CHAPTER IV

Synthesis of new 2-(4-(1-phenyl-3-p-substituted-pyrazol-4-yl) methylene-2-hydrazolyl) -1,3-thiazolidin-5-yl-acetic acids and 2-(4-(1-phenyl-3-(substituted)-pyrazol-4-yl) methylene-2-hydrazolyl)-thiazolidino -4-ones.
Abstract

Chapter IV deals with the synthesis of new 2-(4-(1-phenyl-3-p-substituted-pyrazol-4-yl) methylene-2-hydrazioly) -1,3-thiazolidin-5-yl-acetic acids (4a-g) and 2-(4-(1-phenyl-3-(substituted)-pyrazol-4-yl) methylene-2-hydrazioly)-thiazolidino-4-ones (8a-g). These have been synthesized from 1-((3-(4-substituted phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) thiosemicarbazides (3a-g). The required precursors, 1-((3-(4-substituted phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) thiosemicarbazides (3a-g) were freshly prepared by condensing 3-(4-substituted phenyl)-1-phenyl-1H-pyrazole-4-carbaldehydes (1a-g) with thiosemicarbazide in ethanol in presence of molecular sieves. The synthetic sequence is given in Scheme 4.1.
Introduction

Heteroaromatic compounds have attracted considerable attention in the design of biologically active molecules and advanced organic materials. Pyrazole and its derivatives, a class of well-known nitrogen-containing heterocyclic compounds, have attracted much attention since they play a vital role in synthetic organic chemistry over the years and are important bioactive compounds. The pyrazole ring is a prominent structure motif found in numerous pharmaceutically active compounds.

Pyrazole framework plays an essential role in biologically active compounds and therefore represents an interesting template for combinatorial as well as medicinal chemistry. Pyrazole derivatives are known to possess a wide spectrum of pharmacological properties such as antibacterial, antifungal, antiviral, antitubercular, antioxidant, antiandrogenic etc. Some of these compounds have also exhibited antidiabetic, herbicidal, analgesic and antiparasitic properties. Pyrazole is an important core nucleus found in various drugs viz. PNU-32945 (4.1), Celecoxib (4.2) and Zoniporide (4.3). These drugs act as HIV- reverse transcriptase inhibitors, sodium hydrogen ion exchanger inhibitors and COX-2 inhibitors, respectively.

Pyrazoles are also emerged as potential antihyperglycemic agents. A number of pyrazole compounds specially 1, 3-disubstituted pyrazoles and 1, 3, 5-trisubstituted pyrazoles have been cited in the literature and are found to elicit antihyperglycemic activity. SAH 57-749 (4.4), a pyrazole derivative has shown antidiabetic activity. Substituted pyrazoles are known for their hypoglycemic activity in vivo. Cottineau et al. have synthesized substituted pyrazole-4-carboxylic acids (4.5) as hypoglycemic agents, inhibiting the activity of the ATP-K channel of the beta cell pancreatic membrane, inducing the production of insulin.
In research on new PPARα selective agonists, some ureidofibrates have been reported. One of them, a selective PPARα agonist, pyrazole (4.6) has been generated.\textsuperscript{27} Compound (4.6) demonstrates in vivo activity toward Zucker fatty rats and has also been tested in a rat 7-day toxicological study. Roche reported thiazolidinedione (4.7)\textsuperscript{28} that has been found to activate protein kinase in cells (AMPK). AMP-activated protein kinase (AMPK; adenosine monophosphate-activated protein kinase) is widely recognized as an energy sensor, which plays a key role in maintaining whole body energy homeostasis.

Recently Bristol-Myers Squibb reported a pyrazole derivative (4.8)\textsuperscript{29} with impressive broad scope preclinical validation of efficacy. This compound has shown increased insulin sensitivity but not increased insulin secretion. In diet-induced obese mice, (4.8) showed decreased glucose level.

