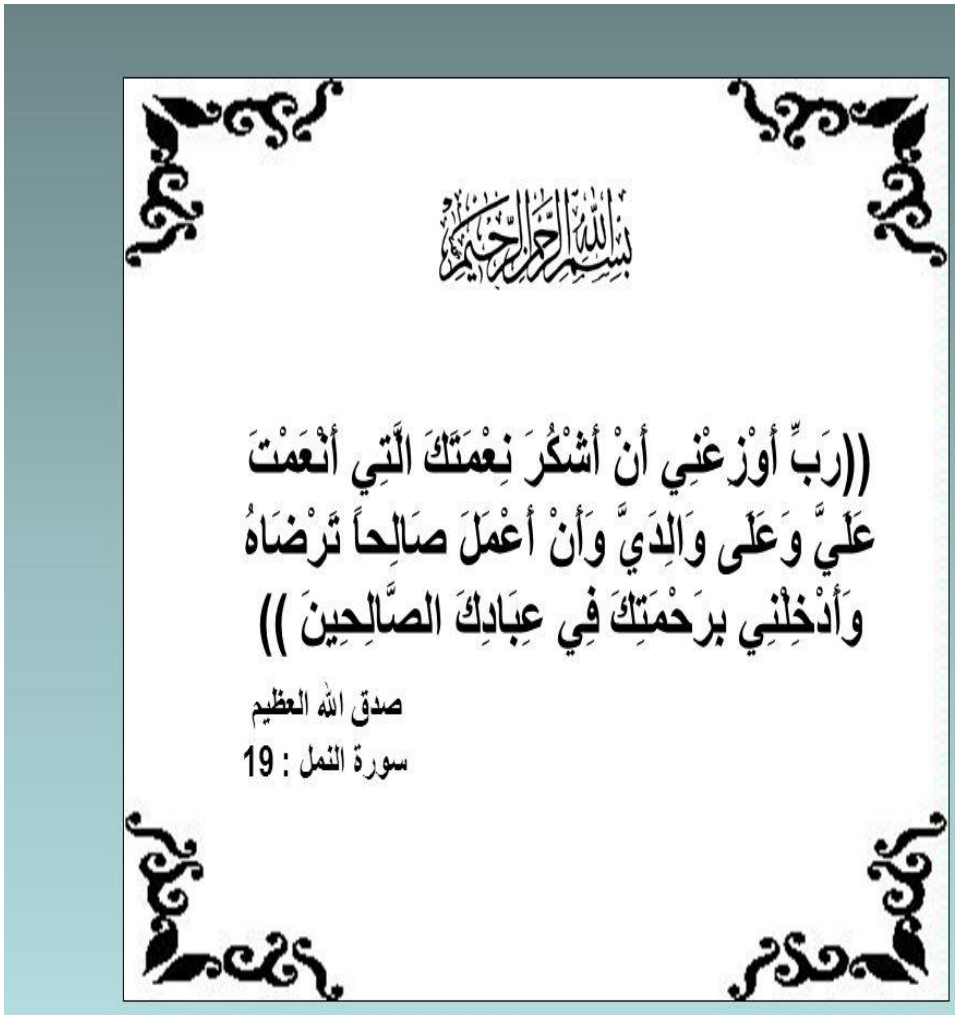
September, 2016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صدق الله العظيم
سورة النمل : 19

DEDICATION

To

My beloved parents

To

My wonderful sister

(Fatima Yusuf)

Acknowledgements

All thanks to my generous God who gave me health, strength and patience to complete this work. I wish to express my sincerest gratitude to my supervisor, Prof. Ahmed Elsadig , who has supported me throughout my thesis with his patience, knowledge, and encouragement . I would also like to express my deepest gratitude to Fatima Alfatih Tajelsir and Dr. Talal Ahmed of Medical Biochemistry Research Department for their invaluable help. My warm thanks and appreciations are also extended to my best friend Hadeel Hassan for her continuous support. I am grateful to my beloved family for their unconditional sacrifice, care and encouragements along the path of my studies.

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Abbreviations

ADT	Auto Dock Tools
ATP	Adenosine Triphosphate
ADMET	Absorption, Distribution, Metabolism, Excretion and Toxicity
BDB	Protein Data Bank
CADD	Computer Aided Drug Design
DSV	Discovery Studio Visualizer
DLG	Docking Log File
HTS	High Throughput Screening
LOG P	Logarithm of octanol water partition coefficient
MDB	Mol2 files Sybyl Data Base
NAD	Nicotinamide Adenine Dinucleotide
PARP	Poly Adenosine di phosphate Ribose Polymerase
QSAR	Quantitative Structural Activity Relationship
VS	Virtual Screening

Abstract

Poly-ADP-ribose polymerases -2 (PARP-2) is an important nuclear enzyme involved in the detection and repair of DNA damage. Inhibition of PARP activity is very useful in cancer therapy. Olaparib also known as AZD2281 or KU-0059436 is a famous potent inhibitor of both PARP-1 and PARP-2, belongs to the class of phthalazinones, used as standard reference in this study. 65 compounds of phthalazinones derivatives were designed, all these compounds have a nicotinamide-based structure aimed at competing with NAD+ for the binding to PARP-2 catalytic site. ACD/Chemical Sketch Software was used to draw chemical structures, calculation of molecular properties and prediction of log P. 45 compounds which have chemical parameters values closes to the reference standard (Olaparib) were chosen to be docked into the inhibitor site of protein by using surflex software (syblyl). Among these derivatives seven compounds showed promising score higher than Olaparib. Docking data revealed that (4-[5-(2-amino-3-cyclopropyl-1,3-dihydroxypropyl)-2-flurobenzyl] phthalazine-1(2H)-one) was the top –ranked result in term of its binding to PARP-2 enzyme, with Surflex score of (-logkd=9.71). Docking results were used to predict molecular interactions; and molecular recognition pattern in PARP-2 inhibitor complexes, were analyzed by online discovery studio software.

الخلاصة

يعتبرانزيم عديد اللأدنين ثنائي نيوكليوتيد فيسفوروز الرايبوزي البوليميريزي-٢ (PARP-2) انزيما نوويا هاما حيث يستخدم في اصلاح تلف الحمض النووي الرايبوزي منقوص اللأوكسجين وتثبيط هذا الانزيم يعتبرا عاملا مهما في علاج السرطان.

اللأولاباريب الذي يعرف ايضا ب(AZD2281) هو احد المثبطات الفعاله المشهوره لنشاط انزيمي-PARP (1) و (PARP-2) ينتمي هذا المركب لمجموعة الفثالازينون وتم استخدامه كمركب مرجعي في هذه الدراسه. تم تصميم خمس وستون مركبا من مشتقات الفثالازينون حيث تشترك جميعها في احتوائها على تركيبة النيكوتيناميد بهدف منافسته لثنائي نيوكليتيد اللأدنين واميد النيكوتين لشغل موقع الترابط مع الانزيم . استخدم البرنامج الحاسوبي ACD/Chemical Sketch أستخدم لرسم التراكيب الكيميائيه وحساب الخصائص الجزيئيه وقيمة(log P) للمركبات المصممه . من مجموع المركبات التي تمت دراستها وجد ان خمس واربعون مركبا كانت لها قيم مقاربه لتلك التي يتميز بها المركب المرجعي تم اختيارها لتخضع لاختبارقوة ونوع الترابط بينها وبين البنيه الثلاثية الأبعاد لانزيم(PARP-2) فيما يسمى بالارساء بأستخدام البرنامج الحاسوبي surflex software (sybyl).

سبع من هذه المركبات الخمس واربعون أحرزت قيم ترابط مع الانزيم اعلى من المركب المرجعي وكان أعلاها المركب [4-(5-(2-amino-3-cyclopropyl-1,3-dihydroxypropyl)-2-flurobenzyl phthalazine-1(2H)-one) بقيمة (logkd=9.7 -). أستخدمت هذه النتائج للتنبؤ بالتداخلات الجزيئيه وتحديد نمط ارتباط المثبطات مع الانزيم وتم تحليلها بأستخدام البرنامج الحاسوبي (discovery studio).

Chapter one

Introduction

1-Introduction

The development of new drugs with potential therapeutic applications is one of the most complex and difficult process in the pharmaceutical industry. Millions of dollars and man-hours are devoted to the discovery of new therapeutically agents. As, the activity of a drug is the result of a multitude of factors such as bioavailability, toxicity and metabolism, rational drug design has been utopias for centuries.

Recently, impressive technological advances in areas such as structural characterization of bio macromolecules, computer sciences and molecular biology have made rational drug design feasible (Ooms, 2000).

Poly (ADP-ribose) polymerase (PARP) inhibition was first introduced as a cancer-targeting strategy in 2005 and has made rapid clinical progression, culminating in the Food and Drug Administration approval of olaparib as a fourth line- and-beyond treatment in relapsed *BRCA*-mutated ovarian cancer in December 2014. This approval follows exciting phase I/II data showing activity in ovarian cancer, with particular success in *BRCA*-deficient and platinum- sensitive populations (Heather *et al*., 2015).

Olaparib has also demonstrated exciting clinical efficacy as a mono therapy of BRCA-1 and BRCA-2 deficient breast cancer (Weil *et al*., 2011) . Therefore the broad spectrum and potent anti-tumor activity of Olaparib has attracted much attention in recent year .

By using structure activity relationship, Olaparib structure could be modified to obtain new compounds, computer base molecular docking studies on the isolated active compounds (ligands) using PARP enzyme could be carried out with the intention to obtain an in-depth picture of the structural bases of the binding of these compounds with the enzyme and therefore, discover new PARP inhibitors.

1.1. Computational Chemistry:

Computational chemistry is a branch of chemistry that uses principles of computer science to assist in solving chemical problems. It uses the results of theoretical chemistry, incorporated into efficient computer programs, to calculate the structures and properties of molecules (Xu and Hagler, 2002).

It is a set of techniques for investigating chemical problems on a computer (Lewars 2004).

Computational chemistry is an exciting and fast-emerging discipline which deals with the modeling and the computer simulation of systems such as biomolecules, polymers, drugs, inorganic and organic molecules, and so on. With high computing power using parallel or grid computing facilities and with faster and efficient numerical algorithms, computational chemistry can be very effectively used to solve complex chemical and biological problems (Ramachandran *et al*., 2008).

Using computational chemistry software you can in particular perform:
Electronic structure determinations, geometry optimizations, frequency calculations, definition of transition structures and reaction paths, protein calculations, i.e. docking, electron and charge distribution calculations, calculations of potential energy surfaces (PES), calculations of rate constants for chemical reactions (kinetics), thermodynamic calculations- heat of reactions, energy of activation and calculation of many other molecular and bulk physical and chemical properties.

The most important numerical techniques are *ab-initio,* semi-empirical and molecular mechanics.

Definitions of these terms are helpful in understanding the use of computational techniques for chemistry:

I. *Ab-initio*, a group of methods in which molecular structures can be calculated using Schrödinger equation, the values of the fundamental constants and the atomic numbers of the atoms present.

II. Semi-empirical techniques use approximations from empirical (experimental) data to provide the input into the mathematical models.

III. Molecular mechanics uses classical physics and empirical or semi-empirical (predetermined) force fields to explain and interpret the behavior of atoms and molecules (Young *et al*., 2001).

1.1.1. Chemoinformatics and Drug Discovery:

Chemoinformatics involves the use of computer technologies to process chemical data. It is the mixing of those information resources to transform data into information and information into knowledge for the intended purpose of making better decisions faster in the area of drug lead identification and organization (Oprea 2004)**.** Initial activities in the field started with chemical document processing. What differentiates chemical data processing from other data processing is that chemical data involves the requirement to work with chemical structures. This requirement necessitated the introduction of special approaches to represent, store and retrieve structures in a computer system. Another challenge faced by this new field was to establish clear relationships between structural patterns and activities or properties (Xu and Hagler, 2002).

Since 1980, with the advent of high throughput screening (HTS), automated techniques have made possible robotized screening through this process; hundreds of thousands of individual compounds can be screened per drug target per year (Gallop *et al*., 1994).

After the pharmaceutical industry adopted high throughput techniques, quick profiling of a compound library with thousands or millions of chemical structures became an important issue , scientists realized that they needed high throughput data

mining approaches. Therefore, cheminformatics was born. The tools to calculate various structure descriptors are available publicly and commercially (Kier and Hall, 1986).

1.1.1.1. Virtual Screening:

In conjunction with high-throughput screening technology, virtual screening has become a main tool for identifying drug leads (Walters *et al*., 1998). Virtual screening involves the use of computer programs to assess whether known compounds are likely to be lead compounds for a particular target. Virtual screening can be used to identify those compounds which are most likely to be active and these would take priority for actual screening.

In order to reduce drug discovery costs, one needs to remove undesired compounds as early as possible. Filters have been built based upon oral bioavailability, aqueous solubility, metabolic clearance and, chemically reactivity or toxic chemical groups *(*Lipinski *et al*., 2001; Zuegge *et al*., 2001). If the target structure is known, one of the structure-based virtual screening methods that can be used is high throughput docking (Abagyan and Totrov, 2001; Diller and Merz, 2001). If the target structure is unknown, but the ligands from the literature or, competitors are known, then, similarity approaches can be applied (Willett, 2000; Makara, 2001). If neither target structure nor ligand structure is known, then SAR patterns can be derived from experimental screening data by statistical approaches (Hopfinger and Duca, 2000; Gedeck and Willett, 2001) Also, virtual screening is a great tool for the design of a combinatorial library with a given target. Analysis of the binding predictions across the virtual library reveals patterns of structure activity information. The patterns are then used to design new focused libraries. A recent review has indicated that HTS and VS are moving toward integration (Good *et al*., 2000).

It is expected that such integration will make HTS more powerful for use in new lead discovery.

1.1.1.2. Computer Aided Drug design (CADD):

Historically, drug absorption, distribution, metabolism, excretion, and toxicity (ADMET) studies in animal models were performed after a lead compound was identified. Now, pharmaceutical companies are employing higher-throughput, *in vitro* assays to evaluate the ADMET characteristics of potential leads at earlier stages of development. This is done in order to eliminate candidates as early as possible, thus avoiding costs, which would have been expended on chemical synthesis and biological testing. Scientists are developing computational methods to select only compounds with reasonable ADMET properties for screening. Molecules from these computationally screened virtual libraries can then be synthesized for high-throughput biological activity screening. As the predictive ability of ADME/Tox software improves, and as pharmaceutical companies incorporate computational prediction methods into programs, the drug discovery process will move from a screening based to a knowledge-based paradigm (Lipinski, 2002).

1.1.1.2.1. Optimization:

The second step of drug design involves the modification of the hits in order to improve the biological properties of the compound by changing its pharmacophore. Using QSAR to modify lead compounds would be less tedious then having to physically synthesize the compounds. Moreover, such *in silico* methods could theoretically help to modify the compounds to exhibit the most potency, most selectivity, best pharmacokinetics and least toxicity. QSAR involves mainly physical chemistry and molecular docking tools that lead to tabulated data of first and second order equations. There are many theories, being the most relevant Hansch's analysis that involves Hammett electronic parameters, and log P parameters (Sprous *et al*., 2006).

1.1.1.2.2. CADD Strategies in the Drug Discovery process:

Strategies for CADD vary depending on the extent of structural and other information available regarding the target (enzyme/receptor) and the ligands. "Direct" and "indirect" design are the two major modeling strategies currently used in the drug design process.

In the indirect approach the design is based on comparative analysis of the structural features of known active and inactive compounds. In the direct design the three-dimensional features of the target (enzyme/receptor) are directly considered (table1.1.).

	Unknown receptor	**known receptor**
Unknown ligand	Homology modeling Generate 3d structure HTS, Comb.chem	Receptor based drug design DE novo design, virtual screening
known ligand	2D, 3D QSAR and pharmacophore searching	Molecular docking

Table (1.1) four major cases in CADD also known as "direct" and "indirect design when the structure of the target is respectively known or unknown (Ooms, 2000).

1.1.2. Molecular Modeling:

Each year, new targets are being identified, structures of those targets are being determined at an amazing rate, and our capability to capture a quantitative picture of the interactions between macromolecules and ligands is accelerating. A receptor in the biochemistry context, is a/are protein molecule(s), found in either the plasma membrane or the cytoplasm of a cell, to which one or more specific kinds of signaling molecules may attach. A molecule which attaches to a receptor is called a ligand, and may be a peptide or other small molecule, such as a neurotransmitter, a hormone, a

pharmaceutical drug, or a toxin. Each kind of receptor can bind only certain ligand shapes. Each cell typically has many receptors, of many different kinds (Sprous *et al*., 2006).

To understand the design concepts of the various types of binding enzyme inhibitors, a basic knowledge of the binding forces between an enzyme's active site and its inhibitors is required. The forces involved in a substrate or an inhibitor binding to an enzyme's active site are, as with a drug binding to a receptor, the same forces that are experienced by all interacting organic molecules. These include ionic (electrostatic) interactions, ion-dipole and dipole-dipole interactions, hydrogen bonding, hydrophobic interactions, and van der Waals interactions.

1.1.2.1. Protein-Ligand docking:

Is used for computational schemes that attempt to find the best matches between a receptor and a ligand. It involves the prediction of ligand conformations and orientation (or ***posing***) within a binding site and attempts to place the ligand into the binding site in configurations and conformations appropriate for interacting with the receptor.

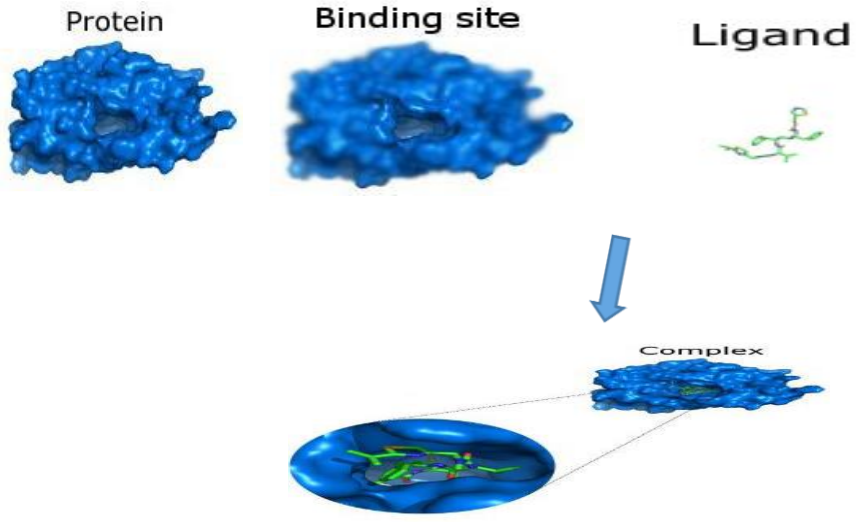


Figure (1.1) Docking Inputs (Boyle ,2012)

1.1.2.1.1. The active site of an enzyme:

The active site of an enzyme (Fig 1.1) has to be on or near the surface of the enzyme if a substrate is to reach it. However, the site could be a groove, hollow, or gully allowing the substrate to sink into the enzyme. Normally the active site is more hydrophobic in character than the surface of the enzyme, providing a suitable environment for many reactions that would be difficult or impossible to carry out in an aqueous environment.

Amino acids present in the active site can have one of two roles:

- Binding: the amino acid residue is involved in binding the substrate to the active site
- Catalytic: the amino acid is involved in the mechanism of the reaction.

1.1.2.1.2. Binding interactions:

In the past, it was thought that a substrate fitted its active site in a similar way to a key fitting a lock (Fischer's lock and key hypothesis). Both the enzyme and the substrate were seen as rigid structures, with the substrate (the key) fitting perfectly into the active site (the lock). However, this scenario does not explain how some enzymes can catalyze a reaction on a range of different substrates. It implies instead that an enzyme has an optimum substrate that fits it perfectly and can be catalyzed very efficiently, whereas all other substrates are catalyzed less efficiently. This is not the case, so the lock and key analogy is invalid. It is now proposed that the substrate is not quite the ideal shape for the active site and when it enters the active site, it forces the latter to change shape—a kind of molding process. This theory is known as Koshland's theory of induced fit since the substrate induces the active site to take up the ideal shape to accommodate it (Danial Koshland , 1994) (Fig 1.2).

Figure (1.2): Binding interaction

1.2. Poly (ADP-ribose) polymerases (PARPs):

Poly Adenosine Di phosphate Ribose polymerases (PARPs) are a family of related enzymes that share the ability to catalyze the transfer of ADP-ribose to target proteins. PARPs play an important role in various cellular processes, including modulation of chromatin structure, transcription, replication, recombination, and DNA repair.

