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PRINT ISSN: 2394-6679 | E-ISSN: 2347-7881

Research Article

Molecular Docking Studies of N-(2-Benzoylphenyl)-L-Tyrosine Derivatives with Anti-Diabetic Activity of Type 2 Diabetes

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ABSTRACT

Type 2 diabetes is one of the major life threatening diseases worldwide. These cases are progressing at an incremental rate every year and number of research works is going on to control the disease by targeting its enzymes or proteins. In modern drug designing, molecular docking is routinely used for understanding drug receptor interaction. In the present study molecular docking were performed on a diverse set of N-(2-benzoylphenyl)-L-tyrosine derivatives that demonstrate antidiabetic activity by stimulating peroxisome proliferator activated receptor- γ. The docking program in Glide dock justifies the correlation between the experimental values and the values derived computationally. Therefore, the dock analysis performed in Glide dock suggests the importance of evaluating the prediction accuracy of scoring functions adopted in various docking program.

Keywords: Molecular Docking, Anti-Diabetic, Computational

INTRODUCTION

Diabetes mellitus is one of the very common chronic diseases across the world and the number of diabetic patients is on the rise. The World Health Organization (WHO) estimates that about 200 million people all over the globe are suffering from diabetes and this figure is likely to be doubled by 2030. WHO says that about 80% of the deaths occur every year due to diabetes in middle-income countries [1]. Type 2 diabetes mellitus (T2DM) is a genetically heterogeneous, polygenic disease with a complex inheritance pattern and is caused by genetic predisposition and environmental factors [2] The disease is characterized by altered expression of many genes and their products in several tissue types [3,4]. The recently published Indian council for medical research-India diabetes (ICMR-INDIAB) national study reported that there are 62.4 million people with type 2 diabetes (T2DM) and 77 million people with prediabetes in India [5]. This will be increased to 100 million by 2030. T2DM predominantly affects older individuals in developed countries, while in developing nations like India; it is affecting the younger population in the prime of their working lives and thus poses an even greater threat to the health of these individuals [5, 6]. Molecular docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex [7] Docking can be defined as an optimization problem, which would describe the ‘‘best-fit’’ orientation of a ligand that binds to a particular protein of interest. Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small

How to cite this article: A Sharma, V Walia, M Gahlawat; Molecular Docking Studies of N-(2-Benzoylphenyl)-L-Tyrosine Derivatives with Anti-Diabetic Activity of Type 2 Diabetes; PharmaTutor; 2015; 3(2); 58-68

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molecule. Hence docking plays an important role in the rational design of drugs [8].

Molecular docking is an efficient tool for investigating receptor-ligand interactions and virtual screening, which plays a key role in rational drug design especially when the crystal structure of a receptor or enzyme is available. Enzymes take a key role in the research of pharmaceutical industry, because they represent targets for the specific development of drugs. A number of docking programs are employed extensively in the pharmaceutical and biotechnology industries, of which the most widely used, appear to Gold, Glide, Autodock, FlexX.

COMPUTATIONAL METHODS

Compound selection

Docking studies has been performed on a series of 79 N-(2-Benzoylphenyl)-L-tyrosine derivatives [9, 10] having PPAR-γ agonistic activity. PPARγ agonistic activity was expressed as pK_i -log of the concentration of test compound required to achieve an apparent *K*i value according to the equation $Ki = IC_{50}/(1 + [L]/K_d)$, where IC_{50} is the concentration of test compound required to inhibit 50% of the specific binding of the radio ligand, [L] is the concentration of the radio ligand used, and K_d is the dissociation constant for the radio ligand at the receptor. Basic structure of the all analogues is shown in the figure 1and the various substituents are enlisted in the Table 1.

Ligand preparation

The LigPrep process consists of a series of steps that perform conversions, apply corrections to the structures, generate variations on the structures, eliminate unwanted structures, and optimize the structures. The molecule were built using Maestro 9.0 and converted to 3D structure from the 2D structure using Ligprep version 5.5 [11]. LigPrep is a robust collection of tool designed to prepare high quality, all-atom 3D structure for large number of drug-like molecule, starting with the 2D or 3D structure in SD or Maestro format. The resulting structures are saved in maestro format. The simplest use of Ligprep produces a single, low-energy, 3D structure with correct chiralities for each successfully proposed input structure. While performing this step, chiralities were determined from 3D structure and original states of ionization were retained [11].

