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SYNTHESIS OF NOVEL PYRAZOLYL-2,4-THIAZOLIDINEDIONES AS ANTI INFLAMMATORY AND ANTI DIABETIC ACTIVITY

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ABSTRACT
Novel pyrazolyl-2,4-thiazolidinediones were prepared via the reaction of appropriate pyrazole carboxaldehydes with 2,4-thiazolidinediones. Different substituted pyrazole carbaldehydes which were synthesized by Vilsmeier-Haack reaction of substituted phenyl hydrazones with POCl3 and dimethyl formamide, hybridized with 2, 4-thiazolidinedione in anhydrous toluene in the presence of glacial acetic acid and piperidine as catalyst. The chemical structures of the synthesized compounds were confirmed using FTIR, Mass and 1H NMR spectral data. The resultant compounds were screened for anti-inflammatory and antidiabetic activities in vitro.The series of synthesized compounds were tested for anti-inflammatory activity by plethysmography. From the data obtained, the mean edema volume and percentage reduction in edema was calculated and the results were represented in Table 4.2.A, 4.2.B. The first series of compounds, pyrazolyl thiazolidinediones **(3a-h)** were found to have significant activity and the compounds **3b**, **3d** and **3e** were found to be equipotent to the standard, diclofenac sodium. The various substituted pyrazolyl-thiazolidinediones were tested in diabetic induced rats. The readings were taken at very fixed intervals of 0 hr, 1 hr, 3 hr and 6 hr of time. Among the series of compounds **3b**,**3d,3e and 3f** have shown the excellent antidiabetic activity.

KEYWORDS: Pyrazoles, 2,4-thiazolidinediones, anti-inflammatory and antidiabetic activity.

INTRODUCTION
Pyrazoles are an interesting class of heterocyclic compounds with synthetic versatility and significant biological activities such as analgesic and anti inflammatory[1-4], antifungal[5-6], antimicrobial[7-10], antidiabetic[11-15], herbicidal[16,17], antitumor[18-21], anti-anxiety[22], and as active pharmacophore in celecoxib (as COX-2 inhibitor)[23] and slidenafil citrate[24] (as cGMP specific phosphodiesterase type 5 inhibitor), etc. On the other hand, thiazolidines are also known for their potential biological activities.2, 4-thiazolidinediones (TZDs) have become a pharmacologically important class of heterocyclic compounds since the introduction of various glitazone and epalrestat into clinical use for the treatment of type II diabetes and diabetic complications[25] Several studies have been reported that TZDs have acquired much importance because of their diverse pharmaceutical applications such as antihyperglycemic[26], bactericidal[27], pesticidal[28], fungicidal[29], insecticidal[30], anticonvulsant[31], tuberculostatic[32], anti-inflammatory[33] etc.

Inspired by the diverse biological properties of thiazolidinedione moiety and pyrazoles, the present study was designed to evaluate the anti-inflammatory and antidiabetic activity of novel pyrazole and thiazolidinedione derivatives.

MATERIALS AND METHODS
All the reagents used in the present work were of analytical grade and were used without any further purification. The reactions were carried out under controlled anhydrous conditions. Melting points were recorded on Analab melting point apparatus by open capillary method and are uncorrected. The IR spectra were recorded on Schimadzu FTIR spectrophotometer using 1% potassium bromide discs. 1H NMR spectra were recorded on Varian 400MHz spectrophotometer using DMSO-*d*6 as solvent and TMS as an internal standard. Mass spectra were taken on Agilent 6430 triple quadruple EI-MS system. Thin layer chromatography was performed using E. Merck 0.25mm silica gel plates, and the spots were visualized under UV light at 256nm.

General procedure for synthesis of 3-(Substituted aryl)-1-phenyl-1*H*-pyrazole-4-carbaldehydes (2a-h)
To an ice cold solution of DMF (0.1mol), was added phosphorus oxychloride(0.012mol) drop-wise and the temperature was maintained below 100C. To the mixture, an ice-cold solution of phenyl hydrazine

(0.01mol) was added in lots wise with stirring under ice cold condition. After the completion of the addition, the reaction mixture was stirred and refluxed at60-700C for 6hr. Solution was cooled and poured into crushed ice with stirring and neutralized with aq.NaHCO3 solution. The solid product obtained was filtered under suction, dried and recrystallized from methanol.

