Section A-Research paper
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IMPOSING COMPUTATIONAL PHARMACOLOGY ON THE PHYTOCONSTITUENTS OF *ARTOCARPUS HETEROPHYLLUS*

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ABSTRACT:

ArtocarpusheterophyllusLam also known as “Jack Fruit”. Because of its medicinal use, it is widely cultivated across many countries in different varieties. It is rich in various minerals, vitamins, amino acids, etc. that help in various conditions like fever, asthma, bone-related disease, and skin disease. The present study was to find out potent phytochemical constituents of Artocarpusheterophyllus against anti-diabetic disease through Computational pharmacology (CP). The CP was used to reduce time consumption in and cost-effective manner. In this, we use SwissADME for finding physiochemical properties and Pharmacokinetic Properties of the ligand molecules. In addition to toxicity and molecular docking, PROTOX-II and Autodock 4.0.respectively. For this, the structure of the ligand molecules was obtained from PubChem and five proteins (Receptor) were downloaded from RCSB-PDB. All the finalized 13 compounds

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exhibited potential binding energy against all the targets and the most promising is compound 8(Artonin-A). Thus, the study suggested that screened chemical constituents in Artocarpusheterophyllus can be used as a therapeutic drug molecule in diabetic management.

KEYWORDS: Docking, Pharmacokinetic, SwissADME, ProTox-II, AutoDock, Diabetic Mellitus, and Jack Fruit.

1 INTRODUCTION:

Over decades, a promising field of study where the extraction of valuable data leads to the successful development of new drugs in this modern pharmaceutical sector is Computational Pharmacology (CP). CP is a predictive technique that integrates the work of computationally acquired data and pharmacology studies [1]. In this field, computational methods are used to manage drug trials, analyze outcomes, model drug systems, and store sensitive information for further analysis. Many theoretical pharmacologists utilize the CP tools to investigate the biological activity of a disease target in relation to a drug or a molecule (drug-protein interactions) or involves in the identification of NCEs (Newer Chemical Entities). Thou a CP method is a predictive tool in the research sector, it plays a vital role in drug design and drug development studies [1-3].

The use of botanical species in the drug discovery process as a starting material has many advantages. The active constituents in the plants are referred to be safer in use and can be used for a longer duration in human life. Due to the intrinsic limits of the original molecule, such methods result in the development of novel molecules derived from the source. For example, toxicities that were dose-limiting were found in podophyllin, which was extracted from Podophyllumhexandrum. Camptothecin inspired the creation of novel anti-cancer molecules like topotecan and irinotecan after being first identified from Camptotheca sp. and then Mappia sp. [4,5].

A delicious edible fruit of one among the Moraceae (Mulberry) Family called Artocarpusheterophyllus Lam (Jackfruit). It is grown in the Western Ghats of India, Central and Eastern Africa, South-Eastern Asia, the Caribbean, Malaysia, Florida, Brazil, etc. Various parts of this Artocarpusheterophyllus Lam like roots, stem, leaves, and fruits were historically used as medicine. The root contains β-sitosterol, ursolic acid, betulinic acid, and cycloartenone which helps with skin diseases and asthma conditions. The leaves and stem of the plant contain Sapogenins, Cycloartenone, and Cycloartenone which aid in fever, wounds, skin disease, and diuretics respectively. The extract from the wood of Artocarpusheterophyllus Lam is highly sedative and abortifacient in nature. Potassium, iron, magnesium, and copper concentration were found to be rich in fruit of Artocarpusheterophyllus Lam that leads to a decrease in blood pressure by reverting the sodium effects in the blood, prevents anemia, aids in calcium absorption in the body which eliminates bone-related diseases, thyroid gland metabolism respectively [4-6].

Despite this, it also has a concentration of phytochemical constituents like Tannins, Sterols, Volatile acids, carotenoids, phenolics, and flavonoids. These functional constituents of

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the Artocarpusheterophyllus Lam also help in a human day-to-day healthy life. The flavonoids and Phenolic obtained from the fruit peel act as a potent anti-oxidant property [7,8]. It has a growth inhibition effect on microorganisms like *Saccharomyces cerevisiae* and *Fusarium moniliforme* thereby acting as anti-fungal activity. In addition, it has anti-bacterial [9], anti-cancer[10,11], anti-inflammatory[12], etc.

Diabetic Mellitus is the major micro-vascular and macro-vascular associated metabolic epidemic disorder in this modern developing world. Artocarpusheterophyllus, has the phenolic compounds artocarpesin, norartocarpesin, and oxyresveratrol identified by spectroscopic studies. These compounds were found to inhibit the lipopolysaccharide (LPS)-activated RAW 264.7 murine macrophage cells, hereby exhibiting a strong immune response. In ancient times, leaf extract was found to reduce the glycemic level in humans. This present study evaluates the phytoconstituents of Artocarpusheterophyllus as an inhibiting factor by binding to the receptors activating the tyrosine-kinase, which triggers the IRS-1. This substrate binds to the PI3K enzyme that phosphorylates to PIP3. This PIP3 is recognized byAKT kinases. Then AKT and AS160 phosphorylated to the active form. AS160 inhibits the GTPase activating domain. This leads to the change of GDP to GTP of Rab proteins. Finally, this Rab protein stimulates the translocation of GLUT4 for the upregulation of glucose to the cellular metabolism. Thereby, leading to the amelioration of the insulin resistance caused by the deficiency in homeostasis [13-18].

2 MATERIALS AND METHODS:

2.1 METHODOLOGY AND SOFTWARE:

Insilico predictions include chemical properties, bioavailability, ADME properties (pharmacokinetic – Adsorption, Distribution, Metabolism, and Excretion) and Toxicity are the significant parameters in the drug discovery process. Many web-based tools have been recently emerged and available on a free platform for developing faster prediction. This helps in reducing the cost and time consumption in identifying an effective candidate. SwissADME, a comprehensive web tool is used for finding the potential of the drug candidate in this study. It also gives a Hexagon Plot and Egg yolk graphs for a better understanding of the results.

Preparing and performing pharmacological complexes between the receptor and the ligand molecules were carried out using Molegro Molecular Viewer and Autodock software (MDL tools). For graphical visualization of the ligand-receptor interactions, Biovia Drug discovery studio was used.

2.2 LIGAND SELECTION AND PREPARATION:

From the PubMed database, all the selected phytoconstituents structures were retrieved. With the help of the ChemDraw software, all the structures were sketched and exported to .pdb format. Followed by, Energy minimization of the compounds was done using Chem3dUltra. All the phytochemical compounds were given in the Table.1.

2.3 RECEPTOR IDENTIFICATION AND PREPARATION:

In this study, an anti-diabetic protein was selected for molecular docking and the sequence of the selected targeted protein in a three-dimensional structure was obtained by Protein Data Bank (RCSB-PDB). The .pdb format was used to download every protein. The

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preparation of the protein was carried out in Molegro Molecular Viewer. In the proteins, the water molecules, fragments, and co-factors were removed. In Autodock 4.0, the receptor was imported in .pdb format. The receptor undergoes the addition of hydrogen atoms and is computed with Gasteiger charges, non-polar atoms are merged, checked for missing atoms, and repaired the missing atoms. Finally exported as .pdbqt format for Molecular docking.