There are at least 18 members of the PARP family that are encoded by different genes, and share homology in a conserved catalytic domain. Isoforms including PARP1 and PARP2 are best known for their involvement in DNA repair processes (Morales *et al*., 2014).

1.2.1. PARP Structure:

PARP is composed of four domains of interest: a DNA-binding domain, a caspase-cleaved domain, an auto-modification domain, and a catalytic domain. The DNA-binding domain is composed of two zinc finger motifs. In the presence of damaged DNA (base pair-excised), the DNA-binding domain will bind the DNA and induce a conformational shift. It has been shown that this binding occurs independent of the other domains. This is integral in a programmed cell death model based on caspase cleavage inhibition of PARP. The auto-modification domain is responsible for releasing the protein from the DNA after catalysis. Also, it plays an integral role in cleavage-induced inactivation. PARP inhibitors that compete with NAD+ at the highly conserved enzyme active site are arisen as new potential therapeutic strategies

as chemo- and radio potentiation and for the treatment of cancers with specific DNA repair defects as single-agent therapies (Jose *et al*., 2010).

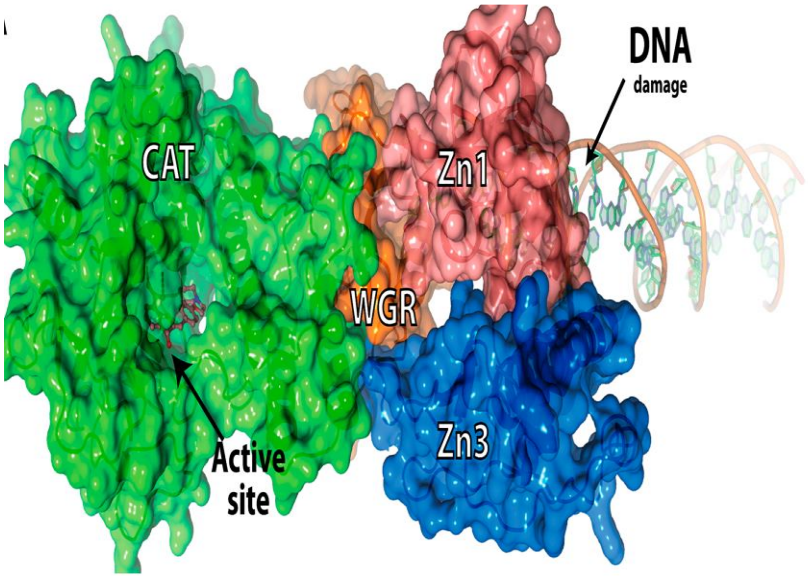


Figure (1.3) crystal structure of inhibitors in the active site of PARP-2 (Maulix *et al*., 2014).

1.2.2. Activity:

The catalytic domain is responsible for Poly (ADP-ribose) polymerization. This domain has a highly conserved motif that is common to all members of the PARP family. PAR polymer can reach lengths of up to 200 nucleotides . The formation of PAR polymer is similar to the formation of DNA polymer from nucleoside triphosphates. Normal DNA synthesis requires that a pyrophosphate act as the leaving group, leaving a single phosphate group linking deoxyribose sugars. PAR is synthesized using nicotinamide (NAM) as the leaving group. This leaves a pyrophosphate as the linking group between ribose sugars rather than single phosphate groups. This creates some special bulk to a PAR bridge, which may have an additional role in cell signaling.

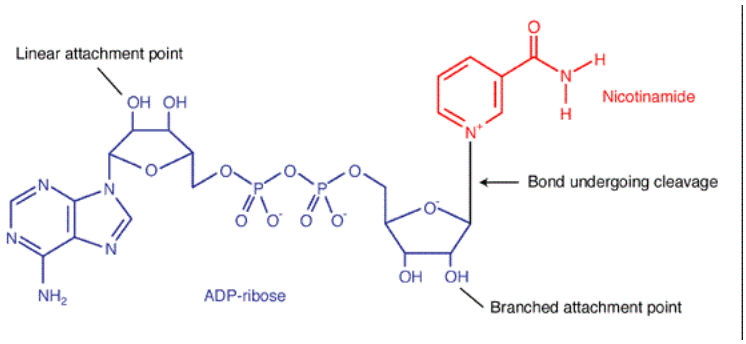


Figure (1.4) the catalytic activity of PARP (Fonfira *et al.*, 2004).

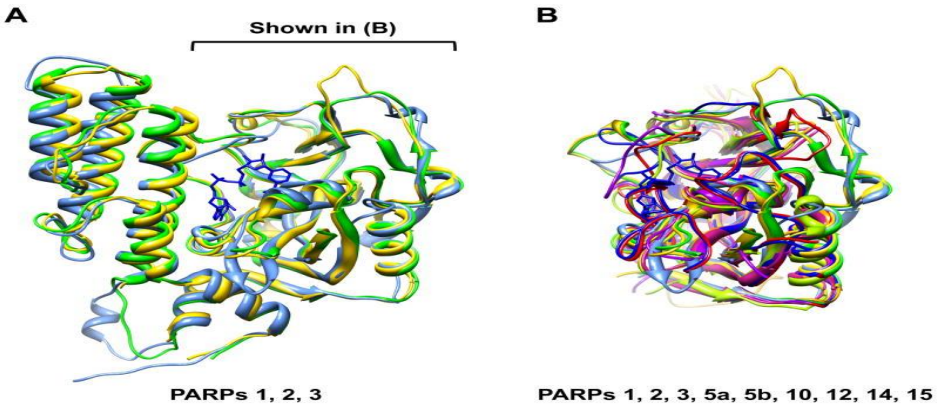


Figure (1.5) (A) Alignment of the catalytic domain structures for PARP-1 (green), PARP-2 (yellow), and PARP-3 (blue), **(B)** Alignment of the catalytic domain structures for PARPs 1, 2, 3, 5a, 5b, 10, 12, 14, 15 (Raga *et al.*, 2011).

1.2.3. Phathalazinones and the early discovery of PARP inhibitors:

Phthalazinones are an important kind of heterocyclic compounds due to their synthetic and pharmacological versatility. This fused heterocycle system represents a common structural feature for many bioactive compounds showing a variety of pharmacological activities such as anticancer, ant diabetic, anti-asthmatic, antihistaminic, antihypertensive, antithrombotic, anti-inflammatory, analgesic, antidepressant or antimicrobial agents, which makes it an attractive scaffold for the design and development of new drugs. They were developed as enzyme inhibitors, such as aldose reductase (AR) inhibitors and poly (ADP-ribose) polymerase (PARP) inhibitors.

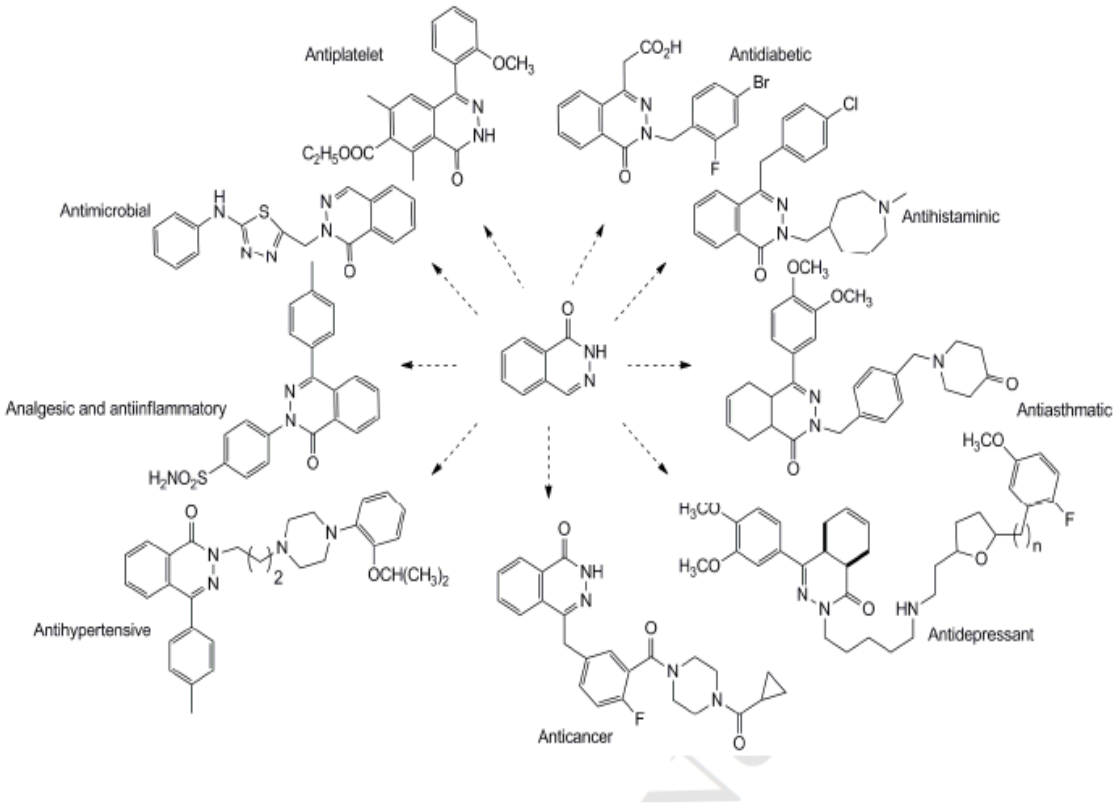


Figure (1.6) wide variety of biological properties of phthalazinones derivatives (Vila *et al*., 2014)

The discovery of poly (ADP-ribose) polymerase (PARP), or as it was called then ADP-ribose transferase (ADPRT), goes hand-in hand with anticancer therapy. The first observation, before the enzyme was discovered, was that the earliest chemotherapy agents, the DNA alkylating agents, caused a profound decrease in glycolysis due to depletion of cellular NAD^+ (Roitt, 1956). ADP-ribose polymers were identified shortly afterwards and finally, the enzyme responsible, PARP, was discovered (Chambon *et al*., 1963). The PARP reaction catalyzes the cleavage of NAD^+ into nicotinamide and ADP-ribose leading to the rapid consumption of NAD^+ when DNA is damaged by alkylating agents. The second product of the reaction, nicotinamide, causes a modest product inhibition of the reaction. Based on this knowledge the first PARP inhibitors were the nicotinamide analogues where the heterocyclic nitrogen at the 3 position was replaced with a carbon to generate a benzamide analogue (Purnell and Whish, 1980). Substitutions at this 3 position

improved solubility and the 3-substituted benzamides, e.g. 3-aminobenzamide helped elucidate the function of PARP. A pivotal study by Sydney Shall's group (Durkacz *et al*., 1980) demonstrated that these compounds inhibited the repair of DNA breaks induced by the DNA alkylating agent, dimethyl sulfate (DMS), and enhanced DMS cytotoxicity. This study was the first to suggest a potential utility of PARP inhibitors in combination with DNA alkylating agents to treat cancer. Of course there is a family of PARP enzymes but, in terms of DNA repair and its exploitation in cancer therapy, PARP1 and PARP2 are the targets, as these enzymes have overlapping function in the repair of DNA breaks by single strand break repair pathway (Schreiber *et al*., 2006). More recently, PARP3 has been shown to co-operate with PARP1 in response to DNA double strand breaks (Boehler, 2011) but the significance of PARP3 inhibition in cancer therapy has not been explored. Most of the inhibitors are active against both PARP1 and 2 and for the rest of this review the term PARP will be used to cover both PARP1 and PARP2.

The initial impetus to the development of PARP inhibitors came from the need to develop tools to study the role of the enzyme and to enhance the activity of DNA damaging agents used to treat cancer.

1.2.4. Identification and development of potent inhibitors:

Despite providing data that help to elucidate the function of PARP, the benzamides were weak; they needed to be used at millimolar concentrations in cell-based studies, which meant they were unsuitable for studies in animals. In addition, they inhibited other cellular pathways (Milam and Cleaver, 1980). Nevertheless, they provided a good starting point for the development of inhibitors with increased potency and virtually all PARP inhibitors in use today have the nicotinamide/benzamide pharmacophore. During the 1990s PARP inhibitors of increasing potency and specificity were discovered using various approaches. 170

compounds were screened for their inhibitory potency, making a major contribution to inhibitor design (Banasik *et al*., 1992). This study identified several compounds with potent PARP inhibitory activity including the isoquinolinones, quinazolinones, quinazoline diones, phthalazinones and phenanthridinones, of which 4-amino-1,8-naphthalimide was the most potent. Several of these compounds have been used as leads for subsequent drug development by various groups. The alternative approach of synthetic chemistry and the development of structure-activity relationships (SAR) led to the identification of 3,4-dihydro-5-methylisoquinolin-1(2*H*)-one (PD128763) and 8-hydroxy-2-methylquinazolin-4-[3*H*]-one (NU1025) (*Suto et al*., 1991; Arundel-Suto *et al*., 1991; Griffin *et al*., 1995 . The more potent inhibitors identified all had the carboxamide group of the benzamide pharmacophore rotationally constrained by incorporation into a second ring, indicating that this was critical for improved potency. The reason why these structural features were associated with potency became apparent when structural biology studies were done. Crystallization of PD128763, 4-amino-naphthalimide and NU1025 in the NAD^+ binding site of the PARP1 catalytic domain demonstrated that the carboxamide group made several important hydrogen bonds with Ser904-OG and the Gly863-N in the catalytic domain and its restriction within a heteroring improved the interaction, in line with the prediction from the increased potency. Based on crystallographic analysis of the binding of 2-(4-hydroxyphenyl)benzamidazole-4-carboxamide (NU1085) several tricyclic lactam indoles and benzamidazoles were developed in which the carboxamide group was held in the favorable orientation by incorporation into a 7-membered ring (Canan-Koch *et al*., 2002; Skalitzky *et al*., 2003; Calabrese *et al*., 2003; Calabrese *et al*., 2004). These compounds, e.g., AG14361 make critical hydrogen bonds with Gly863 and Ser904, and the important catalytic Glu988 residue (Marsischky *et al*., 1995). Further development of AG14361 led to the identification of AG-14447 (Thomas *et al*., 2007), and it was the phosphate salt of this compound

(AG-014699, rucaparib) that was the first PARP inhibitor to enter clinical trial for cancer patients (Plummer *et al*., 2006; Plummer *et al*., 2008). Several academic investigators and pharmaceutical companies have had an active PARP inhibitor development program and several have entered clinical investigation such as Veliparib (ABT-888), which also has low nM Ki against both PARP1 and PARP2 (Penning *et al*., 2009) and olaparib (AZD2281) with nanomolar IC_{50} values against PARP1 and PARP2 (Menear *et al*., 2008; Ferraris, 2010; Javle and Curtin, 2011). Iniparib (BSI-201, 4-iodo-3-nitrobenzamide) has now been shown not to be a PARP inhibitor (Patel *et al*., 2012).

1.3. Olaparib:

Olaparib {4-(4-(4-(cyclopropanecarbonyl) piperazine-1-carbonyl)-3-fluorobenzyl phthalazine-(2*H*)-one} also known as AZD2281 or KU-0059436 (developed by KuDOS pharmaceuticals, and later AstraZeneca) is a potent inhibitor of both PARP-1 and PARP-2. This agent has been used successfully in the context of "synthetic lethality" in the treatment of tumors with BRCA mutations, as well as used in combination with platinum-based drugs. It is currently at the end of phase II clinical trials after successful phase I studies where it was used as a single agent in cancer patients with BRCA1 and BRCA2 mutations (Menar *et al*., 2008) . *In vitro* activity inhibitory for olaparib with PAPR-2 enzyme IC_{50} (nM)[a] =1.94 and EC_{50} (nM)[b] =3.57 (Wang *et al*., 2015).

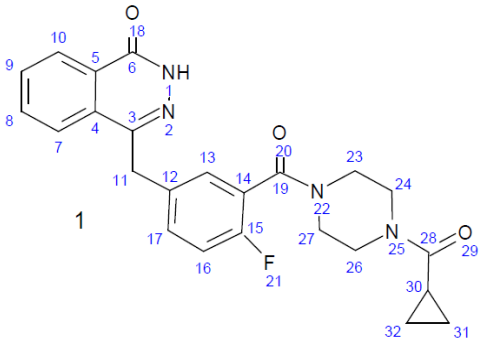


Figure (1.7) olaparib structure

This compound belongs to the class of phthalazinones, it was used as standard reference and it was accessible for various modifications to produce many other compounds.

1.4. ACD/Lab programmer:

ACD/Lab programmer use to draw chemical structures including organics, organometallics and polymers. It also includes calculation of molecular properties (e.g., molecular weight, density, molar refractivity etc.), 2D and 3D structure cleaning and viewing, functionality for naming structures, and prediction of log *P*.

Polarizability:

Polarizability is the relative tendency of a charge distribution, like the electron cloud of an atom or molecule, to be distorted from its normal shape by an external electric field. External field can be due to presence of a nearby ion or solvent. So this effect is very important in understanding the solvent properties and reactivity of some compounds which may change when changing the solvent. Polarizability increases as volume occupied by electrons increases, larger polarizability higher reactivity (Christensen *et al.*, 2002 and Anslyn, 2006).

Log*P*:

The octanol-water partition coefficient, P, is a measure of the differential solubility of a neutral substance between these immiscible liquids and thereby, a descriptor of hydrophobicity (or the lipophilicity) of a neutral substance. It is typically used in its logarithmic form, log*P* (Caillard *et al.*, 1997 and Elkins *et al.*, 1971).

1.5. SYBYL molecular modeling suite (Surflex-Dock):

Complete suite of computational chemistry applications that simplify and accelerate the discovery of lead compounds and development candidates. SYBYL expert molecular modeling environment application include validated solutions for

key computational chemistry and molecular modeling tasks such as ligand-based design, receptor-based design, structural biology, library design, and cheminformatics. Continual innovation creates well-designed, frequently-updated software that saves valuable time, enhances productivity, and can mean the difference between success and failure for in silico discovery programs.

Surflex-Dock uses an empirical scoring function and a patented search engine to dock ligands into a protein‟s binding site. Docking is guided by the protomol, an idealized representation of a ligand that makes every potential interaction with the binding site. The protomol can be generated automatically or defined based on a cognate ligand or known active site.

1.6. Discovery Studio Visualizer (DSV):

Discovery Studio® Visualizer 2.5 allows to view and edit molecular structures, sequences and sequence alignments and Perl scripts created with the Discovery Studio and other applications. Discovery Studio is a comprehensive software suite for analyzing and modeling molecular structures, sequences, and other data of relevance to life science researchers. The product includes functionality for viewing and editing data along with tools for performing basic data analysis. The Discovery Studio Visualizer is a free viewer that can be used to open data generated by other software in the Discovery Studio product line. It is designed to offer an interactive environment for viewing and editing molecular structures, sequences, X-ray reflection data, scripts, and other data.

1.7. Aims and objectives of the current study

Based on the latest statistics published by the World Health Organization (WHO).In 2005, 7.6 million people died of cancer out of 58 million deaths worldwide. Based on projections, cancer deaths will continue to rise with an estimated 9 million people dying from cancer in 2015, and 11.4 million dying in 2030. (PARP) inhibition was introduced as an important cancer-targeting strategy in 2005 and has made rapid clinical progression, discover and development of PARP inhibitors has attracted much attention in recent year.

This study was carried out to discover and to develop new inhibitors of PARP-2 enzyme, the study has included screening of compounds with considerable chemical diversity for PARP inhibition. The main objectives of this study were:

- To design some phthalazinone derivatives and Correlate the structure properties by ACD lab programmer.
- To Conduct molecular docking study of the PARP-2 enzyme on compounds.
- To carry out a structural computational chemistry-based studies on the active compounds to investigate the enzyme-inhibitor molecular recognition and to investigate the possibility of structural optimization of newly discovered inhibitors.
- To obtain active compounds with potency higher than the standard reference (Olaparib).

Chapter Two

Materials and Methods

2. Materials and Methods

2.1. ACD lab programmer

ACD/lab free ware 2012 from www.acdlabs.com

2.1.1. General method of ACD/lab programmer

There were two modes to ACD/ChemSketch, namely Structure and Draw. Structure mode was used to draw chemical molecules, while Draw mode used to create and edit graphical objects. Upon startup, the Draw Normal mode and Carbon were automatically selected. By clicking and dragging the cursor in the window, C-C bonds were created. Clicking on a carbon atom produces branched structure. The change was made by selecting a heteroatom from the element list in the left toolbar and clicking on an atom in the structure to replace it. Radicals were made by selecting it from table which including carbon rings, carbon-based side chains and functional groups. A reaction requires were drawing by using the reaction arrow and reaction plus icons. Bond lengths and bond angle standardized by clicking on Clean Structure. The calculated properties were inserted into the ChemSketch window as a text field; on the tools menu, point to calculate, and choose the desired property as the value of the octanol-water partition coefficient (log P),density , polarizability ,molar volume ,molar refractivity ,formula weight and surface tension (table No 3.1). By selecting a structure and clicking on generate Name for structure, the IUPAC name was generated as a text field underneath the structure (Table No 3.1).

