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Molecular Docking Studies Of Lawsone Derivatives With Tuberculosis Protein (PDB CODE: 1v0j)

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ABSTRACT

*A series of seven numbers of lawsone derivatives are examined for the Insilico molecular docking studies with the tuberculosis protein (**PDB CODE: 1v0j**). The compound **6** shows the lowest inhibition constant 4.82 µM and the compound **7** shows the highest inhibition constant 74.17 µM.*

Keywords: Lawsone derivatives; Molecular docking; Tuberculosis protein; 1v0j.

INTRODUCTION

Lawsone or 2-hydroxy-1,4-naphthoquinone was first isolated from the leaves of Lawsonia inermis L. In 1959 [1], 2-Hydroxy-1,4-naphthoquinone and related compounds have been reported to possess interesting biological activities such as antitumor, antibacterial and antifungal properties [2-4]. It is also used as a hair dye [5] and use an ultra-violet (UV) filter in sunscreen formulation [6]. Naphthoquinones constitute one of the largest and diverse groups of plant secondary metabolites with a broad range of properties [7,8] antifeedent, [9] and allelopathic activity [10] which contribute to plant defense. They also possess important pharmacological activities, such as antioxidant [11], anti-inflammatory [12], anticancer, [13]. With nearly one-third of the global population infected by Mycobacterium tuberculosis (MTB), tuberculosis (TB) is still a major cause of death. Indeed, in 2006 over nine million new cases and 1.7 million deaths occurred due to TB, and there is now a significant concern about the emergence of multi-drug resistant (MDR) strains of TB with an estimated 0.5 million cases worldwide [14].

Docking is the most popular and integrity part of computational data based screening method of compounds in Pharmaceutical Research for drug Discovery efforts. The molecular docking is an important part of virtual screening, means “Ligand-based Screening” to find out the active compound as a template and also focus on comparative molecular similarity analysis of compounds with known and unknown activity by algorithm method. Also helps to predict the toxicity study of designing the formulation or synthesis of New Chemical Entity (NCE) in now a day of Pharmaceutical Research Developments. Docking is an important part of drug designing field of molecular modeling system in which the

orientation by means of interaction through an H - bond or Vander Waal force of one molecule (ligand) to a second molecule (macro molecule or target protein) were bound with each other to form a stable complex. The orientation directly refers to the strength of bond association or bond affinity between these two molecules and also predicted the scoring functions. The scoring function directly influences the biological activity of that relevant molecule Docked [15,16].

Computational Biology and Bioinformatics have the potential not only speeding up the drug discovery process, thus reducing the costs, but also about changing the way drugs are designed. Rational Drug Design (RDD) helps to facilitate and speed up the drug designing process which involves a variety of methods to identify novel compounds [17,18]. One such method is the docking of the drug molecule with the receptor (target). The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor [19]. Docking is the process by which two molecules fit together in 3D space.
In this present study, in continuation of our research work on synthesis of lawsone derivatives [21] we are reporting the *Insilico* molecular docking study of lawsone derivatives with the tuberculosis protein (**PDB CODE: 1v0j**).

MATERIALS AND METHODS

Molecular docking: Docking calculations were carried out using Docking Server. The MMFF94 force field was used for energy minimization of the ligand molecule using Docking Server [20]. Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined. Docking calculations were carried out on ***1v0j - ISOMERASE*** protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools. Affinity (grid) maps of 20×20×20 Å grid points and 0.375 Å spacing were generated using the Autogrid program. AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the Vander Waals and the electrostatic terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method. Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 10 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