Protein Preparation

PPAR-γ (PDB ID 3ET0, 2PRG) X-ray structures were accessed from the protein data bank (PDB). The protein structures with polar hydrogen were prepared using the protein preparation wizard in maestro (12). In this step, bond order were assigned, all hydrogen in the structure were added, and the bond to the metal are deleted and adjust the formal charge on the metal & the neighboring atoms and deleting water that were more than the 5Å specified distance. PPAR were heterodimerize and we have taken all the monomer. With generate Het state option predicted ionization and tautomeric state of the het group at pH 7 was done. The next stage of the protein preparation was to optimize the hydrogen bond network by reorienting hydroxyl group, water molecules, and amide groups of Asn and Gln, and selecting appropriates states and orientation of the rings in the residues. The final step in the preparation process is to refine the structure, with a restrained minimization. Their task is initiated in the impref minimization with the 0.3Å RMSD for the minimization OPLS_2001 force field.

Receptor grid generation

Glide searches for favourable interaction between one or more ligand molecule and a receptor molecule, usually a protein. The shape and properties of the receptor are the represented on a grid by several different sets of field that provide progressively more

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accurate scoring of the ligand poses. For receptors that adopt more than one conformation on binding, grids are prepared for each conformation, to ensure that possible actives are not missed. Ligand molecule is picked so it can be excluded from the grid generation with vanderwaal radius scaling 1.00 and partial charge cut off 0.25. Grids were generated using Glide version 5.5 following the standard procedure recommended by Schrodinger. The docked pose discussed in it were not necessarily the highest scoring, but were selected as the highest scoring pose with reasonable conformation and binding mode as judge by models.

Docking

Glide ligand docking jobs require a set of previously calculated receptor grids and one or more ligand structures. Ligands must satisfy following conditions i.e. they must be three-dimensional (3D), they must have realistic bond lengths and bond angles, and they must each consist of a single molecule that has no covalent bonds to the receptor. The process of docking is repeated until a constant value of docking score is reached. This takes about 12,000–18,000 generation. The final results are parameterized in terms of docking score in kcal/mol.

