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Synthesis, Moleculoar Docking and Antidiabetic Studies of Some 3,5-Disubstituted Thiazolidinediones

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Novel thiazolidinedione derivatives incorporating a naphthylidene moiety were synthesized through Knoevenagel condensation reaction. The structural confirmation of the synthesized compounds was achieved through IR, mass and NMR spectral analyses. These compounds were assessed for their antidiabetic effects in alloxan-induced diabetic rats and *in vivo* antidiabetic analysis indicated that the compounds **IIg** and **IIh** exhibited significant antidiabetic activity. Molecular docking studies on the PPARγ receptor were performed to gain insights into the binding interactions of these designed compounds. The molecular docking studies identified compounds **IIg** and **IIh** as particularly effective against the PPARγ receptor. ADME properties were predicted using the QikProp module from the Schrödinger suite and all compounds complied with Lipinski's rule of five, suggesting good oral absorption. Thus, compounds **IIg** and **IIh** may further be considered as potential antidiabetic agents.

Keywords: Thiazolidinediones, Molecular docking, Naphthylidene, Antidiabetic activity, Lipinski's rule.

INTRODUCTION

Type II diabetes is an age-old disorder which is evident by elevated glucose level in the blood [1]. According to WHO, diabetes mellitus prevalence is increasing in adults above 18 years of age and around 1.5 million deaths are caused every year [2]. Diabetes mellitus leads to other secondary complications such as kidney failure, heart disorders, blindness, hyperlipidemia and many more [3]. Recently, it has been proved that the oxidative stress pivotal role in the precipitation of high levels of glucose in blood [4]. Thiazolidinediones are one of the prominent moieties indicated for the ameliorating diabetes mellitus [5]. Thiazolidinediones activate the peroxisome proliferative activated receptors (PPARγ) [6] and thus ensure glucose metabolism. PPAR receptors are nuclear receptors [7] and exist in three isomeric forms *e.g.*, PPARα, PPARβ/δ and PPARγ [8]. The PPARγ is mainly located in adipose tissue, intestinal cells and macrophages. The PPAR receptors are associated in the breakdown of glucose and lipids. Upon activation, the PPARs binds with retinoid X receptor and bind with the specific peroxisome proliferative response elements on several target genes implicated in the metabolism of carbohydrates and lipids [9].

Naphthyl derivatives, polycyclic aromatic compounds, are known for their versatile pharmacological activities [10]. Naphthyl moieties are reported to have several biological activities like anti-inflammatory [11], antihypertensive [12], antihyperlipidemic [13], antioxidant [14], antimicrobial [15] and many other properties [16], which has gathered a lot of importance in the synthetic chemistry.

All the above rationale laid the zeal for the design and synthesis of compounds with antidiabetic activity that could act as potential lead compounds for treating diabetes mellitus. Owing to the above revelations a series of novel thiazolidinediones fused with naphthyl moieties by a single-atom spacer analogous to pioglitazone by Knoevenagel condensation reaction were integrated [17,18]. The compounds were assessed for *in vivo* and *in silico* antidiabetic potential and studied the possible pharmacophoric contributions of thiazolidinedione and naphthyl units. Docking studies of 5-naphthylidene thiazolidinediones, were studied at PPARγ receptor to recognize the binding affinity of the molecules at the reactive position.

EXPERIMENTAL

Solvents and chemicals utilized in this study were obtained several commercial sources like Merck Ltd. India, Sd Fine

Chemicals Ltd., India and Sigma-Aldrich, USA. Digital melting point apparatus was used to check the melting point of the synthesized conjugates and the melting points are uncorrected. Schimadzu UV visible double spectrophotometer with UV probe 2.71 software was used to measure the absorbance. IR spectra were analyzed with Perkin-Elmer FT-IR spectrophotometer using KBr pellets method. ^{1}H and ^{13}C NMR were done on Bruker 500 MHz NMR spectrophotometer utilizing $CDCl_3$ and DMSO solvents. Mass spectra were performed on Shimadzu mass spectrophotometer (model: QP-2010 Plus (EI, 70 eV).