2.2. In silico studies:

Molecular docking is computer-aided simulation of the ligand-receptor interaction process. Automated docking methods can be used to predict energetically favorable conformations and orientations of ligands in the interior structure of a protein. These methods combine algorithms to generate different poses (docking), and scoring functions to consider the tightness of protein-ligand interactions.

2.2.1. Docking with Surflex-Dock software:

Molecular docking simulations were conducted using Surflex-Dock which is one of the docking engines of SYBYL®-X 1.1, which distributes Surflex v.2.51 from BioPharmics IT.

Surflex-Dock uses an empirical scoring function and a patented search engine to dock ligands into a protein's binding site. Docking is guided by the protomol, an idealized representation of a ligand that makes every potential interaction with the binding site. It is important to mention that the function of protomol is to direct the initial placement of the ligand during docking process and not to be the only and absolute site where the ligand will be docked (Ruppert *et al*., 1997).

Surflex-Dock is particularly successful at eliminating false positive results and can, therefore, be used to narrow down the screening pool significantly, while still retaining a large number of active compounds.

The Docking suite has been improved to better support workflow.

2.2.1.1 Ligand file preparation:

All PARP-2 inhibitors under study were sketched using ACD/ChemSketch and then converted into 3D structures and minimized using SYBYL. Minimization process is a prerequisite of docking. This process included addition of partial charges which were assigned using Gasteiger-Huckel method. Minimization was carried out using SYBYL tripos force field and then inhibitors were saved in mol2 format and put in SYBYL databases ready for docking. SYBYL Database a directory of Mol2 files. The directory has a (mdb) extension.

2.2.1.2 Protein file preparation:

The structure of PARP-2 used was downloaded from protein data bank (http://www.rcsb.org/), PDB Code (4TVJ). To start the protein preparation, the protein structure preparation dialog is displayed. Only one chain was used in docking after removing all water molecules and substructures, and adding hydrogen atoms.

The amino acids side chains were repaired and chain termini were treated and fixed. Protonation type of a residue was set to favor hydrogen bonds with the ligand. AMBER7-FF99 atom types were assigned, Atomic charges were added, side chain amides were fixed automatically, and the receptor was minimized using AMBER7 FF99 force field and finally saved using the Mol2 format.

2.2.1.3 Molecular Docking Procedure

Ligand docking was performed with the Surflex-Dock software of SYBYL package using the procedure reported by A. Jain. (Jain, 2000). Consensus Score module was implemented to calculate and rank the docking scores for the resulting docking conformations. Score integrates a number of popular scoring functions for ranking the affinity of ligands bound to the active site of the receptor. The strengths of individual scoring functions combine to produce a consensus that is more robust and accurate than any single function for evaluating ligand-receptor. Surflex-Dock's initial implementation used the Hammerhead procedure (Hammerhead *etal*.,1996) to screen for the binding of flexible molecules to a protein binding site. Input to Surflex-Dock consists of: The 3D structure of a receptor protein with hydrogens and binding site empty of co-crystallized ligand. The protomol, a set of probes (CH4, N-H, C=O) complementary to the active site, and 3D ligands, with proper atom types, and hydrogens, and in any arbitrary optimized conformation. After docking with Surflex-Dock software was performed the results were appeared with 20 docked poses for every ligand. The final results of these poses were appeared in a final schedule which included just a best high score to the 20 poses of that docked molecule.

Finally, PARP-2 inhibitors to be docked were specified and each docking run was given a job name. Results of each submitted job were automatically posted in the result browser in the form of score value.

2.3. Analysis with Discovery Studio Visualizer (DSV):

Data was viewed, modelled and analyzed with Discovery Studio® Visualizer 2.5 software, which showed that the interaction between compound and residues in the binding site mainly were hydrogen bonds and π- π interactions.

Chapter Three

Results and Discussion

3. Results and discussion:

Poly-ADP-ribose polymerases (PARPs) are cleave (NAD) into ADP-ribose and nicotinamide and transfer the ADP-ribose units into their substrates. All publicly available structures of PARP inhibitor complexes show compound anchoring in the pocket that retains the nicotinamide moiety after NAD cleavage.

Inhibitors that target this site contain a cyclic or acyclic carboxamide pharmacophore, which makes π−π stacking interactions with adjacent tyrosine residues, and form hydrogen bonds with the PARP catalytic site. Optimization efforts that gave rise to these clinical candidates improved potency by restricting the amide conformation of the Carboxamide through intramolecular hydrogen bonding or by locking the amide into a ring .

Olaparib is a potent inhibitor of both PARP-1 and PARP-2 this compound belongs to the class of organic compounds known as phthalazinones. These are compounds containing a phthalazine bearing a ketone group. Olaparib was used as reference standard and it was accessible for various modifications to produce many other compounds.

The criteria of inclusion to lead - like screening libraries is taken into consideration, this criteria for molecules are like to become successful oral drugs:

1. The substance should have a molecular weight of 500 or less.
2. It should have fewer than five hydrogen-bond donating functions.
3. It should have fewer than ten hydrogen-bond accepting functions.
4. The substance should have a calculated log *P* (*c* Log *P*) between approximately −1 to 4+ (Larsen, *et al*., 2002).

65 compounds of Olaparib derivatives were designed using chemoinfomatic programmer (ACD/Lab), all these compounds have a nicotinamide-based structure aimed at competing with NAD+ for the binding to PARP-2 catalytic site. Molecular modeling studies indicate that the Attempts to improve PARP inhibitors' affinity to the binding site have been made by locking the carboxamide group which is usually free to rotate. This locking can be made either by inserting on the aromatic ring heteroatoms or groups able to give an intramolecular hydrogen bond with the amide NH, or enclosing the amide group into a two (or more)-ring heterocycle (Ferraris, 2010).

Based on these findings, a pharmacophore query was created in which the presence of three structural features were imposed:

1) An aromatic ring. 2) A carboxamide moiety with at least one NH or OH group locked into the desired anti-conformation. 3) A side chain extending into the deep pocket located in the auto modification domain of PARP-2.

ACD/ChemSketch software was used to draw the chemical structures, and to perform the calculation of molecular properties (molecular weight, density, molar volume, molar refractivity and polarizability), naming structures and prediction of log P (table No.3.1).

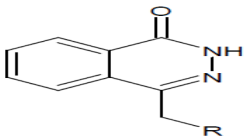
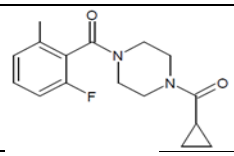
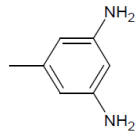
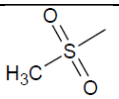
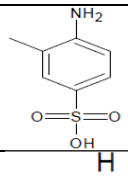
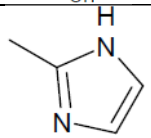
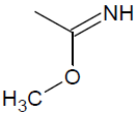
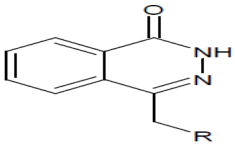
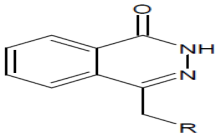


Table No. (3.1) ACD/Lab results

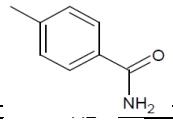
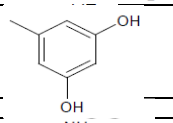
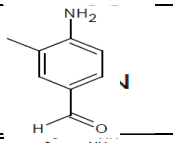
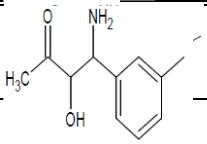
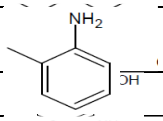
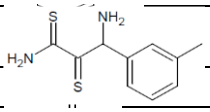
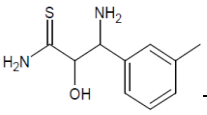
d	R	Log p (+/-0.64-0.76)		Density g/cm^3	Polarizability	Molar volume (cm^3)	Molar refractivity (cm^3)	Surface tension (-7.0) dyne/cm
		0.00		1.43	46.32	301.70	116.85	57.70
		-0.03		1.41	29.65	188.80	74.81	61.40
		-0.23		1.46	23.80	162.70	60.05	58.30
		-0.24		1.30	33.10	209.60	83.50	70.90
		0.27		1.44	25.08	156.30	63.26	61.50
		0.30		1.34	23.07	161.70	58.21	51.50

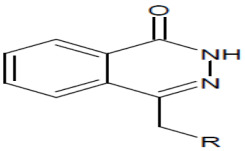


Continue table No (3.1) ACD/Lab results of :

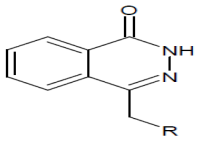


Continue table No (3.1) ACD/Lab results of:

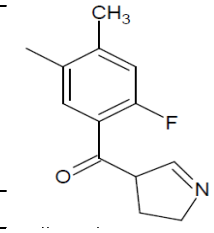
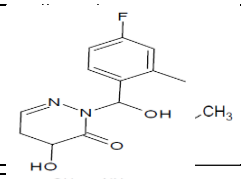
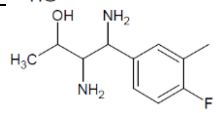
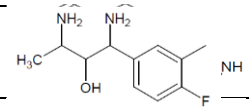
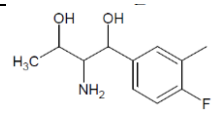
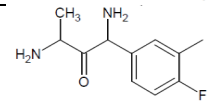
Compound No.	R	Log p (+/-0.64-0.76)	Density g/cm^3	Density g/cm^3	Polarizability	Polarizability	Molar volume (cm^3)	Molar volume (cm^3)	Molar refractivity (cm^3)
14.		0.50	1.29	1.35	27.52	31.06	183.80	205.40	79.38
15.		1.03	1.51	1.58	25.77	28.81	159.7	189.80	72.69
16.		1.18	1.29	1.41	27.52	31.06	183.8	205.40	78.36
17.		1.19	1.45	1.34	38.38	36.81	243	250	96.82
11.		0.66	1.49		27.54		180.20		69.47
18.		1.21		1.35		28.90		192	72.90
12.		0.66	1.58		31.40		202.60		79.21
19.		1.24		1.44		40.64		254.40	103.29
13.		0.73	1.34		27.20		182.90		68.61
20.		1.28		1.45		38.38		243	96.82

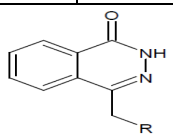


Continue table No (3.1) ACD/Lab results:

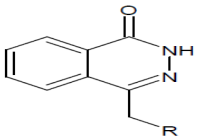


Continue table No (3.1) ACD/Lab results :

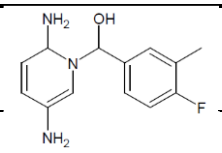
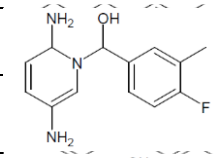
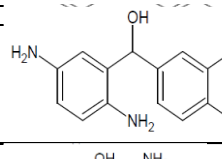
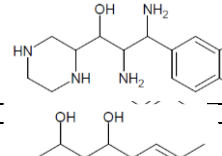
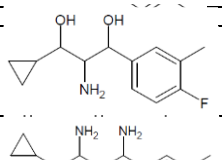
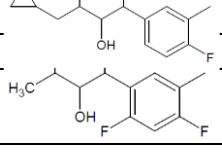
Compound No.	R	Log p (+/-0.64-0.76)	Density g/cm^3	Polarizability	Molar volume (cm^3)	Molar refractiv (cm^3)
25.		0.81	1.36	39.51	267.1	99.68
21.		1.40	1.41	32.08	210.10	82.44
22.		-0.37	1.37	43.60	297.3	110.00
26.		-0.57	1.54	40.00	257.2	100.91
23.		0.33	1.38	40.95	324.3	123.48
27.		0.20	1.41	37.18	252.4	93.78
28.		0.48	1.41	37.18	252.4	93.78
24.		0.43	1.38	39.33	262.7	99.21
29.		1.07	1.41	36.75	252.9	92.72
30.		0.97	1.40	37.18	252.4	93.78

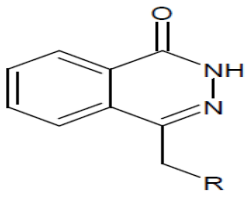


Continue table No (3.1) ACD/Lab results of:



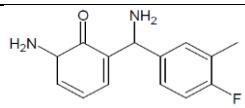
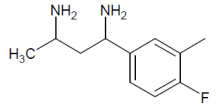
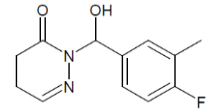
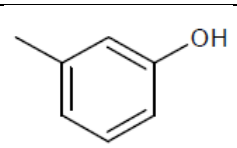
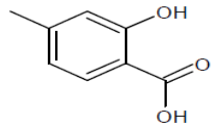
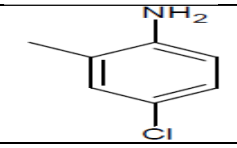
Continue table No (3.1) ACD/Lab results of:

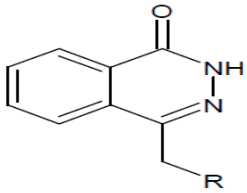
Compound No.	R	Log p (+/-0.64-0.76)	Density g/cm^3	Polarizability	Molar volume (cm^3)	Molar refractiv (cm^3)
38.		0.88	1.46	39.80	267.6	104.59
32.		0.46	1.41	36.75	252.9	92.72
39.		1.58	1.46	41.46	267.6	104.59
33.		2.09	1.41	39.68	266.5	100.11
40.		0.16	1.43	41.72	272.9	105.25
34.		1.69	1.39	40.70	270.8	102.68
41.		0.23	1.37	39.17	269.9	98.36
42.		1.44	1.48	39.47	257.3	99.58
36.		0.62	1.54	33.49	208.4	84.48
43.		1.38	1.45	41.72	272.9	105.25
37.		0.57	1.46	37.12	255.2	93.66



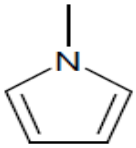
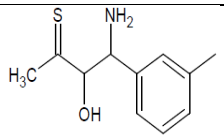
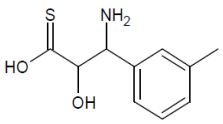
Continue table No (3.1) ACD/Lab results of:

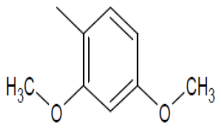
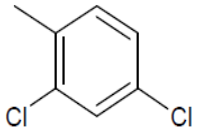
Compound No.	R	Log p (+/-0.64-0.76)	Density g/cm^3	Polarizability	Molar volume (cm^3)	Molar refractiv (cm^3)

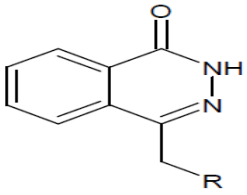
44.		0.43	1.43	41.72	272.9	105.25
45.		0.86	1.33	36.84	255.1	92.93
46.		-0.36	1.46	39.67	260.0	100.06
47.		1.75	1.31	28.47	192.5	71.83
48.		2.33	1.45	30.98	203.1	78.15
49.		2.03	1.41	30.72	201.3	77.50



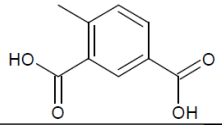
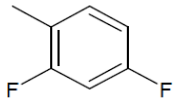
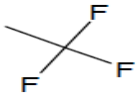
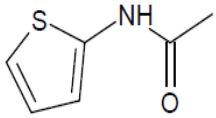
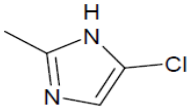
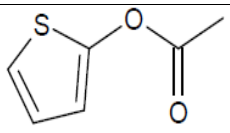
Continue table No (3.1) ACD/Lab results of:

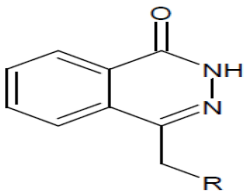
Compound No.	**R**	**Log p (+/-0.64-0.76)**	**Density g/cm^3**	**Polarizability**	**Molar volume (cm^3)**	**Molar refracti (cm^3)**
50.		1.86	1.25	27.88	189.9	70.33
51.		1.60	1.53	39.37	261.4	99.33
52.		1.47	1.45	37.96	243,5	95,75

53.		2.20	1.24	32.75	238.6	82.61
54.		3.69	1.42	31.78	213.8	80.13

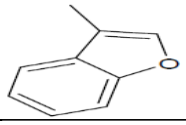
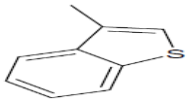
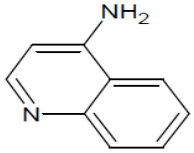
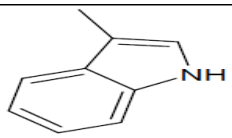
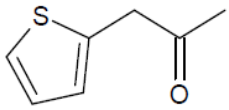


Continue table No (3.1) ACD/Lab results of:

Compound No.	**R**	**Log p (+/-0.64-0.76)**	**Density g/cm^3**	**Polarizability**	**Molar volume (cm^3)**	**Molar refracti (cm^3)**
55.		1.93	1.49	33.14	216.5	83.61
56.		2.63	1.35	28.03	201.0	70.72
57.		2.02	1.44	20.07	157.3	50.63
58.		1.74	1.45	30.95	195.6	78.09
59.		1.64	1.57	26.90	165.7	67.86
60.		2.17	1.44	30.29	197.4	76.43



Continue table No (3.1) ACD/Lab results of:

Compound No.	R	Log p (+/-0.64-0.76)	Density g/cm^3	Polarizability	Molar volume (cm^3)	Molar refracti (cm^3)
61.		2.94	1.34	31.33	205.4	79.04
62.		4.65	1.36	33.88	213.4	85.46
63.		2.64	1.34	35.03	224.4	88.37
64.		2.41	1.35	31.99	203.6	80.70
65.		1.92	1.37	31.57	207.0	79.65

45 compounds which have chemical properties values closes to the reference standard (Olaparib) values were chosen to be docked into the inhibitor site of protein by using surfex software (Sybyl).

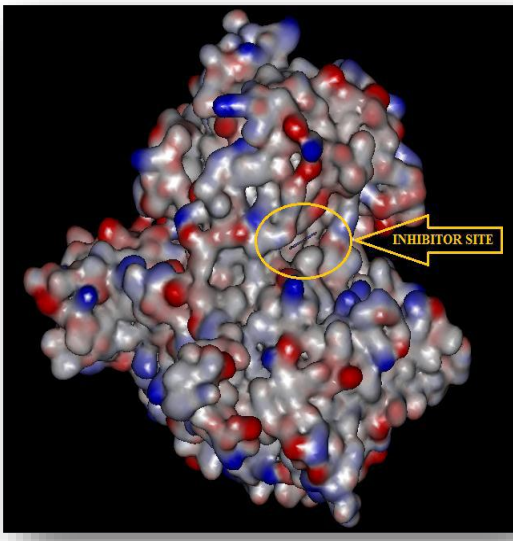
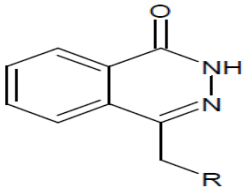


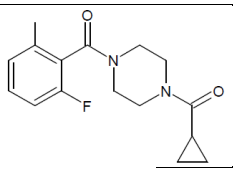
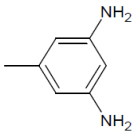
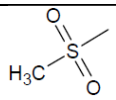
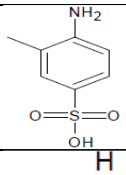
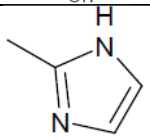
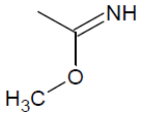
Figure (3.1) inhibitor site of the protein

Docking process guided by the protomol that direct the initial placement of the ligand in to the protein (Table 3.2).

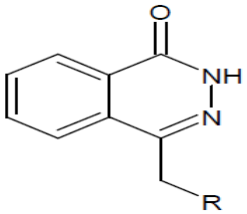
Surflex dock results explained as the total score which integrates a number of popular scoring functions for ranking the affinity of ligands bound to the active site of a receptor and contains, polar score by which docking results that make no hydrogen bonds can be excluded, and crash score) which is the degree of un appropriate penetration by the ligand into the protein. Crash scores close to zero are favorable, the smaller crash score, the better surflex –dock. (Jain, 2000).

