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Docking Of The Isolated Compounds - 3,3',4',5,7-Penta Hydroxy Isoflavone And 5,7,4'- Tri Hydroxy Isoflavone With Various Proteins

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ABSTRACT:-It evaluates the inhibitory effect of the isolated compounds with different drug targets for the anti-cancer and anti-diabetic activities. The present investigation analyses the docking score of the isolated compounds with different proteins. Two types of proteins (Drug targets) were chosen against Breast cancer and Diabetes namely AKT1 – Rac-Alpha Serine/Threonine-protein Kinase (breast cancer drug target) and ACE2-Angiotensin- converting enzyme (diabetes drug target) respectively. These results reveals that the 3,3',4',5,7-penta hydroxyl isoflavone (compound 1) shows seven hydrogen interactions with the docking energy of –8.83 Kcal/mol for drug target AKT1 and seven hydrogen interactions with the docking energy of –8.76 Kcal/mol drug target ACE2 and 5,7,4'- tri hydroxyl isoflavone (compound 2) exihibits four hydrogen interactions with the docking energy of –8.16 Kcal/mol for drug target AKT1 and four hydrogen interactions with the docking energy of -7.61 Kcal/mol for drug target ACE2. This reveals a significant interaction between the target proteins and the selected compounds. Hence, these compounds (3,3',4',5,7-penta hydroxyl isoflavone and 5,7,4'tri hydroxyl isoflavone may offer therapeutic advantages in the treatment and prevention of diabetes and breast cancer.

Keywords: *Isolated compounds, Ipomoea pes-caprae, Drug targets, AKT1, ACE2, Docking scores.*

I. INTRODUCTION

Bioinformatics is the collection, classification, storage, and analysis of biochemical and biological information using computers especially as applied to molecular genetics and genomics. It is a management information system for molecular biology and has many practical applications. Bioinformatics organizes data in a way that allows researchers to access existing information and to submit new entries as they are produced, eg the Protein Data Bank for 3D macromolecular structures [1, 2]. While data-duration is an essential task, the information stored in these databases is essentially useless until analyzed. Bioinformatics also develops tools and resources that aid in the analysis of data. For example, having sequenced a particular protein, it is of interest to compare it with previously characterised sequences. This needs more than just a simple text-based search and programs such as FASTA [3] and PSI-BLAST [4], must consider what comprises a biologically significant match. Biological data are being produced at a phenomenal rate [5]. For example the GenBank repository of nucleic acid sequences contained 8,214,000 entries [6] and the SWISS- PROT database of protein sequences contained 88,166 [7]. On an average, these databases are doubling insize every 15 months [8]. In addition, since the publication of the *H.influenzae* genome [9], complete sequences for over 40 organisms have been released, ranging from 450 genes to over 100,000.

Protein sequence databases are categorized as primary, composite or secondary. Primary databases contain over 300,000 protein sequences and function as a repository for the raw data. Some more common repositories, such as SWISS-PROT [10] and PIR International [11], annotate the sequences as well as describe the proteins' functions, its domain structure and post-translational modifications. Composite databases such as OWL [12] and the NRDB [13] compile and filter sequence data from different primary databases to produce combined non-redundant sets that are more complete than the individual databases and also include protein sequence data from the translated coding regions in DNA sequence database. Secondary databases contain information derived from protein sequences and help the user to determine whether a new sequence belongs to a known protein family. One of the most popular is PROSITE [14], a database of short sequence patterns and profiles that characterise biologically significant sites in proteins. PRINTS [15] expand on this concept and provide a compendium of protein fingerprints – groups of conserved motifs that characterise a protein family. Motifs are usually separated along a protein sequence, but may be contiguous in 3D-space when the protein is folded. By using multiple motifs, fingerprints can encode protein folds and functionalities more flexibly than PROSITE. Pfam [16] contains a large collection of multiple sequence alignments and profile Hidden Markov Models covering many common protein domains. Pfam-A comprises accurate manually compiled alignments

while Pfam-B is an automated clustering of the whole SWISS-PROT database. These different secondary databases have recently been incorporated into a single resource named InterPro [17].

