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# *IN SILICO* DIURETIC ACTIVITY OF BIOACTIVE COMPOUNDS IN *VIGNA RADIATA*

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**ABSTRACT**

Medicinal plants serve as an ethnomedicine and play a pivotal role in healing and curing disease. It has a major role in the identification of drug-lead compounds. The present study shows the molecular synergy of 27 bioactive compounds in *Vigna radiata* (L.) R.Wilczek like Rutin, Syringic acid, p-hydroxybenzoic acid, Gentisic acid, Protocatechuic acid, Gallic acid, Caffeic acid, Apigenin, Cinnamic acid, Ferulic acid, p-Coumaric acid, Chrysin, Vitexin, Genistein, Daidzein, Quercetin, Daidzin, Vanillic acid, Chlorogenic acid, Kaempferol, Isovitexin, Ononin, Myricetin, Formononetin, Naringin, Isoformononetin against diuretic receptors like Human Carbonic anhydrase II (CA II, PDB ID-3HS4) were evaluated and compared with the taken standard drug Acetazolamide. Molecular docking studies were performed using AutoDock Vina 1.1.2 docking software which has a good search algorithm and scoring function respectively, and visualization of interactions can be seen by using Biovia Discovery Studio Visualizer. The docking studies of various small molecules in *Vigna radiata* with the target protein 3HS4 showed good diuretic activity, amongst the compounds screened Ononin and Rutin (Binding energy; 3HS4: -8.4 kcal/mol), Naringin (Binding energy; 3HS4: -8.3 kcal/mol), Myricetin and isovitexin (Binding energy; 3HS4: -8.1 kcal/mol), Quercetin (Binding energy; 3HS4: -8.0 kcal/mol), Acetazolamide, Chrysin, Vitexin and Kaempferol (Binding energy; 3HS4: -7.9 kcal/mol). Ononin ad Rutin showed maximum biological activity for the 3HS4 target when compared with the standard drug Acetazolamide, both these bioactive compounds can be further subjected to *in vitro* and *in vivo* studies to attest their biological activity and can be further leveraged as effective diuretic agents.

**Keywords:** *Vigna radiata*, Carbonic anhydrase II receptor (3HS4), AutoDock Vina, Molecular docking.

## INTRODUCTION

Medicinal plant life serves a major position in displaying biological pastimes because of the presence of diverse secondary metabolites like alkaloids, flavonoids, glycosides, terpenes, etc. Diuretic activity is associated with the treatment of diseases like cardiac problems like arterial hypertension, heart failure, kidney problems, renal problems, glaucoma, and edema due to water and electrolyte imbalances. Diuretics have some side effects like erectile dysfunction, hyperuricemia, hypercalciuria, hypokalemia, ototoxicity, hyperglycemia, immune reactions, and Metabolic acidosis leading to increased bicarbonate loss.

Currently, there are five classes of diuretics are present including thiazide (eg; chlorothiazide), loop diuretics (eg; furosemide), carbonic anhydrase inhibitors (eg; acetazolamide), Potassium-sparing diuretics (eg; Spironolactone),osmotic diuretics (eg; Mannitol). Carbonic anhydrases belong to the metalloenzymes family that breaks down the reversible addition of water or water removal of $CO_2/HCO_3^-$. Carbonic anhydrases are associated with some physiological processes such as calcification, respiration, bone resorption, and photosynthesis.

Computational methods are emerging nowadays due to their reduction in time process, low cost, etc--. The present study wants to execute the docking analysis of 27 bioactive compounds of *Vigna radiata* (see Table 1 and their structures in Table 4) like Rutin, Syringic acid, p-hydroxybenzoic acid, Gentisic acid, Protocatechuic acid, Gallic acid, Caffeic acid, Apigenin, Cinnamic acid, Ferulicacid, p-

Coumaric acid, Chrysin, Vitexin, Genistein, Daidzein, Quercetin, Daidzin, Vanillic acid, Chlorogenic acid, Kaempferol, Isovitexin, Ononin, Myricetin, Formononetin, Naringin, Isoformononetin against diuretic receptors like Human Carbonic anhydrase II (CA II, PDB ID-3HS4) which is one of the most active isoforms of Human Carbonic anhydrase enzyme and binding affinity results of the 27 different bioactive compounds of the plant were compared with the standard drug acetazolamide. A good one may grow into an effective diuretic drug.

## 1. MATERIALS AND METHODS

### 1.1 Selection and Preparation of Protein structure:

Human carbonic anhydrase II complex with acetazolamide (PDB ID-3HS4) with Resolution value 1.1 $A^0$, R-value free 0.14, and R-value work 0.112 were selected in the present study and it is selected by SwissADME Target Prediction (http://www.swisstargetprediction.ch/). The target structures were downloaded from the RCSB protein data bank (https://www.rcsb.org/structure/3HS4) (see Fig 1) which is an open source for obtaining 3D protein structures. It provides all necessary information about chain length, Number of chains, hydrogen atoms, and various charges that need to be added. For the process of docking, all the solvent molecules like water, etc-- and co-crystallized small molecules were removed from the target structure and different ligands, missing atoms, hydrogen atoms, and Gasteiger-Marsili charges can also be inserted to check biological activity by using AutoDock 4.2.6. Active sites were defined, listed, and selected just before the grid generation step (see Table 2 and Fig 2).

### 1.2 Selection and preparation of Ligands:

In the present study, a total of 27 small molecules of Vigna radiata were selected by literature survey and it includes Rutin, Syringic acid, p-hydroxybenzoic acid, Gentisic acid, Protocatechuic acid, Gallic acid, Caffeic acid, Apigenin, Cinnamic acid, Ferulic acid, p-Coumaric acid, Chrysin, Vitexin, Genistein, Daidzein, Quercetin, Daidzin, Vanillic acid, Chlorogenic acid, Kaempferol, Isovitexin, Ononin, Myricetin, Formononetin, Naringin, Isoformononetin were selected respectively. The 3D SDF (Structure Data File) format was retrieved from the PubChem database ( https://pubchem.ncbi.nlm.nih.gov/). But for the docking procedure, the protein and ligands should be in the form of PDB (Protein Data Bank) format. To convert SDF to PDB Format, Open Babel software ( http://openbabel.org/wiki/Main_Page) was used. Open Babel is an open and free access software and it is used to search and convert one format into another different format easily. Preparation of ligands like energy minimization, deleting water molecules, choosing torsional roots, and the number of conformations by using AutoDock 4.2.6 (http://autodock.scripps.edu/).

