ECO-FRIENDLY SYNTHESIS OF THIAZOLIDINONE DERIVATIVES AND THEIR BIOLOGICAL STUDIES

A THESIS SUBMITTED TO THE UNIVERSITY OF THE PUNJAB FOR THE AWARD OF DEGREE OF DOCTOR OF PHILOSOPHY 2010

By

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DEDICATED

TO

My Loving Family

Prof. Dr. Muhammad Nawaz Chaudhry

Prof. Dr. Taseer Hussain

The prayers and guidance of all helped and enabled me to

ACCOMPLISH THIS PROJECT.
CERTIFICATION

I, Muhammad Naeem, declare that this thesis, submitted in fulfillment of the requirement for the award of Doctor of Philosophy, in department of College of Earth and Environmental Sciences, University of the Punjab, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualification at any other academic institution.

Muhammad Naeem
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All praises to the Almighty Allah who induced the man with intelligence, knowledge, sight to observe, mind to think and judge. Peace and blessings of Allah be upon the Holy Prophet (PBUH) and his pure and pious progeny who exhorted his followers to seek knowledge from cradle to grave.

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ABBREVIATIONS

ILs = Ionic Liquids
C = Compound
MW = Microwave
SPC = Solid Phase Catalyst
LPC = Liquid Phase Catalyst
NSAIDs = Nonsteroidal Anti-Inflammatory Drugs
SDA = Saburaud’s Dextrose Agar
MIC = Minimum Inhibition Concentration
DMF = Dimethylformamide
NMR = Nuclear Magnetic Spectrometer
USP = United State Pharmacopia
BP = British Pharmacopia
FTIR = Fourier Transformation Infrared Spectroscopy
TBAB = Tetraethylammonium bromide
TEBAC = Trethylbenzylammonium chloride
PEG = Polyethyleneglycol
DMF = dimethylformamide
SDA = dextrose agar
CFU = Colonies forming unit
Av. = Average
FC = Flash chromatography
TLC = Thin layer chromatography
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Chapter 1</th>
<th>Introduction</th>
<th>Page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>Introduction</td>
<td>02</td>
</tr>
<tr>
<td>1.1</td>
<td>Organic synthesis under microwave</td>
<td>05</td>
</tr>
<tr>
<td>1.2</td>
<td>Chemistry of 4-Thiazolidione</td>
<td>05</td>
</tr>
<tr>
<td>1.3</td>
<td>Microwaves</td>
<td>07</td>
</tr>
<tr>
<td>1.3.1</td>
<td>Microwave equipment used in organic synthesis</td>
<td>09</td>
</tr>
<tr>
<td>1.3.2</td>
<td>Microwave heating</td>
<td>09</td>
</tr>
<tr>
<td>1.3.3</td>
<td>Heating effect of microwaves</td>
<td>12</td>
</tr>
<tr>
<td>1.4</td>
<td>Thiazolidinones; A-Versatile Biologically Active Compounds</td>
<td>13</td>
</tr>
<tr>
<td>1.4.1</td>
<td>Antibacterial activity</td>
<td>13</td>
</tr>
<tr>
<td>1.4.2</td>
<td>Antifungal activity</td>
<td>15</td>
</tr>
<tr>
<td>1.4.3</td>
<td>Anti-inflammatory activity</td>
<td>16</td>
</tr>
<tr>
<td>1.4.4</td>
<td>Anticonvulsant activity</td>
<td>18</td>
</tr>
<tr>
<td>1.4.5</td>
<td>Hypnotic activity</td>
<td>18</td>
</tr>
<tr>
<td>1.4.6</td>
<td>Antitubercular activity</td>
<td>19</td>
</tr>
<tr>
<td>1.4.7</td>
<td>Anthelmintic activity</td>
<td>19</td>
</tr>
<tr>
<td>1.4.8</td>
<td>Cardiovascular effects</td>
<td>21</td>
</tr>
<tr>
<td>1.4.9</td>
<td>Anticancer activity</td>
<td>22</td>
</tr>
<tr>
<td>1.4.10</td>
<td>Antiviral activity</td>
<td>22</td>
</tr>
<tr>
<td>1.4.11</td>
<td>Antihistaminic activity</td>
<td>23</td>
</tr>
<tr>
<td>1.5</td>
<td>Antibacterial Activity of Compounds</td>
<td>24</td>
</tr>
</tbody>
</table>
1.5.1 Cylinder Plate or Hole Plate Method 25
1.5.2 Turbidimetric Method 25
1.5.3 Streak Method 26
1.5.4 Impregnated Filter Paper Disc Method 26
1.5.5 Thin Layer Chromatographic Method 27

<table>
<thead>
<tr>
<th>Chapter 2</th>
<th>Literature Survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Conventional Methods 28</td>
</tr>
<tr>
<td>2.1.1</td>
<td>Reaction dependant upon nucleophilic activity 28</td>
</tr>
<tr>
<td>2.1.1.1</td>
<td>Aldol condensation 29</td>
</tr>
<tr>
<td>2.1.1.2</td>
<td>Reaction with nitrous acid and nitroso compounds 29</td>
</tr>
<tr>
<td>2.1.1.3</td>
<td>Reaction with diazonium salts 30</td>
</tr>
<tr>
<td>2.1.1.4</td>
<td>Reaction with diphenylfomnamidine 31</td>
</tr>
<tr>
<td>2.1.1.5</td>
<td>Reaction with ortho esters 31</td>
</tr>
<tr>
<td>2.1.1.6</td>
<td>Reaction with sodium 32</td>
</tr>
<tr>
<td>2.2</td>
<td>Reaction with electrophilic carbon atoms 32</td>
</tr>
<tr>
<td>2.3</td>
<td>4-thiazolidinone derivatives prepared by other conventional methods 33</td>
</tr>
<tr>
<td>2.4</td>
<td>Non conventional methods 43</td>
</tr>
</tbody>
</table>

| 46 |
| Project Aims |

<table>
<thead>
<tr>
<th>Chapter-3</th>
<th>Materials and Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Instrumentation 48</td>
</tr>
<tr>
<td>3.2</td>
<td>Environment friendly catalysts 49</td>
</tr>
<tr>
<td>3.3</td>
<td>Chemicals and Reagents 49</td>
</tr>
<tr>
<td>3.4</td>
<td>Synthesis of 4-thiazolidinone derivatives 50</td>
</tr>
<tr>
<td>3.4.1</td>
<td>Synthesis of 4-thiazolidinone analogues (88-97) with non conventional procedures 50</td>
</tr>
<tr>
<td>3.4.2</td>
<td>Synthesis of 4-thiazolidinone derivatives (98-107) by adopting non conventional procedures 63</td>
</tr>
<tr>
<td>3.4.3</td>
<td>Synthesis of 4-thiazolidinone derivatives (108-117) with non conventional procedures 72</td>
</tr>
<tr>
<td>3.4.4</td>
<td>Synthesis of 4-thiazolidinone derivatives (118-127) with non conventional procedures 81</td>
</tr>
</tbody>
</table>
3.4.5 Synthesis of 4-thiazolidinone derivatives with non conventional procedures (128-137) 91
3.4.6 Synthesis of 4-thiazolidinone derivatives with non conventional procedures (138-147) 101

Chapter 4 4.0 Results and Discussion 112

4.1 Biological characterization of synthesized compounds 134
4.1.1 Introduction 134
4.1.2 Methodology for antibacterial screening 134
4.1.3 Antibacterial activity of compounds (88-107) 135
4.1.4 Activity of another two series of 4-thiazolidinones derivatives (108-127) 137
4.1.5 In vitro evaluation of antibacterial activity of novel 4-thiazolidinone derivatives (128-147) 138
4.2 Antifungal activity 144
4.2.1 Methodology for antifungal screening 144
4.2.2 Antifungal activity 145
4.3 Discussion of Biological Activity 147
4.3.1 In vitro evaluation of antibacterial activity of compounds 88-97 and 98-107 148
4.3.2 Antibacterial activity of compounds 108-127 148
4.3.3 Antibacterial activity in vitro of compounds 128-147 149
4.3.4 In vitro evaluation of antifungal activity of compounds 88-147 150

Conclusion 153

Chapter 5 References 155

Annexure-I Publications resulted from this work 167
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Serial number</th>
<th>Description</th>
<th>Page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1</td>
<td>Microwave effects on organic reactions</td>
<td>04</td>
</tr>
<tr>
<td>Table 2</td>
<td>Synthesis of novel compounds and intermediates under microwave radiation</td>
<td>114</td>
</tr>
<tr>
<td>Table 3</td>
<td>Percentage yield and time of conventional and non conventional procedures (88-97)</td>
<td>116</td>
</tr>
<tr>
<td>Table 4</td>
<td>Novel compounds synthesized under microwave radiation</td>
<td>118</td>
</tr>
<tr>
<td>Table 5</td>
<td>Percentage yield and time of conventional and non conventional procedures (98-107)</td>
<td>119</td>
</tr>
<tr>
<td>Table 6</td>
<td>Novel compounds under microwave radiation</td>
<td>121</td>
</tr>
<tr>
<td>Table 7</td>
<td>Percentage yield and time of conventional and non conventional methods (108-117)</td>
<td>122</td>
</tr>
<tr>
<td>Table 8</td>
<td>Novel compounds under microwave radiation</td>
<td>124</td>
</tr>
<tr>
<td>Table 9</td>
<td>Percentage yield comparison between conventional and non conventional procedures (128-137)</td>
<td>124</td>
</tr>
<tr>
<td>Table 10</td>
<td>Novel compounds (128-137) under microwave radiation</td>
<td>126</td>
</tr>
<tr>
<td>Table 11</td>
<td>Percentage yield and time of conventional and non conventional procedures (128-137)</td>
<td>127</td>
</tr>
<tr>
<td>Table 12</td>
<td>Novel compounds (138-147) under microwave radiation</td>
<td>129</td>
</tr>
<tr>
<td>Table 13</td>
<td>Percentage yield and time of conventional and non conventional procedures (138-147)</td>
<td>130</td>
</tr>
<tr>
<td>Table 14</td>
<td>Environmental factors of various chemical Industries</td>
<td>131</td>
</tr>
<tr>
<td>Table</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>15</td>
<td>Antibacterial response of compounds (88-107)</td>
<td>136</td>
</tr>
<tr>
<td>16</td>
<td>Antibacterial response of compounds (108-127)</td>
<td>137</td>
</tr>
<tr>
<td>17</td>
<td>Antibacterial response of compounds (128-147)</td>
<td>139</td>
</tr>
<tr>
<td>18</td>
<td>Percentage of inhibition of compounds (88-107) and (98-107) against fungi F1-F7</td>
<td>145</td>
</tr>
<tr>
<td>19</td>
<td>Percentage of inhibition of compounds (108-117) and 118-127 against fungi F1-F7</td>
<td>146</td>
</tr>
<tr>
<td>20</td>
<td>Percentage of inhibition of compounds 128-137 and 138-147 against fungi F1-F7</td>
<td>147</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>Serial number</th>
<th>Description</th>
<th>Page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fig. 1</td>
<td>A modified microwave oven for microwave photochemistry experiments</td>
<td>10</td>
</tr>
<tr>
<td>Fig. 2a</td>
<td>Microwave induced dipole rotation</td>
<td>11</td>
</tr>
<tr>
<td>Fig. 2b</td>
<td>Microwave induced ionic conduction</td>
<td>11</td>
</tr>
<tr>
<td>Fig. 3</td>
<td>Over all percentage yield comparison between conventional, unconventional microwave and microwave with catalysts</td>
<td>133</td>
</tr>
<tr>
<td>Fig. 4</td>
<td>Reaction time comparison between conventional, microwave and microwave with catalysts</td>
<td>133</td>
</tr>
<tr>
<td>Fig. 5</td>
<td>The inhibition zones obtained for the selected compounds on different pathogens in the qualitative screening assay.</td>
<td>140</td>
</tr>
<tr>
<td>Fig. 6</td>
<td>Antifungal activity of compounds (88-107) against the fungi F1-F7</td>
<td>151</td>
</tr>
<tr>
<td>Fig. 7</td>
<td>Antifungal activity of compounds (108-127) against the fungi F1-F7</td>
<td>151</td>
</tr>
<tr>
<td>Fig. 8</td>
<td>Antifungal activity of compounds (128-147) against the fungi F1-F7</td>
<td>152</td>
</tr>
</tbody>
</table>
ABSTRACT

Microwave heating, ionic liquids and solid phase catalysts were employed and studied for the preparation of various 4-thiazolidinone derivatives and for “in vitro” antibacterial and antifungal activity. These techniques revealed several advantages over the conventional methods.

In combination with microwave radiation, ionic liquids were used as phase transfer catalysts (PTC) and montmorillonite clays (K10 and KSF types) were used as solid phase catalysts. The catalytic efficiency of montmorillonite KSF was marginally inferior to that of montmorillonite K10. Compounds pertaining to main six different series were synthesized. In the first series; two methods Microwave procedure-I: Multi-Component Reaction in DMF and Microwave procedure-II: Solvent free, Multi-Component Reaction were used and it was found that first was better in yield ranging from 82.4% to 96.0% while yield in procedure-II ranging from 42.6% to 84.6%. The compound 4,6-dimethylpyrimidin-2-amine was treated with disubstituted aromatic aldehydes in dimethylformamide to form a Schiff base and Schiff base was further treated with sulfanyl acetic acid under microwave radiation to obtain the compounds (88-97). The compounds of first series were synthesized and elucidated as 2-(2,4-dimethylphenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (88), 3-(4,6-dimethylpyrimidin-2-yl)-2-(2-hydroxy-4-methylphenyl)-thiazolidin-4-one (89), 2-(2,4-dihydroxyphenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (90), 2-(2,4-dichlorophenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (91), 3-(4,6-dimethylpyrimidin-2-yl)-2-(2-hydroxy-4-methoxyphenyl)-thiazolidin-4-one (92), 2-(4-chloro-2-methylphenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (93), 3-(4,6-dimethylpyrimidin-2-yl)-2-(4-fluorophenyl)-thiazolidin-4-one (94), 3-(4,6-dimethylpyrimidin-2-yl)-2-(4-nitrophenyl)-thiazolidin-4-one (95), 2-(2,4-difluorophenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (96) and 2-(3-(dimethylamino)phenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (97).

In the second series (98-107); two methods Microwave procedure-I: Multi-Component Reaction using Montmorillonite Clays (K-10 and KSF) and Microwave procedure-II: Solvent free, Multi-Component Reaction were employed. First procedure was found better in yield ranging from (yield 78.4% to 94.1% with K-10 and 68.3% to 88.1% with KSF) while yield in second procedure ranging from 14.3%
to 76.4%. In this procedure Schiff base was treated with mercaptoacetic acid under microwave radiation followed by the condensation reaction of aniline and substituted benzaldehydes. The compounds 2-(3,5-dimethylphenyl)-3-phenyl-thiazolidin-4-one (98), 2-(3-hydroxy-5-methoxyphenyl)-3-phenyl-thiazolidin-4-one (99), 2-(3-chloro-5-methylphenyl)-3-phenyl-thiazolidin-4-one (100), 2-(3,5-dichlorophenyl)-3-phenyl-thiazolidin-4-one (101), 2-(3-nitrophenyl)-3-phenyl-thiazolidin-4-one (102), 2-(3-ethoxyphenyl)-3-phenyl-thiazolidin-4-one (103), 2-(3-methoxyphenyl)-3-phenyl-thiazolidin-4-one (104), 2-[3-(dimethylamino)phenyl]-3-phenyl-thiazolidin-4-one (105), 2-(3,5-difluorophenyl)-3-phenyl-thiazolidin-4-one (106) and 2-(3,5-dihydroxyphenyl)-3-phenyl-thiazolidin-4-one (107) were obtained.

For the compounds (108-117), two methods Microwave procedure-I: Ionic Liquids (PEG, TBAB and TEBAC) and Microwave procedure-II: Solvent free, Multi-Component Reaction were used. The second procedure was found better in yield and environmentally than Ionic Liquids (PEG, TBAB and TEBAC). The yield ranged from 33.4%-48.8% with TBAB, 33.5%-52.2% with PEG and 20.4%-32.4% with TEBAC while in solvent free procedure-II 66.8% to 92.8%. The compounds 1,3-dipyridin-2-ylthiourea, chloroacetic acid and different aromatic aldehydes were used for the preparation of compounds (108-117) of third series named as 5-benzylidene-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (108), 5-(4-methoxybenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (109), 5-(2-hydroxy-4-methoxybenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (110), 5-[4-(dimethylamino)benzylidene]-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (111), 5-(2,4-dichlorobenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (112), 5-(4-nitrobenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (113), 5-(4-ethoxybenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (114), 5-(2,4-difluorobenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (115), 5-(4-ethylbenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (116) and 5-(1,3-benzodioxol-5-ylmethylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (117).

In the forth series; two methods Microwave procedure-I: Multi-Component Reaction using Montmorillonite Clays (KSF and K-10) and Microwave procedure-II: Solvent free, Multi-Component Reaction were used and it was found that first was better in yield ranging from 78.8% to 96.1% with K-10 and 70.8% to 84.2% with KSF.
while yield in second ranging from 34.6% to 78.8%. In this series compounds (118-127) were synthesized by adopting environmentally safe procedure. (4-substituted-phenyl)methylidene]aniline was treated with sulfanyl(thioxo)acetic acid in the presence of montmorillonite clays under microwave radiation for ten to twelve minutes. The compounds (118-127) (5-benzylidene-3-phenyl-2-thioxo-thiazolidin-4-one (118), 5-(4-methylbenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (119), 5-(4-methoxybenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (120), 5-(3-hydroxy-4-methoxybenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (121), 5-[4-(dimethylamino)benzylidene]-3-phenyl-2-thioxo-thiazolidin-4-one (122), 5-(4-nitrobenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (123), 5-(2,4-dichlorobenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (124), 5-(4-ethoxybenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (125), 5-[2-(furan-2-yl)benzylidene]-3-phenyl-2-thioxo-thiazolidin-4-one (126) and 5-(2,4-difluorobenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one) (127) were synthesized.

The compounds (128-137) of fifth series were prepared by using environmentally benign procedure and reaction time was also dramatically reduced. In this series two methods Microwave procedure-I: Multi-Component Reaction using Montmorillonite Clays (KSF and K-10) and Microwave procedure-II: Solvent free, Multi-Component Reaction were employed and procedure-I was found better in yield ranging yields ranging from 78.8% to 94.4% with K-10 and 68.9-% to 88.6% with KSF while yield in procedure-II ranging from 34.4% to 65.3%. Sulfanylacetic acid was reacted with (2,5-disubstituted-phenyl)methylidene-4-methoxypyrimidin-2-amine followed by the condensation between 4-methoxypyrimidin-2-amine and various aldehydes. The compounds 2-(2,5-dimethylphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (128), 2-(4-ethylphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (129), 2-(4-methoxyphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (130), 2-(2-hydroxy-5-methoxyphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (131), 2-(4-ethoxyphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (132), 2-[4-(dimethylamino)phenyl]-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (133), 2-(2,5-dichlorophenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (134), 2-(2,5-difluorophenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (135), 2-(2,5-dihydroxyphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (136), 2-[3-(furan-2-yl)phenyl]-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (137) were thus achieved.
For the compounds (138-147), Microwave procedure-I: Multi-Component Reaction using Ionic Liquids (PEG, TBAB and TEBAC) and Microwave procedure-II: Solvent free, Multi-Component Reaction was used. Yield obtained with Ionic Liquids ranging from 73.4%-88.8% with TBAB, 33.5%-58.2% with PEG and 44.4%-62.4% with TEBAC than yield with second procedure ranging from 12.0% to 64.5%. Ionic liquids (ILs) are advantageous over conventional methods in terms of environment, time and cost. In this series of compounds (138-147) 3-phenyl-2-(phenylimino)-5-(phenylmethylidene)-4-thiazolidinone (138), 5-(4-methylbenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (139), 5-(4-methoxybenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (140), 5-(2-hydroxy-4-methoxybenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (141), 5-(4-ethoxybenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (142), 5-(4-nitrobenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (143), 5-(2, 4-dihydroxybenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (144), 5-(2,4-dichlorobenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (145), 5-(2,4-difluorobenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (146) and 5-[4-(dimethylamino)benzylidene]-3-phenyl-2-(phenylimino)-thiazolidin-4-one (147) were obtained.

Chromatographic techniques such as thin layer chromatography and column chromatography and solvent extraction were used for purification of active ingredients. Structural elucidation of the compounds synthesized were carried out using Infrared, $^1$H-NMR, $^{13}$CNMR, elemental analyzer and Mass Spectrometry.

All the synthesized compounds were screened for antibacterial activities (in vitro); which exhibited different activities depending on the nature and position of the substituents on the thiazolidinones ring. The compounds containing Fluoro group exhibited comparable or higher antibacterial activity than the existing antibiotics like Ciprofloxacin (standard) against E. coli, S. aureus, B. subtilis, and P. aeruginosa. Most of the thiazolidinone analogues showed significant activity against all the strains used in the present studies.
Chapter 1

http://www.goma.demon.co.uk/eco/ecoselect.html
INTRODUCTION

In order to reduce the environmental impact there is a need for clean chemical processes including monitoring analysis, synthetic procedures, catalysts and reaction conditions. To achieve these goals, green chemistry is being developed based on innovative and unconventional synthetic procedures including reactions carried out in water\(^1-^2\) (normal\(^3\) and super heated under high pressure\(^4\)), in supercritical fluids\(^5-^6\), in ionic liquids\(^7\), in micro emulsions\(^8\), in solvent free conditions\(^9\), by ultrasounds\(^10\) and microwaves\(^11-^12\) that must allow regio and stereo selectively products to be prepared with high yields. The concept of green chemistry not only involves the planning of new procedures and the synthesis of new environmentally benign materials, but also requires a new chemical mentality along with new energetic and research development policy.

Thiazolidinone moiety possesses several biological activities\(^13-^14\) and it is essential precursor for microbiological studies even many other applications. In recent years, the literature has shown a great increase both in academic and in commercial research in the preparations, reactions and the physiological activities of these compounds. These observations served as an impetus for the extension of investigation in the field of synthesis of 4-thiazolidione derivatives in the hope of discovering compounds with good pharmacological properties. The peak of research activity is yet to find in this vast and interesting area of study; much more needs to be done and achieved. The synthesis and chemistry of 4-thiazolidinones using non-conventional, environment friendly procedures is investigated in this study.

Today in the modern world scientists are worried and trying to develop and discover new environment friendly synthetic methodologies for organic compounds. Microwave irradiation, as an unconventional energy source, has been used for a variety of applications including organic synthesis\(^15\) wherein chemical reactions are
accelerated because of selective absorption of microwave energy by polar molecules, non-polar molecules being inert to the microwave dielectric loss. The application of microwave irradiation in conjunction with the use of catalysts (ionic liquids and inorganic oxides) and in solvent free conditions enables organic reactions to occur expeditiously at ambient pressure\textsuperscript{16} thus providing unique chemical processes with special attributes such as enhanced reaction rates, higher yields and the associated ease of manipulation. These less cumbersome solvent free methods conducted at ambient pressure have become very popular wherein the neat reactants undergo facile reactions often on the surfaces of inorganic oxides such as alumina, silica and clay or ‘doped’ supports thus minimizing the use of organic solvents\textsuperscript{17}. From a practical standpoint, these reactions can be performed in open glass containers under solvent less conditions and simply involve mixing of neat reactants with the catalyst/promoter or their adsorption on mineral and exposing the reaction mixture briefly to microwaves.

The analogues of 4-thiazolidinone moiety were synthesized by various conventional methods like condensation with aldehydes, with nitrous acid and nitroso compounds, with diazonium salts, with diphenylfornamidim, with ortho esters, with sodium, substituted benzoyl chlorides with various 2-thiono-4-thiazolidinones, phthalic anhydride undergoes condensation at 5\textsuperscript{th} position of various 2-substituted imino-4-thiazolidinones in acetic anhydride and triethylamine.

Several microwave assisted condensation reactions such as aldol and Knoevenagel etc. have been accomplished using relatively benign reagents such as ammonium acetate. The conventional preparation of imines, amines, nitroalkenes and N-sulfonylimines involves the azeotropic removal of water from the condensation reaction intermediates that are usually catalyzed by p-toluenesulphonic acid, titanium(IV)chloride. The aldol condensation was the first reaction of this type to be investigated. The reaction was first performed with rhodanine and benzaldehyde or acetaldehyde, using sulfuric acid as the condensing agent. Later, sodium hydroxide in ethanolic solution, sodium ethoxide in ethanolic solution, anhydrous sodium acetate in acetic acid, anhydrous sodium acetate, acetic anhydride and acetic acid, ammonia and ammonium chloride in ethanolic solution,
ammonium hydroxide in ethanolic solution, diethanolamine, and piperidine were used as condensing agents\textsuperscript{18-25}.

New strategy has recently been developed for non conventional methods in organic synthesis. Microwave irradiation takes a particular place as it induces specific interaction between materials and wave of electromagnetic nature assimilated to dielectric heating. Microwave irradiation ranges from 1cm to 1m in wave length in the electromagnetic spectrum and are located between infrared and radio-radar frequency\textsuperscript{26}. Heating of products submitted to microwaves exposure can result from material-wave interaction. It is brought about by the transformation into heat of the part of energy in the electromagnetic waves. Heating by microwaves is therefore an original procedure to bring the advantages of speed, no inertia, quick energy transfer and no superficial over heating. Microwaves can be used to promote many organic synthesis; the material-wave interactions produce uniform heating of the reaction medium.

The specific heating effects of microwave are observed.

### Table-1 Microwave effects on organic reactions

<table>
<thead>
<tr>
<th>Serial number</th>
<th>Thermal Effects</th>
<th>Non-Thermal Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Dipolar polarization</td>
<td>Variation in activation parameters</td>
</tr>
<tr>
<td>02</td>
<td>Change space polarization Inserted</td>
<td>entropic effects (favoured orientation)</td>
</tr>
<tr>
<td>03</td>
<td>Better homogeneity in temperature</td>
<td>Hot spots (“false MW effects”)</td>
</tr>
<tr>
<td>04</td>
<td>Enhancement in collisions probabilities (A)</td>
<td>High localized microscopic temperature</td>
</tr>
</tbody>
</table>
1.1 Organic synthesis under microwave.

The applications of microwave that can be implemented in organic reactions are divided into two main types:

a) Type-1 reactions

In this type, reactions need long reaction times and high temperatures. Microwaves will bring lower decomposition of products, accelerate the chemical reactions and better yields.

b) Type-II reactions

In second type of reactions; reactions will be equilibrated by vaporization of small polar molecules.

The pioneering works are due to Gedye et al.\textsuperscript{27} and Giguere et al.\textsuperscript{28} who used domestic ovens and solvents for their experiments. The most common benefits achieved in the organic synthesis under microwaves are:

a) Very rapid reactions, a few minutes frequency, brought about by high and homogenous temperature combined with pressure effects (if conducted in closed vessels).

b) Higher degree of purity achieved due to short residence time at high temperatures, no local overheating, minor decomposition and minor occurrence of secondary reactions.

c) Yields often better, obtained within shorter time and with purer products.

Considering the advantages as reported for the organic synthesis by unconventional methods using microwave heating, attempts were made to synthesize 4-thiazolidinone analogues for their commercial and industrial uses.

1.2 Chemistry of 4-Thiazolidinone

4-thiazolidinone (1) is a derivative of thiazolidine (2) with a carbonyl group at 4\textsuperscript{th} position which belongs to an important group of heterocyclic compounds.
The methylene carbon atom at fifth position of 4-thiazolidinone possesses nucleophilic activity and attacks an electrophilic center. The reaction product loses water, forming a 5-unsaturated derivative of the 4-thiazolidinone. The reaction occurs in the presence of a base and the anion of the 4-thiazolidinone is the attacking species. The ease of formation of the anion and hence the degree of the nucleophilic activity is dependent not only on the electron-withdrawing effect of the adjacent carbonyl group, but also on the presence of other electron-withdrawing groups such as those attached to the second carbon atom. The electron attraction of sulfur of 2-thione group is greater than that of the oxygen of a 2-carbonyl group. The nucleophilic activity of 5-methylene carbon atom of 2-aryl-4-thiazolidinone or 2-arylmino-4-thiazolidinone should be influenced by the nature of the substituents attached to the aryl group.

The mobility of the hydrogen atoms in the methylene group depends much upon the electro-negativity and co-planarity of substitution on the exocyclic nitrogen. The aldehydes, however, react only on one 4-thiazolidinone moiety to give the corresponding 5-unsaturated products. The condensation of aldehydes with 2-alkyl- or aryl-4-thiazolidinones does not occur due to acetic acid and sodium acetate, possibly because of the decreased reactivity of the methylene group. The reactivity is increased due to presence of imino or thioxo groups at second position at 4-thiazolidinone. Three components substituted aromatic amines, substituted aromatic aldehydes and a mercapto acid are used to synthesize 4-thiazolidinone derivatives. These processes can be conducted in two ways, one pot (one step) and two step reactions.

4-thiazolidinone is a useful moiety for a variety of heterocyclic products including drugs, dyes and intermediates such as thiazol yellow, thioflavin T., thidiazuron, the uses of this class of chemicals (4-thiazolidinone derivatives) are as herbicides, insecticides etc. The thiazolidinones moiety is also associated
with broad spectrum of biological activities including antibacterial\textsuperscript{39-40}, antifungal, anti-inflammatory, hypnotic, anticonvulsant, antitubercular, antiviral, antihistaminic, anthelmintic, cardiovascular and anticancer. A number of 4-thiazolidinones derivatives were investigated for their inhibitory effects on the oxidation of the substrates of the tricarboxylic cycle and $\beta$-hydroxybutyrate by rat brain homogenates for respiratory activity\textsuperscript{41}.

### 1.3 Microwaves

Microwaves are electromagnetic radiation with a frequency range from 300 to 300,000 MHz with free space wavelengths of 1 m to 1 mm. The energy of microwaves is so low that only molecular rotation could be induced. The frequency used in heating applications is usually 2450 MHz (wavelength 12.2 cm) and for industrial heating applications 915 MHz (wavelength 32.8 cm) can also be used. The development of microwave technology was initiated by the invention of radar. Radar applications needed single frequency microwaves and this demand lead to the development of the magnetron. The heating effect of microwaves was discovered by accident. Percy Spencer from Raytheon Company was the first to realize the potential of microwaves as an everyday life application. Spencer's inventions lead to the first commercial microwave oven in 1954\textsuperscript{42}. The first publication on the use of microwaves in the heating of organic reactions is the modification of starch in 1974\textsuperscript{43}. According to most publications the first reactions to use microwave heating have been carried out in 1986\textsuperscript{44-45}. It took some time before microwave heating was widely accepted in organic synthesis, may be due to the non-reproducible results of the domestic microwave oven. After microwave reactors were developed specially for organic chemistry (pressure, temperature and power can be precisely measured and adjusted) microwave heating has reached ever-growing popularity, especially in pharmaceutical industry. Over the last decade microwaves have been intensively used in organic chemistry as a heating method. There are many excellent reviews on different applications where microwaves have been used\textsuperscript{46-51}. 
Scale up is one of the key questions in the microwave technique but not too many articles have been published yet on the subject. One of the drawbacks of microwaves is the penetration depth of radiation. When polar absorbing solvent is used as a reaction medium, the microwave power halves for every 2.5 cm traveled in medium. This feature limits the reactor diameter, which is a problem in scale-up. The penetration depth depends on the used wavelength, with lower wavelengths having higher penetration but at the same time longer wavelengths having lower energy. So by changing the wavelength it is possible to build bigger reactors. Another way to get around penetration problems is to build flow through reactors\textsuperscript{52}.

Microwave is particularly interesting due to its high efficiency, leading to drastically reduced reaction times, higher yield, purer products and environmentally safer methodologies. Microwave assisted synthesis under controlled conditions has many uses in the field of medical chemistry and pharmaceutical research. Microwave consists of an electric and magnetic field and thus represents electromagnetic energy. This energy can act as a non ionizing radiation that causes molecular motions of ions and rotation of the dipoles, but does not affect molecular structure. The rotation of the dipoles in an alternation field causes friction, which produces heat, up to 10ºC\textsuperscript{53}. The applied microwave field causes the molecules, on average to temporarily spend slightly more time orienting themselves in the direction of the electric field rather than in other directions. When the field is removed, thermal agitation returns the molecules to a disordered state in the relaxation time and thermal energy is released. Microwave assisted digestion, dissolution or extraction constitutes a thriving field gathering the thermal effects of microwaves and their chemical effects. Under microwaves, the energy transfer by dielectric loss. The propensity of a sample to undergo microwave heating depends on the dielectric properties, the dielectric loss factor (\(\varepsilon''\)) and the dielectric constant (\(\varepsilon'\)). The dielectric constant represents the ability of a substance to absorb microwaves, while the dielectric loss factor represents the ability of a substance to transform this energy into heat. Dielectric constants of acetone and ethanol are in the same range but ethanol possesses a much higher loss tangent. For this reason, ethanol couples better with microwave irradiation, resulting in a more rapid temperature increase.
In this high frequency (2450 MH)\(^5\), the charge space polarization\(^6\) can also intervene and can be of prime importance with semiconductors since it concerns materials, which contain free conduction electrons. This phenomenon is essential in heating solid particles, more or less magnetic, such as a variety of mineral oxides or metallic species\(^7\).