The chemistry of carbon-nitrogen double bond of hydrazone is becoming the backbone of condensation reaction in benzo-fused N-heterocycles.\textsuperscript{30} Hydrazones containing azomethine (–NH–N=C) constitutes an important class of compounds for new drug development.\textsuperscript{31} Many researchers have synthesized these compounds as target structures and evaluated their biological activities. Hydrazones have been reported to possess antimicrobial,\textsuperscript{32} antitubercular,\textsuperscript{33} anticonvulsant,\textsuperscript{34} analgesic,\textsuperscript{35} antiinflammatory,\textsuperscript{36} antiplatelet,\textsuperscript{37} anticancer,\textsuperscript{38} antiviral,\textsuperscript{39} antitumoral\textsuperscript{40} and antimalarial\textsuperscript{41} activities.
A series of potent and selective antidiabetic agents mostly from substituted thiazolidinediones has been developed and their blood glucose level lowering activity has been examined in genetically obese and insulin resistant ob/ob mouse. Modification of the 2,4-thiazolidinedione ring at 2, 3, 4 and 5 positions is found to yield synthetic products with a wide spectrum of pharmacological activities and hence now a days considerable attention has been receiving. The 5 position of 2,4-thiazolidinedione, the methylene group with liable hydrogens being relatively more reactive hence most of the modification on 2,4-thiazolidinedione ring are done at 5 position to construct new molecules. 4- Thiazolidinones with carbonyl substituents at the five position introduces an additional diversity point to further structural tuning.

Synthesis of some derivatives of thiazolidine- 2, 4-dione having carboxylic ester appendage at N-3 has been reported to have antihyperglycemic activity.\textsuperscript{42} The ethyl ester of thiazolidine- 2, 4-dione- 3- acetic acid showed higher antihyperglycemic activity than the corresponding ester because the ethyl group is replaced by methylgroup.\textsuperscript{43} Many of these derivatives along with their corresponding carboxylic acids showed significant improvement on post-prandial hyperglycemia in normal rats.\textsuperscript{44} Fresneau et al.\textsuperscript{45} have reported new compounds, 2, 4-dioxo-5-(naphthylmethylene)- 3-thiazolidineacetic acid (4.9) and its 2-thioxo analogue (4.10) as aldose reductase (AR) inhibitors.

![Chemical structures](image)

The acidic functionality of the TZD ring is considered essential for its binding to PPAR\textsubscript{\gamma}, so some PPAR\textsubscript{\gamma} agonists have been developed as bioisosteres of the TZD ring, conserving acidic properties by replacement of this ring with acyclic structures such as carboxylated hydroxyl ureas, \(\alpha\)-heteroatom or \(\alpha\)-carbon-substituted carboxylic acids and 1,3-dicarbonyl compounds.\textsuperscript{46}

Replacement of the TZD ring by a noncyclic 1,3-dicarboxyl moiety led to compounds (4.11), (4.12) and (4.13).\textsuperscript{47} These compounds show interesting insulin-sensitizing and hypoglycemic activities, with levels of glucose and triglyceride correction comparable to those of rosiglitazone in ob/ob mouse studies.
Objectives of the Work

Literature survey revealed that heterocycles *viz.* pyrazoles, thiazolidinediones with having acid functionality have shown antidiabetic activity. Compounds (4.14), (4.15) and (4.16) with acid functionality are highly potent antidiabetic agents. It was also found that there is scanty information on pyrazoles having thiazolidinone and acid pharmacophoric groups.

Considering the pharmacological importance of pyrazoles, thiazolidinones and carboxylic functionality here it was thought worthwhile to bring these active moieties together in one molecular framework with the hope to obtain the new molecules/leads with better antidiabetic activity. Therefore the titled, 2-(4-(1-phenyl-3-p-substituted-pyrazol-4-yl) methylene-2-hydrazolyl) -1,3-thiazolidin-5-yl-acetic acids and 2-(4-(1-phenyl-3-(substituted)-pyrazol-4-yl) methylene-2-hydrazolyl)-imino thiazolidino-4-ones have been synthesized and their antidiabetic activity has been evaluated.