### 1.3 Performance of Molecular Docking:

Molecular docking studies of 27 phytochemical constituents in *Vigna radiata* (L.) R.Wilczek against CA II Target like 3HS4 was carried out by using AutoDock Vina 1.1.2 software(https://vina.scripps.edu/downloads/). Molecular docking studies mainly depend upon the type of search algorithm and scoring function. The presence of the best search algorithm helps in the quick finding of conformations with lower energy which will have a high binding affinity. Scoring Function is used for ranking or numbering a pose or conformation generated by the search algorithm. AutoDock MGL Tools follows the Lamarckian genetic algorithm used for pose optimization. The Experience-based scoring function is used for considering the residue side chains and also used in the determination of the flexibility of ligand molecules. AutoDock Vina is customized better than AutoDock MGL Tools in rate functioning and accuracy of the results made in protein-ligand molecular docking. To run the AutoDock Vina, both protein and ligand should be in the form of PDBQT format and this type of format was achieved by using AutoDock MGL Tools. In AutoDock MGL Tools, after the preparation of both protein and ligand, the grid generation box step is involved and this is the most crucial step involved in the molecular docking program. During the grid generation, the selected X, Y, and Z dimensions are 54, 46, and 64 and the center search space was X- center: -4.103, Y-center: -1.986, Z- center: 14.855 (see Fig 3). After the configuration file generation (see Fig 4), the docking program AutoDock Vina will run by using Command Prompt. The command prompt program should run in the form of the following order

a. Open Command Prompt> cd (copy the folder address where all the PDB files & vina are saved) > Enter.
b. vina.exe --config confi(confi file name which was saved during the procedure. For Eg; confirutin).txt –log log.txt > Enter.
c. Docking Results (Output) were obtained (see Fig 5).
**d.** If visualization needs, then type **Vina_split.exe –input out.pdbqt > Enter.**
e. Then, Out-ligand will be generated in the above-mentioned folder which was copied before.

The stability and number of poses were evaluated by using AutoDock Vina software. The

visualization of 2D (see Fig 6&7) and 3D (see Fig 8&9) molecular interaction has been done by using Biovia Discovery Studio Visualizer software.

## 2. RESULTS

CA II **(**3HS4) is the better receptor for Rutin, Ononin, and Naringin than Acetazolamide which will fit into the protein binding pocket of active site residues like hydrophobic contacts like VAL121, VAL143, LEU198, VAL207, TRP209, and hydrophilic contacts like TYR7, ASN62, HIS64, ASN67, THR199, THR200. High affinity was observed with Rutin, Ononin, Naringin, Isovitexin, Quercetin, and Myricetin, while moderate affinity was predicted for Acetazolamide, Chrysin, Vitexin, Kaempferol, Daidzin, Chlorogenic acid, Genistein, Formononetin, Daidzein, Isoformononetin, and low affinity was observed with p-Hydroxy Benzoic acid, Syringic acid, Vanillic acid, Shikimic acid, Cinnamic acid, Protocatechuic acid with RMSD "0" value. Results, when compared with standard drug, all the phytoconstituents showed nearer values (see Table 3).

## 3. DISCUSSION

Computer-aided drug design (CADD) is one of the huge strategies in the area of drug discovery and improvement in the current years. In the drug discovery process, target identification, HIT identification (HTS, know ledged based approaches, virtual screening), Lead compounds, and Lead Optimization steps are involved. Due to more steps involved in the process, it is a time-eating (appro, 14 years) and high-priced method (appro, 800 US million dollars). CADD is present-day *in silico* technique used within the drug discovery system to perceive and develop a potential lead compound. CADD helped in both academic and pharmaceutical companies like predicting the ADMET parameters, Physico-chemical properties, and experimental testing like removal of undesired atoms or compounds with poor bioavailability, poor solubility, poor absorption, etc--.

*Vigna radiata* (L.) R.Wilczek ( Mung bean) is a legume plant in Asia and its seeds are rich in proteins, antioxidants, fiber, vitamins, minerals, and phytonutrients. Mung bean sprouts have large amounts of niacin, thiamine, and ascorbic acid. Along with nutrient requirements, it has hypoglycemic and hypolipidemic effects, antihypertensive, anticancer, anti-melanogenesis, hepatoprotective, and immunomodulatory properties. China considered mung bean as indigenous medicine used for detoxification and heat stroke purposes. In the present study,the phytochemical constituents of the *Vigna radiata* (L.) R.Wilczek is used to conclude the potential small molecules having diuretic activity when compared with the standard drug acetazolamide.

Carbonic anhydrases belong to the metalloenzymes family that break down the reversible water addition or water removal of $CO_2/HCO_3^-$. Carbonic anhydrases are associated with some physiological processes such as calcification, respiration, bone resorption, and photosynthesis. Among all isoforms, HCA II is the most popular and it has a cone- shaped pocket with active sites formed of Hydrophobic contacts VAL 121, VAL 143, LEU 198, VAL 207, TRP 209, and Hydrophilic contacts TYR 7, ASN 62, HIS 64, ASN 67, THR 199, THR 200. In the mechanism of HCA II, $CO_2$ will bind with the active site of protein in the first step, In the second step, proton transfer will take place.

**Mechanism:**

Step 1: AZnOH- + CO2 ↔ AZnHCO3-↔ AZnH2O + HCO3 –
Step 2: AZnH2O + B ↔ AZnOH- + BH+

The ordinary purpose of this study is to examine and file new insights into how an inhibitor binds within the active site of human CAs. The present study was accomplished to look into whether the phytochemical constituents of Vigna radiata (L.) R.Wilczek as small molecules with HCA II protein 3HS4. Molecular docking was done with 27 bioactive compounds of the plant as small molecules against the single target 3HS4 by using AutoDock Vina respectively. The current study disclosed that amid bioactive compounds screened for diuretic activity against the 3HS4 protein, Rutin and Ononin with a binding energy of -8.4, after that Naringin with -8.3, Isovitexin and Myricetin with a binding energy of -8.1 and these are compared with the standard drug Acetazolamide with a binding energy of -7.9. In this study, Rutin and Ononin revealed the highest inhibitory action against the protein 3HS4 and it has high stability with lower energy levels. Rutin has many biological activities such as antibacterial, antiprotozoal, antitumor, anti-inflammatory, antiallergic, antiviral, cytoprotective, vasoactive, hypolipidemic, antiplatelet, antispasmodic, and antihypertensive. Ononin has advantages, it is an isoflavone that has good oral bioavailability and it has a higher absorption rate in the larger intestine than in the small intestine.

