CHAPTER – VI

Design & synthesis of novel thiazolidine 2,4-diones derived from imidazo[2,1-b][1,3,4]thiadiazoles
INTRODUCTION

Diabetes mellitus is a complex, chronic, progressive disease of glucose metabolism, which eventually can adversely affect function of number of organs as well as the nervous and vascular systems. Diabetes mellitus is of two types,

I. Insulin dependent diabetes mellitus (IDDM), which arises due to absolute lack of insulin.

II. Non-insulin dependent diabetes mellitus (NIDDM), which is characterized by insufficient secretion of insulin and reduction in response of the peripheral target tissue to insulin i.e. insulin resistance. Although the frequency of diabetes is increasing, only two classes of oral hypoglycemic agents are available, namely Sulfonylureas and Biguanides.

Type II diabetes (non-insulin dependent diabetes mellitus; NIDDM) is one of the major causes of several chronic diseases, such as retinopathy, nephropathy, neuropathy and cardiovascular diseases.\(^1\) Long-term hyperglycemia, caused by insufficient insulin secretion from pancreas and / or insulin resistance in muscle, liver and adipose tissues, brings about aggravation of diabetics. Therefore, it is important to regulate the blood glucose level in order to control diabetics.\(^2\)

Treatment of diabetes has been carried out with a combination of diet, exercise and hypoglycemic agents.

Sulfonylurea stimulate pancreatic β-cells and increases secretion of insulin to lower the blood glucose level.\(^3,4\) However sulfonylurea therapy has some problems such as primary or secondary failure of efficacy, enhancement of obesity, weight gain and high incidence of hypoglycemia.\(^5,6\) Biguanides are banned in western countries due to its severe side effects mainly lactic acidosis. A significant advancement has been made with the introduction of new class of compounds thiazolidine-2,4-diones (TZDs) which act as insulin sensitivity enhancers.\(^7\)

The onset of insulin resistance in body, which causes an abnormal effect on glucose metabolism is related not only to the development of type II diabetes but
also to cardiovascular disease. A cluster of other metabolic abnormalities, involving body fat distribution, lipid metabolism, thrombosis and fibrinolysis, blood pressure regulation and endothelial cell function is referred to as the insulin resistance syndrome or the metabolic-syndrome. Since after the pioneering discovery of cigelizone \(^10\) (1), a new class of thiazolidine-2,4-dione based compounds have been developed to treat diabetic patients that can reverse the insulin resistance in non-insulin dependent diabetes mellitus (NIDDM) type II patients. It lowered the elevated blood glucose, plasma insulin and triglyceride level in insulin resistant animals, but showed no hypoglycemic effect in nondiabetic or IDDM animal models. Among various substituted compounds benzyl-2,4-thiazolidinedione compounds, troglitazone \(^11\) (2), englitazone \(^12\) (3), pioglitazone \(^13\) (4) and rosiglitazone \(^14\) (5) are potential antidiabetic compounds that have been clinically examined.

It has been reported that these drugs act as high-affinity ligands for peroxisome proliferator activated receptor gamma (PPAR\(\gamma\)), a receptor subtype to induce adipocyte differentiation.\(^15\) It has also been reported that there is a significant positive relationship between PPAR\(\gamma\) agonism in vitro and hypoglycemic activity of thiazolidinedione compounds in genetically diabetic mice.\(^16\) Specifically the thiazolidinediones improve insulin action and decrease insulin resistance. Treatment of insulin resistant type II diabetic patients with thiazolidinediones not only improves glycemic control and decreases insulin
resistance, but also improves many of the abnormalities as part of the resistant syndrome.

The compounds (thiazolidine-2,4-dione class) are found to be very effective in reducing insulin resistance or to efficiently potentiate insulin in type II non-insulin dependent diabetes mellitus (NIDDM) patients. The structure activity relationship of such related compounds similar to ciglitazone, has resulted into the development of troglitazone, englitazone, pioglitazone and rosiglitazone as new drug entities for diabetes.

Several studies showing that analogues of these classes interact with a nuclear receptor PPAR-γ and transcript the insulin sensitizing genes have been summarized and the synthesis, structural elucidation and screening of hypoglycemic activity of the molecules are described.

Recently from our laboratory\textsuperscript{17} new series of thiazolidine 2,4-dione derivatives of following type of were designed and synthesized. These derivatives I (structure analogue of ciglitazone), II (structure analogue of troglitazone), III (structure analogue of rosiglitazone) and IV (structure analogue of englitazone) were screened for their hypoglycemic, hypolipidemic and antitubercular activities.

B. K. Trivedi \textit{et al.}\textsuperscript{18} have synthesized a new class of oral antidiabetic agents. They have reported the first example of a non-thiazolidine containing oral antidiabetic series, perfluoroanilides that possess a pharmacologic profile similar to that of ciglitazone in two genetic (db/db) mice.
Two novel classes of thiazolidine-2,4-diones and oxazolidinediones with an o-(azolylalkoxy-phenyl) alkyl substituent at the 5-position were prepared and their antidiabatic effects were evaluated in two genetically obese and diabetic animal models (KKAy mice and Wistar fatty rats) by Yu Momose et al.\textsuperscript{19} A large number of 2,4-thia(oxa)-zolidinediones showed potent glucose and lipid-lowering activities. The antidiabetic activities of the 2,4-oxazolidinediones were superior to those of the thiazolidine-2,4-diones.

New series of flavonyl-2,4-thiazolidine dione derivatives were synthesized by Oya et al.\textsuperscript{20} The prepared compounds were tested for their insulinotropic effects in INS-1 cells. Few of the compounds were able to increase insulin release compared with glibenclamide.

A number of highly potent and orally bioavailable 5-Aryl thiazolidine-2,4-diones were reported by Desai\textsuperscript{21} and associates. Efficacy study results of some of these analogues in the db/db mice model of type 2 diabetes showed them superior to rosiglitazone in correcting hyperglycemia hypertriglyceridemia.
Lee et al.\textsuperscript{22} have reported the synthesis and antidiabetic activity of novel substituted thiazolidine diones having pyrimidine moiety. These compounds were evaluated for their glucose and lipid lowering activity in mice. These compounds exhibited considerably more potent biological activity than that of reference compounds, pioglitizone and rosiglitazone.