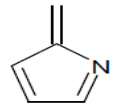
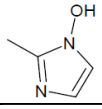
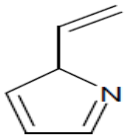
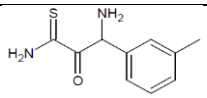
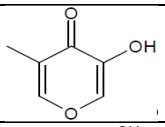
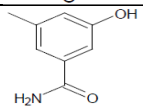
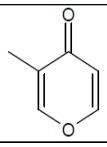
Table No (3.2): Surflex Docking Scores



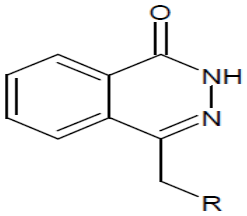
Compound No.	R	Total score	Crash	Polar
1.		8.200	-1.9900	1.9600
2.		5.7100	-0.8700	1.4700
3.		5.7800	-0.7300	2.5400
4.		5.5900	-1.1600	1.1100
5.		5.8700	-0.7700	0.0200
6.		6.1700	-0.4000	3.1200

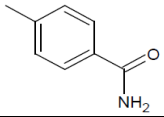
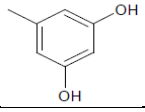
Continue Table No (3.2): Surflex Docking Scores:

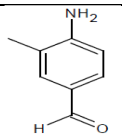
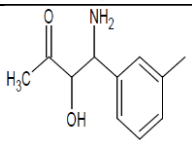
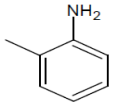
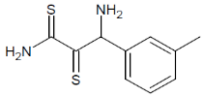
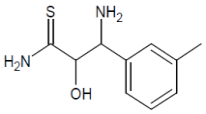


Compound No.	R	Total score	Crash	Polar
7.		5.1900	-0.3500	0.000
8.		6.2800	-0.2300	2.000
9.		5.1100	-0.4300	0.000
10.		6.4600	-1.1100	1.5900
11.		5.5700	-0.3600	1.9200
12.		6.6500	-1.8400	2.2800
13.		4.7500	-1.4400	0.9400

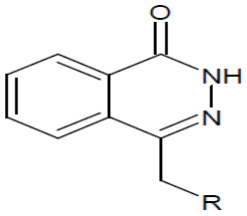
Continue Table No (3.2): Surflex Docking Scores:

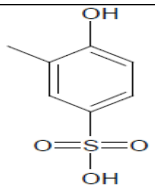
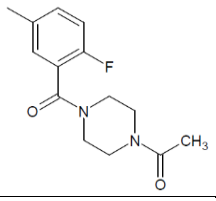
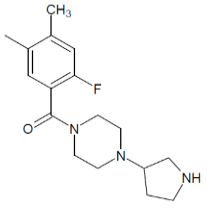


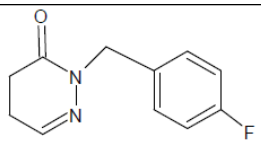
Compound No.	R	Total score	Crash	Polar
14.		5.7700	-0.6900	1.5900
15.		6.6400	-0.3900	1.8600

16.		5.0700	-0.5200	2.1900
17.		7.2500	-1.9400	3.1300
18.		5.0800	-0.9300	2.1200
19.		5.4300	-2.0700	2.0400
20.		5.7700	-1.8500	3.0900

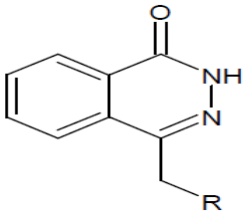
Continue Table No (3.2): Surflex Docking Scores:

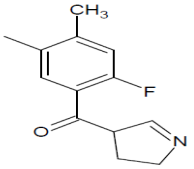
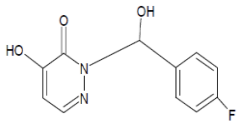
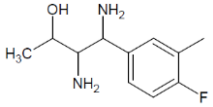
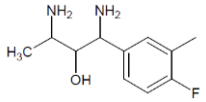
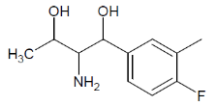
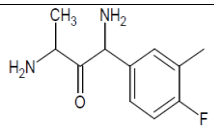


Compound No.	**R**	**Total score**	**Crash**	**Polar**
21.		6.41	-0.53	3.98
22.		5.27	-2.430	1.90
23.		7.23	-1.27	1.7

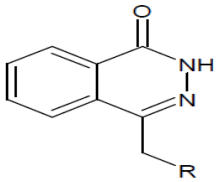
24.		7.04	-1.5	2.35

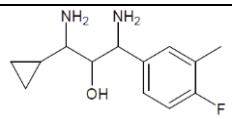
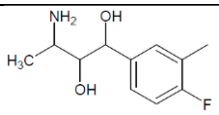
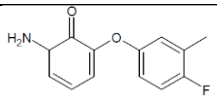
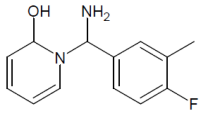
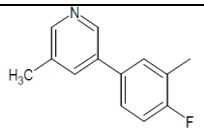
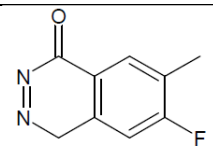
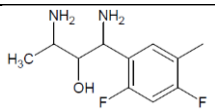
Continue Table No (3.2): Surflex Docking Scores:



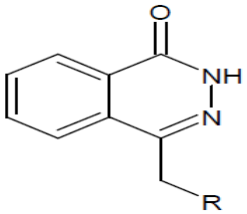
Compound No.	**R**	**Total score**	**Crash**	**Polar**
25.		7.43	-1.51	1.22
26.		7.42	-1.62	2.07
27.		7.92	-2.00	3.06
28.		9.02	-0.93	3.43
29.		7.44	-1.44	2.61
30.		6.92	-1.68	3.47

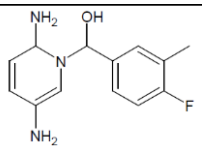
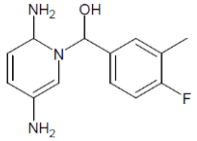
Continue Table No (3.2): Surflex Docking Scores:

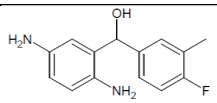
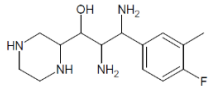
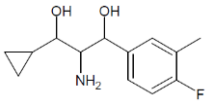
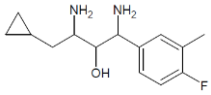
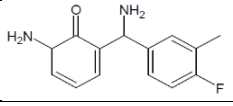


Compound No.	R	Total score	Crash	Polar
31.		8.48	-1.90	2.28
32.		8.54	-1.43	3.02
33.		8.77	-1.5	2.2
34.		6.72	-1.55	1.85
35.		6.33	-1.09	0.00
36.		5.52	-0.72	1.29
37.		5.24	-0.77	1.19

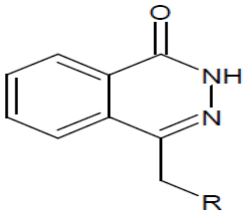
Continue Table No (3.2): Surflex Docking Scores:

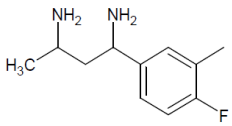
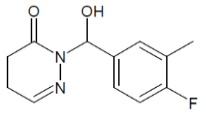


Compound No.	R	Total score	Crash	Polar
38.		7.35	-1.09	2.32
39.		7.83	-1.31	4.32

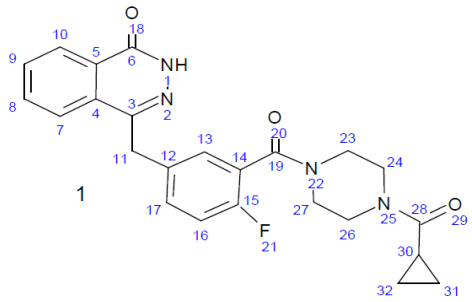
40.		7.79	-1.71	3.07
41.		7.95	-2.19	2.37
42.		9.71	-2.71	4.11
43.		7.09	-1.51	0.97
44.		8.28	-0.70	2.13

Continue Table No (3.2): Surflex Docking Scores:



Compound No.	**R**	**Total score**	**Crash**	**Polar**
45.		7.92	-1.40	1.50
46.		9.06	-0.483	2.78

3.1 The Inhibition of PARP-2 Enzyme by Olaparib (standard reference/compound1)



Molecular modeling studies indicate that Structural features of Olaparib include 2-H,phathalazine-1-one which increases potency by forming π-π interaction, while 4-NH piprazine functionality tolerates bulky substituents that increase solubility without significantly affecting PARP binding affinity, and fluorine atom improve the inhibition and metabolic stability (Curtin, *et al*, .2013).

Results showed that Olaparib exhibited very good inhibitory activity against PARP-2 with total Score 8.2 Table (3.2). TYR473 residue in the binding site was responsible for the most interactions between the enzyme and the compound 1. Two π-π interactions were between TYR473 residue and Phathalazinones rings at distance 3.9 and 3.8 respectively. The other interaction were between TYR473 residue and phenyl ring at distance 3.5 Aº.

Surflex results also show two H-bonds of distance 2.23, 2.46 Aº respectively between and H, HD21 atoms of Gly429 residue and N1, O28 at compound 1 which played the role of acceptor atoms. Other H- bond of distance 2.46 Aº between O18 and the hydrogen of the OH of ASN434 residue at the inhibitor site.

4-NH piprazine functionality didn't affect PARP binding affinity by forming any kind of H- bonding or π-π interactions.

Docking results revealed hydrophobic interactions between the hydrocarbon skeleton of the compound 1 and the hydrophobic network formed by residues Glu553, Tyr462, His428, Tyr473, Phe463, Arg431, Glu332 and Glu335 in the

binding site of the enzyme (Figure 3.2). The surface view of compound 1 inside the inhibitor site of PARP-2 is given in (Figure 3.1).

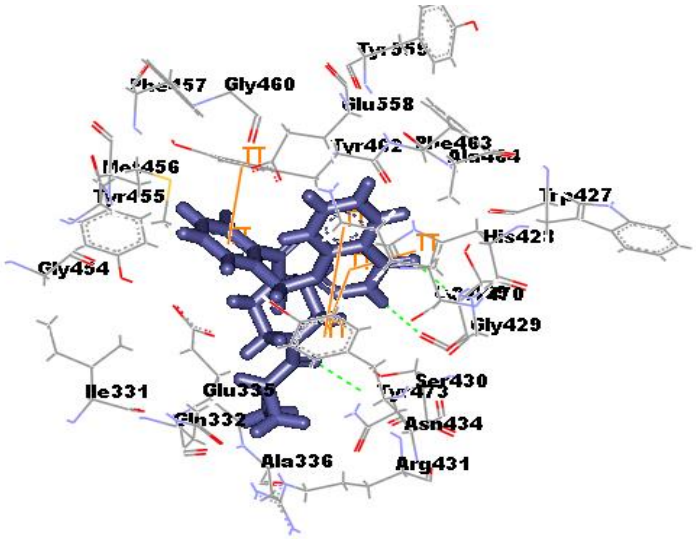


Figure (3-2): Biochemical interactions of compound 1 (Olaparib) with PARP-2 enzyme: schematic diagram obtained by DSV(Discovery Studio Visualizer) software for docking, results of Surflex software represented in ribbon form, with the interacting amino acids represented as sticks, The inhibitor is shown as ball and stick with Dotted green lines indicate enter molecular hydrogen bonding interaction, whereas the dotted orange line indicate $\pi-\pi$ stacking interactions .

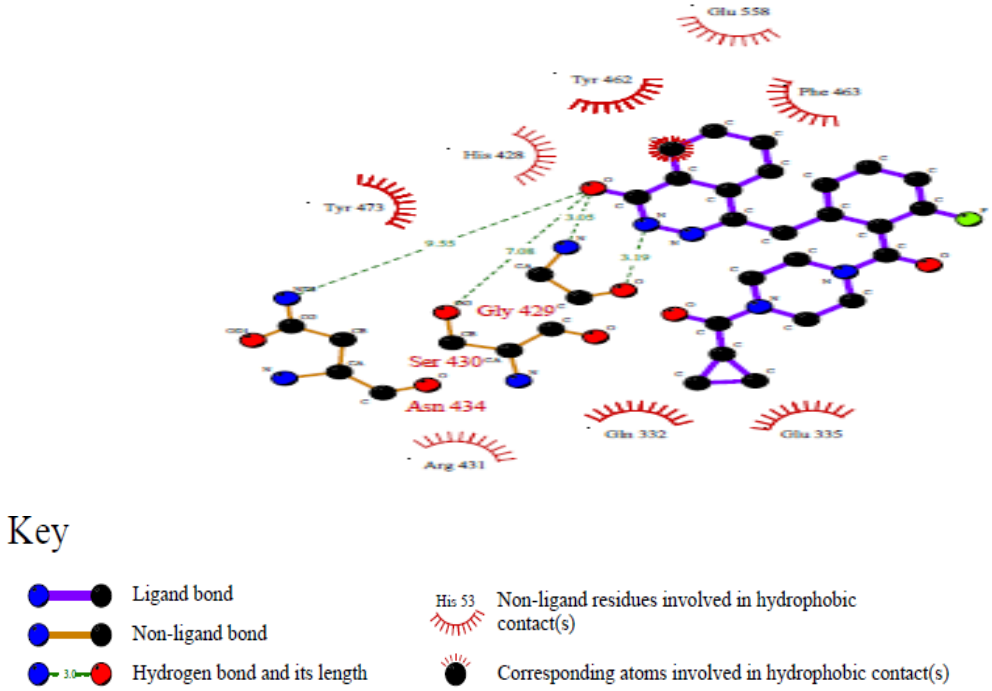
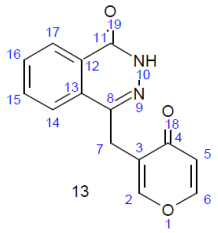


Figure (3-3): Interactions between compound 1 and inhibitor site of the PAPP-2 as predicted by Surflex plotted by Ligplot software

3.2. The Inhibition of PARP-2 Enzyme by designed Phathalazinones derivatives:

From 45 docked compounds, 7 compounds have total score higher than Olaparib and 38 compounds lower than its value. Compound 13 was neutral derivative with no highly electron donating groups has lowest total score due to the large degree of unappropriated penetration by the ligand into the protein, thus the orientation of compound cause steric clashes, assisted by decrease in polar score making poor binding affinity.



Compound 13 forming only one H-bonding between oxygen 1 and the hydrogen of the OH of TYR427 residues in the binding site of distance 2.23A^{o}.

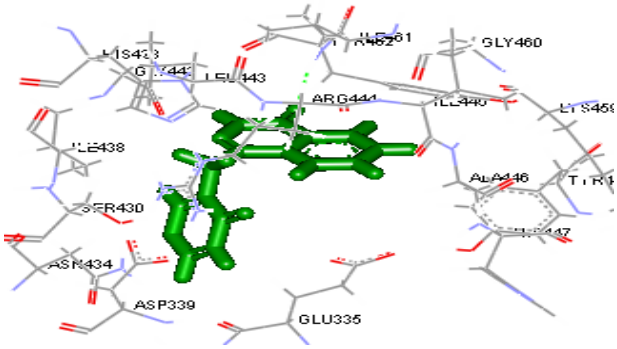
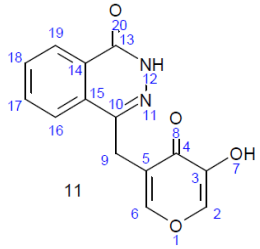


Figure (3-4): Biochemical interactions of compound 13 with PARP-2 enzyme: schematic diagram obtained by DSV software for docking, results of Surflex software represented in ribbon form, with the interacting amino acids represented as sticks, The inhibitor is shown as ball

and stick with Dotted green lines indicate enter molecular hydrogen bonding interaction, whereas the dotted orange line indicate π–π stacking interactions.

The binding affinity increases by substitution of highly donating group (OH) ortho to the carbonyl of pyran ring of the (compound 13) to give new derivative (compound 11).



The compound shows lower clash score, and forming two H-bonds of distance 2.03, 2.13 A° respectively between and hydrogen of the OH and oxygen of the carbonyl of Gly429 residue and O20, H12 of compound 11. Two π-π interactions were between TYR473 residue and Phathalazinones ring of the compound at distance 3.27 and 3.44 respectively. The other interaction was between HIS482 residue and ring at distance 4.76.

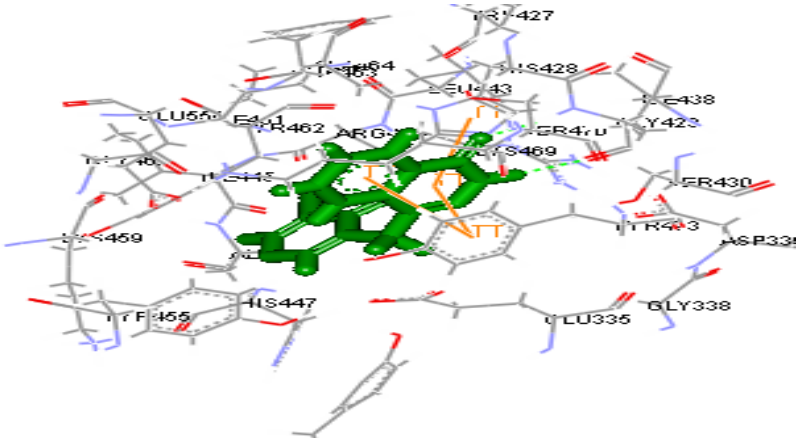
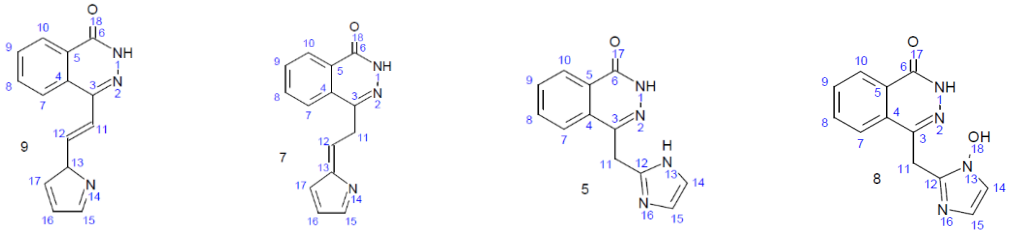


Figure (3-5): Biochemical interactions of compound 11 with PARP-2 enzyme: schematic diagram obtained by DSV software for docking, results of Surflex software represented in ribbon form, with the interacting amino acids represented as sticks, The inhibitor is shown as ball

and stick with Dotted green lines indicate enter molecular hydrogen bonding interaction, whereas the dotted orange line indicate π–π stacking interactions.



Compound 7 and 9 recorded poor affinity due to large degree of unappropriated penetration by the ligand into the protein, add to that, zero value of polarity makes compounds have no H-bonds with the binding site, the interaction was by just by forming two π–π stacking interaction between carboxamide ring of compound 7 with TYR462 of distance 3.77, 3.37 and 5.64 Aº with TYR473 of the residue

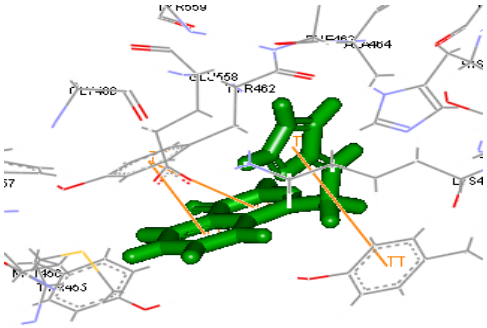


Figure (3-6): Representation of compound 7 binding mode with the PARP-2 residues

Several structural modifications were undertaken in an attempt to increase affinity, firstly by NH2 ortho substitution to the pyrole to give compound5, which was formed two π–π stacking interaction between carboxamide ring with TYR462 of distance 3.16 and 3.16Aº.