RESULTS AND DISCUSSION

Docking energy score : The seven numbers of lawsone derivative compounds (**1-7**) **(Figure 1)** are examined in the *Insilico* molecular docking studies with the tuberculosis protein (**PDB CODE: 1v0j**). All the seven compounds are well docked with the 1v0j protein **(Figure 2)** and the Estimated Free Energy of Binding, Estimated Inhibition Constant, Vander wall + Hydrogen bond + desolv Energy, Electrostatic Energy, Total Intermolecular Energy and Interaction Surface are given in **table 1**. The compound **6** shows the lowest inhibition constant 4.82 μM and the compound **7** shows the highest inhibition constant 74.17 μM. The other compounds (**1-5**) are showing the inhibition constants 18.66, 6.23, 8.74, 9.91 and 13.55 μM respectively. The 2D ligand-Protein images of the compounds (**1-7**) clearly shows that, all the compounds are goes inside the active binding site of protein cavity (**Figure 3**). Compounds are interacted with the amino acids of the protein like Alanine, Tyrosine, Asparagine, Arginine, Methionine, Phenylalanine and Asparagine.

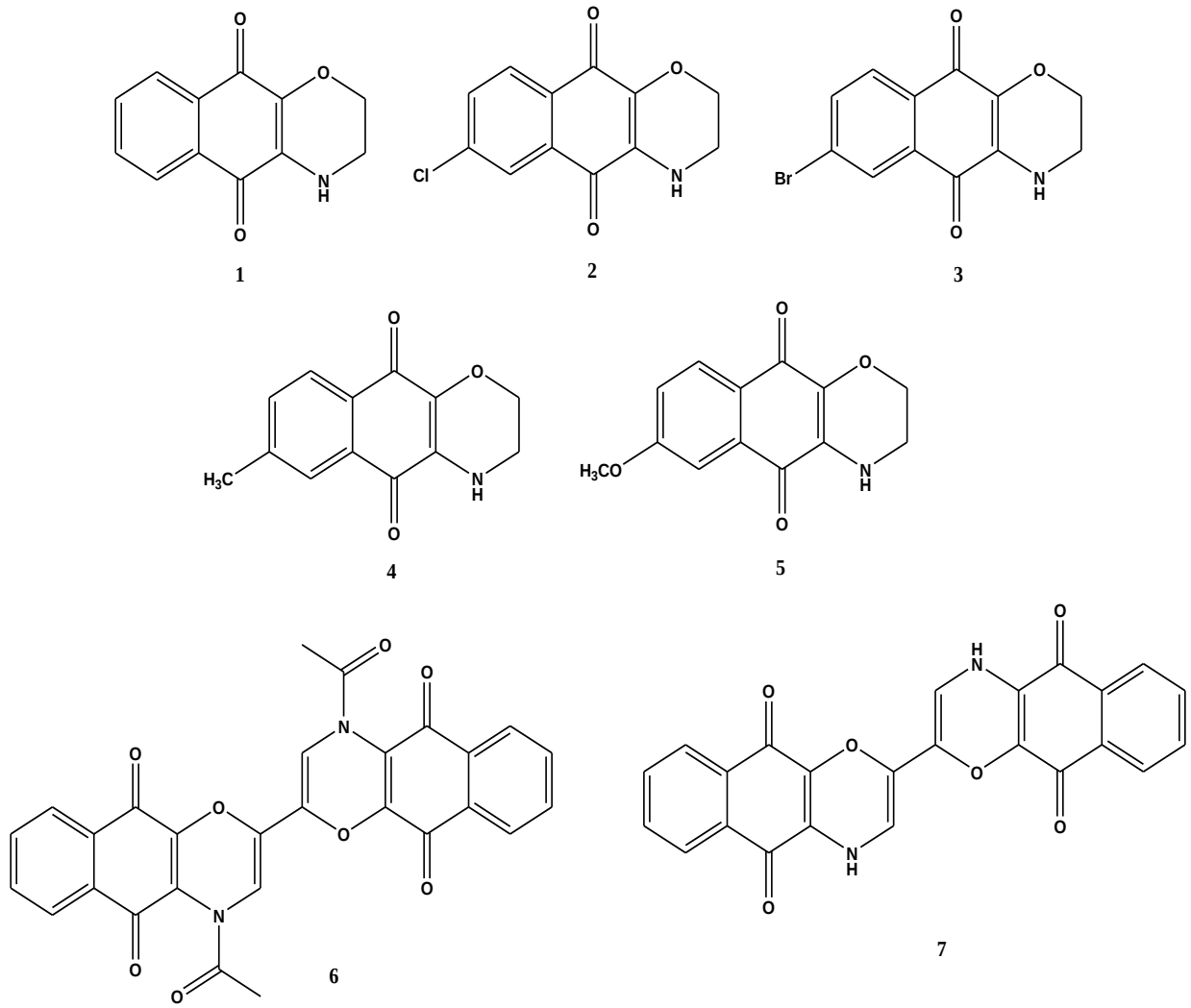


Figure.1 Lawsone derivative compounds (1-7)

Ligand-Protein hydrogen bond: All the compounds (**1-7**) having hydrogen bonds with the amino acids of the selected protein. The nitrogen atom of the compounds (**1-4**) bonded with the alanine with the bond length 2.67, 2.61, 2.79 and 2.76 Å respectively. The nitrogen atom of the compound **5** bonded