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NOVEL SUBSTITUTED THIAZOLIDINEDIONE DERIVATIVES AS ANTI-DIABETIC AGENTS

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ABSTRACT

A set of novel of 5-[4-(substituted) benzylidene] thiazolidinediones were synthesized and evaluated as potential anti-diabetic agents. Thiazolidinediones scaffold- based molecules were synthesized and validated on a mice hyperglycemia model caused by dexamethasone. As a result few derivatives showed anti-hyperglycemic activities against standard drug rosiglitazone. This research provides useful clues for further design and discovery of anti-diabetic agents.

KEYWORDS: Thiazolidinediones, anti-diabetic, anti-hyperglycemic, dexamethasone, rosiglitazone.

1. INTRODUCTION

Type II diabetes is one of the most common metabolic diseases still lacking fully effective therapy and characterized by abnormalities of insulin secretion and by insulin resistance of major target tissues.[1,2]

2,4-Thiazolidinediones (2,4-TZDs) are a new class of anti-diabetic agents, differ markedly from other antidiabetic agents in that they are effective in normalizing glucose and lipid metabolism associated with insulin resistance and are therefore expected to be useful in the treatment of both type 2 diabetes mellitus and obesity.[3,4] There is a greater need to develop a safe and effective promising new approach to the treatment of diabetes.

In this study, we describe further modifications of the 2, 4-TZD derivatives containing thizolyl ring. Here in we outline the anti-diabetic activity of 5-[4-(substituted) benzylidene] thiazolidinediones. The structural evaluation of the compounds was based on the various spectral data.

2. DRUG DESIGN

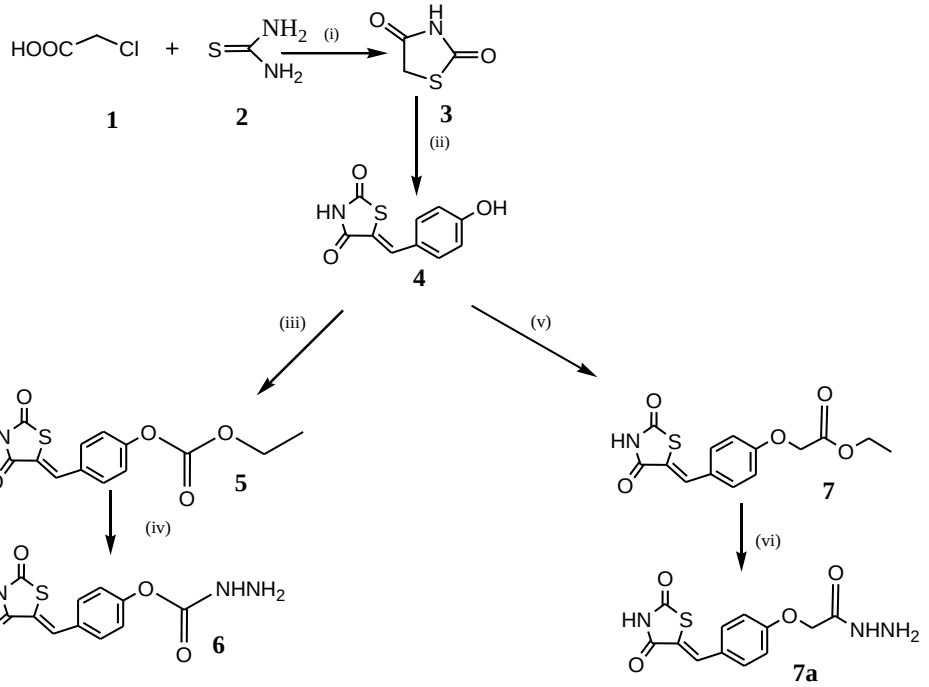
We have performed 2D QSAR on the series reported by using software V-Life MDS 3.5 in our laboratory. It gives the output as an equation containing descriptors such as alignment independent parameters and as an indicative of physicochemical properties required to show biological activity i.e., anti-hyperglycemic activity. The correlation between independent variables (descriptors) and dependent variables (pharmacological activity) was established. The out-put is in the form of regression equation showing descriptors are in the form of positive and negative contributions by using the equation as an output from the QSAR study, we have designed the following derivatives. And further their synthesis has been done followed by hypoglycemic activity using DIIR model in rats.

3. MATERIALS AND METHODS

The chemicals used in the present project work were purchased from Rankem, Merck and Spectrochem. The melting point of the synthesized compound was determined by open capillary with Thiel's melting point tube (capillary tube method). TLC plates were prepared by using Merck Silica Gel 60 GF 254. Visualization was done in UV light chamber at 254 nm, iodine chamber. The IR spectra of the synthesized compounds were recorded on a Fourier Transform Infra Red spectrometer (model Shimadzu 8400 S) in the range of 400-4000 cm^{-1} as KBr pellets. (^1H NMR) data of the compound was carried out in Bruker 200 spectrospin NMR at Astra Zeneca Pharma India Limited, Bangalore and Bruker 400 spectrospin NMR at Indian Institute of Science, Bangalore. The solvent used for NMR was $CDCl_3$.