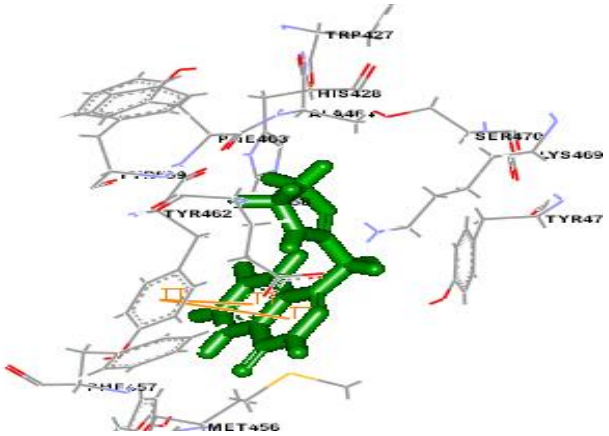


Figure (3-7): Representation of compound 5 binding mode with the PARP-2 residues

Then Further (OH) substitution at the same position to give compound 8 which have good binding affinity to PARP-2 residue. compound 8 occupies a wide cavity surrounded by the following amino acids: HIS428,TYR473, GLY429 and TYR462, the amide carbonyl forms a hydrogen bond with the side-chain of Gly429 of distance 2.03A^{o}, while another H-bond of distance 2.09A^{o} with hydrogen of the amide . It was observed that the phethlizinone moiety of this compound established four π–π interactions with Tyr473 and HIS428 of distances 4.44, 4.85, 3.76 and 5.81A^{o}, while pyrole ring π–π stacking with TYR462 was 3.62A^{o}.

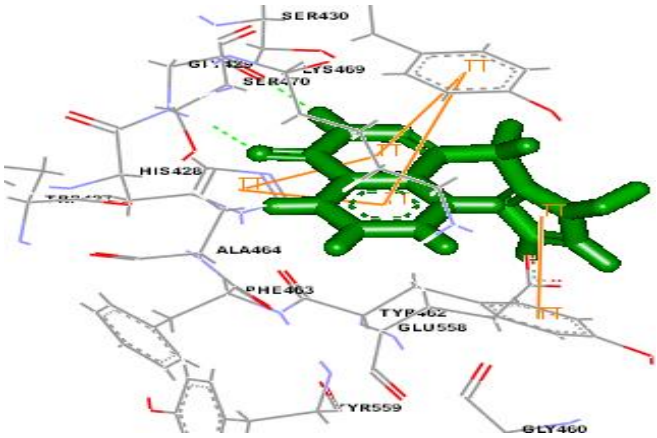
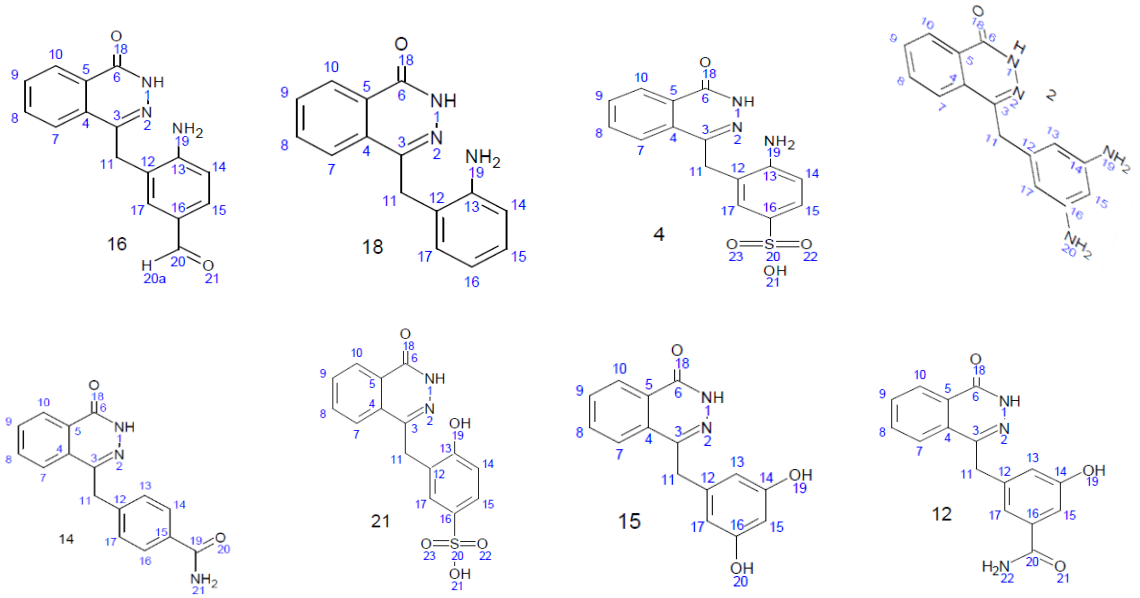


Figure (3-8): Representation of compound8 binding mode with the PARP-2 residues

In order to increase the affinity pyrole ring was replaced by phenyl in position 11 of 4-methylphathalazine-1(2H)-one and many substitutions were undergoing in different positions of the ring, to produce a set of compounds ending with compound 12 which possess two rich donating groups in position para to each other assist the compound to form three strong hydrogen bonds of distance 1.77, 2.14,and 2.47 A^{o} respectively between and OH of Gly429, SER470 and GLU558 residue and O11, H1 and H19 of compound 12 .Another attractive binding was forming five pi-pi interactions between phenyl and carboxamide ring with HIS428, TYR473 and TYR462 residue of parp-2 of distance 14.46, 4.86,4.92,3.32 ,and 4.52 A^{o} respectively.



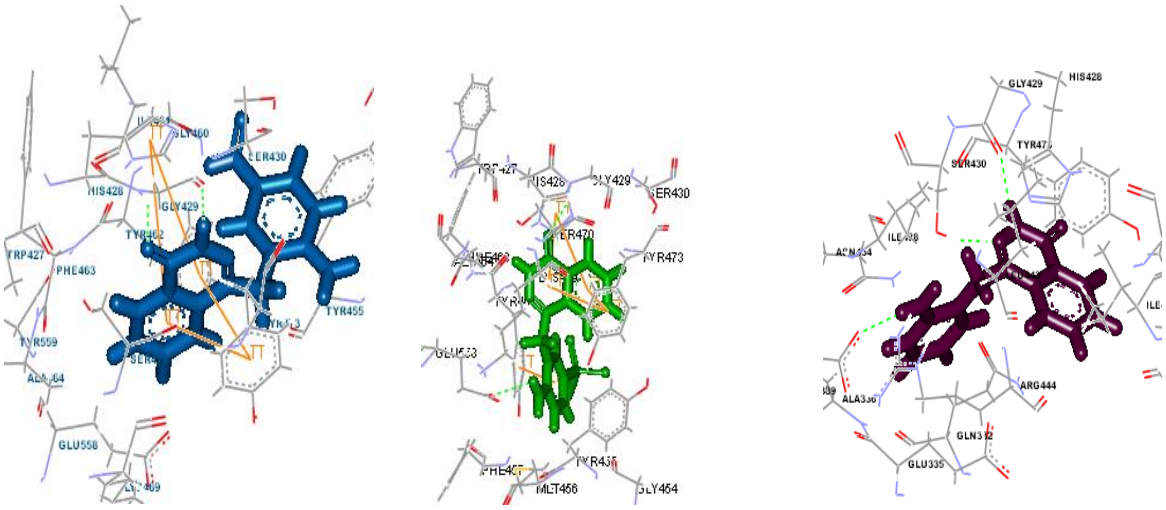


Figure (3-9): Biochemical interactions of compound 16,18,4 respectively with PARP-2 enzyme: schematic diagram obtained by DSV software for docking, results of Surflex software represented in ribbon form, with the interacting amino acids represented as sticks, The inhibitor is shown as ball and stick with Dotted green lines indicate enter molecular hydrogen bonding interaction, whereas the dotted orange line indicate π–π stacking interactions .

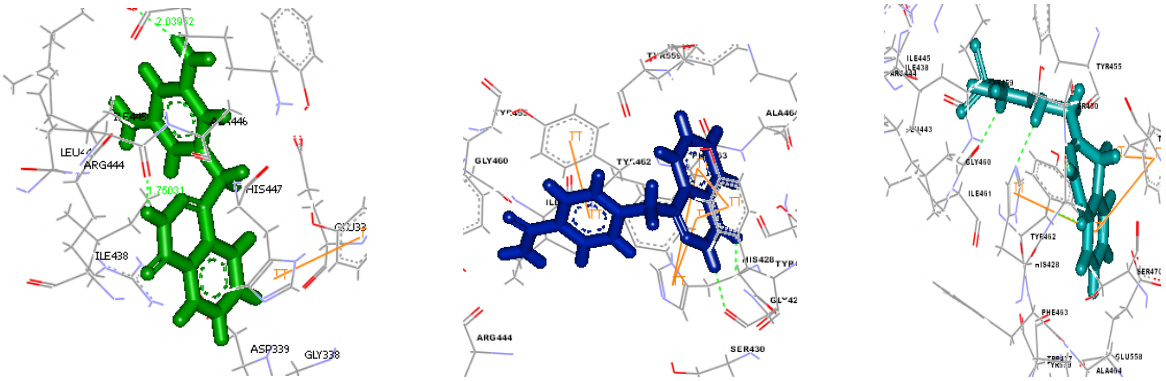


Figure (3-10): Biochemical interactions of compound 2,14.21 respectively with PARP-2 enzyme: schematic diagram obtained by DSV software for docking, results of Surflex software represented in ribbon form, with the interacting amino acids represented as sticks, The inhibitor is shown as ball and stick with Dotted green lines indicate enter molecular hydrogen bonding interaction, whereas the dotted orange line indicate π–π stacking interactions .

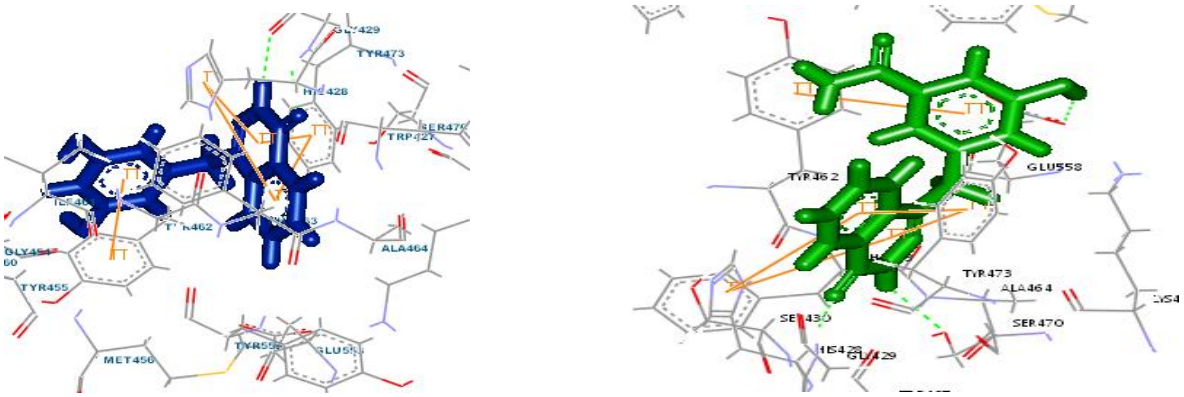
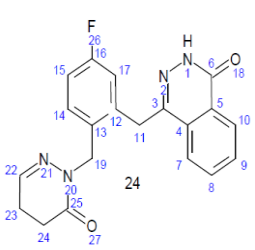
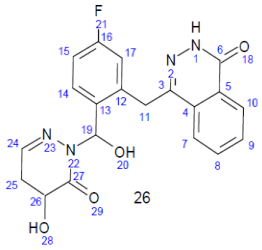


Figure (3-11): Biochemical interactions of compound 15,12 respectively with PARP-2 enzyme: schematic diagram obtained by DSV software for docking, results of Surflex software represented in ribbon form, with the interacting amino acids represented as sticks, The inhibitor is shown as ball and stick with Dotted green lines indicate enter molecular hydrogen bonding interaction, whereas the dotted orange line indicate π–π stacking interactions .





Two hydroxyl substitutions ortho to the carbonyl of pyridazinone ring ,and in position 19 of compound 24 were swapped to give new derivative - compound 26 with better interaction of two H-bonds at distance 2.03and 1.96 Aº between oxygen of OH of Gly429 and Glu335 respectively and two π–π interactions at distance 2.32 and 5.06 Aº with TYR473 and HIS428 while pi-sigma interaction was formed between hydrogen of benzyl and TYR462 side chain at distance 2.44 Aº .

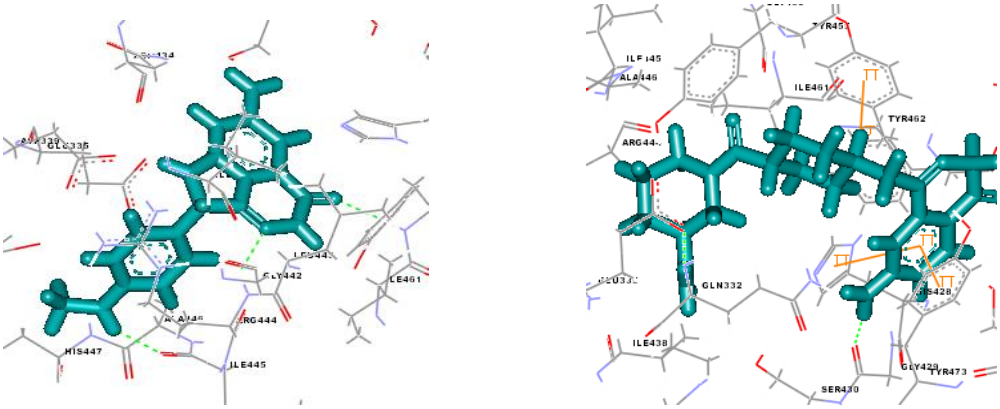
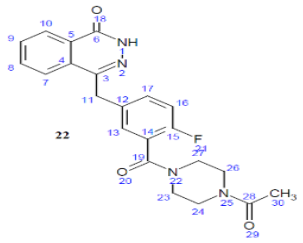
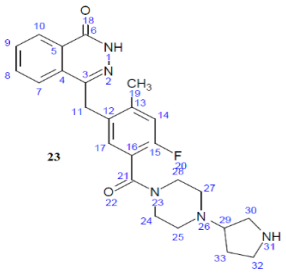


Figure (3-12): Representation of compound 24, 26 binding mode respectively with the PARP-2 residue





Significant inhansement of affinity was observed when acyl group replaced with pyrrolidine ring in N25 position of piprazine , this result in better interaction of four H-bonds with SER470, HIS428 and ASP339 and two pi-pi interactions with TYR473 of the enzyme.

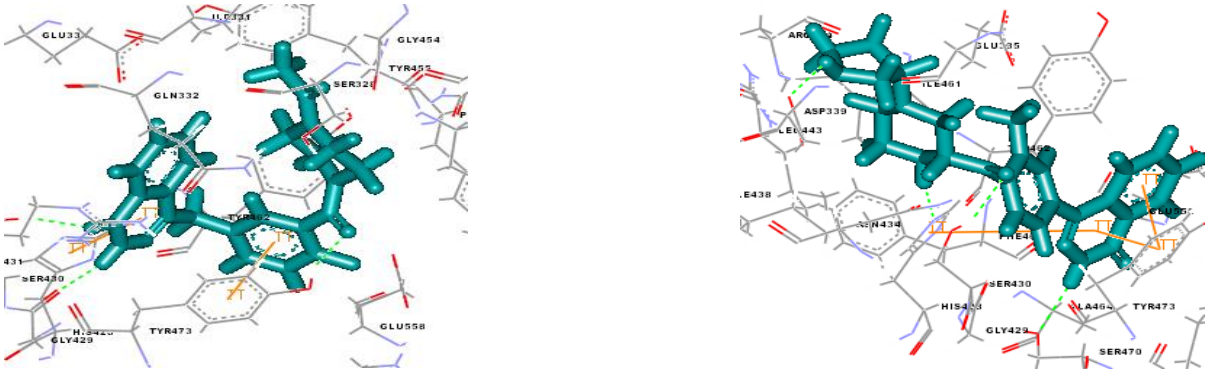
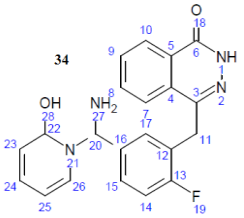
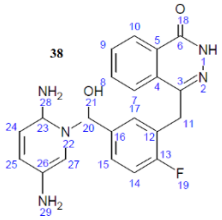


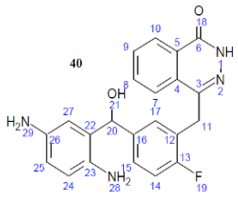
Figure (3-13): Representation of compound22, 23 respectively binding mode with the PARP-2 residue

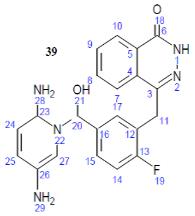
Compound 34 showed moderate affinty (6.72) when comparable with the standard referance, In order to improve its affinity subsets of compounds were designed by making different modifications ,beginning with exchange of amine and hydroxyl group positions, followed by forming ether bond and ending with locking the amide into aring in an attempt to offer another phathlide tail that can insert to the nicotinamide pocket and produce satisfied inhibition for the enzyme ,the attempts were successful by forming compound 46 with binding affinity higher than standard reference (olaparib) with score 9.06 (table3.2) the geometric orientation of Compound46 in the target active site provided three H-bonds interaction of distance 2.10, 1.97,and 2.07 A^{o} respectively between and O atom of carbonyl of Gly429,

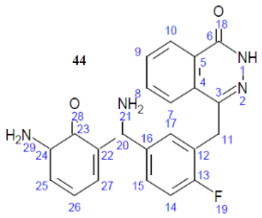
H of OH of TYR462 residue and O18, H1 and N23 of compound 46 . Compound 42 surrounded with such aromatic residues as HIS428, TYR47, TYR462, ILE451, GLY429, GLU558 and PHE463. In particular HIS428, TYR473 and TYR462 forms five π–π interactions with phenyl and carboxamide ring of distance 4.46, 4.54, 3.63, 3.80, and 5.86 A^{o} respectively.

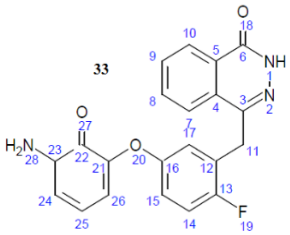


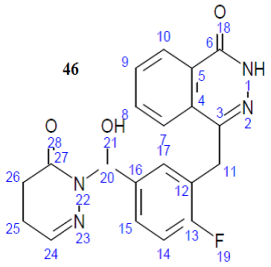


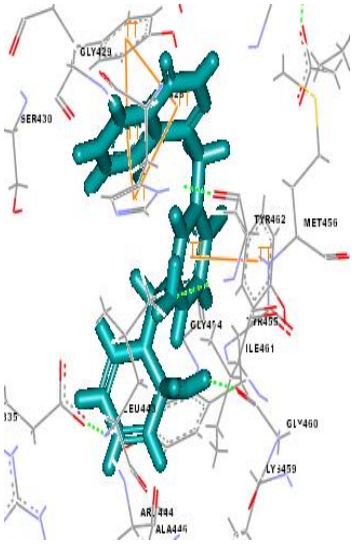


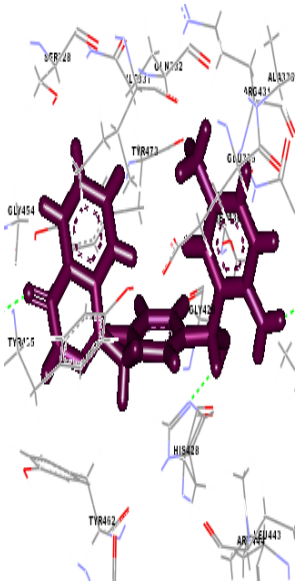












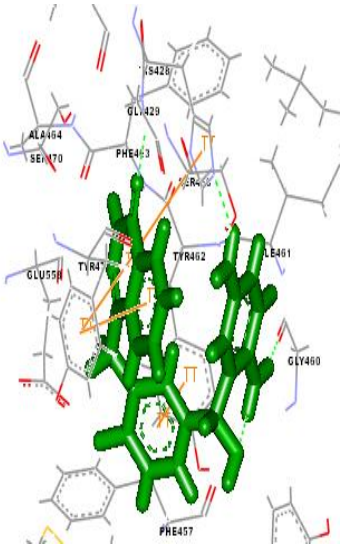


Figure (3-14): Biochemical interactions of compound 34,38,40 respectively with PARP-2 enzyme: schematic diagram obtained by DSV software for docking, results of Surflex software represented in ribbon form, with the interacting amino acids represented as sticks, The inhibitor is shown as ball and stick with Dotted green lines indicate enter molecular hydrogen bonding interaction, whereas the dotted orange line indicate π–π stacking interactions