1.3.1 Microwave equipment used in organic synthesis

In order to carry out more accurately and safely organic reactions, microwave oven is simply modified by piercing a hole on the top of the cavity, this allows the introduction of a tube (acting as a air cooler) surmounted by a water cooler to maintain reactions under solvent reflux, or under inert atmosphere, or allowing the addition of compounds in multi step procedures. Thermocouple p type is adjusted inside the chamber with display on external to view and set the temperature and variable is fixed on magnetron to control the microwave intensity shown in Figure\-1.

1.3.2 Microwave heating

Dielectric loss is the amount of electromagnetic energy absorbed by molecules. Its origin is in how microwave energy is obstructed by matter (dielectric constant) and how energy is dissipated in the sample\(^8\). Molecular dipoles are normally randomly orientated, but they orientate themselves according to the external electric field. For small non-associated molecules (molecular weight < few hundred, no hydrogen bonding) dielectric relaxation times are so short that they follow the external electric field of microwaves and do not heat. Small associated and large molecules (dipoles) have such long relaxation times that they do not have time to orient themselves and thus the rapidly changing electric field cause heating when dipoles hit each other when some are relaxing and some are excited again (Figure 1a).
Figure-2  Microwave used in synthesis

A. Magnetron  
B. Reaction mixture and a magnetic stir bar  
C. Aluminum plate  
D. Magnetic stirrer  
E. Pyrometer,  
F. Circulating water in a glass tube  
G. Sensor to measure the intensity of microwave
Free ions in solution (in liquid or in ionic liquid) tend to follow the changing electric field by migrating with the field. This migration causes a current, which results in losses caused by resistance. Energy is then released in the form of heat. All ions migrate during irradiation, but only a fraction of the current is carried away by the medium. Therefore losses by ionic conduction depend on the concentration; size and charge of ionic species (Figure 1/b).
1.3.3 Heating effect of microwaves

It is well known that microwaves enhance reaction rates, increase selectivities and yields. The microwave heating effect is when a reaction is done in a polar microwave absorbing solvent. There is no microwave effect since the solvent absorbs most of the microwave energy and there is no additional energy going to the reactants. So, no matter what kind of reaction is done, no rate enhancement is detected due the microwave effect. Sometimes, it has been reported that rate enhancements was detected. Usually rate enhancements can be explained by superheating of the solvent. It is possible to achieve 10-15°C higher boiling points in polar solvents when they are heated with microwaves compared to conventional heating\(^{58-59}\). Polar absorbing reagents in non-absorbing solvent are a considerably harder case to explain. In this case microwave energy is mostly absorbed by reactants. The solvent acts as a heat sink, which cools the reactants down. Sometimes in these systems selectivity and yield can be lot better than in conventional heating, because overall temperature is lower than the temperature of the reactants. This prevents products from reacting further to by-products, because the solvent is cooler than the reactants and thus has a lower amount of energy to be released to by-product formation.

The reaction mechanism plays an important role when polar reagents are used in non-polar solvents. The reaction is “pushed” towards product if the transition microwaves state has a long enough life time it can absorb energy from microwaves and energy can be transferred to the activated complex. Microwave effect(s) can be seen in rare cases when the reactant acts as a solvent and no additional solvents are added. Reaction coordinates play an even more important role in this case, since reactants absorbs the microwave energy. This increases the probability of meeting of the activated complexes. There is a proposal that “hot spots” are generated in the reaction mixture and the reaction would take place mostly in the "hot spots". The existence of "hot spots" has been proven in solid and highly viscous materials\(^{60}\).

As a conclusion, using microwaves usually has a beneficial effect on reaction if a reaction needs heating. The specific microwave effect depends on different
factors, but it is quite hard to actually rule out the existence or lack of microwave
effect. Generally reactions give higher selectivity and yields when microwave heating
is used.

Three types of solvent free procedures can be coupled with microwave
activation.

a) Reactions between reactants, needing at least one liquid polar molecule, as
liquid-liquid or liquid-solid systems. In the absence of solvent the radiation is
absorbed directly by the reagents, so the effect of microwaves is more
marked\textsuperscript{61}.

b) Reactions between supported reagents on solid mineral supports in “dry
media” by impregnation of compounds on alumina, silicas or clays\textsuperscript{62-63}.

c) Phase transfer catalysis (PTC) conditions in the absence of organic solvent
when a liquid reagent acts both as a reactant and an organic phase\textsuperscript{64}.

1.4 Thiazolidinones; A Versatile Biologically Active
compounds

Several thiazolidinone analogues have been reported to show considerable
biological activities as antibacterial, antifungal, anti-inflammatory, anticonvulsant,
hypnotic, antitubercular, anthelmintic, cardiovascular, anticancer, antiviral and
antihistaminic. The details of some important activities of thiazolidinones reported
are given below.

1.4.1 Antibacterial activity

Studies have shown that thiazolidinones were more active than thiazoles
against some common bacteria\textsuperscript{65}. Kavitha\textsuperscript{66} reported more then 20 thiazolidinone
derivatives were tested against Bacillus subtilis and Escherichia coli and compared
with reference drugs. He concluded that synthesized compounds exhibited more
activity then reference drugs. This significant inhibitory activity can be attributed to
fluorine atoms and has been observed in thiazolidinone derivatives with different
positions (03).
Several analogues of 4-thiazolidinones (04) were synthesized and employed for their antibacterial studies against different strains like *S. aureus*, *B. subtilis*, *S. typhi* and *E. coli* of bacteria and were found to have significant antibacterial activity. It was seen that the presence of thiazolidinone ring was essential for antibacterial activity\textsuperscript{67}. The functional groups of organic molecules relationship with thiazolidinone proved the importance of basic precursor (thiazolidine).

\begin{align*}
\text{(03)} \\
2-(2,6-Difluoro-phenyl)-3-[2-(1-hydroxycyclohexyl)-2-(4-methoxy-phenyl)-ethyl]-4-thiazolidinone
\end{align*}

\begin{align*}
\text{(04)} \\
\text{Pyrazin-2-yloxy)-acetic acid}[3-(4-ethoxy-phenyl)-4-oxothiazolidin-2-ylidene]-hydrazide
\end{align*}
This antimicrobial activity attracted the attention of Bondock et al.\textsuperscript{68} and they synthesized novel 4-thiazolidinone derivatives of 6-chloro-1-oxo-2,3a,8,9-tetrahydro-1H-thiazolo[3,2-a]quinoline-7-carboxaldehyde and evaluated biological activity (antibiotic). Several 4-thiazolidinone derivatives were screened \textit{in vitro} against different bacterial strains \textit{E. coli} \textit{B. subtilis} and \textit{B. megaterium} by the agar diffusion technique\textsuperscript{69}. Some derivatives of 4-thiazolidinone were prepared and reported considerable biological activity by Vicini \textit{et al.}\textsuperscript{70}.

\subsection{Antifungal activity}

The antifungal activities against \textit{A. niger} at different concentrations of few compounds of 2-thioxo-4-thiazolidinone have been studied by Rao \textit{et al.}\textsuperscript{71}. Better yield and significant antifungal activity has been reported by Matolcsy \textit{et al.}\textsuperscript{72} against \textit{B. allii} and \textit{A. tenius} of 4-oxo-2-thionothiazolidine derivatives. Various 2-[[\textit{methylphenyl}imino]-3-hydroxyphenyl-thiazolidin-4-ones and other 4-thiazolidinone analogues (05) were synthesized and evaluated for antifungal activity against different fungal strains.

\begin{center}
\includegraphics[width=0.3\textwidth]{image.png}
\end{center}

\textit{A. tenius} (conc. of one ratio one thousand, one ratio five thousand and one ratio ten thousand) was found by (Z)-2-
(4-chlorobenzo[d]thiazol-2-ylimino)-3-ethyl-5-methylthiazolidin-4-one and (Z)-2-(5-chlorobenzo[d]thiazol-2-ylimino)-3-ethyl-5-methylthiazolidin-4-one\textsuperscript{73}.

\[
\text{(06)}
\]

8-(2-Amino-3-phenyl-propionyl)-4-dodecyl-1-thia-4-aza-spiro[4.5]decan-3-one

Compound 8-(2-Amino-3-phenyl-propionyl)-4-dodecyl-1-thia-4-aza-spiro[4.5]decan-3-one (06) and its derivatives were prepared and screened by Katti \textit{et al.}\textsuperscript{74} against two strains of \textit{C. albicans} and one strain of \textit{C. neoformans}. They were also evaluated of MIC in 100 mmoles followed double dilution standard method and found that the antifungal activity was of average to higher level against the various fungal strains. Dandia \textit{et al.}\textsuperscript{75} prepared various derivatives of thiazolidinone using microwave and screened it for antifungal activity. Three fungal strains, namely \textit{R. solani}, (causing root rot of okra), \textit{C. capsici}, (causing leaf spot) and \textit{F. oxysporum}, (causing wilt of mustard) were used in this screening and it was seen that the prepared derivatives showed significant antifungal activity against different fungal strains under test. The addition of thiazole ring increased the antifungal activity of these synthesized substances.

\subsection{1.4.3 Anti-inflammatory activity}

Anti-inflammatory agents are used to cure chronic and acute inflammation along with many others diseases. Ottana \textit{et al.}\textsuperscript{76} synthesized 4-thiazolidinone
derivatives and used them as anti-inflammatory agent. They found that 2-(2-(4-oxo-2-pentylthiazolidin-2-yl)ethyl)-2-pentylthiazolidin-4-one and other derivatives were good analgesic and anti-inflammatory agents. Dirosa et al.\textsuperscript{77} and Cuzzocrea et al.\textsuperscript{78} investigated derivatives of 2-imino-4-thiazolidinones and 5-amino-2-(3-hydroxyphenyl)thiophen-3(2\textit{H})-one. These were applied in rats and paw edema for anti-inflammatory activity \textit{in vivo} and received very promising results.

![Chemical structure](image)

\textbf{(07)}

5-bromo-2-(2-(2-flourophenyl)-5-methyl-4-oxothiazolidin-3-yl)benzoyic

\textit{Goel et al.}\textsuperscript{79} described and evaluated novel substituted thiazolidinones for anti-inflammatory activity. These were employed in albino rats as anti-inflammatory agent and showed very good results. The potency of 5-bromo-2-(2-(2-flourophenyl)-5-methyl-4-oxothiazolidin-3-yl)benzoic acid (07) derivatives were compared with reference drug (phenylbutazone) of known potency applied with four different doses i.e. 25, 50, 75 and 100 mmoles. The results were equal to the reference drug. The anti-inflammatory activity of 2-amino-5-(3-hydroxyphenyl)-1,3-thiazolidin-4-one was shown by Ottana \textit{et al.}\textsuperscript{80} Almost all the derivatives showed considerable activity in acute inflammation in rats. (2Z,5Z)-5-(4-methoxycyclohexa-2,4-dien-1-ylidene)-2-(phenylimino)-3-propyl-1,3-thiazolidin-4-one (08) showed very good paw edema inhibition as compared with indomethacin. Consequently, the compounds of 4-thiazolidinone and thiazole were found to show high level of anti-inflammatory activity.\textsuperscript{81}
1.4.4 Anticonvulsant activity

Kumar, Dwivedi, and Gupta et al.\textsuperscript{82-85} conducted anticonvulsant studies of various thiazolidinone derivatives of 2-(arylhydrazono)/(arylimino)-3-aryl/furfuryl/2-pyrimidyl/(alkylaryl)/(substitutedamino)/cycloalkyl/(3-(N-morpholin-4-yl-propyl)-1,3-thiazolidin-4-ones. These derivatives were evaluated against pentylenetetrazol-induced seizures at dose of 100 mg/kg in albino mice. Most of the compounds were found to exhibit protection against pentylenetetrazol-induced seizures and the degree of protection ranged up to 80%. However, no definite structure activity relationship could be observed regarding the anticonvulsant activity possessed by thiazolidinones.

1.4.5 Hypnotic activity

Several 3-(3-(N-morpholin-4-yl-propyl)-2-(arylimino)-4-thiazolidinones\textsuperscript{86} (09) and 2-(arylimino)-3-(pyrimidin-2-yl)-4-thiazolidinones\textsuperscript{87} (10) were evaluated for their ability to potentiate pentobarbital-induced hypnosis in mice at a dose of 100 mg/kg. All thiazolidinones were found to potentiate pentobarbital sleeping time. The increase in the duration of sleep ranged from 10 ±3 min in untreated control to 98.6 ±10 min in mice pretreated with substituted thiazolidinones.
1.4.6 Antitubercular activity

Several studies\(^{88-89}\) have shown that 4-thiazolidinone derivatives are possible antitubercular substances. Moreover Litvinchuk\(^ {90}\) have suggested that some derivatives of rhodanine have proven to exhibit antitubercular activity with minimum toxic effects\(^ {91}\). The structure activity relationship was studied by Kapustayak \textit{et al.}\(^ {92}\) of few 4-thiazolidinone analogues regarding tuberculostatic effects. It was seen that some derivatives inhibited the growth of \textit{H37Rv} strain, in a particular dilution \textit{i.e} 12.5 µg/mL\(^ {93-94}\). Similarly various thiazolidinone derivatives have been reported to be the cause of inhibition in the growth of \textit{H37Rv} strain\(^ {95-96}\). The activity of thiazolidin-4-one containing compounds on other Myobacterium strains has also been studied\(^ {97}\) and was found to give very good results.

1.4.7 Anthelmintic activity

Several derivatives of rhodanine studied were found to be important anthelmintic agents\(^ {98-99}\) against \textit{Hymenolepsis nana} and \textit{Syphacia obvelata} infections in mice, \textit{Asceridia galli} infections of chickens, \textit{Uncinaria stenocephala} infection in horses, \textit{Toxocera canis} in dogs and \textit{Ancylostoma caninum} infection in pigs.
The derivatives of 4-thiazolidinone (11) were reported as very effective anthelmintic agents particularly against horse strongyloids in the range of $10^{-3}$-$10^{-6}$ M\textsuperscript{100}. Some derivatives of 4-thiazolidinone, rhodanine and psedothioydentine showed very promising anathematic activity\textsuperscript{101-102}. They showed not only anthelmintic activity when administered alone but were also effective as anti-inflammatory and antibacterial agents. The compound 3-methyl-5-[(4-nitrophenyl)azo]rhodanine (12) was also reported by Brody \textit{et al.}\textsuperscript{103} as potent anthelmentic compound and Hussain \textit{et al.}\textsuperscript{104} synthesized 2-thiono-3-(4-chlorophnyl)-5-[(4-(4-methylpiperazino)phenyl] azo-4-thiazolidinone possessing anthelmementic activity against \textit{N. dubius} in mice.
1.4.8  Cardiovascular effects

The cardiovascular effects of different thiazolidinone analogues like 2-(cyclohexylimino)cyclopentyl-3-aryl-1,3-thiazolidin-4-one-5-ylacetic acids (13) have been studied in cats\textsuperscript{105}. It was seen that almost all thiazolidinone analogues induced hypotension of different levels. The time of this hypotensive activity was less than 15 minutes.

![Chemical structure of (13)](image1)

\[(\text{13})\]

\[\text{[(2Z)-2-(cyclohexylimino)-3-phenyl-1,3-thiazolidin-5-yl]acetic acid}\]

![Chemical structure of (14)](image2)

\[(\text{14})\]

\[3-(3-(((\text{benzo}[d][1,3]\text{dioxol-4-yloxy})\text{methyl})(\text{methyl})\text{amino})\text{propyl})-2-(3,5-di-\text{tert-butyl-4-hydroxyphenyl})\text{thiazolidin-4-one}\]

The analogues of 4-thiazolidinone induced different cardiovascular effects that depended on the substituents attached with the basic skeleton of thiazolidinone. The analogue (14) also showed positive effects on the myocardial oxygen consumption and the cardiac function in dogs\textsuperscript{106}. 
1.4.9 Anticancer activity

Gududuru\textsuperscript{107} studied a new series of 2-aryl-4-oxo-thiazolidin-3-yl amides and derivatives were synthesized and evaluated for their ability to inhibit the growth of prostate cancer cells. Study reported COX-2 inhibitors as potential drugs aimed at the prevention and treatment of cancer, especially colorectal cancer. Some representative 2-phenylimino-4-thiazolidinones have been investigated as potent inhibitors of the growth of human colon carcinoma cell lines with a different COX-2 expression. The antiproliferative in vitro screening was performed on five cell lines of human colon cancers, such as \textit{DLD-1}\textsuperscript{108}, \textit{HCT-116}\textsuperscript{109}, \textit{HT-29}\textsuperscript{110}, \textit{HCT-8}\textsuperscript{111}, and \textit{H-630}\textsuperscript{112}, obtained from the American Type Culture Collection (Manassas, VA); among them, \textit{HT-29} cell line expresses high COX-2 levels\textsuperscript{113-114}. Derivative 5-(3-trifluoromethyl benzylidene)-2,4-thiazolidinedione which does not interact with COX enzymes, inhibited the growth of HT-29 cells. This compound displayed activity on all cell lines, mainly on the DLD-1\textsuperscript{115}.

1.4.10 Antiviral activity

Some derivatives of thiazolidinone like 2,5-diphenyl-1,3-thiazolidin-4-one showed to have high efficacy in inhibition of various viruses (HIV-1) at very low quantity dilution with minimum cytotoxicity. Their mode of action was seen to be by inhibiting reverse transcriptase enzyme. Multifunctional ability of enzyme plays an important role in the human immunodeficiency virus (HIV). Novel derivatives of 4-thiazolidinone (15) were also reported by Barreca \textit{et al.}\textsuperscript{116} and he found their good anti-viral effects.

\begin{center}
\centering
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\textbf{(15)}
2-(2,6-dichloro-phenyl)-3-(6-methyl-pyridin-2-yl)-4-thiazolidinone
Katti et al.\textsuperscript{117} synthesized few derivatives of thiazolidinone with furfuryl amine and employed these as antiviral agents. These derivatives 2,3-diaryl substituted 4-thiazolidinone, 3-substituted 2-(2,6-dichlorophenyl)-3-(6-methylpyridin-2-yl)-1,3-thiazolidin-4-one and compound (16) showed promising HIV-RT inhibitory activity by determining their ability to inhibit the replication of HIV-1 (IIIB) in MT-4 cells with EC50 value of 0.204 mM.

![Chemical structure of compound 16](image)

2-(2,6-dichloro-phenyl)-3-furan-2-ylmethyl-4-thiazolidinone

1.4.11 Antihistaminic activity

Singh et al.\textsuperscript{118} and Agrawal et al.\textsuperscript{119} discussed the antihistaminic activity of substituted 4-thiazolidinones. The substitution of hydrophobic molecules at the benzene ring and combined effect of negative polar on over all compound increased the efficiency of antihistaminic activity.

![Chemical structure of compound 17](image)

2-(2,6-difluoro-phenyl)-3-(3-dimethylamino-propyl)-4-thiazolidinone
Diurno\textsuperscript{120} prepared novel series of 4-thiazolidinone derivatives (17) and studied their inhibition ability to the specific quantity applied on pig. His study found the new horizon of antihistamine because the synthesized compounds showed excellent results. Emmet \textit{et al.}\textsuperscript{121} have reported twenty derivatives of thiazolidinones (18) as free bases for bio assays. These derivatives were employed on guinea pig ileum and evaluated for their capability to inhibit the contractions by induced-histamine. They have highlighted thiazolidinone as an essential moiety for antihistaminic drugs. Walczynski, \textit{et al.}\textsuperscript{122-123} synthesized thiazolidinone analogues and found the application of cumulative hydrophobic effect in addition to antihistaminic activity.

![Chemical Structure](image)

3-{3-[3-(dimethylamino)propyl]-4-oxo-1,3-thiazolidin-2-yl}benzamide

\subsection*{1.5 Antibacterial Activity of Compounds}

The testing of antibacterial properties of various compounds \textit{in vitro} was carried out by bringing together the micro organisms and the substance under test. With the passage of time, the pharmacologists have developed various technical methods to assess the antibacterial activity of a test substance. The experiments were performed for quantitative and qualitative assessments.

Biological potency is expressed in terms of micro-organism per unit determined by comparing the amount of killing or bacterioatasis of a test organism affected by the substance under test, with that affected by a standard preparation.
under rigidly controlled conditions. This *in vitro* test may further be extended on animate objects to prove the effectiveness of drug in a given infection.

General methods for testing of the antibacterial properties and potencies of compound are as follows.

### 1.5.1 Cylinder Plate or Hole Plate Method

This method is used to determine the potency of antibiotics against various microorganisms. A suspension or solution of a known strength is placed in one set of the steel cylinders, and various dilutions of antibiotics/antibacterial compounds to be tested are placed in the others. The cups rest on a culture medium inoculated with bacteria. The antibacterial action of the antibiotic/antibacterial compound produces a clear zone around the cylinder, the size of which is directly related to the potency of the test compounds.

In the Hole Plate method, seeded agar is spread in the sterilized petridishes instead of the cups in the above procedure. Holes of definite diameter are carved in the seeded agar and the known quantities of standard and the test antibiotics are poured in to these holes.

### 1.5.2 Turbidimetric Method

Turbidimetric method is also known as tube dilution technique. Increasing amount of the antibiotic under examination is placed in a series of culture tubes containing a suitable broth medium inoculated with the test organism. The dosage of drugs used in the test illustrated is indicated by the labels on the tubes in the top rack. The tube at the extreme left is the control tube and contains no antibiotics. After incubation, the concentration of the drugs required to inhibit the growth of the organism used is determined by observing the absence of growth.

It has an advantage of being faster than the hole plate method, since results can be read after three or four hours of incubation. However, a standard curve must be drawn at the start of the work. The presence of other possibly inhibitory substances is more likely to affect this method than the hole plate method. It is
sometimes difficult to interpret results when cloudy or turbid specimens are tested. Turbidimetric assays are only occasionally used for body fluid and tissues because of the laborious pipetting required and inconveniently short incubation.

1.5.3 Streak Method

The strength/potency of an antibacterial/antibiotic can also be determined by Streak method\textsuperscript{125}. The materials to be tested and antibiotic solutions are introduced aseptically into pre sterilized Petri dishes. For testing at 1000 mcg/ml, 10 mg is dissolved or suspended in 0.2 ml of solvent. Water, alcohol, acetone or dimethyl sulfoxide is satisfactory as preliminary studies showing no inhibition of cultures. Trypticase-soy agar is prepared and sterilized in the usual fashion by autoclaving. Before congealing, 10ml of agar medium is added to each of the Petri dishes containing the antibiotics or extracts and the Petri dishes are swirled carefully until the agar begins to set.

The test organisms are maintained on typticase-soy agar slants and are recovered for testing by making suspension in saline before streaking. The organisms are streaked in a radial pattern on the agar containing the various test materials. The plates are incubated at 37\textdegree C and are examined for growth after 24 and 48 hours. Virtually complete suppression of growth is required for a substance to be declared active. Those extracts found to be active are retested for conformation and are tested also at 100mcg/ml. A positive and a negative control are streaked first and last in each test series and all four plates must have the expected appearance or the results are discarded. This avoids, in particular, cross contamination during the streaking operation. This technique is used for isolation of pure culture of bacteria, so that individual cells could grow into distinct, separate colonies.

1.5.4 Impregnated Filter Paper Disc Method

Sensitivity of bacteria to various antibacterial/antibiotics can be determined by applying the impregnated filter paper disc method. In this method Agar culture
medium is melted, cooled to 48°C and then introduced with the organism under test\textsuperscript{126}. The inoculated medium is poured into a sterile petri dish. When the medium has solidified, filter paper disc impregnated with known amounts of various antibiotics are placed on the surface. The drugs diffuse into the medium, and after incubation, zones of inhibition appear which denote sensitivity of the organism to the particular antibiotic or drug\textsuperscript{127-128}.

It is simple, convenient, rapid and economical method and is particularly useful in the fractionation and purification of crude products because of its simplicity and rapidity and when used in conjunction with antimicrobial assay can identify antimicrobial substances that are also cytotoxic to maintain mammalian cells.

\subsection*{1.5.5 Thin Layer Chromatographic Method}

Biological efficiency of antibiotics can be determined by thin layer chromatographic method\textsuperscript{129}. In this technique (TLC) without eluting, the zones or spots have been used to assess the antibacterial efficiency of test materials. The material is charged to a silica gel plate and the plate is developed in some suitable solvents. The developed and dried chromatoplate is placed directly on a seeded agar preparation or more frequently with a sterile filter paper between them\textsuperscript{130}. The chromatoplate with the filter is left on the seeded agar for an optimal time of diffusion, then removed and incubated.

This method can be used for the bioassay of antibacterial compounds in the identification of some of the most important and recently discovered antibiotics from fermentation sources. It is also used for quantitative analysis of antibiotics from fermentation sources, animal tissues, and pharmaceutical preparations. However, it is more suitable for the potent antibacterial compounds. Quantity of the material which can be charged to a thin layer plate is usually small. Kanatiwela \textit{et al}.\textsuperscript{131} developed a method for collection of fungicidal residues and quantitative determination of fungicidal effect by using TLC technique. This technique was applied successfully to detect and quantify fungicide residues in a commercial sample of tomato.
LITERATURE SURVEY

Research work is being carried out all over the world on thiazolidinone nuclei because diverse biological activities are found to be associated with thiazolidinone derivatives. Now a days, emphasis is being placed on synthesizing new derivatives with therapeutic properties in the quest for compounds that will show significant pharmacological efficiency. A comprehensive first review had been written on 4-thiazolidinones in 1961. Later on, a review article appeared which dealt with the use of thiazolidinone derivatives as stabilizers for polymeric materials. Synthesis of known thiazolidinone derivatives along with their various conventional methods is briefly reviewed below:

2.1 Conventional Methods

2.1.1 Reaction dependant upon nucleophilic activity of the methylene carbon atom of 4-thiazolidinone

The methylene carbon atom (at 5\textsuperscript{th} position of 4-thiazolidinone) has nucleophilic activity and it attacks on electrophilic center. The nucleophilic activity of 5-methylene carbon atom is influenced by the nature of the substituents attached to the aryl group.
2.1.1.1 Aldol condensation

Aldol condensation reaction was the first reaction to be investigated. In this condensation methylene group was treated with an aldehyde or ketone by loss of water. The product of the reaction was α,β-unsaturated carbonyl group (19), using sulfuric acid as condensing agent.

\[
\begin{align*}
\text{R}_1 \text{COR}_2 + \text{R}_2 \text{S} + \text{X} & \text{R}_1 \text{COR}_2 \\
\text{R}_1 \text{COR}_2 & \leftrightarrow \text{R}_2 \text{S} + \text{X}
\end{align*}
\]

(19) (20)

Acetaldehyde was one of the first aldehyde to be condensed with rhodanine and aliphatic aldehydes had been reported to be unsuccessful to condense with rhodanine in presence of sulfuric acid. Aliphatic aldehydes condense with rhodanine on refluxing for several hours in acetic acid solution. Rhodanine derivatives of aldehydes and ketones were detected by paper chromatography. Formamide and dimethylformamide used as the mobile phase and \( R_f \) values had been tabulated for various eluting solvents. Variations in the possibilities of hydrogen bonding were used to explain the differences in \( R_f \) values with different solvents.

2.1.1.2 Reaction with nitrous acid and nitroso compounds

Perry et al. reported pseudothiohydantoin on treatment with nitric acid gave a low yield of 5-oximinopseudothiohydantoin. The same product was obtained in better yield by the action of nitrous acid, which was prepared by the reduction of nitric acid or by the addition of sodium nitrite to a hydrochloric acid solution of the pseudothiohydantoin. 3-substituted derivatives of rhodanine (22) were obtained with amyl nitrite or isopropyl nitrite and hydrochloric acid.
Aromatic nitroso compounds reacted with 3-substituted rhodanines and with 2-substituted-imino-4-thiazolidinones forming 5-arylimino derivatives (24).

2.1.1.3 Reaction with diazonium salts

Grishchuk et al.\textsuperscript{137} coupled diazonium salts with 5-methylene group of rhodanine, 2,4-thiazolidinediones and 2-substitutedimino-3-substituted(or hydrogen)-4-thiazolidinones\textsuperscript{138}.

Patnaik et al.\textsuperscript{139} reported reduction of the phenyl-azo group of 2-arylimino-5-phenylazo-4-thiazolidinones with sodium hydrosulfite to yield the corresponding 5-amino-2-arylimino-4-thiazolidinones (26).
2.1.1.4 Reaction with diphenylformamidine

The electrophilic carbon atom of diphenylformamidine was attacked by the
nucleophilic methylene carbon atom of rhodanines\(^{140}\), 2,4-thiazolidinediones and 2-
substituted-imino-4-thiazolidinones\(^{141}\). The product was 5-anilinomethylene
derivative (28) was formed, if the same reaction ran in acetic anhydride then 5-N-
acetalanilinomethylene derivative formed. The ease of formation of the 5-
anilinomethylene derivative depended on the nature of X. If X = S, the reactants
heated in kerosene at 120°C for 1 hour, if X = O, heated for 3 hours at 140-150 °C,
while if X = NC\(_6\)H\(_5\), heated for 5 hours at the same temperature.

![Reaction with diphenylformamidine](image)

2.1.1.5 Reaction with ortho esters

Compounds containing an active methylene group reacted with ortho esters,
with acetic anhydride being used frequently as a condensing agent. In acetic
anhydride solution, rhodanine and 3-substituted derivatives condensed with methyl
or ethyl orthoformate, methyl or ethyl orthoacetate, and ethyl orthopropionate and
form the 5-(alkoxyalkylidene) derivatives\(^{142}\).

![Reaction with ortho esters](image)
2.1.1.6 Reaction with sodium

Behringehr et al.\textsuperscript{143} described the anhydrous ether solution rhodanine reacted with two moles of sodium. The product which would be a dianion, on condensation with ethyl formate and subsequent acidification forms 5-hydroxymethylenerrhodanine (34). The reaction failed with 3-substituted rhodanine derivatives.

\[
\begin{align*}
\text{NH}_2 \quad \text{O} \\
\text{S} \quad \text{S} \\
\text{Na}^+ \\
\text{HCOOC}_2\text{H}_3 \\
\text{S} \quad \text{O} \\
\text{N} \quad \text{S} \\
\text{Na} \\
\text{Na} \\
\text{O} \\
\text{N} \\
\text{S} \\
\text{OH} \\
\text{Na} \\
\text{ON} \\
\text{S} \\
\text{Na} \quad \text{CS}_2 \\
\text{S} \\
\text{Na} \\
\text{R} \quad \text{O} \\
\text{N} \quad \text{S} \\
\text{R} \quad \text{S} \\
\text{O} \\
\text{N} \\
\text{S} \\
\text{CH}_3\text{I} \\
\text{S} \\
\text{C(SCH}_3\text{)_2} \\
\end{align*}
\]

The sodium derivative prepared from 3-substituted rhodanine (35) was treated with carbon disulfide, followed by methyl iodide, to form a 5-di(methylthio)methylene-3-substituted rhodanine\textsuperscript{144} (37).

\[
\begin{align*}
\text{R} \quad \text{N} \quad \text{O} \\
\text{S} \quad \text{S} \\
\text{Na}^+ \\
\text{R} \quad \text{N} \quad \text{O} \\
\text{S} \quad \text{S} \\
\text{Na} \\
\text{CS}_2 \\
\text{S} \\
\text{Na} \\
\text{R} \quad \text{O} \\
\text{N} \quad \text{S} \\
\text{C(SCH}_3\text{)_2} \\
\end{align*}
\]

2.2. Reaction with electrophilic carbon atoms

Heterocyclic compounds with carbon atoms of electrophilic activity were condensed with the nucleophilic carbon atom of the 4-thiazolidinone nucleus in the
presence of a base. The carbonyl and nitrogen portions of an amide group were in
different heterocyclic nuclei and separated by one or more vinyl groups.

Brooker et al.\textsuperscript{145} studied the heterocyclic quaternary ammonium salt with an
active alkylthio or arylthio group attached to an electrophilic carbon atom reacted
with the nucleophilic methylene groups of substituted rhodanines, 2,4-
thiazolidinediones and 2-imino-4-thiazolidinones (or the isomeric 2-amino-4(5H)-
thiazolons). Pyridine\textsuperscript{146}, triethylamine\textsuperscript{147} and acetic anhydride with sodium acetate\textsuperscript{148}
were used as condensing agents.

\[
\begin{align*}
\text{(38)} + \text{(39)} & \rightarrow \text{(40)} \\

\end{align*}
\]

2.3 4-thiazolidinone derivatives prepared by other
conventional methods

Paola et al.\textsuperscript{149} synthesized compounds of 2-thiazolylimino-5-arylidene-4-
thiazolidinones and assayed \textit{in vitro} for their antimicrobial activity against gram
positive and gram negative bacteria, yeasts and moulds.

Elnagdi et al.\textsuperscript{150} described the studies with poly functionally substituted
thiazolines and 1, 2, 4- triazolines: synthesis and chemical reactivity of 4-aryloxo-
2isopropoxy-2-thiazolin-5-ones and of 4-arylidene-2-isopropoxy-2-thiazolin-5-
one.

Another method for the preparation of thiazolidinones was reported by Cesur
\textit{et al.}\textsuperscript{151} and Vicini \textit{et al.}\textsuperscript{152}. In this method alkylisothiocynate, ammonium
thiocyanate and thiocyanate with acetamide/hydrazide were used and finally the
mixture was treated with sodium acetate and ethyl bromoacetate.
Ottana et al.\textsuperscript{153} described the synthesis of 4-thiazolidinones using starting material N-propyl-N-phenylthiourea, obtained by the reaction of propylamine and phenylisothiocyanate in chloroform at room temperature for 4 hrs followed by workup under acidic conditions.

