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Use of Heterogeneous Catalyst in Synthesis of Bioactive Thiazolidinedione (TZD) Derivatives for Antidiabetic Action

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Keywords: antidiabetic, thiazolidinedione, diabetes mellitus, characterization

ABSTRACT

Background: Diabetes is one of the growing health problems worldwide, and scientists have been striving to find effective treatment methods. In this regard, thiazolidinedione has frequently been targeted by many researchers owing to its diverse biological activities. **Methods:** Here, the condensation reaction with 1-naphthyl thiourea with 2-chloroacetic acid was applied to synthesize thiazolidinedione derivatives. Morpholine was used as a heterogenous catalyst used in the preparation of TZD derivatives. The thiazolidinedione derivatives were characterized and evaluated for in-vitro antidiabetic action. Structures of the newly synthesized compounds were found to be by their elemental analyses and spectral data. All the synthesized compounds were checked for their in vitro α-amylase and α-glucosidase inhibitory activities. **Results:** Based on the elemental analysis and spectral analysis, the synthesized compounds were further evaluated for in vitro antidiabetic activity. The synthesized compounds were 5-[(4-bromophenyl)methyl]-3-(naphthalen-1-yl)-1,3-thiazolidine-2,4-dione (2e),5-[(2,4-dichlorophenyl)methyl]-3-(naphthalen-1-yl)-1,3-thiazolidine-2,4-dione (2f), and (5-[(2-fluorophenyl)methyl]-3-(naphthalen-1-yl)-1,3-thiazolidine-2,4-dione (2h). Compound 2h showed the highest inhibitory activity for alpha amylase causing 61% at 125 µg/ml. **Conclusion:** The thiazolidinedione derivatives considered in this study could be used as potential lead compounds in the discovery of effective drugs to treat diabetes mellitus.

1. INTRODUCTION:

Diabetes mellitus is a metabolic disorder with various etiologies. The disease is marked by chronic hyperglycemia, which is associated with the disturbances of carbohydrate, protein and fat metabolism arising from defects in insulin secretion, action, or both. (1) The global diabetes prevalence has been steadily increasing over the past three decades. (2) According to the recent estimation by the International Diabetes Federation (IDF), there were 451 million people with diabetes mellitus in 2017 worldwide and traumatically, this number is expected to rise to 693 million by 2045. (3) Being a global concern, several pharmacological and non-pharmacological diabetes treatment methods have been reported by different studies. In line with this, some drugs are already approved and commercially available, while some are under clinical trial. (4, 5) In this aspect, chalcones and their derivatives are considered one of the promising future antidiabetic drugs and have been targeted by many researchers. (6, 7)