1) Synthesis of 2-(4-(1-phenyl-3-p-substituted-pyrazol-4-yl) methylene-2-hydrazolyl) -1,3-thiazolidin-5-yl-acetic acids (4a-g)

Synthetic Plan

Keeping in view these multifarious applications of pyrazoles, thiazolidinone carboxylic acids and in continuation of our earlier interest to synthesize new analogues of bioactive thiazolidinediones, here it was planned to synthesize 2-(4-(1-phenyl-3-p-substituted-pyrazol-4-yl) methylene-2-hydrazolyl) -1,3-thiazolidin-5-yl-acetic acids (4a-g) using readily available reactants. Accordingly the synthetic route was planned to obtain the titled products (Scheme 4.1).
The precursors, pyrazole aldehydes, required were synthesized by Vilsmeier Haack reaction using hydrazones derived from acetophenones and phenyl hydrazine by following reported method.\textsuperscript{50} The synthetic steps of this route are presented in \textbf{Scheme 4.1} and their details are incorporated in the present work.

\textbf{Present Work}

3-(4-Substituted phenyl)-1-phenyl-1H-pyrazole-4-carbaldehydes (1a-g) were synthesized using reported procedure\textsuperscript{50} i.e. Vilsmeier Haack reaction of phenyl/aryl hydrazones with POCl\(_3\) and DMF. Phenyl hydrazones were obtained by condensing substituted acetophenones and phenyl hydrazine in ethanol. Thus obtained pyrazole aldehydes (1a-g) were then condensed with thiosemicarbazide (2) in ethanol in presence of molecular sieves under reflux for 1h and obtained 1-((3-(4-substituted phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)thiosemicarbazides (3a-g) with excellent yields. The pyrazolyl thiosemicarbazones (3a-g) were then subjected to react with maleic anhydride in refluxed toluene for obtaining new 2-(4-(1-phenyl-3-p-substituted-pyrazol-4-yl) methylene-2-hyrazolyl)-1,3-thiazolidin-5-yl-acetic acids (4a-g), following thia Michel addition reaction, (\textbf{Scheme 4.1, Table 4.1}).

![Scheme 4.1 Synthesis of 2-(4-(1-phenyl-3-p-substituted-pyrazol-4-yl) methylene-2-hyrazolyl) -1,3-thiazolidin-5-yl-acetic acids](image-url)
### Table 4.1: Physical data of 1-((3-(4-substituted phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) thiosemicarbazides (3a-g).

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<thead>
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<th>Entry</th>
<th>Compound</th>
<th>R</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Melting Point (°C)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>-H</td>
<td>92</td>
<td>210-212</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>-CH₃</td>
<td>86</td>
<td>201-202</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>-OCH₃</td>
<td>91</td>
<td>162-163</td>
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<tr>
<td>4</td>
<td>3d</td>
<td>-F</td>
<td>94</td>
<td>218-220</td>
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<td>-Br</td>
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<td>6</td>
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<td>7</td>
<td>3g</td>
<td>-OH</td>
<td>82</td>
<td>215-217</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: substituted pyrazolyl carboxaldehyde (1a-g) (10 mmol), thiosemicarbazide (10 mmol), Ethanol refluxed for 1h. <sup>b</sup>Isolated yields

### Table 4.2: Physical data of 2-(4-(1-phenyl-3-p-substituted-pyrazol-4-yl) methylene-2-hydrazolyl) -1,3-thiazolidin-5-yl-acetic acids (4a-g).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Melting Point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>7</td>
<td>4g</td>
<td>-OH</td>
<td>80</td>
<td>224-226</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: 1-((3-(4-substituted phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) thiosemicarbazide (3a-g) (3 mmol), maleic anhydride (4 mmol), toluene (20 ml) refluxed for 3h. <sup>b</sup>Isolated yields
Experimental