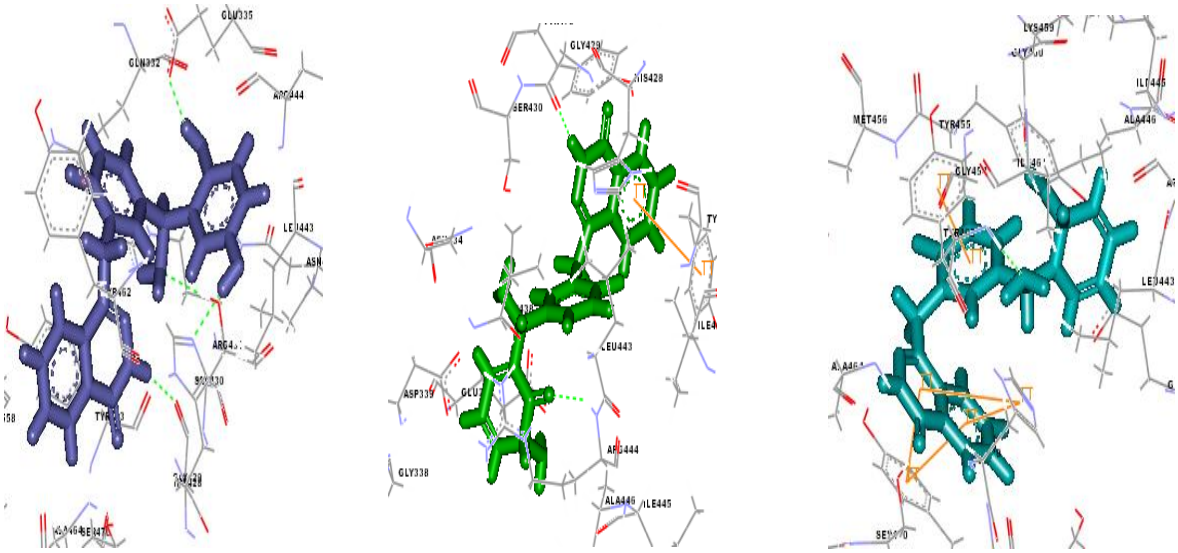


Figure (3-15): Biochemical interactions of compound 39,44,33 respectively with PARP-2 enzyme: schematic diagram obtained by DSV software for docking, results of Surflex software represented in ribbon form, with the interacting amino acids represented as sticks, The inhibitor is shown as ball and stick with Dotted green lines indicate enter molecular hydrogen bonding interaction, whereas the dotted orange line indicate π–π stacking interactions

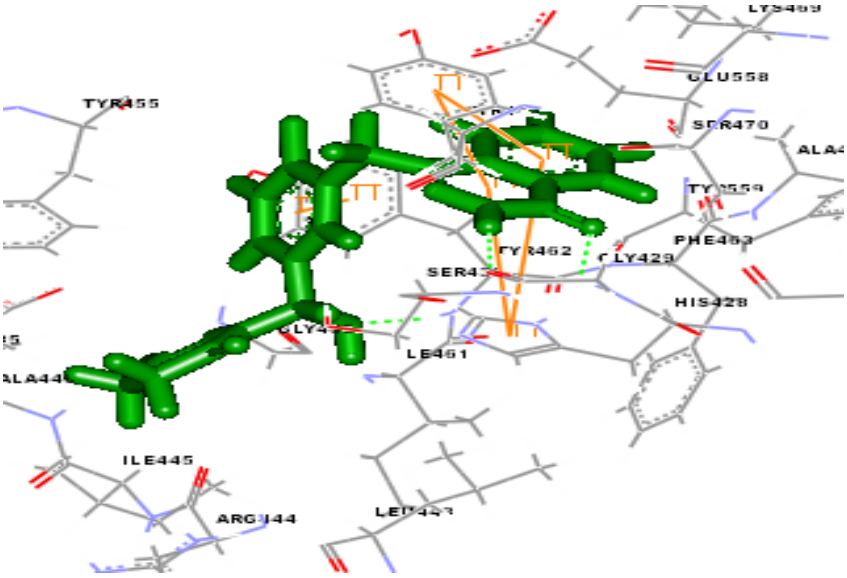
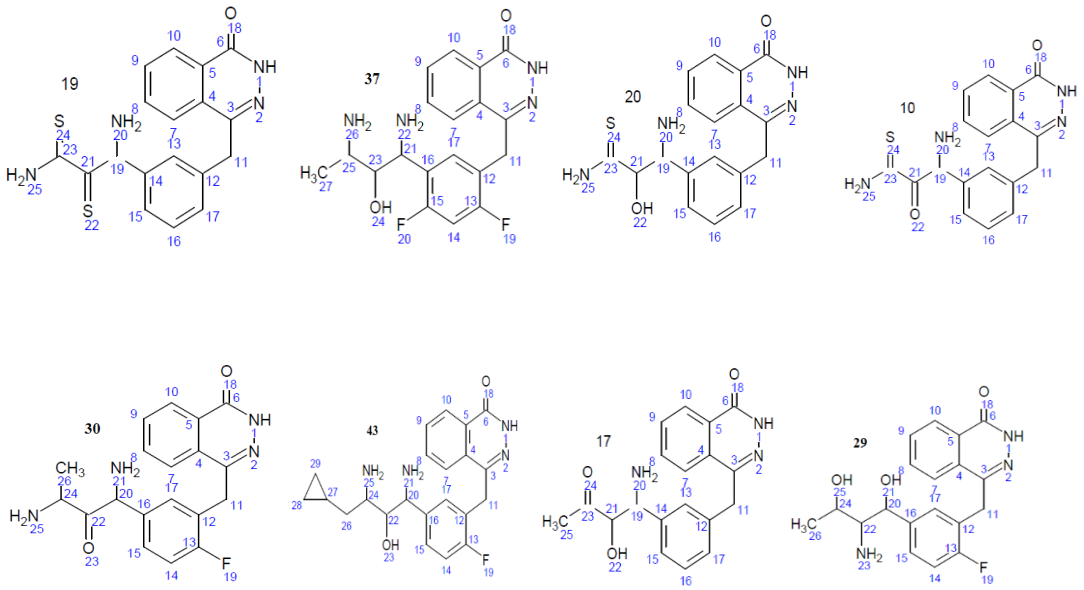


Figure (3-16): Representation of compound46 binding mode with the PARP-2 residue

Compound 19 showed low binding affinity, in order to increase it many modification were taken. substitution were switched to the 18-phenyl ring position , to produce a set of new compounds ending with compound 29 which has attractive interaction of two H-bonds and five pi-pi stacking with the side chain of the enzyme .



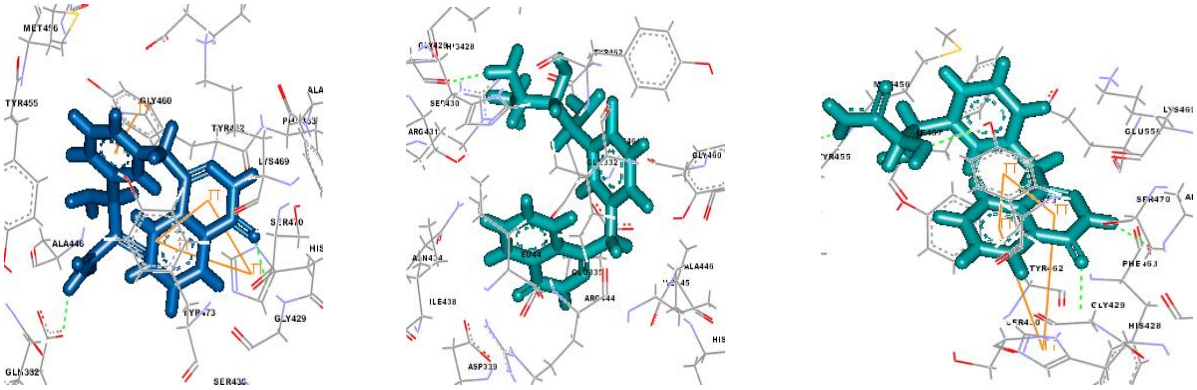


Figure (3-17): Biochemical interactions of compound 19,37,20 respectively with PARP-2 enzyme: schematic diagram obtained by DSV software for docking, results of Surflex software represented in ribbon form, with the interacting amino acids represented as sticks, The inhibitor is shown as ball and stick with Dotted green lines indicate enter molecular hydrogen bonding interaction, whereas the dotted orange line indicate π–π stacking interactions

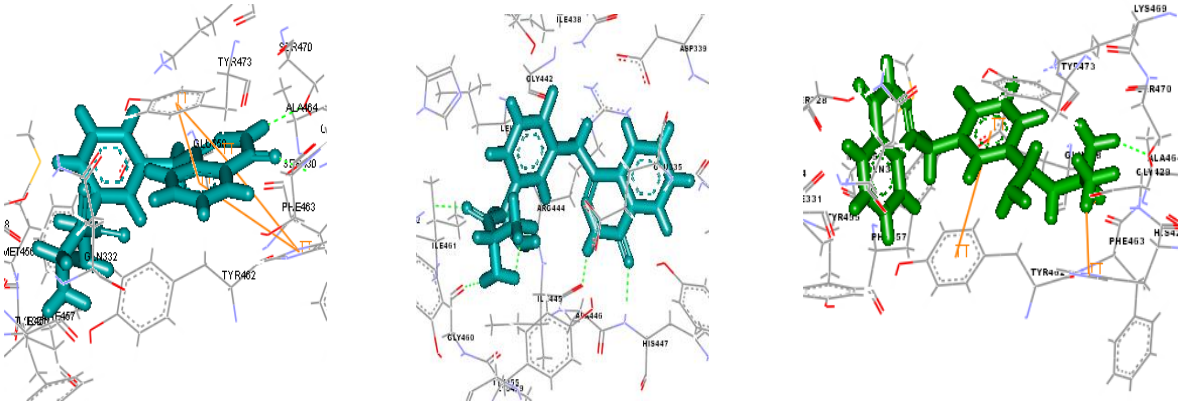


Figure (3-18): Biochemical interactions of compound 20,10,43 respectively with PARP-2 enzyme: schematic diagram obtained by DSV software for docking, results of Surflex software represented in ribbon form, with the interacting amino acids represented as sticks, The inhibitor is shown as ball and stick with Dotted green lines indicate enter molecular hydrogen bonding interaction, whereas the dotted orange line indicate π–π stacking interactions

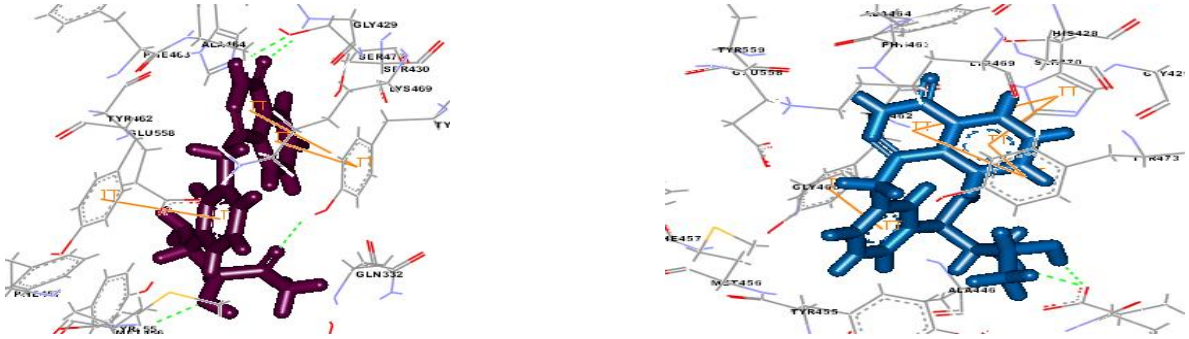


Figure (3-19): Biochemical interactions of compound 17,29 respectively with PARP-2 enzyme: schematic diagram obtained by DSV software for docking, results of Surflex software represented in ribbon form, with the interacting amino acids represented as sticks, The inhibitor is shown as ball and stick with Dotted green lines indicate enter molecular hydrogen bonding interaction, whereas the dotted orange line indicate $\pi-\pi$ stacking interactions**.**

Through the designing of the previous derivatives ,it seems that the presence of donating groups and phenyl ring increase the binding affinity and thus makes good attraction with the side chain of the enzyme ,resulting in good inhibitory effect .

The hypothesis was confirmed when good donating groups were swapped in position (16-phenyl) of the 4-methylphathalazine-1(2H)-one derivative, significant enhancement of affinity was observed when amino and hydroxyl groups were substituted to produce new set of compounds that showed very good interaction with the receptor and finally leading to the designing of compound 42 .Docking data relieved that this compound was top- ranked docking results in terms of its binding to the receptor with total score 9.71 which was higher comparable to the standard reference .Highly donating groups (amine , and two groups of hydroxyl para to each other) assisted the compound to possess high polarity 4.11 (table3.2).The core hexa cyclic group of the compound is tethered to the base of the binding pocket via conserved hydrogen bonding interactions with GLY429 backbone and HIS428 side chain hydroxyl atoms . The cyclic moiety is common found in many PARP inhibitors (Ferras, 2010). Phathalazinone carbonyl involved in a hydrogen bond with nearby hydrogen of OH of GLY428 amino acid of the residue at distance 2.01 A^o, while nitrogen of the amine and Oxygen of OH20 in the compound were formed two H-bonding with hydrogen of OH of His4228 at distance 1.81 and 2.44 A^o respectively. Ser430 in the side chain of the enzyme formed two hydrogen bonds between its nitrogen and oxygen atoms and OH20, OH25 of the compound at distance 2.07 and 1.75 A^o respectively. Docking results revealed hydrophobic interactions between the hydrocarbon skeleton of the compound 42 and the

hydrophobic network formed by residues Glu553, His428, Tyr473, Arg431, Asp335, and Asn434 in the binding site of the enzyme (Figure 3.21). The surface view of compound 42 inside the inhibitor site of PARP-2 is given in (Figure 3.20).

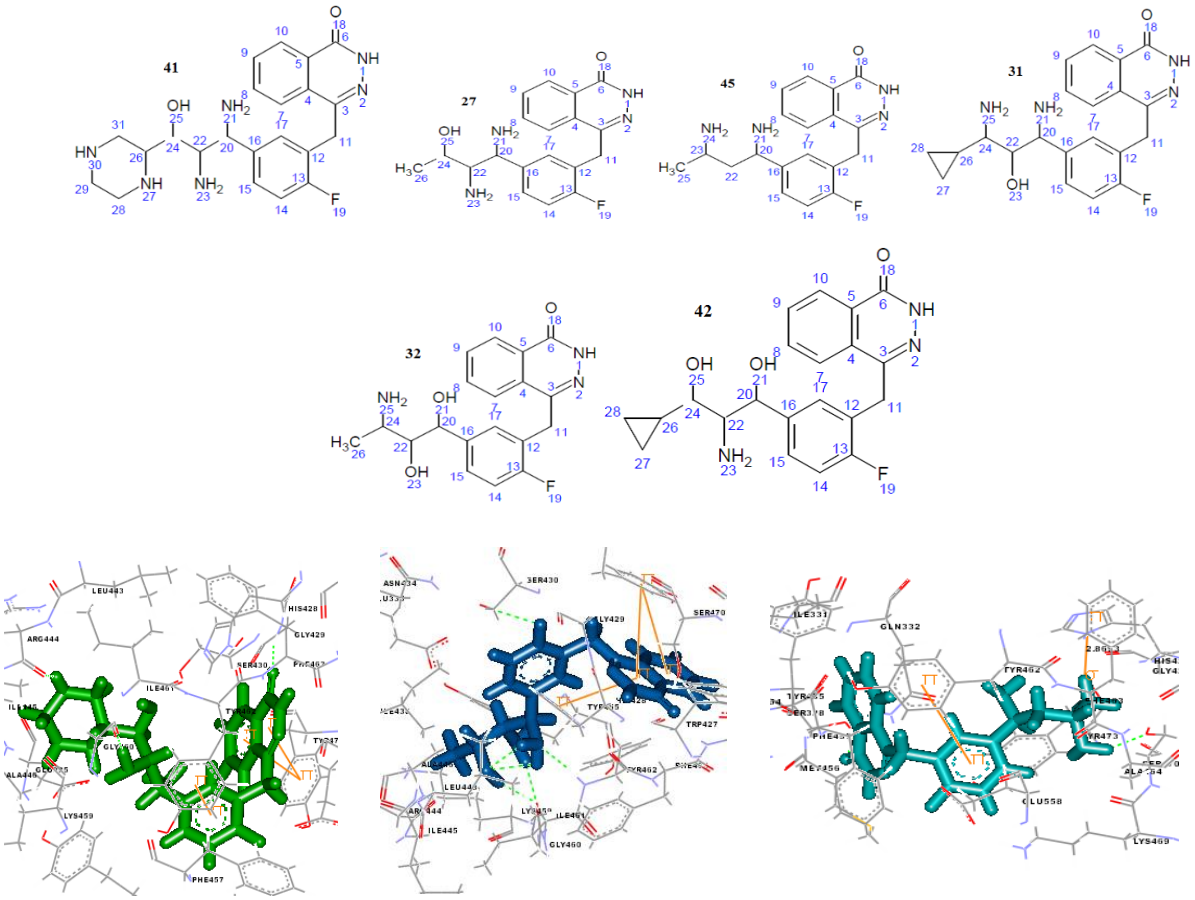


Figure (3-20): Biochemical interactions of compound 41,27,45 respectively with PARP-2 enzyme: schematic diagram obtained by DSV software for docking, results of Surflex software represented in ribbon form, with the interacting amino acids represented as sticks, The inhibitor is shown as ball and stick with Dotted green lines indicate enter molecular hydrogen bonding interaction, whereas the dotted orange line indicate π–π stacking interactions

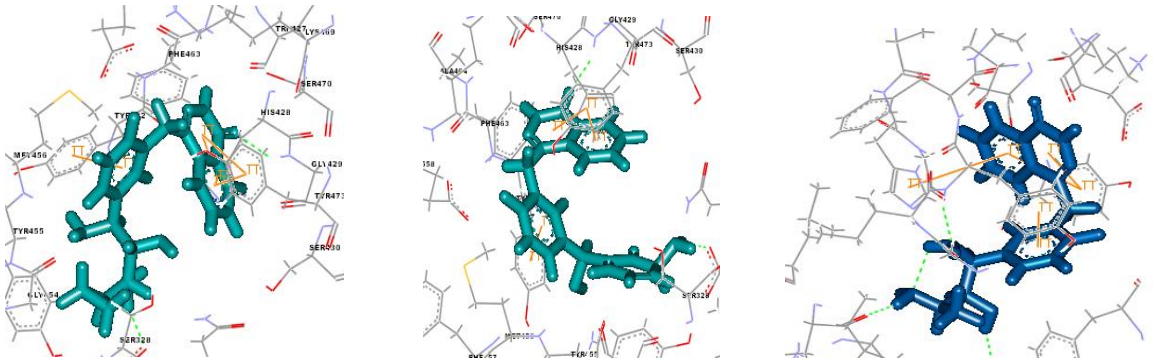


Figure (3-21): Biochemical interactions of compound 31,32,28 respectively with PARP2 enzyme: schematic diagram obtained by DSV software for docking, results of Surflex software represented in ribbon form, with the interacting amino acids represented as sticks, The inhibitor is shown as ball and stick with Dotted green lines indicate enter molecular hydrogen bonding interaction, whereas the dotted orange line indicate π–π stacking interactions

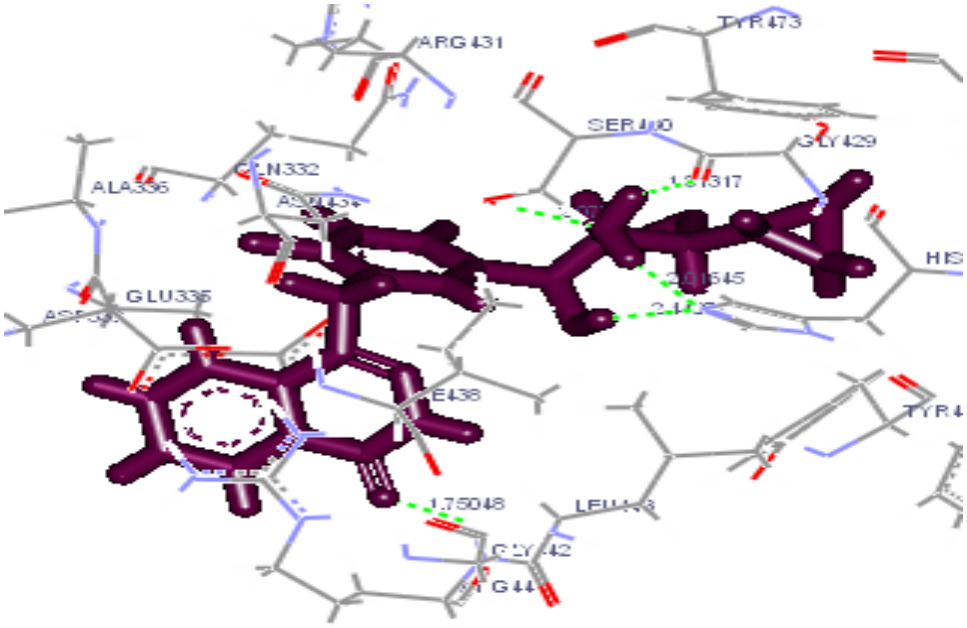


Figure (3-22): Representation of compound 42 binding mode with the PARP-2 residue: schematic diagram obtained by DSV software for docking results of surflex