General procedure for synthesis of 3-(Substituted aryl)-1-phenyl-1*H*-pyrazolyl-2,4-thiazolidinediones (3a-h)

A mixture of 3-(Substituted aryl)-1-phenyl-1*H*-pyrazol-4-carbaldehyde 2a (0.5g, 2mmol) and 1, 3-thiazolidine-2,4-dione (0.4g, 2mmol) in glacial acetic acid (20ml) and 2-3 drops of piperidine was refluxed at 120-1300C for 3-4hr. A solid would separate from the reaction mixture within 15-20min and the refluxing was continued for 3-4hrto completes the reaction. The reaction mixture was then cooled to room temperature, filtered and washed with ethanol to give the pure product.

Spectral analysis

3a.5-[(1,3-diphenyl-1H-pyrazol-4-yl)methylidene]-1,3-thiazolidine-2,4-dione

C19H13N3O2S, IR (KBr, cm-1): 3448.49(N-H str), 3058.89 (Ar C-H str), 1735,1685(C=O str),1593.09 (C=N str**)**. 1H-NMR (DMSO-d6) 12.6 s (1H, NH of thiazolidinedione), 8.7 s(1H, pyrazole), 7.4-8.1 (10H, Ar-H&1H, HC=C-thiazolidinedione). EI-MS (m/z):347.50(M+), 370.50(M+Na) +.

3b. 5-{[3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl] methylidene}-1,3-thiazolidine-2,4-dione

C19H12ClN3O2S, IR (KBr, cm-1):3124.47(N-H str), 3024.16 (Ar C-H str), 1758.95,1685.67(C=O str), 1593.09 (C=N str), 758.04(C-Cl str). 1H-NMR (DMSO-d6)12.6 s (1H, NH of thiazolidinedione), 8.7 s (1H, pyrazole), 7.4-8.0(9H, Ar-H &1H, HC=C-thiazolidinedione).EI-MS m/z: 381.50 (M+), 404.80(M+Na) +.

3c. 5-{[3-(4-methylphenyl)-1-phenyl-1H-pyrazol-4-yl] methylidene}-1,3-thiazolidine-2,4-dione

C20H15N3O2S, IR (KBr cm-1):3120.61(N-Hstr), 3004.69(Ar C-H str),2781.16 (C-H str of CH3), 1735.81,1685.57(C=O str), 1604.65(C=N str).1H-NMR (DMSO-d6) 12.5 s (1H,NH of thiazolidinedione), 8.6 s (1H, pyrazole), 7.3-8.1 (9H,Ar-H&1H, HC=C-thiazolidinedione),2.3-2.5 (3H,CH3). EI-MS m/z: 361.4 (M+), 384.4 (M+Na) +.

3d. 5-{[3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl]methylidene}-1,3-thiazolidine-2,4-dione

C20H15N3O3S, IR (KBr cm-1):3329 (N-H str),3067.57 (Ar C-H str), 2876.1 (C-H str of CH3), 1743,1685(C=O str), 1612.38 (C=N str), 1244.97 (aryl-O str), 1178.43, 1017.38 (CH3-O str).1H-NMR (DMSO-d6) 12.5 s (1H,NH of thiazolidinedione), 8.6 s(1H, pyrazole), 7.3-8.1 (9H,Ar-H&1H, HC=C-thiazolidinedione),2.3-2.5 (3H,CH3).EI-MS m/z:377.41(M+).

3e. 5-{[3-(2-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl]methylidene}-1,3-thiazolidine-2,4-dione

C20H15N3O3S, IR (KBr cm-1):3328 (N-H str), 3120.45 (Ar C-H str), 2869.23 (C-H str of CH3), 1742, 1682(C=O str), 1611.88 (C=N str), 1240.87 (aryl-O str), 1176.22, 1012.68 (CH3-O str). 1H-NMR (DMSO-d6) 12.5 s (1H, NH of thiazolidinedione), 8.6 s (1H, pyrazole, C=CH), 7.3-8.1 (9H, Ar-H&1H, HC=C-thiazolidinedione), 2.3-2.5 (3H, CH3). EI-MS m/z: 377.41(M+).

3f. 5-{[3-(4-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl]methylidene}-1,3-thiazolidine-2,4-dione

C19H13N3O3S, IR (KBr cm-1):3348 (N-H str), 3340.48 (O-H str), 3109.04 (Ar C-H str), 1729, 1690(C=O str), 1596.95 (C=N str). 1H-NMR (DMSO-d6)12.5 s (1H, NH of thiazolidinedione), 8.6 s (1H, pyrazole), 7.3-8.1 (9H, Ar-H&1H, HC=C thiazolidinedione), 5.35 s (1H, OH). EI-MS m/z: 363.38(M+).