Kvitko et al.\textsuperscript{154} reported the reaction of substituted benzoyl chlorides with various 2-thiono-4-thiazolidinones, giving 5-aroyl-4-thiazolidinones (42).

\[
\begin{align*}
\text{(41)} & & \text{(42)}
\end{align*}
\]

Tominaga et al.\textsuperscript{155} conducted a reaction of 3-ethyl-2-thioxothiazolidin-4-one with carbon disulfide in the presence of sodium hydroxide in dimethyl sulfoxide, giving 3-ethyl-5-bis(methylthio)methylene]-2-thioxo-4-thiazolidinone (44). This on treatment with nucleophilic reagents such as amines or active methylenes yields the corresponding replacement products of one (45) or two (46) methylthio group in good yields, respectively. The active ketone thioacetal group was reacted with active methylene compounds in the presence of K\textsubscript{2}CO\textsubscript{3} in dimethyl sulfoxide.
Nakayama et al. studied the introduction of cyclic dithioacetal functions into activated methylene compounds by treatment with 2-alkoxy-1,3-benzodithioles. 5–bis(1,3-benzodithiol-2-yl)rhodanine (49) produced in high yields by the treatment of 2-(3-methylbutoxy)-1,3-benzodithiole with rhodanine in anhydrous acetic acid.

Phthalic anhydride undergoes condensation at 5-position of various 2-substituted imino-4-thiazolidinones in acetic anhydride and triethylamine to give 2-substituted imino-5-phthalyl-4-thiazolidinones (52).
The anhydride was treated spontaneously with 2-imino-3-aryl-4-thiazolidinones at room temperature to give N-chloroacetyl derivatives\textsuperscript{158}.

Krutosikova \textit{et al}. and Raouf \textit{et al}. reported that different 2-thiono-4-thiazolidinones undergo aldol condensation reactions with a variety of aliphatic, aromatic, and heterocyclic aldehydes to give good yields of 5-unsaturated derivatives (56). The reactions were mostly carried out in the presence of anhydrous sodium acetate in benzene or acetic acid with reflux for 6-18 hrs\textsuperscript{159-161}.

Substituted 2-imino-4-thiazolidinones (57) was used to carry aldol condensation with ease in the presence of anhydrous sodium acetate in acetic acid refluxed for 8-10 hrs. A wide variety of aliphatic, aromatic and heterocyclic aldehydes were reported to react with the 4-thiazolidinones\textsuperscript{162-165}.
Karishin et al.\textsuperscript{166} described the condensation where only one carbonyl group of acenaphthenequinone or its halogen derivatives at the 5-position of 2-imino-4-thiazolidinone (58) occur in hot acetic acid and similarly, isatin also condense only with one of its carbonyl groups at position of various 2-imino-4-thiazolidinones and refluxed for 12 hrs.

Snider et al.\textsuperscript{167} studied Friedel-Craft reactions with 5-arylidene-4-thiazolidinones using benzene and anhydrous aluminum chloride. Kononenko et al.\textsuperscript{168} reported aminomethylation reactions of 2-aryl-4-thiazolidinones (59) and 4-thiazolidinediones with formaldehyde and amines by heating in alcohol.
2-(Arylimino)-4-thiazolidinone 1, l-dioxides were treated with aromatic amines in the presence of paraformaldehyde and amine hydrochloride to give 2-(arylimino)-3-(substituted-aminomethyl)-4-thiazolidinone 1, l–dioxides\textsuperscript{169} (60).

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{S} \\
\text{O} \\
\text{O}
\end{array}
\hspace{1cm}
\begin{array}{c}
\text{R} \\
\text{N}
\end{array}
\hspace{1cm}
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{S} \\
\text{O} \\
\text{O}
\end{array}

(60)

Wilson \textit{et al.}\textsuperscript{170} oxidized 2-(Arylimino)-3-substituted-4-thiazolidinones and 2, 3-disubstituted-4-thiazolidinones\textsuperscript{61} with KMnO\textsubscript{4} in glacial acetic acid at 0\textdegree C.

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{S} \\
\text{O} \\
\text{O}
\end{array}
\hspace{1cm}
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{S} \\
\text{O} \\
\text{O}
\end{array}

(61)

Vorobeva \textit{et al.}\textsuperscript{171} prepared seven thiazolidine and oxazolidinethiones in 35-80\% yields by condensing thiones II with CIP (X\textsuperscript{1}) R (OPh). Other reactions phosphorylation and thiophosphorylation of thiazolidine and oxazolidinethiones were also studied.

Litvinov \textit{et al.}\textsuperscript{172} have prepared bis(aminothiazoly) methanes (62) from dichloro diketones and RR\textsuperscript{1}NCSNH\textsubscript{2} and inhibitory activity of their hydrochlorides against acetylcholinesterase was shown to be higher than that of the corresponding free bases.
Solankee et al.\textsuperscript{173} prepared thiazolidinone derivatives (63) by cyclocondensation of R\textsuperscript{1}NHC(NH\textsubscript{2})S with HO\textsubscript{2}C(CH\textsubscript{2})\textsubscript{5}CHBrCO\textsubscript{2}H and tested them for antitubercular activity. The activity of the compounds was enhanced with lengthening of the side chain in position 5 and in some cases the activity was doubled.

Hui ling Liu, \textit{et al.}\textsuperscript{174} discussed the synthesis of 2-Imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones and their fungicidal activity. Andeane \textit{et al.}\textsuperscript{175} described the synthesis (64) of 6-substituted imidazo [2, 1-b] thiazoles with a lactam ring connected, by means of a methane group, to the 5-position. The pharmacological results show that interesting cardiotonic activity is obtained when the lactam ring is pseudothiohydantoin or barbituric acid. Even the substituent at position 6 plays an important role in the pharmacological behavior of these compounds. The activity rank order was observed Ph > Me > Chlorine.
Kassab et al. conducted some reactions involving thiazolidinone with phenylisothiocyanate to give 2-imino-5-phenylcarboxamido-4-thiazolidone (65) that was converted to a thiazolodihydropyrazoles, thiazolopyrazole and thiazolopyridine. Thiazolodihydropyrazoles then reacted with urea in ethanol in the presence of sodium ethoxide generated from sodium and ethanol to give tetrahydropyrimidothiazole in 90% yield (70)\[15\].
Albuquerque et al. reported the synthesis and physico-chemical properties of new 3-benzyl-4-thioxo-5-arylideneimidazolidine-2-ones and 3-benzyl-5-arylideneimidazolidine-2, 4-dione. These compounds were synthesized by condensation reaction from aromatic aldehydes and 3-substituted imidazolidine-2, 4-diones or 4-thioxoimidazolidine-2-ones. He also studied antimicrobial in vitro activity on ten compounds\textsuperscript{[11]}. El-Shafei, A. K. et al. also reported the synthetic studies using 2-imino-4-thiazolidinones and related structures with active Nitriles\textsuperscript{[26]}.

Aysel G et al.\textsuperscript{176} synthesized two series of 2-(3-ethyl-4(3H)-quinazolinone-2ylmercaptoacetylhydrazono)-3-alkyl/aryl-5methyl-4-thazolidinones (a) and 2-arylimino-3-(3-ethyl-4(3H)-quinazolinone-2ylmercaptoacetylamino)-5-methyl-4-thazolidinones (b) by cyclization of 1-(3-ethyl-4(3H)-quinazolinone-2ylmercaptoacetyl)-4-alkyl/aryl thiosemicarbazides (c) with ethyl 2-bromopropionate in the presence of anhydrous sodium acetate in anhydrous ethanolic medium.
Meihsiu et al.\textsuperscript{177} synthesized and evaluated antioxidant activity of 4-methyl-2-[(3-arylsydnone 4-yl-methylene)hydrazono]-2,3-dihydro-thiazole-5-carboxylic acid ethyl ester and 4-phenyl-2-[(3-arylsydnone 4-yl-methylene)hydrazono]-2,3-dihydro-thiazoles.

\begin{center}
\includegraphics[width=0.5\textwidth]{image1.png}
\end{center}

\textbf{(74)}

Nedime et al.\textsuperscript{178} studied 4-[2-(3,4-dimethoxypheny)ethyl]-3-thosemicarbazide was converted into new 1-substituted benzylidene/furfurylidene-4-[2-(3,4-dimethoxypheny)ethyl]-3-thosemicarbazide which furnished 2-(substituted benzylidene/furfurylidene)hydrazono-3-[2-(3,4-dimethoxypheny)ethyl]thiazolidin-4-ones and 1-(substituted benzylidene/furfurylidene)-amino-3-[2-(3,4-dimethoxypheny)ethyl]-2thioxo-4,5-imidazolidinediones on reaction with chloroacetic acid and oxalyl chloride.

\begin{center}
\includegraphics[width=0.8\textwidth]{image2.png}
\end{center}

\textbf{(75)} \hspace{1cm} \textbf{(76)} \hspace{1cm} \textbf{(77)}
Such conventional methods involve long reaction time, use large quantities of organic solvents (toxic) but give unsatisfactory yield. It is the need of hour to carry out reaction in solvent free conditions or non toxic solvents with cost effective methods. Microwave radiation has been employed for the formation of different products under simple operational conditions. So, there is a need to evolve a mechanism, which may give chemical products ever needed but prevents the toxic and pollutant aspects. Hence it will be endeavored to adopt some ecologically favourable procedure for synthesis. Methods of microwave heating has been employed. Due to environmental legislation chemists are forced to replace conventional processes with new clean non conventional processes. One of the major goals of green chemistry is to develop environmentally acceptable route to important organic products.

2.4- NON CONVENTIONAL METHODS

Non conventional route is a rapid and environmentally friendlier approach for organic synthesis and transformations which involve microwave exposure of neat reactants in the presence of ionic liquids (phase transfer catalyst) or recyclable catalysts (solid phase catalyst) such as montmorillonite clays, alumina and silica.

Verma et al.\textsuperscript{179} reported solvent free deprotection procedure using relatively benign reagent, ammonium persulfate on clay, for the regeneration of carbonyl compounds from the corresponding semicarbazone and phenylhydrazone derivatives by microwaves.

\[
\begin{align*}
\text{R}^1\text{C}_4\text{H}_9, \text{Ph}, \text{p-Cl C}_6\text{H}_4, & \quad \text{R}^1\text{=CH}_3, \text{C}_2\text{H}_5 \text{ and R}_2\text{=CONH}_2, \text{Ph}
\end{align*}
\]
Verma et al.\textsuperscript{180} studied a wide variety of heterocyclic compounds assembled rapidly by employing this solvent free approach for the synthesis of flavonoids using Baker-Venkatacharan rearrangement and related cyclization of 2-aminochalcones to 2-aryl-1,2,3,4-tetrahydro-4-quinolones on clay. He also reported remarkable improvement over the conventional two-component synthesis that required lachrymatory α-haloketones and restricted the generation of a diverse library of these molecules.

\[ \text{R} \text{-CHO} \text{+} \text{R}^1 \text{-NC} \xrightarrow{\text{MW, Clay}} \text{(82)} \text{ (83)} \]

Where \( \text{X=} \text{Y=} \text{C, X=} \text{C, Y=} \text{N, X=} \text{N, Y=} \text{C} \)

Guniz et al.\textsuperscript{181} prepared new series of 4-thiazolidinone analogues were screened for various biological activities like antibacterial activity (84), antimycobacterial activity (85), (86) and antiviral activity (87). These derivatives were also employed against various bacteria, fungi and virus strains to determine the efficacy or ability to inhibit their growth and found very promising.
Sarika et al.\textsuperscript{182} adopted an efficient and extremely fast procedure for the synthesis of 7,11-Diphenyl-5,6a,7,11,11a,13a-hexahydro-6H-benzo[h]isoxazolo[3′,4′,4,5][1,3]thiazolo[2,3-b]quinazolines through four-step procedure starting from 2-aryldenetetralin-1-one under microwave irradiation. The reaction rate increased considerably with better yield.

Souad et al.\textsuperscript{183} described a rapid and easy solvent free one-pot synthesis of 5-arylidene-2-imino-4-thiazolidinones by condensation of the thioureas with chloroacetic acid and an aldehyde under microwave irradiation.

Jian et al.\textsuperscript{184} synthesized a series of benzylidenerhodanine derivatives by the crossed aldol condensation of aromatic aldehydes with rhodanine using tetrabutylammonium bromide (TBAB) as phase transfer catalyst in water under microwave irradiation. The reactions were completed in 8~10 min with 71~96% yield, short reaction times, environmentally benign conditions and easy work-up.
Project Aims

The aims of the present piece of work were to prepare potentially biologically active 4-thiazolidinone derivatives from the materials available in the local market in order to gain access to products in cost-effective, rapid, high yield and environment friendly procedures. Environment friendly synthetic Microwave procedures: Multi-Component Reaction in DMF, Solvent free\(^{185-188}\), Multi-Component Reaction, Multi-Component Reaction using Montmorillonite Clays (K-10 and KSF)\(^{189-192}\), have been adopted for the synthesis of 4-thiazolidinone containing compounds in addition to conventional methodology. On the basis of literature novel derivatives of 4-thiazolidinone were synthesized by substituting different functionalities in order to get some potentially bioactive compounds.
MATERIAL AND METHODS

3.1 Instrumentation

Melting points

Melting points of synthesized compounds were determined on digital melting point apparatus (SUPICO) and are uncorrected.

FTIR spectroscopy

The functional groups of organic compounds were determined by IR spectra that were recorded on Bruker FTIR spectrophotometer. Samples were placed directly on sampling probe.

Nuclear Magnetic Resonance

$^1$HNMR spectra were recorded on Bruker AVANCE 300 (300.13 MHz for $^1$H and 75.5 MHz for $^{13}$CNMR). The $^1$HNMR spectra were referenced with respect to the non-deuterated residual solvent in the sample.
Mass Spectrometry

The instrument Bruker Esquire 3000 +ion trap with ESI ionization was used for mass spectrometric analysis.

Elemental analyses

Micro analysis for carbon, hydrogen, nitrogen and sulphur were carried out on 2400-CHN analyzer (Perkin Elmer) and 932 Leco CHNS analyzer (Leco).

Microwave Oven

Microwave irradiations were carried out in a SINEO (MAS-II) microwave system with dynamically adjustable microwave power 0-1000W into ten ranges, increment 100W based on reaction temperature. Calibrated digital dual channel temperature monitor ranging from ambient to 400 °C was used. In this advance microwave system ten reaction methods can be programmed in which four reaction variables are changeable in each e.g. time, temperature, stirring speed and microwave power. Reaction processes were observed with on site camera.

3.2 Environment friendly catalysts

A) Montmorillonite K-10 and KSF

Montmorillonite clays (K-10 and KSF) were purchased from Merck. The characteristics of clays are:

- refractive index = 1.51
- specific gravity = 2.5 g ml
- surface area = 220–270 m²/g,
Montmorillonite K-10 is a strong Bronsted and Lewis acidic catalyst and modification was carried out by exchanging the cations present in the clay with other suitable cations such as Fe, Zn, Pd, Cu, Ru, Rh, Ce etc. 193-194.

B) Ionic Liquids

Ionic liquids TBAB, TEBAC and PEG were purchased from Merck Germany.

3.3 Chemicals and reagents

All chemicals were purchased from Merck, Fluka, Sigma-Aldrich and used as such. TLC coated with silica 60 F254 aluminum plates were purchased from Merck (Germany).

Drying solvents

Toluene was distilled and stored over sodium wire. Dimethylsulfoxide was dried over calcium hydride, distilled under reduced pressure and stored over type 4A molecular sieve. N-N-dimethylformamide was dried by mixing with molecular sieve for 72 hours and then distilled under reduced pressure and stored. Dichloromethane was dried over calcium chloride and stored in brown bottle over Type 3A molecular sieve. Chloroform was dried over Calcium chloride, distilled and stored in amber coloured bottle.
3.4 Synthesis of 4-thiazolidinone derivatives

3.4.1-Synthesis of 4-thiazolidinone analogues (88-97)

2-(2,4-dimethylphenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (88)

**Microwave procedure-I: Multi-Component Reaction in DMF**

4,6-dimethylpyrimidin-2-amine (0.739 g, 6 mmoles) was treated with 2,4-dimethylbenzaldehyde (0.805 g, 6 mmoles) in dimethylformamide (10.0 mL) and irradiated under microwave radiation at 105 °C for 10 minutes to get the Schiff base N-(2,4-dimethylbenzyldiene)-4,6-dimethylpyrimidin-2-amine as an intermediate (Schiff base). Schiff base was then reacted with sulfanyl acetic acid (0.552 g, 6 mmoles) and again irradiated for 8 minutes. The irradiated product was cooled to room temperature, washed, filtered under suction and dried. The irradiated product (88) was purified with preparative TLC (ethyl acetate: n-hexane, 6:4, v/v) followed by recrystallization from ethanol to obtain the compound 2-(2,4-dimethylphenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (88) (yield 94.2%).

**Microwave procedure-II: Solvent free, Multi-Component Reaction**

4,6-dimethylpyrimidin-2-amine (0.739 g, 6 mmoles) and 2,4-dimethylbenzaldehyde (0.805 g, 6 mmoles) were mixed and irradiated under microwave radiation at 105 °C for 8 minutes to get the Schiff base N-(2,4-dimethylbenzyldiene)-4,6-dimethylpyrimidin-2-amine as an intermediate. Schiff base was further treated with sulfanyl acetic acid (0.552 g, 6 mmoles) and again irradiated in microwave oven for 8 minutes. The irradiated product was cooled to room temperature, washed, filtered and dried. The product was recrystallized from ethanol to obtain 2-(2,4-dimethylphenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (yield, 84.6%).
Analytical Data Obtained:

Yield: 94.2%

Melting Point: 218-220 °C

FTIR: 3420, 2968, 1715, 1614 cm\(^{-1}\).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\): 6.84-6.74 (m, 4H, aromatic), 5.92 (s, 1H, C\(_2\)-thiazolidinone), 3.38, 3.28 (s, 2H, C\(_5\)-thiazolidinone), 2.36 (s, 12H, 4CH\(_3\))

\(^1\)C-NMR (75.5 MHz, CDCl\(_3\)) \(\delta\): 166.7(C=O\(_{\text{thiazolidinone}}\)), 165.6, 159.9, 138.0, 136.0, 129.8, 128.7, 126.1, 116.1, 51.5(C\(_2\)-thiazolidinone), 36.3, 21.2, 14.3, 36.3(C\(_5\)-thiazolidinone)

MS m/z: 313.12 (M\(^{+}\)), 207, 107, 101

Anal.: C\(_{16}\)H\(_{15}\)NOS: (313.42): Calculated: C, 65.15; H, 6.11; N, 13.41; O, 5.10; S, 10.23; found: C, 65.13; H, 6.10; N, 13.38; O, 5.08; S, 10.20

3-(4,6-dimethylpyrimidin-2-yl)-2-(2-hydroxy-4-methylphenyl)-thiazolidin-4-one (89)

Microwave procedure-I: Multi-Component Reaction in DMF

Equimolar quantities of 2-hydroxy-4-methylbenzaldehyde (0.680 g, 5 mmoles) and 4,6-dimethylpyrimidin-2-amine (0.616 g, 5 mmoles) were mixed in dimethylformamide (10.0 mL) and irradiated at 105 °C for 8 minutes to get the 2-(((4,6-dimethylpyrimidin-2-ylimino)methyl)-5-methylphenol as an intermediate (Schiff base). This Schiff base was further treated with sulfanyl acetic acid (0.460 g, 5 mmoles) and again irradiated for 8 minutes. The product was cooled to room temperature, filtered under suction and dried. This final product was purified with preparative TLC (ethyl acetate: n-hexane, 4:6, v/v) followed by recrystallization from ethanol to get 3-(4, 6-dimethylpyrimidin-2-yl)-2-(2-hydroxy-4-methylphenyl)-thiazolidin-4-one (89) (yield 82.4%).
Microwave procedure-II: Solvent Free, Multi-Component Reaction

Equimolar quantities of 2-hydroxy-4-methylbenzaldehyde (0.680 g, 5 mmoles) and 4,6-dimethylpyrimidin-2-amine (0.615 g, 5 mmoles) were mixed and irradiated in microwave oven (200 watt) at 105 °C for 6 minutes to get 2-((4,6-dimethylpyrimidin-2-ylimino)methyl)-5-methylphenol as an intermediate. This Schiff base was further treated with sulfanyl acetic acid (0.460 g, 5 mmoles) under the same conditions. The irradiated product was cooled room temperature, washed, dried and followed by recrystallization from ethanol (yield, 42.6%).

Analytical Data Obtained:
Yield: 82.4%
Melting Point: 218-220 °C
FTIR: 3400, 3200, 2968, 1720, 1664 cm⁻¹
¹H-NMR (300MHz, CDCl₃) δ: 7.01 (s, 1H), 6.80 (s, 1H), 6.60-6.40 (d, 2H, J=6.8Hz), 5.96 (s, 1H, C₂-thiazolidinone), 5.0 (s, 1H, OH), 3.33 (d, 2H, C₅-thiazolidinone), 2.36 (s, 9H, 3CH₃)
¹³CNMR (75.5 MHz, CDCl₃) δ: 166.6 (C=O thiazolidinone), 165.6, 159.9, 157.6, 137.5, 130.2, 122.5, 121.7, 116.3, 116.1, 47.8 (C₂-thiazolidinone), 36.3 (C₅-thiazolidinone), 21.2
MS m/z: 315.1(M⁺₁), 209, 107, 102
Anal.: C₁₆H₁₅NOS: (315.39): Calculated: C, 60.93; H, 5.43; N, 13.32; O, 10.15; S, 10.17; found: C, 60.90; H, 5.42; N, 13.29; O, 10.13; S, 10.15

2-(2, 4-dihydroxyphenyl)-3-(4, 6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (90)

Microwave procedure-I: Multi-Component Reaction in DMF

Schiff base 4-((4,6-dimethylpyrimidin-2-ylimino)methyl)benzene-1,3-diol was prepared by mixing 4,6-dimethylpyrimidin-2-amine (0.370 g, 3 mmoles) and 2,4-
dihydroxybenzaldehyde (0.414 g, 3 mmoles) in dimethylformamide (10.0 mL) irradiated in microwave oven at 105 °C for 8 minutes. The (4-((4,6-dimethylpyrimidin-2-ylimino)methyl)benzene-1,3-diol) was further treated with sulfanyl acetic acid (0.276 g, 3 mmoles) under same condition. The irradiated product was cooled to room temperature, filtered under suction and dried to obtain the crude product. The crude product was purified with preparative TLC (n-hexane and ethyl acetate) followed by recrystallization from ethanol to obtain 2-(2,4-dihydroxyphenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (90) (yield, 92.4%).

Microwave procedure-II: Solvent free, Multi-Component Reaction

Schiff base 4-((4,6-dimethylpyrimidin-2-ylimino)methyl)benzene-1,3-diol was prepared by mixing 4,6-dimethylpyrimidin-2-amine (0.370 g, 3 mmoles) and 2,4-dihydroxybenzaldehyde (0.414 g, 3 mmoles) and irradiating in microwave oven at 105 °C for 6 minutes. Schiff base was further treated with sulfanyl acetic acid (0.276 g, 3 mmoles) under the same conditions. The irradiated product was cooled to room temperature and dried followed by recrystallization from ethanol to obtain 2-(2,4-dihydroxyphenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (90) (yield, 46.4%).

Analytical Data Obtained:

Yield: 92.4%
Melting Point: 224-226 °C
FTIR: 3346, 3180, 2968, 1718, 1624 cm⁻¹.
¹H-NMR (300MHz, CDCl₃) δ: 6.96 (s, 1H), 6.72 (s, 1H), 6.17-6.08 (d, 2H, J=6.7Hz), 5.95 (s, 1H, C₂-thiazolidinone), 5.0 (s, 1H, OH), 3.34 (d, 2H, C₅-thiazolidinone), 2.35 (s, 6H, 2CH₃)
¹³CNMR (75.5 MHz, CDCl₃) δ: 166.7 (C=O thiazolidinone), 165.6, 159.9, 159.1, 157.1, 131.7, 118.1, 116.1, 108.2, 102.8, 47.8 (C₂-thiazolidinone), 36.3 (C₅-thiazolidinone), 21.2
MS m/z: 317.08 (M⁺), 211, 109, 107, 101
Anal.: C_{16}H_{15}NOS: (317.36): Calculated: C, 56.77; H, 4.76; N, 13.24; O, 14.11; S, 10.12; found: C, 56.79; H, 4.72; N, 13.22; O, 14.11; S, 10.12

2-(2,4-dichlorophenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (91)

**Microwave procedure-I: Multi-Component Reaction in DMF**

An intermediate product \(N\)-(2,4-dichlorobenzylidene)-4,6-dimethylpyrimidin-2-amine was prepared by 2,4-dichlorobenzaldehyde (0.700 g, 4 mmoles) treated with 4,6-dimethylpyrimidin-2-amine (0.492 g, 4 mmoles) in dimethylformamide (8.0 mL) and irradiated under microwave oven at 105 °C for 6 minutes. The product \(N\)-(2,4-dichlorobenzylidene)-4,6-dimethylpyrimidin-2-amine and sulfanyl acetic acid (0.368 g, 4 mmoles) was further irradiated under microwave oven under the same condition. The irradiated product was cooled to room temperature, filtered under suction and dried. The final product was purified with preparative TLC (ethyl acetate: n-hexane, 6:4, v/v) followed by recrystallization from ethanol to obtain 2-(2,4-dichlorophenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (91) (yield, 88.4%).

**Microwave procedure-II: Solvent free, Multi-Component Reaction**

An intermediate Schiff base \(N\)-(2,4-dichlorobenzylidene)-4,6-dimethylpyrimidin-2-amine was synthesized by 2,4-dichlorobenzaldehyde (0.700 g, 4 mmoles) reacted with 4,6-dimethylpyrimidin-2-amine (0.492 g, 4 mmoles) and irradiated in microwave oven (200 watt) at 105 °C for 6 minutes. \(N\)-(2,4-dichlorobenzylidene)-4,6-dimethylpyrimidin-2-amine and sulfanyl acetic acid (0.368 g, 4 mmoles) were further irradiated under microwave oven (200 watt) under the same conditions. The irradiated product was cooled to room temperature, washed, dried and recrystallized in ethanol (yield, 82.0%).
Analytical Data Obtained:

Yield: 88.4%
Melting Point: 224-226 °C

FTIR: 3410, 3170, 2970, 1724, 1619 cm⁻¹.

¹H-NMR (300 MHz, CDCl₃) δ: 7.20-7.16 (d, 2H, J=7.2 Hz), 6.98 (s, 1H), 6.84 (s, 1H), 5.94 (s, 1H, C₂-thiazolidinone), 3.34 (d, 2H, C₅-thiazolidinone), 2.37 (s, 6H, 2CH₃)

¹³C NMR (75.5 MHz, CDCl₃) δ: 166.7 (C=O thiazolidinone), 165.6, 159.9, 136.8, 135.6, 133.6, 131.7, 129.2, 126.9, 116.1, 48.9 (C₂-thiazolidinone), 36.3 (C₅-thiazolidinone), 21.2 (CH₃)

MS m/z: 353.02 (M+1), 247, 145, 107,

Anal.: C₁₆H₁₅NOS: (354.25): Calculated: C, 50.86; H, 3.70; N, 11.86; O, 4.52; S, 9.05; found: C, 50.88; H, 3.66; N, 11.88; O, 4.50; S, 9.06

3-(4,6-dimethylpyrimidin-2-yl)-2-(2-hydroxy-4-methoxyphenyl)-thiazolidin-4-one (92)

Microwave procedure-I: Multi-Component Reaction in DMF

A mixture of 4,6-dimethylpyrimidin-2-amine (0.615 g, 5 mmoles), 2-hydroxy-4-methoxybenzaldehyde (0.761 g, 5 mmoles) and dimethylformamide (10.0 mL) was irradiated under microwave radiation (200 watt) at 106 °C for 8 minutes. The intermediate (Schiff base) was reacted with sulfanyl acetic acid (0.460 g, 5 mmoles) under the same condition. The irradiated product was cooled room temperature, filtered under suction and dried. The product was purified with preparative TLC (ethyl acetate: n-hexane, 6:4, v/v) followed by recrystallization from ethanol to obtain 3-(4,6-dimethylpyrimidin-2-yl)-2-(2-hydroxy-4-methoxyphenyl)-thiazolidin-4-one (92) (yield, 96.0%).
Microwave procedure-II: Solvent free, Multi-Component Reaction
A mixture of 2-hydroxy-4-methoxybenzaldehyde (0.761 g, 5 mmoles) and 4,6-dimethylpyrimidin-2-amine (0.615 g, 5 mmoles) was placed in a microwave oven (200 watt) and irradiated under microwave radiation at 110 °C for 08 minutes. The intermediate was further treated with sulfanyl acetic acid (0.460 g, 5 mmoles) under the same condition. The irradiated product was cooled to room temperature, dried and recrystallized from ethanol (yield, 66.0%).

Analytical Data Obtained:
Yield: 96.0%
Melting Point: 208-210 °C
FTIR: 3334, 3220, 2954, 1728, 1616 cm⁻¹
¹H-NMR 
(300MHz, CDCl₃) δ: 6.94 (s, 1H), 6.78 (s, 1H), 6.21-6.12 (d, 2H, J=6.3Hz), 5.92 (s, 1H, C₂-thiazolidinone), 5.0 (s, 1H, OH), 3.78(s, 3H, OCH₃), 3.35 (d, 2H, C₅-thiazolidinone), 2.35 (s, 6H, 2CH₃)
¹³CNMR 
(75.5 MHz, CDCl₃) δ: 166.7 (C=Othiazolidinone), 165.6, 161.8, 159.9, 158.7, 131.3, 117.8, 116.1, 106.6, 101.2, 56.0, 47.8(C₂-thiazolidinone), 36.3 (C₅-thiazolidinone), 21.2 (CH₃)
MS m/z: 331 (M⁺¹), 225, 124, 107, 101
Anal.: C₁₆H₁₅NOS: (331.39): Calculated: C, 57.997; H, 5.17; N, 12.68; O, 14.48; S, 9.68; found: C, 60.01; H, 5.17; N, 12.66; O, 14.46; S, 9.70

2-(4-chloro-2-methylphenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (93)

Microwave procedure-I: Multi-Component Reaction in DMF
4-chloro-2-methylbenzaldehyde (0.465 g, 3 mmoles) was treated with 4,6-dimethylpyrimidin-2-amine (0.369 g, 3 mmoles) in dimethylformamide (10.0 mL) irradiated in microwave oven at 105 °C for 8 minutes to get Schiff base N-(4-chloro-
2-methylbenzylidene)-4,6-dimethylpyrimidin-2-amine as an intermediate (Schiff base). The Schiff base was further treated with sulfanyl acetic acid (0.276 g, 3 mmoles) and irradiated for eight minutes. The irradiated product was cooled to room temperature, filtered under suction and dried to get crude product. Preparative TLC (n-hexane : ethyl acetate, 6:4, v/v) was applied to purify the crude product and recrystallized from ethanol to obtain the 2-(4-chloro-2-methylphenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (yield, 88.4%).

Microwave procedure-II: Solvent free, Multi-Component Reaction

4-chloro-2-methylbenzaldehyde (0.465 g, 3 mmoles) was reacted with 4,6-dimethylpyrimidin-2-amine (0.369 g, 3 mmoles) irradiated in microwave oven (200 watt) at 105°C for 6 minutes to get Schiff base \( N\)-[(4-chloro-2-methylphenyl)methylidene]-4,6-dimethylpyrimidin-2-amine as an intermediate. The Schiff base was further treated with sulfanyl acetic acid (0.276 g, 3 mmoles) and again irradiated in microwave oven under the same condition. The crude product was cooled, dried and followed by recrystallization from ethanol to obtain the 2-(4-chloro-2-methylphenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (yield, 56.8%).

Analytical Data Obtained:

Yield: 88.4%
Melting Point: 216-218 °C
FTIR: 3338, 3140, 2946, 1724, 1615 cm\(^{-1}\)
\(^1\)H-NMR (300MHz, CDC\(_3\)) \( \delta \): 7.12-7.08 (d, 2H, \( J=7.5Hz \)), 7.00 (s, 1H), 6.86 (s, 1H), 5.92 (s, 1H, \( C_2\)-thiazolidinone), 3.33 (d, 2H, \( C_5\)-thiazolidinone), 2.35 (s, 9H, 3CH\(_3\))
\(^{13}\)C-NMR (75.5 MHz, CDC\(_3\)) \( \delta \): 166.7 (C=O\(_{\text{thiazolidinone}}\)), 165.6, 159.9, 139.5, 137.1, 132.1, 130.2, 129.5, 125.8, 51.5(C\(_2\)-thiazolidinone), 36.3 (C\(_5\)-thiazolidinone), 21.2 (CH\(_3\))

MS \( m/z \): 334 (M\(^{+1}\)), 227, 125, 107, 101
3-(4,6-dimethylpyrimidin-2-yl)-2-(4-fluorophenyl)-thiazolidin-4-one (94)

**Microwave procedure-I: Multi-Component Reaction in DMF**

Equimolar quantities of 4-fluorobenzaldehyde (0.744 g, 6 mmoles) and 4,6-dimethylpyrimidin-2-amine (0.739 g, 6 mmoles) were mixed in dimethylformamide (10.0 mL) and irradiated in microwave oven at 108 °C for 6 minutes to get Schiff base \( N\)-(4-fluorophenyl)methylidene]-4,6-dimethylpyrimidin-2-amine. This Schiff base was treated with sulfanyl acetic acid (0.552 g, 6 mmoles) under the microwave radiation. The irradiated product was cooled to room temperature, filtered under suction and dried. Preparative TLC (ethyl acetate: n-hexane, 6:4, v/v) was applied to purify the crude product and followed by recrystallization in ethanol to obtain 3-(4,6-dimethylpyrimidin-2-yl)-2-(4-fluorophenyl)-thiazolidin-4-one (94) (yield 90.3%).