Synthesis of 1-((3-(4-phenyl)-1-phenyl-1H-pyrazol-4-yl) methylene) thiosemicarbazide (3a)

A mixture of 3-(4-phenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde (1a) (10 mmol) and thiosemicarbazide (2) (10 mmol) was refluxed in ethanol in the presence of activated molecular sieves of size 4Å^0^ (10 g). After 1h of reflux the reaction mixture was filtered to remove molecular sieves. Ethanol was removed under vacuum. The residual mass was poured on crushed ice. The solid obtained was filtered and washed with water. The crude solid was purified by crystallization.

Similarly the other compounds, (3b-g) of the series were prepared. The melting points and the yields of the derivatives are recorded in Table 4.1.

Spectral analysis:

Following is a spectral data of 1-((3-(4-phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)thiosemicarbazide (3a).

IR (KBr, ν cm^{-1}) Characteristic absorptions:
3410 (N-H stretching), 3100 (Ar-H stretching), 1597 (C=C stretching), 1590 (C=N stretching), 1334 (C-N stretching) and 1250 (C=S stretching).

MS (Scanning mode, ESI^+): m/z (% intensity):
322 (M^+, 100), 323 (22), and 305 (20).

$^1$H-NMR (200 MHz, DMSO-$d_6$, δ ppm):
7.55 (s, 1H, -CH=N-), 8.01 (s, 1H, pyrazoline-H), 8.29-8.77 (m, 10H, Ar-H), 9.10 (s, 1H, NH), 9.36 (s, 1H, NH, tautomeric) and 11.73 (s, 1H, SH, enolic).
Chapter IV

Mass spectrum of compound (3a)

$^1$H-NMR of compound (3a)
Synthesis of 2-(4-(1-phenyl-3-pyrazol-4-yl) methylene-2-hydrazolyl) -1,3-thiazolidin-5-yl-acetic acid (4a)

1-((3-(4-substituted phenyl)-1-phenyl-1H-pyrazol-4-yl)methylene) thiosemicarbazide (3a) (3 mmol) and maleic anhydride (4 mmol) were refluxed in toluene. Thia Michel addition was monitored by thin layer chromatography. After 3h of reflux the reaction mixture was cooled. Excess toluene was removed on rota evaporator. The residual mass was poured on crushed ice and extracted with ethyl acetate. From extract organic medium was removed under reduced pressure. The residual solid obtained was dried and purified by crystallization.

Similarly the other compounds, (4b-g) of the series were prepared. The melting points and the yields of the derivatives are recorded in Table 4.2.

Spectral analysis:

Following is a spectral data of one of the representative products from the series, 2-(4-(1-phenyl-3-pyrazol-4-yl) methylene-2-hydrazolyl) -1,3-thiazolidin-5-yl-acetic acid (4a).

**IR (KBr, ν cm⁻¹)** Characteristic absorptions:

3433 (N-H stretching), 3271 (Ar-H stretching), 2924 (OH stretching), 1643, 1720 (C=O stretching), 1597 (C=N stretching) and 1215 (C-O stretching).

**MS (Scanning mode, ESI⁺):** m/z (% intensity):

420 (M⁺, 100), 421 (28) and 422 (6).

**¹H-NMR (300 MHz, DMSO-d₆, δ ppm):**

2.97-3.34 (dd, overlapped, 2H, methylene, J=8.0 and J=3.50), 4.42 (t, 1H, methine, J=7.6), 7.23-8.02 (m, 10H, Ar-H), 8.42 (s, 1H), 8.94 (s, 1H), 11.31 (s, 1H, NH) and 12.35 (bs, 1H, -COOH).

**¹³C NMR (75 MHz, DMSO-d₆, δ ppm):**

36.80, 43.67, 116.68, 118.85, 127.06, 128.49 (2C), 128.59 (2C), 128.84 (2C), 129.48 (2C), 129.59, 132.00, 138.91, 149.09, 151.64, 171.73 and 175.40.