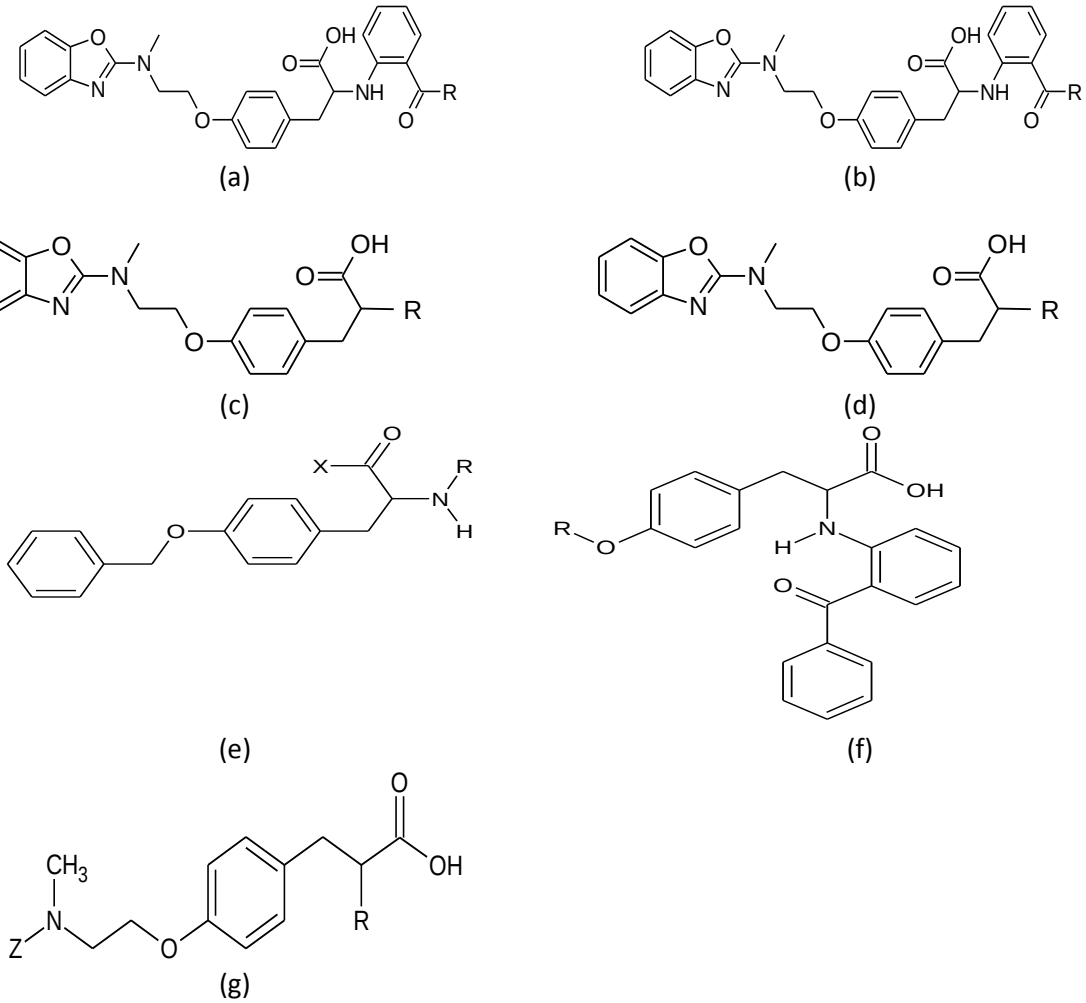

FIG 1: BASIC STRUCTURE OF N-(2-BENZOYLPHENYL)-L-TYROSINES.

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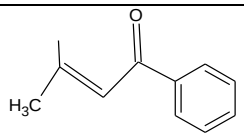
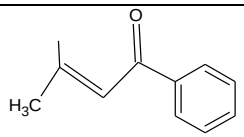
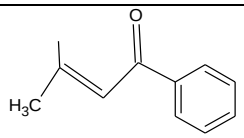
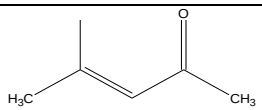
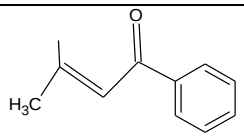
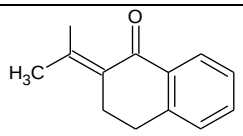
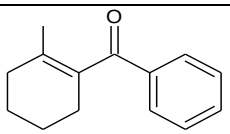
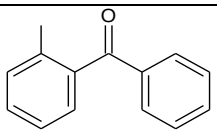
TABLE 1: VARIOUS SUBSTITUTENTS ATTACHED TO BASIC STRUCTURE OF N-(2-BENZOYLPHENYL)-L-TYROSINES.

Compd No.	Series	R	Compd No.	Series	R	X	Z
1	a	H	41	e	NMe_2		
2	a	2-CF_3	42	e	OMe		
3	a	3- CF_3	43	e	OEt		
4	a	4- CF_3	44	e	OPr		
5	a	3-CH_3	45	e	OiPr		
6	a	2-OCH_3	46	e	4-pyridyl		
7	a	3-OCH_3	47	e	OH		
8	a	3-OCH_2Ph	48	f		OH	
9	a	4-OCH_2Ph	49	f		NH_2	
10	a	2-CF_3	50	f		OCH_3	
11	a	2-CH_3	51	f		OH	
12	a	4-CH_3	52	f	H	OH	
13	a	4-OCH_3	53	f		OH	
14	a	4-Ph	54	f		OCH_3	
15	b	Cyclohexyl	55	f		OH	
16	b	2-thienyl	56	f		OH	