Synthesis of 5-[(naphthalen-2yl)methylidene)-1,3-thiazolidine-2,4-diones (II): Naphthalene-2-carbaldehyde (3.2 mmol) and 2,4-thiazolidinedione (**I**) (3.2 mmol) in a round-bottom flask were mixed in 20 mL of ethanol followed by the addition of piperidine (0.5 mL) and then heated for 19 h [19]. Upon cooling, the solid precipitate was filtered, dried and recrystallized with absolute ethanol. Yield: 75.2%, m.p.: 202-204 ºC, R_f: 0.72, FT-IR (KBr, ν_{max}, cm^{-1}): 3223 (N-H), 3034 (Ar-H), 1698 & 1730 (C=O), 1431 (C=C), 1330 (C-N), 750 (C-S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 10.96 (s, 1H, NH), 7.97 (s, 1H, HC=C), 7.6-7.42 (m, 7H, Ar.-H); Mass (ESI): *m/z* 255 $[M]^+$.

Synthesis of 3-substituted-5-[(naphthalen-2-yl)methylidene]thiazolidine-2,4-diones (IIa-i): 5-[(Naphthalen-2-yl)-methylidene)thiazolidine-2,4-dione (**II**, 0.02 mmol) and substituted alkyl/aryl chlorides (0.02 mmol) in a round-bottom flask were mixed. To this mixture, sodium hydroxide (0.02 mmol), 20 mL ethanol:water (1:1) solution were added and then heated for 18-20 h. The solid conjugate was separated out upon cooling. TLC was carried out on silica gel TLC plates using ethyl acetate and ether (4:6) [20] (**Scheme-I**). The products were purified by recrystallization by ethanol.

3-Methyl-5-[(naphthalen-2-yl) methylidene]thiazolidine-2,4-dione (IIa): Yield: 75.6%, m.p.: 214-216 ºC, R_f: 0.66, FT-IR (KBr, ν_{max}, cm^{-1}): 3010 (Ar-H), 2900 (C-H), 1730 & 1670 (C=O), 1470 (C=C), 1310 (C-N), 750 (C-S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.07 (s, 1H, =C-H), 8.01-7.57 (m, 9H, Ar-H), 3.27 (s, 3H, CH_3). ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 168.08 (C=O), 166.50 (C=O), 133-125.96 (Ar-C), 121.67 (C-S), 27.96 (CH_3). Mass (ESI): *m/z* 270.20$[M+1]^+$; Elemental analysis of $C_{15}H_{11}NO_2S$; calcd. (found) %: C, 66.89 (66.86); H, 4.12 (4.08), N, 5.20 (5.22), S: 11.90 (11.92), O: 11.88 (11.86).

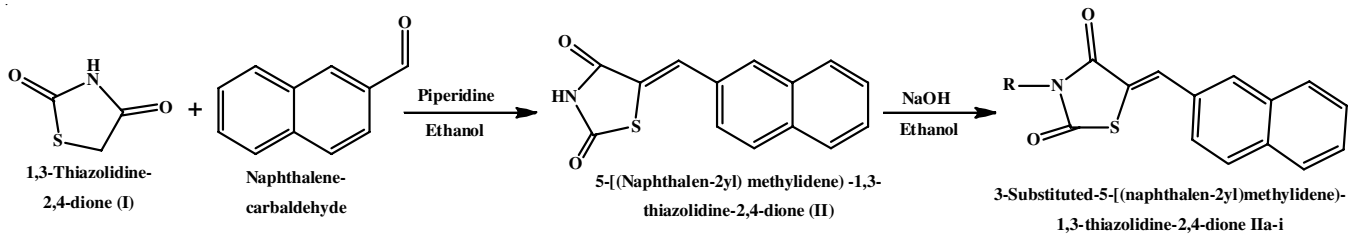
5-[(Naphthalen-2-yl)methylidene]-3-pentyl thiazolidine-2,4-dione (IIb): Yield: 68.46%, m.p.: 223-225 ºC, R_f: 0.69, FT-IR (KBr, ν_{max}, cm^{-1}): 3050 (ArH C=C), 2970 (C-H), 1730 & 1670 (C=O), 1320 (C-N), 710 (C-S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.93 (s, 1H, HC=C), 7.73-7.37 (m, 9H, Ar-H), 3.75 (t, 2H, N-CH_2), 1.67 (d, 2H, CH_2-C-N), 1.55-1.27 (m, 4H, CH_2) 0.88-0.86 (t, 3H, CH_3); ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 177.87 (C=O), 170.82 (C=O), 143.22-126 (Ar-C), 121.9 (C-S), 42.91 (CH_2-N), 29.08-22.67 (aliphatic C); Mass (ESI): *m/z* 325 $[M+1]^+$. Elemental analysis of $C_{19}H_{19}NO_2S$; calcd. (found) %: C, 70.12 (70.09); H, 5.90 (5.87); N, 4.30 (4.32); S, 9.86 (9.87); O: 9.83 (9.85).