**Elemental Analysis:**

Anal. Calcd for C₂₁H₁₇N₅S: C, 60.13; H, 4.09; N, 16.70; S, 7.64 found C, 60.33; H, 4.64; N, 16.57 and S, 7.61.
Chapter IV

Syntheses of Newer Therapeutic Agents for Diabetes Mellitus

Mass spectrum of compound (4a)

H-NMR of compound (4a)
$^{13}$C NMR of compound (4a)
2) Synthesis of 2-(4-(1-phenyl-3-(substituted)-pyrazol-4-yl)methylene-2-hydrazolyl)-4-thiazolidinones. (8a-g)

**Synthetic Plan**

Considering the pharmacological significance of the pyrazoles and thiazolidinones, here a convenient synthetic plan has been made to synthesize new 2-(4-(1-phenyl-3-(substituted)-pyrazol-4-yl)methylene-2-hydrazolyl)-4-thiazolidinones (8a-g). A key step in this plan was the cyclocondensation of pyrazolyl thiosemicarbazones with ethyl bromo acetate.

Nevertheless a common synthetic strategy to construct imino thiazolidinones is the cyclization of thiourea or thiosemicarbazide derivatives with α-halo esters in presence of inorganic base (i.e. NaOAc) in polar solvents using either a conventional or microwave energy. Various synthetic protocols for obtaining imino thiazolidinones were reported. One of the approach for obtaining imino thiazolidinones is the condensation of thioureas with α-haloalkanoic acid derivatives in the presence of a base. Robert and co-workers employed gem-dicyano epoxide as a dicationic ketene for the synthesis of 2-imino-4-thiazolidinone derivatives. Jerome *et al.* has also reported the Reeve’s synthesis of imino thiazolidinones using NaOH in DME-H$_2$O.

The reported methods which are in use are having certain lacunas like, need of catalysts, higher temperatures, also relatively longer reaction time and handling of toxic reactants. Most of the routes require costly reagents, hazardous organic solvents and tedious work up. Hence chemists are paying more attention to modify reaction conditions of the cyclization incorporating green tools.

Design of green processes using cleaner media with less hazards has been gaining special attention due to increase in global environmental concerns. In this regard, many valuable reactions are conducted cleanly and efficiently in water.

For many chemical processes, a major adverse effect to the environment is the consumption of energy for heating and cooling. To overcome such problems, it is highly desirable to develop efficient methods that utilize alternative energy sources such as ultrasound and microwave irradiation to facilitate chemical reactions. Ultrasound technique has increasingly been used in organic synthesis in the recent years. Ultrasonic irradiation enhances the chemical reaction via the process of
acoustic cavitation. The assistance of ultrasonic irradiation efficiently shortens the reaction times. Simple experimental procedure, very high yields, increased selectivity and clean reaction of many ultrasound-induced organic transformations offer additional convenience in the field of synthetic organic chemistry. The chemical effects resulting from the irradiation of aqueous solutions with ultrasound were first time introduced by Loomis and co-workers.

Considering the advantages of water and ultrasound irradiation as green tools and drawbacks associated with the existing routes, used in synthesizing pyrazolyl-2-imino-4-thiazolidinones, here an attempt has been made to develop modified protocol by optimizing the reaction conditions for carrying the one pot cyclocondensation of a 3-(4-substituted phenyl)-1-phenyl-1H-pyrazole-4-carbaldehydes (1a), thiosemicarbazide (2) and ethylbromo acetate (6) in water under ultrasound. The details of the synthetic routes are depicted in Scheme 4.3.

Present work

An environmentally benign and eco-sustainable one pot synthetic protocol has been developed for the synthesis of known 2-phenyl methylene hydrazolyl-4-thiazolidinones (7a-g) by allowing the interactions of aryl aldehydes (5a-g), thiosemicarbazide (2) and ethyl bromoacetate (6) in water under ultrasound irradiation at 50-60°C (Scheme 4.2).