with the Tyrosine with the bond length of 2.91 Å. The oxygen atom of the compound **6** shows the four hydrogen bonds with Asparagine, Arginine and Methionine with the bond length 2.94, 3.06, 3.01 and 2.92 Å. In the compound **7** both oxygen and nitrogen atoms are involved in the hydrogen bond with the Phenylalanine, Asparagine, Arginine and Tyrosine with the bond length 3.16, 3.13, 3.30 and 3.12 Å (**Table 2**). The plots of the Ligand-Protein hydrogen bonds are shown in **figure 4**

APPLICATIONS

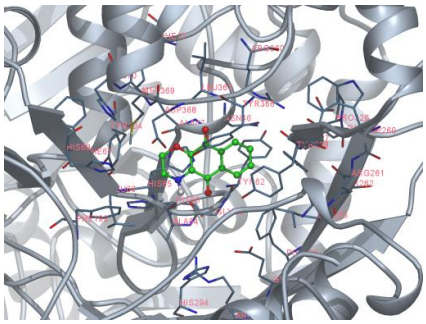
In this present study a series of seven numbers of lawsone derivatives are examined for the *Insilico* molecular docking studies with the tuberculosis protein (**PDB CODE: 1v0j**). All the compounds are showing higher active against the tuberculosis protein in *Insilico* molecular docking studies.

Table-1 Docking energy score of the compound (1-7)

Compound	Rank	Estimated Free Energy of Binding kcal/mol	Estimated Inhibition Constant, Ki µM	Vander wall + Hydrogen bond + desolv Energy kcal/mol	Electrostatic Energy kcal/mol	Total Intermolecular Energy kcal/mol	Interaction Surface
1	1	-6.45	18.66	-6.50	+0.05	-6.45	575.195
2	1	-7.10	6.23	-7.13	+0.02	-7.10	611.014
3	1	-6.90	8.74	-6.81	-0.09	-6.90	581.242
4	1	-6.83	9.91	-6.78	-0.05	-6.83	603.424
5	2	-6.64	13.55	-6.64	-0.30	-6.94	632.139
6	2	-7.25	4.82	-7.35	-0.20	-7.55	1119.574
7	1	-9.73	74.17	-9.73	-0.30	-10.02	966.514

Table-2 Ligand-Protein hydrogen bonds of compound (1-7)

