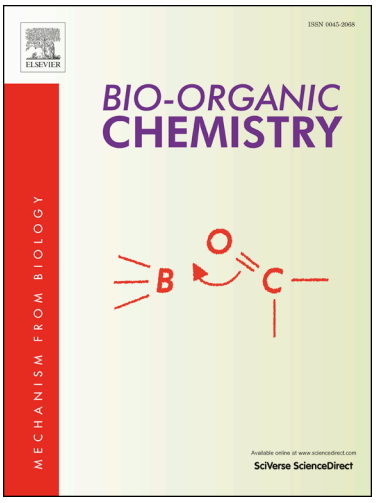

Synthesis, biological evaluation and molecular docking studies of novel 3,5-disubstituted 2,4-thiazolidinediones derivatives

Alok Ranjan Srivastava, Rohit Bhatia, Pooja Chawla

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Synthesis, biological evaluation and molecular docking studies of novel 3,5-disubstituted 2,4-thiazolidinediones derivatives

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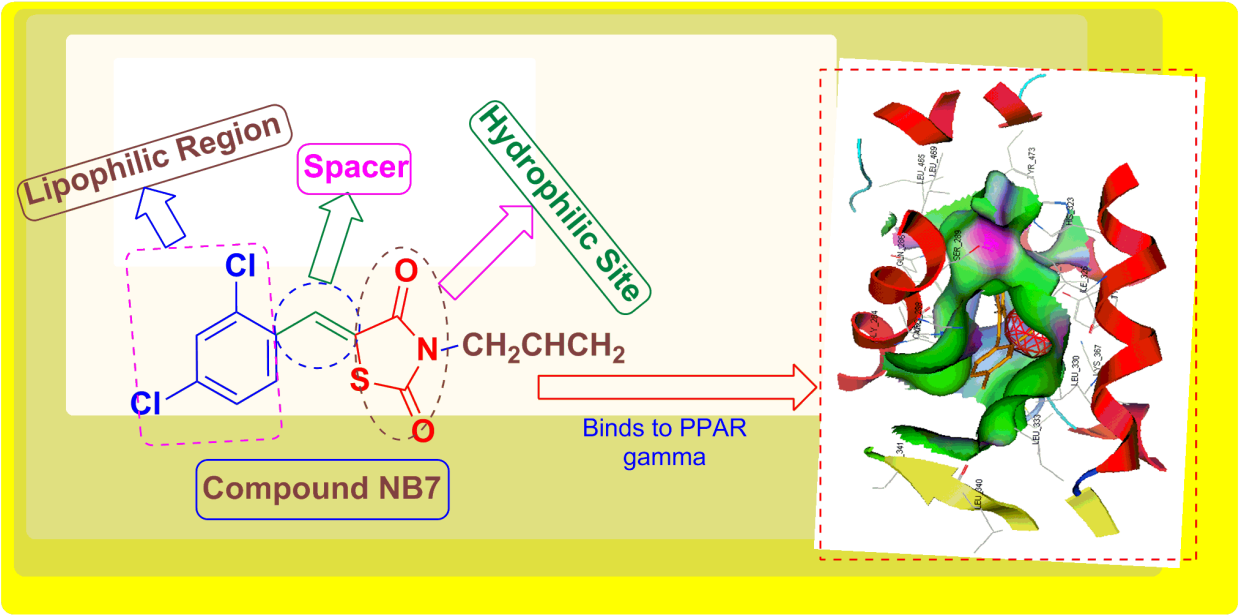
ABSTRACT

A series of thirteen novel 2,4-thiazolidinedione derivatives were synthesized through three step reaction procedure. The title compounds were synthesized by Knoevenagel condensation at the 5th position of the 2,4-thiazolidinedione ring. Various physicochemical and spectral studies were conducted to characterize the synthesized derivatives including- IR, Mass, ^{1}H-NMR, ^{13}C-NMR and elemental analysis. The derivatives were screened for *in vivo* anti diabetic, *in vivo* anti-inflammatory and *in vitro* free radical scavenging activities by carrageenan induced rat paw edema method, alloxan induced diabetes in wistar rats method and FRAP (ferric reducing antioxidant power) method respectively. Some of the derivatives emerged out as potent antidiabetic, anti inflammatory and free radical scavenging agents. Molecular docking was carried out to investigate some possible structural insights into the potential binding patterns of the most potent anti-diabetic molecules NB7,NB12 and NB13 with the active sites of target PPARγ (PDB ID: 2PRG) using MOE software. Dichloro derivative compound **NB-7** has shown great potential in the present study as it not only has maximum antidiabetic activity but also possess excellent anti-inflammatory and antioxidant potential.

Keywords: Thiazolidinedione, anti diabetic, anti inflammatory, anti oxidant, structure activity relationship, docking

GRAPHICAL ABSTRACT



1. Introduction

Diabetes is rapidly spreading life threatening disease with a global prevalence of 171 million in year 2000 and is expected to increase to 366 million by 2030 [1]. Diabetes is a group of diseases characterized by chronic hyperglycemia due to deficiency of insulin action. The deficiency of insulin action, a common basis of diabetes, leads to characteristic abnormalities in the metabolism of carbohydrates, lipids, and proteins which results in chronic complications. Type 2 diabetes (T2D) results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. Despite the abundance of available anti-diabetes therapies, a considerable number of patients with type 2 diabetes continue to have relatively poor glycemic control and are at risk for macrovascular and microvascular disease [2]. Inflammation and injury to the arterial wall in the peripheral or coronary vascular system is thought to result in atherosclerosis which affects the arteries that supply the heart, brain and lower extremities. These also contribute in increased risk of developing cardiovascular disease (CVD) [3]. High glucose results in oxidative stress which leads to formation of free radicals mainly reactive oxygen species (ROS). This results in microvascular complications (damage to smaller blood vessels throughout the body) in retina, renal glomerulus and peripheral nerves [4]. So in hyperglycemic condition increased level of inflammation and oxidative stress are chief contributing factors in development of diabetic complications. Many researchers have proposed that the treatment with antioxidants ameliorates diabetic complications (Fig.1) [5-8]. Contribution of inflammation in development of insulin resistance (IR) [9] and other complications like diabetic nephropathy (DN) [10] and diabetic retinopathy (DR) [11] has been proved by many researchers. So if the drug which is used for antidiabetic therapy possesses anti-inflammatory activity as well as is capable of scavenging free radicals generated during

hyperglycemic conditions, can prove highly effective not only in treatment of diabetes but also for complications arising due to high glucose level in the body.

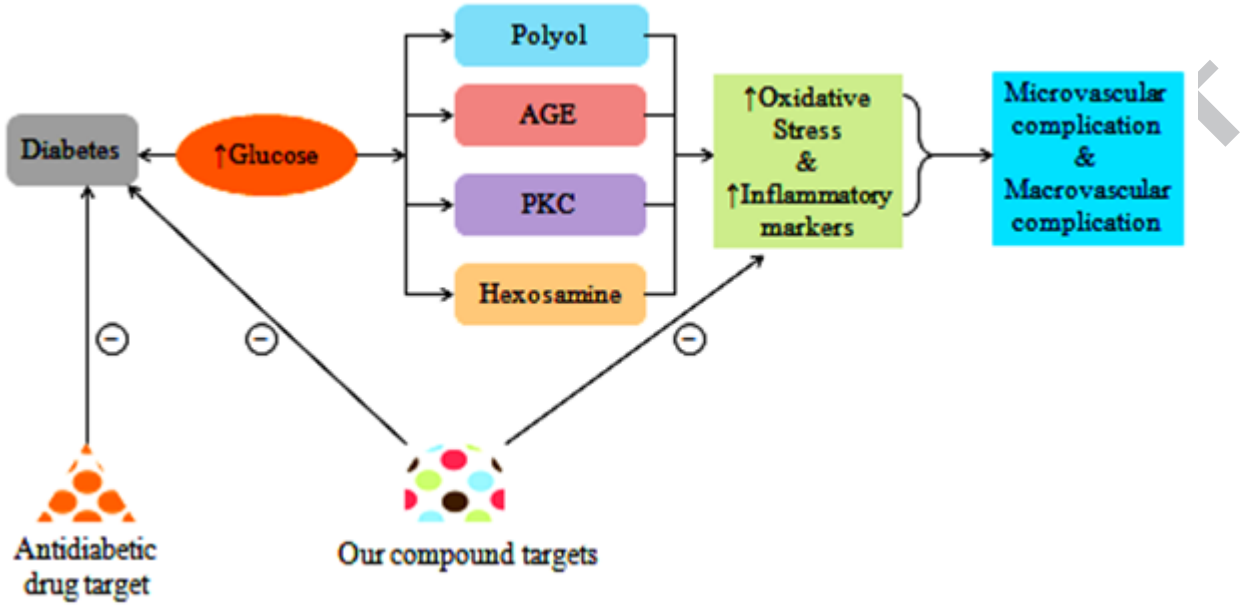


Fig. 1. High glucose level in diabetes and its complications.

Thiazolidnediones (TZDs) constitute an important class of heterocyclic compounds which possess significant anti-diabetic activity along with various other activities like immunostimulatory, antiarthritic, oncostatic, anti-inflammatory, antioxidant *etc*. TZD is insulin sensitizing moiety that acts by selectively binding to the nuclear transcription factor peroxisome-proliferator–activated receptor γ (PPAR γ). Studies have shown the association of PPAR γ with the inflammation [12-14] and free radical generation [15-16]. Even some glitazones are shown to have potential to check the inflammation and free radical generation [12,17-18]. So targeting inflammation and oxidative stress generated due to free radicals can prove beneficial in anti-diabetic therapy as well as to increase the efficacy of treatment.

Our study is based on developing new compounds by utilizing the multifunctionality of TZD nucleus for diabetes which may prove more efficacious than currently available drugs for diabetes. Pharmacophore thiazolidine-2,4-dione is essential for activity; Linker region: flat linker region is favourable for activity; Aryl substituent: group attached to left side of linker provides large area for stearic interaction with the hydrophobic region of receptor. N-terminal (head portion) of the molecule is hydrophilic/cationic site as it forms several H-bonds with nuclear receptor PPARγ; tail portion having arylidine substituent is responsible for stearic interaction with the receptor due to its large area, lipophilicity is favoured in this portion of molecule (Fig. 2). As the developed compound also targets the inflammation along with oxidative stress generated inside cell, it may be of high benefit in diabetes treatment. N-terminal of TZD nucleus is cationic/hydrophilic site which forms hydrogen-bond with Ser 289 of PPARγ receptor, it also forms several hydrogen bonds with critical residues of the activation function helix 2 (AF-2 helix) of PPARγ including His 323, His 449 and Tyr 473 [19-21]. So hydrogen presence is necessary near N-terminal for agonistic activity of PPARγ-ligand. N-terminal of TZD is substituted with allyl group (R_1) by replacing the solitary hydrogen present at 3rd position, as it is

more acidic owing to presence of two carbonyl groups at 2nd and 4th position of TZD which may contribute to gastric irritation. It is evident that substitution of alkyl group at N-terminal results in decreased activity of compound [22]. Allyl group is selected for replacing the hydrogen at 3rd position of TZD as it decreases the acidity of hydrogen alongwith increase in the lipophilicity by maintaining the hydrophilicity as well. The log p value of N-allyl group is in between N-H and N-C_6H_5 group. Selected allyl group may increase the solubility profile of compound as well as its activity profile should also increase as PPARγ receptors are mostly present in adipose tissue [23-24]. As observed during literature review arylidene substitution on 5th position is most beneficial for plasma glucose (PG) level reduction [21,25-26]. [21, 25-26] Electron donating groups at 4th position in arylidene substituted thiazolidinediones (ATZDs) produce a significant reduction in PG [25]. Various substitutents (R_2) (electron donating as well as withdrawing) like -OCH_3, -Cl, -F, -NO_2, -OH are attached at different positions in arylidene group attached to 5th position of TZD to check the activity profile of the compounds.