5-[(Naphthalen-2-yl)methylidene]-3-(prop-2-yn-1-yl)-thiazolidine-2,4-dione (IIc): Yield: 71.6%, m.p.: 216-218 ºC, R_f: 0.7; FT-IR (KBr, ν_{max}, cm^{-1}): 3250 (HC≡CH), 2900 (CH_2), 1720 & 1640 (C=O), 1450 (C=C), 1330 (C-N), 750 (C-S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.11 (s, 1H, HC=C), 8.02-7.58 (m, 7H, Ar.-H), 4.54-4.53 (s, 2H, N-CH_2), 2.3 (s, 1H, HC≡). Mass (ESI): *m/z* 293.90 $[M]^+$; Elemental analysis of $C_{17}H_{11}NO_2S$; calcd. (found) %: C, 69.60 (69.56); H, 3.79 (3.77); N, 4.78 (4.80), S, 10.93 (10.91); O, 10.91 (10.89).

3-(6-Hydroxyhexyl)-5-[(naphthalen-2-yl)methylidene]-thiazolidine-2,4-dione (IId): Yield: 75.6%, m.p.: 232-234 ºC, R_f: 0.8, FT-IR (KBr, ν_{max}, cm^{-1}): 3350 (OH), 3030 (ArH C=C), 2940 (C-H), 1670 & 1630 (C=O), 1380 (C-N), 1080 (C-O), 750 (C-S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.08 (s, 1H, HC=C), 8.05-7.55 (m, 7H, Ar.-H), 3.80 (t, 2H, O-CH_2), 3.44 (t, 2H, N-CH_2), 1.92-1.39 (m, 8H, CH_2). Mass (ESI): *m/z* 356 $[M+1]^+$; Elemental analysis of $C_{20}H_{19}NSO_3$; calcd. (found) %: C, 67.95 (67.97);; H, 5.43 (5.40); N: 3.96 (3.95); S: 9.07 (9.03); O: 13.58 (13.55).

Ethyl{(5-[(naphthalen-2-yl)methylidene]-2,4-dioxo thiazolidin-3-yl}acetate (IIe): Yield: 78.2%, m.p.: 227-229 ºC, R_f: 0.8, FT-IR (KBr, ν_{max}, cm^{-1}): 2910 (C-H), 1734 & 1683 (C=O), 1637 (C=O ester), 1355 (C-N), 1190 (C=C), 1080 (C-O), 750 (C-S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.03 (s, 1H, HC=), 7.95-7.19 (m, 7H, Ar.-H), 4.43-4.22 (s, 2H, CH_2-O), 4.20-4.15 (2H, CH_2-N), 1.26-1.21 (3H, CH_3). Mass (ESI): *m/z* 342 $[M+1]^+$; Elemental analysis of $C_{18}H_{15}NSO_4$; calcd. (found) %: C, 63.32 (63.30); H, 4.44 (4.46); N, 4.10 (4.13); S, 9.39 (9.36); O: 18.75 (18.72).