**Microwave procedure-II: Solvent free, Multi-Component Reaction**

Equimolar quantities of 4-fluorobenzaldehyde (0.744 g, 6 mmoles) and 4,6-dimethylpyrimidin-2-amine (0.739 g, 6 mmoles) were mixed and irradiated under microwave oven at 108 °C for 6 minutes to get Schiff base \( N\)-[(4-fluorophenyl)methylidene]-4,6-dimethylpyrimidin-2-amine. This Schiff base was reacted with sulfanyl acetic acid (0.552 g, 6 mmoles) under the same condition. The irradiated product was cooled to room temperature, washed, filtered, dried and followed by recrystallization from ethanol (yield 80.8%).

**Analytical Data Obtained:**

Yield: 90.3%

Melting Point: 202–204 °C
FTIR: 3424, 3234, 2982, 1720, 1664, 1130 cm⁻¹

¹H-NMR (300 MHz, CDCl₃) δ: 7.04-6.85 (m, 4H), 6.86 (s, 1H), 5.92 (s, 1H, C₂-thiazolidinone), 3.38 (d, H, C₅-a thiazolidinone), 3.28 (d, H, C₅-b thiazolidinone), 2.35 (s, 6H, 2CH₃)

¹³CNMR (75.5 MHz, CDCl₃) δ: 171.2 (C=O thiazolidinone), 164.8, 161.3, 159.9, 134.8, 130.4, 115.4, 109.6, 65.6 (C₂-thiazolidinone), 33.6 (C₅-thiazolidinone), 25.1 (CH₃)

MS m/z: 303.08 (M⁺¹), 197, 107, 95

Anal.: C₁₅H₁₄FN₃OS: (303.08): Calculated: C, 59.39; H, 4.65; N, 13.85; O, 5.27; S, 10.57; found: C, 59.33; H, 4.63; N, 13.81; O, 5.22; S, 10.59

3-(4, 6-dimethylpyrimidin-2-yl)-2-(4-nitrophenyl)-thiazolidin-4-one (95)

**Microwave procedure-I: Multi-Component Reaction in DMF**

Schiff base N-(4-nitrobenzylidene)-4,6-dimethylpyrimidin-2-amine was synthesized by mixing 4,6-dimethylpyrimidin-2-amine (0.616 g, 5 mmoles) and p-nitrobenzaldehyde (0.755 g, 5 mmoles) in dimethylformamide (10.0 mL) and irradiated in microwave oven at 106 °C for 6 minutes. The N-(4-nitrobenzylidene)-4,6-dimethylpyrimidin-2-amine was treated with sulfanyl acetic acid (0.460 g, 5 mmoles) under same condition. The irradiated product was cooled to room temperature, washed, filtered under suction and dried. The crude product was purified with preparative TLC (ethyl acetate: hexane, 6:4, v/v) followed by recrystallization from ethanol to obtain 3-(4,6-dimethylpyrimidin-2-yl)-2-(4-nitrophenyl) thiazolidin-4-one (yield, 82.9%).

**Microwave procedure-II: Solvent free, Multi-Component Reaction**

Schiff base N-(4-nitrobenzylidene)-4,6-dimethylpyrimidin-2-amine was synthesized by mixing 4,6-dimethylpyrimidin-2-amine (0.616 g, 6 mmoles) and 4-nitrobenzaldehyde (0.755 g, 6 mmoles) irradiated in microwave oven (200 watt) at
108 °C for 6 minutes. The N-(4-nitrobenzylidene)-4,6-dimethylpyrimidin-2-amine was further treated with sulfanyl acetic acid (0.460 g, 5 mmoles) under the same condition. The irradiated product was cooled to room temperature, washed, dried and recrystallized from ethanol to obtain 3-(4,6-dimethylpyrimidin-2-yl)-2-(4-nitrophenyl)-thiazolidin-4-one (95) (yield, 76.8%).

**Analytical Data Obtained:**

<table>
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<tr>
<th>Property</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td><strong>Yield:</strong></td>
<td>82.9%</td>
</tr>
<tr>
<td><strong>Melting Point:</strong></td>
<td>202-204 °C</td>
</tr>
<tr>
<td><strong>FTIR:</strong></td>
<td>3336, 3190, 2974, 1722, 1644 cm⁻¹</td>
</tr>
<tr>
<td><strong>¹H-NMR:</strong></td>
<td>(300MHz, CDCl₃) δ: 8.07-7.32 (m, 4H), 6.86 (s, 1H), 5.96 (s, 1H, C₂-thiazolidinone), 3.42 (d, H, C₅-a thiazolidinone), 3.30 (d, H, C₅-b thiazolidinone), 2.35 (s, 6H, 2CH₃)</td>
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<tr>
<td><strong>¹³CNMR:</strong></td>
<td>(75.5 MHz, CDCl₃) δ: 171.2 (C=O thiazolidinone), 164.8, 159.9, 146.8, 145.3, 129.7, 121.0, 109.6, 65.8 (C₂-thiazolidinone), 33.7 (C₅-thiazolidinone), 25.3 (CH₃)</td>
</tr>
<tr>
<td><strong>MS m/z:</strong></td>
<td>330.08 (M⁺¹), 122, 107, 102</td>
</tr>
<tr>
<td><strong>Anal.:</strong></td>
<td>C₁₅H₁₄N₄O₃S: (333.36): Calculated: C, 54.53; H, 4.27; N, 16.96; O, 14.53; S, 9.71; found: C, 54.51; H, 4.25; N, 16.92; O, 14.49; S, 9.67</td>
</tr>
</tbody>
</table>

**2-(2,4-difluorophenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (96)**

**Microwave procedure-I: Multi-Component Reaction in DMF**

A Schiff base N-(2,4-difluorobenzylidene)-4,6-dimethylpyrimidin-2-amine was prepared by treating 2,4-difluorobenzaldehyde (0.568 g, 4 mmoles) with 4,6-dimethylpyrimidin-2-amine (0.492 g, 4 mmoles) in dimethylformamide (10.0 mL) and irradiated in microwave oven at 105 °C for 6 minutes. The intermediate N-(2,4-difluorobenzylidene)-4,6-dimethylpyrimidin-2-amine and sulfanyl acetic acid (0.368 g, 4 mmoles) were further irradiated for 06 minutes at 110 °C. The irradiated product
was cooled to room temperature, washed, filtered under suction and dried. This crude product was purified with preparative TLC (ethyl acetate: hexane, 6:4, v/v) followed by recrystallization from ethanol to obtain 2-(2,4-difluorophenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (96) (yield, 86.6%).

Microwave procedure-II: Solvent free, Multi-Component Reaction

Schiff base N-(2,4-difluorobenzylidene)-4,6-dimethylpyrimidin-2-amine was prepared by treating 2,4-difluorobenzaldehyde (0.568 g, 4 mmoles) with 4,6-dimethylpyrimidin-2-amine (0.493 g, 4 mmoles). The mixture was irradiated by microwave (200 watt) at 105 °C for 6 minutes. The intermediate N-(2,4-difluorobenzylidene)-4,6-dimethylpyrimidin-2-amine and sulfanyl acetic acid (0.368 g, 4 mmoles) were mixed and irradiated in microwave radiation under the same condition. The irradiated product was cooled room temperature, washed, dried and recrystallized from ethanol to get 2-(2,4-difluorophenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (yield, 82.4%).

Analytical Data Obtained:

Yield: 86.6%
Melting Point: 224-226 °C
FTIR: 3402, 3175, 2956, 1726, 1668, 1145 cm\(^{-1}\).
\(^1\)H-NMR (300MHz, CDCl\(_3\)) \(\delta\): 7.02-6.90 (m, 3H aromatic), 6.86 (1s, 1H), 5.94 (s, 1H, C\(_2\)-thiazolidinone), 3.38 (s, H, C\(_5\)-a thiazolidinone), 3.28(s, H, C\(_5\)-b thiazolidinone), 2.35 (s, 6H, 2CH\(_3\))
\(^{13}\)CNMR (75.5 MHz, CDCl\(_3\)) \(\delta\): 171.2 (C=O thiazolidinone), 164.8, 162.9, 160.6, 159.9, 132.0, 111.0, 109.6, 104.6, 97.5, 54.8 (C\(_2\)-thiazolidinone), 33.6 (C\(_5\)-thiazolidinone), 25.1 (CH\(_3\))
MS \(m/z\): 321.07 (M\(^+\)), 225, 113, 107, 101
Anal.: C\(_{16}\)H\(_{17}\)N\(_3\)O\(_2\)S: (321.35): Calculated: C, 56.06; H, 4.08; N, 13.08; O, 4.98; S, 9.98; found: C, 56.08; H, 4.06; N, 13.06; O, 4.97; S, 9.96
2-(4-(dimethylamino)phenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (97)

**Microwave procedure-I: Multi-Component Reaction in DMF**

The compounds 4,6-dimethylpyrimidin-2-amine (0.370 g, 3 mmoles), 4-(dimethylamino)benzaldehyde (0.447 g, 3 mmoles) were mixed and irradiated in microwave oven (200 watt) at 105 °C for 6 minutes to get Schiff base as an intermediate \(N\)-\(4\)-(diaminomethyl)benzylidene-4,6-dimethylpyrimidin-2-amine. \(N\)-(4-diaminomethyl)benzylidene-4,6-dimethylpyrimidin-2-amine was mixed with sulfanyl acetic acid (0.276 g, 3 mmoles) and again irradiated (200 watt) at 108 °C for 06 minutes. The crude product was cooled to room temperature, washed, filtered under suction and dried. Preparative TLC (ethyl acetate: n-hexane, 6:4, v/v) was applied to purify the crude product followed by recrystallization from ethanol to obtain 2-(4-(dimethylamino)phenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (yield, 88.8%).

**Microwave procedure-II: Solvent free, Multi-Component Reaction**

A mixture of 4,6-dimethylpyrimidin-2-amine (0.370 g, 3 mmoles), 4-(dimethylamino)benzaldehyde (0.447 g, 3 mmoles) and sulfanyl acetic acid (0.276 g, 3 mmoles) was irradiated in microwave oven (200 watt) at 105 °C for 8 minutes. The irradiated product was cooled to room temperature, washed, filtered under suction and dried. The irradiated product was purified with preparative TLC (ethyl acetate: n-hexane, 6:4, v/v) followed by recrystallization from ethanol to obtain 2-(4-(dimethylamino)phenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one (yield 72.4%).

**Analytical Data Obtained:**

Yield: 88.8%

Melting Point: 218-200 °C

FTIR: 3360, 3160, 2928, 1724, 1652 cm\(^{-1}\).
\( ^{1}H\text{-NMR}\)  
\( (300\text{MHz, CDCl}_3 \delta: 6.96-6.40 (m, 4H), 6.88 (s, 1H), 5.90 (s, 1H, C_2\text{-thiazolidinone}), 3.40 \text{ (d, H, C}_5\text{-a thiazolidinone)}, 3.31(\text{d, H, C}_5\text{-b thiazolidinone}), 2.85 \text{ (s, 6H, N(CH}_3)_2), 2.38 \text{ (s, 6H, 2CH}_3) \)

\( ^{13}C\text{-NMR}\)  
\( (75.5 \text{ MHz, CDCl}_3 \delta: 171.2 \text{ (C=O thiazolidinone)}, 164.8, 159.9, 149.5, 140.1, 129.6, 118.3, 113.7, 112.7, 109.6, 65.9 \text{ (C}_2\text{-thiazolidinone)}, 40.3, 33.6 \text{ (C}_5\text{-thiazolidinone)}, 25.2 \text{ (CH}_3 \) \)

\( \text{MS m/z:} \)  
328.43 (M\(^+\)), 222, 120, 107, 101

\( \text{Anal.:} \)  
C\(_{17}\)H\(_{20}\)N\(_{4}\)OS: (328.43): Calculated: C, 62.17; H, 6.14; N, 17.06; O, 4.87; S, 9.76; found: C, 62.15; H, 6.16; N, 17.02; O, 4.85; S, 9.72

### 3.4.2-Synthesis of 4-thiazolidinone derivatives (98-107)

**Microwave procedure-I: Multi-Component Reaction using Montmorillonite Clays (K-10 and KSF)**

The compounds of substituted aromatic aldehydes, substituted aromatic amines, mercaptoacetic acid and montmorillonite clays, KSF and K-10 (30% by weight of reactants) in 10 mL water was irradiated in microwave oven (200 Watt) at 105-108 °C for 9-12 minutes. TLC was used to monitor the reaction. Irradiated product was cooled and extracted with ethyl acetate (4 X 25 mL). The final product was recrystallized from ethanol to obtain the compounds (98-107) (yield 78.4% to 94.1% with K-10 and 68.3% to 88.1% with KSF).

**Microwave procedure-II: Solvent free, Multi-Component Reaction**

Compounds (98-107) were synthesized without solvent. The compounds of substituted aromatic aldehydes and substituted aromatic amines were irradiated in microwave oven (200 watt) for 6-8 minutes. The product was further treated with mercaptoacetic acid and again irradiated under microwave radiation under the condition. The irradiated product was cooled to room temperature, washed, filtered under suction and dried. The product was purified with preparative TLC (ethyl
acetate: n-hexane, 5:5, v/v) followed by recrystallization from ethanol. The yields of compounds (98-107) were obtained ranging from 44.3% to 76.4%.

Microwave procedure-I: Multi-Component Reaction using Montmorillonite Clays (K-10 and KSF)

2-(3, 5-dimethylphenyl)-3-phenyl-thiazolidin-4-one (98)

A mixture of aniline (0.465 g, 5 mmoles), 3, 5 dimethyl benzaldehyde (0.670 g, 5 mmoles), mercaptaoactic acid (0.460 g, 5 mmoles) and montmorillonite clays KSF and K-10 (30% by weight of reactants) in 10 mL water was irradiated in microwave oven at 105 °C for 10 minutes. TLC was used to monitor the reaction. Irradiated product (98) was cooled to room temperature and extracted with ethyl acetate (4 X 25 mL). The product was recrystallized from ethanol to obtain the 2-(3,5-dimethylphenyl)-3-phenyl-thiazolidin-4-one (98) (yields 84.4% with K-10 and 78.6% with KSF).

Analytical Data Obtained:

Yield: 84.4%
Melting Point: 180-182 °C
FTIR: 3190, 3000, 1720, 1618 cm⁻¹

1H-NMR (300MHz, CDCl₃) δ: 7.31-7.10 (m, 5H), 6.67 (s, 3H, aromatic), 5.92 (s, 1H, C₂-thiazolidinone), 3.39 (s, 1H, C₅-a thiazolidinone), 3.28 (s, 1H, C₅-b thiazolidinone), 2.35 (s, 6H, 2CH₃)

13CNMR: (75.5 MHz, CDCl₃) δ: 166.7 (C=O thiazolidinone), 140.8, 138.1, 137.5, 128.7, 128.3, 126.6, 124.1, 120.4, 58.6 (C₂-thiazolidinone), 36.5 (C₅-thiazolidinone), 21.5 (CH₃)

MS m/z: 283.10 (M⁺), 207, 179, 105, 77

Anal.: C₁₇H₁₇NOS: (283.39): Calculated: C, 72.05; H, 6.05; N, 4.94; O, 5.65; S, 11.31; found: C, 72.08; H, 6.04; N, 4.96; O, 5.68; S, 11.30
2-(3-hydroxy-5-methoxyphenyl)-3-phenyl-thiazolidin-4-one (99)

Equimolar quantities of aniline (0.279 g, 3 mmoles), 3-hydroxy-5-methoxybenzaldehyde (0.456 g, 3 mmoles), sulfanylacetic acid (0.276 g, 3 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) in 10 mL water were mixed and irradiated under microwave radiation at 106 °C for 10 minutes. Irradiated product was cooled and extracted with ethyl acetate (4 X 25 mL). The product was recrystallized from ethanol to get 2-(3-hydroxy-5-methoxyphenyl)-3-phenyl-thiazolidin-4-one (99) (yields 78.4% with K-10 and 68.2% with KSF).

Analytical Data Obtained:

Yield: 78.4%
Melting Point: 180-182 °C
FTIR: 3320, 3212, 2912, 1721, 1662 cm⁻¹
^1H-NMR (300 MHz, CDCl₃) δ: 7.32-7.14 (m, 5H), 6.13-6.05 (m, 3H), 5.96 (s, 1H, C₂-thiazolidinone), 5.0 (s, H, OH), 3.47 (s, 1H, C₅-a thiazolidinone), 3.38 (s, 1H, C₅-b thiazolidinone), 3.22 (s, 3H, CH₃)
^13CNMR (75.5 MHz, CDCl₃) δ: 166.9 (C=O thiazolidinone), 163.3, 158.2 (CH-OH), 140.8, 140.7, 128.7, 124.1, 120.4, 108.4, 107.1, 99.7, 58.8 (C₂-thiazolidinone), 56.0 (O-CH₃), 36.3 (C₅-thiazolidinone)
MS m/z: 301(M⁺), 225, 123, 77, 101
Anal.: C₁₆H₁₅NO₃S: (301.36): Calculated: C, 63.77; H, 5.02; N, 4.65; O, 15.93; S, 10.64; found: C, 62.24; H, 5.08; N, 4.58; O, 15.96; S, 10.62

2-(3-chloro-5-methylphenyl)-3-phenyl-thiazolidin-4-one (100)

A mixture of aniline (0.372 g, 4 mmoles), 3-chloro-5-methylbenzaldehyde (0.618 g, 4 mmoles), mercaptoacetic acid (0.368 g, 4 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) in 10 mL water was irradiated under microwave radiation at 108 °C temperature for 12 minutes. TLC was used to monitor the reaction. The irradiated product was cooled to room temperature, washed and extracted with ethyl acetate (4 X 25 mL). The product was recrystallized
from ethanol 2-(3-chloro-5-methylphenyl)-3-phenyl-thiazolidin-4-one (100) (yields 88.3% with K-10 and 74.3% with KSF).

Analytical Data Obtained:

Yield: 88.3%  
Melting Point: 201-203 °C  
FTIR: 3320, 3208, 2942, 1712, 1652 cm⁻¹.  
¹H-NMR (300 MHz, CDCl₃) δ: 7.30-7.16 (m, 5H), 6.88 (d, 2H, J=6.7 Hz), 6.74 (s, 1H), 5.92 (s, 1H, C₂-thiazolidinone), 3.40 (s, 1H, C₅-a thiazolidinone), 3.26 (s, 1H, C₅-b thiazolidinone), 2.40 (s, 3H, CH₃)  
¹³C-NMR (75.5 MHz, CDCl₃) δ: 166.8 (C=O thiazolidinone), 140.8, 139.6, 139.0, 133.6, 128.7, 128.0, 126.3, 124.1, 120.4, 57.8 (C₂-thiazolidinone), 36.3 (C₅-thiazolidinone), 20.7 (CH₃)  
MS m/z: 303 (M⁺), 227, 125, 101, 77  
Anal.: C₁₆H₁₄ClNOS: (303.81): Calculated: C, 63.25; H, 4.64; N, 4.61; O, 5.27; S, 10.55; found: C, 63.27; H, 4.63; N, 4.59; O, 5.25; S, 10.53

2-(3, 5-dichlorophenyl)-3-phenyl-thiazolidin-4-one (101)

Equimolar quantities of aniline (0.279 g, 3 mmoles), 3,5-dichlorobenzaldehyde (0.525 g, 3 mmoles), sulfanylacetic acid (0.276 g, 3 mmoles) and montmorillonite clays, K-10 and KSF (30% by weight of reactants) in 10 mL water were mixed and irradiated under microwave radiation at 108 °C for 9 minutes. Irradiated product was cooled to room temperature and extracted with ethyl acetate (4 X 25 mL). Finally the product was recrystallized from ethanol to get 2-(3,5-dichlorophenyl)-3-phenyl-thiazolidin-4-one (101) (yields 86.5% with K-10 and 78.5% with KSF).

Analytical Data Obtained:

Yield: 86.5%  
Melting Point: 212-214°C
FTIR: 3326, 3140, 2934, 1724, 1652 cm^{-1}

$^1$H-NMR (300MHz, CDCl$_3$) δ: 7.28-7.10 (m, 5H), 7.02 (s, 1H), 6.95 (d, 2H, $J$=7.7Hz), 5.90 (s, 1H, C$_2$-thiazolidinone), 3.38 (s, 1H, C$_5$-a thiazolidinone), 3.24 (s, 1H, C$_5$-b thiazolidinone)

$^{13}$CNMR (75.5 MHz, CDCl$_3$) δ: 166.7 (C=O thiazolidinone), 141.1, 140.6, 135.1 (Ar-Cl), 128.7, 127.7, 127.4, 124.1, 120.4, 57.0(C$_2$-thiazolidinone), 36.3 (C$_5$-thiazolidinone)

MS $m/z$: 324 (M$^+$), 145, 101, 77

Anal.: C$_{15}$H$_{11}$Cl$_2$NOS: (324.22): Calculated: C, 55.57; H, 3.42; N, 4.32; O, 4.93; S, 9.89; found: C, 55.55; H, 3.41; N, 4.30; O, 4.95; S, 9.85

2-(3-nitrophenyl)-3-phenyl-thiazolidin-4-one (102)

Aniline (0.558 g, 6 mmoles), 3-nitrobenzaldehyde (0.906 g, 6 mmoles), mercaptoacetic acid (0.552 g, 6 mmoles), montmorillonite clays, K-10 and KSF (30% by weight of reactants) in 10 mL water were mixed and irradiated under microwave radiation at 105 °C for 10 minutes. Irradiated product (102) was cooled to room temperature and extracted with ethyl acetate (4 X 25 mL). The product was recrystallized from ethanol to obtain 2-(3-nitrophenyl)-3-phenyl-thiazolidin-4-one (102) (yields 80.5% with K-10 and 69.8% with KSF).

**Analytical Data Obtained:**

Yield: 80.5%

Melting Point: 190-192 °C

FTIR: 3330, 3160, 2926, 1726, 1634 cm$^{-1}$

$^1$H-NMR (300MHz, CDCl$_3$) δ: 8.00-799 (d, 2H, $J$=7.5Hz), 7.45-7.40 (d, 2H, $J$=6.8Hz), 7.31-7.12 (m, 5H), 5.90 (s, 1H, C$_2$-thiazolidinone), 3.41 (s, 1H, C$_5$-a thiazolidinone), 3.30 (s, 1H, C$_5$-b thiazolidinone)

$^{13}$CNMR (75.5 MHz, CDCl$_3$) δ: 166.6 (C=O thiazolidinone), 148.3, 140.8, 139.2, 135.0, 129.3, 128.7, 124.1, 124.0, 122.0, 120.4, 57.0(C$_2$-thiazolidinone), 36.3 (C$_5$-thiazolidinone)
Mass $m/z$: 300 (M$^{+1}$), 122, 101, 77

Anal.: $C_{16}H_{15}NOS$: (300.33): Calculated: C, 59.99; H, 4.03; N, 9.33; O, 15.98; S, 10.68; found: C, 59.96; H, 4.01; N, 9.31; O, 15.96; S, 10.65

2-(3-ethoxyphenyl)-3-phenyl-thiazolidin-4-one (103)

The equimolar quantities of compounds aniline (0.465 g, 5 mmoles), 3-ethoxybenzaldehyde (0.751 g, 5 mmoles), sulfanylacetic acid (0.460 g, 5 mmoles) and montmorillonite clays, K-10 and KSF (30% by weight of reactants) in 10 mL water were mixed and irradiated under microwave radiation at 105 °C temperature for 10 minutes. Irradiated product was cooled to room temperature and extracted with ethyl acetate (4 X 25 mL). Finally the compound was recrystallized from ethanol to obtain 2-(3-ethoxyphenyl)-3-phenyl-thiazolidin-4-one (103) (yields 82.7% with K-10 and 76.4% with KSF).

Analytical Data Obtained:

Yield: 82.7%

Melting Point: 190-192 °C

FTIR: 3324, 3120, 2912, 1724, 1653 cm$^{-1}$

$^1$H-NMR (300MHz, CDCl$_3$) δ: 7.31-7.10 (m, 5H), 6.62-6.57 (m, 4H), 5.92 (s, 1H, C$_2$-thiazolidinone), 3.98 (s, CH$_2$CH$_3$), 3.43 (s, 1H, C$_5$-a thiazolidinone), 3.33 (s, 1H, C$_5$-b thiazolidinone ), 1.33 (s, CH$_2$CH$_3$)

$^{13}$CNMR (75.5 MHz, CDCl$_3$) δ: 171.2 (C=O$_{thiazolidinone}$), 157.4, 141.7, 139.8, 129.3, 129.0, 124.4, 121.6, 121.2, 120.4, 112.9, 112.8, 65.9(C$_2$-thiazolidinone), 64.7, 36.3(C$_5$-thiazolidinone), 14.8

Mass $m/z$: 299.10 (M$^{+1}$), 121, 101, 77

Anal.: $C_{17}H_{17}NO_2S$: (299.39): Calculated: C, 68.20; H, 5.72; N, 4.68; O, 10.69; S, 10.71; found: C, 68.18; H, 5.68; N, 4.65; O, 10.65; S, 10.73
2-(3-methoxyphenyl)-3-phenyl-thiazolidin-4-one (104)

The compounds aniline (0.279 g, 3 mmoles), 3-methoxybenzaldehyde (0.450 g, 3 mmoles), sulfanylacetic acid (0.276 g, 3 mmoles) and montmorillonite clays, K-10 and KSF (30% by weight of reactants) in 10 mL water were mixed and irradiated under microwave radiation at 105 °C for 10 minutes. The irradiated product (104) was cooled to room temperature and extracted with ethyl acetate (4 X 25 mL). Finally the product was recrystallized from ethanol to get 2-(3-methoxyphenyl)-3-phenyl-thiazolidin-4-one (104) (yields 89.9% with K-10 and 84.6% with KSF).

Analytical Data Obtained:

Yield: 89.9%
Melting Point: 190-192 °C
FTIR: 3320, 3120, 2946, 1726, 1646 cm⁻¹.

¹H-NMR (300MHz, CDCl₃) δ: 7.31-7.10 (m, 5H), 7.01-6.57 (m, 4H), 5.92 (s, 1H, C₂-thiazolidinone), 3.43 (s, 1H, C₅-a-thiazolidinone), 3.33 (s, 1H, C₅-b-thiazolidinone), 3.73 (s, OCH₃)

¹³CNMR (75.5 MHz, CDCl₃) δ: 171.2 (C=O-thiazolidinone), 161.1, 160.6, 141.7, 140.2, 129.7, 129.0, 124.4, 121.6, 121.2, 112.8, 112.7, 65.9 (C₂-thiazolidinone), 55.9, (OCH₃), 33.6 (C₅-thiazolidinone)

MS m/z: 285.08 (M⁺), 209, 107, 101, 77
Anal.: C₁₆H₁₅NOS: (285.36): Calculated (%): C, 67.34; H, 5.30; N, 4.91; O, 11.21; S, 11.24; found: C, 67.31; H, 5.32; N, 4.87; O, 11.19; S, 11.21

2-[3-(dimethylamino)phenyl]-3-phenyl-thiazolidin-4-one (105)

Aniline (0.465 g, 5 mmoles), 3-(dimethylamino)benzaldehyde (0.746 g, 5 mmoles), mercaptoacetic acid (0.460 g, 5 mmoles) and montmorillonite clays, K-10 and KSF (30% by weight of reactants) in 10 mL water were mixed and irradiated under microwave radiation for 10 minutes at 105 °C. Irradiated product was cooled to 25 °C and extracted with ethyl acetate (4 X 25 mL). Finally the product was
recrystallized from ethanol to get 2-[3-(dimethylamino)phenyl]-3-phenyl-thiazolidin-4-one (105) (yields 84.4% with K-10 and 82.6% with KSF).

**Analytical Data Obtained:**

| **Yield:** | 84.4% |
| **Melting Point:** | 168-170 °C |
| **FTIR:** | 3344, 3212, 2964, 1725, 1634 cm⁻¹. |
| **¹H-NMR** (300MHz, CDCl₃) δ: | 7.31-7.10 (m, 5H), 6.96-6.39 (m, 4H), 5.90 (s, 1H, C₂-thiazolidinone), 3.45 (s, 1H, C₅-a thiazolidinone), 3.31 (s, 1H, C₅-b thiazolidinone), 2.85 (s, 6H, N(CH₃)₂) |
| **¹³CNMR** (75.5 MHz, CDCl₃) δ: | 171.2 (C=Othiazolidinone), 149.5, 141.7, 140.1, 129.6, 129.0, 124.4, 121.6, 121.1, 118.3, 113.7, 112.7, 65.6 (C₂-thiazolidinone), 40.3, (N (CH₃)₂), 33.6 (C₅-thiazolidinone) |
| **Mass m/z:** | 298.11 (M⁺), 222, 120, 101, 77 |
| **Anal.:** | C₁₇H₁₈N₂OS: (298.40): Calculated: C, 68.42; H, 6.08; N, 9.39; O, 5.36; S, 10.75; found: C, 68.40; H, 6.10; N, 9.37; O, 5.32; S, 10.70 |

2-(3,5-difluorophenyl)-3-phenyl-thiazolidin-4-one (106)

A mixture of aniline (0.558 g, 6 mmoles), 3,5-difluorobenzaldehyde (0.852 g, 6 mmoles), mercaptoacetic acid (0.552 g, 6 mmoles) and montmorillonite clays, K-10 and KSF (30% by weight of reactants) in 10 mL water was irradiated under microwave radiation at 105 °C for 11 minutes. The irradiated product was cooled to room temperature and extracted with ethyl acetate (4 X 25 mL). Finally the product was recrystallized from ethanol to obtain 2-(3,5-difluorophenyl)-3-phenyl-1,3-thiazolidin-4-one (106) (yields 94.1% with K-10 and 88.4% with KSF).

**Analytical Data Obtained:**

| **Yield:** | 94.1% |
| **Melting Point:** | 178-80 °C |
| **FTIR:** | 3342, 3140, 2937, 1724, 1645 cm⁻¹. |
$^1$H-NMR (300MHz, CDCl$_3$) $\delta$: 7.31-7.10 (m, 5H), 6.83-6.75 (m, 3H), 5.96 (s, 1H, C$_2$-thiazolidinone), 3.47 (s, 1H, C$_5$-a thiazolidinone), 3.27 (s, 1H, C$_5$-b thiazolidinone).

$^{13}$CNMR (75.5 MHz, CDCl$_3$) $\delta$: 171.2 (C=O thiazolidinone), 158.4, 156.9, 141.7, 129.6, 124.4, 121.6, 117.4, 117.0, 115.5, 103.5, 54.8 (C$_2$-thiazolidinone), 33.6 (C$_5$-thiazolidinone).

MS $m/z$: 291.05 (M$^+$), 215, 113, 101, 77

Anal.: C$_{15}$H$_{11}$F$_2$NOS: (291.32): Calculated: C, 61.84; H, 3.81; N, 4.81; O, 5.49; S, 11.01; found: C, 61.81; H, 3.85; N, 4.78; O, 5.46; S, 11.04

2-(3,5-dihydroxyphenyl)-3-phenyl-thiazolidin-4-one (107)

The equimolar quantities of compounds aniline (0.279 g, 5 mmoles), 3,5-dihydroxybenzaldehyde (0.414 g, 5 mmoles), sulfanylacetic acid (0.276 g, 5 mmoles) and montmorillonite clays, K-10 and KSF (30% by weight of reactants) in 10 mL water were mixed and irradiated for 8 minutes under microwave radiation at 105 °C. The irradiated product was cooled to room temperature, washed and extracted with ethyl acetate (4 X 25 mL). Finally the product was recrystallized from ethanol to obtain 2-(3,5-dihydroxyphenyl)-3-phenyl-thiazolidin-4-one (107) (yields 90.2% with K-10 and 82.8% with KSF).

Analytical Data Obtained:

Yield: 90.2%
Melting Point: 204-206 °C
FTIR: 3342, 3125, 2946, 1728, 1645 cm$^{-1}$
$^1$H-NMR (300MHz, CDCl$_3$) $\delta$: 7.31-7.10 (m, 5H), 6.09-6.01 (m, 3H), 5.94 (s, 1H, C$_2$-thiazolidinone), 5.00 (s, 1H, OH), 3.41 (s, 1H, C$_5$-a thiazolidinone), 3.34 (s, 1H, C$_5$-b thiazolidinone)

$^{13}$CNMR (75.5 MHz, CDCl$_3$) $\delta$: 171.2 (C=O thiazolidinone), 159.8, 142.0, 141.7, 129.0, 124.4, 121.6, 107.0, 102.0, 66.2 (C$_2$-thiazolidinone), 33.6 (C$_5$-thiazolidinone)
MS m/z: 287.06 (M+1), 211, 109, 101, 77
Anal.: C_{15}H_{13}NO_{3}S: (287.06): Calculated: C, 62.70; H, 4.56; N, 4.87; O, 16.70; S, 11.16; found: C, 62.67; H, 4.53; N, 4.85; O, 16.68; S, 11.18

3.4.3-Synthesis of 4-thiazolidinone derivatives (108-117)

Microwave procedure-I: Multi-Component Reaction using Ionic Liquids (PEG, TBAB and TEBAC)

A mixture of 1, 3-dipyridin-2-ylthiourea, chloroacetic acid (0.378 g, 4 mmoles) and substituted aromatic aldehydes was taken in the presence of Ionic Liquids (PEG, TBAB, TEBAC) and water (20 mL) was irradiated in microwave oven (200 watt) for 12 minutes at 110 °C. The reaction was monitored by TLC. The crude product was cooled to 25 °C, washed with water and followed by recrystallization from ethanol to get compounds (108-117). The yield ranged from 33.4%-48.8% with TBAB, 33.5%-52.2% with PEG and 20.4%-32.4% with TEBAC.