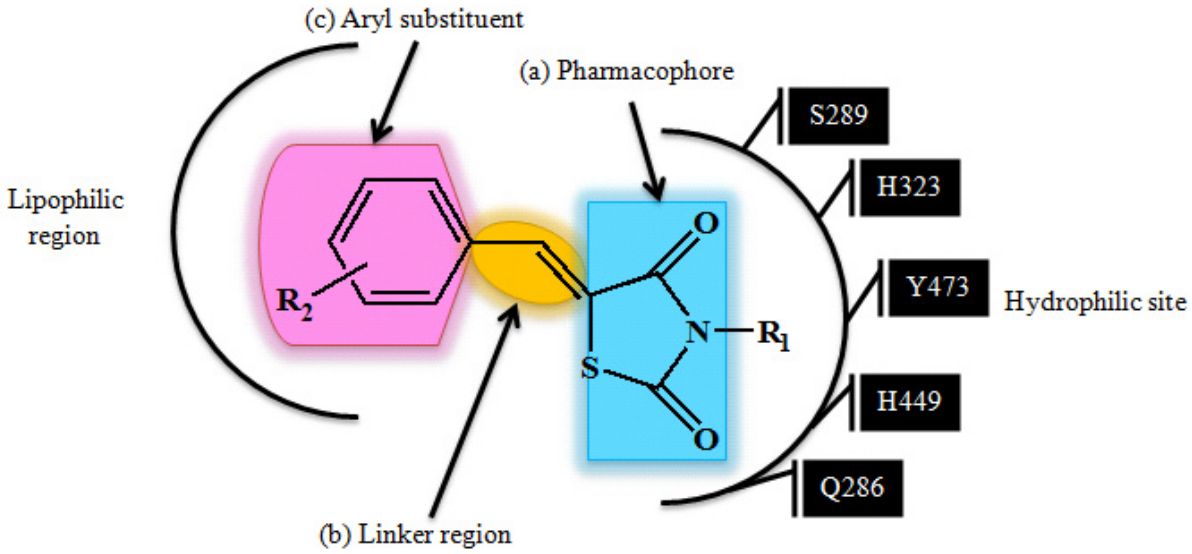
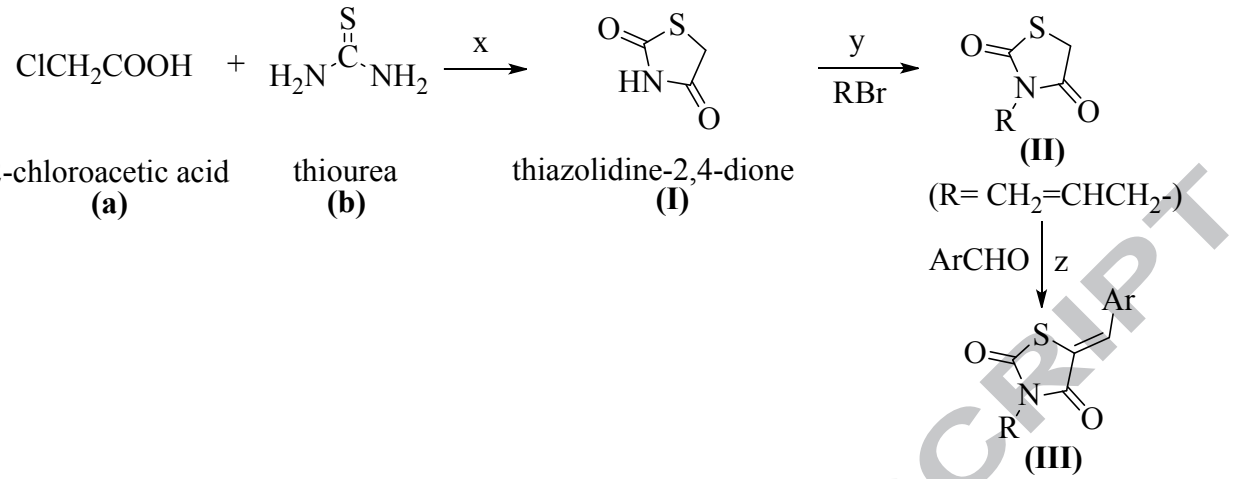


Fig. 2. Regions of molecule required for binding to PPARγ



2-chloroacetic acid **(a)** thiourea **(b)** thiazolidine-2,4-dione **(I)**

Scheme 1. Reagents: (x) HCl; (y) EtOH+water; (z) sodium acetate, hot glacial acetic acid.

2. Results and discussion

2.1 *Chemistry*

The chemicals required were obtained from Hi-media Chem. Ltd, SD-Fine Ltd. and Sigma Aldrich Pvt. Ltd and were used as such. A total of thirteen derivatives (**NB1-NB13**) were synthesized via three step reaction process. The synthetic strategy utilized for preparation of TZD derivatives is outlined in scheme **1**. Thiourea gives thiazoldine-2,4-dione (**I**) with chloroacetic acid [27]. N-allylation of thiazoldine-2,4-dione (**I**) with allylbromide furnished 3-allylthiazoldine-2,4-dione (**II**) [28], which on which on Knoevenagel condensation with various aromatic aldehydes yielded 5-arylidene derivatives (**III**)[29] (figure **3**). Melting points were determined using open capillary tube melting point apparatus and are uncorrected. Reaction progress was monitored by performing thin layer chromatography on silica gel G plates, using iodine vapours and UV chamber as visualizing agents. After physical characterization, the compounds were subjected to spectral analysis. Proton Nuclear Magnetic resonance spectra were recorded on Bruker ultra shield (400 MHz) spectrometer and chemical shifts are reported in parts per million (δ value) from TMS (δ 0 ppm for ^{1}H NMR) as an internal standard. Coupling constant are given in Hertz. Mass spectra were recorded on a JEOL GC-HRMS instrument using ESI. Infrared spectra were taken on Perkin Elmer (FTIR) spectrometer and values are expressed in cm^{-1}.

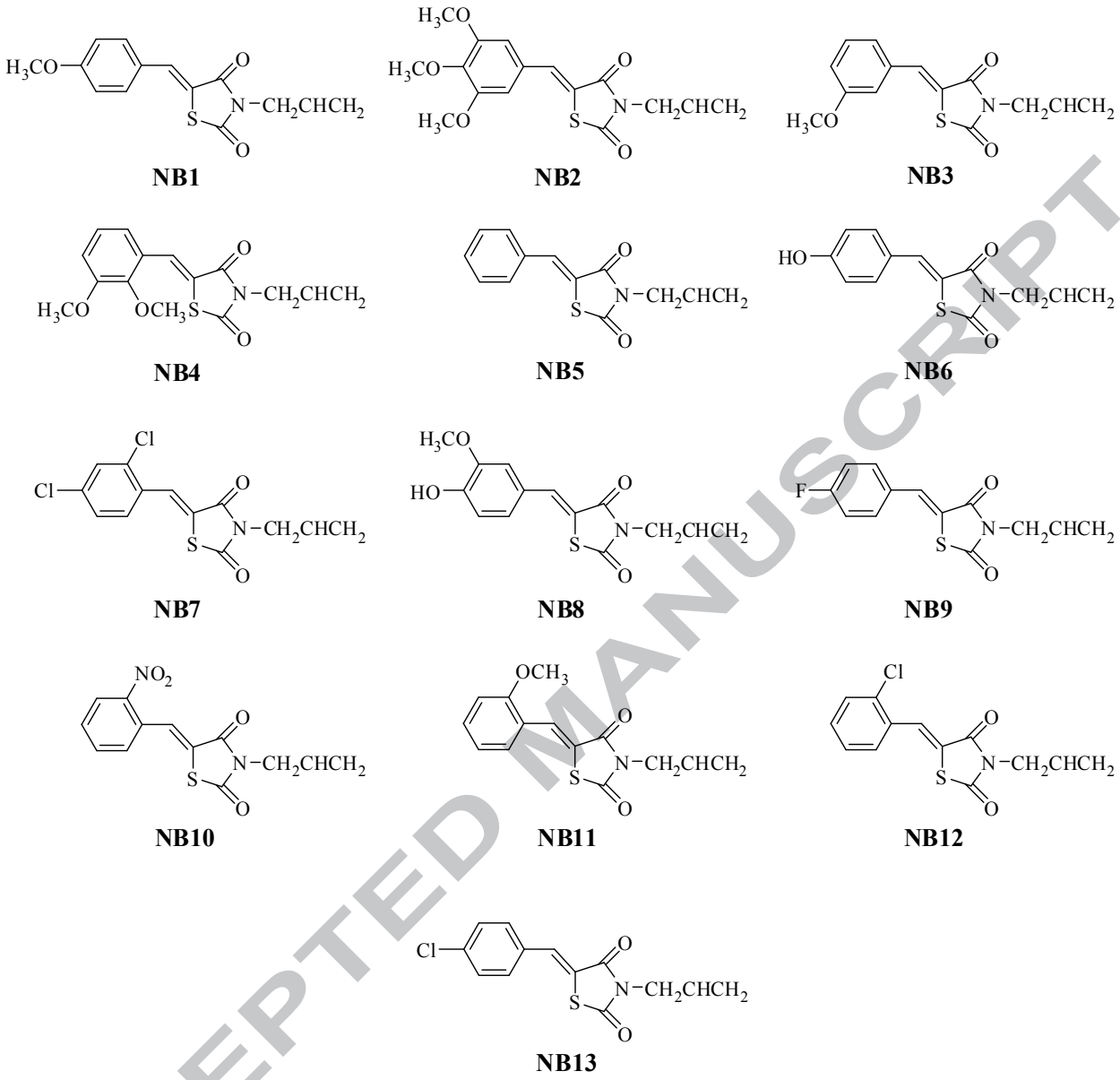


Fig. 3. Structures of synthesized final compounds **III** (**NB1-NB13**).