2.3.1 IRS-1 (INSULIN RECEPTOR SUBSTRATE-1):

The term Insulin Resistance indicates the inability of glucose uptake and utilization in both exogenic and endogenic processes. As far as the mechanism ofinsulin resistance in the human body remains idiopathic. Several factors are associatedwith insulin resistance like Genetic abnormalities, Fetal malnutrition, Visceral obesity, etc [13]. PDB ID 1IRK, an Insulin receptor substrate-1 (IRS), which is a tyrosine kinase domain with 2369 amino acids was chosen as the target. The phosphorylation of tyrosine residue improves insulin resistance.

2.3.2 GLUT4 (GLUCOSE TRANSPORTER TYPE 4):

It is an Insulin-Regulated transporter with 12 transmembrane domains, which exists especially in Skeletal Muscle cells, cardiomyocytes, and adipocytes. In transport vesicles, GLUT4 is stored and timely released primarily when required in the plasma membrane. About 80% of the transporting glucose in the body is carried out in cells present in the muscle. In addition, it has a unique sequence (N- terminal and COOH terminal) which is responsible for signaling and trafficking of insulin membrane. Its primary function is to regulate glucose uptake by the body (Homeostasis) [14,15]. PDB ID 7WSN was chosen as a receptor in representing GLUT4, which contains a 3505 amino acid sequence.

2.3.3 AKT/PKB (PROTEIN KINASE B):

Protein kinase B is the set of serine/threonine kinases. It is also known as AKT protein. It is majorly involved in cellular processes, glucose metabolism, apoptosis, cell migration, proliferation, and transcription. It has three isoforms, namely, AKT1, AKT2, and AKT3. AKT1 performs cellular functions, AKT2 is involved in the insulin signaling pathway and AKT3 is present in brain cells. The AKT isoforms bear the PH or the pleckstrin domain that binds to phosphoinositides and activates cellular signaling involving PI3K phosphorylation. Also stimulates the G protein-coupled receptors like insulin receptors [16]. The PDB ID 1GZO was chosen for docking.

2.3.4 P13K:

PI3K is lipid kinase, it phosphorylates phosphatidylinositol in eukaryotic membranes. The PI3K present on the intracellular membranes phosphorylates phosphatidylinositol 4,5-biphosphate (PIP2) into phosphatidylinositol 3,4,5-triphosphate (PIP3). Its diverse functions involve cellular mechanisms such as cell growth, proliferation, motility, differentiation, and intracellular trafficking. It can also activate the protein kinase B (PKB/Akt) and the mammalian target of rapamycin (mTOR). PI3K is involved in the insulin-signaling pathway. So, the PI3K target (PDB ID 5XGJ) was also selected for docking [16].

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2.3.5 AS160:

AS160 is an AKT substrate of 160kDa and is a Rab GTPase-activating protein encoded by the *TBC1D4* gene in humans. The AKT2 phosphorylates AS160 at threonine and serine residue followed by insulin stimulation. The phosphorylation of AS160 is necessary for the glucose transporter GLUT4 to translocate at the plasma membrane in response to insulin stimulation of fat and muscle cells. 3QYB was employed as the target ofthe AS160 protein [17].

3 RESULTS AND DISCUSSION:

In this present study, the selected phytochemical constituents were docked against five receptors. Also, *insilico* predictions like drug-likeness and the pharmacokinetic properties of the ligand molecules were carried out.

3.1 PHYSIOCHEMICAL AND PHARMACOKINETIC PREDICTIONS:

The chemical structures obtained from the PubChem database were drawn in ChemDraw and converted into SMILES notation. This smiles notation used in the SwissADMEto identify the Chemical properties of the ligand Molecules like Lipinski, Ghose, Veber, Muegge, and Egan violations were predicted and listed in the Table.2.

For orally active drugs, the compound should obey Lipinski's rule of Five. Out of thirteen compounds, β-sitosterol (1), Lakoochanoside (5), Artonin-A (8), Artonin-B (9), and Cycloheterophyllin (13) are the five compounds showed only one Lipinski rule violation rest of the compoundsobeys the conditions. Therefore, the Predicted compounds violations are not more than two thus the compounds are orally active. Similarly, Ghose, Egan, Veber, and Mueggerule have similar findings for the drug candidate. All the compounds showed a 0.55 or 0.56 bioavailability score. This results that the ligand molecules have good pharmacokinetic properties [18].

In addition, the bioavailability radars of the ligand molecules under drug-likeness graphs given by the SwissADME tool, are specified in the shape of hexagons. Each vertex in the hexagons denotes a characteristic (Size, Polarity, Lipophilicity, Flexibility, Solubility, and saturation)of the predicted compounds. The optimal range of the six characteristics wasshown by the pink regions and out of the pink shade region was said to be incapability (white shade region) of that particular characteristic of the ligand molecule. Except for compounds 1, 5, 6, and 13, all the compounds remain inside the pink shade.

The Topological Potential Surface Area (TPSA) of the ligand molecule is the sum of oxygen, nitrogen, and their linked hydrogens (Polar atoms) in the molecules. This gives the drug transporting ability in the intestinal absorption and blood-brain barrier (BBB) penetration. The value of TPSA below 60$Å^2$ and 140 $Å^2$ were said to be good potential in BBB penetration and intestinal absorption respectively. In this study, compound (1) results in 20.33 $Å^2$ TPSA value and other compounds showed a range of 75.99 $Å^2$to167.91 $Å^2$that results in good intestinal absorption.

3.2 TOXICITY PREDICTION:

An easy and Virtual tool for predicting Toxicity in the small molecule drug discovery process was ProTox – II [19]. For all the compounds Organ toxicity including Hepatotoxicity, immunotoxicity, carcinogenicity, mutagenicity, etc are predicted and listed in the Table.3.All the compounds do not show Hepatotoxicity and Cytotoxicity. The compounds Cycloaltilisin (4) and

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Artonin-A (8), and Cycloheterophyllin (13) showed active toxicity of Carcinogenicity and Mutagenicity respectively. Except for the compounds, (Epi)catechin(2), Chromone(3), Lakoochanoside (5), and Oxyresveratrol (6) all the other compounds showed active Immunotoxicity.

3.3 MOLECULAR DOCKING:

In this study, Molecular docking was performed using AutoDock 4.0 Software. Binding Affinity with the RMSD value of all the five targets against 13 compounds is presented in the Table.4. The highest binding docking pose of the ligand molecules with the highest negative docking score was obtained by Discovery Studio software. The docking pose of various targets was analyzed and based on their bonding type (Vander wall's, hydrogen, alkyl) with amino acids are listed in the Table.5 and Table.6.