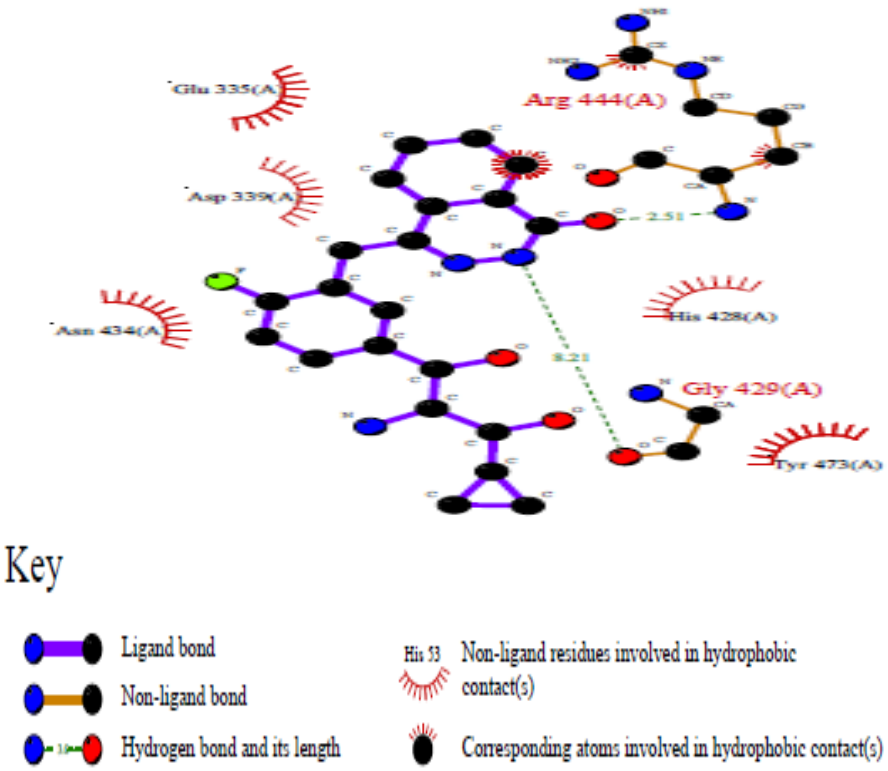


Figure (3-23): Representation of compound 42 binding mode with the PARP-2 residue: schematic diagram obtained by Ligplot software for docking results of surflex

Conclusion and Recommendations

In the current study 65 compounds of phthalazinones derivatives were designed, all these compounds have a nicotinamide-based structure aimed at competing with NAD+ for the binding to PARP-2 catalytic site.

45 compounds which have chemical properties values closes to the reference standard (Olaparib) were chosen to be docked into the inhibitor site of protein by using surflex software (syblyl), among these compounds seven derivatives gave promising score which was higher than Olaparib. Docking data revealed that (4-[5-(2-amino-3-cyclopropyl-1,3-dihydroxypropyl)-2-flurobenzyl] phthalazine-1 (2H)-

one) was the top –ranked compound in term of its binding to PARP-2 enzyme, its Surflex score was (-logkd=9.71). Analysis of the result by Discovery Studio Visualizer showed that the presence of aromatic rings, which allow for π-π interactions to occur and good donating groups which forms hydrogen bonding with the amino acid in the side chain of the enzyme is the most common factor for increasing the binding affinity.

Further studies are recommended to be conducted, such as synthesis and determination of the IC_{50} values of the designed compounds, to study the mechanism of inhibition of the enzyme by the compounds, based on the data of inhibition , kinetics experiments could achieved to test the cytotoxicity. And to assess the ADMET properties of the compounds.

Chapter Four

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4. References

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Appendices

Sybyl results for 20 docked poses of every ligand pose

Total Score/ Crash / Polar

olaparib_000 8.20 -1.99 1.96
olaparib_001 7.95 -1.48 3.01
olaparib_002 7.88 -0.77 3.94
olaparib_003 7.85 -1.26 1.90
olaparib_004 7.20 -1.36 1.42
olaparib_005 7.17 -1.49 3.16
olaparib_006 7.14 -0.80 3.39
olaparib_007 7.10 -1.21 2.70
olaparib_008 7.04 -0.81 1.70
olaparib_009 7.03 -1.51 3.17
olaparib_010 6.93 -0.91 3.28
olaparib_011 6.92 -1.48 3.12
olaparib_012 6.59 -1.41 3.12
olaparib_013 6.54 -1.08 2.42
olaparib_014 6.41 -0.76 1.81
olaparib_015 6.21 -1.05 1.16
olaparib_016 6.04 -0.85 1.49
olaparib_017 6.00 -0.85 1.30
olaparib_018 5.97 -1.25 2.46
olaparib_019 5.85 -2.07 3.15
compound2_000 5.71 -0.87 1.47
compound2_001 5.50 -0.40 0.75
compound2_002 5.50 -0.44 1.86
compound2_003 5.45 -0.32 0.73
compound2_004 5.41 -0.40 0.95
compound2_005 5.40 -0.39 0.75
compound2_006 5.36 -0.41 0.88
compound2_007 5.32 -0.39 0.78
compound2_008 5.27 -0.41 1.72
compound2_009 4.77 -0.43 1.09
compound2_010 4.69 -0.42 2.36
compound2_011 4.63 -0.41 2.34
compound2_012 4.62 -0.44 2.37
compound2_013 4.54 -0.44 2.35
compound2_014 4.43 -0.27 2.12
compound2_015 4.40 -0.41 1.09
compound2_016 4.37 -1.11 1.48
compound2_017 4.23 -1.04 1.57
compound2_018 3.96 -0.43 1.21

compound2_019 3.94 -0.46 1.20
compound3_000 5.78 -0.73 2.54
compound3_001 5.77 -0.76 2.48
compound3_002 4.97 -0.73 1.87
compound3_003 4.08 -0.80 1.48
compound3_004 3.98 -0.38 1.92
compound3_005 3.97 -0.45 1.90
compound3_006 3.95 -0.81 0.26
compound3_007 3.81 -1.39 1.19
compound3_008 3.71 -0.34 2.19
compound3_009 3.71 -0.77 0.39
compound3_010 3.62 -0.33 2.19
compound3_011 3.50 -0.30 1.66
compound3_012 3.42 -0.37 1.08
compound3_013 3.29 -1.14 1.09
compound3_014 3.21 -0.53 2.54
compound3_015 3.18 -0.96 1.37
compound3_016 3.15 -1.31 2.61
compound3_017 3.13 -1.51 1.19
compound3_018 3.13 -1.20 2.62
compound3_019 3.06 -0.45 1.16
compound4_000 5.59 -1.16 1.11
compound4_001 5.58 -1.21 1.02
compound4_002 5.58 -1.34 0.72
compound4_003 5.56 -1.34 1.00
compound4_004 5.56 -1.19 0.81
compound4_005 5.55 -1.41 0.79
compound4_006 5.54 -1.32 0.84
compound4_007 5.54 -1.27 0.82
compound4_008 5.54 -1.20 0.83
compound4_009 5.48 -1.30 1.33
compound4_010 5.46 -1.35 0.83
compound4_011 5.43 -1.39 0.79
compound4_012 5.37 -1.50 0.80
compound4_013 5.30 -1.65 0.85
compound4_014 5.16 -1.16 0.80
compound4_015 5.13 -1.90 0.74
compound4_016 4.89 -1.74 0.78
compound4_017 3.75 -2.42 1.07
compound4_018 3.71 -2.44 1.09
compound4_019 3.69 -2.50 1.04
compound5_000 5.87 -0.77 0.02
compound5_001 5.52 -0.75 0.02
compound5_002 4.95 -0.45 0.08
compound5_003 4.75 -0.42 0.16
compound5_004 4.70 -0.71 0.00
compound5_005 4.64 -0.68 0.00
compound5_006 4.60 -0.63 0.00
compound5_007 4.36 -1.00 2.11
compound5_008 4.14 -0.24 0.87
compound5_009 3.79 -0.20 0.76
compound5_010 3.74 -0.18 0.85
compound5_011 3.72 -0.18 0.83
compound5_012 3.64 -0.24 1.53
compound5_013 3.44 -0.37 0.91
compound5_014 3.32 -0.84 2.13
compound5_015 3.27 -1.27 2.13

compound5_016 3.18 -0.23 0.78
compound5_017 3.10 -1.45 0.90
compound5_018 3.09 -0.72 0.13
compound5_019 3.08 -0.38 1.23
compound6_000 6.17 -0.40 3.12
compound6_001 5.92 -0.22 1.84
compound6_002 5.26 -0.25 2.12
compound6_003 5.15 -0.70 1.63
compound6_004 5.11 -0.48 1.98
compound6_005 5.09 -0.68 1.73
compound6_006 5.07 -0.64 1.62
compound6_007 5.00 -0.60 1.65
compound6_008 4.98 -0.64 1.69
compound6_009 4.86 -0.41 1.71
compound6_010 4.80 -0.32 1.83
compound6_011 4.78 -0.46 1.55
compound6_012 4.76 -0.95 1.78
compound6_013 4.75 -0.82 1.72
compound6_014 4.74 -0.87 1.75
compound6_015 4.72 -0.85 1.64
compound6_016 4.72 -0.44 1.51
compound6_017 4.63 -0.39 1.61
compound6_018 4.62 -0.50 1.48
compound6_019 4.58 -0.96 1.70
compound7_000 5.19 -0.35 0.00
compound7_001 4.87 -0.50 1.76
compound7_002 4.63 -0.34 2.21
compound7_003 4.53 -0.65 0.95
compound7_004 4.29 -0.72 1.59
compound7_005 4.09 -0.69 1.73
compound7_006 3.80 -0.18 1.01
compound7_007 3.78 -0.71 0.80
compound7_008 3.71 -0.78 0.75
compound7_009 3.71 -0.44 1.93
compound7_010 3.55 -0.23 1.07
compound7_011 3.46 -0.48 0.02
compound7_012 3.45 -0.20 1.13
compound7_013 3.42 -0.24 1.12
compound7_014 3.41 -0.20 1.16
compound7_015 3.30 -1.00 2.63
compound7_016 3.19 -0.34 2.36
compound7_017 3.16 -0.36 1.08
compound7_018 3.14 -0.32 0.96
compound7_019 3.13 -0.37 0.98
compound8_000 6.28 -0.23 2.00
compound8_001 5.84 -0.64 1.06
compound8_002 4.68 -0.39 1.02
compound8_003 4.61 -0.33 1.12
compound8_004 4.04 -0.65 2.59
compound8_005 4.00 -1.65 2.04
compound8_006 3.81 -1.06 2.00
compound8_007 3.77 -0.39 0.95
compound8_008 3.61 -0.95 1.28
compound8_009 3.48 -0.46 1.09
compound8_010 3.42 -1.67 2.15
compound8_011 3.31 -0.73 0.72
compound8_012 3.26 -0.96 2.06

compound8_013 3.25 -0.30 1.19
compound8_014 3.06 -0.59 1.67
compound8_015 3.00 -0.52 2.47
compound8_016 2.90 -1.18 3.08
compound8_017 2.76 -0.48 1.00
compound8_018 2.73 -0.38 1.20
compound8_019 2.65 -0.85 0.94
compound9_000 5.11 -0.43 0.00
compound9_001 4.71 -0.73 1.96
compound9_002 4.70 -0.74 1.93
compound9_003 4.55 -1.54 0.76
compound9_004 4.48 -1.39 0.71
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compound9_006 4.01 -0.24 1.18
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compound14_016 4.93 -0.60 1.48
compound14_017 4.84 -0.83 1.32
compound14_018 4.71 -1.54 2.14
compound14_019 3.82 -2.40 1.10
compound15_000 6.64 -0.39 1.86
compound15_001 6.63 -0.30 3.19
compound15_002 6.59 -0.22 3.19
compound15_003 6.55 -0.28 3.18
compound15_004 6.53 -0.34 3.15
compound15_005 6.51 -0.30 3.09
compound15_006 6.50 -0.30 1.99
compound15_007 6.49 -0.31 3.19
compound15_008 6.43 -0.30 3.23
compound15_009 6.43 -0.29 3.11
compound15_010 6.38 -0.27 3.01
compound15_011 6.37 -0.51 3.39
compound15_012 6.33 -0.53 3.36
compound15_013 6.32 -0.33 1.90
compound15_014 6.32 -0.44 3.39
compound15_015 6.31 -0.27 1.92
compound15_016 6.31 -0.35 2.03
compound15_017 6.29 -0.48 3.41
compound15_018 6.28 -0.58 3.44
compound15_019 6.27 -0.51 2.11
compound16_000 5.07 -0.52 2.19
compound16_001 4.89 -1.52 2.83
compound16_002 4.70 -1.87 1.93
compound16_003 4.60 -1.03 0.87
compound16_004 4.48 -0.71 2.17
compound16_005 4.40 -0.80 1.02
compound16_006 4.32 -1.14 3.25
compound16_007 4.17 -0.45 2.31
compound16_008 4.11 -0.59 0.04
compound16_009 4.09 -0.89 0.00
compound16_010 4.05 -0.49 2.28
compound16_011 3.97 -0.79 3.09
compound16_012 3.91 -0.32 2.26
compound16_013 3.88 -0.92 2.87
compound16_014 3.76 -0.65 1.35
compound16_015 3.75 -2.49 1.16
compound16_016 3.73 -0.45 3.45
compound16_017 3.72 -1.77 2.24
compound16_018 3.67 -0.83 2.19
compound16_019 3.64 -0.93 3.05
compound17_000 7.25 -1.94 3.13
compound17_001 6.65 -1.45 0.98
compound17_002 6.63 -1.19 1.08
compound17_003 6.29 -1.32 1.01

compound17_004 6.21 - 1.16 0.81
compound17_005 6.20 - 1.08 1.02
compound17_006 5.94 - 1.29 0.83
compound17_007 5.88 - 1.20 0.96
compound17_008 5.87 - 1.23 0.73
compound17_009 5.80 - 1.17 0.78
compound17_010 5.69 - 1.31 0.82
compound17_011 5.58 - 1.07 0.81
compound17_012 5.54 - 1.29 0.81
compound17_013 5.52 - 1.03 1.78
compound17_014 5.40 - 1.17 0.77
compound17_015 5.36 - 0.97 0.99
compound17_016 4.98 - 1.45 0.98
compound17_017 4.87 - 1.85 0.80
compound17_018 4.86 - 1.64 0.00
compound17_019 4.79 - 1.37 0.85
compound18_000 5.08 - 0.93 2.12
compound18_001 4.24 - 2.09 1.15
compound18_002 4.05 - 1.48 0.91
compound18_003 3.94 - 0.75 1.13
compound18_004 3.66 - 0.85 1.08
compound18_005 3.51 - 1.02 1.17
compound18_006 3.50 - 0.87 1.14
compound18_007 3.43 - 0.86 1.08
compound18_008 3.42 - 0.55 1.15
compound18_009 3.40 - 0.57 1.13
compound18_010 3.34 - 1.05 0.91
compound18_011 3.34 - 1.10 0.95
compound18_012 3.33 - 0.58 1.04
compound18_013 3.31 - 0.55 1.14
compound18_014 3.29 - 1.16 0.73
compound18_015 3.24 - 2.21 1.27
compound18_016 3.10 - 2.01 0.89
compound18_017 3.09 - 1.17 0.18
compound18_018 3.06 - 0.78 1.06
compound18_019 3.06 - 1.88 0.70
compound19_000 5.43 - 2.07 2.04
compound19_001 5.38 - 2.36 1.95
compound19_002 4.84 - 2.35 1.40
compound19_003 4.77 - 2.46 2.01
compound19_004 4.44 - 2.46 2.59
compound19_005 4.42 - 1.49 0.13
compound19_006 4.30 - 1.62 0.79
compound19_007 4.22 - 1.83 0.66
compound19_008 4.16 - 2.00 1.35
compound19_009 4.14 - 2.65 2.00
compound19_010 4.05 - 2.33 1.55
compound19_011 3.98 - 2.30 1.37
compound19_012 3.89 - 1.99 2.32
compound19_013 3.86 - 1.82 2.01
compound19_014 3.77 - 1.84 0.77
compound19_015 3.65 - 2.46 1.10
compound19_016 3.46 - 0.97 0.22
compound19_017 3.44 - 0.85 0.16
compound19_018 3.36 - 1.20 0.29
compound19_019 3.35 - 2.54 2.55
compound20_000 5.77 - 1.85 3.09

compound20_001 5.10 -1.24 2.07
compound20_002 5.05 -1.69 1.67
compound20_003 4.13 -2.47 2.93
compound20_004 3.98 -1.53 0.33
compound20_005 3.85 -2.17 2.14
compound20_006 3.84 -2.14 2.12
compound20_007 3.76 -2.41 1.50
compound20_008 3.46 -2.31 1.85
compound20_009 3.41 -2.17 1.91
compound20_010 3.38 -2.15 1.71
compound20_011 3.35 -2.62 2.09
compound20_012 3.33 -2.24 1.72
compound20_013 3.28 -2.40 1.86
compound20_014 3.24 -2.26 1.56
compound20_015 3.19 -2.30 1.63
compound20_016 3.00 -4.08 2.66
compound20_017 2.88 -2.20 1.25
compound20_018 2.67 -2.39 1.20
compound20_019 2.59 -2.75 1.39
compound21_000 6.41 -0.53 3.98
compound21_001 5.55 -2.10 2.85
compound21_002 5.44 -2.07 2.75
compound21_003 5.30 -1.02 2.31
compound21_004 5.29 -2.21 2.79
compound21_005 5.25 -2.33 2.83
compound21_006 5.08 -2.25 2.83
compound21_007 4.99 -2.66 2.70
compound21_008 4.95 -2.60 2.83
compound21_009 4.76 -2.61 2.79
compound21_010 4.73 -1.07 2.59
compound21_011 4.69 -1.27 1.04
compound21_012 4.65 -2.25 2.17
compound21_013 4.63 -2.75 2.74
compound21_014 4.55 -2.58 2.55
compound21_015 4.38 -2.79 2.63
compound21_016 4.36 -1.48 1.85
compound21_017 4.34 -2.29 2.72
compound21_018 4.22 -3.38 3.02
compound21_019 4.09 -0.80 2.15
compound22_000 5.27 -2.34 1.90
compound22_001 5.24 -3.09 1.08
compound22_002 4.91 -3.12 0.76
compound22_003 4.78 -1.93 1.53
compound22_004 4.67 -2.55 0.98
compound22_005 4.63 -0.73 0.95
compound22_006 4.46 -2.46 0.05
compound22_007 4.44 -2.85 1.01
compound22_008 4.37 -2.62 1.13
compound22_009 4.24 -3.09 0.97
compound22_010 4.22 -2.73 1.20
compound22_011 3.82 -2.27 1.17
compound22_012 3.73 -2.28 1.06
compound22_013 3.70 -2.28 0.90
compound22_014 3.63 -2.28 1.27
compound22_015 3.48 -0.83 0.00
compound22_016 3.40 -3.70 1.03
compound22_017 3.36 -2.69 1.16