2.2. Pharmacological studies

The synthesized derivatives of thiazolidinedione were subjected to pharmacological screening for anti-diabetic activity against alloxan induced diabetes in wistar rats [30-33] (Table 1), anti-inflammatory activity using carrageenan induced rat paw edema model [34-35] (Table 2) and *in vitro* antioxidant activity using FRAP method [36] (Table 3).

2.2.1. Antidiabetic Activity

Results of antidiabetic activity show that halogen containing compound showed excellent activity than others, especially compounds having chloro group at ortho and para position of arylidene ring showed best activity among all the derivatives. **NB7** is found to possess maximum

antidiabetic activity among all derivatives. **NB2** having three $-OCH_3$ groups showed least potency in lowering the blood glucose level (Fig. **4**). From the result it may be concluded that groups like halide attached to molecule which may contribute in lipophilicity of the molecule showed excellent activity. This may be due to the fact that increased lipophilicity may help in easy penetration of compound into PPARγ receptor which is mainly present in high concentration in adipose tissue.

Table 1

Blood glucose levels of alloxan induced diabetic rats.

Treatment (mg/kg, p.o.)	Blood Glucose Level (mg/dL)			
	0 hour	**1 hour**	**3 hour**	**6 hour**
Group I (Control)	251±3.13	253±4.72	252±4.40	254±6.14
Group II (Pioglitazone)	276±4.84	213±3.44	114±5.49	89±3.26
Group III (NB1)	248±6.39	222±6.36	189±7.29	138±9.49
Group III (NB2)	260±4.24	225±7.38	191±5.93	157±6.71
Group III (NB3)	308±6.25	241±6.83	201±7.35	150±4.19
Group III (NB4)	305±9.72	205±5.72	194±3.79	155±8.48
Group III (NB5)	281±7.39	233±4.59	181±5.04	143±5.93
Group III (NB6)	253±5.62	232±6.52	185±6.86	152±9.11
Group III (NB7)	**301±5.43**	**211±4.74**	**166±7.08**	**108±3.95**
Group III (NB8)	264±5.73	225±6.14	189±4.93	145±7.39
Group III (NB9)	245±7.30	208±5.93	161±4.73	129±8.61
Group III (NB10)	244±7.28	208±6.92	178±5.62	133±4.05
Group III (NB11)	261±3.87	230±6.49	172±5.26	149±4.11
Group III (NB12)	298±6.34	213±7.39	170±4.82	122±9.24
Group III (NB13)	283±8.32	238±6.43	167±10.32	111±5.48

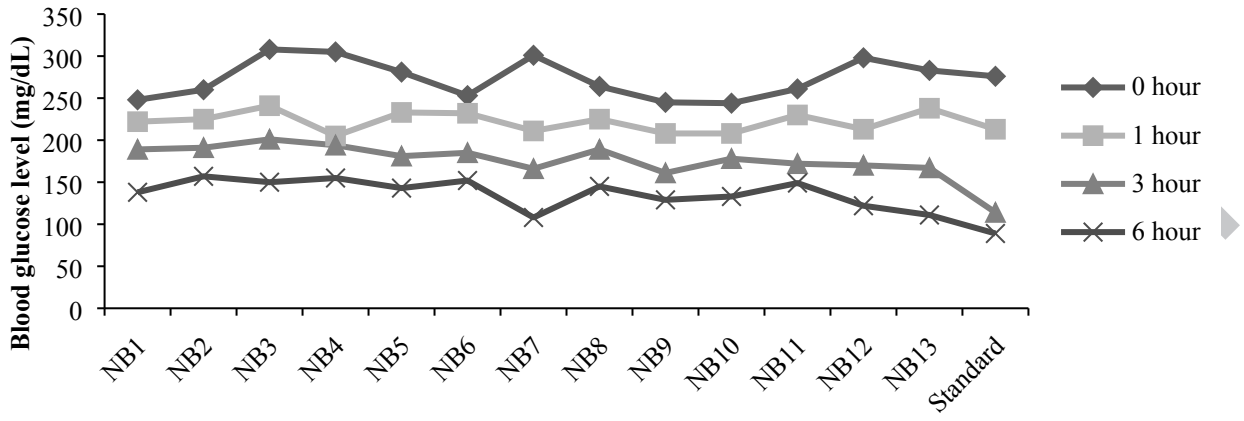


Fig. 4. Blood glucose level of different compounds at 0, 1, 3 and 6 hours

2.2.2. Antiinflammatory Activity

The entire series of investigated compounds exhibited moderate to good anti-inflammatory activity comparable to reference drug diclofenac sodium (10 mg/kg). Compounds **NB7**, **NB13** and **NB9** showed significant anti-inflammatory activity at third hour being 59.5%, 57.1% and 54.7% respectively closer to that of standard drug diclofenac sodium (64.2%).

The data of *in vivo* anti-inflammatory activity of synthesized novel compound evidence that presence of group at 4th position of arylidene substituent attached to TZD is necessary to exhibit good anti-inflammatory activity. Halide derivative compounds of TZD showed good activity among all the derivatives. Even compounds **NB7** and **NB13** showed more activity than standard compound during 0, 1 and 2 hrs. Compound **NB7** showed maximum activity (59.5%) among all the synthesized compounds quite closer to standard compound (64.2%). (Fig. 5).

2.2.3. Antioxidant Activity

Data obtained for antioxidant activity of synthesized compounds shows that compounds bearing electron donating groups like –OH and –OCH_3 showed greater reducing power in comparison to other derivatives. **NB8** showed good reduction potential which may be attributed to presence of –OH and –OCH_3 groups which are capable of donating electrons to electron deficient species (Table 3). The absorption at 100 µg/ml for the thirteen samples was compared with ascorbic acid for the plot was calculated by the equation: $y = 0.0084x + 0.0025$ ($R^2 = 0.994$) (Fig. 6), it was expressed as AAE (ascorbic acid equivalent) means that reducing power of 100µg/ml of each compound is equivalent to reducing power of µg of ascorbic acid or expressed as µg AAE/mg of compound. Data obtained reveals that compound bearing electron donating groups like –OH and –OCH_3 showed greater reducing power in comparison to other derivatives. **NB8** showed good reduction potential which may be attributed to presence of –OH and –OCH_3 groups which are capable of donating electrons. Compounds bearing electron withdrawing group (**NB10**) and unsubstituted derivative (**NB5**) showed least potency which may be outcome of their least ability to donate electron.

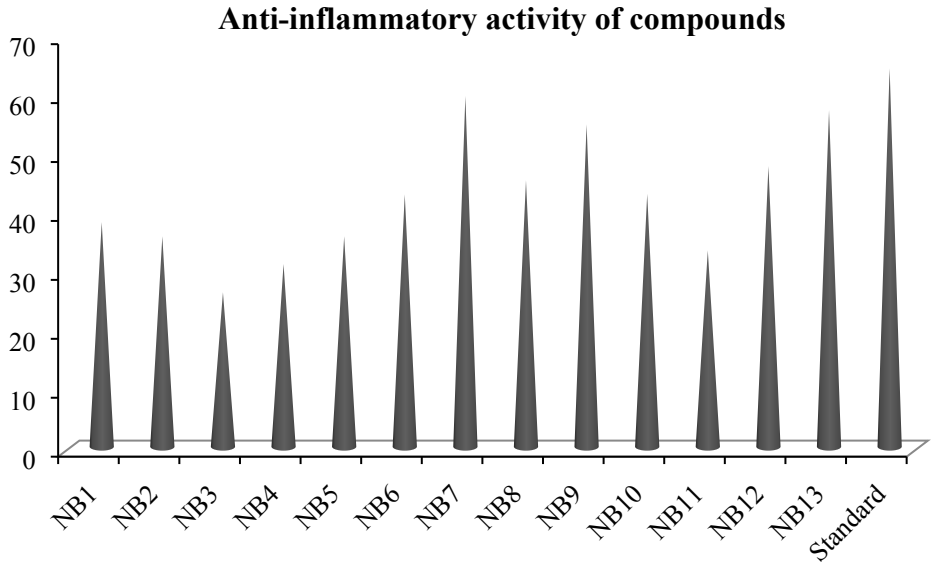


Fig. 5. Anti-inflammatory activity profile of compounds

Table 2

Percent Inhibition value of compounds against carrageenan-induced edema in rats.

Compounds	Normal Paw Volume(ml)	Mean Paw Volume ± SEM(ml) and % inhibition			
		Time After Carrageenan Injection			
		0 hr	**1hr**	**2hr**	**3hr**
Control	0.015±0.005	0.048±0.008	0.048±0.008	0.045±0.005	0.042±0.005
Diclofenac sodium	0.012±0.005	0.042±0.004 (12.5%)	0.036±0.006 (25.0%)	0.033±0.004 (26.7%)	0.015±0.004 (64.2%)
NB1	0.011±0.004	0.042±0.005 (12.5%)	0.037±0.005 (22.9%)	0.032±0.004 (28.9%)	0.026±0.006 (38.1%)
NB2	0.011±0.005	0.045±0.005 (6.2%)	0.039±0.007 (18.7%)	0.030±0.004 (33.3%)	0.027±0.005 (35.7%)
NB3	0.010±0.005	0.043±0.006 (10.4%)	0.039±0.005 (18.7%)	0.032±0.005 (28.9%)	0.031±0.008 (26.2%)
NB4	0.010±0.005	0.040±0.005 (16.7%)	0.038±0.005 (20.8%)	0.035±0.003 (22.2%)	0.029±0.004 (31.0%)
NB5	0.011±0.004	0.041±0.005 (14.6%)	0.036±0.005 (25.1%)	0.032±0.005 (28.9%)	0.027±0.005 (35.7%)
NB6	0.011±0.005	0.037±0.005 (19.9%)	0.035±0.006 (27.1%)	0.027±0.007 (40.0%)	0.024±0.005 (42.8%)
NB7	**0.010±0.006**	**0.038±0.005 (20.8%)**	**0.032±0.005 (33.3%)**	**0.026±0.005 (42.2%)**	**0.017±0.004 (59.5%)**
NB8	0.010±0.005	0.040±0.005 (16.7%)	0.037±0.004 (22.9%)	0.029±0.005 (35.6%)	0.023±0.005 (45.2%)
NB9	0.011±0.004	0.040±0.005 (16.7%)	0.038±0.005 (20.8%)	0.034±0.005 (24.4%)	0.019±0.005 (54.7%)

NB10	0.011±0.006	0.041±0.006 (14.6%)	0.032±0.005 (33.3%)	0.027±0.004 (40.0%)	0.024±0.003 (42.9%)
NB11	0.010±0.004	0.040±0.005 (16.7%)	0.038±0.005 (20.8%)	0.033±0.006 (26.7%)	0.028±0.004 (33.3%)
NB12	0.011±0.005	0.040±0.006 (16.7%)	0.035±0.005 (27.1%)	0.030±0.007 (33.3%)	0.022±0.005 (47.6%)
NB13	0.010±0.005	0.043±0.004 (10.4%)	0.033±0.005 (31.2%)	0.028±0.006 (37.8%)	0.018±.007 (57.1)

Table 3

Concentration of samples (100 µg/ml) equivalent to ascorbic acid (µg/ml).

