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Evaluation of PPAR gamma agonists: A molecular docking and QSAR study of chalcone analog

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ABSTRACT

In recent years, chalcones have attracted researchers with their unique structure and promising potential across a wide range of scientific disciplines. They are naturally occurring 1,3-diphenyl-2-propen-1-ones. As well as regulating cell proliferation, differentiation, and angiogenesis, PPARs are also involved in cell differentiation. The present study evaluates the molecular activity of 60 chalcone analogs and two marketed drugs as potential PPAR gamma agonists. Molecular docking studies, structural property calculations, and 2D QSAR studies were carried out to screen the best molecule in the library. The compound coded with 2i was found to have the highest binding affinity and selectivity for PPAR gamma. Firm interactions within 5.0 Å were considered for the docking analysis. Ramachandran plot interpretations also helped us to justify the firm binding at the catalytic site. The correlational studies using the QSAR model were carried out, and the coefficient of regression was found to be 0.9247, and the results were plotted. The 2i was found to be the most suitable compound from the library.

INTRODUCTION

Diabetes Mellitus (DM) represents a multifaceted metabolic disorder stemming from various causes, including deficiencies in insulin secretion and/or action. DM disrupts glucose homeostasis, inducing metabolic alterations and complications. Effective management strategies are vital to mitigate long-term health risks associated with glycemic dysregulation and metabolic abnormalities.[1–2] Chalcones are a family of naturally occurring 1,3-diphenyl-2-propen-1-ones Figure 1 that have fascinated researchers due to their distinctive structure and the great potential they provide across a wide range of scientific fields [3]. Chalcones exhibit promising anti-inflammatory [4–8] and anticancer activities [9–12], suggesting their potential therapeutic role in managing these severe conditions [13]. Further exploration, particularly regarding their ability to influence diabetes [14], is a crucial area of future research.

Chalcones have been widely explored for several decades and have been used for treating diabetes [15]. Their potential lies in targeting glycemic control and regulating pathways involved in carbohydrate, lipid, and protein metabolism, offering comprehensive management strategies to mitigate long-term health risks associated with diabetes [16]. PPARγ, prominently expressed in adipose tissue, orchestrates adipogenesis and insulin sensitivity, making it a key player in metabolic homeostasis. Dysregulation of PPARγ signaling has been implicated in the pathogenesis of metabolic disorders, underscoring the significance of targeting PPARγ for therapeutic purposes [17]. An important function of PPARs is to regulate the transcription of several target genes that regulate adipocyte differentiation, glucose, and lipid metabolism, as well as insulin sensitivity and inflammation. Moreover, beyond their metabolic regulatory functions, PPARγ exerts pleiotropic effects encompassing cell proliferation, differentiation, angiogenesis, inflammation, and oxidative stress. [18]. Consequently, dysregulated PPARγ activity contributes to the development and progression of metabolic disorders. By

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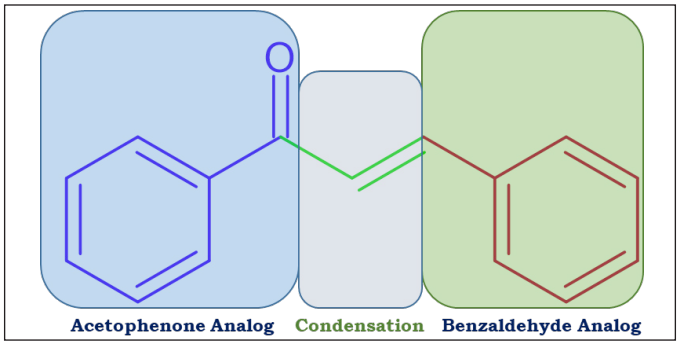

Figure 1. Structure of 1,3-diphenyl-2-propen-1-ones.