A series of hindered phenols were reported by Takao Yoshioka \textit{et al.}\textsuperscript{23} as hypolipidemic and/or hypoglycemic agents with an ability to inhibit peroxidation. They have prepared 1,3-benzoxothioles (1 and 2), phenoxypentanoic acid (3), phenoxy pentanol (4), phenylchloropropionic acid having a chromyl group (5) and a thiazolidinedione compound 6 derived from 5, having a phenol group. They have reported that compound 6 showed the expected biological properties \textit{in vivo} and \textit{in vitro}.

David \textit{et al.}\textsuperscript{24} have reported a series of dihydrobenzofuran and dihydrobenzopyran thiazolidinediones which were synthesized from corresponding aryl aldehydes. These compounds represent conformationally restricted analogues of the novel hypoglycemic ciglitazone. \textit{In vivo} hypoglycemic effects were evaluated in genetically obese mice and structure activity relationship is discussed.
Bernard Hulin et al.\textsuperscript{25} have reported a new series of thiazolidine-2,4-diones which were obtained by replacing the ether function of englitazone with various functional groups \textit{i.e.} a ketone, alcohol or olefin moiety. These compounds lower the blood glucose levels in the genetically obese and insulin resistant ob/ob mice. Appending an oxazole-based group at the terminus of the chain provided highly potent compounds.

In the course of further chemical modification of the novel antidiabetic pioglitazone, Takashi Shoda et al.\textsuperscript{26} have reported a series of 5-[4-(2- or 4-azoyl alkoxy)benzyl- or benzylidine-2,4-thiazolidinediones and evaluated them for hypoglycemic and hypolipidemic activities in insulin resistant, genetically obese and diabetic KKA\textsuperscript{Y} mice. Replacement of the 2-pyridyl moiety of pioglitazone by a 2- or 4-oxazolyl/thiazolyl moiety greatly enhanced \textit{in vivo} potency. The corresponding 5-benzyldine type compounds, in which a methine group was used as a linker between the benzene ring and the thiazolidinedione ring, also had potent biological activity. Among the compounds synthesized, 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy] benzyl}-2,4-thiazolidinedione exhibited the most potent activity, \textit{i.e.} 100 times more than that of pioglitazone. They have also reported the synthesis and structure-activity relationships for this novel series of derivatives.
Cantello and coworkers\textsuperscript{27} have reported a series of [(ureidoethoxy)benzyl]-2,4-thiazolidinediones and [(heterocyclylamino)alkoxy]-benzyl]-2,4-thiazolidinediones which were synthesized from the corresponding aldehydes. Compounds from the urea series, as exemplified by (1), showed antihyperglycemic potency comparable with known agents of the type such as pioglitazone and troglitazone. The benzoxazole (2) a cyclic analogue of (1) was a very potent enhancer of insulin sensitivity and by modification of the heterocycle; an aminopyridine (3) was identified as a lead compound from SAR studies.

\rule{0pt}{1in}

Lohary and associates\textsuperscript{28} have synthesized a series of [(heterocyclyl)ethoxy] benzyl]-2,4-thiazolidinediones. Both unsubstituted thiazolidinedione (1) and its saturated counterpart have shown antihyperglycemic activity. Many of these compounds have shown superior euglycemic and hypolipidemic activity compared to troglitazone. The indole analogue was found to be a very potent insulin sensitizing.

\rule{0pt}{1in}

Prabhakar\textit{ et al.}\textsuperscript{29} have synthesized novel compounds of the following type having a dual pharmacophore and evaluated them for the insulin sensitiser and anti-inflammatory properties in different animal models.
Novel 5-(3-aryl-2-propynyl)-5-(arylsulfonyl)thiazolidine-2,4-diones were reported by Jay Wrobel et al.\textsuperscript{30} as oral antihyperglycemic agents in obese mice. The sulfonylthiazolidine-diones (2) were more potent than the corresponding sulfanylthiazolidine congeners (1).

\begin{center}
\includegraphics[width=0.8\textwidth]{1}
\end{center}

Several thiazolidinedione derivatives having 1-hydroxy-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran moieties and their 5-benzylloxy derivatives (1) and 5-hydroxy-2,4,6,7-tetramethylbenzofuran moieties (2) were synthesized by Anji Reddy et al.\textsuperscript{31} Insertion of an N-Me group (3) in to the linker between thiazolidine-2,4-dione and substituted benzofuran pharmacophores showed considerable improvement in their euglycemic activity. Further improvement has been observed when a pyrrolidine moiety is introduced in the structure (4).

\begin{center}
\includegraphics[width=0.8\textwidth]{2}
\end{center}

A series of imidazopyridine thiazolidine-2,4-diones were designed and synthesized from their corresponding pyridines by Minoru Oguchi et al.\textsuperscript{32} These compounds represent conformationally restricted analogues of the novel hypoglycemic compound Rosiglitazone (1). The compounds from this series were evaluated for their effect on insulin induced 3T3-L1 adipocyte differentiations \textit{in vitro} and its hypoglycemic activity in the genetically diabetic KK mice \textit{in vivo}. 

118
A series of substituted 5-\{4-[2-(6,7-dimethyl-1,2,3,4-tetrahydro-2-oxo-4-
quinoxa- linyl)ethoxyphenyl]methylene\}thiazolidine-2,4-diones were synthesized by Ramesh Chandra et al.\textsuperscript{33} and their euglycemic and hypolipidemic activities were investigated in Wistar male rats. Based on the \textit{in vivo} data in rats, compounds were identified as a potent euglycemic and hypolipidemic agents.

Yanagisawa et al.\textsuperscript{34} have prepared oximes having 5-benzyl-2,4-thiazolidine dione and evaluated them for PPAR \(\gamma\) agonistic and blood glucose lowering activities and reported that bioaromatic and methyl groups attached to the oxime moiety and ethylene bridge are favorable for the biological activities. Thus thiazolidinedione derivatives are novel class of insulin sensitizing agents that have demonstrated \textit{in vivo} antidiabetic activity with least undesired side effects.