Compound	No. of hydrogen bonds	Ligand atoms involved in the of hydrogen bond	Amino acids involved in the of hydrogen bond	Lengths of the hydrogen bond (Å)
1	1	Nitrogen	Alanine	2.67
2	1	Nitrogen	Alanine	2.61
3	1	Nitrogen	Alanine	2.79
4	1	Nitrogen	Alanine	2.76
5	1	Nitrogen	Tyrosine	2.91
6	4	Oxygen	Asparagine, Arginine, Methionine	2.94, 3.06, 3.01, 2.92
7	4	Oxygen, Nitrogen	Phenylalanine, Asparagine, Arginine, Tyrosine	3.16, 3.13, 3.30, 3.12



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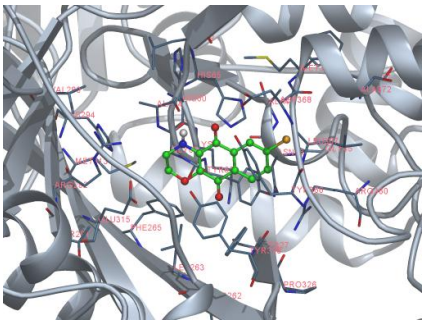

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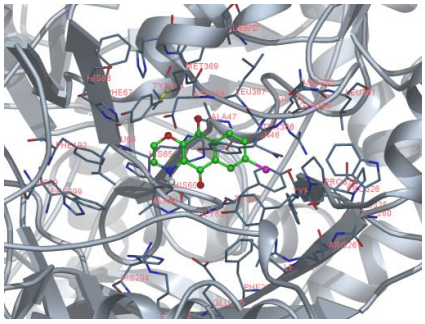

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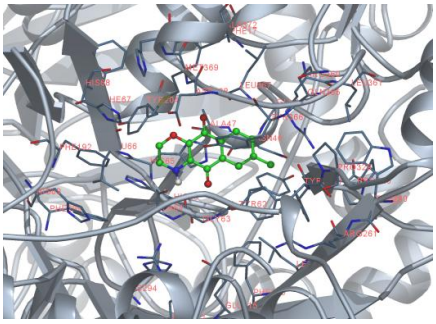

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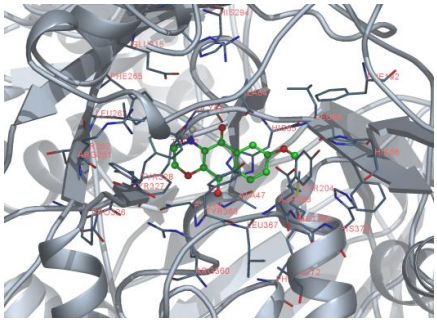

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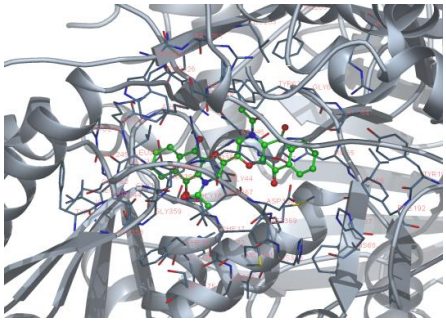

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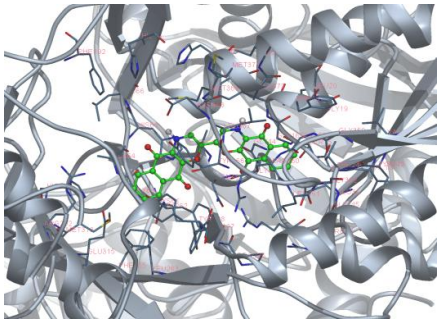

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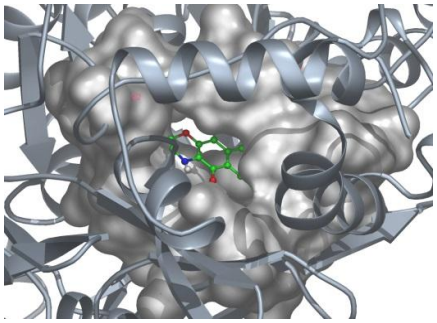
Figure.2 Ligand-Protein docking imagesof compound (1-7)