targeting PPARγ, chalcones offer a comprehensive approach to addressing the multifaceted nature of metabolic dysfunction. Through their modulation of PPARγ activity, chalcones not only impact metabolic processes but also influence cellular functions crucial for overall metabolic health. Understanding the intricate mechanisms underlying chalcone-PPARγ interactions provides insights into novel therapeutic strategies for combatting metabolic disorders, including obesity, diabetes, and atherosclerosis [19,20]. In this work, we critically studied the article Chi-Ting Hsieh *et.al.* [21] entitled Synthesis of chalcone derivatives as potential anti-diabetic agents which were published in Bioorganic & Medicinal Chemistry Letters in 2012 [21]. This study employs a combined computational and experimental approach to screen 61 analogs of 1,3-diphenyl-2-propen-1-ones for potential anti-diabetic properties. Computational analyses predict interactions with key molecular targets involved in diabetes, while animal experiments assess direct effects on blood glucose levels. By correlating computational predictions with empirical data, researchers identify promising compounds for further development as anti-diabetic agents. This integrated strategy aims to advance diabetes treatment by identifying compounds with favorable pharmacological profiles, facilitating subsequent experimental validation and potential therapeutic advancements.

MATERIALS AND METHODS

Library creation

This article from Chi-Ting Hsieh *et al.* [21] provided the authors with information about chalcone analogs that could be used as bioactive. The chalcone analogs were set up using computational software, and they were converted into .pdb format [20] and are represented in Table 1. The initial energy associated with the molecules was minimized before to inhibit the hindrance of that with the binding energies. The .pdb files were further analyzed to determine their reactivity and stability. The results showed that the chalcone analogs had the potential to be used as bioactives. Before the binding energy was inhibited by the initial energy associated with the molecules, these energies were minimized so that the hindrance to that was prevented from occurring. This allowed the molecules to be bound together more tightly, resulting in a stronger bond. In addition, this minimized the energy required to keep the molecules together, leading to more efficient and stable bonds.

Molecular docking

The virtual screening of the bioactive molecules was carried out using molecular docking studies using the referenced software under standard protocol. The autodock software [21] under the Vina module was used for molecular docking studies. A crystal structure of human PPAR-gamma was obtained from the protein database (PDB ID: 2P4Y) (https://www.rcsb.org/) [22] as a .pdb format from the protein databank. Discovery Studio was used to prepare the protein and remove the pre-associated ligand from the protein during its preparation. In Discovery Studio, the active sites of the protein were defined using the define sites module.

It was necessary to construct the ligands as 2D structures using chemsketch software and then convert them to SMILES using Avogadro software. The SMILES were then optimized for the geometry using the Avogadro software. UFF force fields were used to minimize the energy of the molecules in Avogadro software's energy minimization module, and the data were then saved in a file format known as .pdb [23]. Analysis of the results was done using the Maestro suite of Schrodinger software [24] and Discovery Studio [25].

Structural property calculation

The structural property calculation was carried out using DruLiTo software [26]. A QSAR model was developed using the information obtained from the property calculations to predict the best antidiabetic molecules in the library. It was developed in the context of converting the molecules into .sdf files, loading them in the program, and calculating their

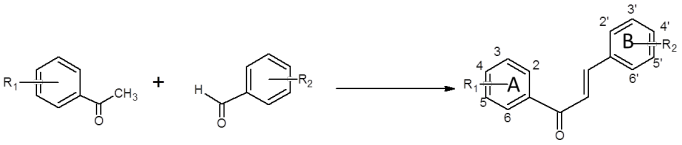

Table 1. Analogs of 1,3-diphenyl-propen-1-ones.

Compound Code	A-Ring				B-Ring		
	2	3	4	5	3'	4'	5'
1a	H	H	H	H	H	H	H
1b	H	H	H	H	H	$-OCH_3$	H
1c	H	H	H	H	$-OCH_3$	H	H
1d	H	H	H	H	OBn	H	H
1e	H	H	H	H	H	-OBn	H
1f	H	H	H	H	H	OH	H
1g	H	H	H	H	H	$-OCH_3$	H
1h	OH	H	H	H	H	H	H
1i	OH	H	H	H	H	$-OCH_3$	H
1j	OH	H	H	H	$-OCH_3$	H	H
1k	OH	H	H	H	-OBn	H	H
1l	OH	H	H	H	H	-OBn	H
1m	OH	H	H	H	H	OH	H
1n	OH	H	H	H	H	$-OCH_3$	H
1o	OH	H	OH	H	H	H	H