## Conclusion

Diuretic activity is associated with the treatment of diseases like cardiac and kidney problems, mung bean (thiazide and loop diuretics) is associated with antioxidant, anti-diabetic, antimicrobial, anti-hyperlipidemic and antihypertensive effects, anti-inflammatory, and anticancer, anti-tumor and anti-mutagenic properties, so there is a need for developing safe and efficacious newer drugs with having no/low toxic effects. Molecular docking studies of bioactive compounds in Vigna radiata (L.) R.Wilczek against a diuretic target like 3HS4 manifested favorable outcomes with notable inhibitory activity noticed with Rutin and Ononin respectively. Thus, the specified bioactive compounds may be used for growing into an amazing diuretic drugs.

**Table 1: Properties of Bioactive compounds of *Vigna radiata* (L.) R.Wilczek**

| S. No. | Compounds | PubChem CID | Molecular Formula | Molecular Weight (g/mol) |
|---|---|---|---|---|
| 1 | Acetazolamide | 1986 | C4H6N4O3S2 | 222.3 |
| 2 | Rutin | 5280805 | C27H30O16 | 610.5 |
| 3 | Syringic acid | 10742 | C9H10O5 | 198.17 |
| 4 | Shikimic acid | 8742 | C7H10O5 | 174.15 |
| 5 | p-hydroxybenzoic acid | 135 | C7H6O3 | 138.12 |
| 6 | Gentisic acid | 3469 | C7H6O4 | 154.12 |
| 7 | Protocatechuic acid | 72 | C7H6O4 | 154.12 |
| 8 | Gallic acid | 370 | C7H6O5 | 170.12 |
| 9 | Caffeic acid | 689043 | C9H8O4 | 180.16 |
| 10 | Apigenin | 5280443 | C15H10O5 | 270.24 |
| 11 | Cinnamic acid | 444539 | C9H8O2 | 148.16 |
| 12 | Ferulic acid | 445858 | C10H10O4 | 194.18 |
| 13 | p-Coumaric acid | 637542 | C9H8O3 | 164.16 |
| 14 | Chrysin | 5281607 | C15H10O4 | 254.24 |
| 15 | Vitexin | 5280441 | C21H20O10 | 432.4 |
| 16 | Genistein | 5280961 | C15H10O5 | 270.24 |
| 17 | Daidzein | 5281708 | C15H10O4 | 254.24 |
| 18 | Quercetin | 5280343 | C15H10O7 | 302.23 |
| 19 | Daidzin | 107971 | C21H20O9 | 416.4 |
| 20 | Vanillic acid | 8468 | C8H8O4 | 168.15 |
| 21 | Chlorogenic acid | 1794427 | C16H18O9 | 354.31 |
| 22 | Kaempferol | 5280863 | C15H10O6 | 286.24 |
| 23 | Isovitexin | 162350 | C21H20O10 | 432.4 |
| 24 | Ononin | 442813 | C22H22O9 | 430.4 |
| 25 | Myricetin | 5280378 | C16H12O4 | 268.26 |
| 26 | Formononetin | 5280378 | C16H12O4 | 268.26 |
| 27 | Naringin | 442428 | C27H32O14 | 580.5 |
| 28 | Isoformononetin | 3764 | C16H12O4 | 268.26 |

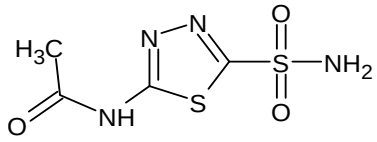
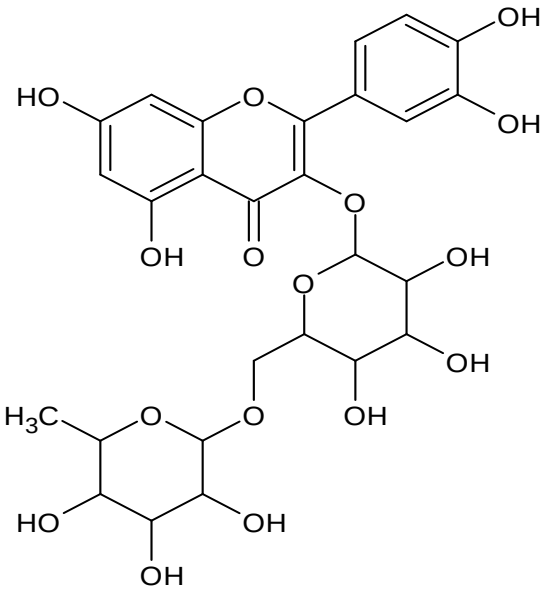
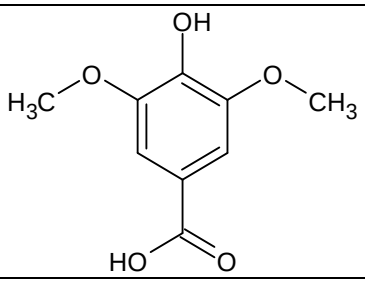
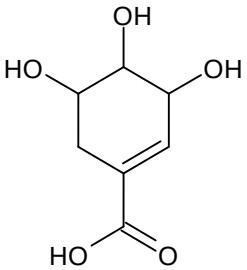
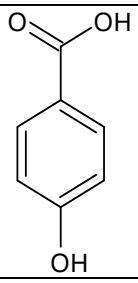
**Table 2: Active binding site residues of Human Carbonic anhydrase II receptor (CA II, PDB ID-3HS4)**