Thiazolidinedione moiety is significant because of its pharmacophoric acidic group in a central flat ring. Structure activity relationship studies have revealed that better activity can be gained by linking a lipophilic fragment such as aromatic/heteroaromatic ring via one or two carbon atom spacer at C\textsubscript{5}-position of the thiazolidinedione moiety. Hence it is proposed to synthesize various thiazolidinedione derivatives by substituting pharmacophorically important group and as a lipophilic fragments like imidazothiadiazoles. Such molecules are expected to exhibit better antidiabetic properties for non-insulin dependent diabetes mellitus (NIDDM) as cited in the literature.
The synthesis of various thiazolidinedione derivatives discussed in this chapter is outlined in following scheme (VI) and explained briefly.

\[
\begin{align*}
&\text{O} \\
&\text{R = } p\text{-methoxybenzyl, } p\text{-fluorobenzyl, thiethyl} \\
a, R' = H; b, R' = \text{Cl; c, } R' = \text{NO}_2; d, R' = \text{Br; e, } R' = \text{OMe; f, } R' = \text{Me; g, } R' = \text{biphenyl; h, } R' = \text{naphthyl; i, } R' = \text{coumarinyl}. \\
\end{align*}
\]

**Reagents and Conditions:**
- i. POCl₃, reflux, 45 min, KOH
- ii. dry ethanol, 18hr, Na₂CO₃
- iii. DMF/POCl₃, Na₂CO₃

**Scheme-V**

The required 2-amino-5-alkyl/aryl-1,3,4-thiadiazoles were prepared by the sulphuric acid/phosphorourous oxychloride cyclisation of various carboxylic acids with thiosemicarbazide. Further 2-aminothiadiazoles were reacted with equimolar quantity of various phenacyl bromides in dry ethanol to get corresponding imidazo[2,1-b][1,3,4]thiadiazole derivatives. By this method the required substituents at 2-and 6-positions have been obtained by starting with appropriately substituted synthons. The respective free bases were obtained by neutralization of the hydrobromide salts with aqueous sodium carbonate solution in good yields. The imidazo[2,1-b][1,3,4]thiadiazoles reacted with DMF and POCl₃ mixture (Vilsmeier Haack reagent) afforded the 5-formyl derivatives in good yields.
Further, these 6-aryl-2-(4-alkyl/aryl)imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehydes on Knoevenagel condensation with thiazolidine-2,4-dione in toluene with catalytic amount of piperidene-acetate yields the corresponding thiazolidine-2,4-dione derivatives of methoxybenzyl/fluorobenzyl/thienyl imidazo[2,1-b][1,3,4]-thiadiazoles (scheme VI). All these derivatives are the structure analogues of ciglitazone, antidiabetic agent.

Reagents and Conditions: iv. piperidine acetate, toluene, reflux.

Scheme-VI
During the present investigation required imidazo[2,1-b][1,3,4]thiadiazoles were prepared by the reaction of 2-amino-1,3,4-thiadiazole (2) with appropriately substituted α-haloketones (phenacyl bromides) in dry ethanol as hydrobromides, which on neutralization with aqueous sodium carbonate solution gave corresponding free bases (3a-g, 28f-29h) in good yields. The absence of vN-H band in IR spectra of the resulting compounds confirms the formation of product, which exhibits imidazole (C5-H) proton in the region δ 7.96-8.31 & methoxy proton at 3.80 ppm in 1H NMR spectra.

Imidazo[2,1-b][1,3,4]thiadiazoles (3a-g, 28f-29h) were further subjected to Vilsmeier Haack reaction, which resulted in the formation of expected imidazo[2,1-b][1,3,4] thiadiazole-5-carbaldehydes (7a-g, 30f-31f) and were confirmed by their spectral and analytical data. The IR spectra of these compounds displayed the aldehydic carbonyl around 1674 cm⁻¹ and vC-H around 2850 cm⁻¹. The structures were further confirmed by the presence of a signal around δ 10.00 for aldehydic proton and absence of C5-H of imidazole in the 1H NMR spectra apart from other aromatic protons.

The intermediate imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehydes (7a-g, 30f-31f) were exploited for the preparation of target molecules (structure analogues of englitazone) by Knoevenagel condensation with thiazolidine-2,4-dione. The reaction underwent smoothly with excellent yields. The formation of compound can be observed in the reaction mixture itself as they come out as intense yellow solid from the clear solution within few minutes. All the thiazolidinedione derivatives were having high melting points compared to its starting materials due to formation of rigid and very stable compound.

The formation of 5-[(2-alkyl/aryl-6-arylimidazo[2,1-b][1,3,4]thiadiazol-5-yl) methylene]-1,3-thiazolidine-2,4-dione (32a-34f) was confirmed by their IR spectra, which displayed the vC=O bands around 1725 and 1690 cm⁻¹. The vN-H was observed in the region 3112-3320 cm⁻¹. Further, they were confirmed by 1H NMR spectra, where aldehydic proton disappeared and the vinylic proton resonated in the region δ 7.60-7.92 as a singlet. The compounds were further confirmed by the
mass spectral data. This series of compounds is characterized by the presence of one carbon atom spacer between thiazolidine-2,4-dione moiety and fused heterocyclic ring.

Newly synthesized compounds were analyzed for their C, H and N compositions and the values are within the allowed limits. Analytical and spectral data for all the compounds is given in the experimental part of this chapter.

All the newly synthesized compounds described in this chapter were screened for their antibacterial, antifungal, euglycemic and hypolipidemic activities.
1. Preparation of 1,3-thiazolidine-2,4-dione:

To the ethanolic solution of thiourea (20g, 0.26mol) was added ethylchloroacetate (32.2g, 0.26mol) slowly over a period of 30 mins and mixture was refluxed for 3 hrs. The reaction mixture was allowed to cool to room temperature. The hydrochloride salt of 4-thiazolidinone or pseudohydantoin was added to water and neutralized with solution of sodium acetate, 4-thiazolidinone crystallizes out on cooling. The product was filtered and dried. Colorless crystals, yield 80%, m.p. 253-255°C (lit.35 255-258°C).

4-Thiazolidinone was hydrolysed by refluxing with 2N hydrochloric acid in ethanol for 30 hrs. The reaction mixture was cooled and neutralized with aqueous sodium bicarbonate solution. After two days, the crude product thiazolidine-2,4-dione was separated as crystals, which were separated by filtration, washed with water and recrystallized from ethanol water (40:60) mixture as colorless cubic crystals. Yield: 70%, m.p. 121-123°C (lit.36 122-124°C).

2. Synthesis of 2-Amino-5-(4-methoxybenzyl)-1,3,4-thiadiazole (2)

General method: A mixture of 4-methoxyphenylacetic acid (16.7 g; 0.1mol) and thiosemicarbazide (9.113g, 0.1mol) in phosphorous oxychloride (30 mL) was refluxed gently for 45 min. The reaction mixture was cooled and quenched (highly exothermic) with cold water (90 mL). The resulting solution was refluxed for additional 4 hrs and filtered hot. The filtrate was cooled and basified with aqueous potassium hydroxide solution. The solid that separated was filtered, washed with water, dried and recrystallized from ethanol, m.p. 195-197°C. (Lit. 196°C)37

In the similar way 2-amino-5-(4-fluorobenzyl)-1,3,4-thiadiazole (19) & 5-thiophen-2-ylmethyl-[1,3,4]thiadiazol-2-ylamine (20) were synthesized from 4-fluorophenylacetic acid & 2-thiopheneacetic acid respectively.