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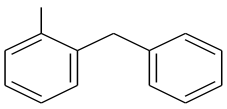
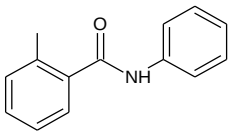
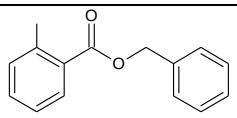
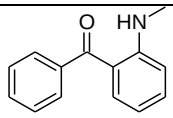
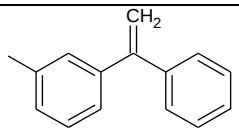
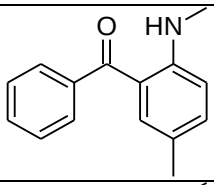
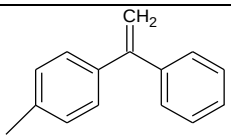
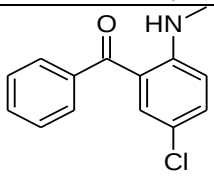
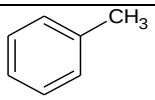
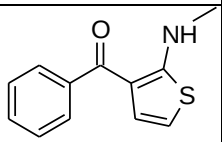
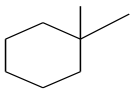
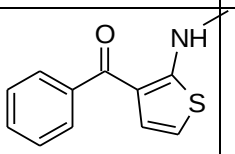
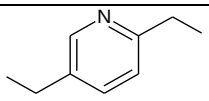
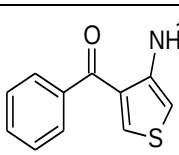
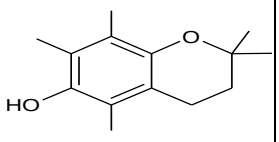
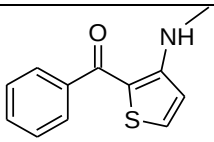
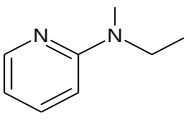
17	b	3-thienyl	57	f		OH	
18	b	1-naphthyl	58	f		OCH_3	
19	b	Cyclohexyl	59	f		OCH_3	
20	c		60	f		OH	
21	c		61	f		OH	
22	c		62	g			
23	c		63	g			
24	c		64	g			
25	c		65	g			
26	c		66	g			

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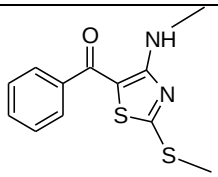
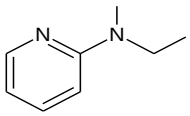
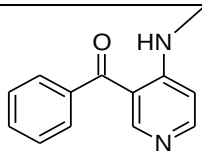
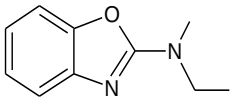
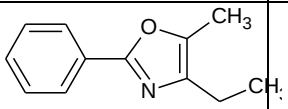
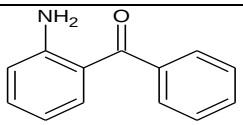
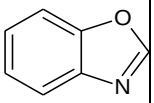
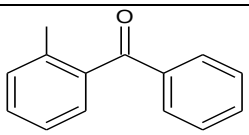
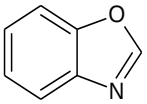
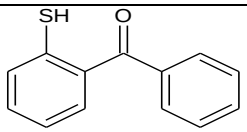
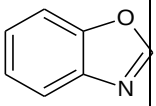
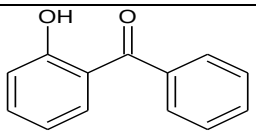
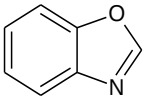
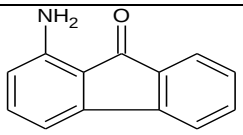
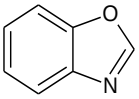
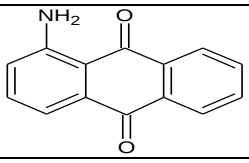
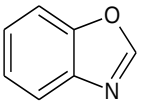
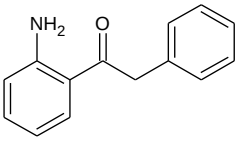
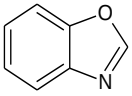
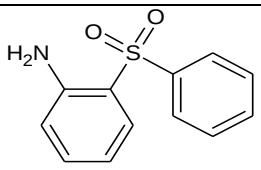
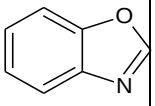
27	c		67	g			
28	c		68	g			
29	d	4-CH_2OH	69	g			
30	d	4-COOH	70	h			
31	d	4-CH_2NMe	71	h			
32	d	3-CH_2OH	72	h			
33	d	3-COOH	73	h			
34	d	3-CH_2NMe	74	h			
35	d	3-NH_2	75	h			
36	d	H	76	h			
37	d	3-NH_2	77	h			