The Protein Data Bank, PDB [18, 19], provides a primary archive of all 3D structures for macromolecules such as proteins, RNA, DNA and various complexes. Most of the ~13,000 structures are solved by x-ray crystallography and NMR, but some theoretical models are also included. As the information provided in individual PDB entries can be difficult to extract, PDBsum [20] provides a separate web page for every structure in the PDB displaying detailed structural analyses, schematic diagrams and data on interactions between different molecules in a given entry. Three major databases classify proteins by structure in order to identify structural and evolutionary relationships: CATH, SCOP [21], and FSSP databases [22]. All comprise hierarchical structural taxonomy where groups of proteins increase in similarity at lower levels of the classification tree. In addition, numerous databases focus on particular types of macromolecules. These include the Nucleic Acids Database, NDB [23], for structures related to nucleic acids, the HIV protease database [24] for HIV-1, HIV-2 and SIV protease structures and their complexes, and ReLiBase [25] for receptor-ligand complexes.

Selected proteins

The present investigation analyses the docking score of the isolated compounds with different proteins. Present study has chosen two types of protein (Drug target) against Breast cancer and Diabetes.

(i) AKT1 for Breast cancer

(ii) ACE2 for diabetes.

(i) AKT1 (v-akt murine thymoma viral oncogene homolog 1) is a protein-coding gene. Diseases associated with AKT1 include proteus syndrome, and proteus syndrome somatic. GO annotations related to this gene include enzyme binding and identical protein binding. An important paralog of this gene is GRK7.

UniProtKB/Swiss-Prot: AKT1_HUMAN, P31749 [26].

(ii) ACE2 (angiotensin I converting enzyme 2) is a protein-coding gene. Diseases associated with ACE2 include neurogenic hypertension, and tetanus neonatorum. GO annotations related to this gene include metallopeptidase activity and virus receptor activity. An important paralog of this gene is ACE.

UniProtKB/Swiss-Prot: ACE2_HUMAN, Q9BYF1 [27].

II. MATERIALS AND METHODS

UniProt

UniProt is a comprehensive, high-quality and freely accessible database of protein sequence and functional information, many entries being derived from genome sequencing projects. It contains a large amount of information about the biological function of proteins derived from the research literature. The UniProt/SwissProt Knowledge base-UniProtKB is the central access point for extensive curated protein information, including function, classification, and cross-reference. It consists of two sections: UniProtKB/Swiss-Prot which is manually annotated and is reviewed and UniProtKB/TrEMBL which is automatically annotated and is not reviewed. The UniProt Reference Clusters UniRef databases provide clustered sets of sequences from the UniProtKB and selected UniProt Archive records to obtain complete coverage of sequence space at several resolutions while hiding redundant sequences [28].

PDB

The Protein Data Bank PDB is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids. The data, typically obtained by X-ray crystallography or NMR spectroscopy and submitted by biologists and biochemists around the world, are freely accessible on the Internet via the websites of its member organizations. The PDB is a key resource in areas of structural biology, such as structural genomics. Most major scientific journals, and some funding agencies, such as the NIH in the USA, now require scientists to submit their structure data to the PDB. If the contents of the PDB are thought of as primary data, then there are hundreds of derived i.e., secondary databases that categorize the data differently. For example, both SCOP and CATH categorize structures according to type of structure and assumed evolutionary relations; GO categorize structures based on genes [29].

Pfam

The Pfam database contains information about protein domains and families. Pfam-A is the manually curated portion of the database that contains over 10,000 entries. For each entry a protein sequence alignment and a hidden Markov model is stored. These hidden Markov models can be used to search sequence databases with the HMMER package written by Sean Eddy. Because the entries in Pfam-A do not cover all known proteins, an automatically generated supplement is provided called Pfam-B. Pfam-B contains a large number of small families derived from clusters produced by an algorithm called ADDA [30].

ACD Chem Sketch

ACD/ChemSketch is an advanced chemical drawing tool and is the accepted interface for the industries best NMR and molecular property predictions, nomenclature, and analytical data handling software.

Autodock

Auto Dock is a suite of automated docking tools. The software is used for modelling flexible small molecule such as drug molecule binding to receptor proteins of known three dimensional structures.

Discovery Studio Visualiser

Molecular visualisation is a key aspect of the analysis and communication of modeling studies. The scheme of the docking methods is given in scheme 1.