Continued

Compound Code	A-Ring				B-Ring		
	2	3	4	5	3'	4'	5'
1p	OH	H	OH	H	H	$-OCH_3$	H
1q	OH	H	OH	H	$-OCH_3$	H	H
1r	OH	H	OH	H	-OBn	H	H
1s	OH	H	OH	H	H	-OBn	H
2a	OH	H	H	F	$-OCH_3$	H	H
2b	OH	H	H	Cl	H	H	H
2c	OH	H	H	Cl	H	$-OCH_3$	H
2d	OH	H	H	Br	$-OCH_3$	H	H
2e	OH	H	H	Br	H	H	H
2f	H	H	H	Br	H	$-OCH_3$	H
2g	OH	H	H	Br	$-OCH_3$	H	H
2h	OH	H	H	Br	H	-OBn	H
2i	OH	H	H	Br	-OBn	H	H
3a	F	H	H	H	H	$-OCH_3$	H
3b	F	H	H	H	$-OCH_3$	H	H
3c	H	F	H	H	H	$-OCH_3$	H
3d	H	F	H	H	$-OCH_3$	H	H
3e	H	H	F	H	$-OCH_3$	H	H
4a	Cl	H	H	H	H	$-OCH_3$	H
4b	H	Cl	H	H	H	H	H
4c	H	Cl	H	H	H	$-OCH_3$	H
4d	H	Cl	H	H	$-OCH_3$	H	H
4e	H	H	Cl	H	H	H	H
4f	H	H	Cl	H	H	$-OCH_3$	H
4g	H	H	Cl	H	$-OCH_3$	H	H
5a	Br	H	H	H	H	H	H
5b	Br	H	H	H	H	$-OCH_3$	H
5c	Br	H	H	H	$-OCH_3$	H	H
5d	H	Br	H	H	H	H	H
5e	H	Br	H	H	H	$-OCH_3$	H
5f	H	Br	H	H	$-OCH_3$	H	H
5g	H	H	Br	H	H	H	H
5h	H	H	Br	H	H	$-OCH_3$	H
5i	H	H	Br	H	$-OCH_3$	H	H
6a	I	H	H	H	H	H	H
6b	I	H	H	H	H	$-OCH_3$	H
6c	I	H	H	H	$-OCH_3$	H	H
6d	I	H	H	H	H	-OBn	H
6e	H	I	H	H	-OBn	H	H
6f	H	I	H	H	H	H	H
6g	H	I	H	H	H	$-OCH_3$	H
6h	H	I	H	H	$-OCH_3$	H	H
6i	H	H	I	H	H	H	H
6j	H	H	I	H	H	$-OCH_3$	H
6k	H	H	I	H	$-OCH_3$	H	H
Pioglitazone	-	-	-	-	-	-	-
Rosiglitazone	-	-	-	-	-	-	-

properties. The model was then used to predict the inhibitory activity of antidiabetic molecules. The model was validated by comparing the predicted values with the experimentally obtained values from molecular docking studies.

QSAR studies

BuildQSAR® open-source software was used to study the correlation of the structural features with the binding affinities obtained by the screening studies [27]. All 60 molecules, along with pioglitazone and rosiglitazone, were included in the study. 10 descriptors were used for the study, and correlational studies were performed with binding energy (Kcal/mol) as activity.

RESULTS AND DISCUSSION

Library creation

A library of 60 analogs and two marketed drugs was created, and the energy of all the molecules was minimized using UFF force fields. All the molecules were saved in the required format in the working directory of the system.

Molecular docking

The results of molecular docking studies are tabulated in Table 2. The studies represent the compounds as 1a to 6k, Pioglitazone and Rosiglitazone, with their binding affinities. Total energy, internal energy, Van der Waal energy, and

Table 2. Results of molecular docking studies.