3. Synthesis of 2-(4-alkyl/aryl)-6-arylimidazo[2,1-b][1,3,4]thiadiazoles : (28f-29h)

General method: A mixture of equimolar quantities of 2-amino-5-(4-aryl)-1,3,4-thiadiazole (0.01 mol) and bromoacetyl compound (0.01 mol) was refluxed in dry ethanol for 18 hrs. The excess of solvent was distilled off and the solid...
hydrobromide salt that separated was collected by filtration, suspended in water and neutralized by aqueous sodium carbonate solution to get free base. It was filtered, washed with water, dried and recrystallized from suitable solvent.

2-(4-Fluoro-benzyl)-6-p-tolyl-imidazo[2,1-b][1,3,4]thiadiazole (28f)

Brown crystalline Solid (ethanol), yield 75%, m.p. 168-170°C; IR (KBr) cm⁻¹: 3124, 2923, 2853, 1602, 1507; ¹H NMR (300MHz, CDCl₃) δ: 2.38 (s, 3H, CH₃), 4.29 (s, 2H, CH₂), 7.06-7.44 (m, 6H, Ar-H), 7.83 (d, J=7.2Hz, 2H, Ar-H), 7.98 (s, 1H, C₅-H, imidazole). Anal. calcd. for C₁₈H₁₄FN₃S: C, 66.85; H, 4.36; N, 12.99. Found: C, 66.81; H, 4.32; N, 12.92%. (Appendices, Spectrum No. 35 & 36).

3-[2-(4-Fluoro-benzyl)-imidazo[2,1-b][1,3,4]thiadiazol-6-yl]-4a,8a-dihydrochromen-2-one (28i)

White needles (ethanol), yield 75%, m.p. 151-153°C; IR (KBr) cm⁻¹: 3010, 2834, 2812, 1718, 1610, 1509; ¹H NMR (300MHz, CDCl₃) δ: 4.26 (s, 2H, CH₂), 6.93-7.04 (m, 4H, Ar-H), 7.30 (d, J=7.6Hz, 2H, Ar-H), 7.74 (d, J=8.2Hz, 2H, Ar-H), 8.24 (s, 1H, C₄-H, coumarin), 8.66 (s, 1H, C₅-H, imidazole); Anal. calcd. for C₂₀H₁₄FN₃O₂S: C, 63.31; H, 3.72; N, 11.08. Found: C, 63.30; H, 3.66; N, 11.03%.(Appendices, Spectrum No. 50).

6-Biphenyl-4-yl-2-(4-fluoro-benzyl)-imidazo[2,1-b][1,3,4]thiadiazole (28g)

White solid (ethanol), yield 80%, m.p. 223-225°C; IR (KBr) cm⁻¹: 3015, 2856, 2816, 1604, 1506; ¹H NMR (300MHz, CDCl₃) δ: 4.29 (s, 2H, CH₂), 7.16-7.49 (m, 11H, Ar-H), 7.76 (d, J=7.5Hz, 2H, Ar-H), 7.98 (s, 1H, C₅-H, imidazole). Anal. calcd. for C₂₃H₁₆FN₃S: C, 71.67; H, 4.18; N, 10.90. Found: C, 71.65; H, 4.17; N, 10.83%.
2-(4-Fluoro-benzyl)-6-naphthalen-2-yl-imidazo[2,1-b][1,3,4]thiadiazole (28h)

Yellow crystalline solid (ethanol), yield 64%, m.p. 212-214°C; IR (KBr) v cm⁻¹: 3107, 2924, 2854, 1603, 1524, 1501; ¹H NMR (300MHz, CDCl₃) δ: 4.31 (s, 2H, CH₂), 7.09-7.66 (m, 10H, Ar-H), 8.1 (s, 1H, C₅-H, imidazole), 8.31 (s, 1H, C₆-H, naphthalene). Anal. calcd. for C₂₁H₁₄FN₃S: C, 70.18; H, 3.93; N, 11.69. Found: C, 70.12; H, 3.88; N, 11.68%.

6-Phenyl-2-thiophen-2-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazole (29a)

Brown crystalline Solid (ethanol), yield 75%, m.p. 195-196°C; IR (KBr) v cm⁻¹: 2923, 2853, 1602, 1507; ¹H NMR (300MHz, CDCl₃) δ: 4.39 (s, 2H, CH₂), 7.06-7.44 (m, 6H, Ar-H), 7.83 (d, J=7.2Hz, 2H, Ar-H), 7.98 (s, 1H, C₅-H, imidazole). Anal. Calcd. for C₁₅H₁₁N₃S₂: C, 60.58; H, 3.73; N, 14.13%. Found: C, 60.52; H, 3.74; N, 14.12%.

6-(4-Chloro-phenyl)-2-thiophen-2-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazole (29b)

Shining white needles (ethanol), yield 70%, m.p. 141-142°C; IR (KBr) v cm⁻¹: 3016, 2859, 2817, 1603, 1504; ¹H NMR (300MHz, CDCl₃) δ: 4.39 (s, 2H, CH₂), 7.05-7.42 (m, 5H, Ar-H), 7.64 (d, J=7.3Hz, 2H, Ar-H), 7.96 (s, 1H, C₅-H, imidazole), Anal. Calcd. for C₁₅H₁₀N₃S₂Cl: C, 54.29; H, 3.04; N, 12.66%. Found: C, 54.27; H, 3.01; N, 12.65%. (Appendices, Spectrum No.39& 40).