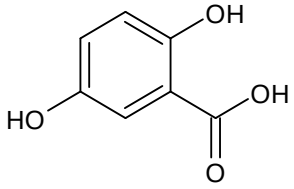
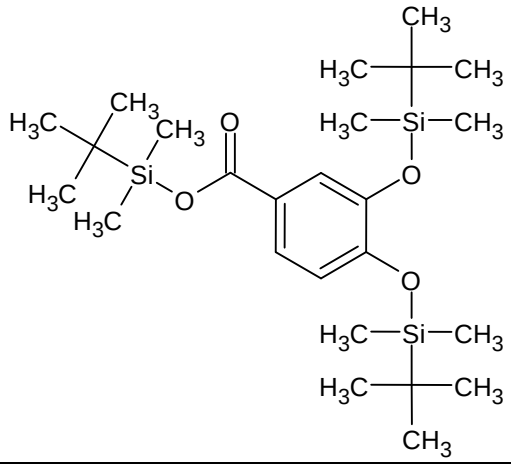
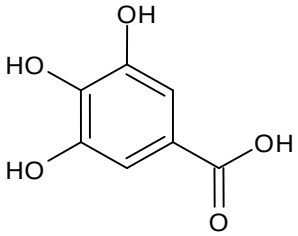
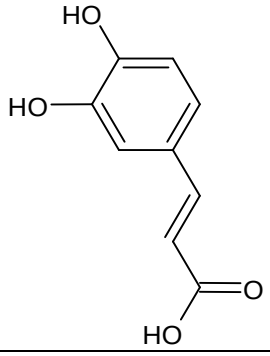
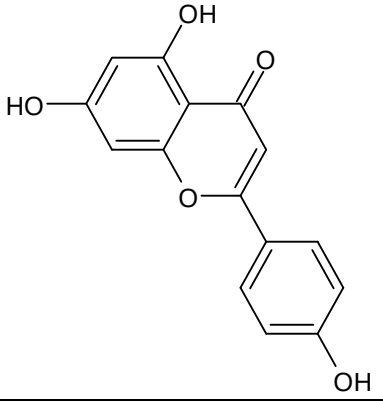
| S. No. | Protein molecule | Contacts | Active site residues |
|---|---|---|---|
| 1 | Human carbonic anhydrase II (3Hs4) | Hydrophobic contacts | VAL 121, VAL 143, LEU 198, VAL 207, TRP 209 |
| | | Hydrophilic contacts | TYR 7, ASN 62, HIS 64, ASN 67, THR 199, THR 200 |

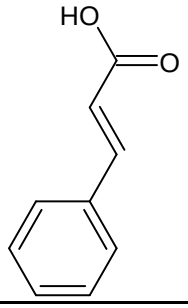
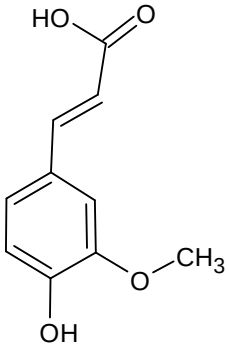
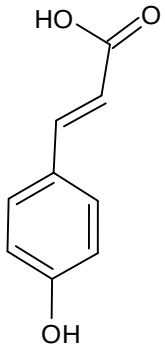
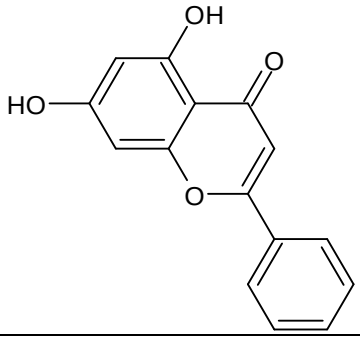
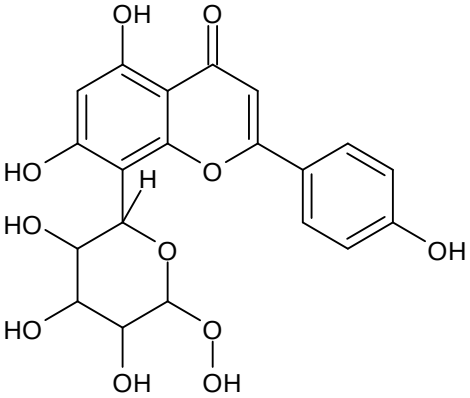
**Table 3: Docking results of Human Carbonic anhydrase II receptor (CA II, PDB ID-3HS4) with respective ligands of *Vigna radiata* (L.)R.Wilczek**

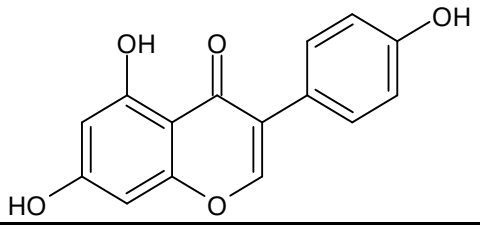
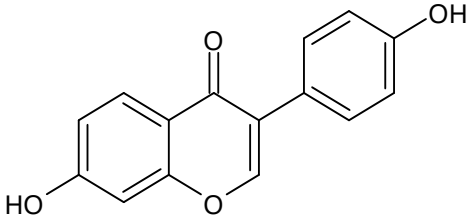
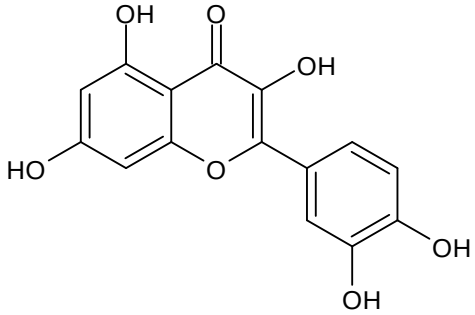
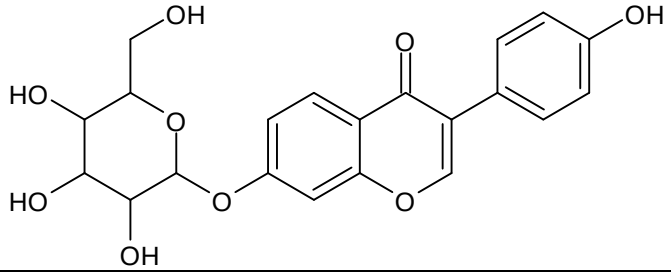
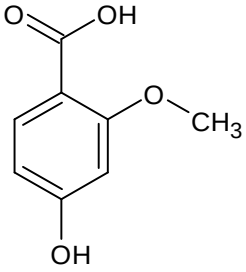
| S. No. | Compound Name | Receptor | No of poses | Best ligand pose energy(kcal/mol) |
|---|---|---|---|---|
| 1 | Acetazolamide | 3hs4 | 9 | -7.9 |
| 2 | Rutin | 3hs4 | 9 | -8.4 |
| 3 | Syringic acid | 3hs4 | 9 | -5.8 |
| 4 | Shikimic acid | 3hs4 | 9 | -6.0 |
| 5 | p-hydroxybenzoic acid | 3hs4 | 9 | -5.7 |
| 6 | Gentisic acid | 3hs4 | 9 | -6.1 |
| 7 | Protocatechuic acid | 3hs4 | 9 | -6.1 |
| 8 | Gallic acid | 3hs4 | 9 | -6.2 |
| 9 | Caffeic acid | 3hs4 | 9 | -6.5 |
| 10 | Apigenin | 3hs4 | 9 | -6.5 |
| 11 | Cinnamic acid | 3hs4 | 9 | -6.0 |
| 12 | Ferulic acid | 3hs4 | 9 | -6.4 |
| 13 | p-Coumaric acid | 3hs4 | 9 | -6.2 |
| 14 | Chrysin | 3hs4 | 9 | -7.9 |
| 15 | Vitexin | 3hs4 | 9 | -7.9 |
| 16 | Genistein | 3hs4 | 9 | -7.3 |
| 17 | Daidzein | 3hs4 | 9 | -7.2 |
| 18 | Quercetin | 3hs4 | 9 | -8.0 |
| 19 | Daidzin | 3hs4 | 9 | -7.8 |
| 20 | Vanillic acid | 3hs4 | 9 | -5.9 |
| 21 | Chlorogenic acid | 3hs4 | 9 | -7.8 |
| 22 | Kaempferol | 3hs4 | 9 | -7.9 |
| 23 | Isovitexin | 3hs4 | 9 | -8.1 |
| 24 | Ononin | 3hs4 | 9 | -8.4 |
| 25 | Myricetin | 3hs4 | 9 | -8.1 |
| 26 | Formononetin | 3hs4 | 9 | -7.4 |
| 27 | Naringin | 3hs4 | 9 | -8.3 |
| 28 | Isoformononetin | 3hs4 | 9 | -7.2 |