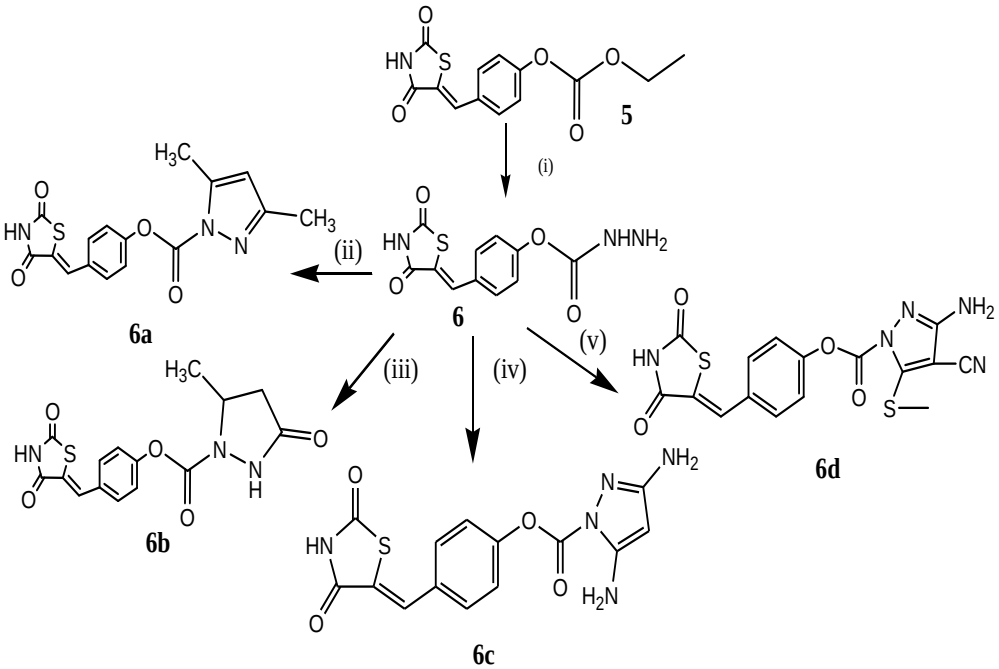
PROTOCOL OF SYNTHESIS

Scheme I



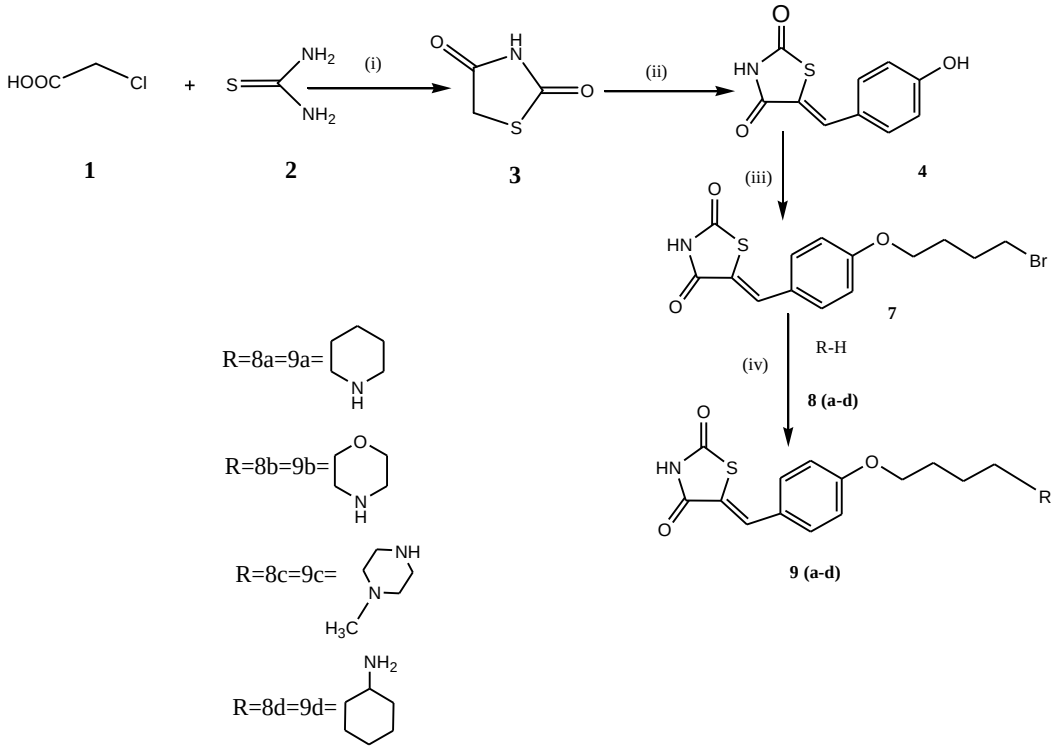
Scheme I. Reagents and conditions: (i) Conc.HCl, H_2O, reflux 10 hrs. (ii) 4-hydroxybenzaldehyde, Benzoicacid, Piperidine, Toluene, stirred at 80^0C, 16 - 20 hrs. (iii) Ethyl chloro formate, Anhydrous K_2CO_3, Dry Acetone stirred over night. (iv) Hydrazine hydrate, Ethanol, refluxed 4hrs. (v) acetylacetone, ethanol, refluxed 4h. (vi) ethylacetoacetate, ethanol reflux 10h. (vii) malanonitrile, ethanol, refluxed, 8h.(viii) 2-(bismethy sulfanyl-methylene)malanonitrile, ethanol, refluxed, 8-12h.

Scheme II



Scheme II. Reagents and conditions: (i) hydrazine hydrate, ethanol, refluxed 4h. (ii) acetylacetone, ethanol, refluxed 4h. (iii) ethylacetoacetate, ethanol reflux 10h. (iv) malanonitrile, ethanol, refluxed, 8h.(v) 2-(bismethy sulfanyl-methylene)malanonitrile, ethanol, refluxed, 8-12h.

Scheme III

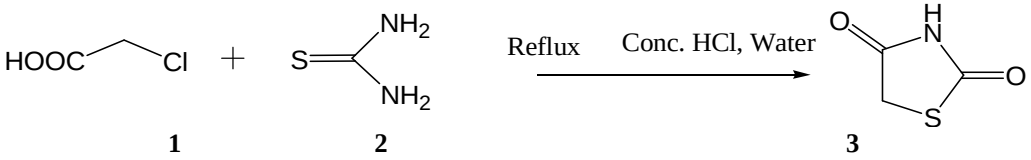


Scheme III. Reagents and conditions: (i) Conc.HCl, H_2O, reflux 10 hrs. (ii) 4 hydroxybenzaldehyde, $PhCO_2H$, Piperidine, toluene, stirred at 80^0C, 16 hrs. (iii) DMSO, NaH, stirred, 2hrs. (iv) for (8a-8d) CH_3CN, Anhydrous K_2CO_3, stirred at 0^0 for 30 min.