Compounds	Binding affinity	Total energy	Internal energy	Van der waal energy	Electrostatic energy
1a	−8.728	21.76	−25.049	−22.606	−2.443
1b	−8.941	23.255	−26.052	−23.66	−2.392
1c	−8.591	23.604	−26.892	−22.258	−4.634
1d	−10.103	50.365	−32.905	−32.107	−0.798
1e	−9.614	53.278	−33.191	−31.596	−1.595
1f	−8.437	11.432	−31.259	−14.915	−16.344
1g	−8.404	13.478	−31.371	−18.014	−13.357
1h	−8.694	14.658	−34.724	−16.669	−18.055
1i	−8.979	17.906	−34.674	−19.87	−14.804
1j	−8.992	14.613	−36.715	−20.04	−16.675
1k	−9.76	53.274	−40.522	−24.464	−16.058
1l	−9.576	39.45	−37.753	−22.849	−14.904
1m	−8.298	10.676	−37.491	−14.528	−22.963
1n	−8.838	11.15	−36.9	−21.694	−15.206
1o	−8.696	9.378	−37.922	−14.219	−23.703
1p	−8.907	12.251	−39.452	−16.74	−22.712
1q	−9.013	10.396	−40.708	−17.299	−23.409
1r	−9.627	40.164	−44.812	−27.245	−17.567
1s	−9.747	50.412	−38.521	−23.872	−14.649
2a	−9.08	15.974	−36.535	−17.657	−18.878

Continued

Compounds	Binding affinity	Total energy	Internal energy	Van der waal energy	Electrostatic energy
2b	−8.491	15.246	−35.691	−18.368	−17.323
2c	−8.798	17.079	−35.957	−21.038	−14.919
2d	−8.855	17.094	−35.777	−21.806	−13.971
2e	−8.654	7.497	−36.276	−20.495	−15.781
2f	−9.009	22.979	−28.471	−27.387	−1.084
2g	−8.821	18.364	−37.456	−21.603	−15.853
2h	−10.094	53.249	−39.864	−28.207	−11.657
2i	−10.191	52.981	−41.455	−28.798	−12.657
3a	−8.611	19.096	−27.435	−24.271	−3.164
3b	−8.943	21.608	−26.51	−24.629	−1.881
3c	−8.774	19.65	−26.992	−21.813	−5.179
3d	−8.475	15.057	−24.897	−14.288	−8.788
3e	−8.822	22.025	−27.534	−23.656	−3.878
4a	−8.792	23.943	−28.484	−24.413	−4.071
4b	−8.983	18.672	−25.766	−24.038	−1.728
4c	−9.184	20.579	−27.583	−25.474	−2.109
4d	−9.288	19.033	−29.429	−26.53	−2.899
4e	−8.769	21.312	−25.955	−24.195	−1.76
4f	−8.659	20.167	−26.188	−24.357	−1.831
4g	−9.077	21.856	−28.259	−26.464	−1.795
5a	−8.58	21.828	−27.418	−23.838	−3.58
5b	−8.839	23.605	−29.642	−25.698	−3.944
5c	−8.89	22.718	−30.058	−25.881	−4.177
5d	−8.991	17.999	−27.895	−25.468	−2.427
5e	−9.208	20.489	−27.573	−25.576	−1.997
5f	−8.77	17.02	−30.13	−26.003	−4.127
5g	−8.507	20.303	−27.117	−24.136	−2.981
5h	−8.486	20.025	−26.98	−23.996	−2.984
5i	−9.101	21.809	−28.616	−26.867	−1.749
6a	−8.658	20.814	−29.1	−25.23	−3.87
6b	−8.591	23.604	−26.892	−22.258	−4.634
6c	−8.944	22.454	−31.372	−27.264	−4.108
6d	−10.034	44.873	−33.201	−31.904	−1.297
6e	−9.788	40.745	−32.158	−31.662	−0.496
6f	−9.1	18.398	−29.114	−26.59	−2.524
6g	−9.457	22.708	−29.546	−29.375	−0.171
6h	−9.109	21.72	−28.648	−28.259	−0.389
6i	−8.582	19.974	−28.018	−24.637	−3.381
6j	−8.949	14.814	−32.29	−26.875	−5.415
6k	−9.075	22.326	−29.091	−29.023	−0.068
Pioglitazone	−9.292	29.54	−36.236	−31.201	−5.035
Rosiglitazone	−9.085	3.372	−37.862	−31.159	−6.703

electrostatic energy were also calculated simultaneously and are represented in Table 2.

The 2i molecule's binding affinity was much higher than the other drugs, meaning it was more likely to bind to its target tissue. This made it a promising candidate to be developed into a drug. Figure 2 shows the results of the docking analysis carried out by maestro suite. Figure 2a represents the interacting amino acids in the periphery of 5.0 Å. The results show that glutamic acid 62 (GLU62) is firmly interacting with the hydroxyl group and glutamic acid 110 (GLU110) is interacting with bromine at the c-2 position. Other close interactions were observed with arginine 55 (ARG55), glutamine 53 (GLN53), isoleucine 108,63 (ILE108,63), serine 109,56 (SER109,56), leucine 107 (LEU107), and glycine 111,51 (GLY111,51). Figure 2b, 2c, and 2d represents the interaction at the active catalytic site. The Ramchandran plot of the interactions is observed in Figure 3.