Selection of Disease
↓
Selection of Macromolecule (Protein) responsible for disease
↓
Check the 3D structure is solved or not using similarity search
↓
Retrieve 3D Structure from PDB Database
↓
Compounds Extracted from LCMS study
(Compounds-1 and Compound-2)
↓
Drawing the 2D structure of inhibitors and converting to 3D
↓
Molecular Docking—Autodock
↓
Evaluation of Docked Structure—Discovery Studio Visualiser

Scheme 1 Schematic representation for the evaluation of docking structure

III. RESULTS AND DISCUSSION

AKT1 (CANCER DRUG TARGET)

Sequence retrieval

The sequence of Rac-Alpha Serine/Threonine-Protein Kinase (AKT1) is retrived from SWISSPROT database and sequence accession number is P31749. The PDB Structure of **AKT1 is** retrieved from PDB database and PDB ID: 4EJN. The domain region of AKT1 is predicted using PFam tool. Domain identified is PH domain 6–108 and PKinase domain 150–408. 3D structure of AKT1 is presented in Figure 1.

ACE (DIABETES DRUG TARGET)

Sequence retrieval

The sequence of Angiotensin-converting enzyme 2 (ACE2) is retrieved from Q9BYF1. The PDB Structure of **ACE2 is** retrieved from PDB database and PDB ID: 1R42; Chain: A. The domain region of ACE2 is predicted using PFam tool (Peptidase_M2 13–613). 3D structure of AKT1 is presented in Figure 2.

Structure of inhibitors

Two inhibitors have been selected for the docking analysis. Selected inhibitors were isolated from *I. pes-caprae*. They have been confirmed by using different spectrometric methods. It is presented in Table 1.

Docking Analysis

Docking Analysis between AKT1 and 3,3',4',5,7-pentahydroxyisoflavone

It shows the combined results of the binding energy, electrostatic energy, intermole energy, torsional energy and the ligand efficiency of the selected inhibitior. The results are presented in Table 2 and Figure 3. Binding affinity as denoted by the docking energy or the docking score is 8.83 Kcal/mol. Docking score of compound-1 with AKT1 is presented in Table 3.

It shows 'O' atom of amino acid THR291 of the target forms a single bond with the 'H' atom of the ligand. 'O' atom of amino acid ILE290 of the target AKT1 forms a bond with another 'H' atom of the ligand. 'O' atom of amino acid THR211 of the target AKT1 forms a bond with another 'H' atom of the ligand. Two 'N' atoms of SER205 forms bonds with two other 'O' atoms of the ligand and the 'O' atom of amino acid GLN203 of AKT1 also forms a 'H' bond with the ligand. The bond distances are 1.94 Å, 1.88 Å, 2.76 Å, 2.11 Å, 2.64 Å, 2.73 Å and 1.99 Å respectively. This reveals a significant interaction between the target protein AKT1 and the compound-1. From this it may be concluded that this isolated compound can be used for further pharmacological or preclinical studies.

Docking Analysis between AKT1 and 5,7,4'- trihydroxyisoflavone

The result exhibits the value of binding energy, electrostatic energy, intermole energy, torsional energy and the ligand efficiency of the selected inhibitior. The results are presented in Table 4 and Figure 4. Binding affinity denoted the docking energy of docking score is -8.16 Kcal/mol. Docking score of compound 5, 7, 4'-trihydroxyisoflavone with AKT1 is presented in Table 5.

The above results demonstrate four interactions between the target AKT1 and the 2nd ligand. These include the formation of a single bond between SER205 of the target and 'O' atom of the ligand. Formation of` a single bond between the 'O' atom of amino acid TYR272 and 'H' atom of the ligand. Formation of a single bond between the 'N' atom of amino acid THR211 and 'O' atom of the ligand. Formation of` a single bond between the OD1 atom of amino acid ASN204 and 'H' atom of the ligand. This reveals a significant interaction between the target protein AKT1 and the selected compound. Thus the isolated compound can be used for further pharmacological or preclinical studies.

Docking Analysis between ACE 2 and 3,3',4',5, 7-pentahydroxyisoflavone

It shows the combined results of the binding energy, electrostatic energy, intermole energy, torsional energy and the ligand efficiency of the selected inhibitior. The results are presented in Table 6 and Figure 5. Binding affinity denoted the docking energy of docking score is -8.76 Kcal/mol. Docking score of compound-1 with ACE2 is presented in Table 7. This reveals a significant interaction between the target protein ACE2 and the selected compound. So the isolated compound can be used for further pharmacological or preclinical studies.