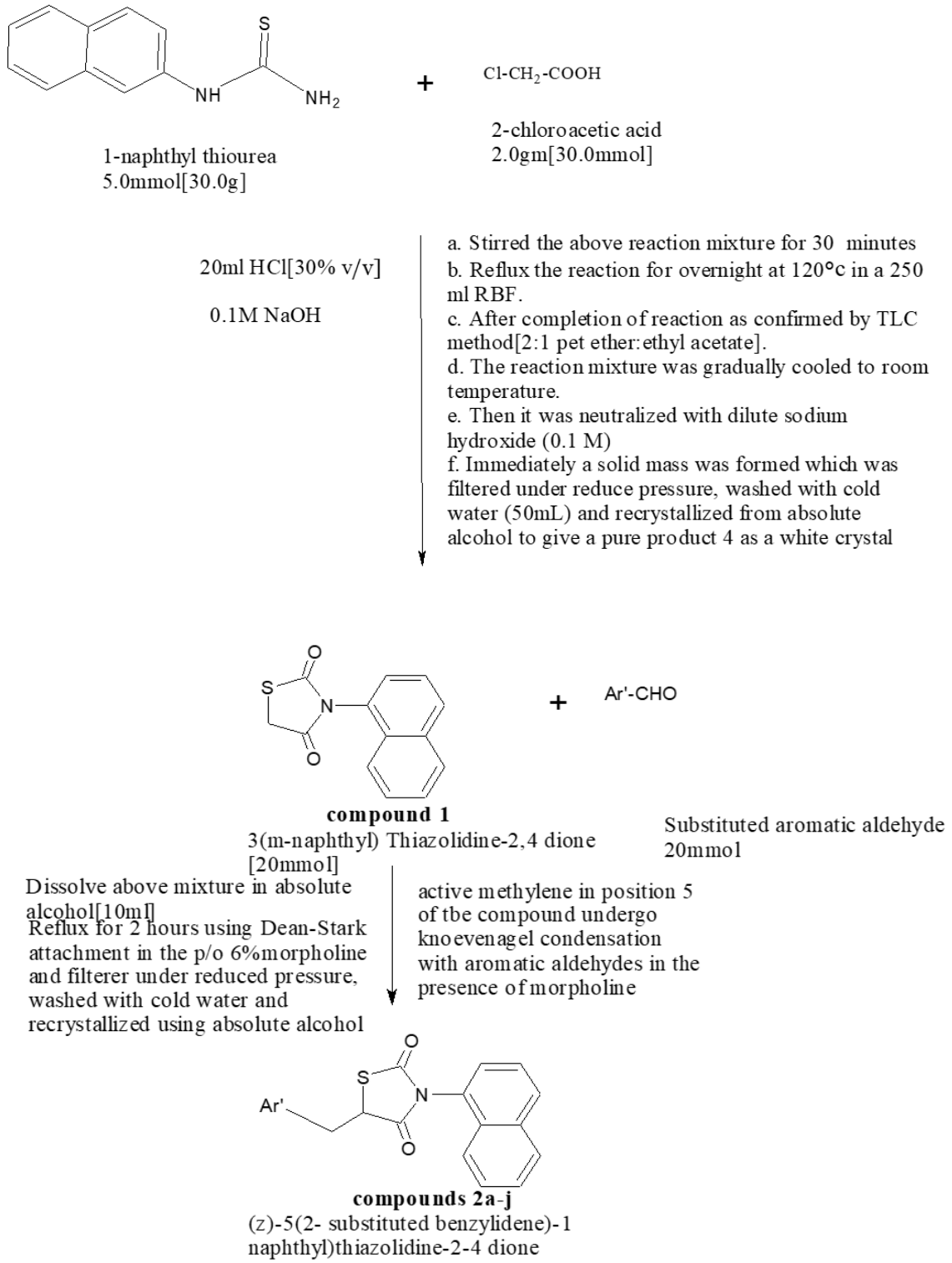
One such five-membered ring heterocycle is a thiazole (1), its non-aromatic analog being thiazolidine (2). When 2 is decorated further with two carbonyl groups at positions 2 and 4, the ring system is termed 2,4-thiazolidinedione (3) (TZD), which is the focus of this review (Figure 1). TZD exists as a white crystalline solid with a melting point of 123–125°C and is bench stable when kept below 30°C. [8] In terms of solubility, TZD is only sparingly soluble in a variety of common organic solvents including water, MeOH, EtOH, DMSO and Et2O.[9] Previous studies have documented that thiazolidinedione derivatives show various biological activities including anti-inflammatory, anti-bacterial, anti-gout, anti-malarial, antioxidant, hypolipidemic, anti-neoplastic, and other related activities. [10-15] In particular, studies on the in-vitro antidiabetic activities of synthetic thiazolidinedione derivative showed promising antidiabetic activities on different concentrations.

2. EXPERIMENTAL:

Chemicals:

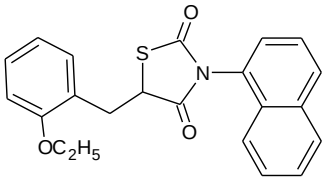
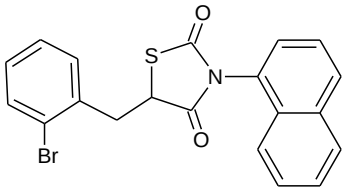
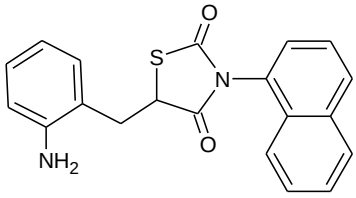
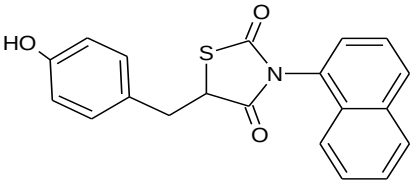
All chemicals and reagents used in this research were obtained from commercial suppliers and were of analytical grade. TLC analysis was performed on a Silica-gel pre- coated plate (Merck, Germany). Silica gel packed (100– 200 mesh size) column chromatography was used for the isolation and purification of the synthesized compounds. IR was recorded on FT-IR spectrometer (SHIMADZU, Japan). 1H NMR, 13C NMR and Mass spectra were recorded on Bruker 400 MHz and 100 MHz spectrometers (Bruker, Germany). Melting points were

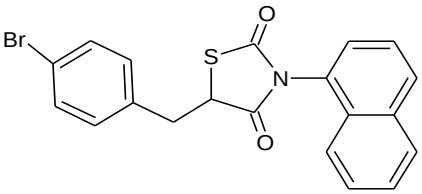
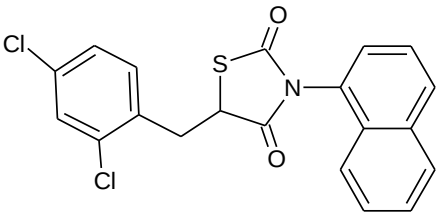
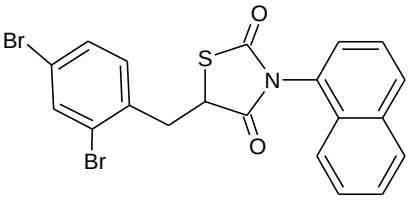
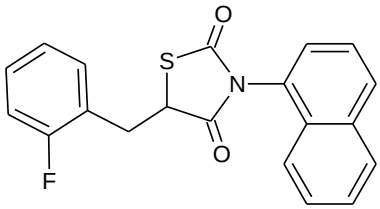
determined using the Stuart melting point apparatus (SMP3, VENDOR) and were uncorrected.