6-(4-Nitro-phenyl)-2-thiophen-2-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazole (29c)

Brown crystalline solid (ethanol), yield 66%, m.p. 212-214°C; IR (KBr) v cm⁻¹: 3107, 2924, 2854, 1603, 1524, 1501; ¹H NMR (300MHz, CDCl₃) δ: 4.51 (s, 2H, CH₂), 7.07-7.39 (m, 5H, Ar-H), 7.91(d, J=8.4Hz, 2H, Ar-H), 8.12 (s, 1H, C₅-H, imidazole). Anal. Calcd. for C₁₅H₁₀N₄O₂S₂: C, 52.67; H, 2.94; N, 16.36%. Found: C, 52.60; H, 2.92; N, 16.38%.
6-(4-Bromo-phenyl)-2-thiophen-2-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazole
(29d)

White needles (ethanol), yield 67%, m.p. 158-160°C; IR (KBr) cm⁻¹: 3013, 2858, 2817, 1601, 1505; ¹H NMR (300MHz, CDCl₃) δ: 4.52(s, 2H, CH₂), 7.24-7.78 (m, 7H, Ar-H), 7.97 (s, 1H, C₅-H Imidazole); Anal. Calcd. for C₁₅H₁₀N₃S₂Br; C, 47.88; H, 2.68; N, 11.17%. Found: C, 47.80 ; H, 2.62; N, 11.18%.
(Appendices, Spectrum No. 41).

6-(4-Methoxy-phenyl)-2-thiophen-2-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazole (29e)

Brown solid (ethanol), yield 74%, m.p. 192-193°C; IR (KBr) cm⁻¹: 3107, 2924, 2854, 1603, 1524, 1501; ¹H NMR (300MHz, CDCl₃) δ: 3.83(s, 3H, OCH₃), 4.51 (s, 2H, CH₂), 7.07-7.39 (m, 5H, Ar-H), 7.91(d, J=8.4Hz, 2H, Ar-H), 7.9 (s, 1H, C₅-H, imidazole). Anal. Calcd. for C₁₆H₁₃N₃OS₂; C, 58.69; H, 4.00; N, 12.83%.Found: C, 58.60 ; H, 4.01; N, 12.82%.

2-Thiophen-2-ylmethyl-6-p-tolyl-imidazo[2,1-b][1,3,4]thiadiazole (29f)

White needles (ethanol), yield 75%, m.p. 161-163°C; IR (KBr) cm⁻¹: 2834, 2812, 1610, 1509; ¹H NMR(300MHz, CDCl₃) δ: 2.38(s, 3H, CH₃), 4.45(s, 2H, CH₂), 6.90-7.71 (m, 7H, Ar-H), 7.98 (s, 1H, C₅-H imidazole); Anal. Calcd. for C₁₆H₁₃N₃S₂; C, 61.71; H, 4.21; N, 13.49%. Found: C, 61.70 ; H, 4.20; N, 13.42%.

6-Biphenyl-4-yl-2-thiophen-2-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazole (29g)

White solid (ethanol), yield 80%, m.p. 223-225°C; IR (KBr) cm⁻¹: 2856, 2816, 1604, 1506; ¹H NMR (300MHz, CDCl₃) δ: 4.39 (s, 2H, CH₂), 7.06-7.69 (m, 10H, Ar-H), 7.76 (d, J=7.5Hz, 2H, Ar-H), 7.98 (s, 1H, C₅-H, imidazole). Anal. calcd. for C₂₁H₁₅N₃S₂; C, 67.53; H, 4.05; N, 11.25. Found: C, 67.51; H, 4.07; N, 11.23%.
6-Naphthalen-2-yl-2-thiophen-2-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazole (29h)

Colorless solid (ethanol), yield 64%, m.p. 212-214°C; IR (KBr) \( \nu \text{cm}^{-1} \): 2924, 2854, 1603, 1524, 1501; \(^1\)H NMR (300MHz, CDCl\(_3\)) \( \delta \): 4.31 (s, 2H, CH\(_2\)), 7.09-7.86 (m, 9H, Ar-H), 8.1 (s, 1H, C\(_2\)-H, imidazole), 8.31 (s, 1H, C\(_1\)-H, naphthalene). Anal. calcd. for C\(_{19}\)H\(_{13}\)N\(_3\)S\(_2\): C, 65.68; H, 3.77; N, 12.09. Found: C, 65.62; H, 3.78; N, 12.08%.

4. Synthesis of 2-(4-alkyl/aryl)-6-arylimidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehydes: (7a-g, 30f-31f)

The procedure for the synthesis of required imidazothiadiazole carbaldehydes is given in chapter-III (page No.65).

2-(4-fluoro-benzyl)-6-\(p\)-tolyl-imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (30f)

Brown solid (Chloroform), Yield 90%, m.p.165°C; IR (KBr) \( \nu \text{cm}^{-1} \): 2923, 1512, 1683; \(^1\)H NMR (300MHz, CDCl\(_3\)) \( \delta \): 2.23 (s, 3H, CH\(_3\)), 4.41 (s, 2H, CH\(_2\)), 6.9-7.84 (m, 8H, Ar-H), 10.02 (s, 1H, CHO); Anal. Calcd. for C\(_{13}\)H\(_{14}\)FN\(_3\)O\(_3\)S; C, 64.94; H, 4.02; N, 11.96%. Found: C, 64.90; H, 4.01; N, 11.91%. (Appendices, Spectrum No.37& 38).

2-(4-fluoro-benzyl)-6-(2-oxo-4a,8a-dihydro-2H-chromen-3-yl)-imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (30i)

White needles (ethanol), yield 86%, m.p. 175-176°C; IR (KBr) \( \nu \text{cm}^{-1} \): 2834, 2923, 1712, 1678, 1513; \(^1\)H NMR (300MHz, CDCl\(_3\)) \( \delta \): 4.4 (s, 2H, CH\(_2\)), 6.93-7.04 (m, 4H, Ar-H), 7.30 (d, \( =7.6\text{Hz}, 2\text{H, Ar-H} \)), 7.74 (d, \( J=8.2\text{Hz}, 2\text{H, Ar-H} \)), 8.34 (s, 1H, C\(_4\)-H, coumarin), 10.20 (s, 1H, CHO); Anal. calcd. for C\(_{21}\)H\(_{14}\)FN\(_3\)O\(_3\)S: C, 61.91; H, 3.46; N, 10.31. Found: C, 61.90; H, 3.41; N, 10.30%. (Appendices, Spectrum No.43& 44).
6-phenyl-2-thiophen-2-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (31a)

Brown crystalline Solid (chloroform), yield 75%, m.p.195-196°C; IR (KBr) vcm⁻¹: 2923, 2853, 1678, 1507; ¹H NMR (300MHz, CDCl₃) δ: 4.39 (s, 2H, CH₂), 7.06-7.44 (m, 6H, Ar-H), 7.83 (d, J=7.2Hz, 2H, Ar-H), 10.03(s, 1H, CHO).