S. No.	Test Sample	Abs. at 700 nm (100µg/ml)	Concentration Equivalent to AAE
1	NB1	0.206	24.35
2	NB2	0.184	21.73
3	NB3	0.123	14.35
4	NB4	0.155	18.15
5	NB5	0.107	12.56
6	NB6	0.305	36.01
7	NB7	0.283	33.39
8	**NB8**	**0.361**	**42.68**
9	NB9	0.117	13.63
10	NB10	0.071	8.03
11	NB11	0.180	21.13
12	NB12	0.210	24.70
13	NB13	0.222	26.13

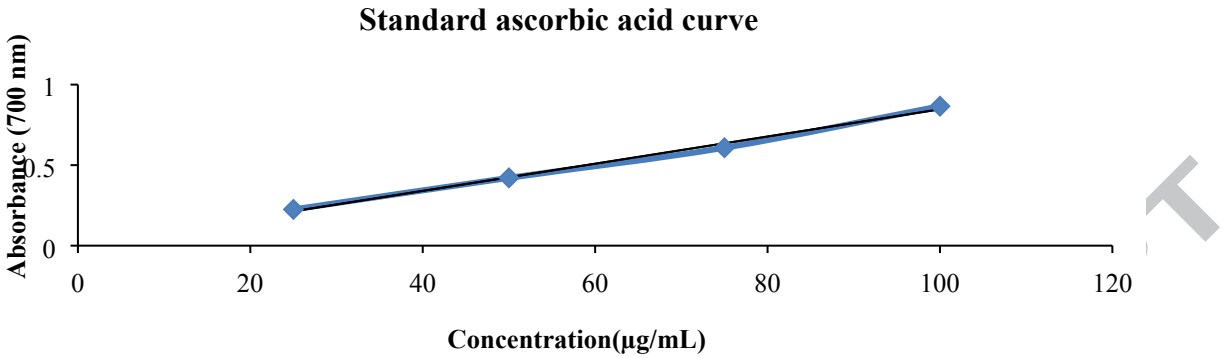
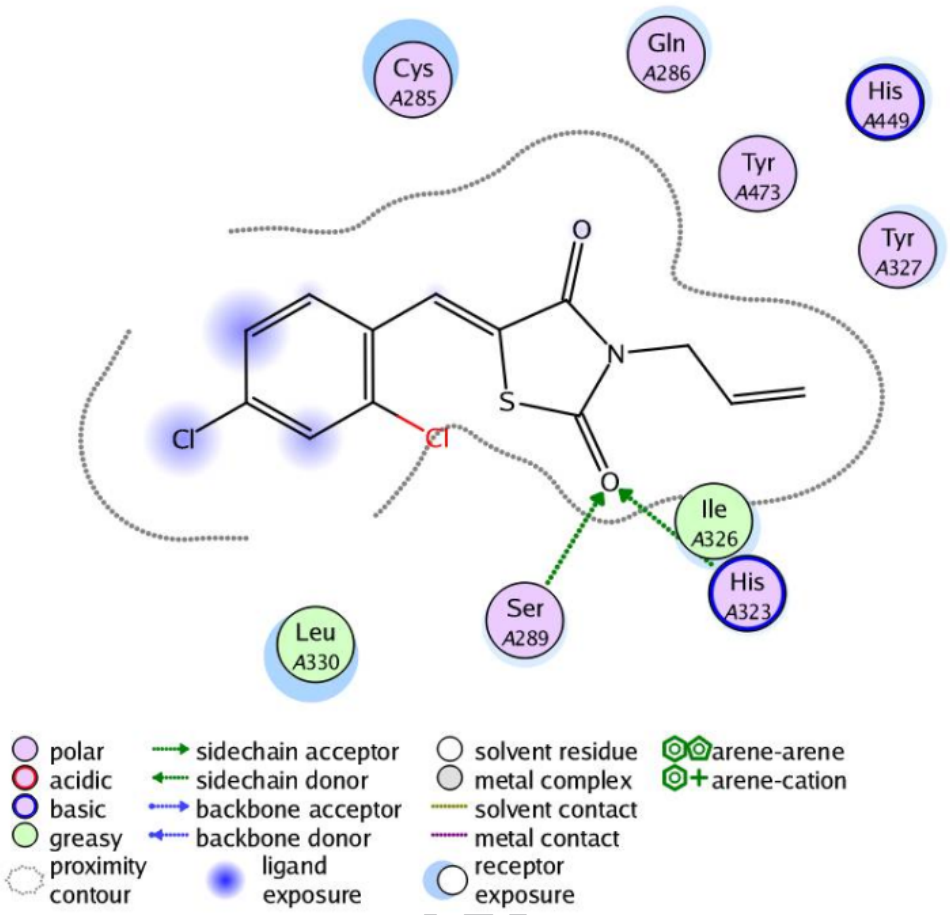


Fig. 6. Standard linearity curve of ascorbic acid.

3. Molecular Docking Studies

Molecular docking was carried out to investigate some possible structural insights into the potential binding patterns of the most potent anti-diabetic molecules NB7,NB12 and NB13 with the active sites of target PPARγ (PDB ID: 2PRG) using MOE software. The various possible interactions and orientations were investigated and compared with the binding patterns of pioglitazone. Compounds NB7, NB12 and NB13 displayed docking scores with values of -11.6930, -10.1553 and -11.1008 which were almost comparable to the reference drug pioglitazone (-12.8116). Compounds NB7 showed two hydrogen bond interactions with amino acid residues Ser A289 (2.86 Å) and His A323 (2.39 Å). The 2D and 3D binding patterns of compound NB 7 have been depicted in **Fig. 7.** One keto group of compound NB12 showed hydrogen bonding interaction (2.86 Å) with water (HOH 604) in association to Ser 342 (3.02 Å); whereas the other keto group showed hydrogen bonding interaction (2.17 Å) with another water molecule (HOH 496) in association to Arg (2.84 Å) **(Fig. 8).** Compound NB13 forms hydrogen bond with Ser A342 (2.54 Å) as depicted in **Fig. 9**. Pioglitazone showed a binding pattern by making a hydrogen bond with Glu A343 (2.81 Å) and another interaction with HOH 604 (3.02 Å) associated with Ser 342. The interactions and biding pattern of pioglitazone to the receptor has been presented in **Fig. 10.**

From the findings it is evident that the pattern of binding in the active site of PPARγ is almost similar to that of pioglitazone which is a well-established therapeutic candidate against PPARγ. Further it is also supported by the *in vivo* activity results in rats where almost equal activity to that of reference drug has been observed. Therefore, the synthesized compound may serve as new leads for the drug development against diabetes.



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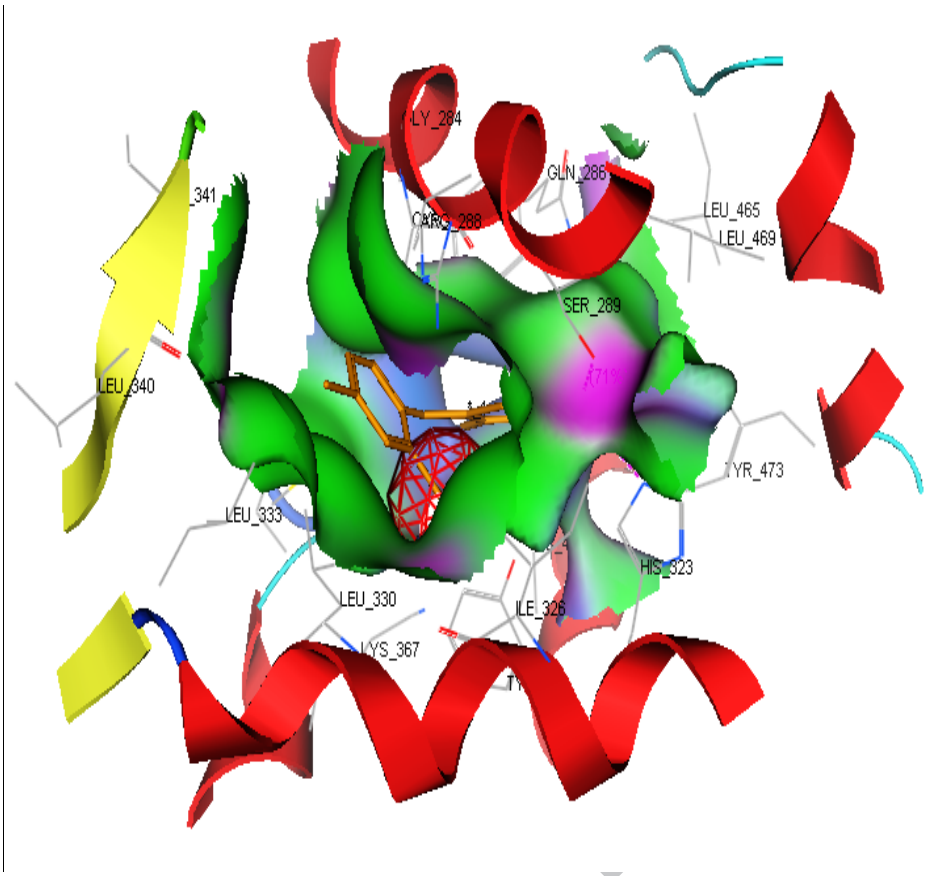