The above results show that the 'O' atom of various amino acids of ACE2 which include GLU208, ASN210, ASP206, SER563 and GLU (OE_2) 564 interacts with different 'H' atoms of the compound-1, forming single bonds with interatomic distances of 1.97 **Å**, 1.92 **Å**, 2.10 **Å**, 1.95 **Å**, 2.07 **Å** and 2.42 **Å** respectively. Similarly, the 'N' atoms of the amino acids ASN210 interacts with different 'O' atoms of the compound-1, forming single bonds with interatomic distances of 3.20 **Å** respectively.

Docking Analysis between ACE2 and 5,7,4'- trihydroxyisoflavone

It shows the value of binding energy, electrostatic energy, intermole energy, torsional energy and the ligand efficiency of the selected inhibitior. The results are presented in Table 8 and Figure 6. Binding affinity denoted the docking energy of docking score is -7.61 Kcal/mol. Docking score of compound-2 with ACE2 is presented in Table 9. This reveals a significant interaction between the target protein ACE2 and the selected compound-2.

The above results depict that the ligand forms 'H' bonds with the amino acids ASP206, ASN210 and GLN98 of the target. Also, an interaction is formed between NE2 of the GLN98 residue of the target and an 'O' atom of the ligand. The results show that there is the 'O' atom of amino acids of ACE2 that of ASP206, and ASP210 interact with the 'H' atom of the compound-2 gives the interatomic distance 1.77 Å, and 2.06 Å respectively. NE2 atom of the GLN98 interacts with the 'O' atom of the compound-2 gives the interatomic distance 3.18 Å and OE1 atom of the GLN98 interacts with the 'H' atom of the selected compound gives the interatomic distance 2,17 Å respectively. From this it may conclude that thus isolated compound can be used for further pharmacological or preclinical studies.

The results of above analysis shows that 3,3',4',5,7-pentahydroxyisoflavone shows seven hydrogen interactions with AKT1 with a docking score of –8.83 Kcal/mol and seven hydrogen interactions with ACE2 with a docking score of –8.76 Kcal/mol. It shows that compounds have inhibitory effect against cancer drug target and that it would possibly possess anti-cancer activity. It is presented Table 10. The other ligand, 5,7,4'- trihydroxyisoflavone shows four hydrogen interactions with AKT1 with a docking score of –8.16 Kcal/mol and four hydrogen interactions with ACE2 with a docking score of –7.61 Kcal/mol. This analysis shows the possible inhibitory effects of the compounds against diabetic drug target and that it should probably possess anti-diabetic activity.

IV. CONCLUSIONS

Analysis of the receptor/ligand complex models generated after successful docking of the compounds was based on the parameters such as hydrogen bond interactions, binding energy and orientation of the docked compound within the active site. The docking poses are ranked according to their docking scores and both the ranked list of docked ligands and their corresponding binding poses may be exported. Hence, these compounds (3,3',4',5,7- pentahydroxyisoflavone and 5,7,4'- trihydroxyisoflavone) may offer therapeutic advantages in the treatment and prevention of diabetes and breast cancer. These results might also be verified with suitable wet laboratory experiments.

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[27] http://www.rcsb.org/pdb/home/home.do
[28] http://www.uniprot.org/
[29] http://www.rcsb.org/pdb/home/home.do
[30] http://pfam.sanger.ac.uk
[31] http://autodock.scripps.edu/resources/tools

Table 1 Selected inhibitiors

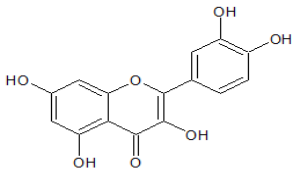
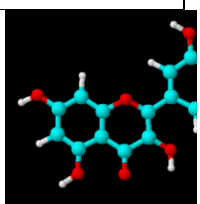
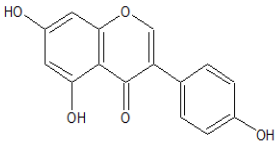
Compound name	Mol. Wt	Mol. Formula	Mol.Structure	3D-Structure
3,3',4',5,7 pentahydroxyisoflavone (Compound 1)	**302.237**	**$C_{15}H_{10}O_7$**		
5,7,4'trihydroxyisoflavone (Compound 2)	**270.236**	**$C_{15}H_{10}O_5$**		