In IRS-1, the binding energy of the ligand molecules lies in the range of -8.8 to -7.2 kcal mol−1. Among the 13 compounds, 9 (Artonin-B), 8(Artonin-A), and 2((Epi)catechin) showed the highest binding affinity of -8.8, -8, and -8.4 kcal mol−1 with 18.571, 17.93, 2.887 RMSD value respectively. The highest binding interaction of 9(Artonin-B) was shown in Figure.1. In this, the amino acid SER A(1003) showed hydrogen bonding and VAL A(1050), PHE A(1054), GLU A(1047), LYS A(1030), PHE A(1151), GLY A(115) MET A(1153), ASN A(1137), ASP A(1132), TYR A(1162), PRO A(1172), HIS A(1130) showed Vanderwal's bonding with 1IRK (PDB ID). In addition, MET A(1051), PHE A(1128), ARG A(1131), and ASP A(1150) resulted in alkyl bonding and steric bonding respectively.

In GLUT4, the ligands showed binding energy in the range of -11.9 to -8.4 kcal mol−1. The compounds, 8 (Artonin-A), 9 (Artonin-B), and 13(Cycloheterophyllin) showed the highest binding affinity of -11.9, -11.5, -11.4 kcal mol−1 with 2.12, 4.923, 2.958 RMSD value respectively. The highest binding energy of 8(Artonin-A) results in showing vanderwal's bonding with eight amino acids like GLY A(154, 424), PRO A(157), ASN A(176, 427), SER A(153), GLN A(177), VAL A(181), PHE A(395, 307), ILE A(42, 184). Also it showed alkyl and steric bonding with ILE A(9), MET A(420) and TRP A(428), PHE A(38), TRP A(404), ILE A(180) respectively. It does not show any hydrogen bonding. Figure 2.Representing the interaction of Artonin-A (8) with GLUT4.

In AKT, the resulting compounds showed binding energy in the range of -8.1 to -6.4 kcal mol-1. The highest binding energy of -8.1 kcal mol-1 was shown by compound 6(Oxyresveratrol) with a 2.087 RMSD value. The amino acids like TYR A(327, 316), VAL A(321, 338), LEU A(317, 348), GLU A(315), PRO A(314), THR A(313), GLY A(335), ASP A(275) showed vanderwal's bonding and ILE A(276), ASP A(332), VAL A(331) showed hydrogen bonding. Also, LYS A(277) showed alkyl bonding with compound 6(Oxyresveratrol) and the binding interaction is given in Figure. 3.

In P13k, the compound showed binding energy in the range of -10.3 to -7.5 kcal mol-1. The compound 8(Artonin-A) results in a binding energy of -10.3 with a 35.643 RMSD value. This compounds with amino acids showed vanderwal's [ASN A(605, 377, 370), ILE A(543),

LYS A(548), GLY B(376), ASP B(349) A(545), ARG B(348), TYR A(361), PRO A(366, 458)], hydrogen [ARG B(373), ASN (378)], alkyl [LEU A(540, 570), PHE A(1016)] and steric bonding with GLU A(542). The binding interactions of this compound showed in Figure.4.

In AS160, the binding energy of the compounds showed a range of -8.7 to -6.1 kcal mol-1. The highest compound with binding energy showed in Figure.5. The compound with -8.7 kcal mol-1 of binding affinity with 4.822 RMSD value is 8(Artonin-A). The compound possessvanderwal's bonding with SER A(1051), GLN A(1058), GLN A(1055), THR A(1114), GLY A(1040), TYR A(1037), LEU A(942) amino acids and GLN A(946) of hydrogen bonding. LYS A(1043) and ILE A(1054) amino acids showed alkyl bonding.

Among all the analyses of the compounds against five targets, compound 8 (Artonin-A) showed the highest anti-diabetic effects by inhibiting in three targets which include GLUT4, P13K, and AS160. Inthe management of toxicity, it is free from Hepatotoxicity, Carcinogenicity, and cytotoxicity with class 4. The rest of the compounds showed good inhibition effects.

4 CONCLUSION:

The computational docking and pharmacokinetic studies of Artocarpusheterophyllus Lam have shown a series of phytochemical constituents that inhibits Diabetic Mellitus. These findings can serve as a framework for the synthetic modification of bioactive phytochemicals, the de novo synthesis of structural motifs, and further research into phytochemicals. The simulated complexes showed stability, and the ligands persisted in the altered protein's active binding pocket. This study found that the phytochemicals it tested could be employed as possible therapeutic drug candidates to prevent diabetes.

5 CONFLICTS OF INTEREST:

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Table.1. photochemical compounds with their structures.

S/N	compound name	Chemical Structure	Mol. Formula

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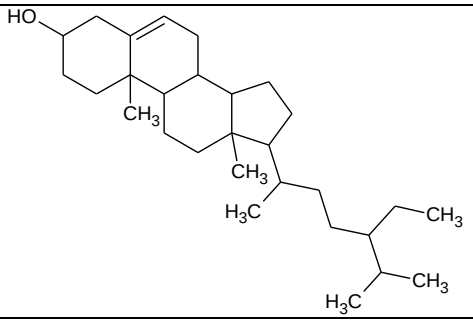
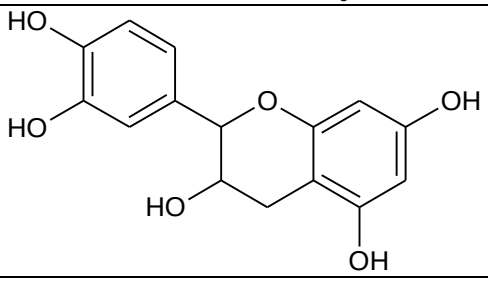
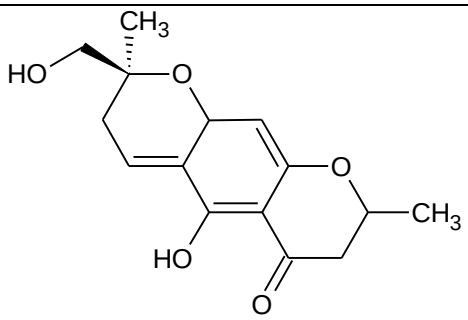
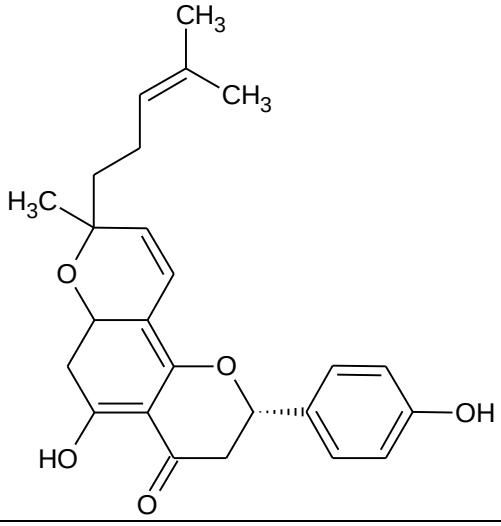
1	β-sitosterol		C29H50O
2	(Epi)catechin		C15H14O6
3	Chromone		C15H18O5
4	Cycloaltilisin 7		C25H28O5