4. EXPERIMENTAL PROCEDURE

Scheme 1

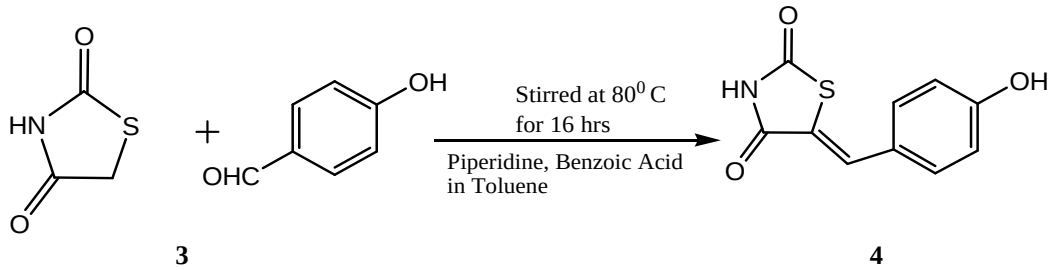
1. Preparation of thiazolidine-2, 4-dione[5]



Procedure

In a 250 ml round bottom flask place (1 g, 0.0131 mol) of Thiourea, Mono chloro acetic acid(2.046 g, 0.11 mol), (6.3 ml) of Hydrochloric acid and 5 ml of Water. The mixture was refluxed for 10 hrs and poured into 250 ml of beaker. The pH was adjusted to 7.0 by adding Sodium bicarbonate. The solution was extracted with 3×50 ml Ethyl acetate. The combined organic layer dried over anhydrous Sodium sulphate and solvent removed in vacuum to obtain the product. The yield was 0.85g, (70%) m.p-126^0C.

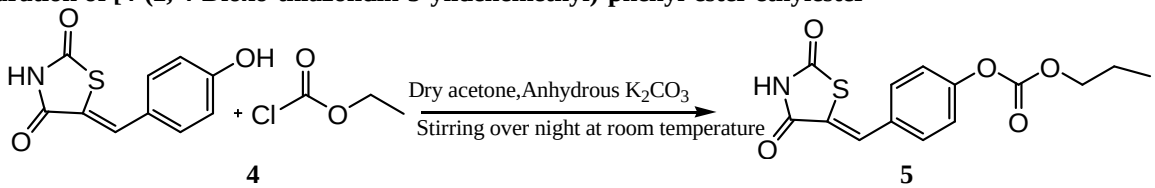
Preparation of 5-(4-hydroxybenzylidene) thiazolidine-2, 4-dione[6]



In a 100 ml round bottom flask place 4-hydroxybenzaldehyde (0.244 g, 0.002 mol), Thiazolidine-2,4-dione (0.250 g 0.002 mol), Piperidine (0.010 g, 0.00017 mol) and Benzoic acid (0.013 g, 0.0001 mol) in 5 ml of Toluene was heated to 80˚C for 16 hrs, with stirring. Cool at room temperature and filter off the yellow solid. Wash the solid with DCM (3×100 ml) and then with methanol: DCM (30:70) {2×100 ml}.

Combine the organic layers and dried in vacuum at 35 ˚C until constant weight. The completion of the reaction was checked by TLC using mobile phase 10% methanol: 90% DCM. The yield was 0.46g (94%) m.p-294^{0}C.

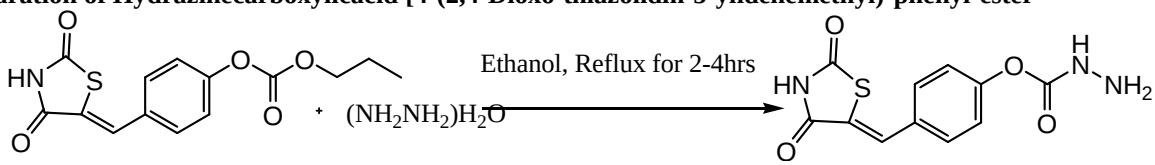
Preparation of [4-(2, 4-Dioxo-thiazolidin-5-ylidenemethyl)-phenyl-ester ethylester[7]



4 **5**

A mixture of 5-(4-hydroxybenzylidene) thiazolidine-2,4-dione (0.05 mol) and Anhydrous K_2CO_3 (0.1mol) in excess of Dry Acetone (100ml) was stirred at reflux temperature for 4h. To stirred suspension mixture of Ethylchloroformate (0.05mol) in dry Acetone was added in a drop wise manner over a period of 30 min at reflux temperature and the refluxing continued for 6h. After keeping the reaction mixture over night, the excess of solvent was removed to get the solid. The solid was re-crystallization from Acetone.

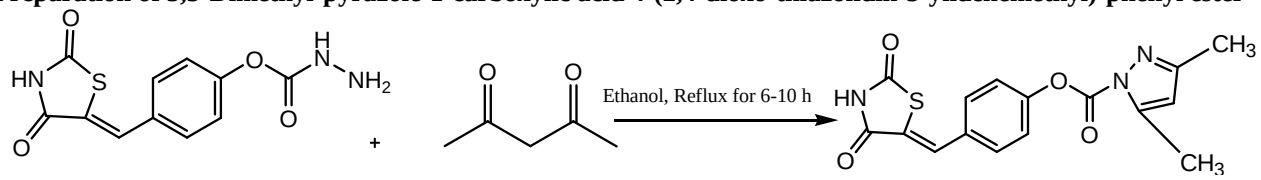
Preparation of Hydrazinecarboxylicacid [4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-phenyl-ester[8]



5 **6**

To a suspension of [4-(2, 4-Dioxo-thiazolidin-5-ylidenemethyl)-phenyl-ester ethyl ester (0.01mol) in 40 ml Ethanol 0.015 mol of Hydrazine hydrate was added and the reaction mixture was refluxed for 2h. The resulting mixture was allowed to cool and filtered. The solid obtained dried and re-crystallization with hot water.