Table 2 Final Conformation Docking energy of compound-1 with AKT1

```
                    binding_energy=-8.83
                  ligand_efficiency=-0.4
                   inhib_constant=335.58
                 inhib_constant_units=nM
                  intermol_energy=-10.62
               vdw_hb_desolv_energy=-10.3
             electrostatic_energy=-0.32
                 total_internal=-1.07
                torsional_energy=1.79
                unbound_energy=-1.07
                  filename=best.dlg
                      clRMS=0.0
                    refRMS=59.17
                     rseed1=None
                     rseed2=None
                4 hydrogen bonds formed:
pentahydroxyisoflavone-3: :LIG1:H :          4EJN_2:A:THR211:O
      4EJN_2:A:SER205:HN :  pentahydroxyisoflavone-3: :LIG1:O
      4EJN_2:A:THR211:HN :  pentahydroxyisoflavone-3: :LIG1:O
pentahydroxyisoflavone-3: :LIG1:H :          4EJN_2:A:ILE290:O
```

Figure 1 3D Structure of AKT1

j 

Figure 2 3D Structure of ACE2

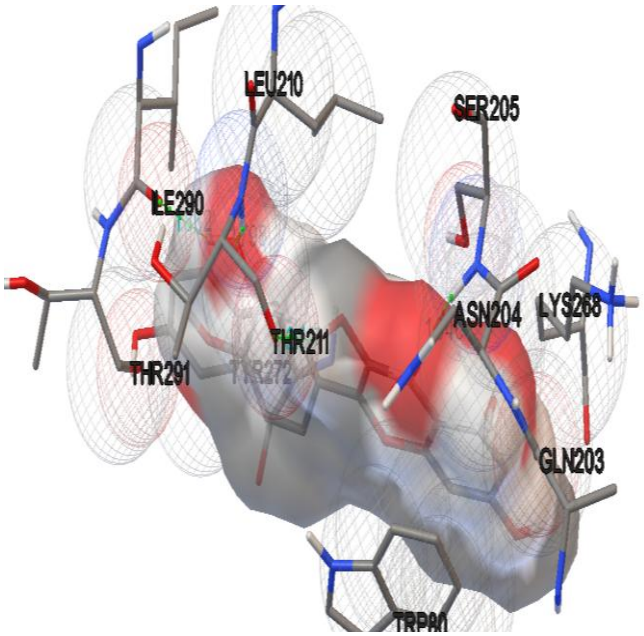


Figure 3 Interactions between AKT1 and 3, 3, 4', 5, 7-pentahydroxyisoflavone Visualised using Autodock

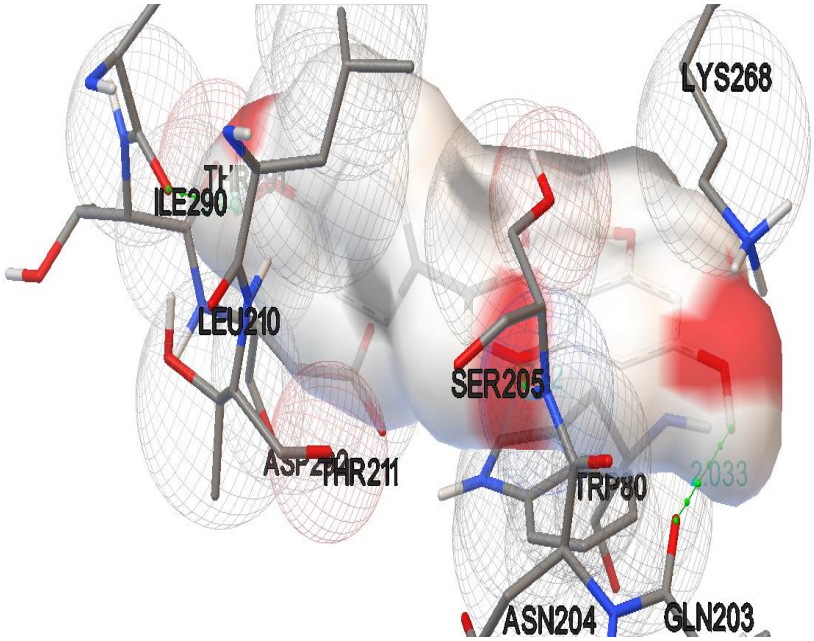


Figure 4 Interactions between AKT1 and 5,7,4'- trihydroxyisoflavoneVisualised using Autodock.