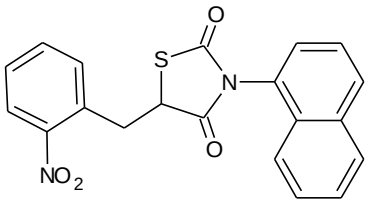
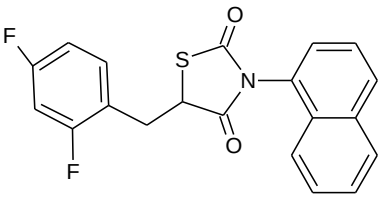


Scheme 1: Synthesis of thiazolidinedione derivatives

Table 1: IUPAC names and structure of synthesized compounds

Derivatives	**Ar'(Substituted benzaldehyde)**	**Chemical name of Compound & Structure**
2a	2-ethoxy benzaldehyde	 5-[(2-ethoxyphenyl)methyl]-3-(naphthalen-1-yl)-1,3-thiazolidine-2,4-dione
2b	2-Bromo benzaldehyde	 5-[(2-bromophenyl)methyl]-3-(naphthalen-1-yl)-1,3-thiazolidine-2,4-dione
2c	2-Amino benzaldehyde	 5-[(2-aminophenyl)methyl]-3-(naphthalen-1-yl)-1,3-thiazolidine-2,4-dione
2d	4-Hydroxy benzaldehyde	

		5-[(4-hydroxyphenyl)methyl]-3-(naphthalen-1-yl)-1,3-thiazolidine-2,4-dione
2e	4-Bromo benzaldehyde	 5-[(4-bromophenyl)methyl]-3-(naphthalen-1-yl)-1,3-thiazolidine-2,4-dione
2f	2,4 dichloro benzaldehyde	 5-[(2,4-dichlorophenyl)methyl]-3-(naphthalen-1-yl)-1,3-thiazolidine-2,4-dione
2g	2,4 dibromo benzaldehyde	 5-[(2,4-dibromophenyl)methyl]-3-(naphthalen-1-yl)-1,3-thiazolidine-2,4-dione
2h	2-Fluoro benzaldehyde	

		5-[(2-fluorophenyl)methyl]-3-(naphthalen-1-yl)-1,3-thiazolidine-2,4-dione
2i	2-nitro benzaldehyde	 3-(naphthalen-1-yl)-5-[(2-nitrophenyl)methyl]-1,3-thiazolidine-2,4-dione
2j	2,4 difluoro benzaldehyde	 5-[(2,4-difluorophenyl)methyl]-3-(naphthalen-1-yl)-1,3-thiazolidine-2,4-dione

In-vitro antidiabetic activity: Synthesized compounds of TZD used in in vitro studies were prepared by using suitable solvents (Carboxy methyl cellulose). A total of 500 µl of test samples and standard drug (100-1000µg/ml) were added to 500 µl of 0.20 mM phosphate buffer (pH 6.9) containing α-amylase (0.5mg/ml) solution and were incubated at 25°C for 10 min. After these, 500 µl of a 1% starch solution in 0.02 M sodium phosphate buffer (pH 6.9) was added to each tube. The reaction mixtures were then incubated at 25°C for 10 min. The reaction was stopped with 1.0 ml of 3, 5 dinitro salicylic acid color reagent. The test tubes were then incubated in a boiling water bath for 5 min, and cooled to room temperature. The reaction mixture was then diluted after adding 10 ml distilled water and absorbance was measured at 540 nm. Control represents 100% enzyme activity and were conducted similarly by replacing extract with the vehicle. The synthesized sulfonylurea derivatives showed

significant activity (60%, 60%, and 61%) against α-amylase enzyme at different concentrations. The results of the experiment are summarized in Table 1.

RESULTS AND OBSERVATION:

Table 2: Chemical Properties of Synthesized Compounds (2a-2j)