Microwave procedure-II: Solvent free, Multi-Component Reaction

Compounds 1,3-dipyridin-2-ylthiourea, chloroacetic acid and substituted aromatic aldehydes were mixed and irradiated by microwaves at 105-108 °C for 9-12 minutes. The irradiated product was cooled to room temperature. The crude mixture was subjected to solvent extraction using dichloromethane. The product was dried under suction followed by recrystallization from ethanol: water (80:20, v/v) to obtain (108-117) yield ranging from 82.4% to 92.8%.
Microwave procedure-II: Solvent free, Multi-Component Reaction

5-benzylidene-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (108)

Compounds 1,3-dipyridin-2-ylthiourea (0.920 g, 4 mmoles), chloroacetic acid (0.378 g, 4 mmoles) and benzaldehyde (0.424 g, 4 mmoles) were mixed and irradiated by microwaves at 106 °C for 12 minutes. The reaction was monitored by TLC. The irradiated product was cooled to room temperature and the crude mixture was subjected to solvent extraction using dichloromethane. Finally the product was dried under suction followed by recrystallization from ethanol: water (80:20, v/v) to obtain 5-benzylidene-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (108) (yield, 82.4%).

Analytical Data Obtained:

Yield: 82.4%
Melting Point: 238-240 °C
FTIR: 3140, 2868, 1712, 1662 cm⁻¹
¹H-NMR (300MHz, CDCl₃) δ: 8.55 (d, 2H, J=6.7Hz), 8.11 (d, 2H, J=4.3Hz), 7.74 (d, 2H, J=5.6Hz), 7.30 (m, 5H), 6.80 (s, 1H, CH=C₅hod), 6.60 (d, 2H, J = 4.3 Hz)
¹³C-NMR (75.5 MHz, CDCl₃) δ: 170.3, 164, 163, 161.1, 151.1, 148.9, 142, 138.0, 137.0, 134.9, 128.4, 127.7, 126.2, 122.1, 120, 117.1, 113.0, 108.9,
MS m/z: 358 (M⁺), 280, 203, 90, 78
Anal.: C₂₀H₁₄N₄O₅: (358.42): Calculated: C, 67.02; H, 3.94; N, 15.63; O, 4.46; S, 8.95; found: C, 67.06; H, 3.96; N, 15.61; O, 4.44; S, 8.97
5-(4-methoxybenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (109)

5-(4-methoxybenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one was synthesized by mixing 1,3-dipyridin-2-ylthiourea (1.150 g, 5 mmoles), chloroacetic acid (0.473 g, 5 mmoles) and 4-methoxybenzaldehyde (0.680 g, 5 mmoles) was irradiated by microwave at 108 °C for 9 minutes. The irradiated product was cooled to room temperature and the mixture was subjected to solvent extraction using dichloromethane. The product was dried under suction followed by recrystallization from ethanol: water (80:20, v/v) to get 5-(4-methoxybenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (109) (yield, 92.3%).

Analytical Data Obtained:

Yield: 92.3%
Melting Point: 238-240 °C
FTIR: 3138, 2870, 1710, 1665 cm⁻¹
¹H-NMR (300MHz, CDCl₃) δ: 8.22-7.54 (m, 8 H of two pyridine molecule), 7.19 (d, 2H, J=5.7Hz ), 7.02 (d, 2H, J=6.3Hz ), 6.80 (s, 1H, CH=C₅-rhod), 6.72 (d, 2H, J=4.8Hz ), 6.62 (d, 2H , J = 4.5Hz), 3.73 (s, 3H, CH₃)
¹³CNMR (75.5 MHz, CDCl₃) δ: 170.3, 164, 163, 161.1, 151.1, 148.9, 142, 138.0, 137.0, 127.2, 122.1, 120, 117.1, 114.0, 113.0, 108.9, 56.0
MS m/z: 388 (M⁺), 281, 203, 120, 92
Anal.: C₂₁H₁₆N₄O₂S: (388.44): Calculated: C, 64.93; H, 4.15; N, 14.42; O, 8.24; S, 8.25; found: C, 64.95; H, 4.12; N, 14.44; O, 8.26; S, 8.22

5-(2-hydroxy-4-methoxybenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (110)

Compounds 3-hydroxy-4-methoxybenzaldehyde (0.912 g, 6 mmoles), chloroacetic acid (0.658 g, 6 mmoles) and 1, 3-dipyridin-2-yl-thiourea (1.382 g, 6
mmoles) were mixed and irradiated under microwave radiation (200 Watt) at 106 °C temperature for 10 minutes. The irradiated product was cooled to room temperature and the mixture was subjected to solvent extraction using dichloromethane. Finally the product was dried under suction followed by recrystallization from ethanol: water (80:20, v/v) to get 5-(2-hydroxy-4-methoxybenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (110) (yield, 86.2%).

**Analytical Data Obtained:**

Yield: 86.2%

Melting Point: 224-226 °C

FTIR: 3142, 2874, 1716, 1667 cm⁻¹

¹H-NMR (300MHz, CDCl₃) δ: 8.42-7.68 (m, 8 H of two pyridine molecule), 7.07 (s, 1H, CH=C₅-rhod), 7.02 (s, 1H aromatic, J=6.28Hz), 6.68 (d, 2H aromatic, J=5.2Hz), 5.02(s, 1H, OH), 3.72 (s, 3H, CH₃)

¹³CNMR (75.5 MHz, CDCl₃) δ: 170.3, 164, 163, 162.6, 161.1, 156.0, 151.1, 148.9, 142, 138.0, 137.0, 128.6, 122.1, 120, 117.1, 114.4, 113.0, 108.9, 106.6, 101.2, 56.0

MS m/z: 404 (M⁺) 327, 281, 136, 92

Anal.: C₂₁H₁₆N₄O₃S: (404.44): Calculated: C, 62.36; H, 3.99; N, 13.85; O, 11.87; S, 7.93; found: C, 62.38; H, 4.02; N, 13.84; O, 11.86; S, 7.94

5-[4-(dimethylamino)benzylidene]-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (111)

Equimolar quantities of 1, 3-dipyridin-2-thioureia (0.690 g; 3 mmoles), 4-(dimethylamino)benzaldehyde (0.447 g, 3 mmoles) and chloroacetic acid were mixed and irradiated in microwave oven at 108 °C for 10 minutes. The crude mixture was subjected to solvent extraction using dichloromethane. The product was dried under suction followed by recrystallization from ethanol: water (80:20, v/v) to obtain 5-[4-(dimethylamino)benzylidene]-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (111) (yield, 89.7%).
Analytical Data Obtained:

Yield: 89.7%
Melting Point: 234-236 °C
FTIR: 3144, 2869, 1722, 1669 cm⁻¹

¹H-NMR (300MHz, CDCl₃) δ: 8.40-7.72 (m, 8 H of two pyridine molecule), 7.22 (d, 2H, J=6.2Hz), 6.98 (d, 2H, J=5.7Hz), 6.78 (s, 1H, CH=C₅-rhod), 2.85 (s, 6H, (CH₃)₂)

¹³CNMR (75.5 MHz, CDCl₃) δ: 170.3, 164, 163,161.1, 155.9, 151.1, 148.9, 145.1, 142, 138.0, 137.0, 128.5, 122.1, 120, 117.1, 113.0, 111.6, 108.9, 105.6, 101.2, 100.2, 43.6, 43.6

MS m/z: 334 (M⁺) 309, 281,133, 92

Anal.: C₂₂H₁₉N₅OS: (401.48): Calculated: C, 65.81; H, 4.77; N, 17.44; O, 3.99; S, 7.99; found: C, 65.82; H, 4.78; N, 17.46; O, 3.96; S, 7.98

5-(2,4-dichlorobenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (112)

A mixture of 2,4-dichlorobenzaldehyde (0.875 g, 5 mmoles), chloroacetic acid (0.470 g, 5 mmoles) and 1, 3-dipyridin-2-ylthiourea (1.150 g, 5 mmoles) was irradiated under microwave radiation at 105 °C for 10 minutes. The irradiated product was subjected to solvent extraction using dichloromethane, dried under suction and followed by recrystallization from ethanol : water (80:20, v/v) to obtain 5-(2,4-dichlorobenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (112) (yield, 92.8%)

Analytical Data Obtained:

Yield: 92.8%
Melting Point: 228-230 °C
FTIR: 3146, 2868, 1718, 1667 cm⁻¹
5-(4-nitrobenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)thiazolidin-4-one (113)

1, 3-dipyrrold-2-ylthiourea (0.920 g, 4 mmoles), chloroacetic acid (0.376 g, 4 mmoles) and 4-nitrobenzaldehyde (0.604 g, 4 mmoles) were mixed and irradiated under microwave radiation (200 Watt) at 108 °C for 12 minutes. The irradiated product was cooled to room temperature. The product was subjected to solvent extraction using dichloromethane, dried under suction and followed by recrystallization from ethanol: water (80:20, v/v) to obtain 5-(4-nitrobenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (113) (yield, 66.8%).

Analytical Data Obtained:

<table>
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<tr>
<th>Property</th>
<th>Value</th>
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<tr>
<td>Yield</td>
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<tr>
<td>Melting Point</td>
<td>228-230 °C</td>
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<tr>
<td>FTIR</td>
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</tr>
<tr>
<td>¹H-NMR (300MHz, CDCl₃) δ:</td>
<td>8.32-7.85 (m, 8 H of two pyridine molecule), 7.65 (d, 2H, J=5.5Hz), 7.56 (d, 2H, J=5.5Hz), 6.87 (s, 1H, CH=C₅-rhod)</td>
</tr>
<tr>
<td>¹³CNMR (75.5 MHz, CDCl₃) δ:</td>
<td>170.3, 164.0, 163.0, 161.1, 151.1, 148.9, 147.6, 142.0, 141.0, 138.0, 137.0, 127.1, 123.5, 122.1, 120.0, 117.1, 113.0, 108.9</td>
</tr>
<tr>
<td>MS m/z:</td>
<td>403 (M⁺¹) 325, 281, 135, 92</td>
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</tbody>
</table>
5-(4-ethoxybenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (114)

The compounds 4-ethoxybenzaldehyde (0.912 g, 6 mmoles), chloroacetic acid (0.658 g, 7.0 mmoles) and 1, 3-dipyridin-2-ylthiourea (1.382 g, 6 mmoles) were mixed and irradiated under microwave radiation at 108 °C for 12 minutes. The crude mixture was subjected to solvent extraction using dichloromethane, dried under suction and followed by recrystallization from ethanol: water (80:20, v/v) 5-(4-ethoxybenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (114) (yield, 84.4%)

Analytical Data Obtained:

Yield: 84.4%
Melting Point: 220-222 °C
FTIR: 3140, 2858, 1718, 1665 cm⁻¹
¹H-NMR (300MHz, CDCl₃) δ: 8.42-7.68 (m, 8 H of two pyridine molecule), 7.19 (d, 2H, J=5.5Hz), 6.97 (d, 2H, J=5.7Hz), 6.77 (s, 1H, CH=Cs-rhod), 3.98 (d, 2H, CH₂), 1.78 (d, 3H, CH₃)
¹³CNMR (75.5 MHz, CDCl₃) δ: 170.3, 164.0, 163.0, 161.1, 151.1, 148.9, 147.6, 142.0, 141.0, 138.0, 137.0, 127.1, 123.5, 122.1, 120.0, 117.1, 113.0, 108.9
Mass m/z: 402 (M⁺) 310, 281, 134, 92
Anal.: C₂₂H₁₈N₄O₂S: 402.47; Calculated; C, 65.65; H, 4.51; N, 13.92; O, 7.95; S, 7.97; Found: C, 65.67; H, 4.49; N, 13.91; O, 7.93; S, 7.95
5-(2,4-difluorobenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (115)

A mixture of 1, 3-dipyridin-2-ylthiourea (1.382 g, 6 mmoles), chloroacetic acid (0.658 g, 7.0 mmoles) and 2,4-difluorobenzaldehyde (0.852 g, 6 mmoles) was irradiated under microwave radiation at 108 °C for 11 minutes. The reaction was monitored by TLC. The crude product was subjected to solvent extraction using dichloromethane, dried under suction followed by recrystallization from ethanol: water (80:20, v/v) to get 5-(2,4-difluorobenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (115) (yield, 88.1%).

Analytical Data Obtained:
Yield: 88.1%
Melting Point: 232-234 °C
FTIR: 3148, 2866, 1724, 1662 cm⁻¹
¹H-NMR (300MHz, CDCl₃): δ: 8.42-7.68 (m, 8 H of two pyridine molecule), 7.36 (d, 2H, J=5.3Hz), 7.14 (s, 1H, J=6.9Hz), 6.87 (s, 1H, CH=C₅-rho)
¹³CNMR (75.5 MHz, CDCl₃): δ: 170.3, 164.0, 163.0, 161.1, 151.1, 148.9, 147.6, 142.0, 141.0, 138.0, 137.0, 127.1, 123.5, 122.1, 120.0, 117.1, 113.0, 108.9
MS m/z: 394 (M⁺) 281, 126, 92
Anal.: C₂₀H₁₂F₂N₄O₅S: 394.0; Calculated: C, 60.91; H, 3.07; N, 14.21; O, 4.06; S, 8.13; Found: C, 60.90; H, 3.05; N, 14.19; O, 4.04; S, 8.11

5-(4-ethylbenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (116)

1, 3-dipyridin-2-yl-thiourea (1.382 g, 6 mmoles), chloroacetic acid (0.658 g, 7.0 mmoles) and 4-ethylbenzaldehyde (0.804 g, 6 mmoles) were mixed and irradiated under microwave radiation at 108 °C for 8 minutes. The irradiated product
was subjected to solvent extraction using dichloromethane, dried under suction and followed by recrystallization from ethanol: water (80:20, v/v) to obtain 5-(4-ethylbenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (116) (yield, 72.4%).

**Analytical Data Obtained:**

**Yield:** 84.2%

**Melting Point:** 212-214 °C

**FTIR:** 3152, 2868, 1726, 1660 cm⁻¹

**¹H-NMR** (300MHz, CDCl₃) δ: 8.36-7.28 (m, 8 H of two pyridine molecule), 7.21 (d, 2H, J=6.5Hz), 7.01 (s, 1H), 6.79 (s, 1H, CH=C₅-rhod), 2.59 (d, 2H, CH₂CH₃), 1.28 (t, 2H, CH₂CH₃)

**¹³CNMR** (75.5 MHz, CDCl₃) δ: 166.9, 163.0, 156.5, 150.4, 148.2, 147.7, 142.0, 138.3, 138.7, 137.3, 132.4, 127.7, 126.3, 122.4, 116.2, 115.9, 113.3, 109.9, 32.4, 14.6

**MS m/z:** 386.12(M⁺¹) 281, 203,118, 92

**Anal.:** C₂₂H₁₈N₄O₄S: 386.47; Calculated: C, 68.37; H, 4.69; N, 14.50; O, 7.414, S, 8.30; Found: C, 68.37; H, 4.69; N, 14.50; O, 7.414, S, 8.28.

**5-(1, 3-benzodioxol-5-ylmethylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (117)**

A mixture of chloroacetic acid (0.658 g, 7.0 mmoles) 1, 3-dipyrindin-2-ylthiourea (1.382 g, 6 mmoles) and 1,3-benzodioxole-5-carbaldehyde (0.90 g, 6 mmoles) was irradiated under microwave radiation at 105 °C for 12 minutes. The reaction was monitored by TLC. The crude mixture was subjected to solvent extraction using dichloromethane, dried under suction and followed by recrystallization from ethanol: water (80:20, v/v) 5-(1, 3-benzodioxol-5-ylmethylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one (117) (yield, 67.6%)
Analytical Data Obtained:

Yield: 67.6%
Melting Point: 223-225 °C
FTIR: 3155, 2863, 1729, 1657 cm⁻¹
¹H-NMR (300MHz, CDCl₃) δ: 8.39-7.31 (m, 8 H of two pyridine molecule), 7.11 (d, 2H, J=7.3Hz), 6.97 (s, 1H), 6.78 (s, 1H, CH=C₅-rhod), 5.90 (d, 2H, O-CH₂-O)
¹³CNMR (75.5 MHz, CDCl₃) δ: 170.3, 164.0, 163.0, 161.1, 151.1, 148.9, 147.6, 142.0, 141.0, 138.0, 137.0, 127.1, 123.5, 122.1, 120.0, 117.1, 113.0, 108.9
MS m/z: 388.44 (M⁺) 324, 281, 134, 92
Anal.: C₂₁H₁₆N₄O₂S: 388.44 Calculated; C, 64.93; H, 4.15; N, 14.42; O, 8.24; S, 8.25; Found: C, 64.91; H, 4.17; N, 14.40; O, 8.21; S, 8.23

3.4.4-Synthesis of 4-thiazolidinone derivatives (118-127)

Microwave procedure-I: Multi-Component Reaction using Montmorillonite Clays (KSF and K-10)

A mixture of substituted aromatic amines, substituted benzaldehydes, sulfanyl(thioxo)acetic acid, 10 mL water and montmorillonite clays, KSF and K-10 (30% by weight of reactants) was mixed and irradiated under microwave radiation (200 watt) at 110 °C temperature for 12 minutes. The reaction was monitored by TLC and the crude product was cooled to 25 °C. It was washed with water, dried under suction and recrystallized from DMF: H₂O (5:5 by v/v) to get compounds (118-127) yields ranging from 78.8% to 96.1% with K-10 and 68.9% to 86.4% with KSF.
Microwave procedure-II: Solvent free, Multi-Component Reaction

A mixture of substituted aromatic amines, substituted benzaldehydes, sulfanyl(thioxo)acetic acid and irradiated under microwave radiation (200 watt) at 110 °C for 12 minutes. The reaction was monitored by TLC and the product was cooled to room temperature. The crude product washed with water, dried under suction and recrystallized from DMF: H₂O (5:5 by v/v) to get compounds (118-127) (ranged from 34.6% to 78.8%).

Microwave procedure-I: Multi-Component Reaction using Montmorillonite Clays (KSF and K-10)

5-benzylidene-3-phenyl-2-thioxo-thiazolidin-4-one (118)

A mixture of phenyl amine (0.465 g, 5 mmoles), benzaldehyde (0.53 g, 5 mmoles), sulfanyl(thioxo)acetic acid (0.55 g, 5 mmoles) and montmorillonite clays, KSF and K-10 (30% by weight of reactants) was irradiated under microwave radiation (200 watt) at 110 °C temperature for 12 minutes. The final product was cooled to 25 °C, washed with water, dried under suction and recrystallized from DMF: H₂O (5:5 by v/v) to obtain the compound 5-benzylidene-3-phenyl-2-thioxo-thiazolidin-4-one (118) (yields 87.6% with K-10 and 78.4%.with KSF).

Analytical Data Obtained:

Yield: 87.6%
Melting Point: 223-225 °C
FTIR: 3266, 3020, 2934, 1714 cm⁻¹
¹H-NMR (300MHz, CDCl₃) δ: 7.58-7.04 (10 H, aromatic protons) [7.58 (d, 2H, J=7.7Hz), 7.30 (d, 2H, J=6.6Hz), 7.24 (d, 2H, J=5.7Hz), 7.21 (d, 2H, J=5.3Hz), 7.14 (s, 1H), 7.04 (s, 1H)], 6.80 (s, 1H). (CH=CS₅-thiazolidinoe).
13CNMR (75.5 MHz, CDCl₃) δ: 193.0 (C=S), 163.8 (C=O), 142.0 (CH=C₅-thiazolidinoe), 138.2, 134.9, 128.7, 128.4, 127.7, 126.2, 124.1, 120.4, 120.0

MS m/z: 297.03 (M⁺) 219, 206, 143, 90, 77

Anal.: C₁₆H₁₁NOS₂: (297.39): Calculated (%): C, 64.62; H, 3.73; N, 4.71; O, 5.38; S, 21.56; found: C, 64.68; H, 3.67; N, 4.66; O, 5.32; S, 21.53

5-(4-methylbenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (119)

Compounds sulfanyl(thioxo)acetic acid (0.55 g, 5 mmoles), aniline (0.465 g, 5 mmoles), 4-methylbenzaldehyde (0.60 g, 5 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of total of reactants) were taken in a round bottom flask equipped with a reflux condenser and irradiated in microwave oven (200 watt) at 108 °C for 12 minutes. The reaction was monitored by TLC and the mixture was cooled to solidify. The solid was collected and washed with 5 ml water. It was dried and recrystallized from 6ml DMF: H₂O (50:50 by v/v) to get the compound of 5-(4-methylbenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (119) (yields 89.1% with K-10 and 80.8% with KSF).

Analytical Data Obtained:

Yield: 89.1%
Melting Point: 223-225 °C
FTIR: 3265, 3018, 2914, 1716 cm⁻¹
¹H-NMR (300MHz, CDCl₃) δ: 7.60-7.04 (9 H, aromatic protons), [7.60 (d, 2H, J=7.6Hz), 7.24 (d, 2H, J=6.7Hz), 7.18 (d, 2H, J=5.8Hz), 7.10 (d, 2H, J=6.5Hz), 7.04 (s, 1H)], 6.76 (CH=C₅-thiazolidinoe), 2.35 (s, 3H, CH₃),

¹³CNMR (75.5 MHz, CDCl₃) δ: 193.0 (C=S), 163.8 (C=O), 142.0 (CH=C₅-thiazolidinoe), 138.2, 136.9, 131.9, 129.1, 128.7, 126.1, 124.1, 120.4, 120.0, 20.9

MS m/z: 311.04 (M⁺), 219, 129, 104
(5-(4-methoxybenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one)

Equimolar quantities of sulfanyl(thioxo)acetic acid (0.55 g, 5 mmoles), aminobenzene (0.465 g, 5 mmoles), 4-methoxybenzaldehyde (0.68 g, 5 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) were mixed and exposed under microwave radiation (200 watt) at 110 °C for 12 minutes. The crude mixture was cooled to 25 °C, washed with 5 mL water, dried under suction and recrystallized from 6 mL DMF: H2O (5:5 by v/v) to get the 5-(4-methoxybenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (120) (yields 89.9% with K-10 and 79.8% with KSF).

Analytical Data Obtained:

Yield: 89.9%
Melting Point: 202-204 °C
FTIR: 3278, 3034, 2944, 1719 cm⁻¹.

¹H-NMR (300MHz, CDCl₃) δ: 7.62-7.04 (9 H, aromatic protons) [7.62 (d, 2H, J=7.5Hz), 7.26 (d, 2H, J=6.6Hz), 7.16 (d, 2H, J=6.8Hz), 7.12 (s, 1H), 7.04 (d, 2H, J=6.0Hz)], 6.74 (CH=C 5-thiazolidinoe), 3.73 (s, 3H, OCH₃)

¹³C NMR (75.5 MHz, CDCl₃) δ: 193.0 (C=S), 163.8 (C=O), 142.0 (CH=C₅-thiazolidinoe), 148.4, 138.2, 129.8, 128.7, 128.6, 124.1, 120.4, 120.0, 119.8, 115.4, 114.4, 56.3 (OCH₃)

MS m/z: 327.04(M⁺), 220, 143, 120, 77

Anal.: C₁₇H₁₃NO₂S₂: (327.42): Calculated (%): C, 62.36; H, 4.00; N, 4.28; O, 9.77; S, 19.59; found: C, 62.32; H, 4.06; N, 4.25; O, 9.76; S, 19.54
5-(3-hydroxy-4-methoxybenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (121)

Benzenamine (0.465 g, 5 mmoles), 3-hydroxy-4-methoxybenzaldehyde (0.76 g, 5 mmoles), sulfanyl(thioxo)acetic acid (0.55 g, 5 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) were mixed and irradiated under microwave radiation (200 watt) at 110 °C temperature for 12 minutes. The product was washed with water, dried under suction and recrystallized from DMF: H2O (5:5 by v/v) to get 5-(3-hydroxy-4-methoxybenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (121) (yields 92.6% with K-10 and 84.2% with KSF).

**Analytical Data Obtained:**

**Yield:** 92.6%

**Melting Point:** 198-200 °C

**FTIR:** 3348, 3260, 3023, 2929, 1720 cm⁻¹.

**¹H-NMR**

(300MHz, CDCl₃) δ: 7.64-7.02 (9 H, aromatic protons) [7.64 (d, 2H, J=7.8Hz), 7.24 (d, 2H, J=7.00Hz), 7.16 (d, 2H, J=6.8Hz), 7.12 (s, 1H), 7.02 (d, 2H, J=6.0Hz)] 6.72 (CH=C₅-thiazolidine), 5.0 (s, 1H, OH), 3.73 (s, 3H, OCH₃)

**¹³CNMR**

(75.5 MHz, CDCl₃) δ: 193.0 (C=S), 163.8 (C=O), 148.4, 142.8, 142.0 (CH=C₅-thiazolidine), 138.2, 128.7, 128.6, 124.1, 120.4, 120.0, 119.8, 115.4, 114.4, 56.3 (OCH₃)

**MS m/z:** 343.03 (M⁺), 219, 136, 77

**Anal.:** C₁₇H₁₃NO₃S₂: (343.42): Calculated (%): C, 59.46; H, 3.82; N, 4.08; O, 13.98; S, 18.67; found: C, 59.48; H, 3.88; N, 4.12; O, 13.90; S, 18.65

5-[4-(dimethylamino)benzylidene]-3-phenyl-2-thioxo-thiazolidin-4-one (122)

A mixture of aminobenzene (0.465 g, 5 mmoles), 4-(dimethylamino)benzaldehyde (0.745 g, 5 mmoles), sulfanyl(thioxo)acetic acid (0.55
g, 5 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) was irradiated under microwave radiation (200 watt) at 110 °C for 10 minutes. The crude mixture was cooled to 25 °C, washed with water, dried under suction and recrystallized from DMF:H₂O (5:5 by v/v) to obtain 5-[4-(dimethylamino)benzylidene]-3-phenyl-2-thioxo-thiazolidin-4-one (122) (yields 94.2% with K-10 and 81.6% with KSF).

**Analytical Data Obtained:**

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</tr>
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<tr>
<td><strong>Yield:</strong></td>
<td>94.2%</td>
</tr>
<tr>
<td><strong>Melting Point:</strong></td>
<td>210-212 °C</td>
</tr>
<tr>
<td><strong>FTIR:</strong></td>
<td>3220, 3012, 2932, 1714 cm⁻¹</td>
</tr>
<tr>
<td><strong>¹H-NMR</strong></td>
<td>(300MHz, CDCl₃) δ: 7.64-6.98 (9 H, aromatic protons) [7.64 (d, 2H, J=7.8Hz), 7.28 (d, 2H, J=7.00Hz), 7.18 (d, 2H, J=6.8Hz), 7.12 (s, 1H), 6.98 (d, 2H, J=6.0Hz)], 6.78 (CH=C₅-thiazolidinoe), 2.85 (s, 6H, N(CH₃)₂)</td>
</tr>
<tr>
<td><strong>¹³C-NMR</strong></td>
<td>(75.5 MHz, CDCl₃) δ: 193.0 (C=S), 163.8 (C=O), 143.7, 142.0, (CH=C₅-thiazolidinoe), 138.2, 128.7, 127.1, 124.4, 124.1, 120.4, 120.0, 113.0, 43.6 (N(CH₃)₂)</td>
</tr>
<tr>
<td><strong>MS m/z:</strong></td>
<td>340.07 (M⁺), 219, 143, 133, 77</td>
</tr>
<tr>
<td><strong>Anal.:</strong></td>
<td>C₁₈H₁₆N₂O₃S₂: (340.46): Calculated (%): C, 63.50; H, 4.74; N, 8.23; O, 4.70; S, 18.84; found: C, 63.56; H, 4.78; N, 8.27; O, 4.76; S, 18.80</td>
</tr>
</tbody>
</table>

5-(4-nitrobenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (123)

Compounds sulfanyl(thioxo)acetic acid (0.55 g, 5 mmoles), phenylamine (0.465 g, 5 mmoles), 4-nitrobenzaldehyde (0.835 g, 5 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) were exposed for 10 minutes under microwave radiated (200 watt) at 110 °C. The crude product cooled to 25 °C, washed with water, dried under suction, recrystallized from DMF : H₂O (4:6 by v/v) to get 5-(4-nitrobenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (123) (yields 78.8% with K-10 and 72.4% with KSF).
Analytical Data Obtained:

**Yield:** 78.8%

**Melting Point:** 224-226 °C

**FTIR:** 3264, 3030, 2934, 1718 cm\(^{-1}\).

**\(^1\)H-NMR**  
(300 MHz, CDCl\(_3\)) \(\delta\): 7.98-7.18 (9 H, aromatic protons) [7.98 (d, 2H, \(J=5.7\)Hz), 7.64 (d, 2H, \(J=6.30\)Hz), 7.52 (d, 2H, \(J=6.5\)Hz), 7.26 (d, 2H, \(J=6.3\)Hz) 7.18 (s, 1H)] 6.78 (CH=C\(_5\)-thiazolidine)

**\(^13\)CNMR**  
(75.5 MHz, CDCl\(_3\)) \(\delta\): 193.0 (C=S), 163.8 (C=O), 147.6, 142.0, (CH=C\(_5\)-thiazolidine), 141.0, 138.2, 128.7, 127.1, 124.1, 123.5, 120.4, 120.0.

**MS m/z:** 342.01 (M\(^+\)), 219, 143, 135, 77

**Anal.:** C\(_{16}\)H\(_{10}\)N\(_2\)O\(_3\)S\(_2\): (342.39): Calculated (%): C, 56.13; H, 2.94; N, 8.18; O, 14.02; S, 18.73; found: C, 56.09; H, 2.98; N, 8.12; O, 14.06; S, 18.68

### 5-(2, 4-dichlorobenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (124)

Equimolar quantities of sulfanyl(thioxo)acetic acid (0.55 g, 5 mmoles), aminobenzene (0.465 g, 5 mmoles), 2,4-dichlorobenzaldehyde (0.875 g, 5 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) were mixed and exposed under microwave radiation (200 watt) at 110 °C for 12 minutes. The crude product was cooled to 25 °C, washed with water, dried and recrystallized from DMF: H\(_2\)O (4:6 by v/v) to obtain 5-(2, 4-dichlorobenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (124) (yields 84.3% with K-10 and 70.8% with KSF).

Analytical Data Obtained:

**Yield:** 84.3%

**Melting Point:** 218-220 °C

**FTIR:** 3246, 3034, 2946, 1716 cm\(^{-1}\).
1H-NMR
(300MHz, CDCl3) δ: 7.64-7.14 (8 H, aromatic protons) [7.64 (d, 2H, J=7.3Hz), 7.26 (d, 2H, J=6.7Hz), 7.18 (d, 2H, J=5.6Hz), 7.14 (s, 1H), 7.10 (s, 1H)], 6.93 (CH=C5-thiazolidine)

13CNMR
(75.5 MHz, CDCl3) δ: 193.0 (C=S), 163.8 (C=O), 147.6, 142.0, (CH=C5-thiazolidinoe), 141.0, 138.2, 128.7, 127.1, 124.1, 123.5, 120.4, 120.0

MS m/z: 364.95 (M+1), 219, 157, 143, 77

Anal.: C16H9Cl2NOS2 (366.28): Calculated (%): C, 52.46; H, 2.48; N, 3.82; O, 4.37; S, 17.51; found: C, 52.43; H, 2.52; N, 3.80; O, 4.33; S, 17.53

5-(4-ethoxybenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (125)
Benzenamine (0.465 g; 5 mmoles), 4-ethoxybenzaldehyde (0.75 g, 5 mmoles), sulfanyl(thioxo)acetic acid (0.55 g, 5 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) were mixed and irradiated under microwave radiation (200 watt) 110 °C for 10 minutes. The crude product was cooled to 25 °C, washed with 5 mL water, dried under suction and recrystallized from DMF: H2O (5:5, v/v) to get 5-(4-ethoxybenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (125) (yields 85.7% with K-10 and 76.2% with KSF).

Analytical Data Obtained:

Yield: 85.7%
Melting Point: 226-228 °C
FTIR: 3248, 3036, 2944, 1716, 1591 cm⁻¹.
1H-NMR
(300MHz, CDCl3) δ: 7.64-7.12 (9 H, aromatic protons) [7.64 (d, 2H, J=6.7Hz), 7.28 (d, 2H, J=7.3Hz), 7.20 (d, 2H, J=5.5Hz), 7.19 (d, 2H, J=6.3Hz), 7.08(s, 1H)], 6.78 (CH=C5-thiazolidinoe), 3.98 (d, 2H, CH2), 1.98 (t, 3H, CH3)
5-[2-(furan-2-yl)benzylidene]-3-phenyl-2-thioxo-thiazolidin-4-one (126)

A mixture of aminobenzene (0.465 g, 5 mmoles), 2-(furan-2-yl)benzaldehyde (0.86 g, 5 mmoles), sulfanyl(thioxo)acetic acid (0.55 g, 5 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) was mixed and irradiated under microwave radiation (200 watt) at 110 °C for 10 minutes. The crude mixture was cooled to 25 °C, washed with 5 mL water and dried under suction. It was recrystallized from DMF: H2O (4:6, v/v) to obtain 5-[2-(furan-2-yl)benzylidene]-3-phenyl-2-thioxo-4-thiazolidin-4-one (126) (yields 96.1% with K-10 and 84.9% with KSF).