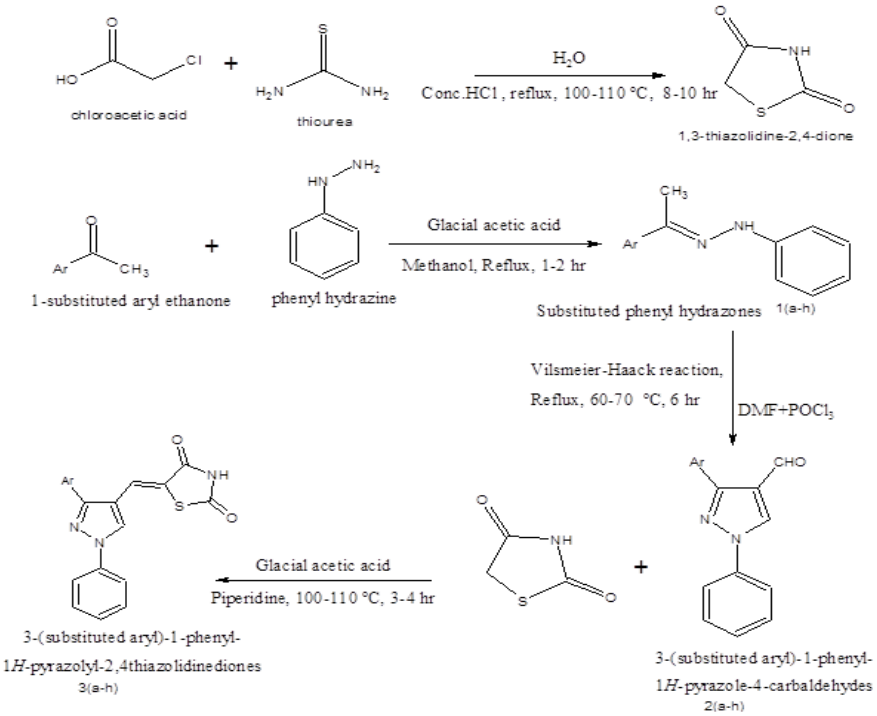
3g.5-{[3-(2-hydroxyphenyl)-1-phenyl-1H-pyrazol-4-yl] methylidene}-1,3-thiazolidine-2,4-dione

C19H13N3O3S, IR (KBr cm-1):3348(N-H str), 3342.45 (O-H str), 3103.06 (Ar C-H str), 1729, 1688(C=O str), 1595.82 (C=N str). 1H-NMR (DMSO-d6) 12.5 s (1H, NH of thiazolidinedione), 8.6s (1H, pyrazole), 7.3-8.1 (9H Ar-H &1H, HC=C-thiazolidinedione), 5.25 s (1H, OH). EI-MS m/z: 363.38(M+).

3h. 5-{[3-(naphthalen-1-yl)-1-phenyl-1H-pyrazol-4-yl] methylidene}-1,3-thiazolidine-2,4-dione

C23H15N3O2S, IR (KBr cm-1): 3337 (N-H str), 3047.32 (Ar C-H str), 1735, 1596(C=O str), 1596.95 (C=N str). 1H-NMR (DMSO-d6) 12.5 s (1H, NH of thiazolidinedione), 8.4 s (1H, pyrazole), 7.3-8.1 (12H, Ar- H& 1H, HC=C-thiazolidinedione). EI-MS m/z: 397.5(M+).

Scheme



Ar	-C_6H_5	4-Cl-C_6H_4	4-CH_3-C_6H_4	4-OCH_3-C_6H_4	2-OCH_3-C_6H_4	4-OH- C_6H_4	2-OH- C_6H_4	napthyl
compd	a	b	c	d	e	f	g	h

RESULTS AND DISCUSSION

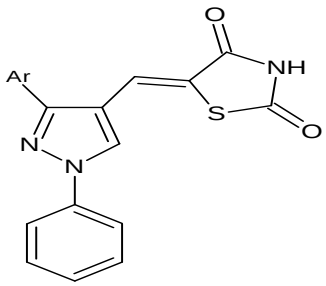
Chemistry

The synthetic methodology followed to obtain the target compounds is outlined under Scheme 1. 2, 4-thiazolidinedione was prepared as per the procedure mentioned in literature.[24] Cyclization of different phenyl hydrazones was done by Vilsmeier-Haack reaction to give 1-phenyl-3-substituted phenyl-1*H*-pyrazole-4-carbaldehydes (2a-h), which on condensation with 2, 4-thiazolidinedione in glacial acetic acidand catalytic amounts of piperidine afforded title compounds(3a-h) in reasonable yields. The compounds were characterized on the basis of physical and spectral data.