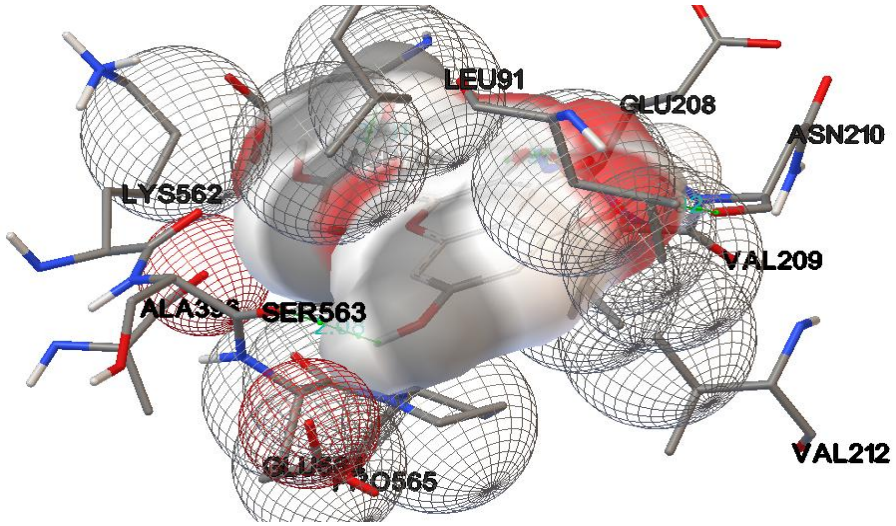


Figure 5 Interactions between ACE 2 and 3,3',4',5, 7-pentahydroxyisoflavone Visualised using Autodock

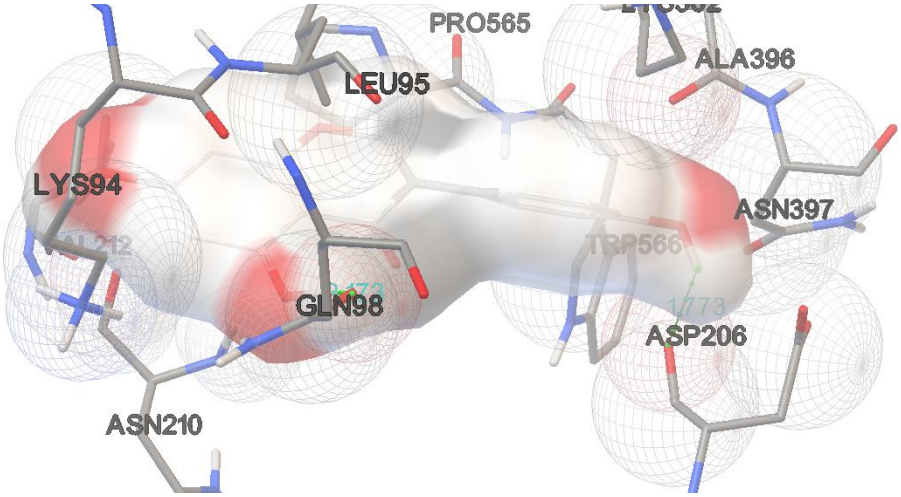


Figure 6 Interactions between ACE2 and 5,7,4' - trihydroxyisoflavoneVisualised using Autodock

Table 3 Docking score of compound-1 with AKT1

AKT1		**3,3',4',5,7-pentahydroxyisoflavone**	**Distance (Å)**	**Docking Energy (Kcal/Mol)**
Residue	**Atom**	**(LIGAND 1)**		
THR291	O	H	1.94	
ILE290	O	H	1.88	
THR211	N	O	2.76	
THR211	O	H	2.11	
SER205	N	O	2.64	
SER205	N	O	2.73	
GLN203	O	H	1.99	–8.83