1d molecule showed the second-best binding affinity towards the catalytic site of the receptor. Firm interactions with histidine 216 (HIS 216, 90), serine 56 (SER56), isoleucine 63, 92, 93 (ILE63, 92, 93), tyrosine 94 (TYR94), methionine 96 (MET96), and leucine 97,100 (leucine97,100). The interactions of the molecule on the catalytic side are shown in Figure 4a.2h, 6d, and 6e molecules showed significant bioactivities in comparison to the other 62 molecules in the library. The interactions are represented in Figure 4b, Figure 4c, and Figure 4d.

Docking studies are vital in drug discovery, predicting how potential drugs interact with target proteins. Validating these studies is crucial for reliability, comparing predicted binding affinities with experimental data. When consistent amino acid patterns are seen in binding across different molecules, it suggests key interactions at the catalytic site, aiding drug design optimization. Identifying these key residues helps modify lead compounds for better binding affinity and specificity. Overall, validation and interpretation of docking results guide rational drug design, facilitating the discovery of new therapies for diseases like diabetes.

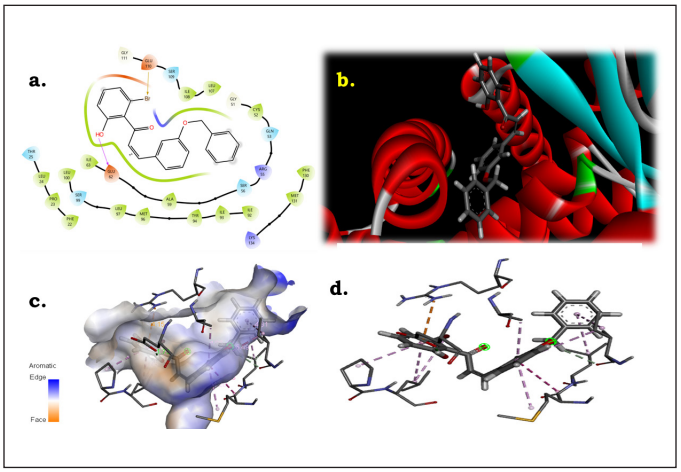

Figure 2. Interactions of 2i molecule with amino acids.