ANTIINFLAMMATORY STUDIES

The series of synthesized compounds were tested for anti-inflammatory activity by plethysmography. From the data obtained, the mean edema volume and percentage reduction in edema was calculated and the results were represented in Table 4.2.A, 4.2.B. The first series of compounds, pyrazolylthiazolidinediones**(3a-h)** were found to have significant activity and the compounds **3b**, **3d** and **3e** were found to be equipotent to the standard, diclofenac sodium.

Anti-inflammatory data of 3-(substituted aryl)-1-phenyl-1*H*-pyrazolyl-2,4- thiazolidinediones (3a-h)



3-(substituted aryl)-1-phenyl-1*H*-pyrazolyl-2,4thiazolidinediones 3(a-h)

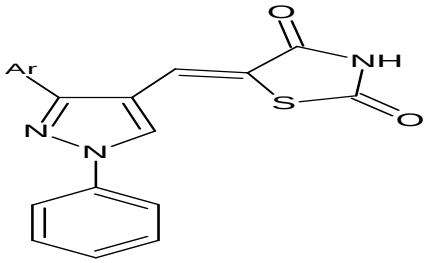
TABLE 4.2 A Mean paw edema volume in ml.

Treatment	**Ar**	**Dose (mg/kg)**	**Mean paw edema volume in ml**			
			0.5 hr	**1 hr**	**2 hr**	**3 hr**
Control	-	100	2.5 ± 0.02	2.75 ± 0.01	2.90 ± 0.08	3.15 ± 0.01
Standard (Diclofenac sodium)	-	100	1.67 ± 0.04	1.15 ± 0.05	0.80 ± 0.03	0.50 ± 0.05
3a	-C_6H_5	100	1.8 ± 0.06	1.65 ± 0.07	1.45 ± 0.06	1.5 ± 0.01
3b	4-Cl-C_6H_4	100	1.6 ± 0.06	1.20 ± 0.08	0.90 ± 0.02	0.70 ± 0.05
3c	4-CH_3-C_6H_4	100	1.5 ± 0.01	1.35 ± 0.04	1.40 ± 0.05	1.45 ± 0.08

3d	4-OCH_3-C_6H_4	100	1.78 ± 0.02	1.50 ± 0.06	1.10 ± 0.08	0.88 ± 0.05
3e	2-OCH_3-C_6H_4	100	1.74 ± 0.03	1.40 ± 0.02	1.20 ± 0.06	1.0 ± 0.02
3f	4-OH- C_6H_4	100	1.6 ± 0.06	1.4 ± 0.08	1.3 ± 0.03	1.2 ± 0.06
3g	2-OH- C_6H_4	100	1.9 ± 0.02	1.45 ± 0.06	1.35 ± 0.08	1.30 ± 0.05
3h	napthyl	100	1.70 ± 0.04	1.55 ± 0.06	1.40 ± 0.06	1.35 ± 0.01

Edema volume = (Mean ± SEM)

Percentage protection against edema formation by 3-(substituted aryl)-1-phenyl-1*H*-pyrazolyl-2, 4-thiazolidinediones (3a-h)

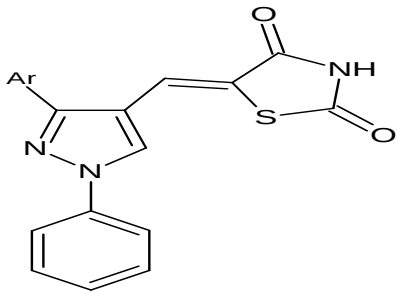


3-(substituted aryl)-1-phenyl-1*H*-pyrazolyl-2,4thiazolidinediones 3(a-h)