Derivatives	Chemical For.	M.W	Composition								M.P.(°C)
			C	H	N	O	S	Br	Cl	F	
2a	$C_{22}H_{19}NO_3S$	377.45	70.0 %	5.07%	3.71%	12.72	8.50	--	--	--	122°C
2b	$C_{20}H_{14}BrNO_2S$	412.30	58.26 %	3.42%	3.40%	7.76%	7.78	19.38	--	--	126°C
2c	$C_{20}H_{16}N_2O_2S$	348.41	68.94 %	4.63%	8.04%	9.18%	9.20%	--	--		123°C
2d	$C_{20}H_{15}NO_3S$	349.40	68.75 %	4.33%	4.01%	13.74%	9.18%	---	--	---	128°C
2e	$C_{20}H_{14}BrNO_2S$	412.30	58.26 %	3.42%	3.40%	7.76%	7.78%	19.38 %	---	--	125°C
2f	$C_{20}H_{13}Cl_2NO_2S$	402.29	59.71 %	3.26%	3.48%	7.95%	7.97%	----	17.63 %	---	129°C
2g	$C_{20}H_{13}Br_2NO_2S$	419.19	4.89 %	2.67%	2.85%	6.51%	6.53%	32.53 %	---	---	118°C
2h	$C_{20}H_{14}FNO_2S$	351.39	68.36 %	4.02%	3.99%	9.11%	9.13%	--	---	5.41 %	121°C
2i	$C_{20}H_{14}N_2O_4S$	378.40	69.48 %	3.73%	7.40%	16.91%	8.47%	---`	---	---	128°C
2j	$C_{20}H_{13}F_2NO_2S$	369.38	65.03 %	3.55%	3.79%	8.66%	8.68%	---	----	10.29 %	124°C

Table 3: Physical and chemical properties of synthesized compound (2a-2j)

Code	Chemical Formula	Color	Rf value	% yield
2a	$C_{22}H_{19}NO_3S$	Pale yellow solid	0.58	59.35%
2b	$C_{20}H_{14}BrNO_2S$	Light yellow solid	0.60	62.0%
2c	$C_{20}H_{16}N_2O_2S$	Light brown solid	0.54	56.0%
2d	$C_{20}H_{15}NO_3S$	Yellow colour solid	0.66	48.0%
2e	$C_{20}H_{14}BrNO_2S$	Brown solid	0.60	61.0%
2f	$C_{20}H_{13}Cl_2NO_2S$	Light yellow solid	0.50	70.0%
2g	$C_{20}H_{13}Br_2NO_2S$	Dark yellow	0.69	58.0%
2h	$C_{20}H_{14}FNO_2S$	Pale yellow	0.66	72.0%
2i	$C_{20}H_{14}N_2O_4S$	Dark yellow solid	0.70	65.0%
2j	$C_{20}H_{13}F_2NO_2S$	Light yellow solid	0.59	69.0%

IR Spectral data of Compound 2e:

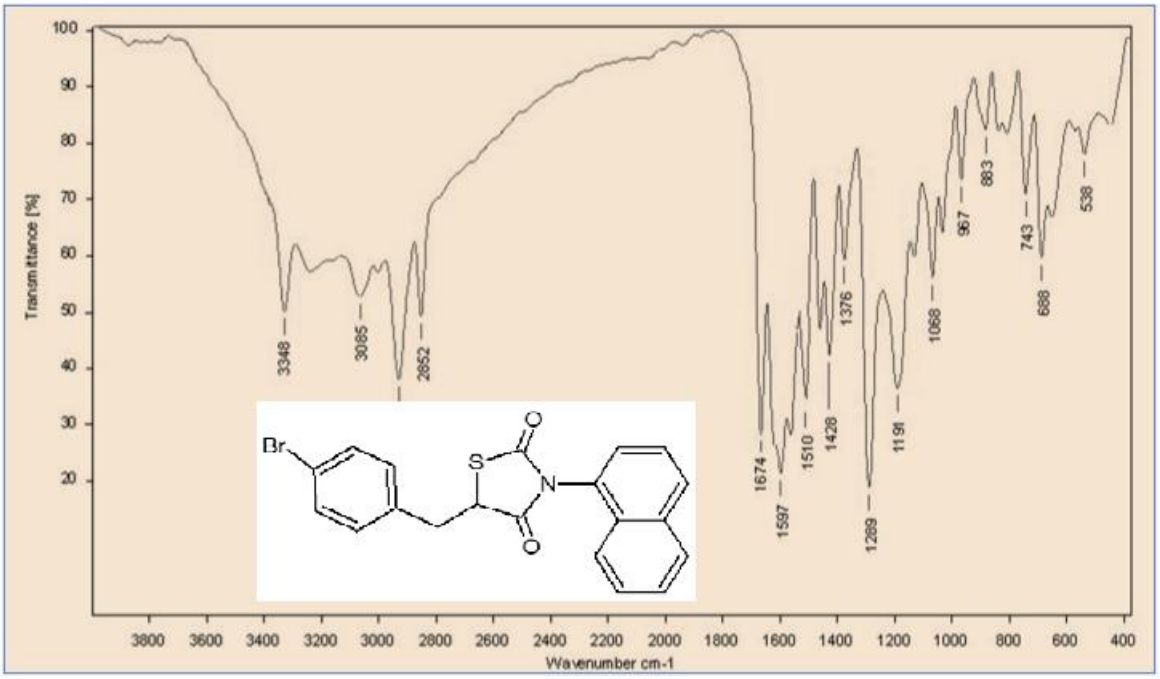


Figure 2: FTIR Spectra of Compound 2e

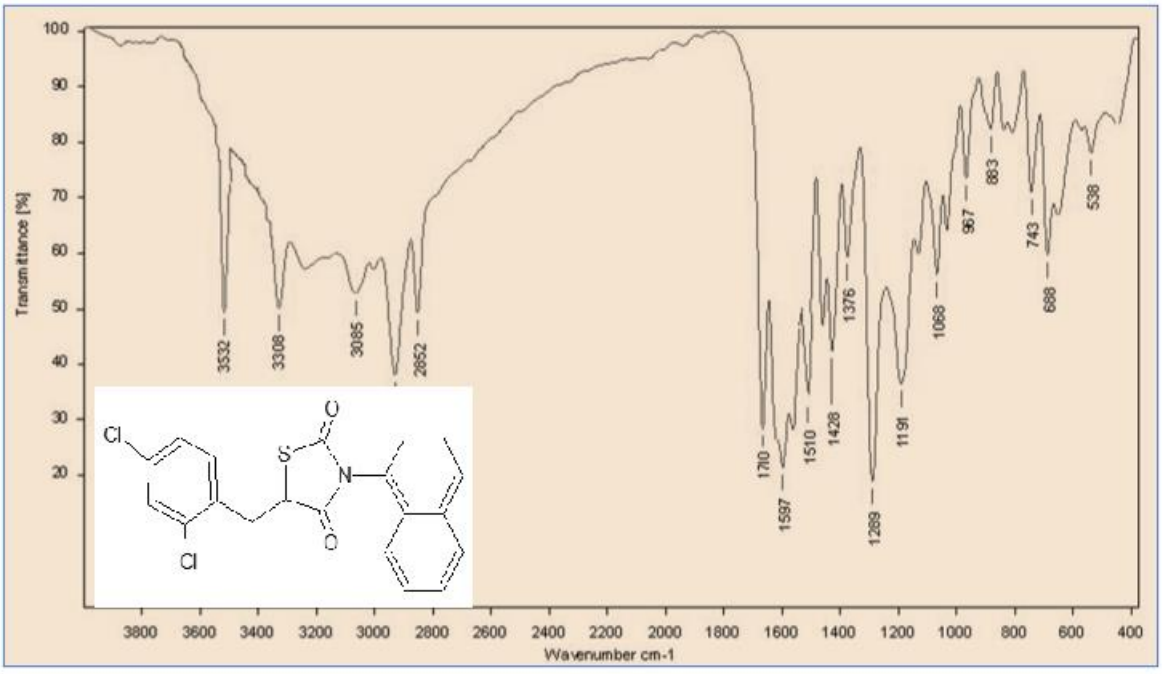


Figure 3: FTIR Spectra of Compound 2f

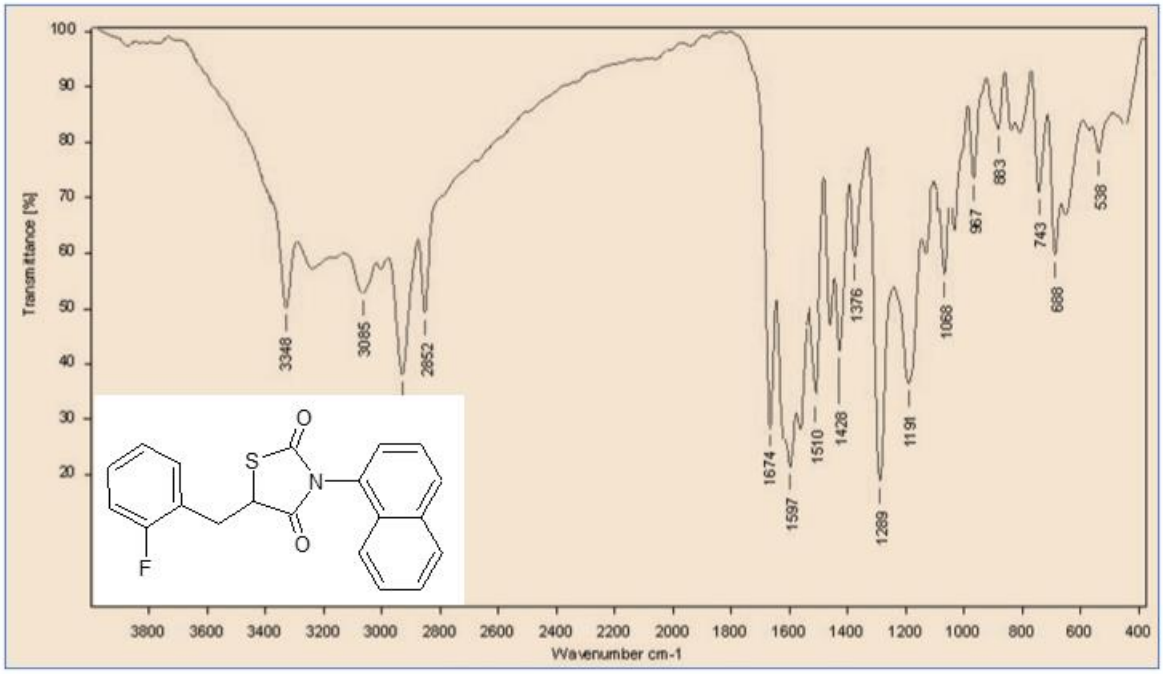


Figure 4: FTIR Spectra of Compound 2h

NMR SPECTRAL DATA

Figure 5: 1H-NMR Spectra of Compound 2e

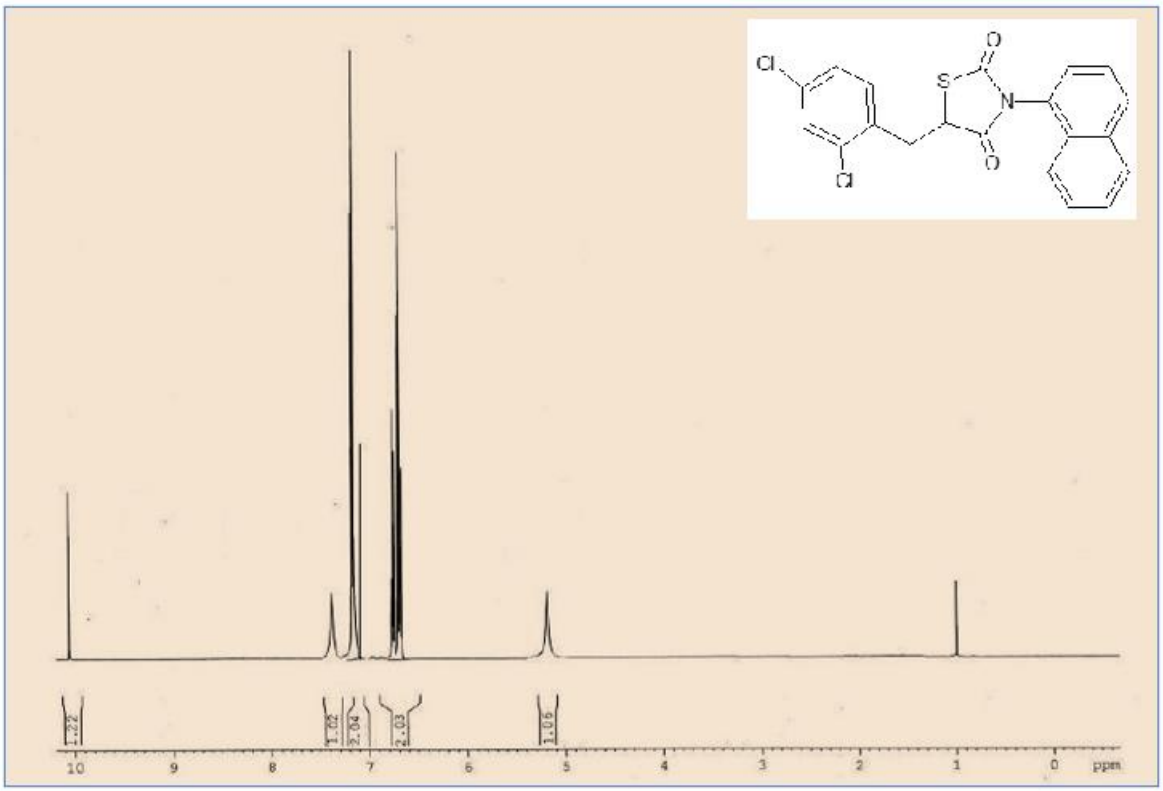


Figure 6: 1H-NMR Spectra of Compound 2f

Figure 7: 1H-NMR Spectra of Compound 2h

MASS SPECTRAL DATA

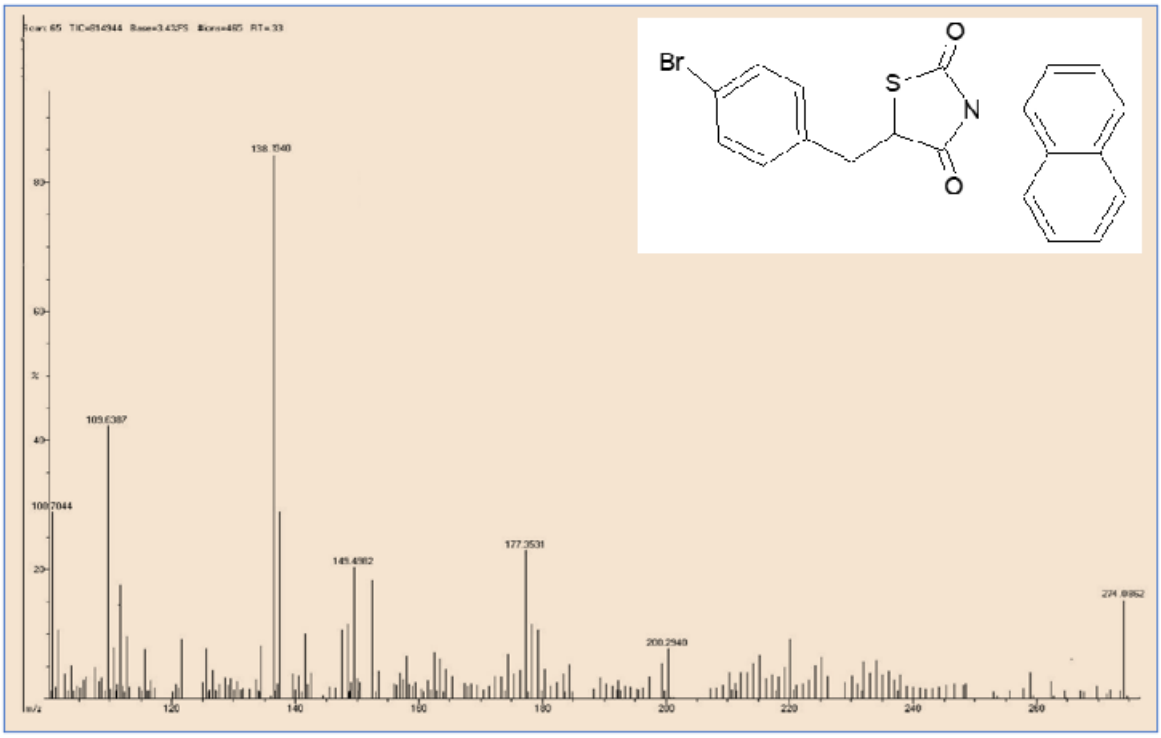


Figure 8: 1H-NMR Spectra of Compound 2e

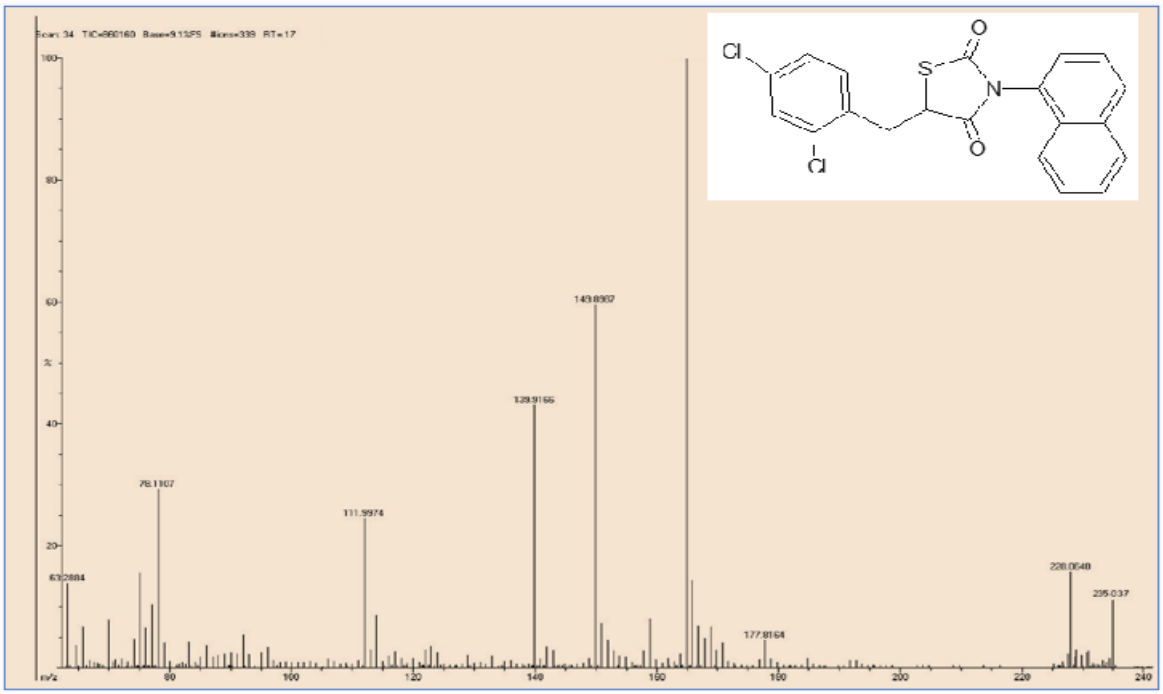


Figure 9: MASS Spectra of Compound 2f

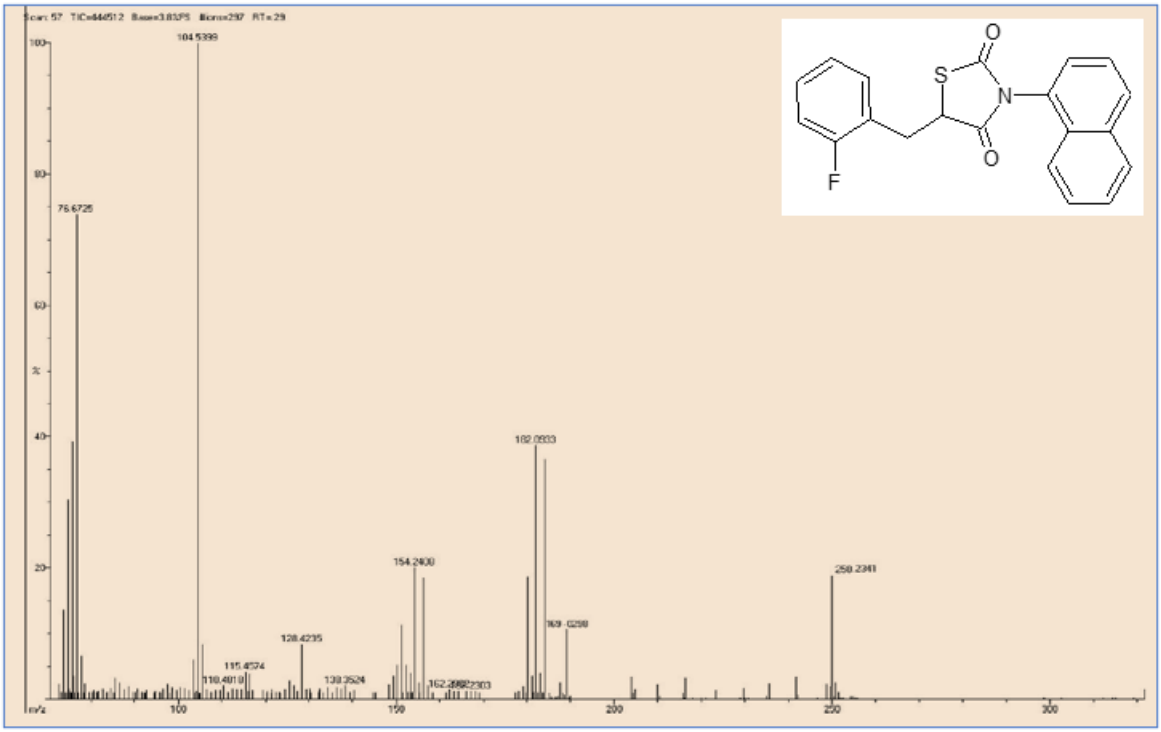


Figure 10: MASS Spectra of Compound 2h

Table 4: α-Amylase Inhibition of Synthesized Compound of TZD