3-Benzyl-5-[(2-naphthalenyl)methylidene]thiazolidine-2,4-dione (IIf): Yield: 78.2%, m.p.: 231-233 ºC, R_f: 0.72, FT-IR (KBr, ν_{max}, cm^{-1}): 3010 (ArH), 2970 (H-C), 1680 & 1630 (C=O), 1360 (C-N), 1190 (C=C), 750 (C-S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.07 (1H, HC=C), 7.99-7.26 (m, 12H, Ar-H), 4.93 (s, 2H, CH_2). Mass (ESI): *m/z* 345.10 $[M]^+$; Elemental analysis of $C_{21}H_{15}NO_2S$; calcd. (found) %: C, 73.01 (73.04); H, 4.39 (4.35); N, 4.06 (4.03); S: 9.28 (9.25); O, 9.26 (9.24).



where,	Conjugate	R	Conjugate	R	Conjugate	R
	IIa	CH_3	IId	$C_6H_{13}O$	IIg	(3,5-OCH_3)-C_6H_3-CH_2-
	IIb	C_5H_{11}	IIe	Et-O-CO-CH_2	IIh	(3-CF_3)-C_6H_4-CH_2-
	IIc	HC≡C-CH_2-	IIf	C_6H_5-CH_2-	IIi	3-NC_6H_4-CH_2-

Scheme-I: Synthesis of 3-substituted-5-[(naphthalen-2yl)-methylidene)-1,3-thiazolidine-2,4-dione

3-[(3,5-Dimethoxyphenyl)methyl]-5-[(naphthalen-2-yl)methylidene]thiazolidine-2,4-dione (IIg): Yield: 85.8%, m.p.: 243-245 ºC, R_f: 0.8, FT-IR (KBr, ν_{max}, cm^{-1}): 2940 (Ar-H), 1670 & 1600 (C=O), 1450 (C=C), 1330 (C-N), 1270 (C-O), 750 (C-S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.07 (s, 1H, CH=C), 8.00-7.56 (m, 7 H, Ar-H), 6.6 (m, 2H, HC-C-O), 6.4 (t, 1H, O-C-CH-C-O), 4.86 (s, 2H, H_2C-N), 3.79 (s, 6H, OCH_3); ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 167.77 (C=O), 166.06 (C=O), 161.01 (ArC-O), 161.01 (Ar C-O), 137.25 (C=C-CH-), 134.24-125.96 (Ar C), 121.66 (C-S), 106.69 (O-C-CH Ar), 100.29 (O-C-CH), 55.39 (C-O), 45.34 (CH_2). Mass (ESI): *m/z* 405.30 $[M]^+$; Elemental analysis of $C_{23}H_{19}NO_4S$; calcd. (found) %: C, 68.14 (68.11); H, 4.73 (4.76); N, 3.45 (3.48); S, 7.91 (7.89); O, 15.78 (15.79).

3-{[3-(Trifluoromethyl)phenyl]methyl}-5-[(naphthalen-2-yl)methylidene]thiazolidine-2,4-dione (IIh): Yield: 68.2%, m.p.: 247-249 ºC, R_f: 0.86, FT-IR (KBr, ν_{max}, cm^{-1}): 3010 (ArH), 2920 (H-C), 1730 & 1680 (C=O), 1440 (C=C), 1360 (C-N), 1190 (C-F), 750 (C-S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.08 (s, 1H, HC=C-CF), 8.00 (s, 1H, HC=C-CF), 7.97 (1H, HC=C), 7.90-7.48 (m, 9H, Ar-H), 4.97 (s, 2H, CH_2); ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 167.77 (C=O), 166.06 (C=O), 161.01 (ArC-O), 137.00-125.00 (Ar C), 123.00 (C-F), 121.66 (C-S), 44.73 (CH_2). Mass (ESI): *m/z* 415.60 $[M+2]^+$; Elemental analysis of $C_{26}H_{23}NO_4S$; calcd. (found) %: C, 70.09 (70.06); H, 5.21 (5.24); N, 3.14 (3.11); S, 7.20 (7.22); O, 14.37 (14.38).