In order to find the best experimental conditions, the cyclocondensation of benzaldehyde, (5a) thiosemicarbazide (2) and ethylbromo acetate (6) in water under ultrasound irradiation was considered as a standard model reaction. An effort was made to carry out the cyclocondensation in ethanol in two steps. In the first step, mixture of benzaldehyde and thiosemicarbazide was refluxed in ethanol in the presence of molecular sieves for 1h and thiosemicarbazone with 90% yield was obtained. Then, the cyclocondensation of the thiosemicarbazone was carried out separately with ethyl bromoacetate in ethanol and acetic acid in presence of base,
NaOAc, which yielded 80% and 67% of 2-phenyl methylene hydrazolyl-4-thiazolidinone (7a), respectively. To evaluate the effect of the solvents and to do the one pot cyclocondensation the model reaction was run in different solvents namely ethanol and water without using base NaOAc under reflux for 2h gave 80% and 82% yield of the 2-imino-4-thiazolidinone, respectively.

From the above results, it was confirmed that water promote formation of the intermediate, thiosemicarbazone, as well as subsequent cyclization of thiosemicarbazone with ethyl bromo acetate, leading to the desired 2-phenyl methylene hydrazolyl-4-thiazolidinone (7a). Above referred utility of water as a reaction medium has promoted us to attempt one-pot cyclocondensation of model reaction at room temperature but there was no reaction. Therefore one pot cyclocondensation of model reaction was then carried in water under ultrasound irradiation at 50-60°C. The reaction proceeded successfully and within 30 min gave 92% yield of desired product (7a).

With all the above optimized conditions in hand, then the above approach was applied to condense various aryl aldehydes, thiosemicarbazide and ethyl bromoacetete in water under ultrasound irradiation and obtained 2-phenyl methylene hydrazolyl-4-thiazolidinones (7b-g) with excellent yields (Table 4.3). It is noteworthy to mention that the methodology worked well to both electron donating and withdrawing substituents on the aryl aldehydes (Table 4.3).

Keeping these results in mind then the attention was paid to synthesize new 2-(4-(1-phenyl-3-(substituted) -pyrazol-4-yl)methylene-2-hydrazolyl)-4-thiazolidinones (8a-g) by carrying one pot cyclocondensation of pyrazolyl aldehydes, thiosemicarbazide and ethyl bromoacetate in water under ultrasound irradiation. But reaction was not occurred. Therefore to dissolve the starting materials and make the reaction mixture homogenous, separate aqueous emulsion of surfactants, CTAB/TTAB/SDS were used to carry the cyclocondensation. It was observed that the condensation of a mixture of (1a), thiosemicarbazide and ethyl bromo acetate has been found to run successfully and gave the titled 2-(4-(1-phenyl-3-pyrazol-4-yl)methylene-2-hydrazolyl)-4-thiazolidinone (8a) in aqueous emulsion of the surfactant at 50-60°C under ultrasonication, (Scheme 4.3, Table 4.4).
To examine the catalytic efficiency of cationic and anionic surfactants particularly quaternary ammonium bromides, the one pot cyclocondensation was carried. For this we used sodium dodecyl sulphate (SDS), tetraethyl ammonium bromide (TEAB), tetrabutyl ammonium bromide (TBAB), TTAB and CTAB for the model reaction. It was noted that the product yields were increased with increasing alkyl chain length of the surfactants. SDS, TEAB, TBAB and TTAB gave 76%, 59%, 61% and 76% yield (Table 4.4), respectively. However CTAB gave excellent product with 82% yield (Table 4.4, entry-5) within 1h.