TABLE 4.2. B

Treatment	Ar	Dose (mg/kg)	Percentage protection against edema formation			
			0.5 hr	1 hr	2 hr	3 hr
Standard (Diclofenac sodium)	-	100	33	58	72	84
3a	-C_6H_5	100	28	40	50	52
3b	4-Cl-C_6H_4	100	36	56	69	77
3c	4-CH_3-C_6H_4	100	40	51	52	53
3d	4-OCH_3-C_6H_4	100	28	45	62	72
3e	2- OCH_3-C_6H_4	100	30	49	59	68
3f	4-OH- C_6H_4	100	36	49	53	62
3g	2-OH- C_6H_4	100	36	47	53	58
3h	napthyl	100	32	43	52	57

Percentage protection against edema formation by 3-(substituted aryl)-1-phenyl-1*H*-pyrazolyl-2, 4-thiazolidinediones (3a-h)

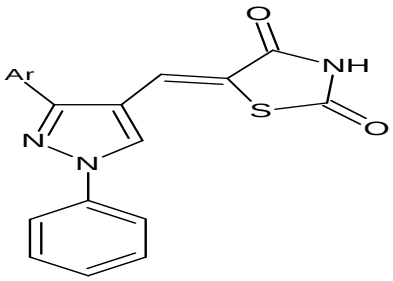


3-(substituted aryl)-1-phenyl-1*H*-pyrazolyl-2,4thiazolidinediones 3(a-h)

TABLE 4.2. B

Treatment	Ar	Dose (mg/kg)	Percentage protection against edema formation			
			0.5 hr	1 hr	2 hr	3 hr
Standard (Diclofenac sodium)	-	100	33	58	72	84
3a	$-C_6H_5$	100	28	40	50	52
3b	$4\text{-Cl-}C_6H_4$	100	36	56	69	77
3c	$4\text{-}CH_3\text{-}C_6H_4$	100	40	51	52	53
3d	$4\text{-}OCH_3\text{-}C_6H_4$	100	28	45	62	72
3e	$2\text{-}OCH_3\text{-}C_6H_4$	100	30	49	59	68
3f	$4\text{-OH-}C_6H_4$	100	36	49	53	62
3g	$2\text{-OH-}C_6H_4$	100	36	47	53	58
3h	napthyl	100	32	43	52	57

Percentage protection against edema formation by 3-(substituted aryl)-1-phenyl-1*H*-pyrazolyl-2, 4-thiazolidinediones (3a-h)

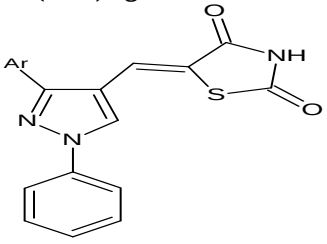


3-(substituted aryl)-1-phenyl-1*H*-pyrazolyl-2,4thiazolidinediones 3(a-h)

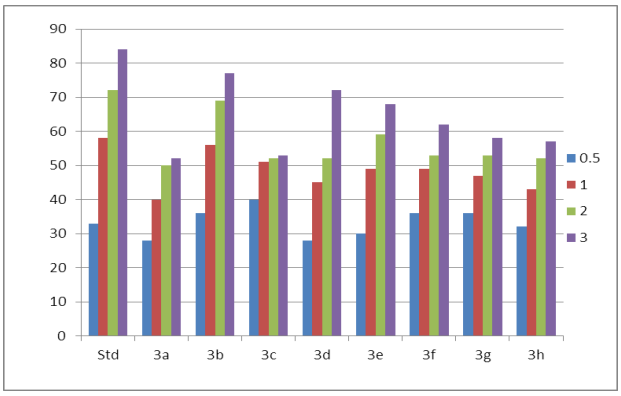
TABLE 4.2.B

Treatment	Ar	Dose (mg/kg)	Percentage protection against edema formation			
			0.5 hr	1 hr	2 hr	3 hr
Standard (Diclofenac sodium)	-	100	33	58	72	84
3a	$-C_6H_5$	100	28	40	50	52
3b	$4\text{-Cl-}C_6H_4$	100	36	56	69	77
3c	$4\text{-}CH_3\text{-}C_6H_4$	100	40	51	52	53
3d	$4\text{-}OCH_3\text{-}C_6H_4$	100	28	45	62	72
3e	$2\text{-}OCH_3\text{-}C_6H_4$	100	30	49	59	68
3f	$4\text{-OH-}C_6H_4$	100	36	49	53	62
3g	$2\text{-OH-}C_6H_4$	100	36	47	53	58
3h	napthyl	100	32	43	52	57