Anal. Calcd. for C₁₆H₁₁N₃O₅S₂; C, 59.06; H, 3.41; N, 12.91%. Found: C, 59.00 ; H, 3.40; N, 12.92%.

6-(4-chloro-phenyl)-2-thiophen-2-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (31b)

Brown Solid (chloroform), yield 70%, m.p. 141-142°C; IR (KBr) vcm⁻¹: 2859, 2817, 1675, 1504; ¹H NMR (300MHz, CDCl₃) δ: 4.39 (s, 2H, CH₂), 7.05-7.42 (m, 5H, Ar-H), 7.64 (d, J=7.3Hz, 2H, Ar-H), 10.02(s, 1H, CHO).

Anal. Calcd. for C₁₆H₁₀N₃S₂OCl; C, 53.40; H, 2.80; N, 11.68%. Found: C, 53.37 ; H, 2.81; N, 11.62%.

6-(4-nitro-phenyl)-2-thiophen-2-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (31c)

Brown crystalline solid (chloroform), yield 66%, m.p. 212-214°C; IR (KBr) vcm⁻¹: 2924, 2854, 1671, 1524, 1501; ¹H NMR (300MHz, CDCl₃) δ: 4.31 (s, 2H, CH₂), 7.07-7.89 (m, 7H, Ar-H), 10.24(s, 1H, CHO).

Anal. Calcd. for C₁₆H₁₀N₃O₅S₂; C, 51.88; H, 2.72; N, 15.13%. Found: C, 51.81 ; H, 2.71; N, 15.10%.

6-(4-bromo-phenyl)-2-thiophen-2-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (31d)

Brown Solid (chloroform), yield 67%, m.p. 188-190°C; IR (KBr) vcm⁻¹: 2858, 2817, 1676, 1505; ¹H NMR (300MHz, CDCl₃) δ: 4.53 (s, 2H, CH₂), 7.24-7.78 (m, 7H, Ar-H), 10.02 (s, 1H, CHO).

Anal. Calcd. for C₁₆H₁₀BrN₃OS₂; C, 47.53; H, 2.49; N,10.39%. Found: C, 47.50 ; H, 2.46; N, 10.38%.

(Appendices, Spectrum No. 42).
6-(4-methoxy-phenyl)-2-thiophen-2-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (31e)

Brown solid (chloroform), yield 74%, m.p. 212-214°C; IR (KBr) v cm⁻¹: 2924, 2854, 1678, 1524, 1501; ¹H NMR (300MHz, CDCl₃) δ: 3.83 (s, 3H, OCH₃), 4.31 (s, 2H, CH₂), 7.07-7.79 (m, 7H, Ar-H), 10.02 (s, 1H, CHO). Anal. Calcd. for C₁₇H₁₃N₃O₂S₂: C, 57.45; H, 3.69; N, 11.82%. Found: C, 57.42; H, 3.68; N, 11.80%.

2-thiophen-2-ylmethyl-6-p-tolyl-imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (31f)

Brown needles (chloroform), yield 75%, m.p. 201-202°C; IR (KBr) v cm⁻¹: 2834, 2812, 1673, 1509; ¹H NMR (300MHz, CDCl₃) δ: ¹H NMR (300MHz, CDCl₃) δ: 2.38 (s, 3H, CH₃), 4.25 (s, 2H, CH₂), 6.90-7.71 (m, 7H, Ar-H), 10.02 (s, 1H, CHO); Anal. Calcd. for C₁₇H₁₃N₃O₂S₂: C, 60.15; H, 3.86; N, 12.38%. Found: C, 60.11; H, 3.83; N, 12.36%.

5. Synthesis of 5-[[2-(4-alkyl/aryl)-6-arylimidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene]-1,3-thiazolidine-2,4-dione. (32a-34f)

**General method:** A mixture of 2-alkyl/aryl-6-arylimidazo[2,1-b][1,3,4] thiadiazole-5-carbaldehyde (0.001mol) and 1,3-thiazolidine-2,4-dione (0.001mol) was refluxed in toluene (25mL) with catalytic amount of piperidine-acetate for 2 hrs. The yellow solid was collected by filtration, washed with hot benzene and methanol. The products were recrystallized from dimethylformamide.

5-[2-(4-methoxybenzyl)-6-phenylimidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene] thiazolidine-2,4-dione (32a).

Yellow granules (DMF), yield 95%, m.p. 295-296°C; IR (KBr) v cm⁻¹: 3016, 2859, 2817, 1722, 1603, 1504; ¹H NMR (300MHz, DMSO, d₆) δ: 3.83 (s, 3H, OCH₃), 4.34 (s, 2H, CH₂), 7.31-7.76 (m, 7H,
Ar-H), 7.88 (d, J=7.6 Hz, 2H, Ar-H), 7.96 (s, 1H, vinylic proton), 12.20 (s, 1H, NH, D₂O exchangeable), Anal. calcd. For C₂₂H₁₆N₄O₃S₂: C, 58.91; H, 3.60; N, 12.49. Found: C, 58.89; H, 3.60; N, 12.46%.

(Appendices; Spectrum No. 45, 46 & 47).

5-[(6-(4-chlorophenyl)-2-(4-methoxy benzyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl methylene]thiazolidine-2,4-dione (32b).

Yellow granules (DMF), yield 90%, m.p. >300°C; IR (KBr) cm⁻¹: 3016, 2859, 2817, 1725, 1603, 1504; ¹H NMR (300 MHz, DMSO, d₆) δ: 3.83 (s, 3H, OCH₃), 4.46 (s, 2H, CH₂), 7.54-7.81 (m, 6H, Ar-H), 7.90 (d, J=7.9 Hz, 2H, Ar-H), 7.92 (s, 1H, vinylic proton), 12.21 (s, 1H, NH, D₂O exchangeable). Anal. calcd. for C₂₂H₁₅ClN₄O₃S₂: C, 54.71; H, 3.13; N, 11.60. Found: C, 54.70; H, 3.12; N, 11.52%.

5-[2-(4-methoxybenzyl)-6-(4-nitrophenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl methylene]thiazolidine-2,4-dione (32c).