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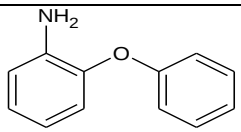
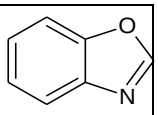
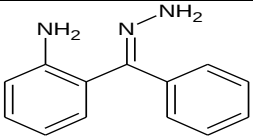
PHARMACY INFOPEDIA
PRINT ISSN: 2394-6679 | E-ISSN: 2347-7881

38	e	3-pyridyl	78	h			
39	e	4-pyridyl	79	h			
40	e	NHMe					

RESULTS AND DISCUSSION

Glide dock is used to study the docking molecules within the active site region of protein 3ETO and number of H-bond and amino acid involved in H-bond were determined. Docking studies may help elucidating the mechanism of PPARγ receptor-ligand interactions. Key feature of the modeling results include logical interaction of the ligand with the putative binding site of the receptor. The binding pocket within the PPARγ receptor is formed by Glu 295, Arg 288, Ser 302, Asp 381, Leu330 and Leu 333. Some of the newly designed molecules have glide score more than -7.029, which is the glide score of Pioglitazone. Hence further proof was provided by plotting a graph between experimental values and glide score, where it is clear that they represented a correlation of 0.634. Glide score and number of hydrogen bond interaction and hydrogen bond length of the docked ligand are shown in the Table 2. The docking study reveals following information with respect to N-(2-benzoylphenyl)-l-tyrosines derivatives.

TABLE 2: GLIDE SCORE, NUMBER OF HYDROGEN BOND AND AMINO ACIDS INVOLVED IN HYDROGEN BOND INTERACTION

Molecule	Activity (pKi)	Glide score	No. of H-bonds	Amino acids (Bond length Å)
1	8.83	-5.87	1	Glu 295(1.230)
2	8.57	-3.60	-	-
3	8.58	-4.46	1	Glu 295(1.252)
4	8.29	-5.50	2	Leu 333(0.946), Ser 332(1.090)
5	8.65	-5.22	1	Glu 295(1.230)
6	8.57	-6.65	3	Leu 330(1.344), Arg 288(1.338), H_2O 559(1.00)
7	8.55	-5.45	2	Leu 330(1.537), Arg 288(1.019)
8	8.76	-4.35	3	Gly 344(1.456), Arg 288(1.536), H_2O 559(1.08)
9	8.64	-4.71	1	Phe 368(1.538)
10	8.25	-5.79	3	Arg 288(1.538, 1.341), H_2O 559(1.089)
11	7.27	-4.19	3	Arg 288(1.008), H_2O 559(1.00), H_2O 548(1.001)
12	7.18	-2.486	3	Arg 288(1.008),Ser 288(0.946), H_2O 548(1.001)
13	7.31	-6.04	2	Arg 288 (1.008), H_2O 559(0.999)
14	8.19	-5.77	1	Arg 288 (1.008)
15	5.81	-2.09	1	Arg 288 (1.008)
16	8.39	-4.23	1	Arg 288(1.008)

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PRINT ISSN: 2394-6679 | E-ISSN: 2347-7881

