INTRODUCTION

The imidazo[2,1-b][1,3,4]thiadiazoles is a rapidly growing and increasingly important class of heterocyclic compounds. In the previous chapters we have highlighted the synthesis of various derivatives and their biological properties. Consequently work on imidazothiadiazoles has resulted in some biologically potent molecules. Moreover 5-formyl imidazo[2,1-b][1,3,4]thiadiazoles are synthetically versatile molecules with reactive carbonyl group towards nucleophiles allowing the synthesis of wide variety of heterocycles, which are of considerable pharmacological significance. There are numerous examples in the literature, wherein coupling of biologically important heterocycles with each other have resulted in biologically active lead compounds.

In continuation of our work in this direction, the present chapter comprises the condensation of methoxy containing formyl imidazothiadiazoles to the active methylene compounds like thiohydantoin & barbituric acid.

Herein we have given a brief note on the interesting biological/pharmacological importance of thiohydantoins & barbituric acid derivatives as background information.

Thiohydantoins are sulfur analogs of hydantoins with one or both carbonyl groups replaced by thiocarbonyl groups. Among the known thiohydantoins, 2-thiohydantoins are most notably known due to their hypolipidemic, anticarcinogenic, antimitagenic, antithyroidal, antiviral (e.g., against herpes simplex virus, HSV), human immune-deficiency virus (HIV), tuberculosis, antimicrobial, anti-ulcer and anti-inflammatory activities as well as pesticides. Additionally 2-thiohydantoins have been used as reference standards for the development of C-terminal protein sequencing as reagents for the development of dyes, textile printing, metal cation complexation and polymerization catalysis.

Joshi et al. have synthesized the thiohydantoins containing benzothiophene moiety and the compounds were screened for their antimicrobial and antitubercular activities.
Christa. E. Muller et al.\textsuperscript{16} have synthesized the thiohydantoin derivatives and investigated in radiobinding ligand studies of GABA\textsubscript{A} receptors in rat brain cortical membranes.

\[
\begin{align*}
\text{Z} &= \text{CH, N, R}^6 = 2-\text{Cl, 2-F, 2-Br, R}^7 = \text{H, R}^8 = \text{H} \\
\end{align*}
\]

Various thiohydantoins of 3-formyl chromones have been reported by Youssef Lotfy Aly.\textsuperscript{17}

David Thomas et al.\textsuperscript{18} have reported the synthesis of thiohydantoin derivatives (I, II& III) and the compounds were screened for their anti-inflammatory and antiallergic activities.

Khodair et al.\textsuperscript{19} have synthesized the compounds of following type (I & II) by condensation of 2-thiohydantoin derivatives with naphthaldehyde. Bisglycosylation took place on reaction of I with glycosyl halides under alkaline conditions. This hydantoin glycosyl halides when tested showed significant activity against HIV & HSV.
Zhang et al. applied fluorous tagging strategy to solution-phase parallel synthesis of a library containing hydantoin and thiohydantoin analogs.

Fluorous synthesis of hydantoin / thiohydantoin analogues

O. V. Bakbardina et al. synthesized a series of pseudo-thiohydantoins and their 5-arylidene derivatives. Reactions of acid hydrolysis of pseudo-thiohydantoins with the formation of the corresponding 5-arylidene-3-aminothiazolid-2,4-one hydrochlorides have been performed. The antifungal activity of the synthesized compounds has been evaluated.

Romashkina et al. self-organized monolayers (SOMs) of 2-thiohydantoins on gold modified with lipoic acid esters using contact angle measurements. The feasibility of complexing SOMs with cobalt (II) ions was demonstrated. Optimal parameters were determined for generating surface metal complexes on gold.

Balya et al. synthesized new 2,5-diamino-1,3-thiazole and 2-Thiohydantoin derivatives by condensation of N-(2-Aryl-1-chloro-2-oxoethyl) carboxamides with thioureas.