5-[(Naphthalen-2-yl)methylidene]-3-[(pyridin-3-yl)-methyl]thiazolidine-2,4-dione (IIi): Yield: 76.9%, m.p.: 245-247 ºC, R_f: 0.8, FT-IR (KBr, ν_{max}, cm^{-1}): 3010 (ArH), 2970 (H-C), 1680 & 1630 (C=O), 1360 (C-N), 1190 (C=C), 750 (C-S); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.74 (d, 1H, HC-N), 8.58 (t, 1H, -HC-N), 8.08 (d, 1H, HC=C), 8.00-7.26 (m, 9H, Ar-H), 4.94 (s, 2H, CH_2); ^{13}C NMR (500 MHz, $CDCl_3$) δ ppm: 167.77 (C=O), 165.77 (C=O), 150.55 (C-N), 149.88 (C-N), 136.00-123.69 (Ar C), 121.1 (C=C), 42.93 (CH_2). Mass (ESI): *m/z* 347.30 $[M+1]^+$; Elemental analysis of $C_{20}H_{14}N_2O_2S$; calcd. (found) %: C, 69.32 (69.30); H, 4.08 (4.10); N, 8.09 (8.06); S, 9.26 (9.28); O, 9.23 (9.24).

Pharmacological activity

Animals: Healthy male Wistar albino rats weighing approximately 170-230 g were purchased from Prasad Vyas Lab, Hyderabad, India and housed in the animal house polypropylene cages under conventional laboratory conditions of temperature 25 ºC ± 5 ºC, 12 h/12 h and the animals were free to access feed and H_2O. The Institutional Animal Ethics Committee (IAEC) approved all the study protocols related to the antidiabetic activity evaluation constituted under the Committee for Control and Supervision of Experiments on Animals, New Delhi.01/MRIPS/CPCSEA-IAEC/Hyd/2023.

Antidiabetic activity: The animals were habituated in the laboratory for 1 week. Rats were kept without feed overnight before the induction of diabetes through alloxan. Alloxan was given once in 0.5 mL of saline at 120 mg/kg [21] and then granted to drink 5% glucose solution overnight to get-over the drug-induced hypoglycemia. After 2 days, the rats were checked for glucose levels and rats over 250 mg/dL of glucose were chosen for the activity. All the compounds were administered through i.p. route by dissolving in DMSO at 20 mg/kg of rat [22]. Rats were divided into groups of normal control, diabetic control, standard control (pioglitazone) and 5 groups administered with the synthesized compounds. Blood was obtained from the tail vein utilizing anaesthetic (ethyl ether) and, 1 h later the injection of the compounds for 0, 7, 14 and 21 days. The blood samples were analyzed using the ACCU Check glucose monitoring device.

In silico studies

Docking studies: Initial structure derived from ternary complex of PPARγ crystallized with rosiglitazone (PDB ID: 2PRG), obtained from the Protein Data Bank (PDB) [23]. Protein structure was prepared using the Schrödinger suite 2021-4 protein preparations wizard module [24]. The protein size has been minimized using the optimized potentials for simulations-3 (OPLS-3), with the RMSD of the crystallographic atom set at 0.3 Å [25].

Using the G-module (XP) of the Schrödinger suite 2021-4version docking was done using default parameters on the compounds obtained by the LigPrep module (Schrödinger suite). The best G scores exhibiting good binding mode were selected and compared with the glide score of the standard pioglitazone [26].

ADME studies: The *in silico* ADME properties were conducted for the synthesized compounds (**II**, **IIa-IIi**) by utilizing the Schrödinger suite 2021 QikProp module. The prepared conjugates were studied for their ADME properties like weight, total solvent accessible surface areas, hydrogen bond donors and acceptors, oral absorption, log P values and violations of the rule of five [27]. The evaluation of the molecular properties of any compound involves several key parameters, each with particular constraints defining its possible use as a therapeutic candidate [28,29].

RESULTS AND DISCUSSION

The strategy to synthesize disubstituted thiazolidinediones (**IIa-i**) was obtained in good yields. The FT-IR spectra revealed that the functional groups of the synthesized compounds appeared at 750, 1160, 1360, 1730 and 1680 cm^{-1}, which are attributed due to the characteristic frequency of C-S, C-N, C=O stretch respectively. The chemical shift (δ) value of methyl group was observed in the range of 2.3-4.5 ppm, δ of methylene group attached to nitrogen ranged from 4.23-4.96 ppm, the δ of aromatic protons ranges from 7.23-8.00 ppm, the δ of C of methyl group ranged from 1.39-1.92 ppm, the δ of the aliphatic carbons ranged from 22.-29.08 ppm, the δ of the aromatic carbons ranged from 123.0-143.22 ppm, the δ of C=O group of thiazolidinediones ring ranged from 166.50-177.87 ppm and the mass yield of the synthesized compounds ranged between 255-445 g. All the above data referred that the compounds were in good yields by the conventional methods.