17	7.40	-4.62	2	Arg 288 (1.008), H_2O 559(0.999)
18	8.56	-6.91	3	Leu 333 (1.091), Arg 288(1.008). H_2o 559(1.23)
19	8.63	-6.32	3	Arg 288 (1.008), Tyr 327 (1.000), H_2O 548(1.001)
20	8.49	-4.82	1	Arg 288(1.008)
21	8.83	-4.90	-	
22	7.87	-1.44	3	Glu 343(1.001), Arg 288(1.008), H_2O 559(1.00)
23	8.06	-5.22	-	
24	7.63	-7.67	3	Leu 333 (1.091), Arg 288(1.008). H_2O 559(1.00)
25	8.59	-4.51	1	Arg 288(1.008)
26	8.01	-4.82	1	Lys 230(1.015)
27	6.81	-6.18	2	Arg 288(1.008), H_2O 559(1.000)
28	7.37	-4.15	2	Arg 288(1.008), H_2O 548(1.000)
29	8.94	-5.31	2	Arg 288(1.008), H_2O 559(1.000)
30	8.38	-5.89	3	Ser 332(0.946), Arg 288(1.008), H_2O 559(1.00)
31	6.19	-3.93	1	H_2O 559(1.000)
32	7.81	-8.39	3	Glu 343 (1.250, 1.230), H_2O 548(1.000)
33	8.47	-6.34	3	Arg 288(1.008), Leu 330(1.00), Asp 381(1.251)
34	6.09	-0.84	4	Arg 288(1.008), H_2O 559(1.000)
35	5.94	-7.96	1	Leu 228(1.232)
36	8.49	-5.07	2	Arg 288(1.008), Lys 354(1.538)
37	8.79	-5.41	2	Ser 332 (0.946), Asp 381(1.250)
38	6.720	-5.52	2	Ser 382(1.091), Asp 381(1.091)
39	9.03	-5.81	1	Lys 230(1.010)
40	8.74	-5.66	1	Glu 295(1.253)
41	5.5	-5.42	1	Arg 288(1.008)
42	7.81	-5.88	1	Arg 288(1.008)
43	6.60	-3.63	-	-
44	8.43	-4.87	2	Leu 228(1.232), H_2O 559(1.001)
45	8.52	-5.80	2	Arg 234(1.339), Lys 230(1.424)
46	8.62	-5.89	2	Arg 288(1.008), H_2O 548(1.000)
47	9.01	-5.51	2	Arg 288(1.008), H_2O 548(1.000)
48	7.93	-4.16	2	Arg 288(1.008), H_2O 548(1.000)
49	5.88	-6.86	3	Asp381(1.251), Ser 332(0.946), Met 329(1.228)
50	6.12	-6.47	2	Asp381(1.251), Ser 332(0.946)
51	5.71	-5.94	1	Ser 302(1.415)
52	5.5	-8.00	1	Asp381(1.251)
53	5.50	-7.44	3	Arg 288(1.008), Glu 369(1.091), H_2O 548(1.00)
54	5.5	-6.39	2	Asp 381(1.251), Ser 332(0.946)
55	6.1	-7.26	3	Arg 288(1.008), Glu 369(1.091), H_2O 548(1.00)
56	6.79	-5.32	1	Leu 228(1.232)
57	5.50	-6.39	2	Arg 288(1.008), Leu 333(1.464)
58	5.50	-3.79	3	Arg 288(1.008), Glu 295(1.0), H_2O(1.252)

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PHARMACY INFOPEDIA
PRINT ISSN: 2394-6679 | E-ISSN: 2347-7881

59	5.50	-6.63	1	Ser 302 (1.415)
60	5.50	-5.73	3	Arg 288(1.338, 1.008), Leu 330(1.537)
61	5.90	-6.32	2	Arg 288 (1.008, 1.010)
62	6.79	-2.32	3	Ser 332(0.946), Leu 340(1.09), Arg 288(1.008)
63	7.29	-6.02	3	Leu 330(1.537), Arg 288(1.008), H_2O559(1.000)
64	8.19	-4.45	1	Glu 295(1.230)
65	8.28	-6.49	4	Arg 288(1.008, 1.001), Glu 295(1.235), H_2O 559(1.000)

66	8.85	-8.30	-	-
67	6.98	-3.53	1	Arg 288(1.008)
68	8.83	-5.34	2	Glu 295(1.252), Arg 288(1.008)
69	8.94	-4.5	1	Arg 288(1.008)
70	8.83	-4.50	1	Glu 295(1.230)
71	7.55	-5.14	2	Arg 288(1.009), H_2O 559(1.000)
72	7.48	-4.75	2	Arg 288(1.008), H_2O 559(1.000)
73	7.49	-3.95	2	Arg 288(1.225), H_2O 548(1.000)
74	7.07	-4.29	2	Arg 288(1.019), H_2O 559(1.089)
75	8.29	-3.60	3	Ser 332(0.946), Arg 288(1.008), H_2O 559(1.000)
76	8.48	-5.07	1	H_2O 559(0.999)
77	6.91	-5.71	2	Arg 288(1.008), H_2O 559(1.000)
78	8.43	-5.12	3	Glu295(1.252), Arg 288(0.946), H_2O(1.0)
79	6.79	-6.13	2	Glu295(1.252), Arg 288(1.008),