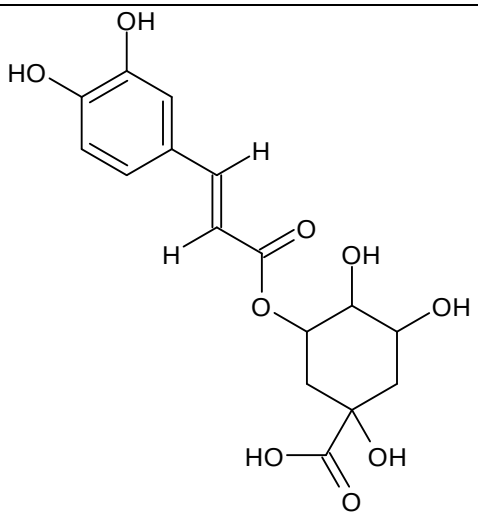
**Table 4: 2D structures of 27 bioactive compounds of *Vigna radiata (L.) R.Wilczek***

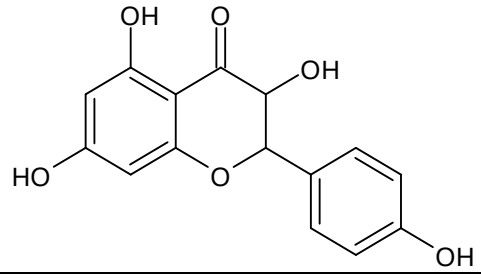
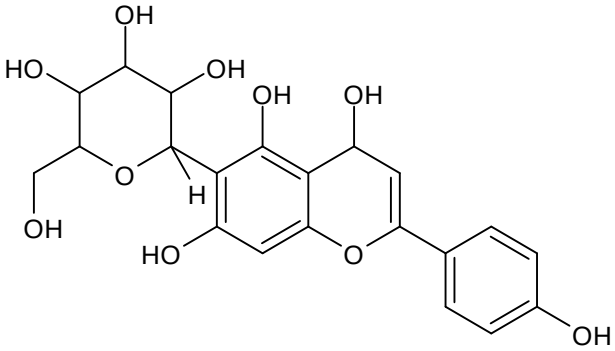
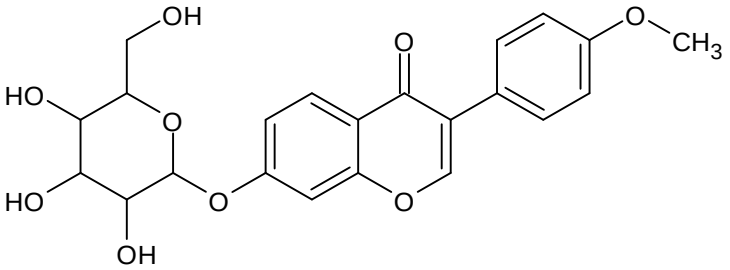
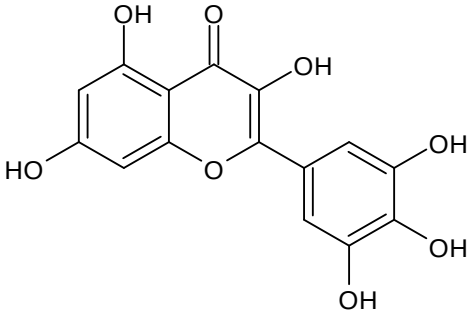
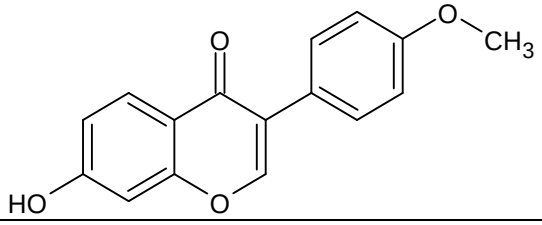
| S. No. | Compounds | 2D Structures |
|---|---|---|
| 1 | Acetazolamide |  |
| 2 | Rutin |  |
| 3 | Syringic acid |  |
| 4 | Shikimic acid |  |
| 5 | p-hydroxybenzoic acid |  |