Graphical representation of percentage protection of 3-(substituted aryl)-1-phenyl-1*H*-pyrazolyl-2, 4-thiazolidinediones (3a-h) against edema formation



3-(substituted aryl)-1-phenyl-1*H*-pyrazolyl-2,4thiazolidinediones 3(a-h)

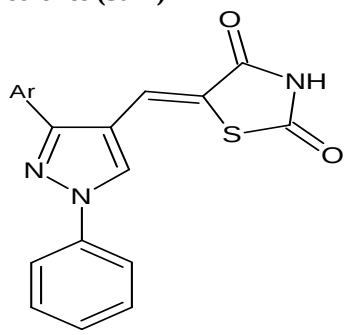


Anti diabetic Activity

The synthesized compounds were screened for antidiabetic activity by tail vein tip method in wistar rats.The wistar rats of either sex weighing between 240-280 g were taken in 10 groups. Blood glucose level was increased by inducing alloxan 120mg/kg body weight. The various substituted pyrazolyl-thiazolidinediones were tested in diabetic induced rats. The readings were taken at very fixed intervals of 0 hr, 1 hr, 3 hr and 6 hr of time.

Among the series of compounds **3b**,**3d,3e and 3f** have shown the excellent antidiabetic activity.

Antidiabetic Activity of SynthesizedCompounds 3-(substituted aryl)-1-phenyl-1*H*-pyrazolyl-2, 4-thiazolidinediones (3a-h)



3-(substituted aryl)-1-phenyl-1*H*-pyrazolyl-2,4thiazolidinediones 3(a-h)

TABLE 4.3 A

Compound	Time in Hours			
	0	1	3	6
Control/ Water	123.3 ±6.00	120.7±5.54	122.3±5.81	123±6.4
Control / Alloxan	200.3±9.59	182.3±8.68	170.3±5.23	146.33.38
3a	295.3±7.42*	233.3±23.8	193±13.86	159.3±12.12
3b	261.6±11.2	197±2.6	162.3±7.44	115.3±5.2*
3c	259±36.6	214±35.3	168±17.77	149.67±8.9
3d	203±13.79	156±13.5	123±4.3*	101±4.5**
3e	214±14.00	163±9.7	146±11.13	115.3±3.8*
3f	224.3±22.06	168±11.0	111±1.45**	107.3±3.4**
3g	263±7.80	252±9.40	242±23.65	232±17.54
3h	263±8.56	242±21.56	228±11.54	221±15.21

* P<0.05 – Non significant
** P<0.01 – Significant
*** P<0.0001 (One way ANOVA followed by Dunnet 't' test Vs. Time 0)

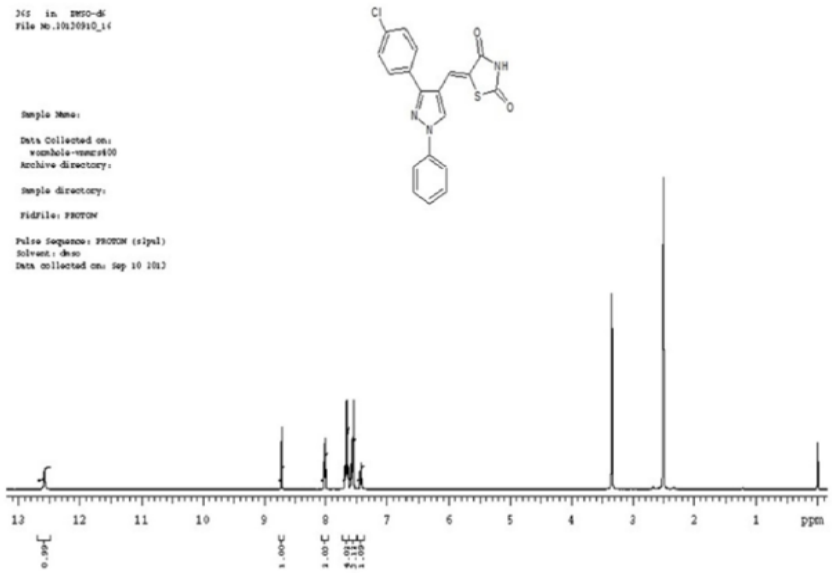


Fig. 1: 1H NMR Spectrum of 5-{[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl] methylidene}-1,3-thiazolidine-2,4-dione (3b).