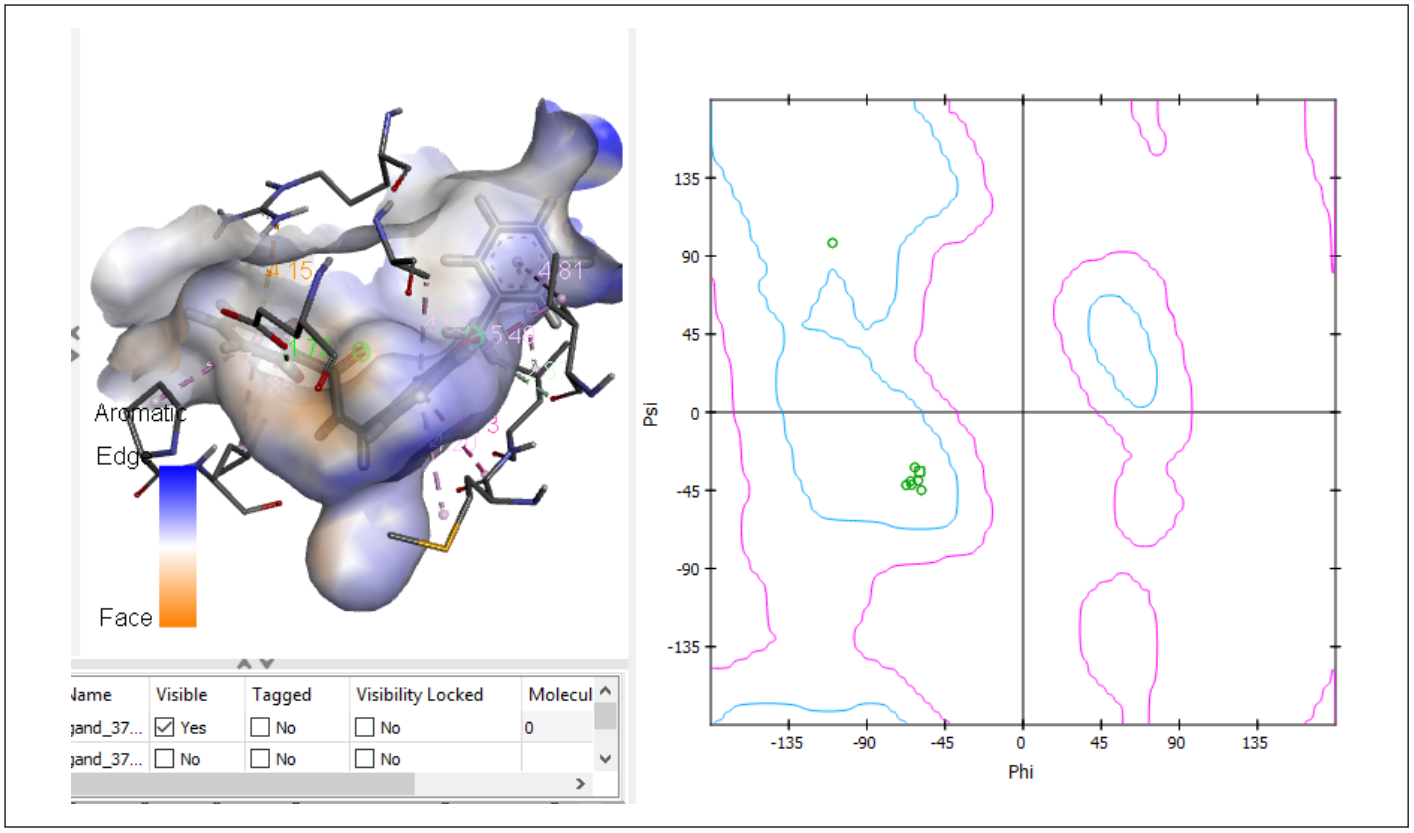

Figure 3. Ramachandran plot of interactions.

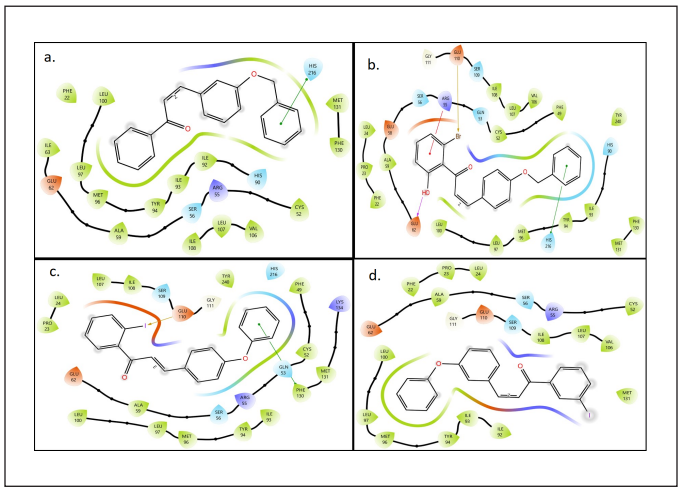

Figure 4. a. Interactions of 1d molecule with amino acid, b. Interactions of 2h molecule with amino acids, c. Interactions of 6d molecule with amino acids, and d. Interactions of 6e molecule with amino acids.

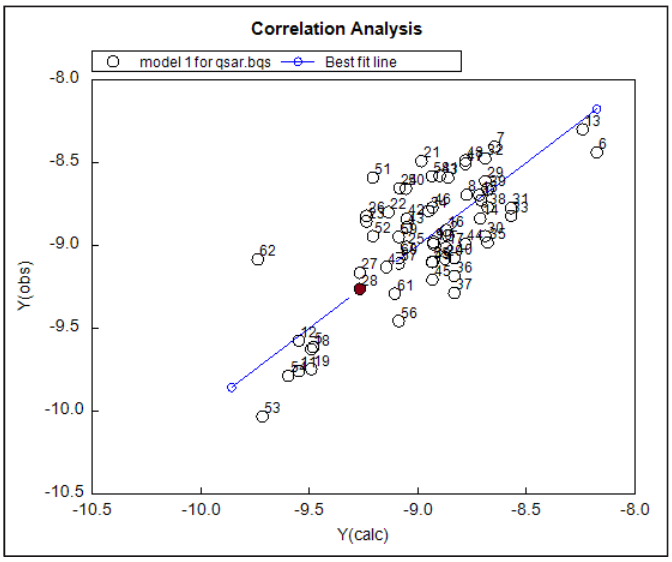

Figure 5. Results of correlational studies.