The success of CTAB as an efficient catalyst could be related to the number of carbon atoms in its hydrophobic chain reaching to saturation. Initially 20 mol% CTAB was used for condensation. It was noted that the yield of product was found to be increased (70-82%) with increasing concentration of the surfactant (5-20 mol%) in its aqueous emulsion (Table 4.4, entry-5). On increasing the load of the catalyst from 20 to 30 mol%, the yield of desired product was not affected. From the results it was clear that the optimized concentration of surfactant required is 20 mol%. In absence of surfactants and ultrasound irradiation the cyclocondensation/model reaction could not run in water even at reflux.

To optimize the reaction temperature the reactions were carried out at different temperatures, ranging from room temperature to 60 °C. We found that at room temperature the rate of reaction was too slow and yield of the product was improved when it was run at 50 to 60 °C. Therefore the condensation was carried under ultrasound irradiation in presence of aqueous emulsion of CTAB at 60 °C.

After optimizing the conditions of cyclocondensation, to expand the scope of the reaction, the other 3-(4-substitutedphenyl)-1-phenyl-1H-pyrazole-4-carbaldehydes (1b-g) have also been separately cyclocondensed with thiosemicarbazide and ethyl
bromoacetate under optimized conditions and obtained good to better yields of 2-(4-(1-phenyl-3-(4’-substituted phenyl)-pyrazol-4-yl) methylene-2-hydrazolyl)-thiazolidino-4-ones (8b-g).
**Table 4.3:** Physical data of 2-phenyl methylene hydrazolyl-4-thiazolidinone (7a-g).\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R</th>
<th>Yield (%)</th>
<th>Melting Point (°C)</th>
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<td>1</td>
<td>7a</td>
<td>-H</td>
<td>92</td>
<td>255-257</td>
</tr>
<tr>
<td>2</td>
<td>7b</td>
<td>-CH(_3)</td>
<td>78</td>
<td>266-267</td>
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<td>-OCH(_3)</td>
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<td>254-256</td>
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<td>7f</td>
<td>-NO(_2)</td>
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<td>240-241</td>
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<td>7</td>
<td>7g</td>
<td>-Br</td>
<td>87</td>
<td>247-248</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: benzaldehyde (5a-g) (10 mmol), thiosemicarbazide (10 mmol), ethylbromo acetate (11 mmol), water (15 ml), at 50-60 °C for 30 min.

**Table 4.4:** Screening of surfactants for the synthesis of 2-(4-(1-phenyl-3-pyrazol-4-yl) methylene-2-hydrazolyl)-thiazolidino-4-ones (8a).\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surfactant</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
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<tr>
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<td>TEAB</td>
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<tr>
<td>5</td>
<td>CTAB (5, 10, 15, 20 mol%)</td>
<td>70, 71, 78, 82</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 1a (3 mmol), thiosemicarbazide (3 mmol), ethylbromoacetate (4 mmol), surfactant in water (15 mL), at 50-60 °C; \(^b\)Isolated yields.
Table 4.5: Physical data of 2-(4-(1-phenyl-3-(4’-substituted phenyl)-pyrazol-4-yl)methylene-2-hydrazolyl)-thiazolidino-4-ones (8a-g).a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R</th>
<th>Yield (%)</th>
<th>Melting Point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8a</td>
<td>-CH₃</td>
<td>78</td>
<td>250-252</td>
</tr>
<tr>
<td>2</td>
<td>8b</td>
<td>-H</td>
<td>82</td>
<td>284-286</td>
</tr>
<tr>
<td>3</td>
<td>8c</td>
<td>-OCH₃</td>
<td>80</td>
<td>198-200</td>
</tr>
<tr>
<td>4</td>
<td>8d</td>
<td>-Cl</td>
<td>74</td>
<td>202-204</td>
</tr>
<tr>
<td>5</td>
<td>8e</td>
<td>-Br</td>
<td>69</td>
<td>273-274</td>
</tr>
<tr>
<td>6</td>
<td>8f</td>
<td>-NO₂</td>
<td>72</td>
<td>287-289</td>
</tr>
<tr>
<td>7</td>
<td>8g</td>
<td>-OH</td>
<td>71</td>
<td>297-298</td>
</tr>
</tbody>
</table>

aReaction conditions: 3-(4-substitutedphenyl)-1-phenyl-1H-pyrazole-4-carbaldehydes (3 mmol), thiosemicarbazide (3 mmol), ethylbromo acetate (4 mmol), CTAB (20 mol%), water (15 ml) at 50-60 °C for 1h.
Experimental