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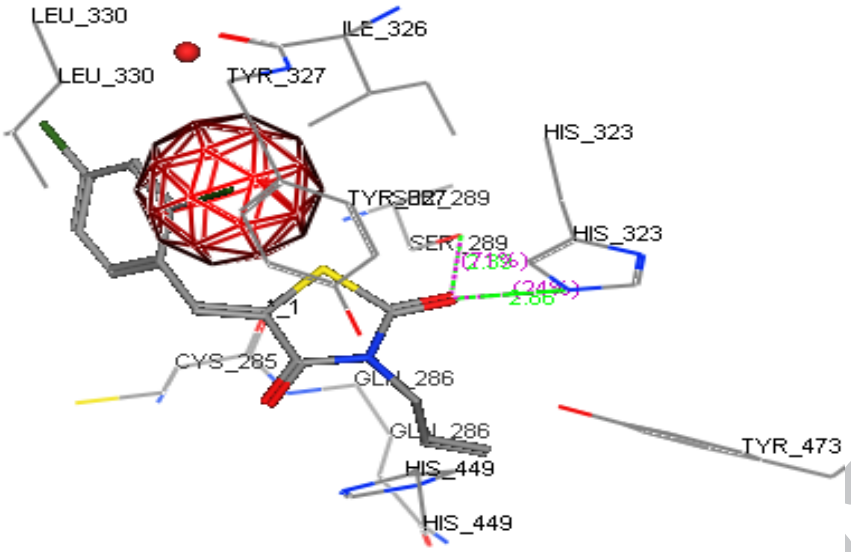
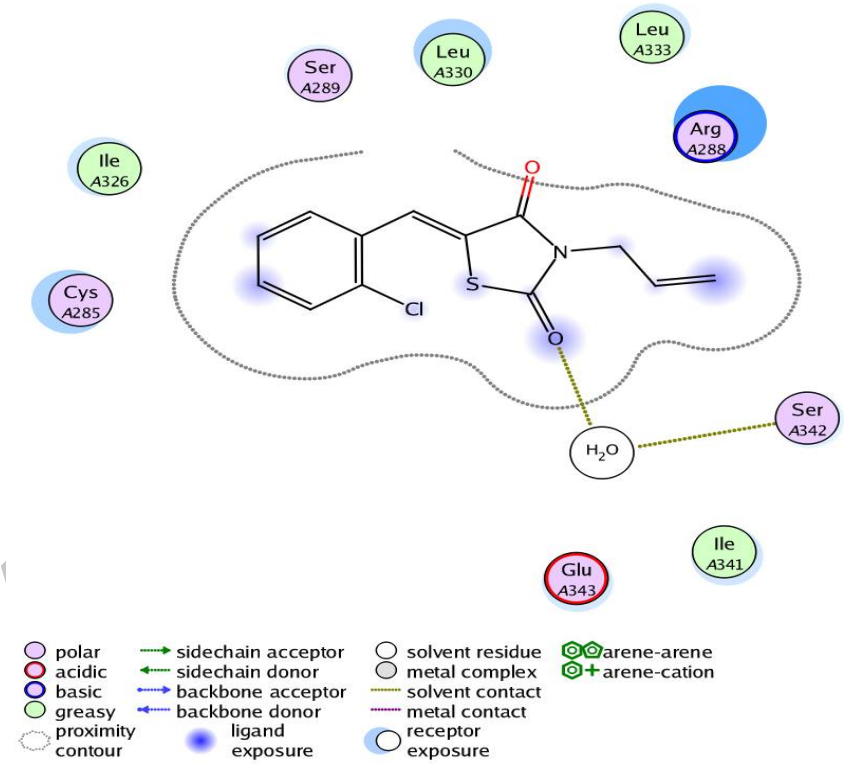


(c)

Fig. 7. (a) 2D interactions of NB 7 with PPARγ (b) 3D pose of embedded ligand inside the pocket (c) Possible interactions between ligand and receptor.



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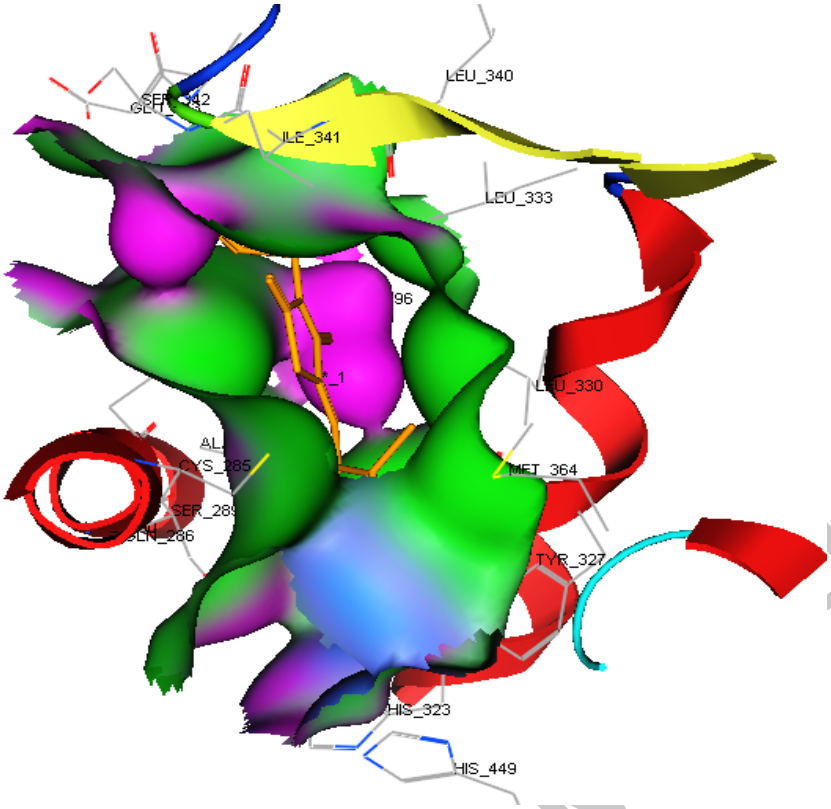

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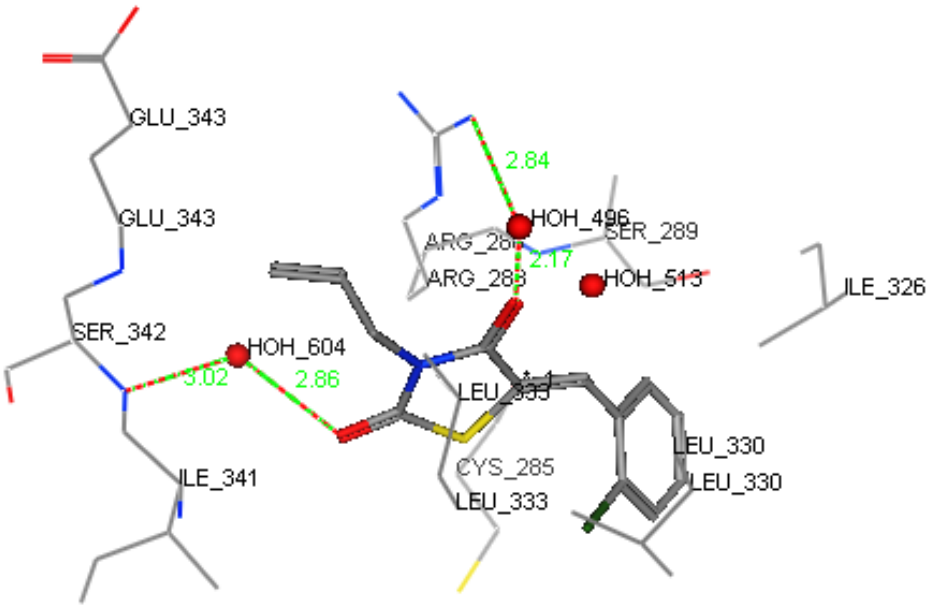
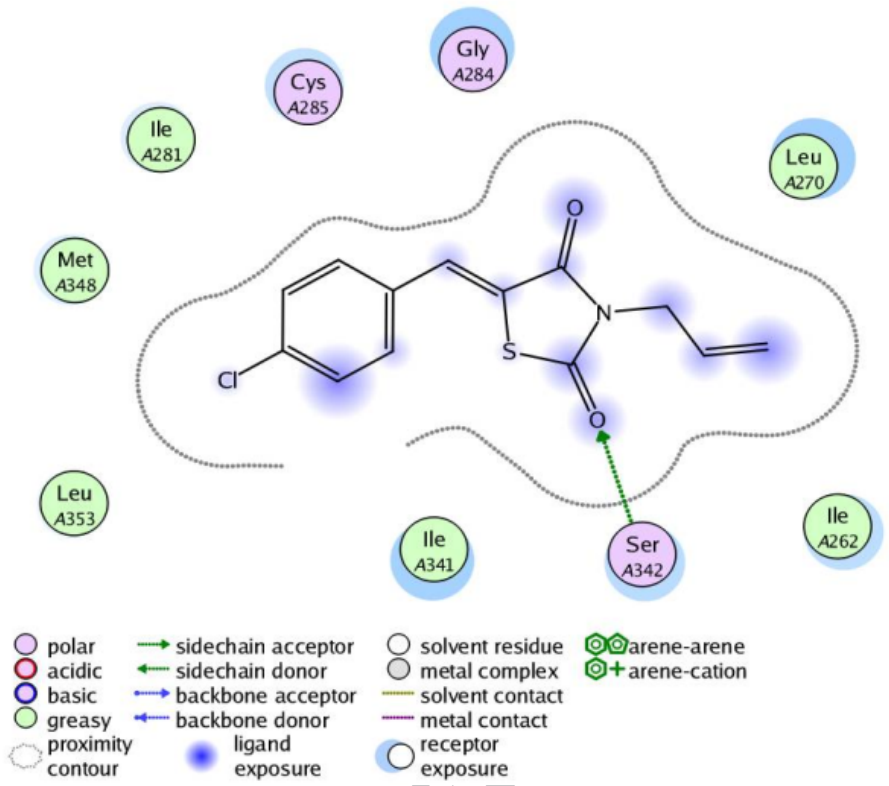
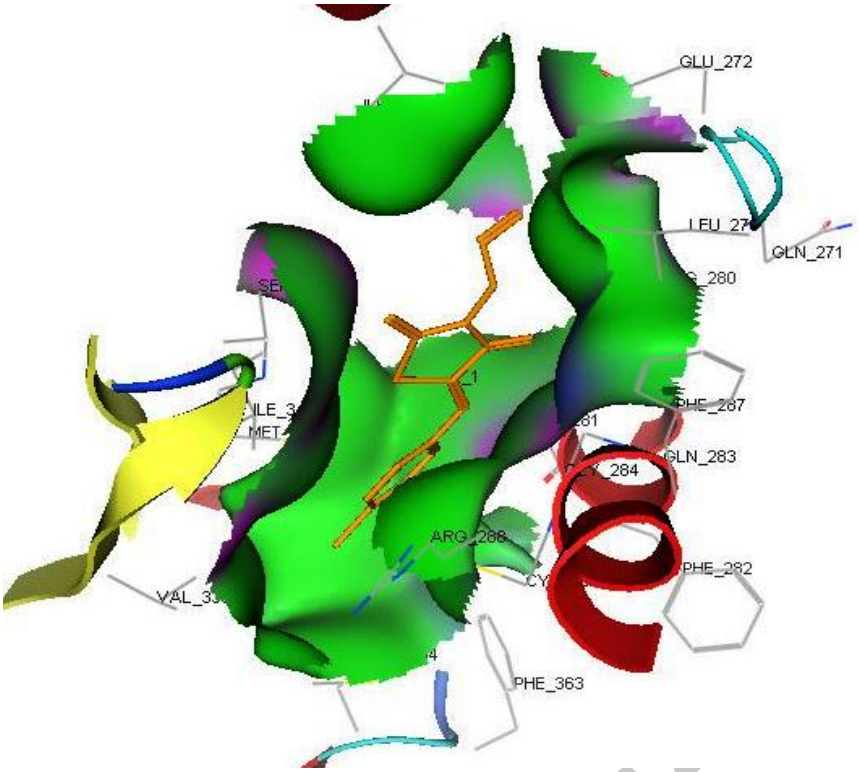


(c)

Fig. 8. (a) 2D interactions of NB 12 with PPARγ (b) 3D pose of embedded ligand inside the pocket (c) Possible interactions between ligand and receptor.