compound22_018 3.26 -0.68 0.08
compound22_019 3.09 -2.48 0.00
compound23_000 7.23 -1.27 1.70
compound23_001 7.09 -1.44 2.01
compound23_002 7.05 -1.40 2.00
compound23_003 6.89 -1.32 1.83
compound23_004 6.43 -0.75 0.00
compound23_005 6.14 -2.30 1.14
compound23_006 5.73 -1.84 0.01
compound23_007 5.62 -1.05 0.00
compound23_008 5.53 -1.69 0.00
compound23_009 5.44 -3.20 0.76
compound23_010 5.12 -2.22 0.04
compound23_011 4.72 -1.74 0.80
compound23_012 4.13 -1.95 0.50
compound23_013 4.12 -2.23 0.01
compound23_014 3.82 -1.90 1.83
compound23_015 3.71 -4.01 0.04
compound23_016 3.55 -1.64 2.12
compound23_017 3.35 -4.06 0.06
compound23_018 2.90 -1.67 0.12
compound24_000 7.04 -1.5 2.35
compound24_001 5.60 -0.79 1.85
compound24_002 5.45 -0.89 1.50
compound24_003 5.44 -0.68 1.79
compound24_004 5.26 -1.30 1.04
compound24_005 5.19 -1.28 0.90
compound24_006 4.87 -0.41 1.24
compound24_007 4.87 -0.90 1.95
compound24_008 4.72 -0.95 1.87
compound24_009 4.45 -0.40 1.29
compound24_010 4.38 -0.65 2.37
compound24_011 4.24 -0.77 1.19
compound24_012 4.22 -0.42 0.66
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compound24_018 3.59 -0.52 1.20
compound24_019 3.55 -0.68 1.26
compound25_000 7.43 -1.51 1.22
compound25_001 7.43 -1.52 1.20
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compound25_006 6.84 -1.60 0.85
compound25_007 6.77 -0.81 2.17
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compound25_009 6.63 -1.23 0.04
compound25_010 6.62 -0.53 1.75
compound25_011 6.59 -1.80 0.56
compound25_012 6.53 -0.65 1.44
compound25_013 6.40 -2.19 0.83
compound25_014 6.34 -0.41 1.60
compound25_015 6.34 -0.53 1.61

compound25_016 6.31 -0.37 1.71
compound25_017 6.20 -0.51 1.89
compound25_018 6.18 -0.48 1.70
compound25_019 6.17 -0.22 2.47
copound26_000 7.42 -1.62 2.07
copound26_001 6.31 -1.05 1.04
copound26_002 6.28 -1.19 0.92
copound26_003 6.24 -1.26 1.03
copound26_004 6.21 -1.26 0.97
copound26_005 6.19 -0.81 1.06
copound26_006 6.16 -0.61 0.81
copound26_007 6.00 -0.83 1.01
copound26_008 5.99 -2.92 1.36
copound26_009 5.99 -0.90 1.02
copound26_010 5.97 -0.91 1.05
copound26_011 5.89 -0.85 1.10
copound26_012 5.85 -1.27 1.57
copound26_013 5.84 -1.58 1.17
copound26_014 5.57 -1.77 1.47
copound26_015 5.51 -0.94 1.10
copound26_016 5.50 -0.95 0.66
copound26_017 5.48 -0.95 1.06
copound26_018 5.47 -0.93 1.13
copound26_019 5.29 -1.35 1.15
compound27_000 7.92 -2.00 3.06
compound27_001 7.79 -2.12 3.14
compound27_002 7.65 -1.65 2.89
compound27_003 7.56 -2.16 3.54
compound27_004 7.32 -1.46 2.33
compound27_005 7.31 -2.12 3.60
compound27_006 7.19 -1.94 1.92
compound27_007 7.05 -1.15 2.63
compound27_008 6.13 -1.33 2.10
compound27_009 6.05 -1.65 1.81
compound27_010 5.94 -1.38 2.04
compound27_011 5.83 -1.21 2.27
compound27_012 5.75 -0.71 1.05
compound27_013 5.71 -1.12 0.74
compound27_014 5.62 -1.88 0.35
compound27_015 5.61 -1.50 2.22
compound27_016 5.47 -1.30 1.04
compound27_017 5.44 -0.96 1.05
compound27_018 5.33 -1.55 2.20
compound27_019 5.31 -1.18 0.95
compound28_000 9.02 -0.93 3.43
compound28_001 8.82 -0.99 3.40
compound28_002 8.80 -1.08 3.48
compound28_003 8.67 -1.12 3.34
compound28_004 8.43 -1.41 2.91
compound28_005 7.37 -1.36 1.95
compound28_006 7.19 -0.67 2.12
compound28_007 6.99 -2.88 3.66
compound28_008 6.74 -0.71 2.73
compound28_009 6.71 -1.17 2.26
compound28_010 6.68 -1.28 2.20
compound28_011 6.68 -1.15 2.93
compound28_012 6.51 -1.84 2.32

compound28_013 6.50 -1.52 2.76
compound28_014 6.46 -1.44 2.12
compound28_015 6.45 -1.42 1.24
compound28_016 6.38 -1.38 2.32
compound28_017 6.34 -0.96 2.26
compound28_018 6.32 -0.68 1.06
compound28_019 6.26 -2.64 2.35
compound29_000 7.44 -1.44 2.61
compound29_001 7.42 -1.17 3.22
compound29_002 7.21 -1.44 4.09
compound29_003 7.15 -1.40 4.06
compound29_004 7.11 -1.44 3.80
compound29_005 7.09 -1.53 4.00
compound29_006 7.04 -1.34 3.06
compound29_007 7.03 -1.54 3.91
compound29_008 6.97 -1.52 3.77
compound29_009 6.88 -1.39 2.78
compound29_010 6.82 -1.41 2.62
compound29_011 6.77 -2.62 3.77
compound29_012 6.72 -1.44 2.80
compound29_013 6.70 -1.67 2.29
compound29_014 6.63 -1.83 1.97
compound29_015 6.61 -1.69 3.78
compound29_016 6.53 -1.70 2.01
compound29_017 6.45 -0.87 1.01
compound29_018 6.42 -1.12 2.44
compound29_019 6.34 -2.14 3.90
compound30_000 6.92 -1.68 3.47
compound30_001 6.86 -1.56 2.26
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compound30_003 6.60 -2.61 3.03
compound30_004 6.59 -1.30 1.93
compound30_005 6.47 -2.33 3.14
compound30_006 6.47 -1.50 1.92
compound30_007 6.37 -1.43 2.06
compound30_008 6.36 -1.57 3.71
compound30_009 6.15 -1.28 2.53
compound30_010 6.07 -2.50 2.91
compound30_011 6.05 -1.56 1.44
compound30_012 6.05 -1.79 2.02
compound30_013 6.01 -2.13 2.75
compound30_014 5.92 -1.92 4.13
compound30_015 5.86 -1.42 1.12
compound30_016 5.84 -2.67 2.98
compound30_017 5.66 -2.51 3.10
compound30_018 5.54 -0.88 1.04
compound30_019 5.54 -1.86 1.71
compound31_000 8.48 -1.90 2.28
compound31_001 7.07 -1.44 2.34
compound31_002 6.99 -1.62 3.44
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compound31_005 6.49 -1.19 1.93
compound31_006 6.30 -2.82 3.18
compound31_007 6.29 -1.76 2.29
compound31_008 6.14 -1.40 2.21
compound31_009 6.11 -1.66 1.59

compound31_010 6.08 - 2.86 2.70
compound31_011 6.07 - 3.03 2.56
compound31_012 6.01 - 2.87 2.67
compound31_013 5.96 - 2.88 2.57
compound31_014 5.89 - 1.36 1.23
compound31_015 5.83 - 2.02 2.44
compound31_016 5.77 - 2.96 2.51
compound31_017 5.72 - 3.08 2.54
compound31_018 5.68 - 3.21 2.56
compound31_019 5.67 - 2.03 2.38
compund32_000 8.54 - 1.43 3.02
compund32_001 8.50 - 1.34 2.97
compund32_002 8.43 - 1.48 3.00
compund32_003 8.39 - 1.57 3.18
compund32_004 8.32 - 1.41 2.93
compund32_005 7.25 - 0.70 2.43
compund32_006 7.23 - 1.16 2.33
compund32_007 7.22 - 1.30 2.33
compund32_008 7.21 - 1.16 2.31
compund32_009 7.12 - 1.09 2.25
compund32_010 7.00 - 1.50 2.36
compund32_011 6.97 - 1.32 2.02
compund32_012 6.96 - 0.62 2.10
compund32_013 6.94 - 1.04 2.19
compund32_014 6.90 - 0.96 2.00
compund32_015 6.87 - 1.11 2.16
compund32_016 6.68 - 0.81 2.29
compund32_017 6.62 - 1.24 2.01
compund32_018 6.58 - 1.50 1.63
compund32_019 6.38 - 1.22 2.25
compound33_000 8.77 - 1.50 2.20
compound33_001 8.14 - 1.74 1.47
compound33_002 8.06 - 1.36 2.71
compound33_003 8.04 - 1.42 2.78
compound33_004 7.88 - 1.50 2.65
compound33_005 7.83 - 1.39 3.05
compound33_006 7.75 - 1.78 1.26
compound33_007 7.71 - 1.53 2.73
compound33_008 7.57 - 1.85 1.17
compound33_009 7.16 - 1.14 1.06
compound33_010 6.82 - 1.27 1.11
compound33_011 6.70 - 1.24 1.01
compound33_012 6.63 - 1.60 0.99
compound33_013 6.60 - 1.74 1.09
compound33_014 6.52 - 1.94 0.01
compound33_015 6.50 - 1.71 0.68
compound33_016 6.47 - 1.73 0.79
compound33_017 6.46 - 1.70 0.85
compound33_018 6.44 - 1.51 1.03
compound33_019 6.42 - 1.59 0.86
compound34_000 6.72 - 1.55 1.85
compound34_001 6.55 - 1.64 1.82
compound34_002 6.42 - 1.09 0.87
compound34_003 6.36 - 1.61 1.77
compound34_004 6.14 - 1.47 3.07
compound34_005 6.13 - 2.19 1.73
compound34_006 6.08 - 2.74 2.03

compound34_007 6.06 -1.73 1.82
compound34_008 5.87 -1.66 2.46
compound34_009 5.65 -1.72 2.75
compound34_010 5.59 -1.74 2.65
compound34_011 5.28 -1.97 2.11
compound34_012 5.24 -1.84 0.82
compound34_013 5.23 -1.04 1.08
compound34_014 5.12 -3.29 3.43
compound34_015 5.02 -2.79 2.82
compound34_016 4.99 -2.51 2.81
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compound34_018 4.75 -2.12 1.54
compound34_019 4.71 -2.34 2.09
compound35_000 6.33 -1.09 0.00
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compound35_002 6.08 -0.47 1.48
compound35_003 4.99 -3.36 0.89
compound35_004 4.81 -0.89 0.89
compound35_005 4.66 -2.73 0.95
compound35_006 4.58 -1.63 0.00
compound35_007 4.57 -1.25 0.02
compound35_008 4.49 -1.32 1.49
compound35_009 4.35 -1.11 1.52
compound35_010 4.25 -0.51 0.00
compound35_011 4.24 -1.78 0.63
compound35_012 4.12 -0.52 0.20
compound35_013 4.04 -2.44 1.33
compound35_014 4.03 -1.32 0.00
compound35_015 4.03 -0.82 0.93
compound35_016 4.00 -0.47 0.01
compound35_017 3.98 -0.67 0.00
compound35_018 3.92 -1.29 0.04
compound35_019 3.91 -1.55 1.05
compound36_000 5.52 -0.72 1.29
compound36_001 5.26 -0.49 1.18
compound36_002 5.16 -0.84 1.08
compound36_003 5.01 -1.27 1.92
compound36_004 4.33 -0.66 1.96
compound36_005 4.12 -1.01 0.84
compound36_006 3.85 -0.78 1.17
compound36_007 3.35 -1.48 1.94
compound36_008 3.23 -0.69 0.00
compound36_009 3.00 -1.52 0.00
compound36_010 2.97 -0.56 0.01
compound36_011 2.84 -1.59 0.11
compound36_012 2.81 -1.34 0.19
compound36_013 2.74 -1.56 0.07
compound36_014 2.72 -1.48 0.03
compound36_015 2.71 -2.38 0.01
compound36_016 2.67 -0.64 0.01
compound36_017 2.66 -2.84 1.76
compound36_018 2.62 -1.24 0.23
compound36_019 2.53 -0.71 0.68
compound37_000 5.24 -0.77 1.19
compound37_001 4.39 -2.10 0.05
compound37_002 3.91 -2.55 1.48
compound37_003 3.68 -3.74 1.67

compound37_004 3.12 -2.32 0.54
compound37_005 3.06 -2.56 0.74
compound37_006 2.84 -1.27 0.00
compound37_007 2.55 -2.48 0.50
compound37_008 2.33 -5.40 1.87
compound37_009 2.16 -1.83 0.00
compound37_010 2.07 -5.53 1.88
compound37_011 1.63 -3.72 1.15
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compound37_013 1.32 -4.51 0.75
compound37_014 0.70 -3.95 0.00
compound37_015 -0.74 -7.75 2.09
compound37_016 -0.94 -8.47 2.46
compound37_017 -1.35 -8.40 1.60
compound37_018 -1.73 -7.65 2.00
compound37_019 -2.21 -8.36 2.00
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compound38_004 7.01 -1.36 1.81
compound38_005 6.62 -1.48 0.79
compound38_006 6.61 -1.67 0.81
compound38_007 6.59 -2.05 0.78
compound38_008 6.57 -1.65 1.20
compound38_009 6.55 -1.95 0.80
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compound38_014 6.22 -1.23 1.81
compound38_015 6.16 -1.00 0.78
compound38_016 6.13 -1.08 0.86
compound38_017 6.07 -1.58 0.10
compound38_018 5.91 -1.77 0.05
compound38_019 5.88 -1.99 1.92
compound39_000 7.83 -1.31 4.32
compound39_001 7.23 -0.78 2.98
compound39_002 6.78 -0.71 2.51
compound39_003 6.52 -0.91 3.30
compound39_004 6.39 -2.25 3.37
compound39_005 5.91 -2.68 3.11
compound39_006 5.67 -1.36 2.57
compound39_007 5.62 -1.06 2.51
compound39_008 5.58 -1.05 2.54
compound39_009 5.39 -2.11 1.59
compound39_010 5.31 -0.99 2.13
compound39_011 5.30 -0.89 1.42
compound39_012 5.28 -1.23 2.43
compound39_013 5.23 -1.08 1.53
compound39_014 5.21 -1.80 1.04
compound39_015 4.90 -1.46 2.57
compound39_016 4.79 -4.08 1.85
compound39_017 4.75 -2.85 3.47
compound39_018 4.71 -0.89 1.05
compound39_019 4.64 -1.46 2.86
compound40_000 7.79 -1.71 3.07

compound40_001 7.43 - 1.79 2.71
compound40_002 7.35 - 1.98 2.87
compound40_003 7.23 - 2.10 3.82
compound40_004 6.35 - 1.34 0.87
compound40_005 6.08 - 1.84 1.90
compound40_006 6.07 - 2.53 1.24
compound40_007 6.06 - 2.10 2.77
compound40_008 5.98 - 1.42 2.17
compound40_009 5.97 - 1.58 2.33
compound40_010 5.83 - 1.97 0.82
compound40_011 5.67 - 1.30 0.00
compound40_012 5.29 - 0.90 0.01
compound40_013 5.25 - 0.98 0.00
compound40_014 5.05 - 1.02 0.01
compound40_015 4.97 - 2.30 1.22
compound40_016 4.95 - 1.32 1.94
compound40_017 4.82 - 3.83 2.19
compound40_018 4.77 - 1.81 1.47
compound40_019 4.39 - 0.92 1.05
compound41_000 7.95 - 2.19 2.37
compound41_001 7.94 - 1.74 2.02
compound41_002 7.82 - 2.49 1.44
compound41_003 7.75 - 1.58 2.96
compound41_004 7.70 - 2.64 3.26
compound41_005 7.63 - 4.97 1.85
compound41_006 7.52 - 1.49 2.08
compound41_007 7.44 - 2.97 2.23
compound41_008 7.25 - 1.70 2.42
compound41_009 7.24 - 2.09 2.25
compound41_010 7.22 - 2.14 2.90
compound41_011 7.18 - 2.31 3.03
compound41_012 7.02 - 1.85 3.31
compound41_013 6.98 - 2.05 1.72
compound41_014 6.82 - 1.44 2.10
compound41_015 6.82 - 2.47 3.55
compound41_016 6.78 - 1.99 2.76
compound41_017 6.73 - 1.77 1.57
compound41_018 6.73 - 3.02 3.64
compound41_019 6.70 - 1.51 2.02
compound42_000 9.71 - 2.71 4.11
compound42_001 7.75 - 2.83 3.82
compound42_002 7.51 - 1.05 4.42
compound42_003 7.50 - 1.55 2.83
compound42_004 7.42 - 1.55 2.80
compound42_005 7.39 - 1.97 2.86
compound42_006 7.34 - 1.60 2.84
compound42_007 7.32 - 1.74 2.80
compound42_008 7.17 - 1.58 3.64
compound42_009 6.84 - 4.08 2.85
compound42_010 6.81 - 3.74 2.63
compound42_011 6.79 - 2.05 2.86
compound42_012 6.79 - 2.24 2.89
compound42_013 6.78 - 2.44 4.13
compound42_014 6.61 - 1.09 1.07
compound42_015 6.59 - 1.13 2.10
compound42_016 6.56 - 2.06 2.75
compound42_017 6.51 - 1.83 2.75

compound42_018 6.47 -1.98 2.73
compound42_019 6.46 -0.82 2.17
compound43_000 7.09 -1.51 0.97
compound43_001 6.82 -2.53 1.87
compound43_002 6.79 -2.26 1.32
compound43_003 6.72 -1.92 1.49
compound43_004 6.29 -1.91 1.12
compound43_005 6.16 -4.89 2.29
compound43_006 6.01 -1.76 1.15
compound43_007 5.93 -2.64 1.47
compound43_008 5.89 -2.96 1.06
compound43_009 5.80 -1.24 0.20
compound43_010 5.77 -1.95 1.46
compound43_011 5.74 -1.25 0.00
compound43_012 5.12 -2.26 1.08
compound43_013 5.10 -2.60 0.20
compound43_014 5.06 -2.57 1.86
compound43_015 5.01 -2.79 1.90
compound43_016 4.75 -3.06 1.87
compound43_017 4.58 -3.96 1.98
compound43_018 4.57 -1.94 0.00
compound43_019 4.49 -1.59 0.00
compound44_000 8.28 -0.70 2.13
compound44_001 7.66 -1.56 2.61
compound44_002 7.41 -4.19 2.08
compound44_003 6.84 -2.26 0.78
compound44_004 6.49 -1.57 0.88
compound44_005 6.22 -1.37 1.76
compound44_006 6.01 -0.73 1.72
compound44_007 5.82 -1.97 2.35
compound44_008 5.80 -1.40 1.42
compound44_009 5.63 -2.70 3.88
compound44_010 5.50 -2.78 3.89
compound44_011 5.15 -4.62 4.55
compound44_012 5.14 -1.32 2.74
compound44_013 5.07 -2.32 1.41
compound44_014 5.05 -4.54 4.46
compound44_015 5.00 -4.65 4.52
compound44_016 4.60 -1.54 0.97
compound44_017 4.58 -3.99 3.00
compound44_018 4.51 -1.60 0.86
compound44_019 4.38 -0.85 0.16
compound45_000 7.92 -1.40 1.50
compound45_001 7.57 -1.52 1.08
compound45_002 7.52 -1.62 1.71
compound45_003 7.40 -2.01 0.81
compound45_004 7.37 -1.83 1.32
compound45_005 7.14 -1.33 1.45
compound45_006 7.05 -1.11 1.43
compound45_007 6.98 -1.62 0.86
compound45_008 6.78 -0.99 1.68
compound45_009 6.72 -1.41 2.03
compound45_010 6.33 -2.41 0.86
compound45_011 6.18 -1.47 2.00
compound45_012 6.17 -1.43 2.00
compound45_013 6.01 -1.72 1.61
compound45_014 5.89 -1.26 0.00

compound45_015 5.87 - 1.57 2.35
compound45_016 5.78 - 1.51 1.70
compound45_017 5.66 - 2.88 1.33
compound45_018 5.57 - 0.62 0.43
compound45_019 5.50 - 2.68 0.97
compound46_000 9.06 - 0.48 2.78
compound46_001 8.63 - 0.56 2.89
compound46_002 8.56 - 0.56 2.80
compound46_003 8.49 - 0.58 2.76
compound46_004 8.47 - 0.50 2.65
compound46_005 7.69 - 0.98 3.77
compound46_006 7.61 - 2.09 2.90
compound46_007 7.12 - 2.27 2.89
compound46_008 7.04 - 1.11 3.71
compound46_009 5.98 - 1.97 1.05
compound46_010 5.94 - 0.64 1.85
compound46_011 5.83 - 1.18 1.69
compound46_012 5.34 - 1.61 1.99
compound46_013 5.07 - 3.71 2.88
compound46_014 4.19 - 2.31 1.11
compound46_015 4.18 - 4.83 2.22
compound46_016 4.18 - 3.00 0.94
compound46_017 4.16 - 4.56 2.19
compound46_018 4.10 - 1.17 0.01
compound46_019 4.10 - 4.85 2.26