Synthesis of 2-phenyl methylene hydrazolyl-4-thiazolidinone (7a)

A mixture of benzaldehyde (10 mmol), thiosemicarbazide (10 mmol) and ethylbromo acetate (11 mmol) in water (15 ml) was subjected to ultrasound irradiation at 50-60°C. Progress of the reaction was monitored by thin layer chromatography. After 30 min the solid was obtained and was filtered, dried and purified by crystallization using ethanol.

Similarly the other compounds, (7b-g) of the series were prepared. The melting points and the yields of the derivatives are recorded in Table 4.3.

Spectral analysis

Following is a spectral data of one of the representative products from the series, 2-phenyl methylene hydrazolyl-4-thiazolidinone (7a).

**IR** (KBr, ν cm⁻¹) Characteristic absorptions:
3447 (N-H stretching), 3234 (Ar-H stretching), 2930 (C-H stretching), 1690 (C=O stretching) and 1632 (C=N stretching).

**MS** (Scanning mode, ESI⁺): m/z (% intensity):
219.9 (M⁺, 9), 218.9 (65) and 190.9 (100).

**¹H-NMR** (200 MHz, DMSO, δ ppm):
4.21 (s, 2H), 7.85-8.20 (m, 5H, Ar-H), 8.90 (s, 1H, -HC=N-N=) and no signal up to 9.35 for amido NH.
Chapter IV

Syntheses of Newer Therapeutic Agents for Diabetes Mellitus

Mass of compound (7a)

\[ \text{H-NMR of compound (7a)} \]

\[ \text{1H-NMR of compound (7a)} \]
Synthesis of 2-(4-(1-phenyl-3-pyrazol-4-yl) methylene-2-hydrazolyl)-imino thiazolidino-4-one (8a)

A mixture of 1,3-phenyl-4-methyl phenyl-1H-pyrazole-4-carbaldehyde (1a) (3 mmol), thiosemicarbazide (3 mmol), ethyl bromoacetate (4 mmol) and CTAB (20 mol%) was irradiated under ultrasound in water (15ml) at 50-60°C. Reaction was monitored by thin layer chromatography. After 1h of ultrasound irradiation, reaction mixture extracted with ethyl acetate. Organic layer was concentrated under reduced pressure. Solid obtained was purified by crystallization.

Similarly the other compounds, (8b-g) of the series were prepared. The melting points and the yields of the derivatives are recorded in Table 4.5.

Spectral analysis:
Following is a spectral data of one of the representative products from the series, 2-(4-(1-phenyl-3-pyrazol-4-yl) methylene-2-hydrazolyl)-imino thiazolidino-4-ones (8a).

**IR (KBr, ν cm⁻¹) Characteristic absorptions:**
3433 (N-H stretching), 3113 (Ar-H stretching), 2928 (C-H stretching), 1674 (C=O stretching) and 1640 (C=N stretching).

**MS (Scanning mode, ESI⁺):** m/z (% intensity):
375 (M⁺, 100), 377 (26) and 378 (10).

**¹H-NMR (200 MHz, CDCl₃, δ ppm):**
2.43 (s, 3H, CH₃), 3.87 (s, 2H, CH₂), 7.35-7.90 (m, 9H, Ar-H), 8.40 (s, 1H, -HC=N-N=) and 8.55 (s, 1H, pyrazolyl-H)
Chapter IV

Syntheses of Newer Therapeutic Agents for Diabetes Mellitus

Mass spectrum of compound (8a)

\[\text{Mass spectrum of compound (8a)}\]

\[\text{1H-NMR of compound (8a)}\]
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