(a)



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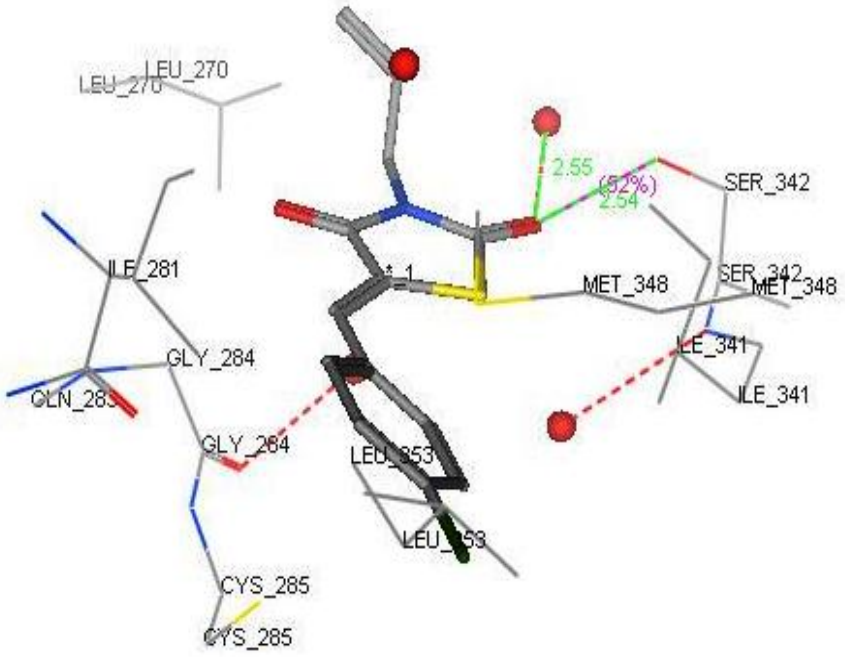
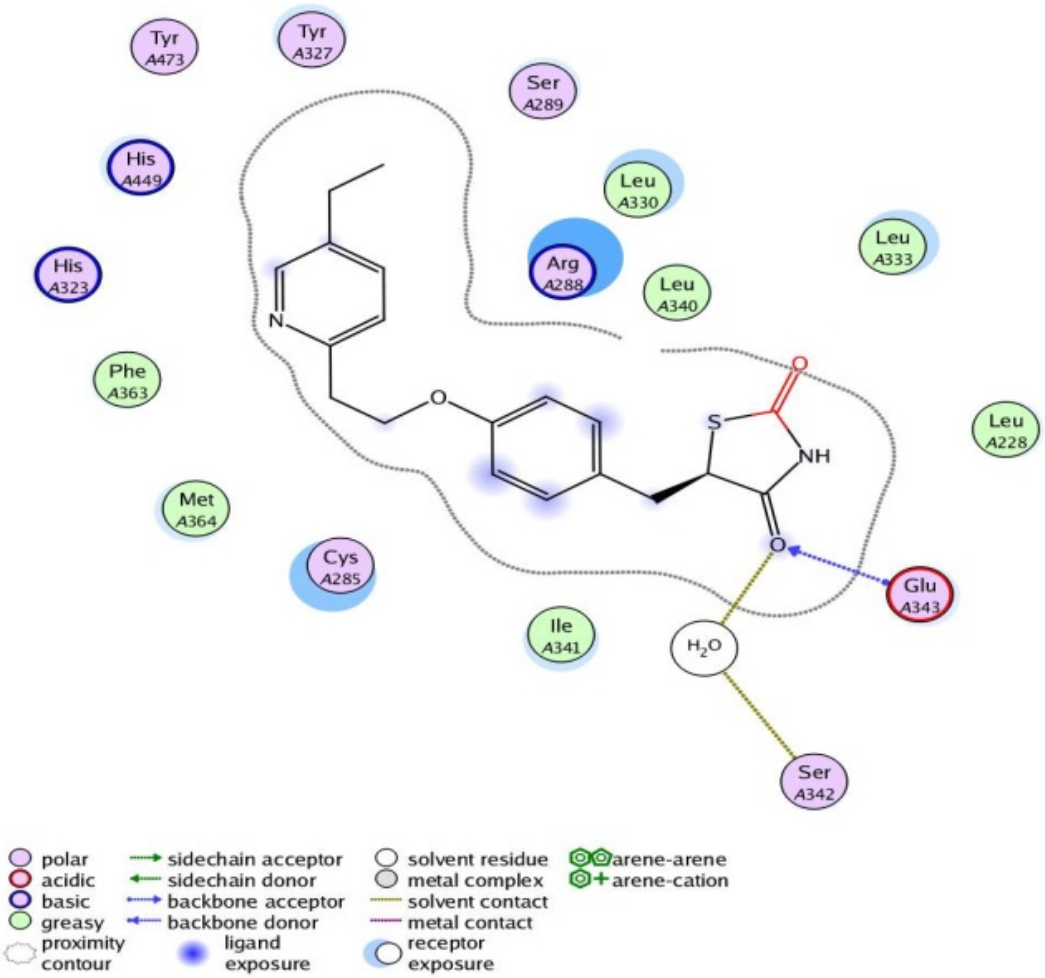
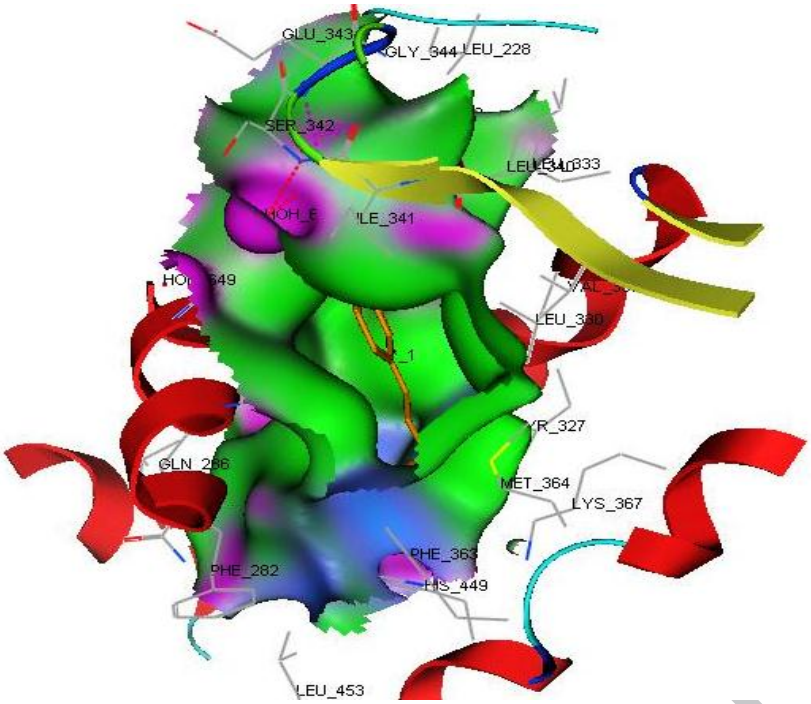


(c)

Fig. 9. (a) 2D interactions of NB 13 with PPARγ (b) 3D pose of embedded ligand inside the pocket (c) Possible interactions between ligand and receptor.



(a)



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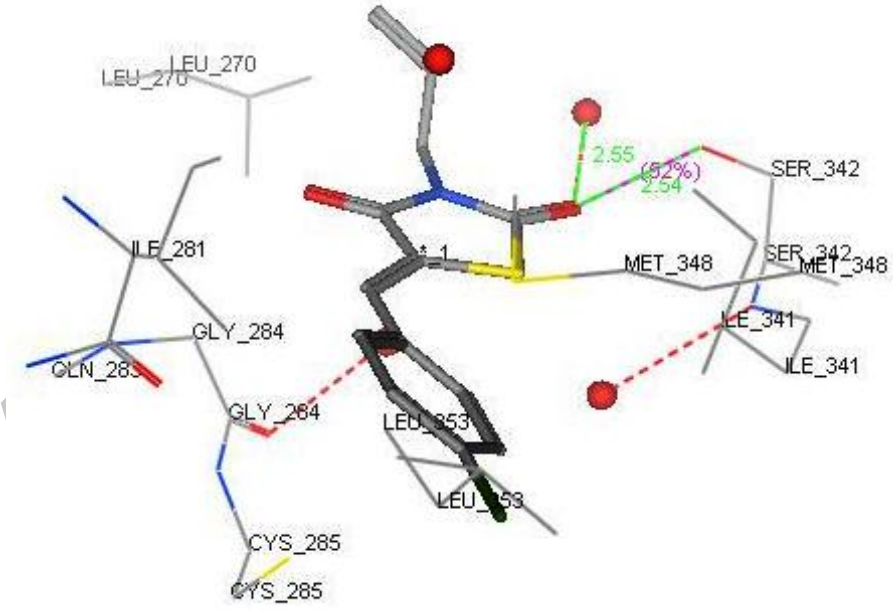

(c)

Fig. 10. (a) 2D interactions of pioglitazone with PPARγ (b) 3D pose of embedded ligand inside the pocket (c) Possible interactions between ligand and receptor.