Analytical Data Obtained:

Yield: 96.1%
Melting Point: 210-212 °C
FTIR: 3268, 3024, 2938, 1714, 1595 cm⁻¹.
¹H-NMR (300MHz, CDCl₃) δ: 7.66-7.14 (9 H, aromatic protons) [7.66 (d, 2H, J=7.7Hz), 7.42 (d, 2H, J=6.5Hz), 7.24 (d, 2H, J=5.7Hz), 7.16 (d, 2H, J=6.3Hz), 7.14(s, 1H)]. 6.76 (CH=C₅-thiazolidino), 6.30(m, 3H, C₄H₄O)
¹³CNMR (75.5 MHz, CDCl₃) δ: 193.0 (C=S), 163.8 (C=O), 147.6, 142.0, (CH=C₅-thiazolidino), 141.0, 138.2, 128.7, 127.1, 124.1, 123.5, 120.4, 120.0.

MS m/z: 341.05 (M⁺), 219, 155, 121, 77
Anal.: C₁₈H₁₅NO₂S₂: (341.45): Calculated (%): C, 63.32; H, 4.43; N, 4.10; O, 9.37; S, 18.78; found: C, 63.30; H, 4.41; N, 4.08; O, 9.34; S, 18.76.
**MS m/z:** 363.04 (M⁺), 207, 156, 67  
**Anal.:** C₂₀H₁₃NO₂S₂: (363.45): Calculated (%): C, 66.09; H, 3.61; N, 3.85; O, 8.80; S, 17.64; found: C, 66.05; H, 3.59; N, 3.82; O, 8.78; S, 17.62

**5-(2,4-difluorobenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one**  
(127)

Equimolar quantities of sulfanyl(thioxo)acetic acid (0.55 g, 5 mmoles), aminobenzene (0.46 g, 5 mmoles), 2,4-difluorobenzaldehyde (0.70 g, 5 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) were mixed and irradiated under microwave radiation (200 watt) at 110 °C for 12 minutes. The crude mixture was cooled to 25 °C, washed with water, dried under suction and recrystallized from DMF: H₂O (5:5 by v/v) to get 5-(2,4-difluorobenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one (127) (yields 86.4% with K-10 and 79.3% with KSF).

**Analytical Data Obtained:**

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<td><strong>Yield:</strong></td>
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<tr>
<td><strong>Melting Point:</strong></td>
<td>208-210 °C</td>
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<tr>
<td><strong>FTIR:</strong></td>
<td>3264, 3034, 2948, 1714, 1173 cm⁻¹.</td>
</tr>
<tr>
<td><strong>¹H-NMR</strong></td>
<td>(300MHz, CDCl₃) δ: 8.14 (d, 2H, J=7.7Hz), 7.64 (d, 2H, J=7.2Hz), 7.54 (d, 2H, J=5.6Hz), 7.48 (CH=C₅-thiazolidinoe), 7.24 (d, 2H, J=6.3Hz), 7.00(s, 1H)</td>
</tr>
<tr>
<td><strong>¹³C-NMR</strong></td>
<td>(75.5 MHz, CDCl₃) δ: 193.0 (C=S), 163.8 (C=O), 147.6, 142.0, (CH=C₅-thiazolidinoe), 141.0, 138.2, 128.7, 127.1, 124.1, 123.5, 120.4, 120.0</td>
</tr>
<tr>
<td><strong>MS m/z:</strong></td>
<td>333.01 (M⁺), 219, 126, 77</td>
</tr>
<tr>
<td><strong>Anal.:</strong></td>
<td>C₁₆H₉F₂NOS₂: (333.37): Calculated (%): C, 57.64; H, 2.72; N, 4.20; O, 4.80; S, 19.24; found: C, 57.62; H, 2.68; N, 4.16; O, 4.82; S, 19.23</td>
</tr>
</tbody>
</table>
3.4.5-Synthesis of 4-thiazolidinone derivatives (128-137)

Microwave procedure-I: Multi-Component Reaction using Montmorillonite Clays (KSF and K-10)

A mixture of substituted aromatic amines, substituted aromatic aldehydes, thioglycolic acid and montmorillonite clays K-10 and KSF (30% by weight of reactants) was irradiated under microwave radiation (200 watt) for 10-15 minutes at 110-115 °C. TLC was used to monitor the reaction. The crude product was cooled to 25 °C, ethyl acetate (25 mL) was added and neutralized with a solution of sodium bicarbonate. The product was purified by preparative TLC (CH₃Cl:H₂O, 6:4, v/v) followed by recrystallization from ethanol to get the final compounds (128-137) yields ranging from 78.8% to 94.4% with K-10 and 68.9% to 86.4% with KSF.

Microwave procedure-II: Solvent free, Multi-Component Reaction

In second procedure reactions were conducted without solvent. In this procedure compounds substituted aromatic amines, substituted aromatic aldehydes, thioglycolic acid were mixed and irradiated under microwave radiation (200 watt) for 10-15 minutes at 110-115 °C. The crude product was cooled to 25 °C, washed, dried under suction and recrystallized from ethanol to get compounds (128-137) yields ranging from 32.5% to 66.4%.

Microwave procedure-I: Multi-Component Reaction using Montmorillonite Clays (KSF and K-10)

2-(2,5-dimethylphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (128)

A mixture of 4-methoxypyrimidin-2-amine (0.625 g, 5 mmoles), 2,5-dimethylbenzaldehyde (0.670 g, 5 mmoles), thioglycolic acid (0.460 g, 5 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) was irradiated
under microwave radiation (200 watt) for 10 minutes at 115 °C. TLC was used to monitor the reaction. The crude product was cooled to 25 °C, ethyl acetate (25 mL) was added and neutralized with a solution of sodium bicarbonate. The product was purified by preparative TLC (CH3Cl:H2O, 6:4, v/v) followed by the recrystallization from ethanol to get the product of 2-(2,5-dimethylphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (yields 92.3% with K-10 and 80.4% with KSF).

Analytical Data Obtained:

Yield: 92.3%
Melting Point: 186-188 °C
FTIR: 3340, 2814, 1718, 1624 cm⁻¹.

¹H-NMR (300MHz, CDCl₃) δ: 8.61 (s, 1H of pyrimidine), 6.82-6.75 (m, 3H), 6.66 (s, 1H of pyrimidine), 5.92 (C₂-thiazolidine), 3.73 (s, 3H, OCH₃), 3.38 (s, 1H), 3.24 (s, 1H), 2.35 (s, 6H, 2CH₃)

¹³C-NMR (75.5 MHz, CDCl₃) δ: 171.2 (C=O), 170.6 (C-O-CH₃), 158.5, 157.0, 138.9, 135.3, 133.6, 130.5, 128.9, 127.4, 105.1, 59.4(C₂-thiazolidine), 55.9 (OCH₃), 33.6 (C₅-thiazolidine), 24.6, 17.4 (CH₃)

MS m/z: 315.10 (M⁺¹), 109, 105, 101

Anal.: C₁₆H₁₇N₃O₂S: (315.39): Calculated (%): C, 60.93; H, 5.43; N, 13.32; O, 10.15, S, 10.17, Found: C, 60.96; H, 5.42; N, 13.35; O, 10.10, S, 10.18

2-(4-ethylphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (129)

Compounds 4-methoxypyrimidin-2-amine (0.375 g, 3 mmoles), 4-ethylbenzaldehyde (0.402 g, 3 mmoles), 2-mercaptoacetic acid (0.276 g, 3 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) was mixed and irradiated under microwave radiation (200 watt) at 115 °C for 14 minutes. The crude mixture was cooled to room temperature, ethyl acetate (25mL) was added and
neutralized with sodium bicarbonate. The crude product was purified with preparative TLC (CH$_3$Cl:H$_2$O, 6:4, v/v) and recrystallized from ethanol to obtain 2-(4-ethylphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (129) (yields 90.9% with K-10 and 78.8% with KSF).

**Analytical Data Obtained:**

**Yield:** 90.9%

**Melting Point:** 223-225 °C

**FTIR:** 3338, 2824, 1720, 1628 cm$^{-1}$.

**$^1$H-NMR**

(300MHz, CDCl$_3$) δ: 8.60 (s, 1H of pyrimidine), 6.95-6.84 (m, 4H), 6.70 (s, 1H of pyrimidine), 5.90 (C$_2$-thiazolidinoe), 3.73 (s, 3H, OCH$_3$), 3.40 (s, 1H), 3.30 (s, 1H), 2.59 (d, 2H, CH$_2$), 1.24 (t, 3H, CH$_3$)

**$^{13}$CNMR**

(75.5 MHz, CDCl$_3$) δ: 171.2 (C=O), 170.6 (C-O-CH$_3$), 158.5, 157.0, 139.4, 139.1, 129.3, 128.6, 126.2, 126.0, 105.1, 65.9(C$_2$-thiazolidinoe), 55.9 (OCH$_3$), 33.6 (C$_5$-thiazolidinoe), 32.7, 14.6(CH$_3$)

**MS m/z:** 315.10 (M$^+$), 109, 105, 101

**Anal.:**

C$_{16}$H$_{17}$N$_3$O$_2$S: 315.39  Calculated (%): C, 60.93; H, 5.43; N, 13.32; O, 10.15, S, 10.17  Found: C, 60.90; H, 5.45; N, 13.30; O, 10.18, S, 10.12

2-(4-methoxyphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (130)

4-methoxypyrimidin-2-amine (0.375 g, 3 mmoles), sulfanylacetic acid (0.276 g, 3 mmoles), 4-methoxybenzaldehyde (0.408 g, 5 mmoles) and montmorillonite clays KSF and K-10 (30% by weight of reactants) were mixed and irradiated under microwave radiation (200 watt) at 115 °C for 12 minutes. The mixture was cooled to 25 °C, ethyl acetate (25 mL) was added and neutralized with sodium bicarbonate. The crude product was purified with preparative TLC (CH$_3$Cl:H$_2$O, 6:4, v/v) and
recrystallized from ethanol to get 2-(4-methoxyphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (yields 89.9% with K-10 and 84.3% with KSF).

**Analytical Data Obtained:**

**Yield:** 89.9%

**Melting Point:** 202-204 °C

**FTIR:** 3342, 2833, 1724, 1632 cm$^{-1}$.

**$^1$H-NMR**

(300MHz, CDCl$_3$) δ: 8.54 (s, 1H of pyrimidine), 7.03-6.57 (m, 4H), 6.70 (s, 1H of pyrimidine), 5.92 (C$_2$-thiazolidinoe), 3.73 (s, 6H, 2OCH$_3$), 3.38 (s, 1H C$_5$-thiazolidinoe), 3.28 (s, 1H C$_5$-thiazolidinoe).

**$^{13}$CNMR**

(75.5 MHz, CDCl$_3$) δ: 171.2 (C=O), 170.6 (C-O-CH3), 160.6 (C-O-CH3), 158.5, 157.0, 140.2, 129.7, 121.1, 112.8, 112.7, 105.1, 65.9(C$_2$-thiazolidinoe), 55.9 (OCH$_3$), 33.6 (C$_5$-thiazolidinoe)

**MS m/z:** 317.08 (M$^{1+}$), 205, 109, 107, 101

**Anal.:** C$_{15}$H$_{15}$N$_3$O$_3$S; 317.36: Calculated (%): C, 56.77; H, 4.76, N, 13.24; O, 15.12; S, 10.10, Found: C, 56.78; H, 4.75, N, 13.28; O, 15.10; S, 10.08

**2-(2-hydroxy-5-methoxyphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (131)**

2-hydroxy-5-methoxybenzaldehyde (0.760 g, 5 mmoles), 4-methoxypyrimidin-2-amine (0.625 g, 5 mmoles), thioglycolic acid (0.460 g, 5 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) were mixed and irradiated under microwave radiation (200 watt) at 115 °C for 12 minutes. The crude mixture was cooled to room temperature, ethyl acetate (25 mL) was added, neutralized with sodium bicarbonate and dried. The final compound was purified with preparative TLC (CH$_3$Cl: H$_2$O, 6:4, v/v) and recrystallized from ethanol to obtain 2-(4-methoxyphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (131) (yields 94.4% with K-10 and 86.4% with KSF).
Analytical Data Obtained:
Yield: 94.4%
Melting Point: 212-214 °C
FTIR: 3340, 2832, 1726, 1626 cm⁻¹.
¹H-NMR (300MHz, CDCl₃) δ: 8.65 (s, 1H of pyrimidine), 6.70 (s, 1H, of pyrimidine), 6.50-6.41 (m, 3H), 5.92 (C₂-thiazolidinoe), 5.0 (s, 1H, OH), 3.73 (s, 6H, 2OCH₃), 3.36(s, 1H C₅-thiazolidinoe), 3.25(s, 1H C₅-thiazolidinoe).
¹³CNMR (75.5 MHz, CDCl₃) δ: 171.2 (C=O), 170.6 (C-O-CH₃), 158.5, 157.0, 153.2 (C-O-CH₃), 148.2, 119.2, 116.8, 114.2, 114.1, 105.1, 55.9 (OCH₃), 55.7(C₂-thiazolidinoe), 33.6 (C₅-thiazolidinoe).
MS m/z: 333.08 (M⁺), 225, 123, 109, 101
Anal.: C₁₅H₁₅N₃O₄S: Calculated (%): C, 54.04; H, 4.54; N, 12.60; O, 19.20; S, 9.62, Found: C, 54.02; H, 4.55; N, 12.56; O, 19.22; S, 9.60.

2-(4-ethoxyphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (132)
A mixture of 4-ethoxybenzaldehyde (0.600 g, 4 mmoles), 4-methoxypyrimidin-2-amine (0.500 g, 4 mmoles), 3-ethoxybenzaldehyde (0.368 g, 4 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) was irradiated under microwave radiation (200 watt) at 115 °C for 14 minutes. The crude mixture was cooled to 25°C, added ethyl acetate and neutralized with sodium bicarbonate. Preparative TLC were used to purify the crude product (CH₃Cl: H₂O, 6:4, v/v), recrystallized from ethanol to get 2-(4-ethoxyphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (132) (yields 89.9% with K-10 and 82.8% with KSF)

Analytical Data Obtained:
Yield: 86.9%
Melting Point: 214-216 °C

FTIR: 3336, 2824, 1720, 1628 cm⁻¹.

¹H-NMR (300MHz, CDCl₃) δ: 8.71 (s, 1H of pyrimidine), 6.78 (s, 1H of pyrimidine), 6.62-6.57 (m, 4H), 5.92 (s, 1H, C₂-thiazolidinoe), 3.98 (d, 2H, OCH₂CH₃), 3.73 (s, 3H, OCH₃), 3.38(s, 1H, C₅-thiazolidinoe), 3.28(s, 1H, C₅-thiazolidinoe), 1.33 (t, 3H, OCH₂CH₃)

¹³CNMR (75.5 MHz, CDCl₃) δ: 171.2 (C=O), 170.6 (C-O-CH₃), 158.5, 157.4 (C-CHOCH₃), 157.0, 139.8, 129.3, 120.4, 112.9, 112.8, 105.1, 65.9 (C₂-thiazolidinoe), 64.7, 55.9 (OCH₃), 33.6 (C₅-thiazolidinoe), 14.8

MS m/z: 331.1 (M⁺), 223, 121, 109, 101

Anal.: C₁₆H₁₇N₃O₃S: 331.39: Calculated (%): C, 57.99; H, 5.17; N, 12.68; O, 14.48; S, 9.68. Found: C, 57.97; H, 5.15; N, 12.70; O, 14.46; S, 9.64

2-[4-(dimethylamino)phenyl]-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (133)

Compounds 4-methoxypyrimidin-2-amine (0.375 g, 3 mmoles), 4-(dimethylamino)benzaldehyde (0.447 g, 3 mmoles), thioglycolic acid (0.276 g, 3 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) were mixed and irradiated under microwave radiation (200 watt) for 14 minutes at 112 °C. The product was cooled to 25 °C, ethyl acetate (25 mL) was added and neutralized with sodium bicarbonate. Preparative TLC was used to purify the crude product (CH₃Cl: H₂O, 6:4, v/v). It was recrystallized from ethanol to obtain 2-[4-(dimethylamino)phenyl]-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (133) (yields 78.8% with K-10 and 74.3% with KSF)

Analytical Data Obtained:

Yield: 78.8%

Melting Point: 224-226 °C

FTIR: 3338, 2828, 1722, 1630 cm⁻¹.
\(^1\text{H-NMR}\) (300MHz, CDCl\(_3\)) \(\delta\): 8.67 (s, 1H of pyrimidine), 6.92 (s, 1H of pyrimidine), 6.80 (d, 2H, \(J=5.6\text{Hz}\)), 6.57 (d, 2H, \(J=6.3\text{Hz}\)), 5.90 (s, 1H, C\(_2\)-thiazolidinoe), 3.38 (s, 1H, C\(_5\)-thiazolidinoe), 3.28 (s, 1H, C\(_5\)-thiazolidinoe), 2.90 (s, 6H, 2).

\(^{13}\text{CNMR}\) (75.5 MHz, CDCl\(_3\)) \(\delta\): 193.0 (C=S), 163.8 (C=O), 147.6, 142.0, (CH=C\(_5\)-thiazolidinoe), 141.0, 138.2, 128.7, 127.1, 124.1, 123.5, 120.4, 120.0.

**MS** \(m/z\): 331.12 (M\(^+\)) 222, 120, 109, 101

**Anal.:** C\(_{16}\)H\(_{10}\)N\(_2\)O\(_3\)S\(_2\): (330.40): Calculated (%): C, 58.16; H, 5.49; N, 16.96; O, 9.68; S, 9.70; found: C, 58.14; H, 5.47; N, 16.94; O, 9.65; S, 9.68

**2-(2,5-dichlorophenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (134)**

Equimolar quantities of 4-methoxypyrimidin-2-amine (0.750 g, 5 mmoles), 2,5-dichlorobenzaldehyde (5 mmoles; 0.875 g), thioglycolic acid (0.460 g, 5 mmoles) and montmorillonite (30% by weight of reactants) were mixed and irradiated under microwave radiation (200 watt) for 12 minutes at 114 °C. The mixture was cooled to 25 °C, ethyl acetate (25 mL) was added and neutralized with sodium bicarbonate. Preparative TLC was used to purify the crude product (CH\(_3\)Cl: H\(_2\)O, 6:4, v/v) and recrystallized from ethanol to get **2-(2,5-dichlorophenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (134)** (yields 86.9% with K-10 and 78.5% with KSF)

**Analytical Data Obtained:**

Yield: 86.9%

Melting Point: 226-228 °C

FTIR: 3332, 2820, 1716, 1624 cm\(^{-1}\).

\(^1\text{H-NMR}\) (300MHz, CDCl\(_3\)) \(\delta\): 8.71(s, 1H of pyrimidine), 7.10-7.01 (m, 3H), 6.70 (s, 1H of pyrimidine), 5.88 (s, 1H, C\(_2\)-thiazolidinoe), 3.73 (s, 3H, OCH\(_3\)), 3.38 (s, 1H, C\(_5\)-thiazolidinoe), 3.28 (s, 1H, C\(_5\)-thiazolidinoe).
2-(2,5-difluorophenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (135)

4-methoxypyrimidin-2-amine (0.625 g, 5 mmoles), 2,5-difluorobenzaldehyde (0.710 g, 5 mmoles), sulfanylacetic acid (0.460 g, 5 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) were mixed and irradiated under microwave radiation (200 watt) for 12 minutes at 110 °C. The product was cooled, added ethyl acetate (25 mL) and neutralized with sodium bicarbonate. The crude product was purified with preparative TLC (CH₃Cl: H₂O, 6:4, v/v) and recrystallized from ethanol to get 2-(2,5-difluorophenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (135) (yields 88.6% with K-10 and 82.6% with KSF)

Analytical Data Obtained:

Yield: 88.6%
Melting Point: 221-223 °C
FTIR: 3328, 2818, 1712, 1620, 1181 cm⁻¹.

¹H-NMR (300MHz, CDCl₃) δ: 8.69 (s, 1H of pyrimidine), 6.83-6.75 (m, 3H), 6.70 (s, 1H of pyrimidine), 5.92 (s, 1H, C₂-thiazolidinoe), 3.73 (s, 3H, OCH₃), 3.38 (s, 1H, C₅-thiazolidinoe), 3.26 (s, 1H, C₅-thiazolidinoe)

¹³CNMR (75.5 MHz, CDCl₃) δ: 171.2 (C=O), 170.6 (C-O-CH₃), 158.5, 157.0, 132.3, 130.2, 130.0, 128.7, 105.1, 104.0, 56.0 (C₂-thiazolidinoe), 55.9 (OCH₃), 33.6 (C₅-thiazolidinoe)
MS m/z: 323.05 (M+), 215, 113, 109, 101

Anal.: C_{14}H_{11}F_{2}N_{3}O_{2}S: 323.32: Calculated (%): C, 52.01; H, 3.43; N, 13.00; O, 9.90; S, 9.92; Found: C, 52.03; H, 3.45; N, 13.02; O, 9.92; S, 9.94.

2-(2,5-dihydroxyphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (136)

A mixture of 4-methoxypyrimidin-2-amine (0.750 g, 6 mmoles), 2,5-dihydroxybenzaldehyde (0.828 g, 6 mmoles), thioglycolic acid (0.552 g, 6 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of reactants) was irradiated under microwave radiation (200 watt) for 14 minutes at 114 °C. The crude mixture was cooled to 25 °C, ethyl acetate (25 mL) was added in the mixture and neutralized with sodium bicarbonate. Preparative TLC was used to purify (CH$_3$Cl: H$_2$O, 6:4, v/v) and recrystallized from ethanol to obtain 2-(2,5-dihydroxyphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (136) (yields 94.3% with K-10 and 85.3% with KSF)

Analytical Data Obtained:

Yield: 94.3%
Melting Point: 206-208 °C
FTIR (KBr): 3348, 2824, 1718, 1612 cm$^{-1}$.
$^1$H-NMR (300MHz, CDCl$_3$) $\delta$: 8.67 (s, 1H of pyrimidine), 6.70 (s, 1H of pyrimidine), 6.44-6.36 (m, 3H), 5.92 (s, 1H, C$_2$-thiazolidinoe), 5.0 (s, 2H, 2OH), 3.73 (s, 3H, OCH$_3$), 3.38 (s, 1H C$_5$-thiazolidinoe), 3.28 (s, 1H C$_5$-thiazolidinoe)

$^{13}$CNMR (75.5 MHz, CDCl$_3$) $\delta$: 171.2 (C=O), 170.6 (C-O-CH$_3$), 157.0, 151.0, 148.5, 119.6, 117.2, 115.8, 115.7, 105.1, 55.9 (OCH$_3$), 55.7 (C$_2$-thiazolidinoe), 33.6 (C$_5$-thiazolidinoe)

MS m/z: 319.06 (M$^+$), 211, 109, 101
Anal.: \( \text{C}_{14}\text{H}_{13}\text{N}_{3}\text{O}_{4}\text{S} \): Calculated (%): C, 52.66; H, 4.10; N, 13.16; O, 20.04; S, 10.04; Found: C, 52.68; H, 4.12; N, 13.14; O, 20.02; S, 10.01

2-[3-(furan-2-yl)phenyl]-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (137)

Compounds 4-methoxypyrimidin-2-amine (0.500 g, 4 mmoles), 3-(furan-2-yl)benzaldehyde (0.688 g, 4 mmoles), thioglycolic acid (0.368 g; 5 mmoles) and montmorillonite clays K-10 and KSF (30% by weight of total of reactants) were mixed and irradiated under microwave radiation (200 watt) for 10 minutes at 120 °C. The final product was cooled to 25 °C. Ethyl acetate (25 mL) was added to the mixture and neutralized with sodium bicarbonate. Preparative TLC was used to purify the crude product (CH\(_3\)Cl: H\(_2\)O, 6:4, v/v) and recrystallized from ethanol to get 2-[3-(furan-2-yl)phenyl]-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one (137) (yields 82.9% with K-10 and 68.9% with KSF)

Analytical Data Obtained:

Yield: 82.9%
Melting Point: 198-200 °C
FTIR: 3218, 2812, 1722, 1614 cm\(^{-1}\)
\(^1\)H-NMR (300MHz, CDCl\(_3\)) \( \delta \): 8.67 (s, 1H of pyrimidine), 7.28-7.02 (m, 4H), 6.80 (s, 1H of pyrimidine), 5.92 (s, 1H, C\(_2\)-thiazolidinoe), 3.73 (s, 3H, OCH\(_3\)), 3.38 (s, 1H, C\(_5\)-thiazolidinoe), 3.26 (s, 1H, C\(_5\)-thiazolidinoe)
\(^13\)CNMR (75.5 MHz, CDCl\(_3\)) \( \delta \): 171.2 (C=O), 170.6 (C-O-CH\(_3\)), 158.5, 157.0, 154.0, 142.9, 139.7, 130.3, 130.1, 129.2, 128.7, 125.9, 107.2, 105.1, 105.0, 65.3 (C\(_2\)-thiazolidinoe), 55.9 (OCH\(_3\)), 33.6 (C\(_5\)-thiazolidinoe)

MS \( m/z \): 353.08 (M\(^+\)), 245, 143, 109, 101, 67
Anal.: $\text{C}_{18}\text{H}_{15}\text{N}_{3}\text{O}_{3}\text{S}$: 353.40: Calculated (%): C, 61.18; H, 4.28; N, 11.89; O, 13.58; S, 9.07; Found: C, 61.16; H, 4.26; N, 11.87; O, 13.54, S, 9.03

3.4.6- Synthesis of 4-thiazolidinone derivatives (138-147)

Microwave procedure-I: Multi-Component Reaction using Ionic Liquids (PEG, TBAB and TEBAC)

A mixture of 3-phenyl-2-(phenylimino)-thiazolidin-4-one and substituted aromatic aldehyde was taken in the presence of Ionic Liquids (PEG, TBAB, TEBAC) and water (15 mL) was irradiated in microwave oven (200 watt) for 8-10 minutes at 105-110 °C and the reaction was monitored by TLC. The crude product was cooled to 25 °C, washed with water and followed by recrystallization in ethanol to get compounds (138-147). The yield ranged from 73.4%-88.8% with TBAB, 33.5%-58.2% with PEG and 44.4%-62.4% with TEBAC.

Microwave procedure-II: Solvent free, Multi-Component Reaction

The compounds 3-phenyl-2-(phenylimino)-thiazolidin-4-one, substituted aromatic aldehyde and water (15 mL) was irradiated in microwave oven (200 watt) for 8-10 minutes at 105-110 °C. TLC was used to monitor the reaction. The crude product was cooled to room temperature, washed and recrystallized from ethanol to obtain the compounds (138-147) with yield ranging from 44.2% to 64.5%.
Microwave procedure-I: Multi-Component Reaction using Ionic Liquids (PEG, TBAB and TEBAC)

3-phenyl-2-(phenylimino)-5-(phenylmethylidene)-thiazolidin-4-one (138)

A mixture of 3-phenyl-2-(phenylimino)-thiazolidin-4-one (0.804 g, 3 mmoles) and benzaldehyde (0.318 g, 3 mmoles), tetrabutylammonium bromide (TBAB) (0.483 g, 1.5 mmoles) and water (15 mL) was irradiated in purpose built microwave oven (200 watt) for 8 minutes at 105 °C. The reaction was monitored by TLC and the crude product was cooled to 25 °C, washed with water and recrystallized from ethanol to get 3-phenyl-2-(phenylimino)-5-(phenylmethylidene)-thiazolidin-4-one (138) (yield, 80.4%).

Analytical Data Obtained:

Yield: 80.4%
Melting Point: 208 °C
FTIR (KBr): 3460 (–N= thiazolidinone), 3040-3010 (Ar-C-), 1724 (C=O, thiazolidinone) cm⁻¹.
¹H-NMR (300MHz, CDCl₃) δ: 7.64-7.21 (m, 15H aromatic proton), 6.80 (s, 1H, CH=C5).
¹³C NMR (75.5 MHz, CDCl₃) δ: 166.9 (C=O), 163, 149.0, 142, 135.2, 132.8, 130.1, 129.0, 128.7, 128.0, 127.3, 126.4, 124.6, 124.4, 122.3, 121.6, 115.9
MS m/z: 356.10 (M⁺, 100%), 294, 281, 91, 77
Anal.: C₂₂H₁₉N₂O₅: 356.44: Calculated (%): C, 74.13; H, 4.52; N, 7.86; O, 4.49; S, 9.00; Found: C, 74.11; H, 4.50; N, 7.83; O, 4.47; S, 9.01
5-(4-methylbenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (139)

The compounds 3-phenyl-2-(phenylimino)-4-thiazolidinone (0.804 g, 3 mmoles), 4-methylbenzaldehyde (0.360 g, 5 mmoles), TBAB (0.483 g, 1.5 mmoles) and water (20 mL) were mixed and irradiated in purpose built microwave oven (200 watt) for 8 minutes at 108 °C. The crude product was cooled to 25 °C, washed and recrystallized from ethanol to get 5-(4-methylbenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (139) (yield, 73.4%).

Analytical Data Obtained:

Yield: 73.4%
Melting Point: 206 °C

FTIR: 3450 (–N=thiazolidinone), 3040-3010 (Ar-C-), 1730 (C=O, thiazolidinone) cm⁻¹.

¹H-NMR (300MHz, CDCl₃) δ: 7.63-7.24 (m, 14H aromatic proton), 6.80 (s, 1H, CH=C₅), 2.35 (s, 3H, CH₃)

¹³C-NMR (75.5 MHz, CDCl₃) δ: 166.9 (C=O), 163, 149.0, 142, 137.6, 132.8, 132.2, 130.1, 129.0, 127.3, 126.3, 124.4, 122.3, 121.6, 115.9, 24.3 (CH₃)

MS m/z: 370.11 (M⁺), 279, 104, 91

Anal.: C₂₃H₁₈N₂OS: 370.47: Calculated (%): C, 74.57; H, 4.90; N, 7.56; O, 4.32; S, 8.66; Found: C, 74.55; H, 4.89; N, 7.55; O, 4.31; S, 8.64

5-(4-methoxybenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (140)

3-phenyl-2-(phenylimino)-4-thiazolidinone (1.072 g, 4 mmoles) was treated with 4-methoxybenzaldehyde (0.544 g, 4 mmoles) in the presence of TBAB (0.515 g, 1.6 mmoles) and water (20 mL). The reaction mixture was irradiated under microwave radiation (200 watt) for 10 minutes at 106 °C. The crude product was cooled to 25 °C, washed and recrystallized from ethanol to obtain 5-(4-
methoxybenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (140) (yield, 78.6%).

**Analytical Data Obtained:**

**Yield:** 75.6%

**Melting Point:** 209 °C

**FTIR:** 3430 (–N= thiazolidinone), 3024-3002 (Ar-C-), 1740 (C=O, thiazolidinone) cm⁻¹.

**¹H-NMR** (300MHz, CDCl₃) δ: 7.64-7.19 (m, 14H aromatic proton), 6.78 (s, 1H, CH=C5), 3.73 (s, 3H, OCH₃)

**¹³CNMR** (75.5 MHz, CDCl₃) δ: 166.9 (C=O), 163, 159.9, 149.0, 142, 132.8, 130.1, 129.0, 127.5, 127.4, 127.3, 124.4, 122.3, 121.6, 115.9,114.2, 55.9 (CH₃)

**MS m/z:** 386.11 (M⁺), 295, 120, 91

**Anal.:** C₂₃H₁₈N₂O₂S: 386.47: Calculated (%): C, 71.48; H, 4.69; N, 7.25; O, 8.28; S, 8.30; Found: C, 71.50; H, 4.67; N, 7.23; O, 8.26; S, 8.31

5-(2-hydroxy-4-methoxybenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (141)

3-phenyl-2-(phenylimino)-4-thiazolidinone (1.34 g, 5mmoles), 2-hydroxy-4-methoxybenzaldehyde (0.760 g, 5 mmoles), TBAB (0.515 g, 1.6 mmoles) and water (20 mL) were mixed and irradiated in purpose built microwave oven (200 watt) for 10 minutes at 110 °C. Finally the crude mixture was cooled to 25 °C, washed and recrystallized from ethanol to obtain 5-(2-hydroxy-4-methoxybenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (141) (yield, 75.5%).

**Analytical Data Obtained:**

**Yield:** 75.5%

**Melting Point:** 209 °C
5-(4-ethoxybenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (142)

3-phenyl-2-(phenylimino)-4-thiazolidinone (0.804 g, 3 mmoles), 4-ethoxybenzaldehyde (0.450 g, 5 mmoles), TBAB (0.515 g, 1.6 mmoles) and water (20 mL) were mixed and irradiated under microwave radiation (200 watt) for 10 minutes at 108 °C. The crude mixture was cooled, washed and recrystallized from ethanol to obtain 5-(4-ethoxybenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (142) (yield, 80.7%).