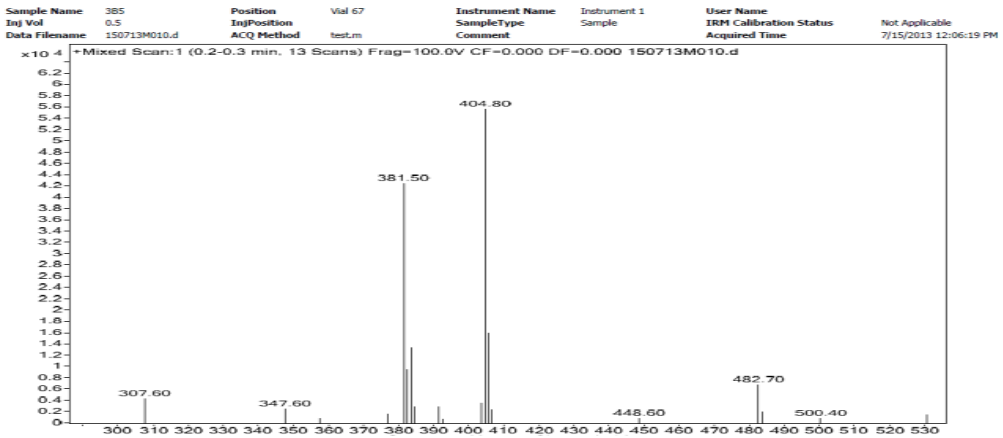


Fig. 2: EI-Mass Spectrum of 5-{[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl] methylidene}-1,3-thiazolidine-2,4-dione (3b).

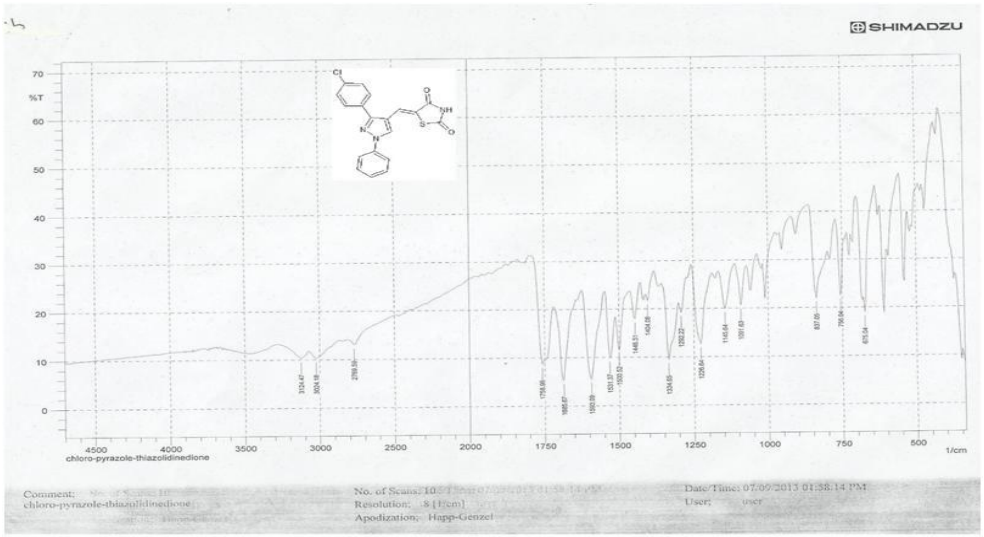


Fig. 3: IR Spectrum of 5-{[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl] methylidene}-1,3-thiazolidine-2,4-dione (3b).

CONCLUSION

In the present investigation, a total of eight new thiazolidinedione incorporated pyrazole derivatives were synthesized by employing hybridization approach and the structures of the synthesized compounds were confirmed on the basis of FTIR, Mass and 1H NMR spectral data.

The series of synthesized compounds were tested for anti-inflammatory activity by plethysmography. From the data obtained, the mean edema volume and percentage reduction in edema was calculated and the results were represented in Table 4.2.A, 4.2.B. The first series of compounds, pyrazolylthiazolidinediones**(3a-h)** were found to have significant activity and the compounds **3b**, **3d** and **3e** were found to be equipotent to the standard, diclofenac sodium.

The various substituted pyrazolyl-thiazolidinediones were tested in diabetic induced rats. The readings were taken at very fixed intervals of 0 hr, 1 hr, 3 hr and 6 hr of time. Among the series of compounds **3b**,**3d,3e and 3f** have shown the excellent antidiabetic activity.

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