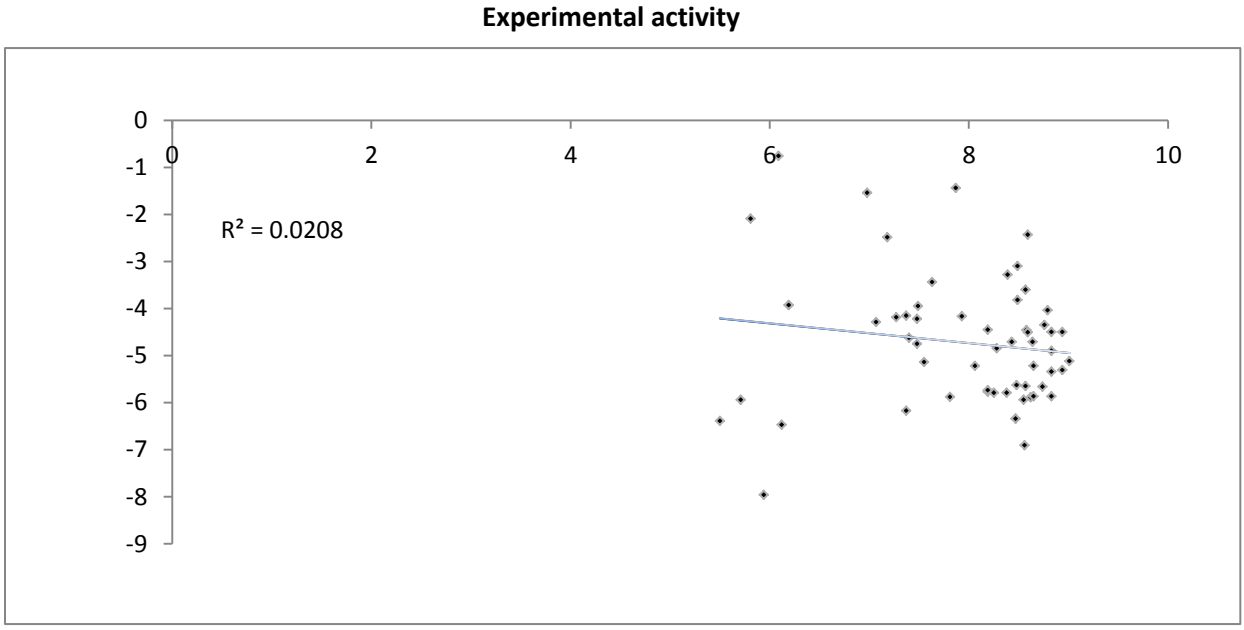

FIG 2: RELATION BETWEEN GLIDE SCORE & EXPERIMENTAL ACTIVITY

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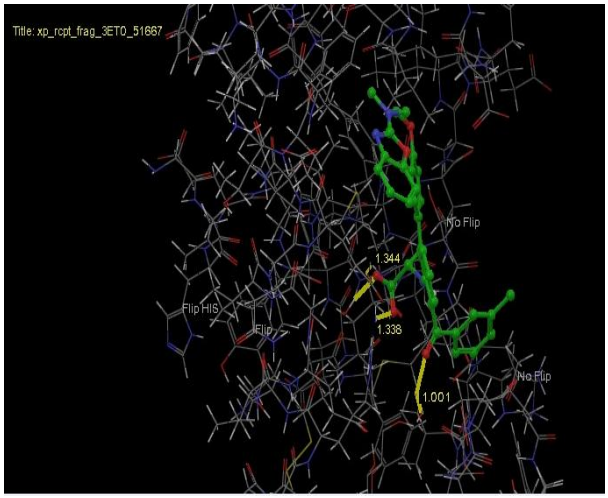

FIG 3: BINDING MODE OF COMPOUND 6.