4. Conclusion

Despite the abundance of available antidiabetes therapies, a considerable number of patients with type 2 diabetes continue to have relatively poor glycemic control and are at risk for macrovascular and microvascular disease. This study can provide an excellent diabetic control to the patient as well as the synthesized compounds can also check the complications arising due to diabetes which is proved to be result of increased inflammation and oxidative stress in hyperglycemic condition. Dichloro derivative compound **NB-7** has shown great potential in the present study as it not only possesses maximum antidiabetic activity but also has excellent anti-inflammatory and antioxidant potential. Docking studies were carried out on the most potent compounds to get an insight to the drug-receptor interactions. The compound **NB7** (docking score -11.6930) revealed similar fashion of binding pattern as in case of marketed anti-diabetic drug pioglitazone (docking score -12.8116). A general SAR is prepared for the synthesized thiazoldinedione derivative on the basis of data obtained from various activities. Compounds bearing halide group at arylidine substituent attached to 5^{th} position of TZD pharmacophore showed best antidiabetic activity while those having groups like $–OCH_3$ and –OH showed least activity. Presence of groups at 4^{th} position of arylidene substituent is essential for reduction in level of inflammation. Compounds having methoxy group at 2^{nd} or 3^{rd} position in arylidine substituent results in loss of anti-inflammatory activity. Electron donating groups like -OH and -OCH_3 play a central in radical scavenging potential of compounds, while those having electron withdrawing or unsubstituted derivative showed least activity. Lipophilicity of compounds played a major role in reduction of blood glucose level. Molecular docking studies were performed using MOE version 2008.10 software. The 3D structure of PPARγ (PDB ID: 2PRG) was procured from protein data bank and was prepared by deletion of ligand, addition of hydrogens, polar hydrogens followed by preparation of dummies using site finder wizard. The ligands were energy minimized by selecting force field MMFF94x, Austin model 1 (AM 1) with gradient value of 0.0001 kcal/mol and were saved as mdb format. The docking simulations were predicted by docking the prepared ligands in the binding pocket of PPARγ and results were displayed in database viewer. 2D and three 3D interactions of ligands with the receptor was predicted using compute tool. The docking results were compared to the standard drug pioglitazone. The employed docking protocol was validated by calculating the RMSD value.

5. Experimental section

Melting points were determined by open capillary method with electric melting point apparatus and are uncorrected. All the reagents for synthesis were obtained from Sigma Aldrich Pvt. Ltd., Rankem, Thomas Baker, SD fine chemical Ltd., Himedia and were used as such. Thin layer chromatography was used to monitor the progress of reactions, and the spots on TLC plates were visualized by iodine vapours, and UV irradiation at 254 nm. IR spectra were recorded on a FT-IR (Shimadzu-8400S) spectrometer using KBr pellets from 400-4000 cm-1. 1H NMR spectra were recorded on JEOL AL 300 FT-NMR spectrophotometer (400 MHz) in $CDCl_3$ using tetramethylsilane as an internal standard. The chemical shifts were expressed in δ ppm. The following notations expressed the peak types in the spectra: singlet (s), doublet (d), triplet (t) and multiplet (m). ESI mass spectra were recorded using Agilent 6530 Accurate-Mass Q-TOF mode.

Elemental analysis (C, H, N) was carried out using X-SUPREME 8000-EDXRF analyser and were found within range of ±0.4% of theoretical values.

5.1 Chemistry

5.1.1 Preparation of thiazolidine-2,4-dione ***(I)***

A mixture of 56.5 gm (0.6 mol) of 2-chloroacetic acid in 60 ml of water and 45.6 gm (0.6 mol) of thiourea in 60 ml of water was stirred for 15 min. The reaction mixture was cooled and white precipitates were formed. To this reaction mixture 60 ml of concentrated hydrochloric acid was added with the help of dropping funnel. Then the mixture was refluxed for 30-40 hrs. After completion of reaction, the whole content was transferred in to crushed ice, white solid product was obtained. Filtered and washed the solid with water. Recrystallized from ethanol and thus obtained a pure thiazolidine-2,4-dione **(I)**. The progress of reaction was monitored by TLC using chloroform and ethylacetate (60:40). Yield = 89%; IR (KBr) 1737.74, 1670.24, 3481.72, 1340.43, 3051.18, 1390.85 cm^{-1}; MS, ESI^{+}: 117.01$[M+H]^{+}$.

5.1.2 Preparation of 3-allylthiazolidine-2,4-dione ***(II)***

Mixture of 60 % ethyl alcohol (EtOH) and 40 % water was stirred for 10 min. Thiazolidine-2,4-dione (0.01 mol) **(I)** was added to above mixture and stirred for 30 min. Allylbromide (0.012 mol) was added to resulting mixture and stirred for 20 hrs at room temperature. Product was separated as oil which was taken up by chloroform added to it and washed with water. Obtained product was dried over sodium sulphate. Resulting product was recrystallized from ethanol to obtain **3-allylthiazolidine-2,4-dione (II).** The progress of reaction was monitored by TLC using ethylacetate and toluene (7:3). Yield = 73%; IR (KBr) 1742.32, 1671.28, 1337.41, 3068.12, 3123.37, 984.13, 923.57, 1637.19 cm^{-1}; MS, ESI^{+}: 157.49 $[M+H]^{+}$.

5.1.3 General method for preparation of compound ***(III)***

Refluxed the mixture of 1.57 gm of 3-allylthiazolidine-2,4-dione (II) and 0.01 mol of substituted benzaldehyde on an oil bath in the presence of 3.38 gm (0.04 mol) of sodium acetate and 10 ml of hot glacial acetic acid. The reaction was completed within 30 min. Filtered and washed it with water. On drying the solid product was obtained and recrystallized from ethanol. The reaction was monitored by using thin layer chromatography in chloroform and methanol (90:10) as solvent and iodine vapours as visualizing agent.

5.1.3.1. 3-allyl-5-(4-methoxybenzylidine)thiazolidine-2,4-dione ***(NB1)***

Yield = 81%; IR (KBr) 1728.42, 1668.56, 1335.82, 2965.37, 3122.56, 825.73, 1635.10 cm^{-1}; ^{1}H NMR (DMSO) δ 3.834 (s, 3H, CH_3), 5.194-5.191 (d, 1H,CH, J=1.2), 5.216-5.213 (d, 2H,CH, J=1.2), 5.227-5.224 (d, 1H,CH, J=1.2), 5.879-5.858 (m, 1H,CH), 6.942-6.939 (d, 1H,ArH, J=1.2), 7.622-7.619 (d, 1H,ArH, J=1.2), 7.954 (s, 1H, CH); MS, ESI^{+}: 275.05 $[M+H]^{+}$.

*5.1.3.2. 3-allyl-5-(3,4,5-trimethoxybenzylidine)thiazolidine-2,4-dione (****NB2****)*

Yield = 85%; IR (KBr) 1726.77, 1669.42, 1369.73, 2971.77, 3129.63, 883.10, 1622.44 cm^{-1}; ^{1}H NMR (DMSO) δ 3.834 (s, 3H, CH_3), δ 5.194-5.191 (d, 1H,CH, J=1.2), δ 5.216-5.213 (d, 2H,CH,

J=1.2), δ 5.227-5.224 (d, 1H,CH, J=1.2), δ 5.879-5.858 (m, 1H,CH), δ 6.784-6.781 (d, 1H, ArH, J=1.2), δ 7.954 (s, 1H, CH); MS, ESI^+: 335.10 $[M+H]^+$.

*5.1.3.3. 3-allyl-5-(3-methoxybenzylidine)thiazolidine-2,4-dione (**NB3**)*

Yield = 79%; IR (KBr) 1719.57, 1678.32, 1342.45, 2973.62, 3133.49, 784.95, 1635.48 cm^{-1}; ^1H NMR (DMSO) δ 3.834 (s, 3H, CH_3), δ 5.194-5.191 (d, 1H,CH, J=1.2), δ 5.216-5.213 (d, 2H,CH, J=1.2), δ 5.227-5.224 (d, 1H,CH, J=1.2), δ 5.879-5.858 (m, 1H,CH), δ 6.874-6.869 (d, 1H, ArH, J=2.0), δ 7.164-7.158 (d, 1H, ArH, J=2.4), δ 7.592-7.585 (t, 1H, ArH), δ 7.954 (s, 1H, CH); MS, ESI^+: 275.00 $[M+H]^+$.

*5.1.3.4. 3-allyl-5-(2,3-dimethoxybenzylidine)thiazolidine-2,4-dione (**NB4**)*

Yield = 83%; IR (KBr) 1743.30, 1681.44, 1348.39, 2960.48, 3115.94, 819.21, 1632.26 cm^{-1}; ^1H NMR (DMSO) δ 3.834 (s, 3H, CH_3), δ 5.194-5.191 (d, 1H,CH, J=1.2), δ 5.216-5.213 (d, 2H,CH, J=1.2), δ 5.227-5.224 (d, 1H,CH, J=1.2), δ 5.879-5.858 (m, 1H,CH), δ 6.763-6.760 (d, 1H, ArH, J=1.2), δ 7.157-7.151 (t, 1H, ArH), δ 7.224-7.221 (d, 1H, ArH, J=1.2), δ 8.220 (s, 1H, CH); MS, ESI^+: 305.07 $[M+H]^+$.

*5.1.3.5. 3-allyl-5-benzylidinethiazolidine-2,4-dione (**NB5**)*

Yield = 74%; IR (KBr) 1709.28, 1664.58, 1338.70, 3126.76, 859.84, 1625.72 cm^{-1}; ^1H NMR (DMSO) δ 5.194-5.191 (d, 1H,CH, J=1.2), δ 5.216-5.213 (d, 2H,CH, J=1.2), δ 5.227-5.224 (d, 1H,CH, J=1.2), δ 5.879-5.858 (m, 1H,CH), δ 7.329-7.326 (d, 1H, ArH, J=1.2), δ 7.481-7.475 (t, 1H, ArH), δ 7.621-7.618 (d, 1H, ArH, J=1.2), δ 7.954 (s, 1H, CH); MS, ESI^+: 245.10 $[M+H]^+$.

*5.1.3.6. 3-allyl-5-(4-hydroxybenzylidine)thiazolidine-2,4-dione (**NB6**)*

Yield = 80%; IR (KBr) 1722.35, 1670.26, 1328.21, 3372.84, 3124.38, 862.74, 1624.83, 1253.89 cm^{-1}; ^1H NMR (DMSO) δ 5.198-5.195 (d, 1H,CH, J=1.2), δ 5.213-5.210 (d, 2H,CH, J=1.2), δ 5.221-5.219 (d, 1H,CH, J=1.2), δ 5.876-5.855 (m, 1H,CH), δ 6.658-6.655 (d, 1H, ArH, J=1.2), δ 7.561-7.558 (d, 1H, ArH, J=1.2), δ 9.496 (s, 1H, OH); ESI^+: 261.07. $[M+H]^+$.

*5.1.3.7. 3-allyl-5-(2,4-dichlorobenzylidine)thiazolidine-2,4-dione (**NB7**)*

Yield = 89%; IR (KBr) 1726.52, 1659.20, 1328.46, 3141.97, 831.06, 1632.71 cm^{-1}; ^1H NMR (DMSO) δ δ 5.193-5.190 (d, 1H,CH, J=1.2), δ 5.217-5.214 (d, 2H,CH, J=1.2), δ 5.223-5.220 (d, 1H,CH, J=1.2), δ 5.882-5.861 (m, 1H,CH), δ 7.324-7.321 (d, 1H, ArH, J=1.2), δ 7.489 (s, 1H, ArH), δ 7.619-7.616 (d, 1H, ArH, J=1.2), δ 8.227 (s, 1H, CH); MS, ESI^+: 313.03 $[M+H]^+$.