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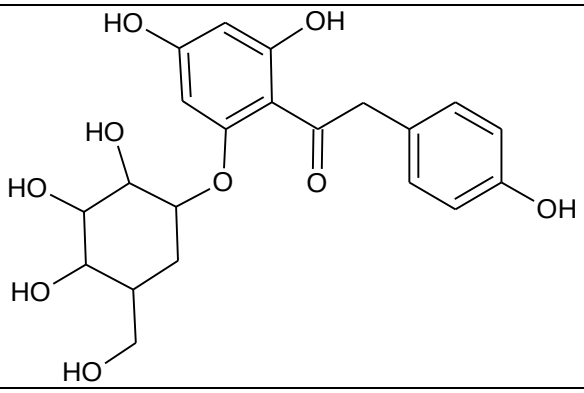
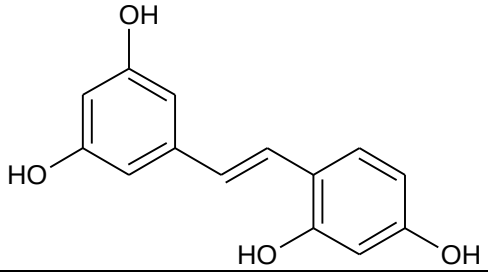
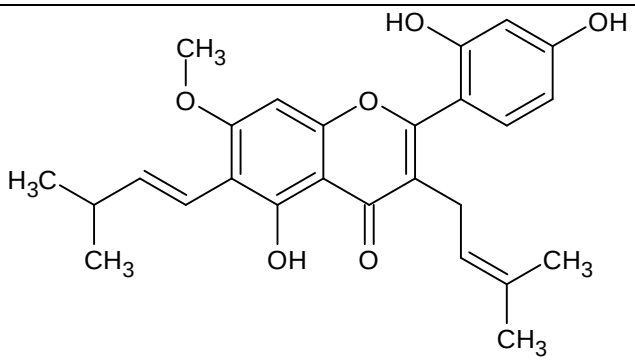
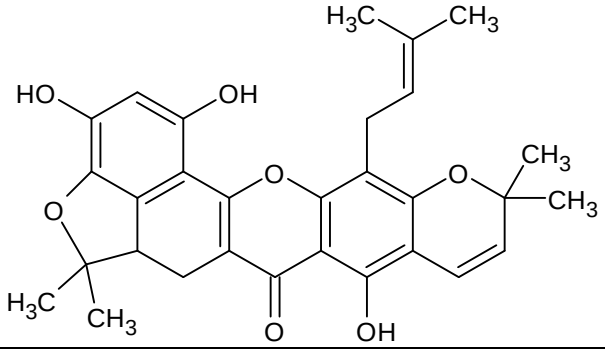
5	Lakoochanoside		C21H24O9
6	Oxyresveratrol		C14H12O4
7	Artocarpin		C26H28O6
8	Artonin A		C30H30O7

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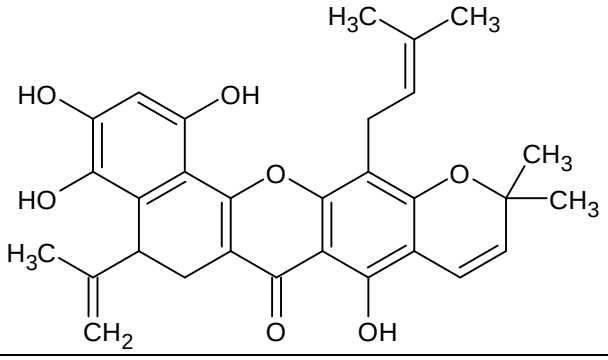
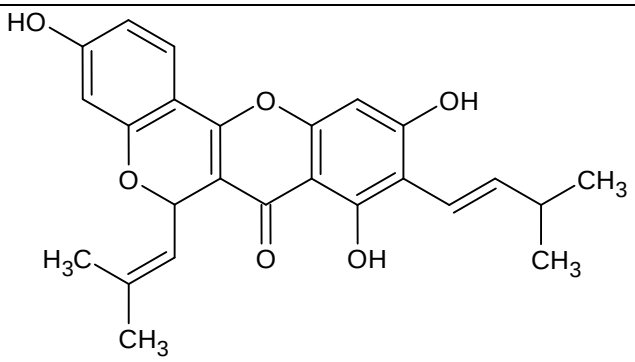
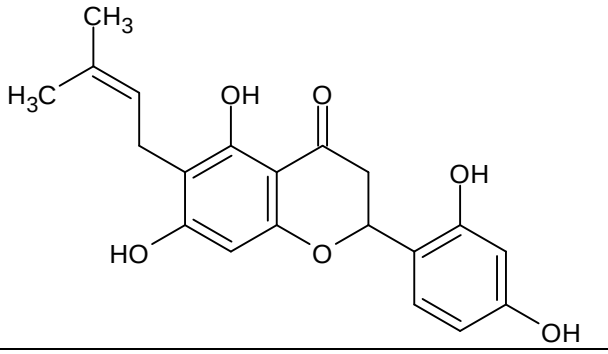
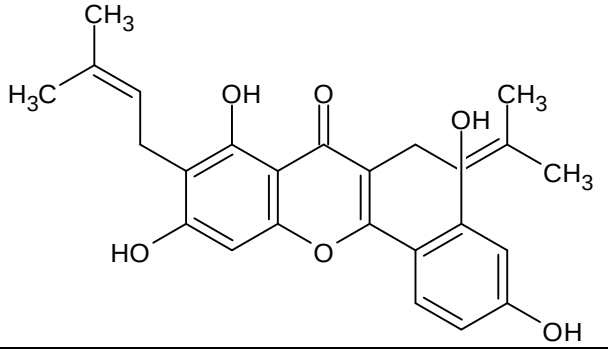
9	Artonin B		C30H30O7
10	Brosimone I		C25H24O6
11	Cudraflavon B		C20H20O6
12	Cudraflavon C		C25H26O6

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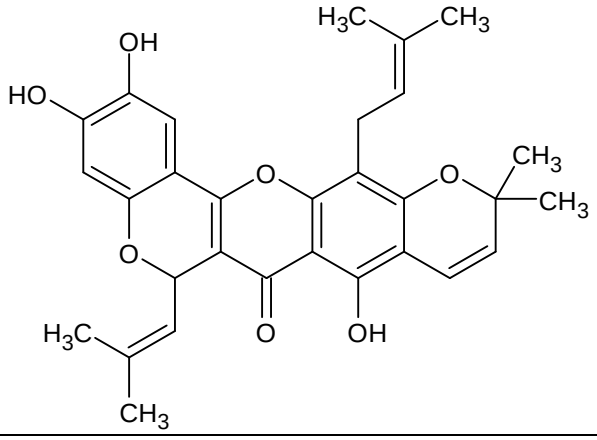
13	Cycloheterophyllin		C30H30O7

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Table. 2. Physiochemical properties of the ligand molecules from SwissADME

Compound no	MW	#Heavy atoms	#H-bond accept	#H-bond donors	MR	TPSA	Lipinski #violations	Ghose #violations	Veber #violations	Egan #violations	Muegge #violations
1	414.71	30	1	1	133.23	20.23	1	3	0	1	2
2	290.27	21	6	5	74.33	110.38	0	0	0	0	0
3	278.3	20	5	2	71.6	75.99	0	0	0	0	0
4	408.49	30	5	2	115.7	75.99	0	0	0	0	0
5	420.41	30	9	7	105.06	167.91	1	0	1	1	2
6	244.24	18	4	4	69.9	80.92	0	0	0	0	0
7	436.5	32	6	3	128.71	100.13	0	1	0	0	1
8	502.56	37	7	3	143.68	109.36	1	3	0	1	1
9	502.56	37	7	4	145.62	120.36	1	3	0	1	1
10	420.45	31	6	3	121.79	100.13	0	0	0	0	1
11	356.37	26	6	4	97.31	107.22	0	0	0	0	0
12	422.47	31	6	4	123.45	111.13	0	0	0	0	1
13	502.56	37	7	3	145.12	109.36	1	3	0	1	1

Table.3. Toxicity of the ligand molecules from ProTox-II.