Analytical Data Obtained:

Yield: 80.7%
Melting Point: 223 °C
FTIR: 3450 (–N= thiazolidinone), 3030-3020 (Ar-C-), 1735(C=O, thiazolidinone) cm⁻¹.
¹H-NMR (300MHz, CDCl₃) δ: 7.64-7.24 (m, 10H aromatic proton), 7.19 (d, 2H, J=7.2Hz), 6.92(d, 2H, J=6.5Hz), 6.80 (s, 1H, CH=C5), 3.98 (d, 2H, OCH₂), 1.33 (s, 3H, OCH₂CH₃)
5-(4-nitrobenzylidene)-3-phenyl-2-(phenylimino)-1,3-thiazolidin-4-one (143)

A mixture of 3-phenyl-2-(phenylimino)-4-thiazolidinone (1.608 g, 6 mmoles) and 4-nitrobenzaldehyde (0.906 g, 6 mmoles), TBAB (0.515 g, 1.6 mmoles) and water (20 mL) was irradiated in microwave oven (200 watt) for 8 minutes at 106 °C. The crude product was cooled to 25 °C, washed and recrystallized from ethanol to get 5-(4-nitrobenzylidene)-3-phenyl-2-(phenylimino)-1,3-thiazolidin-4-one (143) (yield, 84.4%).

Analytical Data Obtained:

Yield: 84.4%
Melting Point: 218 °C
FTIR: 3440 (–N= thiazolidinone), 3030-3015 (Ar-C-), 1740 (C=O, thiazolidinone) cm⁻¹.

¹H-NMR (300MHz, CDCl₃) δ: 8.14 (d, 2H, J=7.5Hz), 7.66(d, 2H, J=7.0Hz), 7.60-7.28 (m, 10H aromatic proton), 6.94 (s, 1H, CH=C5)

¹³CNMR (75.5 MHz, CDCl₃) δ: 166.9 (C=O), 163, 149.0, 147.6, 142, 141.3, 132.8, 130.1, 129.0, 127.3, 124.4, 122.3, 121.6, 121.0, 115.9, 114.3

MS m/z: 401.08 (M⁺), 310, 279, 135, 91
5-(2, 4-dihydroxybenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (144)

The compounds 3-phenyl-2-(phenylimino)-thiazolidin-4-one (1.342 g, 5 mmoles), 2,4-dihydroxybenzaldehyde (0.69 g, 5 mmoles), TBAB (0.515 g, 1.6 mmoles) and water (20 mL) were mixed and the mixture was exposed under microwave radiation (200 watt) for 10 minutes at 108 °C. The reaction was monitored by TLC. Finally the crude product was cooled to 25 °C, washed and recrystallized from ethanol to get 5-(2,4-dihydroxybenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (144) (yield, 78.5%).

Analytical Data Obtained:

Yield: 78.5%
Melting Point: 238 °C

**FTIR**

3420 (–N= thiazolidinone), 3220 (-OH), 3030-3015 (Ar-C), 1740 (C=O, thiazolidinone) cm⁻¹.

**¹H-NMR**

(300MHz, CDCl₃) δ: 7.64-7.24 (m, 10H aromatic proton), 7.07 (s, 1H, CH=C5), 6.96 (s, 1H), 6.24 (s, 1H), 6.15 (s, 1H), 5.0 (s, 1H, OH)

**¹³CNMR**

(75.5 MHz, CDCl₃) δ: 166.9 (C=O), 163, 159.7, 159.1, 149.0, 142, 132.8, 130.1, 129.2, 129.0, 127.3, 124.4, 122.3, 121.6, 115.9, 109.2, 108.4, 103.5

**MS m/z:** 388.09 (M⁺), 297, 279, 122, 91

Analytical Data Obtained:

C₂₂H₁₅N₃O₃S: 401.44: Calculated (%): C, 65.82; H, 3.77; N, 10.47; O, 11.96; S, 7.99; Found: C, 65.80; H, 3.79; N, 10.49; O, 11.98; S, 8.01
5-(2,4-dichlorobenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (145)

3-phenyl-2-(phenylimino)-thiazolidin-4-one (1.608 g, 6 mmoles) was treated with 2,4-dichlorobenzaldehyde (1.050 g, 6 mmoles) in the presence of TBAB (0.515 g, 1.6 mmoles) and water (20mL). The mixture was irradiated in purpose built microwave oven (200 watt) for 8 minutes at 108 °C. The crude mixture was cooled to 25 °C, washed and recrystallized from ethanol to obtain the compound 5-(2,4-dichlorobenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (145) (yield, 82.7%).

Analytical Data Obtained:

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<th>Property</th>
<th>Value</th>
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<td>Yield</td>
<td>82.7%</td>
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<tr>
<td>Melting Point</td>
<td>224 °C</td>
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<tr>
<td>FTIR</td>
<td>3440 (--N=thiazolidinone), 3044-3010 (Ar-C-), 1716 (C=O,thiazolidinone), 660 (-Cl) cm⁻¹.</td>
</tr>
<tr>
<td>¹H-NMR</td>
<td>δ: 7.64-7.30 (m, 10H aromatic proton), 7.21(s, 1H), 7.16 (s, 1H), 7.10 (s, 1H), 6.84 (s, 1H, CH=C5)</td>
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<td>¹³C-NMR</td>
<td>δ: 166.9 (C=O), 163, 149.0, 142, 134.9, 132.8, 132.6, 131.2, 130.3, 130.1, 129.2, 129.0, 127.3, 126.9, 124.4, 122.3, 121.6, 115.9</td>
</tr>
<tr>
<td>MS m/z</td>
<td>424.02 (M⁺), 332, 279, 157, 91</td>
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<tr>
<td>Anal.</td>
<td>C₂₂H₁₄Cl₂N₂O₃S: 425.33: Calculated (%): C, 62.12; H, 3.32: N, 6.59; O, 3.76; S, 7.54; Found: C, 62.10; H, 3.31: N, 6.57; O, 3.74; S, 7.54</td>
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</tbody>
</table>

5-(2, 4-difluorobenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (146)

3-phenyl-2-(phenylimino)-thiazolidin-4-one (1.340 g, 5 mmoles), 2,4-difluorobenzaldehyde (0.710 g, 5 mmoles), TBAB (0.515 g, 1.6 mmoles) and water (20 mL) were mixed and the mixture was irradiated in purpose built microwave oven
(200 watt) for 10 minutes at 106 °C. The mixture was cooled to 25 °C, washed and recrystallized from ethanol to get fine product of 5-(2,4-difluorobenzylidene)-3-phenyl-2-(phenylimino) thiazolidin-4-one (146) (yield, 80.5%).

**Analytical Data Obtained:**

Yield: 80.5%

Melting Point: 228 °C

FTIR: 3440 (–N=thiazolidinone), 3044-3010 (Ar-C-), 1716 (C=O,thiazolidinone), 1126 (-F) cm⁻¹.

**¹H-NMR**  
(300MHz, CDCl₃) δ: 7.63-7.24 (m, 13 H, aromatic protons), 6.80 (s, 1H, CH=C5)

**¹³CNMR**  
(75.5 MHz, CDCl₃) δ: 166.9 (C=O), 163.7, 163, 158.5, 149.0, 142, 132.8, 130.1, 129.6, 129.0, 127.3, 124.4, 122.3, 121.6, 118.7, 115.9, 111.0, 104.6

**MS m/z:** 392.08 (M⁺), 301, 279, 126, 91

**Anal.:**  
C₂₂H₁₄F₂N₂OS: 393.42: Calculated (%): C, 67.33; H, 3.60; N, 7.14; O, 4.08; S, 8.17; Found: C, 67.31; H, 3.58; N, 7.16; O, 4.06; S, 8.17

5-[4-(dimethylamino)benzylidene]-3-phenyl-2-(phenylimino)-thiazolidin-4-one (147)

3-phenyl-2-(phenylimino)-4-thiazolidinone (1.072 g, 4 mmoles), 4-(dimethylamino)benzaldehyde (0.596 g, 5 mmoles), TBAB (0.515 g, 1.6 mmoles) and water (20mL) were mixed and the mixture was irradiated in purpose built microwave oven (200 watt) for 8 minutes at 110 °C. The crude mixture was cooled to 25 °C, washed and recrystallized from ethanol to obtain 5-(2,4-difluorobenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one (147) (yield, 88.8%).

**Analytical Data Obtained:**

Yield: 88.8%
Melting Point: 210 °C

FTIR: 3414 (–N= thiazolidinone), 3040-3010 (Ar-C-), 1740 (C=O, thiazolidinone) cm⁻¹.

¹H-NMR (300MHz, CDCl₃) δ: 7.64-7.24 (m, 10H aromatic proton), 7.12 (d, 2H, J=7.3Hz), 6.80 (s, 1H, CH=C5), 6.54 (d, 2H, J=6.7Hz), 2.85 (s, 6H)

¹³C-NMR (75.5 MHz, CDCl₃) δ: 166.9 (C=O), 163, 149.0, 148.8, 142, 132.8, 130.1, 129.0, 127.3, 124.7, 124.4, 122.3, 121.6, 115.9, 114.2, 40.3

MS m/z: 399.14 (M⁺¹), 322, 308, 133, 91

Anal.: C₂₄H₂₁N₃OS: 399.51: Calculated (%): C, 72.15; H, 5.30: N, 10.52; O, 4.00; S, 8.03; Found: C, 72.13; H, 5.30: N, 10.50; O, 3.99; S, 8.01
http://www.goma.demon.co.uk/eco/ecoselect.html
RESULTS AND DISCUSSION

Thiazolidinone derivatives are a class of important five member heterocyclic organic compounds which possess diversified biological and pharmacological activities\textsuperscript{195-197}. This research work is primarily concerned with the application of environmentally benign (non-conventional) and economic procedures in the preparation of compounds possessing 4-thiazolidinone ring as an essential moiety.

In the first phase of the research endeavour, synthesis of various starting materials was carried out from respective reagents. First step in the synthesis of starting materials substituted aromatic aldehydes; substituted aromatic amines and thioglycolic acid. However, simple substituted benzaldehydes, mercaptoacetic acid, aminobenzene etc. were directly purchased from the market due to being cheap and their abundant availability. In the next step, substituted benzaldehydes were reacted with 4,6-dimethylpyrimidin-2-amine and the mixture was subjected to microwave irradiation to form Schiff bases as intermediate products.

Scheme-4.1: Synthesis of Schiff bases and thiazolidinone derivatives
The intermediate products were further treated with mercaptoacetic acid under microwave irradiation to form 4-thiazolidinone derivatives and recrystallized from ethanol.

In first series, two methods Microwave procedure-I: Multi-Component Reaction in DMF and Microwave procedure-II: Solvent free, Multi-Component Reaction were used for the synthesis of compounds (88-97). Microwave procedure-I was found better in yield ranging from 82.4% to 96.0% with time 12 to 18 minutes while yield in procedure-II was 42.6% to 84.6% with time 12 to 16 minutes. In this series, 4,6-dimethylpyrimidin-2-amine was treated with 2,4-dimethylbenzaldehyde in dimethylformamide to form a Schiff base and Schiff base was further treated with sulfanyl acetic acid under microwave irradiation. The compounds 88, 92, 93, 94 and 97 were obtained higher yields 94.2, 96.0, 88.4, 90.3, 88.8 respectively and were synthesized by using Microwave procedure-I. The final products were identified by FTIR, $^1$H-NMR and $^{13}$C-NMR. In FTIR spectra peaks which appeared at 1715 cm$^{-1}$ and 1614 cm$^{-1}$ due to thiazolidinone, C=O and C=N. In compounds 90 and 92 Ar-OH bands displayed at 3331-3346 cm$^{-1}$ and bands of Ar-F were displayed in the range 1130-1145 cm$^{-1}$ for the compounds 94 and 96. In $^1$H-NMR signal appearing at 5.92 ppm indicated the presence one proton (s, H, C$_2$-thiazolidinone), peaks at 3.38 and 3.28 confirmed the presence of two protons (2H, C$_5$-thiazolidinone) and intense signals appeared at 2.35 for 4(CH$_3$). The multiplet appeared in the range 6.84-6.74 ppm for
four aromatic protons. On the other hand $^{13}$CNMR signals were recorded at 166.7 (C=O thiazolidinone), 51.5 (C$_2$-thiazolidinone) and 36.3 (C$_5$-thiazolidinone), while rest of the carbon atoms produced peaks regarding their environment. Final conformation of synthesized was done by Mass spectrometer and elemental analyzer. The mass spectra of compound (88) was recorded and the fragment 207, 107, 77 also confirmed the formation of compound. Similarly other spectral data of each compound are presented in experimental section. In this first series microwave coupled with DMF lead to high yields, clean, environmentally benign and shorter reaction times.

**Table-2 Synthesis of novel compounds and intermediates under microwave irradiation**

<table>
<thead>
<tr>
<th>Compound number</th>
<th>Intermediate product Schiff base</th>
<th>Final product</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
<td>$N$-(2,4-dimethylbenzylidene)-4,6-dimethylpyrimidin-2-amine</td>
<td>2-(2,4-dimethylphenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one</td>
</tr>
<tr>
<td>89</td>
<td>2-[(4,6-dimethylpyrimidin-2-ylimino)methyl]-5-methylphenol</td>
<td>3-(4,6-dimethylpyrimidin-2-yl)-2-(2-hydroxy-4-methylphenyl)-thiazolidin-4-one</td>
</tr>
<tr>
<td>90</td>
<td>4-[(4,6-dimethylpyrimidin-2-ylimino)methyl]benzene-1,3-diol</td>
<td>2-(2,4-dihydroxyphenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one</td>
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<tr>
<td>91</td>
<td>$N$-(2,4-dichlorobenzylidene)-4,6-dimethylpyrimidin-2-amine</td>
<td>2-(2,4-dichlorophenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one</td>
</tr>
<tr>
<td>92</td>
<td>$N$-(4-methoxy-2-methylbenzylidene)-4,6-dimethylpyrimidin-2-amine</td>
<td>3-(4,6-dimethylpyrimidin-2-yl)-2-(2-hydroxy-4-methoxyphenyl)-thiazolidin-4-one</td>
</tr>
<tr>
<td></td>
<td>Reaction 1</td>
<td>Reaction 2</td>
</tr>
<tr>
<td>---</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>93</td>
<td>N-(4-chloro-2-methylbenzylidene)-4,6-dimethylpyrimidin-2-amine</td>
<td>2-(4-chloro-2-methylphenyl)-3-(4,6-dimethylpyrimidin-2-yl)-thiazolidin-4-one</td>
</tr>
<tr>
<td>94</td>
<td>N-[(4-fluorophenyl)methylidene]-4,6-dimethylpyrimidin-2-amine</td>
<td>3-(4,6-dimethylpyrimidin-2-yl)-2-(4-fluorophenyl)thiazolidin-4-one</td>
</tr>
<tr>
<td>95</td>
<td>N-(4-nitrobenzylidene)-4,6-dimethylpyrimidin-2-amine</td>
<td>3-(4,6-dimethylpyrimidin-2-yl)-2-(4-nitrophenyl)thiazolidin-4-one</td>
</tr>
<tr>
<td>96</td>
<td>N-(2,4-difluorobenzylidene)-4,6-dimethylpyrimidin-2-amine</td>
<td>2-(2,4-difluorophenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one</td>
</tr>
<tr>
<td>97</td>
<td>N-[(4-dimethylamino)benzylidene]-4,6-dimethylpyrimidin-2-amine</td>
<td>2-(4-(dimethylamino)phenyl)-3-(4,6-dimethylpyrimidin-2-yl)thiazolidin-4-one</td>
</tr>
</tbody>
</table>

The yield of compounds (88-97) and dramatically reduced reaction times shown in Table-3 and Figure-4 respectively. The procedure-II: Solvent free coupled with microwave was more environment friendly but the compounds 89, 90, 92 and 93 did not produce good result (yield). Over all conventional procedures were also tried and compared with non conventional procedures. It was observed that the procedure using microwave with DMF gave better then rest of all. The differences were observed in yield, cost, time and environmental effects.
Table-3 Percentage yield and time of conventional and non conventional procedures

<table>
<thead>
<tr>
<th>Serial number</th>
<th>Conventional method</th>
<th>Non conventional method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percent yield</td>
<td>Time (hours)</td>
</tr>
<tr>
<td>88</td>
<td>44.6</td>
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<td>89</td>
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<td>90</td>
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<td>54.3</td>
<td>12</td>
</tr>
<tr>
<td>92</td>
<td>60.0</td>
<td>12</td>
</tr>
<tr>
<td>93</td>
<td>56.3</td>
<td>12</td>
</tr>
<tr>
<td>94</td>
<td>62.4</td>
<td>12</td>
</tr>
<tr>
<td>95</td>
<td>54.8</td>
<td>12</td>
</tr>
<tr>
<td>96</td>
<td>48.2</td>
<td>12</td>
</tr>
<tr>
<td>97</td>
<td>56.4</td>
<td>12</td>
</tr>
</tbody>
</table>

**MCR in DMF = Microwave procedure-I: Multi-Component Reaction in DMF

*SMCR = Microwave procedure-II: Solvent free, Multi-Component Reaction

In the second series, Microwave procedure-I: Multi-Component Reaction using Montmorillonite Clays K-10 and KSF and Microwave procedure-II: Solvent free, Multi-Component Reaction were applied for the preparation of compounds (98-107). In procedure-I, two environmentally benign catalysts K-10 and KSF were used and K-10 was better in yield raging 78.4% to 94.1% than the yields with KSF 68.3% to 88.1% while yield 14.3% to 76.4% were obtain by procedure-II. In this procedure Schiff base was treated with mercaptoacetic acid under microwave irradiation followed by the condensation reaction of aniline and substituted aromatic aldehydes. Some of the compounds 99, 100, 103, 104, 105 and 107 prepared by solvent free procedure did not show good results 16.6%, 14.3%, 28.8%, 26.3%, 34.8%, 36.4%
and few of them i.e. 98, 100, 102 and 106 showed good results 76.4%, 72.3%, 74.4%, 68.8% respectively. The yield with solvent free coupled with microwave radiation was lower as compared with the solid phase catalysts as shown in Table-5. In this procedure two catalysts K-10 and KSF were used. K-10 showed slightly better efficiency as compared to KSF. In general, consistent yield was obtained by using the montmorillonite clays (K-10 and KSF). Because montmorillonite clays are often very poor conductors of heat but behave as very efficient microwave adsorbents, thus resulting in a very rapid and homogeneous heating. Consequently, these clays display very strong specific microwave effects with significant improvements in temperature homogeneity and heating rates enabling faster reactions and less degradation of final products as compared to classical heating198-199. They can be reused after washing with ethanol. The details of spectral data of each compound are given in the experimental section.

The characterization of compounds (98-107) was done by FTIR, 1H-NMR, 13C-NMR, mass spectrometer and elemental analysis. In FTIR spectra, absorption bands appeared at 1720 cm⁻¹ and 1618 cm⁻¹ due to C=O and C=N of thiazolidinone respectively. The absorption bands were displayed at 3331-3346 cm⁻¹ for hydroxyl group in compounds (99 and 107) and bands were displayed 1130-1145 cm⁻¹ due to fluoro group in compound 106.

In 1H-NMR spectra the compounds (98-107) signal appeared at 7.31-7.10 as multiplet due to aromatic protons clustered in this region. A singlet appeared at 6.67 ppm indicated three aromatic protons. Peak appeared at 5.92 ppm indicated the presence one proton (s, H, C2-thiazolidinone), peaks at 3.39 ppm and 3.28 ppm confirmed the presence of two protons (d, 2H, C5-thiazolidinone) and intense signal appeared at 2.35 for six proton 2CH3. In 13CNMR spectra, signals were recorded at 166.7 (C=O, thiazolidinone), 58.6 (C2-thiazolidinone), 36.5 (C5-thiazolidinone) and 24.9 for CH3. Other carbon atoms produced peaks regarding their environment.

Molecular ion peak for compound 98 at m/z 283 confirmed the molecular weight of corresponding compound. The mass spectra of rest of the compounds (98-
showed molecular ion peaks corresponding to their molar masses. A
fragmentation pattern was 207, 179, 105 and 77. For further conformation elemental
analysis data also corresponded to the proposed formula.

Table 4: Novel compounds synthesized under microwave irradiation

<table>
<thead>
<tr>
<th>Compound number</th>
<th>Intermediate product</th>
<th>Final product</th>
</tr>
</thead>
<tbody>
<tr>
<td>98</td>
<td>[(3,5-dimethylphenyl)methylidene]aniline</td>
<td>2-(3,5-dimethylphenyl)-3-phenyl-thiazolidin-4-one</td>
</tr>
<tr>
<td>99</td>
<td>3-methoxy-5-[(phenylimino)methyl]phenol</td>
<td>2-(3-hydroxy-5-methoxyphenyl)-3-phenyl-thiazolidin-4-one</td>
</tr>
<tr>
<td>100</td>
<td>N-[(3-chloro-5-methylphenyl)methylidene]aniline</td>
<td>2-(3-chloro-5-methylphenyl)-3-phenyl-thiazolidin-4-one</td>
</tr>
<tr>
<td>101</td>
<td>[(3,5-dichlorophenyl)methylidene]aniline</td>
<td>2-(3,5-dichlorophenyl)-3-phenyl-thiazolidin-4-one</td>
</tr>
<tr>
<td>102</td>
<td>[(3-nitrophenyl)methylidene]aniline</td>
<td>2-(3-nitrophenyl)-3-phenyl-thiazolidin-4-one</td>
</tr>
<tr>
<td>103</td>
<td>[(3-ethoxyphenyl)methylidene]aniline</td>
<td>2-(3-ethoxyphenyl)-3-phenyl-thiazolidin-4-one</td>
</tr>
<tr>
<td>104</td>
<td>[(3-methoxyphenyl)methylidene]aniline</td>
<td>2-(3-methoxyphenyl)-3-phenyl-thiazolidin-4-one</td>
</tr>
<tr>
<td>105</td>
<td>N,N-dimethyl-3-[(phenylimino)methyl]aniline</td>
<td>2-[3-(dimethylamino)phenyl]-3-phenyl-thiazolidin-4-one</td>
</tr>
<tr>
<td>106</td>
<td>N-[(3,5-difluorophenyl)methylidene]aniline</td>
<td>2-(3,5-difluorophenyl)-3-phenyl-thiazolidin-4-one</td>
</tr>
<tr>
<td>107</td>
<td>5-[(phenylimino)methyl]benzene-1,3-diol</td>
<td>2-(3,5-dihydroxyphenyl)-3-phenyl-thiazolidin-4-one</td>
</tr>
</tbody>
</table>
Table-5 Percentage yield and time of conventional and non-conventional procedures of (98-107)

<table>
<thead>
<tr>
<th>Serial number</th>
<th>Conventional method</th>
<th>Non conventional method percentage yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage yield</td>
<td>Time (hours)</td>
</tr>
<tr>
<td>98</td>
<td>48.4</td>
<td>16</td>
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<tr>
<td>99</td>
<td>54.6</td>
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<td>44.4</td>
<td>14</td>
</tr>
<tr>
<td>101</td>
<td>58.2</td>
<td>15</td>
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<tr>
<td>102</td>
<td>64.0</td>
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<td>103</td>
<td>54.8</td>
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<td>104</td>
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<td>105</td>
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<td>106</td>
<td>64.6</td>
<td>16</td>
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<tr>
<td>107</td>
<td>66.3</td>
<td>16</td>
</tr>
</tbody>
</table>

**MCR with K-10 and KSF = Microwave procedure-I: Multi-Component Reaction using Montmorillonite Clays (K-10 and KSF)

*SMCR = Microwave procedure-II: Solvent free, Multi-Component Reaction

Using non-conventional methodology, it was possible to design a new process scheme for the preparation of organic chemicals on an industrial scale with a high efficiency. For the compounds (108-117), two methods Microwave procedure-I: Multi-Component Reaction by using Ionic Liquids (PEG, TBAB and TEBAC) and Microwave procedure-II: Solvent free, Multi-Component Reaction were used. Procedure-II was found better in yield and environmentally than Ionic Liquids (PEG, TBAB and TEBAC). The yield ranged from 33.4%-48.8% with TBAB, 33.5%-52.2% with PEG and 20.4%-32.4% with TEBAC while yield in solvent free procedure-II 67.6% to 92.8%. The compounds 1,3-dipyridin-2-ylthiourea, chloroacetic acid and...
different aromatic aldehydes were used for the preparation of compounds (108-117) of third series. Ionic Liquids Tetraethylammonium bromine (TBAB), Triethylbenzylammonium chloride (TEBAC), Polyethyleneglycol (PEG) were used as catalysts for synthesis of compounds (108-117) of this series under microwave radiation for the period of eight to twelve minutes and water was used as reaction medium. The procedure-II was found more environment friendly, cost effective and yield. The compounds 109, 111, 112, 115 were obtain maximum yield 92.3, 89.7, 92.8 and 88.1 respectively than Ionic Liquids.

The IR spectra of compound (108-117) showed two intense stretching vibrations due to carbonyl group of thiazolidinone at 1710 cm\(^{-1}\) and 1665 cm\(^{-1}\) respectively. In compounds 110 and 115 bands were displayed at 3335 cm\(^{-1}\) and 1138 cm\(^{-1}\) for hydroxyl and flouro groups respectively.

In \(^1\)HNMR spectra, the signals of two doublets appeared at 7.19 (\(J=6.3\) Hz) and 7.02 (\(J=6.5\) Hz) integrating to four protons due to \((\text{C}_6\text{H}_4\text{O-CH}_3)\) and a singlet appeared at 6.80 ppm indicated the presence one proton (s, H, CH=C\text{2-thiazolidinone}) in compound (109). A mutiplet appeared at 8.22-7.54 ppm of two pyridine molecules and signal appeared at 3.73 ppm for CH\(_3\) further confirmed the formation of 5-(4-methoxybenzylidene)-3-(pyridine-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one. The mass spectrum also corresponded to the molar mass of the product m/z 388\(^+\) (100%) and their fragmentation pattern was m/z 388, 296, 108. The details of compounds (108-117) were given in experimental section. For further conformation elemental analysis data also corresponded to the proposed formula.
## Table-6 Novel compounds under microwave irradiation

<table>
<thead>
<tr>
<th>Compound number</th>
<th>Final product</th>
</tr>
</thead>
<tbody>
<tr>
<td>108</td>
<td>5-benzylidene-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one</td>
</tr>
<tr>
<td>109</td>
<td>5-(4-methoxybenzylidene)-3-(pyridine-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one</td>
</tr>
<tr>
<td>110</td>
<td>5-(2-hydroxy-4-methoxybenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one</td>
</tr>
<tr>
<td>111</td>
<td>5-[4-(dimethylamino)benzylidene]-3-(pyridin-2-yl)-2-(pyridine-2-ylimino)-thiazolidin-4-one</td>
</tr>
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<td>112</td>
<td>5-(2,4-dichlorobenzylidene)-3-(pyridine-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one</td>
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<td>113</td>
<td>5-(4-nitrobenzylidene)-3-(pyridin-2-yl)-2-(pyridine-2-ylimino)-thiazolidin-4-one</td>
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<td>5-(4-ethoxybenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one</td>
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<tr>
<td>115</td>
<td>5-(2,4-difluorobenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one</td>
</tr>
<tr>
<td>116</td>
<td>5-(4-ethylbenzylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one</td>
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<td>117</td>
<td>5-(1,3-benzodioxol-5-ylmethylidene)-3-(pyridin-2-yl)-2-(pyridin-2-ylimino)-thiazolidin-4-one</td>
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</tbody>
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Tabl-7 Percentage yield and time of conventional and non conventional methods of (108-117)

<table>
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<tr>
<th>Serial number</th>
<th>Conventional method</th>
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<th>Time (minutes)</th>
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<td>*SMCR</td>
<td>MCR with **PEG</td>
<td>MCR with **TEBAC</td>
<td>MCR with **TBAB</td>
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<td>26.2</td>
<td>67.6</td>
<td>40.8</td>
<td>24.4</td>
<td>33.4</td>
</tr>
</tbody>
</table>

**MCR with ILs = Microwave procedure-I: Multi-Component Reaction using Ionic Liquids (PEG, TBAB and TEBAC)

*SMCR = Microwave procedure-II: Solvent free, Multi-Component Reaction

A fourth series of 4-thiazolidinone derivatives (118-127) were prepared by using two methods Microwave procedure-I: Multi-Component Reaction using Montmorillonite Clays (KSF and K-10) and Microwave procedure-II: Solvent free, Multi-Component Reaction and it was found that first was better in yield ranging from 78.8% to 96.1% while yield in procedure-II ranging from 34.6% to 78.8%. In this series; sulfanyl(thioxo)acetic acid was treated with Schiff base followed by condensation reaction of substituted aromatic amines with substituted aromatic aldehydes under microwave irradiation coupled with solid phase catalysts (K-10 and KSF types) procedure-I and procedure-II. When a mixture of sulfanyl(thioxo)acetic
acid, aromatic amine and substituted aromatic aldehyde was irradiated in a microwave, the reaction completed in 10-12 minutes. The reaction mixture was then washed with a small amount of ethanol. The crude products were purified by recrystallization from ethanol to afford products with good yields (78.8% to 96.1%). The results for the synthesis of these compounds are given in Table-9. The microwave with K-10 (montmorillonite catalyst) showed excellent results than other procedure in this study. The compounds 119, 120, 121, 122 and 126 were synthesized in good yield 89.1, 89.9, 92.6, 94.2 and 96.1 respectively with procedure-I.

The IR spectra showed absorption bands in the range 1714-1720 cm\(^{-1}\) due to the presence of C=O of 4-thiazolidinone (118-127), absorption bands around 3340-3360 cm\(^{-1}\) due to the presence of hydroxyl group (121) and 1173 cm\(^{-1}\) for Flouro group (127) respectively.

The \(^1\)HNMR spectra the compound (118) showed peaks in the range 7.58-7.04 ppm due to aromatic protons clustered in this region. The singlet appeared at 6.80 of one proton (CH=thiazolidinone). The detailed \(^1\)HNMR data is presented in the experimental section. In \(^{13}\)CNMR spectra, signals were recorded at 193.5 (C=S, thiazolidinone) 166.9 (C=O thiazolidinone), 142(C=thiazolidinone), 115.9 (CH=CH-thiazolidinone), while rest of the carbon atoms produced peaks regarding their environment.

Molecular ion peak for compound 118 at m/z 297 confirmed the molecular weight of corresponding compound. The mass spectra of rest of the compounds (119-127) showed molecular ion peaks corresponding to their molar masses. The fragmentation pattern was 219, 206, 143, 90 and 77. The elemental analysis data also corresponded to the proposed formula.
Table-8 Novel compounds under microwave irradiation

<table>
<thead>
<tr>
<th>Compound number</th>
<th>Final product</th>
</tr>
</thead>
<tbody>
<tr>
<td>118</td>
<td>5-benzylidene-3-phenyl-2-thioxo-4-thiazolidin-4-one</td>
</tr>
<tr>
<td>119</td>
<td>5-(4-methylbenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one</td>
</tr>
<tr>
<td>120</td>
<td>5-(4-methoxybenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one</td>
</tr>
<tr>
<td>121</td>
<td>5-(3-hydroxy-4-methoxybenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one</td>
</tr>
<tr>
<td>122</td>
<td>5-[4-(dimethylamino)benzylidene]-3-phenyl-2-thioxo-thiazolidin-4-one</td>
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<td>123</td>
<td>5-(4-nitrobenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one</td>
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<td>124</td>
<td>5-(2,4-dichlorobenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one</td>
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<td>5-(4-ethoxybenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one</td>
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<td>126</td>
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<tr>
<td>127</td>
<td>5-(2,4-difluorobenzylidene)-3-phenyl-2-thioxo-thiazolidin-4-one</td>
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Table-9 Percentage yield comparison between conventional and non conventional procedures

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<th>Serial number</th>
<th>Conventional method</th>
<th>Non conventional method</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Percentage yield</td>
<td>Time (hours)</td>
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<tr>
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<td>44.2</td>
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<tr>
<td>119</td>
<td>42.6</td>
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<td>120</td>
<td>43.8</td>
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<tr>
<td>121</td>
<td>46.7</td>
<td>06</td>
</tr>
<tr>
<td>122</td>
<td>40.3</td>
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MCR with K-10 and KSF = Microwave procedure-I: Multi-Component Reaction using Montmorillonite Clays (K-10 and KSF)

SMCR = Microwave procedure-II: Solvent free, Multi-Component Reaction

In fifth series (128-137), two environment friendly procedures were tried and found the procedure “Multi-Component Reaction using Montmorillonite Clays (KSF and K-10)” better regarding yield and reaction time. The yields ranging from 78.84% to 94.43% with K-10 and 64.6-% to 78.8% with KSF while yields in procedure-II ranging from 32.5% to 66.4%. Sulfanylacetic acid was reacted with (2,5-disubstituted-phenyl)methylidene-4-methoxypyrimidin-2-amine followed by the condensation between 4-methoxypyrimidin-2-amine and various aldehydes. The compounds (128-137) of this series were synthesized under microwave irradiation for ten to fourteen minutes and non toxic solvent like water was used as a reaction medium with montmorillonite clays (K-10 and KSF). In the conventional methods such reactions require longer reaction times and use toxic solvents (pyridine, dimethyl formamide, dimetyl sulphoxide, dry benzene etc) with a considerable amount of catalyst200-201. The combination of microwave and solid phase catalysts considerably enhanced reaction rate, provided cleaner products and simplified the whole process under non polluting conditions. It is pertinent to mention that the present reactions under microwave radiation dramatically reduce the reaction time from 12–24 hours (conventional method) to a few minutes and data for the same are shown in experimental section. The results are presented in Table-11 and Figure-4. Consequently, environment friendly catalyst K-10 (montmorillonite clay) showed excellent results regarding consistent and high yield, more repeatability factor and uniform heating.
The IR spectra showed characteristic absorption bands around 3340-3360 cm\(^{-1}\) due to the presence of hydroxyl group (131 and 136) and absorption bands in the range 1714-1724 cm\(^{-1}\) due to the presence of C=O of 4-thiazolidinone (128-137) and 1181 cm\(^{-1}\) for Flouro group (135) respectively.