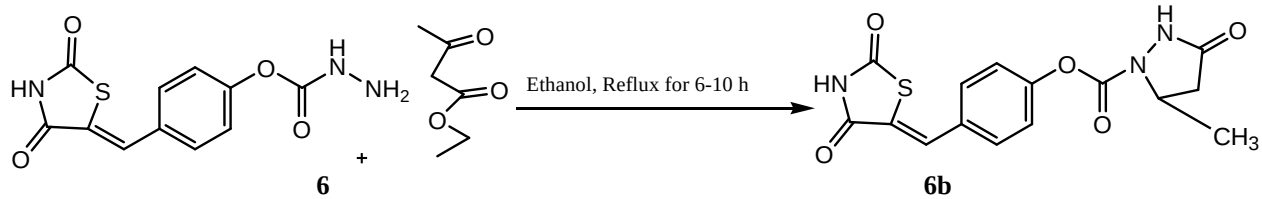
Preparation of 3,5-Dimethyl-pyrazole-1-carboxylic acid 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl ester[9]



6 **6a**

A series of novel pyrazole derivatives were synthesized by the cycloaddition of acetyl acetone with the respective hydrazine derivatives. The sequences of the reactions are done for the formation of novel pyrazole derivatives. Hydrazine derivative (0.2 mol) and acetyl acetone (0.2 mol) in ethanol (10ml) was refluxed with continous stirring for 6-10 h. The reaction was monitered by TLC after the completion of reaction mixture was cooled at room temperature and stirred for 10-15 mins, the resulting solid mass was filtered, washed with small amount of ethanol and dried. Re-crystalization using ethanol.

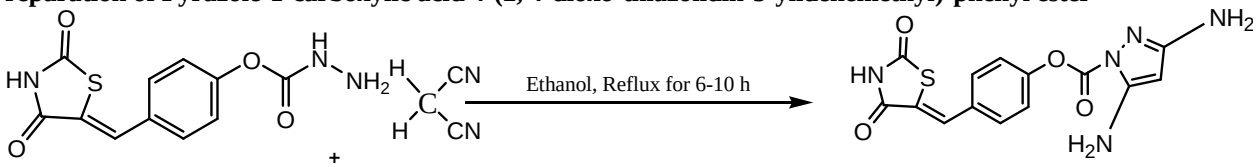
Preparation of 5-Methyl-3-oxo-pyrazolidine-1-carboxylic acid 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl ester[10]



6 **6b**

Ethyl acetoacetate (0.1mol) was taken in conical flask and hydrazinecarboxylic acid[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-phenyl-ester (0.2 mol) in ethanol (20 ml) was added dropwise to it with stirring. The temperature is raised during this addition and it was maintained at 60^{o}C when a crystalline solid separated. The reaction mixture was further stirred for 1 h at room temperature then cooled in an ice bath to complete the crystallization. Separated solid was washed with ice cold ethanol. Re-crystallization is by ethanol.

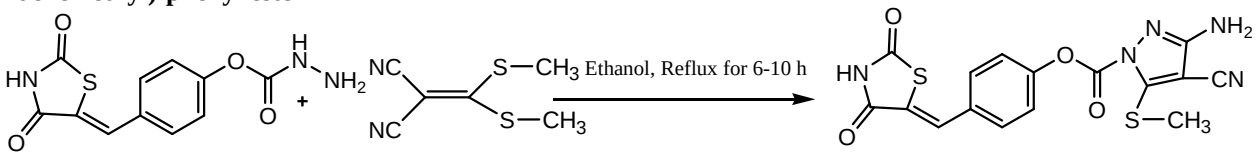
Preparation of Pyrazole-1-carboxylic acid 4-(2, 4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl ester[11]



6 **6c**

Hydrazine carboxylic acid [4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-phenyl-ester (0.01mol) and malanonitrile (0.01mol) in ethanol (10ml) was refluxed with continuous stirring. The reaction was monitered by TLC after the completion of reaction it was cooled at room temperature and stirred for 10-15 mins, the resulting solid mass was filtered, washed with small amount of ethanol and dried. Re-crystallization is by ethanol.

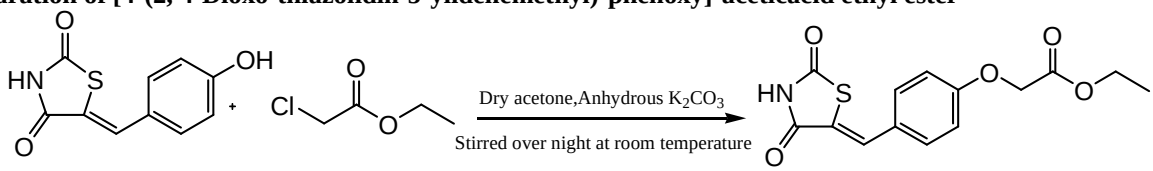
Preparation of 3-Amino-4-cyano-5-methylsulfalyl -Pyrazole-1-carboxylic acid 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl ester[11]



6 **6d**

Hydrazine carboxylic acid [4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-phenyl-ester (0.1mol) and 2-(Bismethylsulfanyl-methylene)-malanonitrile (0.1mol) placed in RBF to which added 50ml ethanol and refluxed for 6-10 h. The reaction was monitered by TLC after the completion of reaction. The reaction mixture was poured into crushed ice and the solid that separates outs in filtered. Re-crystallization is by ethanol.

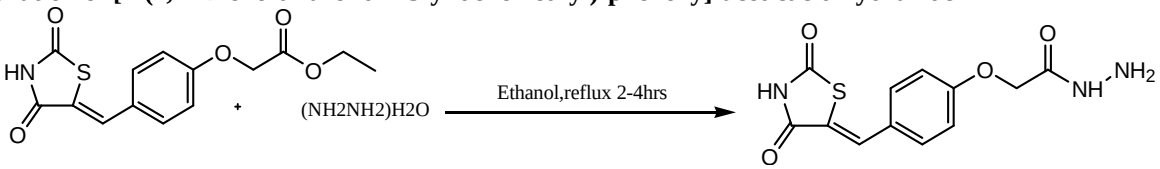
Preparation of [4-(2, 4-Dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-aceticacid ethyl ester[8]



5 **7**

A mixture of 5-(4-hydroxybenzylidene)thiazolidine-2,4-dione (0.05 mol) and anhydrous K_2CO_3 (0.1mol) in excess of dry Acetone (100ml) was stirred at reflux temperature for 4h. To stirred suspension mixture of Ethylchloroacetate (0.05mol) in dry Acetone was added in a drop wise manner over a period of 30 min at reflux temperature and the refluxing continued for 6h. After keeping the reaction mixture over night, the excess of solvent was removed to get the solid. The solid was re-crystallization from Acetone.