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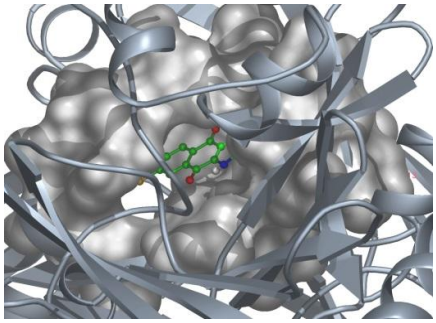

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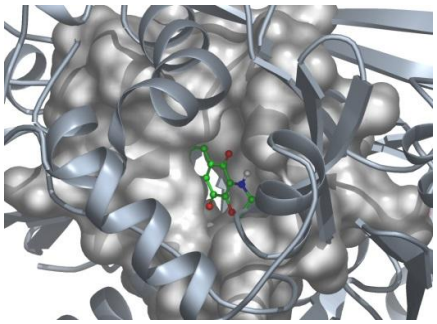

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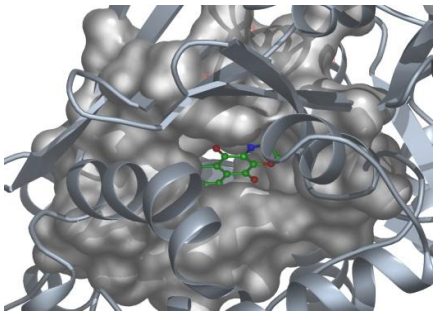

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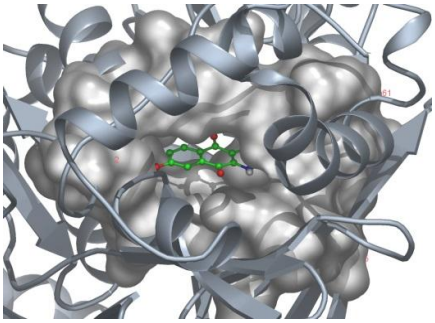

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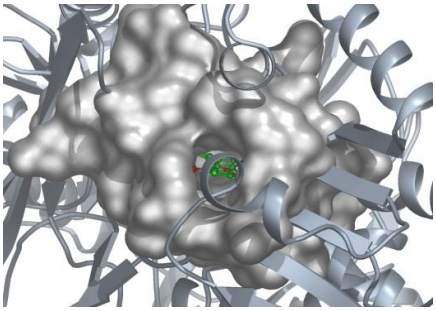

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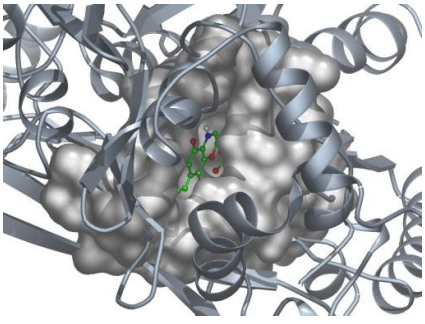

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Figure.3 Ligand-Protein docking 3D-images of compound (1-7)