Bright yellow granules (DMF), yield 93%, m.p. >300°C; IR (KBr) cm⁻¹: 3425, 2928, 2853, 1726, 1694, 1606, 1508; ¹H NMR (300 MHz, DMSO, d₆) δ: 3.83 (s, 3H, OCH₃), 4.47 (s, 2H, CH₂), 7.41-8.12 (m, 7H, Ar-H & vinylic proton), 8.29 (d, J=8.1 Hz, 2H, Ar-H) 12.03 (s, 1H, NH, D₂O exchangeable). Anal. calcd. for C₂₂H₁₅N₅O₅S₂: C, 53.54; H, 3.06; N, 14.19. Found: C, 53.43; H, 3.05; N, 14.11%.

5-[6-(4-bromophenyl)-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl methylene]thiazolidine-2,4-dione (32d).

Yellow granules (DMF), yield 89%, m.p. 279-281°C; IR (KBr) cm⁻¹: 3430, 2925, 2854, 1727, 1696, 1607, 1509; ¹H NMR (300 MHz, DMSO, d₆) δ: 3.83 (s, 3H, OCH₃), 4.52 (s, 2H, CH₂), 7.18-7.72 (m, 9H, Ar-H & vinylic proton), 12.21 (s, 1H, NH,
Chapter-VI

D$_2$O exchangeable). Anal. calcd. for C$_{22}$H$_{13}$BrN$_4$O$_3$S$_2$: C, 50.10; H, 2.87; N, 10.62. Found: C, 50.07; H, 2.81; N, 10.60%.

5-[2-(4-methoxybenzyl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl methylene]thiazolidine-2,4-dione (32e).

Bright yellow granules (DMF), yield 89%, m.p. 285-287°C; IR (KBr) νcm$^{-1}$: 3429, 2923, 2851, 1724, 1694, 1605, 1506; $^1$H NMR (300MHz, DMSO, $d_6$) δ: 3.92 (s, 6H, OCH$_3$), 4.41 (s, 2H, CH$_2$), 7.17-7.69 (m, 6H, Ar-H), 7.56 (d, $J$=7.3Hz, 2H, Ar-H), 7.81 (s, 1H, vinylic proton), 12.2 (s, 1H, NH, D$_2$O exchangeable). Anal. calcd. for C$_{23}$H$_{18}$N$_4$O$_3$S$_2$: C, 57.73; H, 3.79; N, 11.71. Found: C, 57.71; H, 3.72; N, 11.70%.

5-[2-(4-methoxybenzyl)-6-(4-methylphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl methylene]thiazolidine-2,4-dione (32f).

Bright yellow granules (DMF), yield 91%, m.p. 280-281°C; IR (KBr) νcm$^{-1}$: 3429, 2923, 2851, 1724, 1694, 1605, 1506; $^1$H NMR (300MHz, DMSO, $d_6$) δ: 2.38 (s, 3H, CH$_3$), 3.90 (s, 3H, OCH$_3$), 4.41 (s, 2H, CH$_2$), 7.17-7.69 (m, 6H, Ar-H), 7.56 (d, $J$=7.3Hz, 2H, Ar-H), 7.81 (s, 1H, vinylic proton), 12.2 (s, 1H, NH, D$_2$O exchangeable). Anal. calcd. for C$_{23}$H$_{18}$N$_4$O$_3$S$_2$: C, 59.72; H, 3.92; N, 12.11. Found: C, 59.71; H, 3.89; N, 12.10%.

5-[2-(4-fluorobenzyl)-6-`$p$`-tolyl-imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene]thiazolidine-2,4-dione (33f).

Yellow granules (DMF), yield 95%, m.p. 295-296°C; IR (KBr) νcm$^{-1}$: 3016, 2859, 2817, 1722, 1603, 1504; $^1$H NMR (300MHz, DMSO, $d_6$) δ: 2.34 (s, 3H, CH$_3$), 4.34 (s, 2H, CH$_2$), 7.31-7.76 (m, 6H, Ar-H), 7.88 (d, $J$=7.6Hz, 2H, Ar-H), 7.96 (s, 1H, vinylic proton), 12.20 (s, 1H, NH, D$_2$O exchangeable). Anal. calcd. For C$_{22}$H$_{13}$FN$_4$O$_3$S$_2$: C, 58.65; H, 3.36; N, 12.44. Found: C, 58.63; H, 3.32; N, 12.41%.

132
5-[2-(4-fluoro-benzyl)-6-(2-oxo-4a,8a-dihydro-2H-chromen-3-yl)-imidazo[2,1-
b][1,3,4]thiadiazol-5-ylmethylene]-thiazolidine-2,4-dione (33i).

Yellow granules (DMF), yield 85%, m.p. >300°C; IR (KBr) vcm⁻¹: 3016, 2859, 2817, 1722, 1603, 1504; ¹H NMR (300MHz, DMSO, d₆) δ: 4.4 (s, 2H, CH₂), 6.93-7.04 (m, 4H, Ar-H), 7.30 (d, J=7.6Hz, 2H, Ar-H), 7.74 (d, J= 8.2Hz, 2H, Ar-H), 7.96 (s, 1H, vinylic proton), 8.34 (s, 1H, C₄-H, coumarin), 12.24 (s, 1H, NH, D₂O exchangeable). Anal. calcd. for C₂₄H₁₅FN₄O₄S₂: C, 56.91; H, 2.98; N, 11.06. Found: C, 56.90; H, 2.91; N, 11.01%.

5-(6-phenyl-2-thiophen-2-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazol-5-yl methylene)-thiazolidine-2,4-dione (34a).

Yellow granules (DMF), yield 95%, m.p. 275-276°C; IR (KBr) vcm⁻¹: 3016, 2859, 2817, 1722, 1603, 1504; ¹H NMR (300MHz, DMSO, d₆) δ: 4.34 (s, 2H, CH₂), 7.31-7.76 (m, 6H, Ar-H), 7.88(d, J=7.6Hz, 2H, Ar-H), 7.96 (s, 1H, vinylic proton), 12.20 (s, 1H, NH, D₂O exchangeable), Anal. calcd. for C₁₉H₁₂N₄O₂S₃: C, 53.76; H, 2.85; N, 13.20. Found: C, 53.72; H, 2.80; N, 13.18%.

5-[6-(4-chloro-phenyl)-2-thiophen-2-ylmethyl-imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene]-thiazolidine-2,4-dione (34b).