Concentration (µg/ml)	IC_{50} %						
	2b	**2c**	**2e**	**2f**	**2h**	**2i**	**2j**
0	0	0	0	0	0	0	0
25	23	26	24	28	29	25	25
50	30	31	33	35	36	31	32
75	41	42	45	46	47	44	43
100	52	53	55	56	56	53	53
125	58	59	60	60	61	57	58

DISCUSSION AND CONCLUSION:

In summary, a new series of 4-substituted benzylidene thiazolidinedione derivatives were synthesized. These title compounds containing seven different substituents at C-5 were screened for their invitro anti-diabetic activity. Most of the test compounds were found to exhibit significant anti-diabetic activity. Among the substituents at C-5, 4-dimethylaminocinnamoyl phenyl substituent showed maximum potency, while 2-hydroxy phenyl substituent showed equipotent activity but the 4-dimethylamino) phenyl,4-methoxyphenyl and but-2- enylidene substituents exhibited least activity when compare to other substituents.

Synthetic route depicted in scheme outline the chemistry part of the present work. The 4-(4-substituted) benzylidene) thiazolidine-2,4-diones (2a-2j) were obtained by the catalyst morpholine of thiazolidine-2,4-diones with substituted aldehydes in the presence of alcohol. The formations of the thiazolidine-2, 4-diones were confirmed by the presence of characteristic peaks in the IR spectra. It showed characteristic peaks around 3380 cm-1 for NH stretching, peaks around 3085 cm-1 for CH_3 stretching, peak around 1700 cm-1 due to the presence of C=O stretching and peak at around 688 cm-1for C-S-C groups. The NMR spectra of the compounds 2a-2j showed the characteristic peak at around δ 2.80 ppm for CH3 group, δ 3.00 ppm for CH_2 and δ 10.00 ppm for NH and also shows multiplet in the range of δ 6.70-7.54 ppm owing to aromatic protons. The appearance of peak due to chlorine, bromine and fluorine in IR spectra around 700 -800 cm^{-1} and the formation M+2 peak in the mass spectra.

Among the test compounds, compound 5-[(2-fluorophenyl)methyl]-3-(naphthalene-1-yl)-1,3-thiazolidine-2,4-dione (2h) was found to be the most active agent which showed 61 percentage of cell inhibition against the enzyme in the highest concentration, which have 2-Fluoro benzaldehyde group at 5th position in the thiazolidinedione nucleus. Hence this molecule can be selected as a lead molecule of the present study for further exploitation.

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