The thiohydantoin system possesses reactive sites which can be suitably modified by the introduction of different heterocyclic moieties to yield the potent COX-1/COX-2 inhibitors. Bearing this in mind, twelve new fused compounds containing isoxazole and pyrazole moieties were synthesized by Dabholkar and Ansari et al. in order to act as active pharmaceutical agents.
Luis et al.\textsuperscript{25} synthesized new Imidazolidin-2,4-dione and 2-Thioximidazolidin-4-ones \textit{via} C-Phenylglycine derivatives. Focus of this study was to investigate the acute cardiovascular effects induced by IM-7 in rats. In addition, the effects of 5-(4-ethylphenyl)-3-phenylimidazolidin-2,4-dione on the Central Nervous System was investigated.

\[
\begin{align*}
\text{X= O, S} & \quad \text{R= Me, OMe, Et}
\end{align*}
\]

Ashraf H. Abadi \textit{et al.}\textsuperscript{26} investigated the synthesis, molecular modeling, and biological evaluation of novel Tetrahydro-\(\beta\)-carboline hydantoin and Tetrahydro-\(\beta\)-Carboline Thiohydantoin derivatives as Phosphodiesterase 5 Inhibitors.

\[
\begin{align*}
tetrahydro-\beta\text{-carboline thiohydantoin}
\end{align*}
\]

M. M. Ghanbari \textit{et al.}\textsuperscript{27} investigated that the adducts produced in the reaction between trialkyl phosphites and acetylenic esters were trapped by thiohydantoins to produce highly functionalized 5-oxo-2-thioxo imidazolidines and 4,5-dihydro-2-(methylthio)-5-oxoimidazoles.

Barbituric acid derivatives\textsuperscript{28,29} have occupied special place in the field of pharmaceutical chemistry, they produce an inhibiting action on the central nervous system and are widely used in medicine as calming, hypnotic, and anticonvulsant drugs.\textsuperscript{30} In clinics, these compounds are employed for the treatment of epilepsy, chorea and spastic paralysis.\textsuperscript{31,32} More recently there are reports on its applications as anticancer and antisteoporosis agents.
Barbituric acid is a versatile lead molecule for designing potential bioactive agents. A large number of 5-substituted barbituric acid derivatives have been reported to exhibit a broad spectrum of biological activities like anticonvulsant, anaesthetic, antiparkinsonian, sedative, and hypnotic activities. Barbital sodium and barbamyl – drugs belonging to the group of barbituric acid derivatives – are of interest as compound producing rapid pharmacological effect. These substances are readily dissolved and rapidly absorbed in the gastrointestinal tract. However, both barbital sodium and barbamyl are characterized by pronounced toxicity leading to inhibition of the cerebral cortex, suppression of the respiratory center and cardiac activity, toxic damage of cerebral capillaries, and a strong hypotensive effect.

M. Guzman-Chozas et al. investigated the synthesis, purification, elemental analysis, and spectroscopic studies to characterize the structure of the red adduct 2:1 thiobarbituric acid (TBA)-malonaldehyde involved in the evaluation of oxidative rancidity in fats and oils.

A. P. Arzamastsev et al. presented a review suggesting methods for the analysis and standardization of drugs belonging to the class of barbituric acid derivatives.

S. A. Andronati et al. synthesized and analysed 5-HT\textsubscript{1A} receptor affinity of arylpiperazinylbutyl derivatives of 5,5-disubstituted barbituric acid. The purpose of this study was to synthesize new phenylbutylpiperazine derivatives containing residues of disubstituted barbituric acids in the N-terminal fragment, and characterize the affinity of the new compounds to 5-HT\textsubscript{1A} receptors.

E. A. Mamina & V. V. Bolotov et al. done the analysis of barbituric acid derivatives in biological objects. The aim of this study was to select the optimum conditions for the extraction of poisons belonging to barbituric acid derivatives from the tissues of cadaveric liver, since liver is the organ involved in the localization and detoxication of poisons.