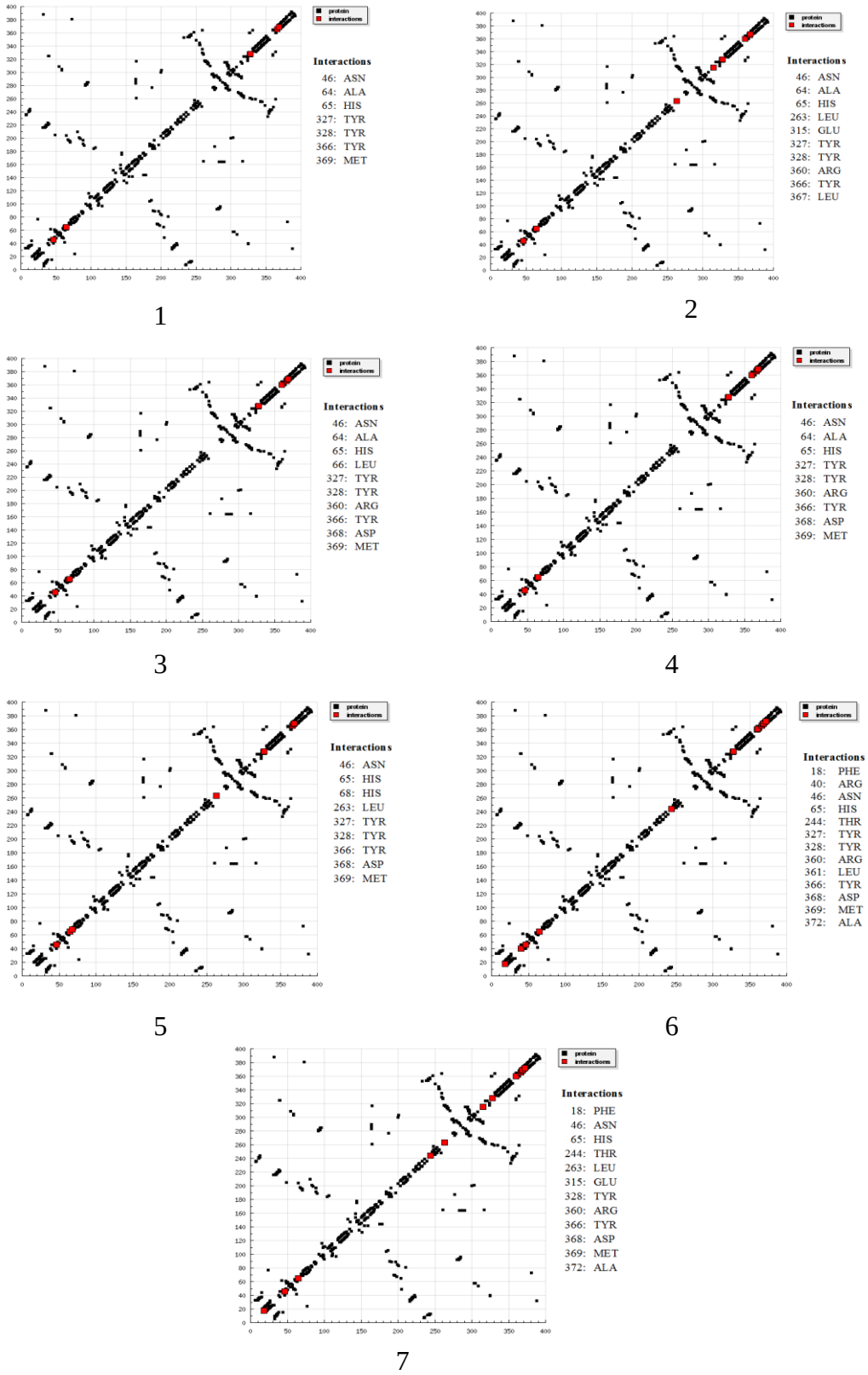

Figure.4 Hydrogen bond plots of compound (1-7)

CONCLUSIONS

A series of seven numbers of lawsone derivatives are examined for the *Insilico* molecular docking studies with the tuberculosis protein (**PDB CODE: 1v0j**). The compound **6** shows the lowest inhibition constant 4.82 µM and the compound **7** shows the highest inhibition constant 74.17 µM. The oxygen atom of the compound **6** shows the four hydrogen bonds with Asparagine, Arginine and Methionine with the bond length 2.94, 3.06, 3.01 and 2.92 Å. In the compound **7** both oxygen and nitrogen atoms are involved in the hydrogen bond with the Phenylalanine, Asparagine, Arginine and Tyrosine with the bond length 3.16, 3.13, 3.30 and 3.12 Å.

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