Structural property calculation and QSAR studies

The results of the structural property calculation are represented in Table 3. The properties like molecular weight, logP, hydrogen bond acceptors (HBAs), hydrogen bond donors (HBDs), total polar surface area (TPSA), number of rotatable bonds (nRBs), number of atoms (nAtoms), number of rigid bonds (nRigid Bs), number of aromatic ring (nArom Ring), and number of hydrogen bonds (nHBs) were calculated by using DruLiTo® software. These calculated properties were truly considered as the descriptors and the binding affinities as the activity. The following structural information was used to generate the 2D QSAR model. The QSAR equation generated by the software is as follows.

Table 3. Results of structural property calculation.

Compounds	Binding energy	Molecular weight	logP	HBA	HBD	TPSA	nRB	nAtom	nRigid B	nArom Ring	nHB
1a	−8.728	208.09	3.171	1	0	17.07	3	28	14	2	1
1b	−8.941	238.1	2.356	2	0	26.3	4	32	15	2	2
1c	−8.591	238.1	2.356	2	0	26.3	4	32	15	2	2
1d	−10.103	314.13	3.448	2	0	26.3	6	42	20	3	2
1e	−9.614	314.13	3.448	2	0	26.3	6	42	20	3	2
1f	−8.437	224.08	2.035	2	1	37.3	3	29	15	2	3
1g	−8.404	254.09	1.784	3	1	46.53	5	33	15	2	4
1h	−8.694	224.08	3.097	2	1	37.3	3	29	15	2	3
1i	−8.979	254.09	2.282	3	1	46.53	4	33	16	2	4
1j	−8.992	254.09	2.282	3	1	46.53	4	33	16	2	4
1k	−9.76	330.13	3.374	3	1	46.53	6	43	21	3	4
1l	−9.576	330.13	3.374	3	1	46.53	6	43	21	3	4
1m	−8.298	240.08	1.961	3	2	57.53	3	30	16	2	5
1n	−8.838	270.09	1.71	4	2	66.76	5	34	16	2	6
1o	−8.696	240.08	2.805	3	2	57.53	3	30	16	2	5
1p	−8.907	270.09	1.99	4	2	66.76	4	34	17	2	6
1q	−9.013	270.09	1.99	4	2	66.76	4	34	17	2	6
1r	−9.627	346.12	3.082	4	2	66.76	6	44	22	3	6
1s	−9.747	346.12	3.082	4	2	66.76	6	44	22	3	6
2a	−9.08	272.08	2.187	3	1	46.53	4	33	17	2	4
2b	−8.491	258.04	3.463	2	1	37.3	3	29	16	2	3
2c	−8.798	288.06	2.648	3	1	46.53	4	33	17	2	4
2d	−8.855	332	2.824	3	1	46.53	4	33	17	2	4
2e	−8.654	301.99	3.639	2	1	37.3	3	29	16	2	3
2f	−9.009	316.01	2.687	2	0	26.3	4	32	16	2	2
2g	−8.821	332	2.824	3	1	46.53	4	33	17	2	4
2h	−10.094	408.04	3.916	3	1	46.53	6	43	22	3	4
2i	−10.191	408.04	3.916	3	1	46.53	6	43	22	3	4
3a	−8.611	256.09	2.05	2	0	26.3	4	32	16	2	2
3b	−8.943	256.09	2.05	2	0	26.3	4	32	16	2	2
3c	−8.774	256.09	1.839	2	0	26.3	4	32	16	2	2
3d	−8.475	256.09	2.05	2	0	26.3	4	32	16	2	2
3e	−8.822	256.09	1.839	2	0	26.3	4	32	16	2	2
4a	−8.792	272.06	2.511	2	0	26.3	4	32	16	2	2
4b	−8.983	242.05	3.115	1	0	17.07	3	28	15	2	1
4c	−9.184	272.06	2.3	2	0	26.3	4	32	16	2	2