Yellow granules (DMF), yield 90%, m.p. >300°C; IR (KBr) vcm⁻¹: 3016, 2859, 2817, 1725, 1603, 1504; ¹H NMR (300MHz, DMSO, d₆) δ: 4.46 (s, 2H, CH₂), 7.54-7.81 (m, 5H, Ar-H), 7.90 (d, J=7.9Hz, 2H, Ar-H), 7.92 (s, 1H, vinylic proton), 12.03 (s, 1H, NH, D₂O exchangeable). Anal. calcd. for C₁₉H₁₁ClN₄O₂S₃: C, 49.72; H, 2.42; N, 12.21. Found: C, 49.70; H, 2.42; N, 12.19%.
5-[(4-nitro-phenyl)-2-thiophen-2-ylmethy1-imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene]-thiazolidine-2,4-dione (34c).

Bright yellow granules (DMF), yield 93%, m.p. >300°C; IR (KBr) v cm⁻¹: 3425, 2928, 2853, 1726, 1694, 1606, 1508; ¹H NMR (300MHz, DMSO, d₆) δ: 4.47 (s, 2H, CH₂), 7.41-8.12 (m, 7H, Ar-H & vinylic proton), 12.23 (s, 1H, NH, D₂O exchangeable). Anal. calcd. for C₁₉H₁₁N₈S₃: C, 48.60; H, 2.36; N, 14.92. Found: C, 48.63; H, 2.35; N, 14.91%.

5-[(4-bromo-phenyl)-2-thiophen-2-ylmethy1-imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene]-thiazolidine-2,4-dione (34d).

Yellow granules (DMF), yield 89%, m.p. 290-291°C; IR (KBr) v cm⁻¹: 3430, 2925, 2854, 1727, 1696, 1607, 1509; ¹H NMR (300MHz, DMSO, d₆) δ: 4.52 (s, 2H, CH₂), 7.18-7.72 (m, 7H, Ar-H), 7.80 (s, 1H, vinylic proton), 12.21 (s, 1H, NH, D₂O exchangeable). Anal. calcd. for C₁₉H₁₁BrN₈S₃: C, 45.33; H, 2.20; N, 11.13. Found: C, 45.27; H, 2.21; N, 11.10%.

5-[(4-methoxy-phenyl)-2-thiophen-2-ylmethy1-imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene]-thiazolidine-2,4-dione (34e).

Bright yellow granules (DMF), yield 89%, m.p. 281-282°C; IR (KBr) v cm⁻¹: 3429, 2923, 2851, 1724, 1694, 1605, 1506; ¹H NMR (300MHz, DMSO, d₆) δ: 3.92 (s, 3H, OCH₃), 4.41 (s, 2H, CH₂), 7.17-7.69 (m, 5H, Ar-H), 7.56 (d, J=7.3Hz, 2H, Ar-H), 7.81 (s, 1H, vinylic proton), 12.2 (s, 1H, NH, D₂O exchangeable). Anal. calcd. for C₂₀H₁₄N₄O₃S₃: C, 52.85; H, 3.10; N, 12.33. Found: C, 52.81; H, 3.12; N, 12.30%.
5-(2-thiophen-2-ylmethyl-6-\(\beta\)-tolyl-imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene)-thiazolidine-2,4-dione (34f).

Bright yellow granules (DMF), yield 91%, m.p. 270-271°C; IR (KBr) \(\text{cm}^{-1}\): 3429, 2923, 2851, 1724, 1694, 1605, 1506; \(^1\)H NMR (300MHz, DMSO, \(d_6\)) \(\delta\): 2.38 (s, 3H, \(\text{CH}_3\)), 4.41 (s, 2H, \(\text{CH}_2\)), 7.17-7.69 (m, 5H, Ar-H), 7.56 (d, \(J=7.3\text{Hz}\), 2H, Ar-H), 7.81(s, 1H, vinylic proton), 12.2 (s, 1H, NH, D\(_2\)O exchangeable). Anal. calcd. for C\(_{20}\)H\(_{14}\)N\(_4\)S\(_3\): C, 54.77; H, 3.22; N, 12.78. Found: C, 54.71; H, 3.20; N, 12.73%. 

Chapter-VI

5-(2-thiophen-2-ylmethyl-6-\(\beta\)-tolyl-imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene)-thiazolidine-2,4-dione (34f).

Bright yellow granules (DMF), yield 91%, m.p. 270-271°C; IR (KBr) \(\text{cm}^{-1}\): 3429, 2923, 2851, 1724, 1694, 1605, 1506; \(^1\)H NMR (300MHz, DMSO, \(d_6\)) \(\delta\): 2.38 (s, 3H, \(\text{CH}_3\)), 4.41 (s, 2H, \(\text{CH}_2\)), 7.17-7.69 (m, 5H, Ar-H), 7.56 (d, \(J=7.3\text{Hz}\), 2H, Ar-H), 7.81(s, 1H, vinylic proton), 12.2 (s, 1H, NH, D\(_2\)O exchangeable). Anal. calcd. for C\(_{20}\)H\(_{14}\)N\(_4\)S\(_3\): C, 54.77; H, 3.22; N, 12.78. Found: C, 54.71; H, 3.20; N, 12.73%. 

Chapter-VI

5-(2-thiophen-2-ylmethyl-6-\(\beta\)-tolyl-imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene)-thiazolidine-2,4-dione (34f).
REFERENCES

1. Jr. D. Porte, M.W. Schwartz, 

2. The diabetes Control and complications, Trial Research Group, 

3. W.L. Isley, 

4. UK Prospective Diabetes Study Group, 

5. A. Melander, P.O. Bitzen, O. Faber, L. Groop, 


7. T. Sohda, K. Mizuno, Y. Sugiyama, T. Fujita and Y. Kawamatsu, 

8. O. G. Kolterman, R. S. Gravy, J. Griffin, P. Burstein, J. Insel, J.A. Scarlett and J.M. Olefsky, 


10. a) T. Sodha, K. Mizuno, H. Tawada, Y. Sugiyama, T. Fujita and Y. Kawamatsu, 

    b) T. Shoda, K. Mizuno, E. Imamiya, Y. Sugiyama, T. Fujita and Y. Kawamatsu, 

    c) T. Shoda, K. Mizuno and Y. Kawamatsu, 

11. a) T. Yoshioka, T. Fujata, T. Kanai, Y. Aizawa, T. Kurumada, K. Hasegawa and H. Horikoshi, 

     b) T. Fujiwara, A. Okuno, S. Yoshioka and Horikoshi, 

Chapter VI


17. a) G. D. Kolavi, Ph.D Thesis (2005), Karnataka University, Dharwad
    b) V. S. Hegde, Ph.D Thesis (2006), Karnataka University, Dharwad


Chapter-VI