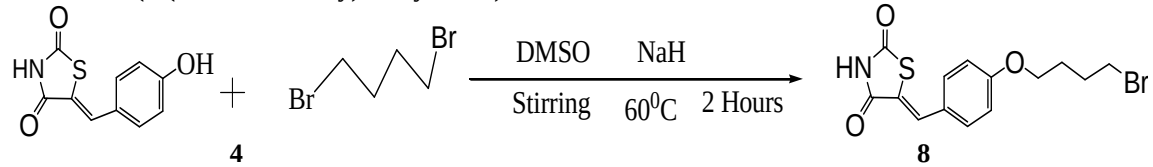
Preparation of [4-(2, 4-Dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-aceticacid hydrazide[8]



7 **7a**

To a suspension of **[**4-(2, 4-Dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-aceticacid ethyl ester (0.01mol) in 40 ml Ethanol 0.015 mol of Hydrazine hydrate was added and the reaction mixture was refluxed for 2h. The resulting mixture was allowed to cool and filtered. The solid obtained dried and re-crystallization with hot water.

Preparation of 5-(4-(4-bromobutoxy)benzylidene)thiazolidine-2,4-dione[8]



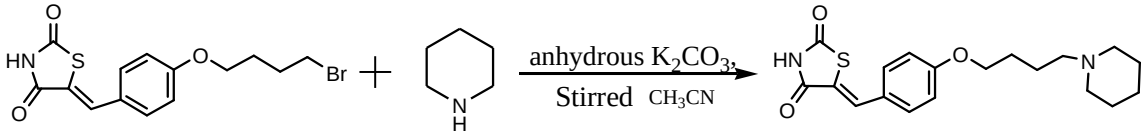
4 **8**

In a 100 ml round bottom flask placed 5-(4-hydroxybenzylidene) thiazolidine-2, 4-dione (0.3 g, 0.0013mol) in 20 ml DMSO. To this NaH (0.0645g, 0.0269mol) added. The reaction mixture was stirred at 0˚C for 30 min. and then added 1, 4-dibromobutane (0.16 ml, 0.00134mol) and further stirred for 2 hrs. At room temperature. The completion of the reaction was checked by TLC using 2:1 hexane and ethylacetate as mobile phase. The reaction mixture was poured into 100 ml water and extracted with (3×25 ml) ethylacetate. The crude mixture was purified by column chromatography using silica gel 100:200 and ethylacetate: hexane solvent system. The yield was 0.24 g, (49%) m.pt of the compound was 136˚C.

General procedure of derivative from 5-(4-(4bromobutoxy)benzylidene)thiazolidine-2,4-dione.

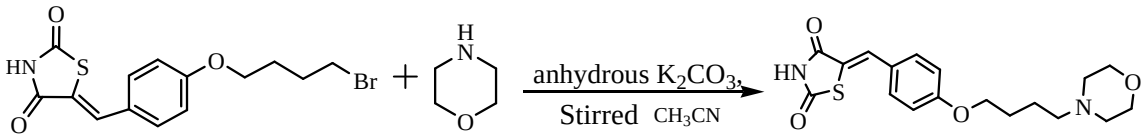
Placed 5-(4-(4-bromobutoxy)benzylidene)thiazolidine-2,4-dione (0.1g, 0.00028mol, 1 eq), acetonitrile (5 ml) and anhydrous K_2CO_3 (3 eq.) in a round bottom flask and stirred at 0˚C for 30 min. To this was added corresponding amine (1.5 eq.) and further stirred at 60˚C for 6 hrs. The acetonitrile was removed in vacuum and remaining mixture poured into 100 ml of water. The aqueous layer was extracted with (3×25 ml) ethylacetate. Combined the organic layers and washed with brine solution and dried over anhydrous sodium sulphate. The solvent removed under vacuum. The completion of the reaction was checked by TLC and mobile phase used hexane: ethylacetate: methanol (5:5:0.2).

Preparation of 5-(4-(4-(piperidin-1-yl) butoxy) benzylidene) thiazolidine-2,4dione



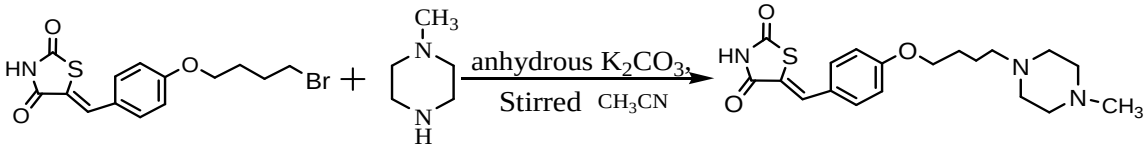
8 **8a** **9a**

Preparation of 5-(4-(4-morpholinobutoxy) benzylidene) thiazolidine-2,4-dione



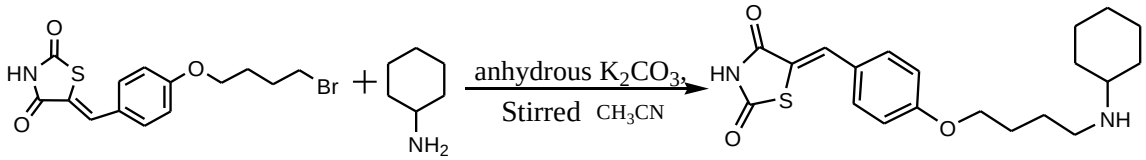
8 **8b** **9b**

Preparation of 5-{4-[4-(4-Methyl-piperazin-1-yl)-butoxy]-benzylidene}-thiazolidine-2,4-dione



8 **8c** **9c**

Preparation of 5-(4-(4-(cyclohexylamino) butoxy) benzylidene) thiazolidine-2, 4-dione



8 **8d** **9d**

***5. IN VITRO* SCREENING FOR ANTIDIABETIC ACTIVITY[12]**

Dexamethasone induced insulin resistance in rats

Exogenous administration of glucocorticoids (Ex: dexamethasone) in rats causes hyperglycemia, hyperinsulinaemia, associated with insulin resistance. Institution of Animals Ethics Committee has approved the experimental protocol (DSU/PhD/IAEC/09/2017-18).