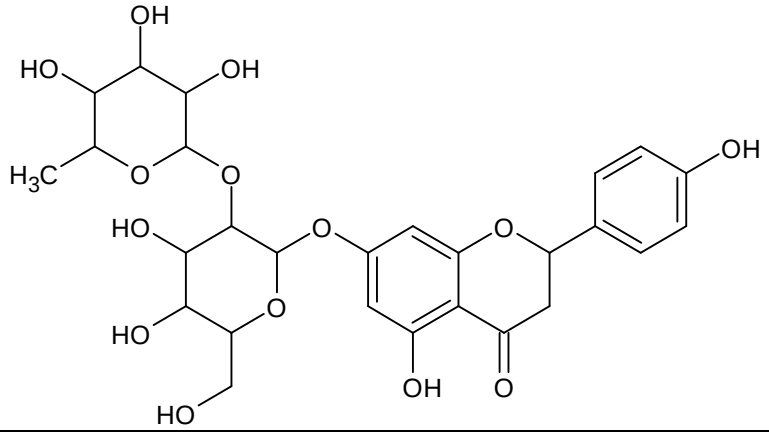
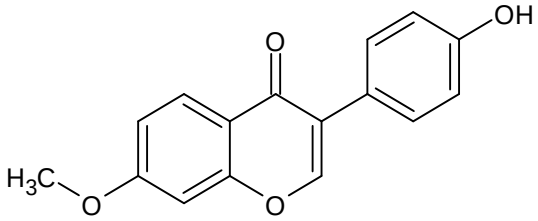
| | | |
|---|---|---|
| 6 | Gentisic acid |  |
| 7 | Protocatechuic acid |  |
| 8 | Gallic acid |  |
| 9 | Caffeic acid |  |
| 10 | Apigenin |  |

| | | |
|---|---|---|
| 11 | Cinnamic acid |  |
| 12 | Ferulic acid |  |
| 13 | p-coumaric acid |  |
| 14 | chrysin |  |
| 15 | Vitexin |  |

| | | |
|---|---|---|
| 16 | genistein |  |
| 17 | Daidzein |  |
| 18 | Quercetin |  |
| 19 | Daidzin |  |
| 20 | Vanillic acid |  |

| | | |
|---|---|---|
| 21 | Chlorogenic acid |  |

| | | |
|---|---|---|
| 22 | Kaempferol |  |
| 23 | Isovitexin |  |
| 24 | Ononin |  |
| 25 | Myricetin |  |
| 26 | Formononetin |  |