*5.1.3.8. 3-allyl-5-(4-hydroxy-3-methoxybenzylidine)thiazolidine-2,4-dione (**NB8**)*

Yield = 89%; IR (KBr) 1738.41, 1672.86, 1341.26, 3368.11, 3109.28, 860.24, 1629.78, 1251.80 cm^{-1}; ^1H NMR (DMSO) δ 3.834 (s, 3H, CH_3), δ 5.197-5.194 (d, 1H,CH, J=1.2), δ 5.216-5.213 (d, 2H,CH, J=1.2), δ 5.222-5.219 (d, 1H,CH, J=1.2), δ 5.874-5.853 (m, 1H,CH), δ 6.993-6.990 (d, 1H, ArH, J=1.2), δ 7.123 (s, 1H, ArH), δ 7.167 (s, 1H, ArH), δ 7.954 (s, 1H, CH), δ 9.834 (s, 1H, OH); MS, ESI^+: 291.23 $[M+H]^+$.

*5.1.3.9. 3-allyl-5-(4-fluorobenzylidine)thiazolidine-2,4-dione (**NB9**)*

Yield = 86%; IR (KBr) 1728.31, 1666.10, 1362.24, 3100.37, 841.08, 1642.57 cm^{-1}; ^1H NMR (DMSO) δ 5.197-5.194 (d, 1H,CH, J=1.2), δ 5.213-5.210 (d, 2H,CH, J=1.2), δ 5.222-5.219 (d, 1H,CH, J=1.2), δ 5.874-5.853 (m, 1H,CH), δ 7.193-7.190 (d, 1H, ArH, J=1.2), δ 7.723-7.720 (d, 1H, ArH, J=1.2), δ 7.951 (s, 1H, CH); MS, ESI^+: 263.03 $[M+H]^+$.

*5.1.3.10. 3-allyl-5-(2-nitrobenzylidine)thiazolidine-2,4-dione (**NB10**)*

Yield = 92%; IR (KBr) 1731.78, 1658.65, 1365.52, 3048.06, 782.53, 1636.11, 1518.13 cm^{-1}; ^1H NMR (DMSO) δ 5.193-5.189 (d, 1H,CH, J=1.6), δ 5.216-5.213 (d, 2H,CH, J=1.2), δ 5.228-5.223 (d, 1H,CH, J=2.0), δ 5.873-5.852 (m, 1H,CH), δ 7.793-7.877 (t, 1H, ArH), δ 7.895-7.887 (t, 1H, ArH), δ 8.009-8.004 (d, 1H, ArH, J=2.0), δ 8.214-8.210 (d, 1H, ArH, J=1.6), δ 8.513 (s, 1H, CH); MS, ESI^+: 290.06 $[M+H]^+$.

*5.1.3.11. 3-allyl-5-(2-methoxybenzylidine)thiazolidine-2,4-dione (**NB11**)*

Yield = 84%; IR (KBr) 1741.35, 1668.42, 1340.17, 2972.18, 3113.47, 879.01, 1640.34 cm^{-1}; ^1H NMR (DMSO) δ 3.834 (s, 3H, CH_3), δ 5.198-5.195 (d, 1H,CH, J=1.2), δ 5.213-5.210 (d, 2H,CH, J=1.2), δ 5.221-5.219 (d, 1H,CH, J=1.2), δ 5.876-5.855 (m, 1H,CH), δ 6.941-6.937 (d, 1H, ArH, J=1.6), δ 6.968-6.963 (d, 1H, ArH, J=2.0), δ 7.227-7.221 (t, 1H, ArH), δ 7.663-7.657 (d, 1H, ArH, J=2.4), δ 8.228 (s,1H, CH); MS, ESI^+: 275.09 $[M+H]^+$.

*5.1.3.12. 3-allyl-5-(2-chlorobenzylidine)thiazolidine-2,4-dione (**NB12**)*

Yield = 90%; IR (KBr) 1729.11, 1655.38, 1336.42, 3108.42, 758.09, 1632.24 cm^{-1}; ^1H NMR (DMSO) δ 5.194-5.191 (d, 1H,CH, J=1.6), δ 5.216-5.212 (d, 2H,CH, J=1.6), δ 5.227-5.222 (d, 1H,CH, J=2.0), δ 5.879-5.858 (m, 1H,CH), δ 7.274-7.268 (t, 1H, ArH), δ 7.305-7.299 (t, 1H, ArH), δ 7.360-7.357 (d, 1H, ArH, J=1.2), δ 7.457-7.453 (d, 1H, ArH, J=1.6), δ 8.219 (s, 1H, CH); MS, ESI^+: 279.24 $[M+H]^+$.

*5.1.3.13. 3-allyl-5-(4-chlorobenzylidine)thiazolidine-2,4-dione (**NB13**)*

Yield = 88%; IR (KBr) 1727.25, 1653.82, 1341.19, 3128.10, 791.49, 1634.24 cm^{-1}; ^1H NMR (DMSO) δ 5.193-5.180 (d, 1H,CH, J=1.2), δ 5.219-5.214 (d, 2H,CH, J=2.0), δ 5.224-5.220 (d, 1H,CH, J=1.6), δ 5.882-5.861 (m, 1H,CH), δ 7.450-7.446 (d, 1H, ArH, J=1.6), δ 7.689-7.684 (d, 1H, ArH, J=2.0), δ 7.951 (s, 1H, CH); MS, ESI^+: 279.40 $[M+H]^+$.

5.2. Molecular docking studies

Molecular docking studies were performed using MOE version 2008.10 software. The 3D structure of PPARγ (PDB ID: 2PRG) was procured from protein data bank and was prepared by deletion of ligand, addition of hydrogens, polar hydrogens followed by preparation of dummies using site finder wizard. The ligands were energy minimized by selecting force field MMFF94x, Austin model 1 (AM 1) with gradient value of 0.0001 kcal/mol and were saved as mdb format. The docking simulations were predicted by docking the prepared ligands in the binding pocket of PPARγ and results were displayed in database viewer. 2D and three 3D interactions of ligands with the receptor was predicted using compute tool. The docking results were compared to the standard drug pioglitazone. The employed docking protocol was validated by calculating the RMSD value.

5.3. Biological activity

5.1 Biology

Rats were housed in groups of six in clean poly acrylic cages. Rice husk as bedding material of the cages was changed every day. The animals were maintained under natural day and night cycle. Animals were acclimatized for one week to the laboratory conditions before starting the experiment. Animals were given standard pellet diet and allowed water *ad libitum*. All the animal studies were conducted in accordance with the guidelines for animal care. The protocol was approved by the Institutional Animal Ethics Committee (IAEC) (Reg No. BBDNITM/IAEC/Clear/04/2012).

5.1.1 Antidiabetic Activity

Male Albino Wistar rats, weighing about 150-250gm were used for antidiabetic studies. Animals were divided into following groups consisting of six rats. Group 1: Consisted of healthy rats and received 0.5 ml of 0.9% normal saline; Group 2: Treated with standard drug Pioglitazone at a dose of 10 mg/kg; Group 3-15: All the test compounds (**NB1-NB13**) were given as oral dose of 10 mg/kg suspended in carboxy methyl cellulose (CMC) by using oral gastric gavages. Rats were fasted overnight and next day anaesthetized with ethyl ether and hyperglycemia was induced by a single intra peritoneal injection of freshly prepared Alloxan (120 mg/kg body weight dissolved in 0.9% w/v saline) solution. Diabetes (blood glucose level more than 250 mg/dl) was confirmed on 4th day by determining the blood glucose concentration using a Glucometer (Accu Chek). The blood glucose levels of the animals were measured at 0, 1st, 3rd and 6th hour by withdrawing 0.1-0.2 ml of blood from tail vein under mild ether anesthesia [30-33].

5.1.2 Anti-inflammatory Activity

Male Albino Wistar rats, weighing about 110-170g were used for anti-inflammatory studies. Animals were divided in three groups each containing 6 animals. Animals in group 1 recieves the vehicle CMC, group 2 was given Diclofenac sodium (10 mg/kg, p.o.) and test compounds **NB1-NB13** in group 3 has given 10mg/kg through oral route. All the compounds were administered 30 minutes prior to carrageenan injection. A mark was put on the leg at the mallaleus region to facilitate the dipping of the leg to the same level at the second and subsequent times. Acute inflammation was induced by injecting carrageenan (0.1 ml of 1% suspension in 0.5% CMC) in sub-plantar region and paw volume was measured at 0, 1, 2 and 3hours with the help of plethysmometer. The mean paw volume at different times was calculated for all groups [34-35].

Percentage reduction in edema volume was calculated by using the formula,

$$\text{Percentage reduction} = 1 - \frac{Vt}{Vc} \times 100$$

Where, V_c = Volume of the paw of control at time‘t’ and V_t = Volume of the paw of drug treated at time‘t’.

5.1.3 In vitro Antioxidant Activity

The *in vitro* antioxidant activities were carried out with FRAP models. In this method four concentrations (25, 50, 75, 100 µg/ml) of each sample and standard in DMSO were prepared and mixed (2.5 ml) with phosphate buffer (2.5 ml, 0.2 M, pH 6.6) and 1.0 % potassium ferricyanide (2.5 ml). The mixture was incubated at 50 ºC for 20 minutes. Aliquots of 10 % trichloro acetic acid (2.5 ml) were added to the mixture, centrifuged at 5000 rpm for 10 min. The upper layer of solution (2.5 ml) was mixed with distilled water (2.5 ml) and a freshly prepared ferric chloride solution (0.5 ml, 0.1 %) and allowed to stand for 30 minutes in dark to complete the reaction. The control solution was prepared as above, taking water in place of samples. The absorbance was measured at 700 nm [36]. All tests and analysis were run in triplicates and the result obtained was averaged and expressed as mean ± standard deviation.

5.1.4 Molecular Docking Studies

Molecular docking studies were performed using MOE version 2008.10 software. The 3D structure of PPARγ (PDB ID: 2PRG) was procured from protein data bank and was prepared by deletion of ligand, addition of hydrogens, polar hydrogens followed by preparation of dummies using site finder wizard. The ligands were energy minimized by selecting force field MMFF94x, Austin model 1 (AM 1) with gradient value of 0.0001 kcal/mol and were saved as mdb format. The docking simulations were predicted by docking the prepared ligands in the binding pocket of PPARγ and results were displayed in database viewer. 2D and three 3D interactions of ligands with the receptor was predicted using compute tool. The docking results were compared to the standard drug pioglitazone. The employed docking protocol was validated by calculating the RMSD value.

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Research Highlights

- The manuscript describes the simple synthetic protocol towards potent multiple-action 2,4-thiazolidinedione derivatives.
- The corroboration of the pharmacological activity with in-silico evaluation has also been reported.
- The synthesized compounds are promising dual action or even triple action drug candidates.
- Hence free radicals which are responsible for inflammation can be curbed and thus inflammation accompanied by pain can be tackled with these agents.

Graphical abstract