Group I: Normal control - Received 0.25% CMC p.o and sterile water for injection i.m.

Group II: Dexamethasone control - Received 0.25% CMC p.o and Dexamethasone 0.7 mg/Kg i.m.

Group III: Rosiglitazone treated - Received Rosiglitazone 0.72 mg/Kg in 0.25% CMC p.o and Dexamethasone 0.7 mg/Kg i.m.

Group IV: IVa treated - Received **IVa**, 0.72 mg/Kg in 0.25% CMC p.o and dexamethasone 0.7 mg/Kg i.m.

Group V: IVb treated - Received **IVb**, 0.72 mg/Kg in 0.25% CMC p.o and dexamethasone 0.7 mg/Kg i.m.

Treatment was continued for 10 days. On day 10, after overnight fasting, blood samples were collected from all the animals by puncturing the retro orbital plexus under mild ketamine anesthesia.

TABLE - 1: List of compounds synthesized.

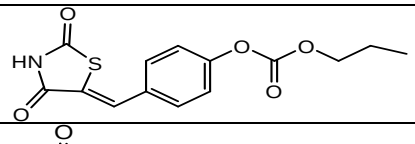
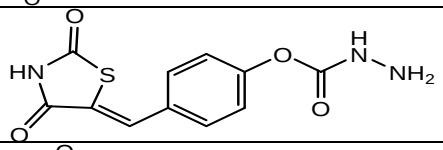
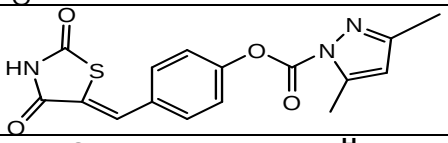
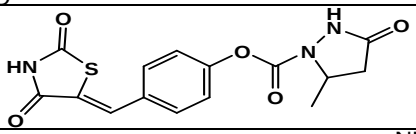
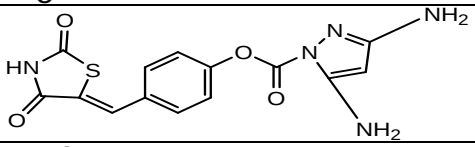
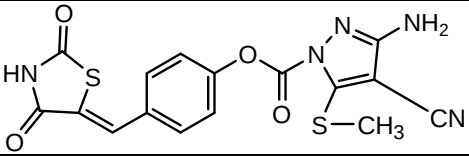
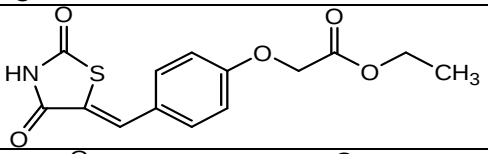
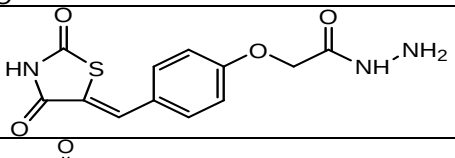
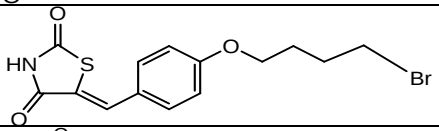
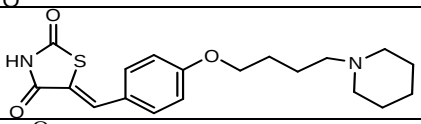
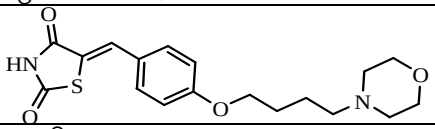
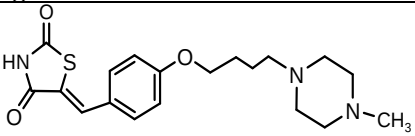
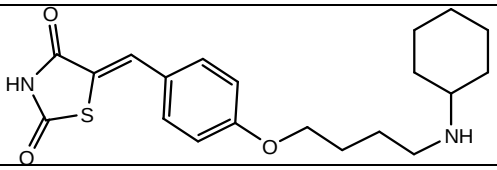
Sl. no	Comp code	Chemical Name	Structure
1	**5**	[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-phenyl-ester ethyl ester	
2	**6**	Hydrazinecarboxylic acid[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-phenyl-ester	
3	**6a**	3,5-Dimethyl-pyrazole-1-carboxylic acid 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl ester	
4	**6b**	5-Methyl-3-oxo-pyrazolidine-1-carboxylic acid 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl ester	
5	**6c**	Pyrazole-1-carboxylic acid 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl ester	
6	**6d**	3-Amino-4-cyano-5-methylsulfalyl -Pyrazole-1-carboxylic acid 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl ester	
7	**7**	[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-acetic acid ethyl ester	
8	**7a**	[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-acetic acid hydrazide	
9	**8**	5-(4-(4-bromobutoxy) Benzylidene)thiazolidine-2,4-dione	
10	**9a**	5-[4-(4-Piperidin-1-yl-butoxy)-benzylidene]-thiazolidine-2,4-dione	
11	**9b**	5-[4-(4-Morpholin-4-yl-butoxy)-benzylidene]-thiazolidine-2,4-dione	
12	**9c**	5-{4-[4-(4-Methyl-piperazin-1-yl)-butoxy]-benzylidene}-thiazolidine-2,4-dione	
13	**9d**	5-[4-(4-Cyclohexylamino-butoxy)-benzylidene]-thiazolidine-2,4-dione	

TABLE-2: Physicochemical properties of synthesized compounds.