| | | |
|---|---|---|
| 27 | Naringin |  |
| 28 | Isoformononetin |  |

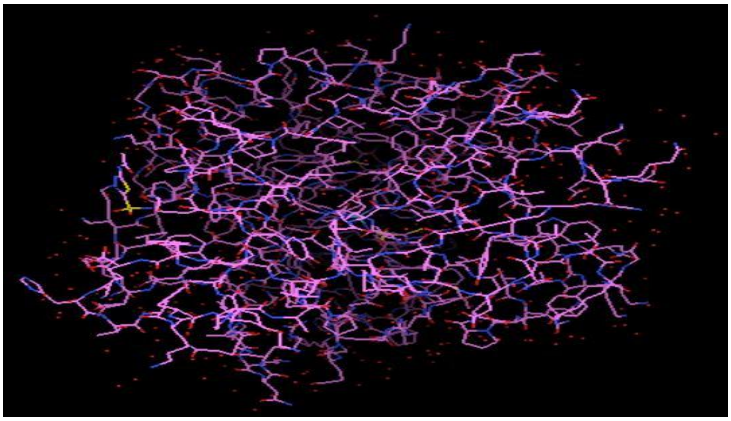


**Fig. 1: Crystal structure of CA II receptor (PDB ID- 3HS4)**

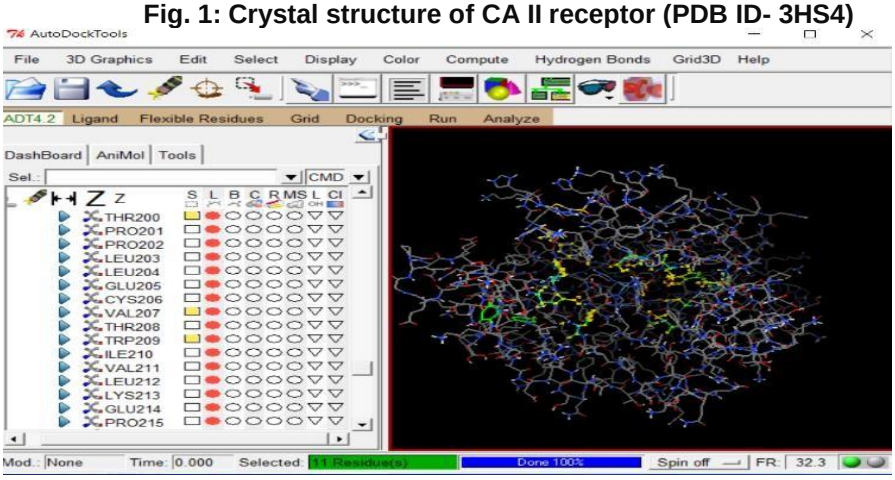



**Fig. 2: Selection of Active binding sites after the preparation of both ligand and protein**

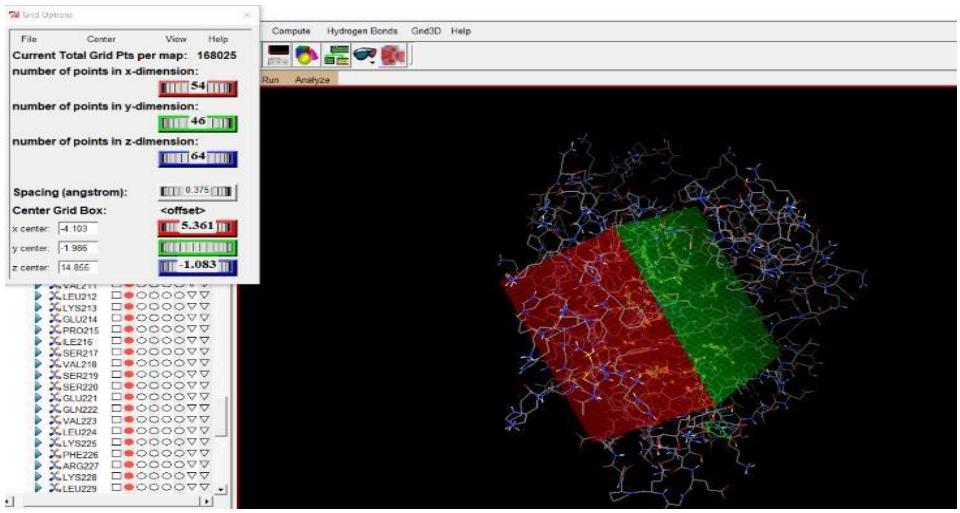



**Fig. 3: Grid generation box**

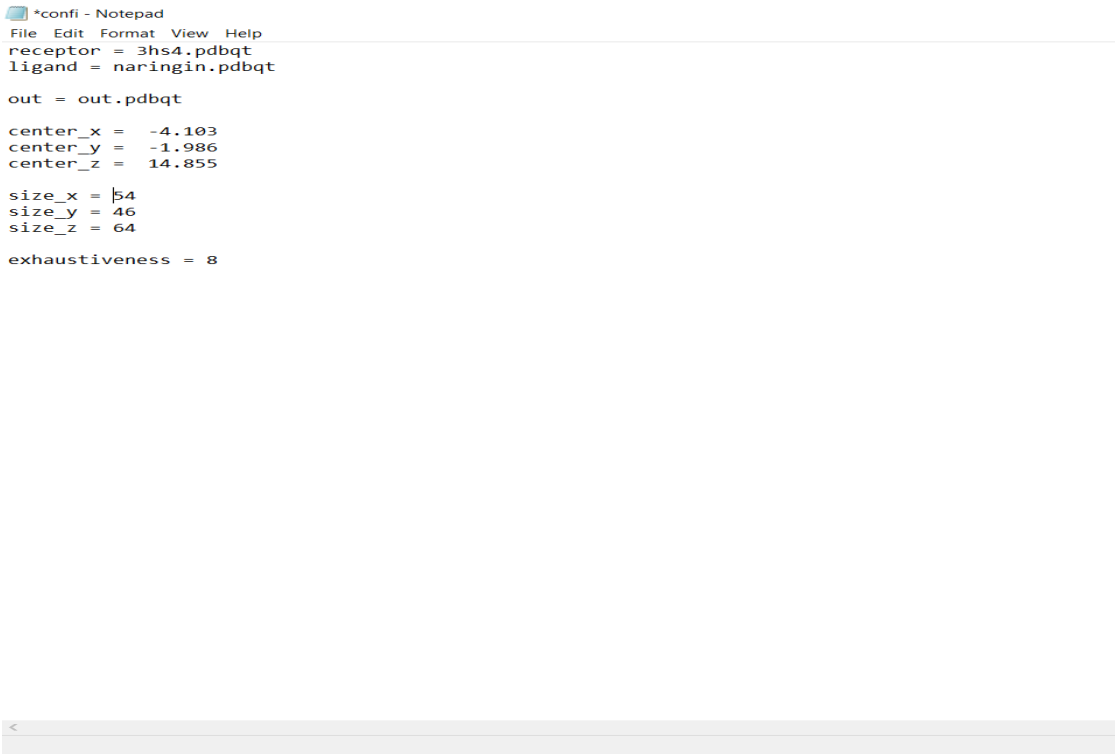



**Fig. 4: Configuration File**

```
Command Prompt

C:\Users\MounicaKanamarlaputi>cd C:\Users\MounicaKanamarlaputi\OneDrive\Desktop\project

C:\Users\MounicaKanamarlaputi\OneDrive\Desktop\project>vina.exe --config confinaringin.txt --log log.txt
#################################################################
# If you used AutoDock Vina in your work, please cite:          #
#                                                               #
# O. Trott, A. J. Olson,                                        #
# AutoDock Vina: improving the speed and accuracy of docking    #
# with a new scoring function, efficient optimization and       #
# multithreading, Journal of Computational Chemistry 31 (2010)  #
# 455-461                                                       #
#                                                               #
# DOI 10.1002/jcc.21334                                         #
#                                                               #
# Please see http://vina.scripps.edu for more information.      #
#################################################################

WARNING: The search space volume > 27000 Angstrom^3 (See FAQ)
Detected 8 CPUs
Reading input ... done.
Setting up the scoring function ... done.
Analyzing the binding site ... done.
Using random seed: -543061168
Performing search ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************
done.
Refining results ... done.

mode |    affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1          -8.3      0.000      0.000
   2          -8.3      5.396     13.414
   3          -8.1      2.519      4.950
   4          -7.9      2.734      5.135
   5          -7.8      2.302      6.076
   6          -7.8      4.298      8.670
   7          -7.6      2.211      5.800
   8          -7.6     11.234     14.715
   9          -7.5      9.334     14.177
Writing output ... done.

C:\Users\MounicaKanamarlaputi\OneDrive\Desktop\project>vina_split.exe --input out.pdbqt
Prefix for ligands will be out_ligand_
Prefix for flexible side chains will be out_flex_

C:\Users\MounicaKanamarlaputi\OneDrive\Desktop\project>
```

**Fig. 5: Docking analysis of Naringin by Autodock vina using command prompt program**

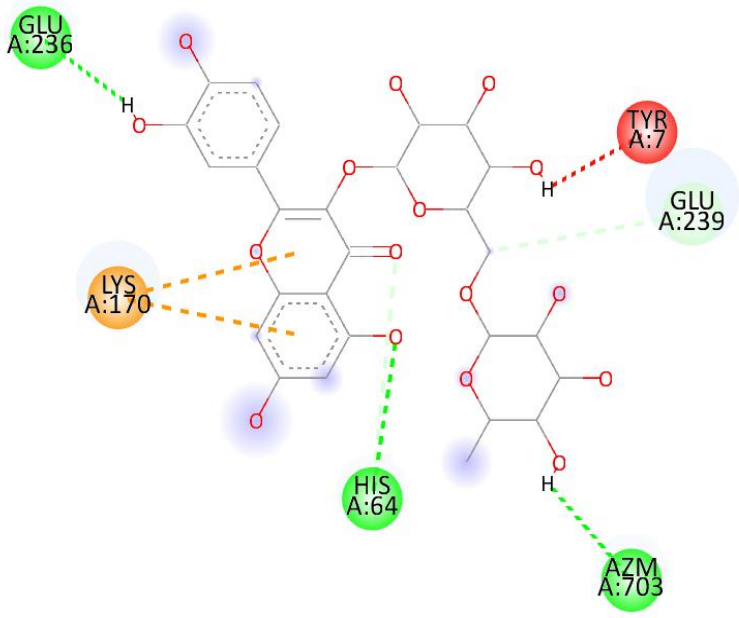



**Fig. 6: 2D molecular interaction of Rutin with active binding sites of CA II receptor PDB ID 3HS4 by using Biovia Discovery Studio Visualizer**