Compound No	LD50 value (mg/kg)	class of toxicity	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
1	890	4	Inactive	Inactive	Active	Inactive	Inactive
2	10000	6	Inactive	Inactive	Inactive	Inactive	Inactive
3	5105	6	Inactive	Inactive	Inactive	Inactive	Inactive
4	5105	6	Inactive	Active	Active	Inactive	Inactive
5	6000	6	Inactive	Inactive	Inactive	Inactive	Inactive
6	1560	4	Inactive	Inactive	Inactive	Inactive	Inactive
7	4000	5	Inactive	Inactive	Active	Inactive	Inactive
8	2500	5	Inactive	Inactive	Active	Active	Inactive

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9	3000	5	Inactive	Inactive	Active	Inactive	Inactive
10	475	4	Inactive	Inactive	Active	Inactive	Inactive
11	2000	4	Inactive	Inactive	Active	Inactive	Inactive
12	159	3	Inactive	Inactive	Active	Inactive	Inactive
13	5000	5	Inactive	Inactive	Active	Active	Inactive

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Table.4. Binding Score of the ligand molecules against five targets.

Compound No	1GZO - AKT	RMSD/UB	1IRK - IRS-1	RMSD/UB	3QYB - AS160	RMSD/UB	5XGJ - PI3K	RMSD/UB	7WSN - GLUT4	RMSD/UB
1	-6.9	25.4	-7	26.699	-6.1	3.507	-7.7	4.482	-8.5	7.3
2	-7	7.002	-8.4	2.887	-6.6	9.388	-8.2	35.041	-8.4	7.113
3	-6.5	3.436	-7.2	25.606	-6.1	15.016	-7.7	29.528	-8.6	7.189
4	-7.7	23.541	-8.1	2.422	-7.8	29.061	-9.7	9.133	-10.4	1.984
5	-7.2	5.425	-7.7	7.51	-6.7	1.959	-8.3	29.2	-8.8	4.707
6	-8.1	2.087	-7.6	2.826	-6.1	9.297	-7.5	7.421	-8.4	1.959
7	-7.2	22.089	-7.6	15.34	-6.7	8.161	-8.4	13.136	-10	1.857
8	-7.8	15.814	-8.8	18.517	-8.7	4.822	-10.3	35.643	-11.9	2.122
9	-7.4	31.077	-8	17.933	-7.6	5.813	-9.9	5.015	-11.5	4.923
10	-7.6	21.427	-8.3	8.156	-7.7	6.757	-9.2	24.722	-9.8	9.241
11	-7.4	30.403	-7.9	3.206	-7.1	2.492	-8.9	16.474	-9.2	3.758
12	-7.5	22.733	-8.2	8.126	-7.1	32.877	-8.5	2.917	-9.6	9.319
13	-7.1	24.671	-8.2	23.305	-7.9	5.419	-10.3	8.076	-11.4	2.958

Table.5. Binding interactions of the ligand molecules against 1GZO – AKT, 1IRK - IRS-1, and 3QYB - AS160.

Comp. NO	**Binding Recpetor**											
	1GZO - AKT				**1IRK - IRS-1**				**3QYB**			
	VANDER WAALS	**HYDROGEN BONDING**	**ALKYL**	**STERIC**	**VANDER WAALS**	**HYDROGEN BONDING**	**ALKYL**	**STERIC,**	**VANDER WAALS**	**HYDROGEN BONDING**	**ALKYL**	**STERIC**

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1	VAL A(187), ILE A(188), LEU A(183), GLU A(200), ARG A(274), THR A(199), VAL A(271)				SER A(1086), ASP A(1083), ASP (1156), TYR A(1158), ARG A(1136), ASP A(1150), ASN A(1137), GLY A(1152), PHE A(1151), LEU A(1048), GLU A(1012), MET A(1079), ARG A(1000), ALA A(1080), HIS A(1081), GLY A(1082)		MET A(1153), LEU A(1002)		PHE A(1118), GLN A(1055), SER A(1051), ARG A(1046), PRO A(943), LEU A(942), GLN A(946), ARG A(1042), GLY A(1040), TYR A(1037), THR A(1114)		LYS A(1043)	
2	PRO A(314), LEU A(348), TYR A(351), TYR A(316), GLU A(342), LEU A(358, HIS A(355), ASP A(354), THR A(313)	PHE A(350), GLY A(346)	ARG A(347)		GLY A(1082), MET A(1139), TYR A(1158), TYR A(1162), THR A(1154), ASN A(1137), GLY A(1152), ASP A(1150)	PHE A(1151), MET A(1153)	AG A(1136), LEU A(1002)	ASP A(1083)	LYS A(945), PRO A(948), LEU A(1002), ASP A(1003), GLN A(946), LEU A(942), MET A(1036), GLY A(1040)	GLU A(1005), ARG A(1042)	PRO A(949)	TYR A(1037)
3	ASN A(233), ARG A(176), TYR A(231), TYR A(178), LYS A(216), ALA A(214), LYS A(290), LYS A(420), GLU A(230), GLU A(433)	ARG A(208)		TYR A(177)	LEU A(1002), MET A(1079), GLY A(1082), ASP A(1083), GY A(1152), TYR A(1158), ASP A(1150), MET A(1153), ASP A(1156), GLY A(1003)	ARG A(1136), ASN A(1137)	MET A(1139), PHE A(115), LEU A(1078)		LYS A(1033), PRO A(948), GLN A(947), ARG A(937)	GLU A(1030), ASP A(1038), LEU A(942)	ARG A(941)	