Continued

Compounds	Binding energy	Molecular weight	logP	HBA	HBD	TPSA	nRB	nAtom	nRigid B	nArom Ring	nHB
4d	−9.288	272.06	2.3	2	0	26.3	4	32	16	2	2
4e	−8.769	242.05	3.115	1	0	17.07	3	28	15	2	1
4f	−8.659	242.05	3.115	1	0	17.07	3	28	15	2	1
4g	−9.077	272.06	2.3	2	0	26.3	4	32	16	2	2
5a	−8.58	286	3.502	1	0	17.07	3	28	15	2	1
5b	−8.839	316.01	2.687	2	0	26.3	4	32	16	2	2
5c	−8.89	316.01	2.687	2	0	26.3	4	32	16	2	2
5d	−8.991	286	3.291	1	0	17.07	3	28	15	2	1
5e	−9.208	316.01	2.476	2	0	26.3	4	32	16	2	2
5f	−8.77	316.01	2.476	2	0	26.3	4	32	16	2	2
5g	−8.507	286	3.291	1	0	17.07	3	28	15	2	1
5h	−8.486	286	3.291	1	0	17.07	3	28	15	2	1
5i	−9.101	316.01	2.476	2	0	26.3	4	32	16	2	2
6a	−8.658	333.99	3.772	1	0	17.07	3	28	15	2	1
6b	−8.591	364	2.957	2	0	26.3	4	32	16	2	2
6c	−8.944	364	2.957	2	0	26.3	4	32	16	2	2
6d	−10.034	426.01	3.853	2	0	26.3	5	39	21	3	2
6e	−9.788	426.01	3.642	2	0	26.3	5	39	21	3	2
6f	−9.1	333.99	3.561	1	0	17.07	3	28	15	2	1
6g	−9.457	364	2.746	2	0	26.3	4	32	16	2	2
6h	−9.109	364	2.746	2	0	26.3	4	32	16	2	2
6i	−8.582	333.99	3.561	1	0	17.07	3	28	15	2	1
6j	−8.949	364	2.746	2	0	26.3	4	32	16	2	2
6k	−9.075	364	2.746	2	0	26.3	4	32	16	2	2
Pioglitazone	−9.292	356.12	0.425	5	1	93.06	7	45	20	2	6
Rosiglitazone	−9.085	357.11	0.461	6	1	96.3	7	44	20	2	7

Binding Energy = - 0.0001 (± 0.0025) MW–0.5643 (± 0.2177) LogP–0.6106 (± 0.2386) HBA + 0.5035 (± 0.2568) HBD–6.2982 (± 0.5709) (n = 62 ; R = 0.790 ; s = 0.285 ; F = 23.722 ; p < 0.0001 ; Q2 = 0.507 ; SPress = 0.327 ; SDEP = 0.316).

The results QSAR studies are as follows:

R^2	0.9247	SDEP	0.3157
Q2	0.5072	C.V.	−3.1649

The plot of the correlational matrix is represented in Figure 5 and shows that serial number 28, i.e., 2i is the best-fit molecule.

CONCLUSION

It was possible to effectively carry out molecular docking investigations in the library. The computation of the structural properties of the whole library was carried out, and the findings were computed with the assistance of software that is open source. In the course of the docking study, the compound with the code 2i was determined to be the most effective molecule. The QSAR investigations were used to carry out the correlational examinations of the structural attributes with the binding affinities that were ultimately achieved. It was determined that the 2i molecule, which had a serial number of 28, was the most suitable for the whole research and the most effective peroxisome proliferator-activated receptor-γ agonists when compared to medications that are already on the market. Studies on the link between structural activity and bioactivity revealed that the presence of a hydroxy group in the ortho position of the acetophenone analog is necessary for bioactivity. A large amount of activity is shown by the electron-withdrawing groups that have been replaced on the benzaldehyde derivatives.

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AUTHOR CONTRIBUTION

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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The authors report no financial or any other conflicts of interest in this work.

CONSENT TO PARTICIPATE

All authors agree to publish the article.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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