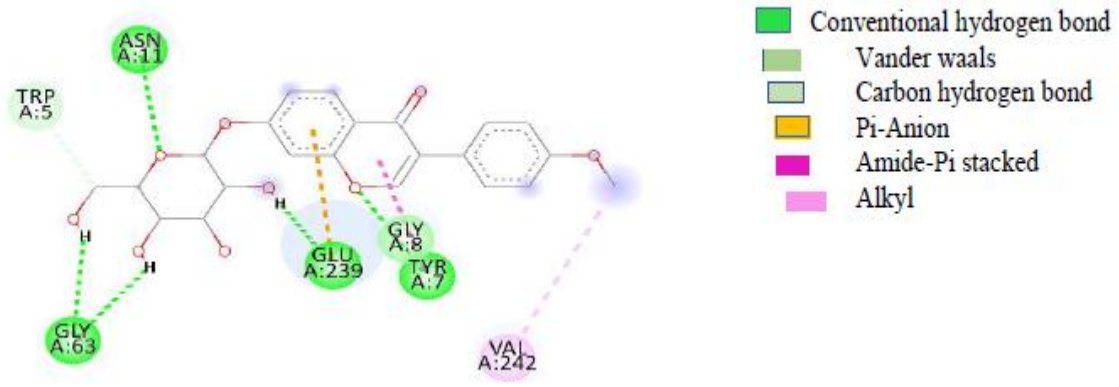



**Fig. 7: 2D molecular interaction of Ononin with active binding sites of CA II receptor PDB ID 3HS4 by using Biovia Discovery Studio Visualizer**

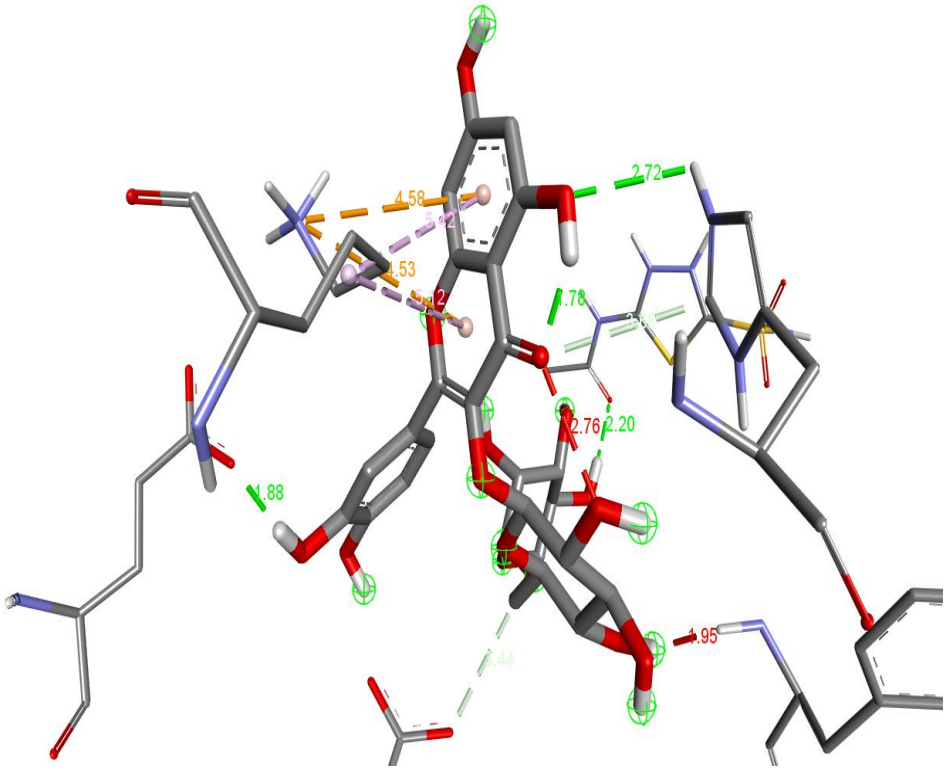



**Fig. 8: 3D molecular interaction of Rutin with active binding sites of CA II receptor PDB ID 3HS4 by using Biovia Discovery Studio Visualizer**

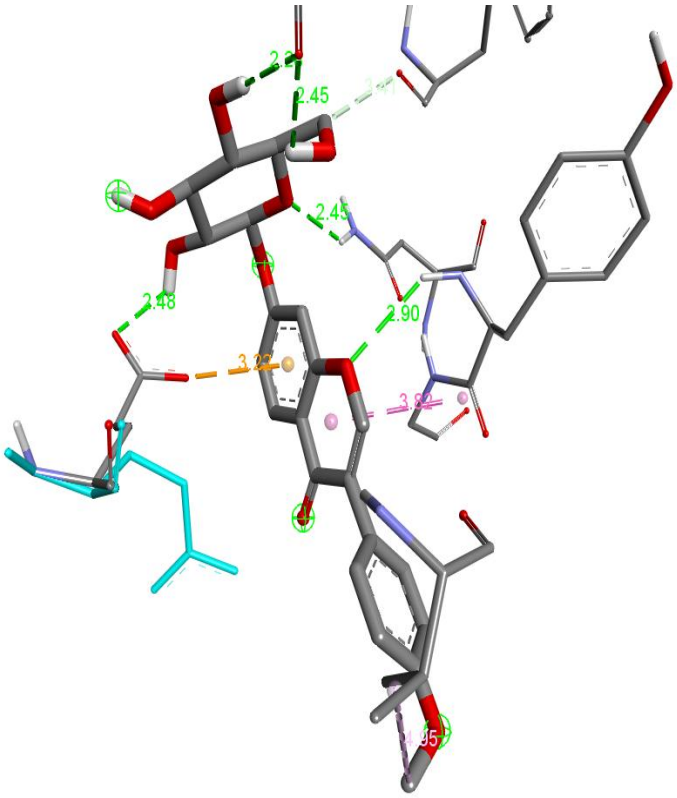



**Fig. 9: 3D molecular interaction of Ononin with active binding sites of CA II receptor PDB ID 3HS4 by using Biovia Discovery Studio Visualizer**

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