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4	ASP A(275), PHE A(294), GLY A(295), LYS A(181), ASP A (293), GLU A(200), THR A(213), LEU A(212), LEU A(266), THR A(207), VAL A(271), VAL A(272), THR A(199)	ARG A(274)		PHE A(163), TYR A(273), LEU A(204)	LEU A(1002), MET A(1139), GLY A(1082), ASP A(1083), GY A(1152), TYR A(1158), ASP A(1150), ASP A(1156), GLY A(1003), GLN A(1004), PHE A(1151), TYR A(1158), ILE A(1157), ARG A(1155), THR A(1154)	ASN A(1137)	MET A(1153), ARG A(1136)		GLN A(1010), ARG A(973), PHE A(9775), PRO A(976), THR A(977), SER A(1095), ALA A(1094), PHE A(1097), SER A(1098), GLU A(881), TYR A(880), PRO A(979)	GLN A(1096), HIS A(978)	LEU A(1099), PHE A(1014)	ASP A(879)
5	VAL A(434), ASN A(233), TYR A(231), LEU A(212)	TYR A(177), LYS A(420), PRO A(210), GLU A(230)	LYS A(216), ALA A(214), ARG A(176)	GLU A(433), TYR A(178), ARG A(208), HIS A(209), LYS A(290)	LEU A(1002), ARG A(1000), ARG A(1136), ASN A(1137), PHE A(1151), GLY A(1152), ASP A(1150), TYR A(1158), ASP A(1156), ILE A(1157), SER A(1086) MET A(1139), MET A(1079), ALA A(1080), LEU A(1078), GLY A(1082), HIS A(1081)			MET A(1153), ASP A1083)	GLN A(1096), ASP A(1151), PRO A(1150), MET A(1152), PHE A(1097), SER A(1095), ALA A(1094), PHE A(1014), PHE A(975), PRO A(976), HIS A(978), TYR A(880), ASP A(879), PRO A(979), GLU A(881)	SER A(1098), THR A(977)	LEU A(1099)	
6	TYR A(327), VAL A(321), LEU A(317), GLU A(315), PRO A(314), THR A(313), LEU A(348), TYR A(316), VAL A(338), GY A(335), VAL A(338), ASP A(275)	ILE A(276), ASP A(332), VAL A(331)	LYS A(277)	TRP A(332), ARG A(274), ALA A(318), GLU A(279)	MET A(1079), GLY A(1082), PHE A(115), ASP A(1083), ASP A(1150), ASN A(1137), TYR A(1162), TYR A(1158)		LEU A(1002), ARG A(1136)	GLY A(1152), MET A(1139), MET A(1153)	TYR A(936), ASP A(1038), PRO A(943), TYR A(1037), ARG A(1042), ARG A(1046)	GLN A(946), HIS A(940)	LEU A(942)	ARG A(941)

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7	THR A(207), VAL A(272), THR A(199), LYS A(181)	TYR A(273)	VAL A(203), VAL A(271), LEU A(204), LEU A(266), LEU A(212)	ASP A(275), ARG A(274), PHE A(163)	ALA A(1080), ARG A(1000), GLU A(1012), TYR A(1158), TYR A(1162), ASP A(1150), GLY A(1152), GLY A(1003), ILE A(1157), GLN A(1004), ASP A(1156)	PHE A(1151), MET A(1153)	ARG A(1136), MET A(1079), LEU A(1002), LEU A(1078)	ASP A(1083), GLY A(1082), MET A(1139), MET A(1153)	LYS A(1043), GLU A(1005), GLN A(947), TYR A(1037), GLN A(946), GLY A(1040), PRO A(948)	ARG A(1046)	PRO A(949), PRO A(943), LEU A(942)	ARG A(1042)
8	ARG A(347), CYS A(345), PRO A(370), MET A(344), LEU A(373), GLU A(249), THR A(248)	THR A(372)	ARG A(245)	VAL A(246)	ARG A(1131), GLU A(1047), ARG A(1136), ASN A(1137), THR A(1154), GLY A(115), ILE A(1148), GLY A(1149), HIS A(1130)	TYR A(1162), ASP A(1150), ASP A(1132)	PHE A(1054), MET A(1051), VAL A(1050)	PHE A(1128)	SER A(1051), GLN A(1058), GLN A(1055), THR A(1114), GLY A(1040), TYR A(1037), LEU A(942)	GLN A(946)	LYS A(1043), ILE A(1054)	ARG A(1042), ARG A(1046)
9	PHE A(238), SER A(242), GLU A(342), GLY A(346), LEU A(348), HIS A(355), TYR A(316)	GLN A(353), PHE A(350), ASP A(354)	PRO A(314), ARG A(347) TYR A(351)		VAL A(1050), PHE A(1054), GLU A(1047), LYS A(1030), PHE A(1151), GLY A(115) MET A(1153), ASN A(1137), ASP A(1132), TYR A(1162), PRO A(1172), HIS A(1130)	SER A(1006)	MET A(1051), PHE A(1128), ARG A(1131)	ASP A(1150)	SER A(1051), ARG A(1046), GLY A(1040), GLN A(946), LEU A(942), PRO A(943), ARG A(941), HIS A(940), ASP A(1038), GLY A(1113), THR A(1114), PHE A(1118)	GLN A(1055)	LEU A(1039), TYR A(936), LYS A(1043)	
10	THR A(199) VAL A(271), THR A(207), VAL A(203), GLU A(200), ASP A(293), LYS A(181), PHE A(294)	VAL A(272)	LEU A(204), LEU A(212), LEU A(266), TYR A(273)	ARG A(274), PHE A(163)	ARG A(1000), GLU A(1012), ALA A(1080), ASN A(1137), THR A(1162), GLY A(1082, SER A(1086), ASP A(1150), TYR A(1162), THR A(1154)	MET A(1153), MET A(1079)	LEU A(1078) LEU A(1002), TYR A(1158), ILE A(1157), ARG A(1136)	PHE A(1151), ASP A(1083), MET A(1139)	ARG A(1046), SER A(1051), THR A(1114), GLY A(1040), GLN A(946), TYR A(1037), LEU A(942), GLN A(947), PRO A(948), PRO A(949)		LYS A(1043)	ARG A(1042), GLU A(1005)