Table 4 Final Conformation Docking energy of compound-2 with AKT1

```
                binding_energy=-8.16
              ligand_efficiency=-0.41
                inhib_constant=1.04
              inhib_constant_units=uM
                intermol_energy=-9.36
            vdw_hb_desolv_energy=-9.14
            electrostatic_energy=-0.22
               total_internal=-0.99
             torsional_energy=1.19
              unbound_energy=-0.99
                filename=best.dlg
                    clRMS=0.0
                  refRMS=62.18
                  rseed1=None
                  rseed2=None
             3 hydrogen bonds formed:
      4EJN_2:A:SER205:HN :  trihydroxyisoflavon-3: :LIG1:O
trihydroxyisoflavon-3: :LIG1:H :         4EJN_2:A:GLN203:O
trihydroxyisoflavon-3: :LIG1:H :         4EJN_2:A:ILE290:O
```

Table 5 Docking score of compound-2 with AKT1

AKT1		**5,7,4'trihydroxyisoflavone**	**Distance (Å)**	**Docking Energy (Kcal/Mol)**
Residue	**Atom**	**(LIGAND 2)**		
SER205	N	O	2.87	
TYR272	O	H	1.90	
THR211	N	O	2.84	
ASN204	OD1	H	2.11	–8.16

Table 6 Final Conformation Docking energy of compound-1 with ACE2

```
                binding_energy=-8.76
              ligand_efficiency=-0.4
                inhib_constant=379.43
              inhib_constant_units=nM
                intermol_energy=-10.55
            vdw_hb_desolv_energy=-10.21
            electrostatic_energy=-0.34
               total_internal=-1.39
             torsional_energy=1.79
              unbound_energy=-1.39
                filename=best.dlg
                    clRMS=0.0
                  refRMS=99.05
                  rseed1=None
                  rseed2=None
             4 hydrogen bonds formed:
pentahydroxyisoflavone-3: :LIG1:H :         1R42_2:A:GLU208:O
pentahydroxyisoflavone-3: :LIG1:H :         1R42_2:A:ASN210:O
pentahydroxyisoflavone-3: :LIG1:H :         1R42_2:A:ASP206:O
pentahydroxyisoflavone-3: :LIG1:H :         1R42_2:A:SER563:O
```

Table 7 Docking score of compound-1 with ACE2

ACE2		3,3',4',5,7-pentahydroxyisoflavone	Distance (Å)	Docking Energy (Kcal/Mol)
Residue	**Atom**			
GLU208	O	H	1.97	–8.76
ASN210	O	H	1.92	
ASN210	N	O	3.20	
ASP206	O	H	2.10	
ASP206	O	H	1.95	
SER563	O	H	2.07	
GLU564	OE2	H	2.42	

Table 8 Final Conformation Docking energy of compound-2 with ACE2

```
                binding_energy=-7.61
              ligand_efficiency=-0.38
                inhib_constant=2.66
              inhib_constant_units=uM
                intermol_energy=-8.8
            vdw_hb_desolv_energy=-8.62
           electrostatic_energy=-0.18
              total_internal=-0.95
            torsional_energy=1.19
            unbound_energy=-0.95
              filename=best.dlg
                 clRMS=0.0
               refRMS=100.32
                rseed1=None
                rseed2=None
          2 hydrogen bonds formed:
trihydroxyisoflavone-3: :LIG1:H :        1R42_2:A:ASP206:O
trihydroxyisoflavone-3: :LIG1:H :       1R42_2:A:GLN98:OE1
```

Table 9 Docking score of compound-2 with ACE2

ACE2		5,7,4'trihydroxyisoflavone	Distance (Å)	Docking Energy (Kcal/Mol)
Residue	**Atom**			
GLN98	NE2	O	3.18	–7.61
GLN98	OE1	H	2.17	
ASP206	O	H	1.77	
ASN210	O	H	2.06	

Table 10 Final Docking Scores

Drug target	Compound 1 and 2	Socking score (Kcal/Mol)	Number of interactions
AKT1	3,3',4',5,7-pentahydroxyisoflavone (Compound -1)	–8.83	7
AKT1	5,7,4'-trihydroxyisoflavone (Compound -2	–8.16	4
ACE2	3,3',4',5,7-pentahydroxyisoflavone	–8.76	7
ACE2	5,7,4'-trihydroxyisoflavone	–7.61	4