Sl. no	C.C.*	Molecular formula	M.Wt.	% yield	State	R_f	Mobile Phase
1.	5	$C_{13}H_{11}NO_5S$	293.30	75.7 %	semisolid	0.68	n-Hex : EA 2 : 1
2.	6	$C_{11}H_9N_3O_4S$	279.27	78.5%	semisolid	0.60	n-Hex :EA 2 : 1
3.	6a	$C_{16}H_{13}N_3O_4S$	343.36	65.7%	semisolid	0.62	n-Hex : EA 2 : 1
4.	6b	$C_{15}H_{13}N_3O_5S$	347.35	76.5%	semisolid	0.60	n-Hex : EA 2 : 1
5.	6c	$C_{14}H_9N_3O_4S$	315.30	66.7 %	semisolid	0.57	n-Hex : EA 2 : 1
6.	6d	$C_{15}H_{12}N_4O_4S$	355.33	63.2%	semisolid	0.69	n-Hex : EA 2: 1
7.	7	$C_{13}H_{11}NO_5S$	293.30	75.7 %	semisolid	0.68	n-Hex : EA 2 : 1
8.	7a	$C_{11}H_9N_3O_4S$	279.27	78.5%	semisolid	0.60	n-Hex :EA 2 : 1
9.	8	$C_{14}H_{14}N_1O_3Br$	226.5	55.7 %	semisolid	0.64	n-Hex :EA 2 : 1
10.	9a	$C_{19}H_{24}N_2O_3S$	374.5	57.7 %	semisolid	0.68	n-Hex : EA : CH_3OH 5 : 5 : 0.02
11.	9b	$C_{19}H_{24}N_2O_3S$	362.13	54.6%	semisolid	0.60	n-Hex : EA : CH_3OH 5 : 5 : 0.02
12.	9c	$C_{19}H_{25}N_3O_3S$	360.15	65.7%	semisolid	0.62	n-Hex : EA : CH_3OH 5 : 5 : 0.02
13.	9d	$C_{19}H_{24}N_2O_3S$	375.15	56.5%	semisolid	0.60	n-Hex : EA : CH_3OH 5 : 5 : 0.02

C.C. * = Compound Code, n-Hex: EA = n-Hexane: Ethyl Acetate, Methanol.

TABLE - 3: spectral data of the synthesized compounds.

Comp Code	Elemental analysis	I.R. values (cm^{-1})
3	C=30.76; H= 2.58; N= 11.96; O= 27.32; S= 27.38	3470.06, (-N-H), 2915.19, 29 74.61 (C-H str.) 1776.50,1737.99 (keto C=O str.), 1522(C=C str.)
4	C=54.29; H=3.19; N= 6.33; O=21.70; S=14.49	3429.29, (-OH str.), 3236.66 (-NH str.), 1718,1703(C=O), 1680, 1664.31 (C=C str.), 1275(C-C)
5	C= 53.24; H=3.78; N= 4.78; O=27.28; S=10.93	3398.69(N-H str.), 2982.05, 2908.75(aliphatic C-H),1749.49,1732.13 (C=O str), 3020.63 (aromatic C-H str.), 1205.55,1242.20 (C-O str)
6	C= 47.31; H=3.25; N=15.05; O=22.92; S, 11.48	3290.67, 3178.79 (NH2 str), 3165.29 (NH str), 2935.36 , 2812.31 (C-H str.) 1730.21,1685.8(C=O str.), 1269.55,1174.69 (C-O str.)
6a	C= 55.97; H=3.82; N= 12.24; O= 18.64; S=9.34	3390.69, 3460.23 (N-H str), 2982.06, 2908.75 (aliphatic C-H str.), 3020.63 (aromatic C-H str.), 1749.49, 1732.13 (C=O str.), 1242.20 (C-O str.),
6b	C=51.87; H=3.77; N=12.10; O=23.03; S= 9.23	3468.13, 3398.69 (N-H str), 2982.05, (aliphatic C-H str.), 3020.63 (aromatic C-H str.), 1749.49, 1693.56 (C=O str.), 1205.55 (C-O str.)
6c	C=53.33; H= 2.88; N= 13.33; O=20.30; S= 10.17	3336.98,3166.51 (N-H str), 2980.08, 2905.85 (aliphatic C-H str.), 3020.63 (aromatic C-H str.), 1749.49, 1732.13 (C=O str.), 1242.20 (C-O str.)
6d	C= 50.70; H=2.55; N=19.71; O=18.01; S=9.02	3448.84 (N-H str), 3066.92, 3039.91 (aromatic C-H str.), 1707.06, 1610.61 (C=O str.), 763.84 (C-Hstr.).

7	C= 53.24; H=3.78; N= 4.78; O=27.28; S=10.93	3398.69(N-H str.), 2982.05, 2908.75(aliphatic C-H),1749.49,1732.13 (C=O str), 3020.63 (aromatic C-H str.), 1205.55,1242.20 (C-O str)
7a	C= 47.31; H=3.25; N=15.05; O=22.92; S, 11.48	3290.67, 3178.79 (NH2 str), 3165.29 (NH str), 2935.36, 2812.31 (C-H str.) 1730.21,1685.8(C=O str.), 1269.55,1174.69 (C-O str.)
8	C= 47.31; H=3.25; N=15.05; O=22.92; Br= 61.08	3290.67, 3178.79 (NH2 str), 3165.29 (NH str), 2935.36, 2812.31 (C-H str.) 1730.21,1685.8(C=O str.), 1269.55,1174.69 (C-O str.),550(C-Br)
9a	C= 64.14, H= 7.00, N= 7.48, O= 12.82, S= 8.56	3371.6 (N-H str.), 2956.97 (C-H str.), 1734.06, 1664.62 (C=O str.), 1503.61, 1437.02 (C=C Ar str.), 1283.31 (Ph-O-C str.)
9b	C= 60.78, H= 6.71, N= 11.19, O= 12.78, S= 8.54	3379.40 (-N-H), 2935.36, 2812.31 (C-H str.) 1730.21, 1672.36 (C=O str.), 1269.55, 1174.69 (C-O str.
9c	C= 63.31, H= 6.71, N= 7.77, O= 13.32, S= 8.90	3390.69 (N-H str.), 2982.06, 2908.75 (aliphatic C-H str.), 3020.63 (aromatic C-H str.), 1749.49, 1732.13 (C=O str.), 1242.20 (C-O str.)
9d	C= 59.65, H= 6.12, N= 7.73, O= 17.66, S= 8.85	3468.13, 3398.69 (N-H str.), 2982.05, (aliphatic C-H str.), 3020.63 (aromatic C-H str.), 1749.49, 1693.56 (C=O str.), 1205.55 (C-O str.)