Pharmacological evaluation: Based upon the molecular docking analysis, five compounds (**IIb**, **IId**, **IIg**, **IIh** and **IIi**) were assessed for the antidiabetic activity in rats with diabetes. Pioglitazone was used as standard and the results are displayed

TABLE-1
ANTIDIABETIC POTENTIAL OF 3,5-DISUBSTITUTED THIAZOLIDINE-2,4-DIONES IN DIABETIC RATS

Groups	0 day	7 day	14 day	21 day
Normal control	94.63 ± 2.54	96.27 ± 2.66	97.29 ± 2.08	95.23 ± 2.14
Disease control	308.24 ± 3.97	310.43 ± 4.83	301.17 ± 2.26	299.67 ± 2.87
Standard control	311.87 ± 1.73	175.36 ± 3.97**	137.68 ± 2.76**	83.33 ± 1.94**
IIb	305.84 ± 1.65	225.74 ± 1.97	154.81 ± 1.56	120.32 ± 1.78
IId	307.54 ± 1.95	236.96 ± 2.84	145.96 ± 1.87	115.64 ± 1.96
IIg	307.78 ± 2.36	185.85 ± 1.89**	141.75 ± 1.84**	85.62 ± 1.63**
Iih	307.96 ± 2.85	187.96 ± 1.63**	140.46 ± 1.79**	86.39 ± 1.65**
IIi	309.21 ± 2.96	234.78 ± 2.97	156.59 ± 2.96	112.85 ± 2.55

Antidiabetic effect at a dose of 20 mg per kg at 0th (pre-drug values), 7th, 14th and 21st day (post-drug values) for each group of test samples and analyzed with disease-control. Data calculated by one way ANOVA using graph prism pad method and is considered significant if $p < 0.05$* and $p < 0.005$**.

as mean ± standard error means in Table-1. It was revealed that all the five derivatives enhanced the glucose levels in the hyperglycemic rats and compounds **IIg** and **IIh** with dimethoxy and trifluoromethyl groups on the benzyl group decreased the blood glucose levels equipotent with the standard pioglitazone which further confirms that the existence of hydrophobic groups on the benzyl ring at the third position of thiazolidinedione ring increases the antidiabetic activity as reported in earlier works [30].

In silico studies

Molecular docking: The glide scores and binding free energies of the moieties are recorded in Table-2. The compounds showed *in silico* activity at the PPARγ receptor with the D score ranging from -5.48 to -7.80 kcal/mol. Compounds **II**, **IId** and **IIh** showed good binding interaction with a glide docking score of -7.579, -7.328 and -7.605 Kcal/mol and binding energies of -41.83, -44.47 and -48.59 Kcal/mol, respectively. Compound **IIg** showed a G score (-7.8004 kcal/mol) and a binding energy of -47.909 Kcal/mol which is almost equal to the G score of standard pioglitazone (-7.878 kcal/mol).

TABLE-2
GLID E XP GSCORE VALUES (kcal/mol) AND
PRIME MMGBSA BINDING FREE ENERGY
VALUES (kcal/mol) IN THE PRIME SITE OF PPARγ

Conjugate	Glide d score (kcal/mol)	Binding energy (kcal/mol)	Amino acids interacted
II	-7.57907	-41.8354	Gln286, Hie323
IIa	-5.48073	-34.9052	Hie 449
IIb	-6.13295	-41.4711	Hie449
IIc	-6.48587	-37.8381	Ser 289
IId	-7.32815	-44.4755	Ser342, Hie449
IIe	-6.7153	-42.898	Gln286
IIf	-5.99481	-44.4832	Ser289
IIg	-7.80049	-47.9094	Gln286, Ser342, Hie 449
IIh	-7.60594	-48.5917	Ser 342, Hie 449
IIi	-5.9397	-34.8421	Hie323
Standard	-7.87843	-50.5857	Ser342, Hie449