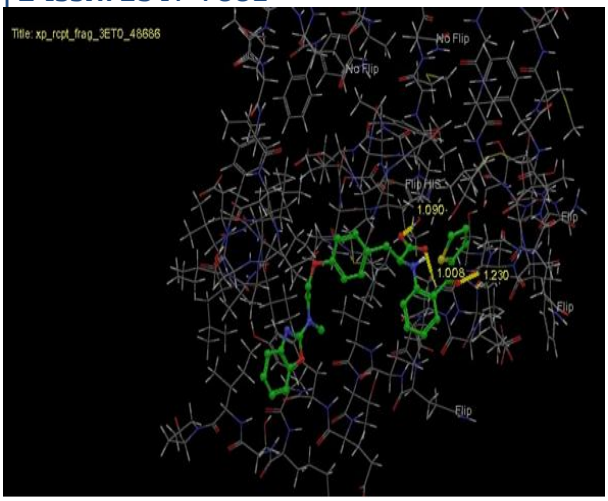

FIG 4: BINDING MODE OF COMPOUND 18

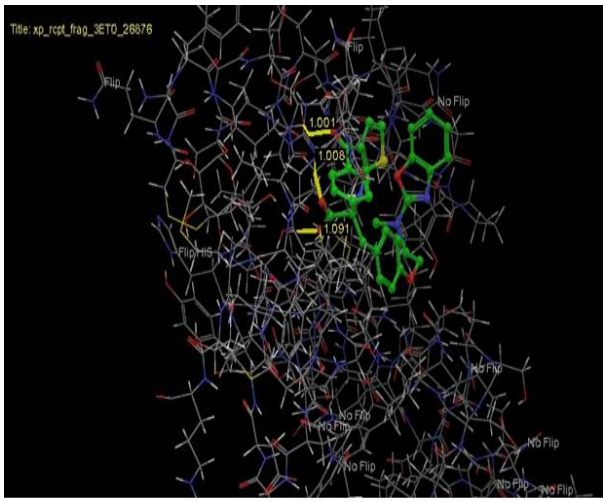

FIG 5: BINDING MODE OF COMPOUND 24

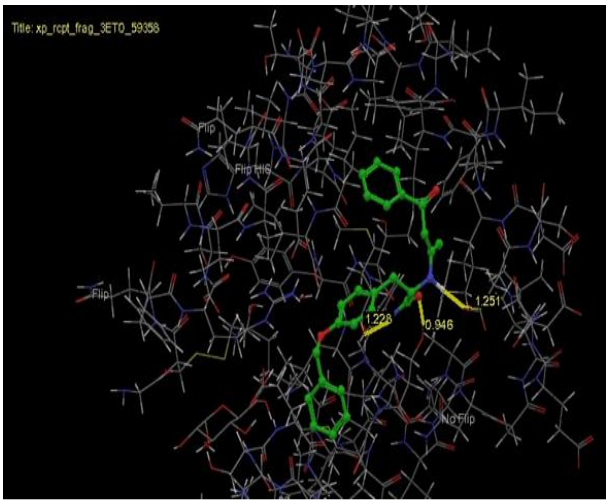

FIG 6: BINDING MODE OF COMPOUND 49

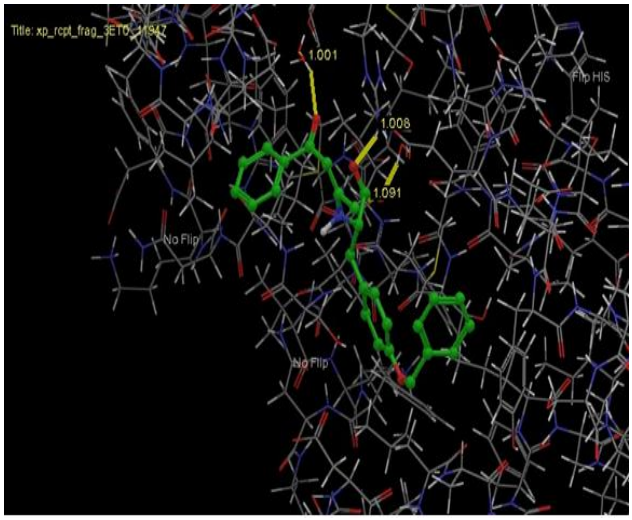

FIG 7: BINDING MODE OF COMPOUND 53

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CONCLUSION

N-(2-Benzoylphenyl)-L-tyrosine PPARγ agonists exhibited positive correlation with experimental data. Glu 295, Arg 288, Ser 302, Asp 381, Leu330 and Leu 333 H-bond interactions are seen in most molecules. The docking program in Glide dock justifies the correlation between the experimental values and the values derived computationally. Therefore, the dock analysis performed in Glide dock suggests the importance of evaluating the prediction accuracy of scoring functions adopted in various docking program. In Glide dock a positive correlation was observed between experimental values and computational glide scores.

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