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11	ALA A(214), TYR A(178), LYS A(290), HIS A(290), PO A(210), ASN A(233), TYR A(177), ALA A(232), ASP A(284)	TYR A(231), LYS A(285)	ARG A(176), VAL A(434)	GLU A(433), GLU A(230), LYS A(420)	THR A(1154), TYR A(1162), ASP A(1150), GLY A(1152), GLYA(1082), MET A(1079), LEU A(1078), ALA A(1080), GLY A(1003), TYR A(1158)	PHE A(1151), ASN A(1137)	ARG A(1136), LEU A(1002)	ASP A(1083), MET A(1139), MET A(1153)	TYR A(1037), GLN A(946), LEU A(942), PRO A(943), ASP A(1038), GLY A(1113), THR A(1114), GLY A(1040)		TYR A(936), LEU A(1039)	ARG A(1042)
12	LYS A(216), TYR A(178), ARG A(208) PRO A(210), LYS A(420), ASP A(284), LYS A(285), GLU A(433), VAL A(434), ASN A(233), ALA A(232)	TYR A(231). TYR A(177)	ARG A(176)	GLU A(230	GLY A(1003, ASP A(1156), PHE A(1151), ALA A(1080), ARG A(1000), GLU A(1012), GLY A(1082), TYR A(1158), THR A(1154), TYR A(1162), ASP A(1150)	MET A(1079), ASN A(1137)	ARG A(1136), LEU A(1002), LEU A(1078)	ASP A(1083), MET A(1139), MET A(1153), GLYA(1152)	LYS A(945), GLN A(947), PRO A(948), TYR A(1037), GLY A(1040), PRO A(943), LYS A(1043), ARG A(046)	ARG A(1042), GLN A(946)	LEU A(942), PRO A(949)	GLU A(1005)
13	ILE A(188), VAL A(187), THR A(162), THR A(199), ARG A(274), GLU A(200), VAL A(203), LEU A(204), VAL A(27!), VAL A(272), TYR A(273), ASP A(293), ASN A(280), LYS A(181)		PHE A(163)		ASP A(1156), GLY A(1003), GLY A(1152), MET A(1153), ASP A(1150), ASP A(1150), PHE A(1151), TYR A(1158), ARG A(1136), GLY A(1082), ALA A(1080)	MET A(1139), ARG A(1000)	LEU A(1002, ILE A(1157)	ASP A(1083)	ASP A(1038), LEU A(942), HIS A(940), PR A(943), ARG A(941), GLN A(946), GLY A(1040), ARG A(1046), SER A(1051), PHE A(1118), GLN A(1055), GLN A(1058), THR A(1114)	TYR A(936)	TYR A(1037), ARG A(1042), LYS A(1043)	

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Table.6. Binding interactions of the ligand molecules against 5XGJ - PI3K, and 7WSN - GLUT4.

Comp. No	Binding Receptors							
	5XGJ				7WSN			
	VANDER WAALS	**HYDROGEN BONDING**	**ALKYL**	**STERIC,**	**VANDER WAALS**	**HYDROGEN BONDING**	**ALKYL**	**STERIC**
1	PRO A(449), THR A(679), ASN A(677), GLN B(475), TYR A(467), HIS A(676), ASP A(843), ARG A(808), PRO A(1011), TYR B(470), THR B(471), SER B(474), LYS A(678)	ASP A(806)	PRO A(447), TRP A(446), TRP A(424)		GLN A(177), ASN A(176), PHE A405), PRO A(401), GLY A(400), GLN A(298), PHE A(395), GLU A(396), ASN A(304), GLN A(299), ASN A(431), TRP A(428), ILE A(42), PHE A(38), ILE A(303), PHE A(30&)M ILE A(180), VAL A(181)		TRP A(404)	
2	GLU A(365), GLY B(376), ASN A(370), TYR A(361), LEU A(456), LEU A(455), ASP A(454), LEU B(347), ASN B(344), GLU A(542), ASP B(349)	ASN B(378), ARG B(373), ASN B(377)	PRO A(366), ARG B(348)	ARG A(357)	PHE A(395), ASN A(304), TYRA(308), ASN A(431), PHE A(88), GLN A(299), SER A(153), GLY A(154), SER A(96), ILE A(99), GLY A(424), TRP A(404), ASN A(427)	GLN A(298)	ILE A(42)	PHE A(38), TRP A(428)
3	SER A(464), GLY A(463), GLN A(643), ASN A(428), TYR A9644), THR A(462), VAL A(461), VAL A(680), THR A(679), LEU A(645), TYR A(432)	GLU A(135), GLN A(682), ARG A(683)		ASP A(133)	GLN A(177), GLU A(396), VAL A(181), THR A(337), VAL A(181), ILE A(180), ASN A(333), PHE A(307), ILE A(184), ILE A(42), TYR A(308), ASN A(431), PHE A(38), GLN A(299), ASN A(427)GLN A(298), GLY A(400), PHE A(395)	ASN A(304)		TRP A(428)

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4	TRP A(446), GLY A(1009), ASN A(677), LYS A(640), VAL A(461), GLY A(460), PRO A(449), TRP A(424), THR B(471), TYR B(470), SERB(474), PRO (447), ASN A(465), GLN B(475), GLN B(478)	GLY A(1007), HIS B(450), TYR B(467)	LYS A(678), HIS A(676)	THR A(679)	PRO A(401), PHE A(38), ILE A(42), ASN A(304), ASN A(431), ASN A(427), GLY A(424), SER A(153), GLY A(154), MET A(420), PRO A(157), ASN A(176), GLY A(173), GLN A(177), THR A(174)	TRP A(428), GLN A(299)	TRP A(404), PHE A(405)	
5	ASN A(756), TYR A(836), GLLY A(837), GLN A(630), GLN A(815), CYS A(838), ILE A(633), PRO A(835), SER A(629), LEU A(632)	GLU A(849), LEU A(814), HIS A(670)		PHE A(666), ARG A(818)	PRO A(157), SER A(153), GLY A(424), ILE A(180), PHE A(395), GLY A(400), GLN A(177), ASN A(427), PHE A(38), ILE A(42)	GLN A(298), TRP A(404), ASN A(304)		ASN A(176), TRP A(428), GLN A(299), ASN A(431)
6	TRP A(780), SER A(854), MET A(922), ILE A(800), LEU A(814), ASP A(810), ASP A(933), LEU A9807), LYS A(802), VAL A(851), VAL A(850), PHE A(930)	GLU A(849)		TYR A(836), ILE A(932), ILE A(848)	PRO A(157), SER A(153), GLY A(424), ILE A(42), TRP A(404), PHE A(38), GLY A(154), GLN A(299), ASN A(431), PHE A(425), ALA A(421), ILE A(99), SER A(96), MET A(420)	ASN A(427), ASN A(304)		TRP A(428)
7	TRP A(446), GLNB(478), ASN A(467), PRO A(447), THR B(471), HIS A(676)	ASP A(843), GLN A(475), SER B(474), ASN A(465)	MET B(479), LYS A(678)		GLY A(400), GLN A(299), ASN A(304), ASN A(431), GLN A(298), TRP A(404), ASN A(427), PHE A(88), GLY A(424), SER A(96), ALA A(421), GLY A(154), SER A(153)	TRP A(428)	ILE A(42), ILE A(99), PHE A(38), MET A(420), ILE A(180), PRO A(147)	
8	ASN A(605), ILE A(543), LYS A(548), ASN B(377), GLY B(376), ASP B(349), ARG B(348), TYR A(361), PRO A(366), ASN A(370), PRO A(366), ASP A(454), PRO A(458)	ARG B(373), ASN (378)	LEU A(540), PHE A(1016), LEU A(570)	GLU A(542)	GLY A(154), PRO A(157), ASN A(176), SER A(153), GLN A(177), VAL A(181), PHE A(395), PHE A(307), ILE A(42), ILE A(18$), ASN A(427), GLY A(424)		ILE A((9), MET A(420)	TRP A(428), PHE A(38), TRP A(404), ILE A(180)