Fig. 1 represents the 2D interactions of **IIg** at the active site. The designed compounds interacted at the active site majorly through hydrophobic interactions with the amino acids Phe 282, Cys 285, Val 339, leu 340, Ile 341, Ile 326, Tyr327, Leu330, Leu 333. The other interactions observed were pi-pi

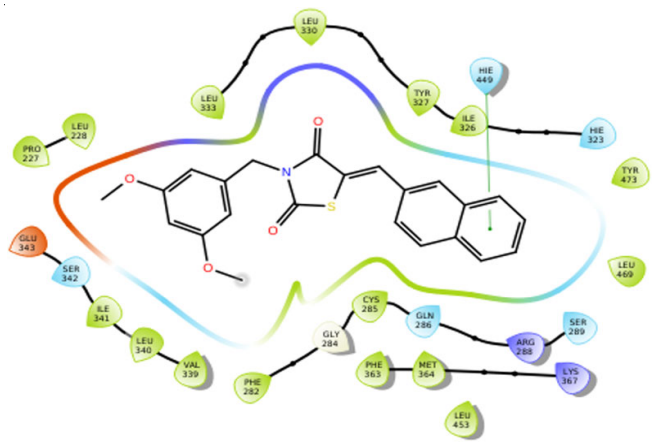


Fig. 1. 2D-Interaction of the compound **IIg** at the active site PPARγ

stacking with aminiacid Hie 449, charged positive interactions and polar interactions were observed mainly with the binding site residues: Gln 286, Arg 288, Ser 289, Hie323.Ser 342.

ADME properties: ADME properties have been determined using the QikProp Schrödinger Suite 2021 and reported in Table-3. The molecular weight of the synthesized molecules ranged from 255-413 g suggested that the compounds might show good permeability and oral absorption. The total solvent-accessible area was 453-686 indicating larger molecular sizes, the donor hydrogen bonds were less than 2 and the acceptor hydrogen bonds ranged from 3 to 5 show that the compounds can form hydrogen bonds when given through oral route. Based on the values of QPlog P and the human oral absorption, the synthesized compounds might likely get absorbed when given through oral route. All the molecules were observed to follow the Lipinski's rule of five.

Conclusion

In summary, 3-substitued-5-naphthylidene thiazolidine-2,4-diones (**IIa-i**) were synthesized, characterized and screened for the *in vivo* antidiabetic potency. The results revealed that two compounds **IIg** and **IIh** were found to be as equipotent with the standard pioglitazone. The *in vivo* studies also revealed that disubstituted thiazolidinediones exhibited significant antidiabetic activity than monosubstituted thiazolidinediones. Further, it can be understood that the presence of a hydrophobic groups like higher alkyl groups or substituted benzyl at the position 3rd of thiazolidinedione may be responsible for the

TABLE-3
QikProp ADME PROPERTIES

CPD	MWT	SASA	HB donor	HB accept	Qplog Po/w	QPlogS	Human oral absorption (%)	Rule of five
II	255.291	453.928	1.0	3.0	2.392	-3.329	90.616	0
IIa	269.317	509.790	0	3.0	3.156	-4.127	100	0
IIb	325.425	636.439	0	3.0	4.797	-5.752	100	0
IIc	293.339	555.798	0.5	3.0	3.813	-4.853	100	0
IId	355.451	671.177	1.0	4.7	4.179	-5.452	100	0
IIe	341.381	626.401	0	5.0	3.448	-4.798	96.114	0
IIf	345.415	618.767	0	3.0	4.998	-5.871	100	0
IIg	405.467	686.301	0	4.5	5.159	-6.034	100	1
IIh	413.413	669.590	0	3.0	6.014	-7.334	100	1
IIi	346.403	623.612	0	4.0	4.394	-5.461	100	0

increased binding interactions at the PPARγ receptor, which accounted for their efficient antidiabetic activity. These observations were further made evident from the molecular docking analysis at the site of the receptor. Moreover, all the synthesized compounds exhibited good oral absorption from the ADME studies.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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