The \(^1\)HNMR spectra of the compounds (128-137) showed peaks of pyrimidine at 8.61 and 6.66 ppm. Peaks due to aromatic protons clustered in the region of 6.82-6.75 and appeared as multiplet. The methylene proton of second position of thiazolidinone appeared as singlet at 5.92 ppm. Protons of O-CH\(_3\) resonated as singlet in NMR spectra at 3.73 ppm. The methylene protons of fifth position appeared as two singlets at 3.38 ppm and 3.24 ppm. Peaks integrating to six protons resonating around 2.35 ppm were attributed to Ar-(CH\(_3\))\(_2\). The detailed \(^1\)HNMR data is presented in the experimental section. \(^13\)CNMR signals were recorded at 171.2 (C=O thiazolidinone), 170.6 (C-O-CH\(_3\)), 59.4 (C\(_2\)-thiazolidinone), 55.9 (O-CH\(_3\)) and 33.6(C\(_5\)-thiazolidinone), 17.4 (CH\(_3\)), while rest of the carbon atoms produced peaks regarding their environment.

Molecular ion peak for compound 128 at m/z 315 confirmed the molecular weight of corresponding compound. The mass spectra of rest of the compounds (129-137) showed molecular ion peaks corresponding to their molar masses. The fragmentation pattern was 207, 110, 105 and 100. For further conformation elemental analysis data also corresponded to the proposed formula.

Table-10 Novel compounds (128-137) under microwave irradiation

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<td>2-(4-methoxyphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one</td>
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<td>2-(2-hydroxy-5-methoxyphenyl)-3-(4-methoxypyrimidin-2-yl)-thiazolidin-4-one</td>
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<tr>
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<tr>
<td>136</td>
<td>34.4</td>
</tr>
<tr>
<td>137</td>
<td>37.6</td>
</tr>
</tbody>
</table>

**MCR with K-10 and KSF = Microwave procedure-I: Multi-Component Reaction using Montmorillonite Clays (K-10 and KSF)**

*SMCR = Microwave procedure-II: Solvent free, Multi-Component Reaction
In sixth series, two methods Microwave procedure-I: Multi-Component Reaction using Ionic Liquids (PEG, TBAB and TEBAC) and Microwave procedure-II: Solvent free, Multi-Component Reaction were used for the preparation of compounds (138-147). Microwave procedure-I ionic liquids (PEG, TBAB and TEBAC) was advantageous over procedure-II and conventional methods in terms of environment time and cost. Particularly in environment IL’s are used in very small quantities and reduce the reaction time as compared with the other conventional catalysts. The yields obtained with Ionic Liquids ranging from 73.4%-88.8% with TBAB, 33.5%-58.2% with PEG and 44.4%-62.4% with TEBAC and yields with procedure-II ranging from 12.0% to 64.5%. A mixture of was taken in the presence of Ionic Liquids (PEG, TBAB, TEBAC) and water (15 mL) was irradiated in microwave oven (200 watt) for 8-10 minutes at 105-110 °C and the reaction was monitored by TLC. The crude product was cooled to 25 °C, washed with water and followed by recrystallization in ethanol to get compounds (138-147). The yield ranged from 73.4%-88.8% with TBAB, 33.5%-58.2% with PEG and 44.4%-62.4% with TEBAC.

Previously under microwave irradiation, a reaction of 3-phenyl-2-(phenylimino)-thiazolidin-4-one and substituted aromatic aldehyde was conducted without TBAB using water as solvent and 8 minutes reaction time. The target compounds were not obtained because 3-phenyl-2-(phenylimino)-thiazolidin-4-one and substituted aromatic aldehyde was non-miscible mixture of oil and water. Then phase transfer catalysts (TBAB, TEBAC, PEG) were tried and it was found that TBAB was best in molar ratio 3:10:10. Increase in the quantity of TBAB had no effect on yield and reaction time. The compounds 143, 145 and 147 were obtained with better yields of 84.4%, 82.7% and 88.8% respectively. The comparison of percentage yield and time between conventional and non conventional procedures is shown in Table-13 and time difference is presented in Figure-4.

Tetra-alkylammonium cations are preferred in heterogeneous two-phase system, one phase containing reacting base generates organic anions and the second phase contains organic reactant. The Tributylammonium bromide serves both as a
phase-transfer catalyst and a base because the reactants would exist as a non-miscible mixture of oil and water in the absence of Tributylammonium bromide and 3-CH$_2$ of 4-thiazolidinone cannot remove the alkali effect. The enolate ions would not be formed in the reaction that explains the reaction does not take place in the presence of polyethylene glycol, or in the absence of TBAB$^{203-204}$. Tributylammonium bromide (TBAB) as phase transfer catalyst in non toxic solvent was used to examine their combined effect.

The characterization of compounds (138-147) was done by using IR, NMR and Mass spectral and elemental analysis techniques. IR spectra of compound 138-147 showed absorption bands from 3040-3010 cm$^{-1}$ due to Ar-C and 1724 cm$^{-1}$ stretching of C=O. For compound 141 and 144 showed absorption band at 3220 cm$^{-1}$ for OH stretching. IR bands were displayed at 1126 cm$^{-1}$ due to Flouro group in compound 146. In $^1$HNMR aromatic protons clustered as multiplet in the range from 7.63-7.24 ppm and singlet appeared at 6.80 due to one proton of CH=C$_5$ thiazolidinone. $^{13}$CNMR signals were recorded at 166.9 (C=O thiazolidinone), 163 (N=C$_2$-thiazolidinone), 142 (CH=C$_5$-thiazolidinone), 115.9 (CH=C$_5$-thiazolidinone), while rest of the carbon atoms produced peaks regarding their environment. Mass spectrum of all the synthesized compounds showed M$^+$ peak corresponding to the molecular mass of the products. The other common fragments showed peaks at 356 (C$_{22}$H$_{16}$N$_2$OS, 100%), 294, 281, 91, 77. Finally the elemental analysis data also corresponded to the proposed formula.

Table-12 Novel compounds (138-147) under microwave irradiation

<table>
<thead>
<tr>
<th>Compound number</th>
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</tr>
</thead>
<tbody>
<tr>
<td>138</td>
<td>3-phenyl-2-(phenylimino)-5-(phenylmethylidene)-4-thiazolidinone</td>
</tr>
<tr>
<td>139</td>
<td>5-(4-methylbenzylidene)-3-phenyl-2-(phethylene)-thiazolidin-4-one</td>
</tr>
<tr>
<td>140</td>
<td>5-(4-methoxybenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one</td>
</tr>
<tr>
<td>141</td>
<td>5-(2-hydroxy-4-methoxybenzylidene)-3-phenyl-2-(phenylimino)-thiazolidin-4-one</td>
</tr>
<tr>
<td>Serial number</td>
<td>Conventional method</td>
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<tr>
<td>---------------</td>
<td>---------------------</td>
</tr>
<tr>
<td></td>
<td>Percentage yield</td>
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<tr>
<td>138</td>
<td>44.9</td>
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<td>139</td>
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<td>146</td>
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<td>147</td>
<td>42.8</td>
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</table>

**MCR with ILs = Microwave procedure-I: Multi-Component Reaction using Ionic Liquids (PEG, TBAB and TEBAC)**

*SMCR = Microwave procedure-II: Solvent free, Multi-Component Reaction
Microwave heating, solid phase catalysts and phase transfer catalysts allow scientists to open new unexplored functionalizations of complex systems. Serious improvements and simplifications over conventional methods originate from the rapidity, enhancements in yields, purities of products and environmental factor. Environmental factor represents the amount of waste produced per kg of product. It is dire need to control or reduce the environmental factor because Pharmaceutical and Fine Chemical Industries have high environmental factor (Table-14) that may reflect the continual use of reagent or the use of multi step synthesis.

**Table-14 Environmental factors of various chemical Industries**

<table>
<thead>
<tr>
<th>Industry</th>
<th>Product tonnage</th>
<th>Ratio kg by-products/ kg product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil refinery</td>
<td>$10^5$-$10^3$</td>
<td>$\sim$0.1</td>
</tr>
<tr>
<td>Commercial chemicals</td>
<td>$10^4$-$10^6$</td>
<td>$&lt;1$-$5$</td>
</tr>
<tr>
<td>Analytical chemicals</td>
<td>$10^2$-$10^4$</td>
<td>5-$50$</td>
</tr>
<tr>
<td>Pharmaceuticals raw material</td>
<td>$10^1$-$10^2$</td>
<td>25-$100+$</td>
</tr>
</tbody>
</table>

Other important green aspects of these techniques are reduction in time, less or no solvent usage and cost effectiveness. This helps to implement the green aspect from basic research to the multi-ton industrial process.

With the goal to reduce the cost and environmental burden, non-conventional techniques *i.e.* microwave irradiation, phase transfer catalysts and solid phase catalysts were used instead of conventional techniques. The combination of these two techniques (i.e. microwave and catalysts) showed excellent results in terms of high reaction rates, formation of cleaner products and operational simplicity. While the conventional methods require twelve to seventy two hours of reflux in toxic
solvents like carbon disulfide, pyridine, toluene etc. The average yield with conventional method was 52 to 81%, with microwave heating 78-94% and microwave heating with catalyst 84 to 96%. Over all results of yields and time are summarized graphically in Figure-3 and Figure-4.
Figure-3: Over all percentage yield comparison between conventional, non-conventional microwave and microwave with catalysts

![Percentage Yield Comparison](image)

Series-1 Yield obtained by using conventional heating method
Series-2 Yield obtained by using microwave heating method
Series-3 Yield obtained by using microwave catalyzed SPC and ILS.

Figure-4: Reaction time comparisons between conventional, microwave and microwave with catalysts

![Reaction Time Comparison](image)

Series-1 Reaction time in conventional heating
Series-2 Reaction time in microwave heating
Series-3 Reaction time in microwave heating with catalysts
4.1 Biological characterization of synthesized compounds

4.1.1 Introduction

Bacteria are developing resistance against existing antibiotics. There is always need to develop new antibiotics. 4-thiazolidinone derivatives are known to possess diversified antibacterial, antifungal and antiviral properties. For this reason, a variety of 4-thiazolidinone based compounds and intermediates have been prepared in this study. The analogues of 4-thiazolidinone were tested against laboratory strains (nine bacterial species and seven fungal species).

Keeping in view, a number of novel compounds were prepared and were tested for diverse biological activities. Biological details of these studies are presented below.

4.1.2 Methodology for antibacterial screening

The activity of synthesized compounds was estimated by comparing the inhibition zones of sensitive micro-organisms produced by known concentrations of synthesized compounds and the broad spectrum antibiotics as reference standards. Mueller-Hinton agar (MHA) medium\(^\text{207}\) was prepared by dissolving agar in 250 mL distilled water with slow heating and stirring to dissolve the medium completely. It was sterilized in autoclave at 15 PSI pressure and 121°C temperature for 15 minutes. The sterilized medium was immediately poured into petri dishes to form a uniform layer (2 mm to 5 mm thick). The petri dishes were stored in incubator so that no appreciable growth of the microorganisms was observed before the dishes were used\(^\text{208}\). Solutions of synthesized compounds (50 mg/mL) and reference substances were prepared that were presumed to be of equal concentration. The solutions of 10µL of synthesized compound and reference standard were applied to the surface of the medium (6 mm in diameter) in triplicate, in cavities prepared in the agar. Negative controls were prepared by using N,N-dimethylformamide (DMF), which was employed to dissolve the test compounds. Ciprofloxacin, Sulfamethoxazole, Erythromycin and Cefixime with the 50 mg/mL concentration were used as reference
standards to determine the sensitivity of each microbial species tested. The inoculated plates were incubated at 37°C for 24 to 48 hours. Antibacterial activities of synthesized compounds were calculated quantitatively (bio assay) by measuring the zone of inhibition (mm) against test organisms of synthesized compounds and compared with the zone of inhibition of reference standards (measured the diameters with a precision of at 0.1 mm). All bacterial strains were cultured on their respective medium for further bacterial propagation.

4.1.3 - Antibacterial activity of compounds (88~107)

The synthesized compounds (88~97 and 98-107) were tested in vitro for their antibacterial activity against Staphylococci aureus, Bacillus subtilis, Escherichia coli, Salmonella typhi, Proteus vulgaris, Psudomonas Shigella, Listeria monocytogenes and Pseudomonas aeruginosa. The activity of the compounds was the average zone inhibition values in millimeter using well dip method in triplicate. Ciprofloxacin, Sulfamethoxazole, Erythromycin and Cefixime were used for gram positive and gram negative bacteria as reference standards. The results of antibacterial activity are given in Table 15. The minimum inhibition concentration (MIC) was determined using the tube dilution method according to the standard procedure. All compounds showed different antibacterial activity that depends on the nature of group attached with the main skeleton. Compound 96 and 106 showed significant antibacterial activity against all strains due to the presence of Fluoro group.
### Table-15 Antibacterial response of compounds 88-107

<table>
<thead>
<tr>
<th>Compound number</th>
<th>Antibacterial activity of compounds 88-107</th>
<th></th>
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<tr>
<td></td>
<td>Gram positive</td>
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</tr>
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<td>+++</td>
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<td>+++</td>
<td>+++</td>
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<td>+++</td>
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<td>++</td>
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<tr>
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<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
</tbody>
</table>

**Key to symbols:**
- **Highly active** = ++++ (inhibition zone > 20 mm)
- **Highly active** = +++ (inhibition zone 15-20 mm)
- **Active** = ++ (inhibition zone 10-15 mm)
- **Slightly active** = + (inhibition zone 5-10 mm)
- **Inactive** = - (inhibition zone < 5mm)
4.1.4 Activity of another two series of 4-thiazolidinones derivatives (108-117 & 118-127)

Another two series (108-117 and 118-127) were screened in vitro for their antimicrobial activity against a variety of bacterial strains such as *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Salmonella typhi*, *Proteus vulgaris*, *Psudomonas Shigella*, *Listeria monocytogenes* and *Pseudomonas aeruginosa*. The standard drugs Ciprofloxacin, Sulfamethoxazole, Erythromycin and Cefixime were used for comparison against synthesized compounds and both were prepared at same concentrations (25 µg/mL). The minimum inhibition concentration (MIC) 8 µg/mL was determined using the tube dilution method according to the standard procedure\textsuperscript{214-215}. Antibacterial activity was carried out by well dip method and average zone of inhibition values were recorded in millimeters in triplicate and are shown in Table 16.

**Table 16 Antibacterial response of compounds 108-127**

<table>
<thead>
<tr>
<th>Compound Number</th>
<th>Gram positive</th>
<th>Gram negative</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>S. aureus</td>
<td>B. subtilis</td>
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<tr>
<td>108</td>
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</tr>
<tr>
<td>120</td>
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</tbody>
</table>
4.1.5 *In vitro* evaluation of antibacterial activity of novel 4-thiazolidinone derivatives (128~137 & 138~147)

The synthesized compounds (128-147) were tested *in vitro* for their antibacterial activity. All test compounds were dissolved in DMSO; it was observed that the solvent showed no activity in these assays at the level used for screening. 4-thiazolidinone derivatives were assayed for antibacterial activity. These compounds were examined against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Salmonella typhi*, *Proteus vulgaris*, *Psudomonas Shigella*, *Listeria monocytogenes* and *Pseudomonas aeruginosa* using 25 mg/mL concentration of prepared 4-thiazolidinone derivatives. The minimum inhibition concentration (MIC) of 10 µg/mL was determined using the tube dilution method according to the standard procedure\(^{216-217}\). Antibacterial activity was carried out by well dip method and average zone of inhibition values were recorded in millimeters in triplicate and results of antibacterial activity are presented in Table 17.
## Table-17 Antibacterial response of compounds 128-147

<table>
<thead>
<tr>
<th>Compound number</th>
<th>Antibacterial activity of compounds 128-147</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gram positive</td>
</tr>
<tr>
<td>S. aureus</td>
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<tr>
<td>B. subtilis</td>
<td></td>
</tr>
<tr>
<td>B. pumilus</td>
<td></td>
</tr>
<tr>
<td>L. monocytogenes</td>
<td></td>
</tr>
<tr>
<td>E. coli</td>
<td></td>
</tr>
<tr>
<td>S. typhi</td>
<td></td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td></td>
</tr>
<tr>
<td>P. vulgaris</td>
<td></td>
</tr>
<tr>
<td>P. Shigella</td>
<td></td>
</tr>
<tr>
<td>128</td>
<td>-</td>
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<td>129</td>
<td>-</td>
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<td>146</td>
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</tr>
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<td>147</td>
<td>+</td>
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<tr>
<td>CLR.</td>
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<td>CIM</td>
<td>+++</td>
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<tr>
<td></td>
<td>Gram negative</td>
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<td></td>
</tr>
<tr>
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<td>Highly active</td>
</tr>
<tr>
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<td>= +++</td>
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<tr>
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<td>(inhibition zone &gt; 20 mm)</td>
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<td>Highly active</td>
</tr>
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<tr>
<td></td>
<td>(inhibition zone 15-20 mm)</td>
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<tr>
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<td>Active</td>
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<td>= ++</td>
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<td>(inhibition zone 10-15 mm)</td>
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<td>Slightly active</td>
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<td>(inhibition zone 5-10 mm)</td>
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<td>Inactive</td>
</tr>
<tr>
<td></td>
<td>= -</td>
</tr>
<tr>
<td></td>
<td>(inhibition zone &lt; 5mm)</td>
</tr>
</tbody>
</table>

**Key to symbols:**

CIP. = Ciprofloxacin
CLR = Clarithromycin
SMZ= Sulfamethoxazole
CIM = Cefixime
Figure-05: The inhibition zones obtained for the selected compounds on different pathogens in the qualitative screening assay.
4.2 Antifungal Activity

4-thiazolidinone derivatives are important compounds due to their broad range of biological activity\textsuperscript{218-221} and 2-imino-4-thiazolidinones are found to have antifungal activity\textsuperscript{222-223}. The derivatives of 4-thiazolidinone were screened for antifungal activity against the seven fungal strains \textit{Aspergillus flavus} (F1), \textit{Aspergillus niger} (F2), \textit{Rhodotorula rubra} (F3), \textit{Lipomyces lipofera} (F4) \textit{Fusarium graminearium} (F5), \textit{Pleurotus ostreatus} (F6) and \textit{Candida albicans} (F7). The concentration of the test compounds was 50 ppm. After 48 hours treatment, the growth diameter of the fungus on the agar was measured and percentage inhibition of growth by an inhibitor was calculated by comparison with the growth in controls. The experiments were performed in triplicate. The antifungal activity of the synthesized compounds was also determined by well dip method by using saboraud's dextrose agar (SDA). The average experimental results i.e. average zones of inhibition in millimeters are given in Table-18, 19 and 20.

4.2.1 Methodology for antifungal screening

Suspension of 100 µL containing $10^{6}$ colony (CFU/mL) of fungi was spread on saboraud's dextrose agar medium\textsuperscript{224}. The discs (6 mm in diameter) impregnated with 10 µL of the test compounds at the concentration of 50ppm (in triplicate) were placed on the inoculated agar. Clotrimazole, miconazole and fluconazole (10 µg/disc) were used as reference standard to determine the sensitivity of each microbial species and compared with the activity of synthesized compounds. The inoculated plates were incubated at 25°C for 48 hours for fungal strains. Antifungal activities were evaluated by measuring the average diameter of zone of inhibition against the test organisms. The responses of tested 4-thiazolidinone derivatives against the fungal species under study were found significantly different and the difference among their responses was also found to be significant.
4.2.2 Antifungal Activity

The derivatives of 4-thiazolidinone were screened for antifungal activity against the seven fungal strains Aspergillus flavus, Aspergillus niger, Rhodotorula rubera, Lipomyces lipofera, Fusarium graminearium, Pleurotus ostreatus and Candida albicans. The antifungal activity of the synthesized compounds was also determined by well dip method by using Saburaud’s dextrose agar. The experimental results in percentage are given in Table 18, 19 and 20.

The results were calculated by using formula.

\[
\text{Percentage of inhibition} = \frac{\text{Average of inhibition of synthesized compounds}}{\text{Average of inhibition of reference standard}} \times 100
\]

Table 18 Percentage of inhibition of compounds 88-107 and 98-107 against the fungi F1-F7

<table>
<thead>
<tr>
<th>Compound number</th>
<th>Percentage Inhibition of compounds 88-107 and 98-107 at 50ppm against F1-F7</th>
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<tbody>
<tr>
<td>88</td>
<td>F1 24.4 F2 28.6 F3 35.6 F4 0.0 F5 0.0 F6 12.9 F7 18.8</td>
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<tr>
<td>89</td>
<td>F1 68.5 F2 72.6 F3 8.6 F4 2.0 F5 6.8 F6 4.0 F7 66.5</td>
</tr>
<tr>
<td>90</td>
<td>F1 76.1 F2 70.2 F3 49.4 F4 58.5 F5 44.6 F6 0.0 F7 76.8</td>
</tr>
<tr>
<td>91</td>
<td>F1 96.2 F2 90.2 F3 68.4 F4 82.5 F5 78.6 F6 34.8 F7 92.8</td>
</tr>
<tr>
<td>92</td>
<td>F1 0.0 F2 16.3 F3 4.6 F4 11.8 F5 18.6 F6 2.8 F7 14.8</td>
</tr>
<tr>
<td>93</td>
<td>F1 05.8 F2 03.9 F3 16.8 F4 20.1 F5 4.8 F6 9.6 F7 12.4</td>
</tr>
<tr>
<td>94</td>
<td>F1 28.5 F2 18.3 F3 14.7 F4 27.8 F5 8.9 F6 11.4 F7 24.8</td>
</tr>
<tr>
<td>95</td>
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</tr>
<tr>
<td>96</td>
<td>F1 98.4 F2 95.4 F3 56.3 F4 84.5 F5 88.6 F6 55.3 F7 97.5</td>
</tr>
<tr>
<td>97</td>
<td>F1 44.8 F2 48.9 F3 44.8 F4 49.0 F5 24.6 F6 36.7 F7 29.8</td>
</tr>
<tr>
<td>98</td>
<td>F1 11.8 F2 7.4 F3 5.6 F4 2.9 F5 0.0 F6 4.6 F7 1.8</td>
</tr>
<tr>
<td>99</td>
<td>F1 18.9 F2 12.9 F3 8.9 F4 6.5 F5 3.9 F6 8.0 F7 4.6</td>
</tr>
<tr>
<td>100</td>
<td>F1 17.6 F2 18.8 F3 9.6 F4 11.6 F5 12.8 F6 14.8 F7 21.6</td>
</tr>
<tr>
<td>101</td>
<td>F1 92.2 F2 86.2 F3 74.4 F4 78.4 F5 76.6 F6 44.8 F7 88.0</td>
</tr>
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<td>F1 24.4 F2 18.4 F3 28.9 F4 26.8 F5 12.0 F6 15.8 F7 26.6</td>
</tr>
<tr>
<td>103</td>
<td>F1 88.6 F2 84.8 F3 70.4 F4 84.2 F5 66.8 F6 46.6 F7 87.4</td>
</tr>
<tr>
<td>104</td>
<td>F1 39.4 F2 34.5 F3 28.9 F4 24.0 F5 32.8 F6 38.8 F7 26.7</td>
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### Table-19 Percentage of inhibition of compounds 108-117 and 118-127 against the fungi F1-F7

<table>
<thead>
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<th>Compound number</th>
<th>Percentage inhibition of compounds 108-117 and 118-127 at 50ppm against F1-F7</th>
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</tr>
<tr>
<td>108</td>
<td>2.4</td>
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<tr>
<td>Fluconazole</td>
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</table>
Table-20 Percentage of inhibition of compounds 128-137 and 138-147 against the fungi F1-F7

<table>
<thead>
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<th>Compound number</th>
<th>Percentage inhibition of compounds 128-137 and 138-147 at 50ppm against F1-F7</th>
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</thead>
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<td>F1</td>
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<td>128</td>
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<td>Clotrimazole</td>
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<td>80.0</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>89.6</td>
</tr>
</tbody>
</table>

4.3 Discussion of Biological Activity

The synthesized compounds were tested in vitro for their antimicrobial activity and showed significant difference in the antimicrobial potentials of different compounds. 4-thiazolidinone analogues exhibited various biological activities and are widely used in medicine, especially as antibacterial and antifungal agents. We focused on a quantitative screening assay of the antimicrobial properties (adapted
well dip methods) against microbial gram-positive, gram-negative and fungal strains. The data of antibacterial activity (inhibition zone) is shown in Tables-15, 16, 17, 18, 19 and 20.

4.3.1 *In vitro evaluation of antibacterial activity of compounds 88-97 and 98-107*

Compounds (88-97) exhibited significantly higher antibacterial potential against gram negative strains especially *E. coli*, *S. tyhi*, *P. aeruginosa* as compared to the compounds 98-107. Among the various 4-thiazolidione derivatives under study, the compounds 96 and 106 have shown highest antibacterial activity against gram negative bacterial strains particularly *E. coli*, *S. tyhi*, *P. aeruginosa*. Among the rest of compounds 91 and 101 were found to be effective against *S. aureus* and *B. subtilis*. The compounds 92 and 99 showed significant zone of inhibition against *S. aureus* and *B. subtilis*. From the data in Table-15, the substituted groups 4-methoxy, methyl, ethoxy were not found to inhibit the bacterial growth significantly. The antibacterial effects are probably because of their structural feature i.e. the compounds bearing fluoro, chloro, dimethyl amine and hydroxyl could possibly induce the activity. Compounds 96 and 106 exhibited maximum bacterial growth due to two Fluoro groups and comparable with standard drug Ciprofloxacin. The broad spectrum antibiotics Ciprofloxacin (fluoroquinolones), Sulfamethoxazole (sulfonmides), Clarithromycin (macrolides) and Cefixime (3rd generation of cephalosporins) as reference standards were used for comparison. In general, the compounds 88-97 inhibited more bacterial growth against gram negative bacteria *E. coli*, *S. tyhi*, and *P. aeruginosa* than the compounds 98-107.

4.3.2 Antibacterial activity of compounds 108-117 and 118-127

The synthesized compounds 108-127 showed antibacterial activity, however, in this case antibacterial potential observed was slightly lower as compared to reference standard but in 4th series (118-127) compounds showed significant activity
against gram negative bacteria *E. coli*, *P. shigella*, *S. typhi*, and *P. aeruginosa*. The compounds 115 and 127 have shown more antibacterial potential against gram negative bacteria under test than rest of the compounds. Among the tested compounds, 112 and 124 were found to be effective against *S. aureus* and *B. subtilis*; the compound 126 showed good antibacterial potential against *E. coli* and *P. shigella* and *P. vulgaris* as compared to the other tested compounds of this series. In general, 4-thiazolidinone derivatives showed different activities due to the presence of different groups. The compounds 115 and 127 showed excellent results due to the presence of Fluoro group; the compounds 112 and 124 showed significant results against *S. aureus* and *B. subtilis* due to the presence of Chloro group and the compounds 126 produced good results against *P. vulgaris* and *P. shigella* due to the presence of furan group. All compounds of 3rd series inhibited the bacterial growth against gram positive bacteria *S. aureus*, *B. subtilis* and *L. monocytogenes* due to more quantity of nitrogen. The basic molecule of 4th series showed almost similar behaviour as shown by standard drug sulfamethoxazole due to the presence of more sulfur content. The groups 4-methoxy and methyl, ethoxy did not effect bacterial growth. The results of two series are presented in Table-16.

### 4.3.3 Antibacterial activity *in vitro* of compounds 128-137 and 138-147

The effects of newly synthesized 4-thiazolidinone analogues were studied against nine bacterial strains and data is presented in Table 15. The activities of fifth series of 4-thiazolidinone derivatives (128-137) were good but the compounds of sixth series (138-147) had not shown better result, although some compounds showed little inhibition of bacterial growth. From the data obtained (Table-16), the compounds 135 and 146 exhibited high activity against negative bacterial strains as compared to the other compounds of these two series. These compounds (135 and 146) showed high activity due to the presence of highest electronegative group. The compounds 134 and 145 exhibited high activity against gram positive bacterial strains under study. The substituted dimethyl amino group was also found to
increase the zone of inhibition against gram positive bacterial strains *S. aureus* and *B. subtilis*. The substituted methoxy, ethoxy and hydroxyl groups participated a little in the zone of inhibition against the gram positive bacterial growth as shown in Table-17. Other substituents *i.e* methanol and benzene did not affect the zone of inhibition against the bacterial strains under study.

**4.3.4 In vitro evaluation of antifungal activity of compounds 88-147**

Compounds (88–147) were tested for *in vitro* antifungal activity against seven fungi *Aspergillus flavus* (F1), *Aspergillus niger* (F2), *Rhodotorula rubera* (F3), *Lipomyces lipofera* (F4) *Fusarium graminearium* (F5), *Pleurotus ostreatus* (F6) and *Candida albicans* (F7). The results of quantitative assay for the antifungal activity of the new 4-thiazolidnone derivatives are presented in Table-18, 19 and 20. These results showed that the tested compounds exhibited a specific antifungal activity, depending on the nature of the substituents and their position on the benzene ring. Compounds 91, 101, 112, 124, 134 and 145 showed higher antifungal activity against *A. flavus*, *A. niger* and *C. albicans*. The percentage inhibition of 96, 106, 116, 127, 135 and 145 against *A. flavus*, *A. niger*, *F. graminearium* and *C. albicans* were higher then 90. From the data Table 18, 19 and 20, most of the compounds did not show the inhibition against *R. rubera*, *F. graminearium* and *P. ostreatus*. Dimethylamine, Fluoro, Chloro and Furan groups found to increase the inhibition but Dimethyl amine was found to be more effective at para position than ortho and meta positions. Basic precursor 4-thiazolidinone also showed good activity against *C. albicans* and *A. flavos*. 
Figure-06: Antifungal activity of compounds 88-107 against the fungi F1-F7

Figure-07: Antifungal activity of compounds 108-127 against the fungi F1-F7
Figure-08: Antifungal activity of compounds 128-147 against the fungi F1-F7
CONCLUSION

Eco-friendly approaches *i.e.* Solvent free, Multi-Component Reaction, Multi-Component Reaction using Montmorillonite Clays (K-10 and KSF), Multi-Component Reaction in DMF and Multi-Component Reaction using Ionic Liquids (PEG, TBAB and TEBAC) coupled with microwave radiation were tried. These approaches open up numerous possibilities for conducting rapid organic synthesis more efficiently. A distinct advantage of these protocols is that since they provide elimination of solvents thereby preventing pollution in organic synthesis ‘at source’. Solvent free procedure was found better in three major constraints *i.e.* cost, time and environment. Pharmaceuticals and Fine Chemicals Industries have relatively high environmental factor\(^\text{225}\) that may reflect the continual use of more reagents or the use of multi-step synthesis.

Multi-Component Reaction using Montmorillonite Clays (K-10 and KSF) provided consistent yield. Because mineral oxides (SPC) are very good microwave adsorbents and result in very rapid and homogenous heating and less degradation of final products as compared to conventional heating. This method is more advantageous towards environment because SPC (K-10 and KSF) can be reused after washing with ethanol. Moreover the separation of final products and catalysts is easy. High yields were obtained with K-10 from rest of all procedures and 10% less yield was obtained with KSF as compared with K-10.

The third approach of Multi-Component Reaction using Ionic Liquids (PEG, TBAB and TEBAC) was tried and it was found that TBAB was best in molar ratio 3:10:10 and even increase in the quantity of TBAB had no effect on yield and time.
The high yield with TBAB (Ionic Liquid) was obtained ranging from 73.4 to 88.8%. The main difference between Ionic Liquids and conventional procedure was high yields, clean reactions, shorter reaction times, nontoxic solvents and environmentally benign because very small quantity of ILs used.

The synthesized compounds were tested for antibacterial activity and showed very promising results with positive activity as compared with standard reference drugs. Compounds 96, 106, 115, 127 146 and 147 exhibited better inhibition as compared to reference drugs. The compounds 124 and 127 are viable alternatives to existing sulfonamides. Compound 112, 124, 133, 134 and 145 showed inhibition against S. aureus hence it may be used for the cure of S. aureus infection.
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PUBLICATION RESULTED FROM THIS WORK

1. Greener Approach synthesis of 4-Thiazolidinone derivatives using PTCs under microwave oven

2. An eco-friendly synthesis of 4-Thiazolidinone derivative using TBAB under microwave oven

3. Environmental friendly procedure for the synthesis of potentially biologically active compounds containing 4-Thiazolidinone.

4. An eco-friendly synthesis of 4-Thiazolidinone derivative using montmorillonite clays (K-10 and KSF) under microwave radiation

5. One pot synthesis of 4-Thiazolidinone containing compounds using Solvent free, Multi-Component reaction under microwave radiation
   *[Chinese Chem. Soc., Submitted]*

6. An eco-friendly synthesis of 4-Thiazolidinone derivative using Solid Phase Catalysts Coupled with microwave radiation
   *[Manuscript under preparation for Molecule]*