9	ARG A(662), LYS A(271), SER A(629), ILE A(633), GLN A(815), LEU A(814), CYS A(838), TYR A(836), GLY A(837), GLU A(849), HIS A(759), ASN A(756)	ASN A(170), MET A(811)	LEU A(755)	ARG A(818), PHE A(666), PRO A(835)	GLY A(400), GLN A(299), ASN A(304), ASN A(431), GLN A(298), TRP A(428), ASN A(427), PHE A(395), SER A(153),PRO A(157), PHE A(38), SER A(153), MET A(420), ILE A(184), PHE A(307), ILE A(42), ILE A(180), GLN A(177)PHE A(405)			TRP A(404)
10	GLY A(1009), ASN A(457), GLY A(460), TRP A(446), ASN A(465), ASN A(467), ARG B(481), GLN B(478), SER B(474), THR B(471), GLN B(475), HIS A(676), ASP A(843), ASN A(677)	TRP A(424)	PRO A(449), LYS A(678)	PRO A(447), THR A(679)	GLN A(299), ASN A(304) ASN A(431), AN A(427), GLY A(424), ALA A(421), GLY A(154), PRO A(157), SER A(153), PHE A(38)		TRP A(404), MET A(420), MET A(420), ILE A(42)	TRP A(428), ILE A(99)
11	LYS A(678), SER A(681), VAL A(680), THR A(679), ARG A(683), TYR A(644), ASN A(428), ASP A(431), VAL A(437), ILE A(427), SER A(464), THR A(462), GLY A(463)	GLU A(135), GLN A(643), LEU A(645)		GLN A(682)	PHE A(307), ASN A(304), GLN A(299), ASN A(427), SER A(96), GLY A(424), ILE A(99), ALA A(421), SER A(153), ILE A 180), PHE A(38)	ASN A(431), TRP A (428)	ILE A(303), ILE A(42), PHE A(395)	TRP A(404), MET A(420)
12	GLY A(1009), ASN A(457), GLY A(460), TRP A(446), ASN A(465), ASN A(467), GLY A(1009), SER B(474), TYR B(470), GLN B(475), LYS A(678), TYR B(556), HIS A(676), GLN A(1014), GLY A(1007)	ASN A(677)	PRO A(449)	THR A(679), PRO A(447)	MET A(420), GLY A(424), ASN A(427), GLN A(299), ASN A(304), PHE A(395), GLN A(298), PRO A(401), GLU A(396), THR A(337), VAL A(181), GLN A(17), ILE A(180), PHE A(38), PRO A(157), SER A(153), TRP A(428), GLY A(154), ILE A(99)	GLY A(400)	ILE A(42), PHE A(307), ILE A(184)	
13	GLU A(341), ASP A(1017), ASN B(344), ARG B(348), GLU B(345), ARG B(373),	PRO A(539)	PHE A(1016), ALA A(1020), LEU A(570), LEU	GLU A(542)	SER A(96), ILE A(99), SER A(153), GLY A(154), PRO A(157), GLN A(177),	GLY A(424), ASN A(176)	ILE A(42), TRP A(428), PHE A(38),	TRP A(404)

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	ASN B(378), ASN B(377), LYS A(548), ILE A(543), TYR A(606), ASN A(605), LEU A(540)		B(380)		VAL A(181), VAL A(181), GLU A(396), PHE A(395), PHE A(307), ASN A(333), ILE A(184), GLN A(299), ASN A(431), PHE A(88), ASN A(427)		ILE A(180), MET A(420)	

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Figure.1. Binding interaction of 9 (Artonin-B) in IRS-1

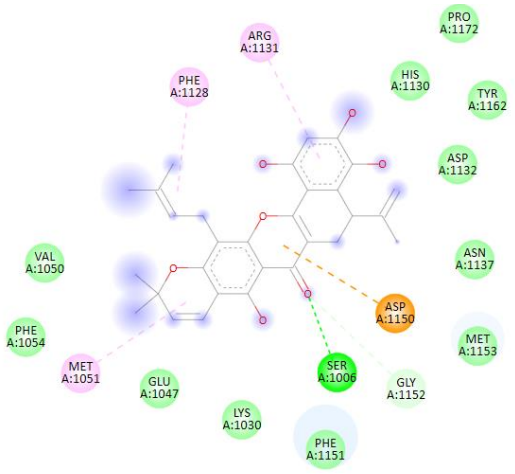

Figure.2. Binding interaction of 8 (Artonin-A) in GLUT4.

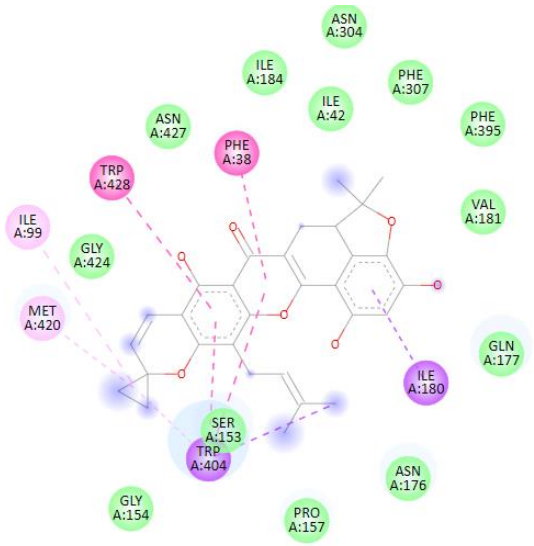

Figure.3. Binding interaction of 6 (Artocarpin) in AKT.

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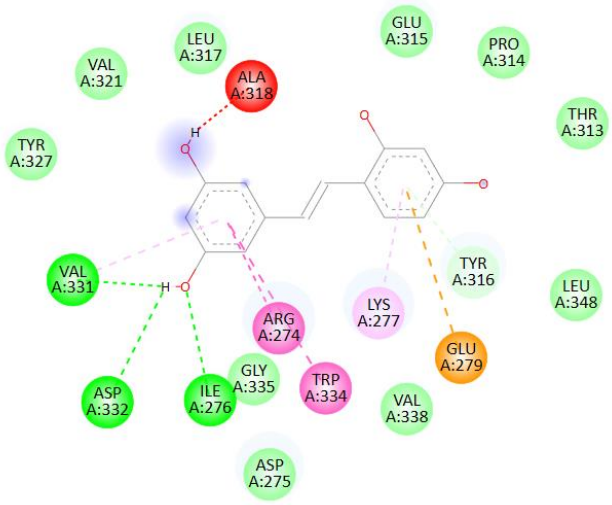

Figure.4. Binding interaction of 8 (Artonin-A) in P13K.

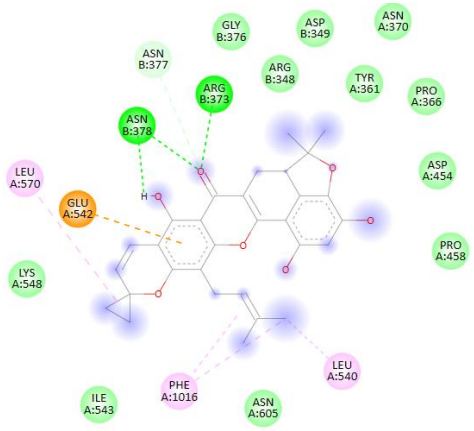

Figure.5. Binding interaction of 8 (Artonin-A) in AS160.

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