Sl.no	Compound code	NMR In(DMSO-d6) (δ) value in ppm from TMS
1	**3**	4.130 (s, 2H,-S-CH_2-C=O) 11.98(1s, 1H, -NH-).
2	**4**	6.89-6.949 (d, 2H, Ar-H at 2, 6, J=8.6H_3), 7.44-7.48 (d, 2H, Ar at 3,5, J=8.6 H_3)7.70 (s, 1H, vinylic-H), 10.31 (s, 1H, Ar-OH), 12.46 (s,1H,NH).

TABLE-4: Effect of derivatives on blood glucose levels (mg/dl) in dexamethasone induced insulin resistance model in rats.

GROUPS ⟶	GROUP 1 NORMAL CONTROL	GROUP 2 DEXA CONTROL	GROUP 3 DEXA + Rosiglitazone	GROUP4 DEXA + 9b	GROUP5 DEXA + 9d
Serum glucose (mg/dl) MEAN ± SEM ⟶	86.08 ± 3.164	261.1 ± 6.298 ^{a***}	111.5 ± 3.123^{b***}	100.47 ± 1.495^{b***}	111.9 ± 1.630^{b***}

Values are expressed as mean ± S.E.M., n = 6, DEXA = dexamethasone 0.7 mg/kg, i.m.
Rosiglitazone = Rosiglitazone 0.36 mg/kg, p.o., twice a day,
IVa = **IVa** 0.36 mg/kg, p.o., twice a day,
IVb = **IVb** 0.36 mg/kg, p.o., twice a day,
^{a} when compared with normal control; ^{b} when compared with dexamethasone control.
***p<0.001 highly significant;

6. RESULT AND DISCUSSION

The structure of new compounds prepared during present investigation has been authentically established by their UV, IR and ^{1}H NMR. In following reaction the spectral studies of some selected compounds have been dealt.

The synthesis of scaffold TZD (**3**) was done by refluxing Thiourea, monochloroaceticacid and Con HCl. It was proved by comparing observed m.p with literature m.p. IR show prominent carbonyl stretching at 1775.50 cm^{-1}, 1739.99 cm^{-1}. Further proof was obtained from ^{1}H NMR spectra, which clearly shows two singlets at 4.31 and 11.98 indicating the presence of –CH_2 and –NH. Further substitution reaction with 4-hydroxybenzaldehyde leads to 5-(4-hydroxybenzylidene) thiazolidinediones. The formation of compounds were confirmed by visualizing agents (2,4 DNP, Phosphomolybdicacid) and IR , which shows vinylic –CH stretching at 1664.31 cm-1 and 1562.91 cm-1. The phenolic benzylidene intermediate was subjected to reaction with Ethylchloroformate and Ethylchloroacetate, Anhydrous K_2CO_3, Dry acetone with guard tube to obtain esters **5**. The IR spectrum showed at 1442 cm^{-1} due to CH_3 str, 1654 cm^{-1} due to C=O str (carbonyl) as shown in **scheme I**. This was then made to react with Hydrazine hydrate using ethanol as solvent to get respective hydrazino derivatives **6**.

The IR spectrum showed at 3290.67, 3178.79 (NH2 st), 3165.29 (NH st). These compounds were treated with different diketones Acetylacetone, ethylacetoacetate. Ethanol used as solvent to obtain compounds **6a-d** as described in **scheme II**. The product formed by cyclo-addition reaction determined from TLC by comparing R_f values of starting material and by IR and NMR data. The

IR spectrum of **6b** showed at 3020.63 (aromatic C-H 3390.69, 3460.23 (N-H st), which showed the peaks at 5.84 indicating the presence of 1-pyrazole. The IR spectrum of **5c** showed 693.56 cm^{-1}(C=O str.), 1205.55 cm^{-1}(C-O str.), 3468.13 cm^{-1}, 3398.69 cm^{-1} (N-H st), indicating presence of pyrazolidine.

The IR spectrum showed at 3290.67 cm^{-1}, 3178.79 cm^{-1} (NH_2 str), 3165.29 cm^{-1} (NH str). The phenolic benzylidene intermediate was subjected to reactions to obtain products **9a- d** as described in scheme **III**.

The other derivatives have been identified by similar manner. In chemexper data + sign indicate favourable drug and – sign indicate unfavorable drug and mole-inspiration shows vice-versa. Physical and spectroscopical data described in **Table 1-3**. The anti-diabetic activity of 5-[4-(substituted) benzylidene] thiazolidinediones against dexamethasone induced diabetes. The 5-[4-(substituted) benzylidene] derivatives were generally more active than the analogous thiazolidinediones. It has been seen that rosiglitazone showed a decrease in BGL in 30 min. while **9b** and **9d** shows a sudden decrease in BGL within a span of 30 min, and then a constant decrease appeared. While remaining showed a decrease in first 30 min, but after that they fail to show a decrease in the blood glucose level (BGL) and a further increase in BGL has been observed.

7. CONCLUSION

By using 2D QSAR, the physicochemical properties required for hypoglycemic activity have been used to synthesize new derivatives. The hypoglycemic activities of 5-[4-(substituted) benzylidene] thiazolidinediones were evaluated by the DIIR model. The amine derivatives have shown nearly equal hypoglycemic activities comparable with the standard used Rosiglitazone.

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