B. B. Semenov et al. synthesised indole-containing 2-thiobarbituric acid derivatives. This study was aimed at the synthesis of barbituric acid derivatives containing α-phenylskatyl residues substituted at C(5) position to obtain a series of 2-thio barbituric acid derivatives, which are expected to possess antioxidant, membrane protector, and radioprotector properties.
Krasnov, Kartsev et al.\textsuperscript{43} synthesised the spiroheterocyclic systems from barbituric acids and $n,n$-disubstituted $o$-aminobenzaldehydes.

Synthesis and biological evaluation of some new spiro derivatives of barbituric acid been analyzed by Shailee Kesharwani et al.\textsuperscript{44}. All the synthesized compounds were screened \textit{in vivo} for their anticonvulsant activity and acute toxicity. All the synthesized compounds were evaluated for the phenobarbitone-induced hypnosis potentiation test. All tested compounds showed sedative-hypnotic and anticonvulsant activity, but spiro compounds were the most potent sedative hypnotic and anticonvulsant agents.

\textbf{Spiro-azepines}

J. M. Khurana, K. Vij et al.\textsuperscript{45} synthesized range of biologically important arylidene barbiturates by the knoevenagel condensation of aromatic aldehydes with barbituric acids and 2-thiobarbituric acids in the presence of polyvinyl pyrrolidone (PVP) stabilized Ni nanoparticles in ethylene glycol.
Maghsoodlou et al.\(^{46}\) synthesized the 5-aryl-1,3-dimethyl-6-(alkyl- or aryl-amino) furo [2,3-\(d\)]pyrimidine derivatives by reaction between isocyanides and pyridinecarbaldehydes in the presence of 1,3-dimethylbarbituric acid without any prior activation or modifications.

Badiger et al.,\(^ {47}\) synthesized 5-[6-aryl-2-(4-methoxybenzyl)imidazo[2,1-b] [1,3,4] thiaazol-5-yl-methylene]-pyrimidine-2,4,6-triones (2) and 5-[6-aryl-2-(4-methoxy benzyl)imidazo[2,1-b][1,3,4] thiaazol-5-yl]methylene-2-thiooximidazolidin-4-one (1) derivatives from 5-formyl derivatives of 2-(4-methoxybenzyl)-6-aryl imidazo [2,1-b][1,3,4]thiaazole by the knoevenagel condensation with barbituric acid & thiohydantoin. These newly synthesized compounds were screened for their antibacterial and antifungal activities.

Looking to the high degree of bioactivity shown by the compounds and the importance of a foresaid heterocycles, it was thought of interest to construct a system, which combines these biolabile rings with imidazothiadiazoles in a single molecular frame work and to evaluate the additive effects towards their biological activities.
PRESENT WORK:

The synthetic approach followed for the preparation of imidazothiadiazoles is depicted in the following schemes. The work carried out in the present investigation includes preparation of 5-formyl imidazo[2,1-b][1,3,4]thiadiazoles and the Knoevenagel condensation with active methylene compounds.

![Scheme IIa]

Reagents and Conditions:

1. DMF/POCl₃, Na₂CO₃
2. thiohydantoin, sod.acetate, AcOH, reflux
3. barbituric acid, sod.acetate, AcOH, reflux

(Scheme IIb)
The required imidazo[2,1-b][1,3,4]thiadiazoles (3a-g) were prepared as per the procedure described in chapter II. Imidazothiadiazoles were further reacted with DMF and POCl₃ mixture (Vilsmeier Haack reagent) to afford the 5-formyl derivatives 7a-g in good yields.

Formyl imidazothiadiazoles (7a-g) on knoevenagel condensation with thiohydantoins & barbituric acid in acetic acid in presence of fused sodium acetate yielded the respective 5-[6-aryl-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4] thiadiazol-5-yl]methylene-2-thioxoimidazolidin-4-one (8) & 5-[6-aryl-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl-methylene]-pyrimidine-2,4,6-triones (9) derivatives in good yields. Knoevenagel condensation of 6-aryl-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4] thiadiazole-5-carbaldehydes with barbituric acid leads to the formation of novel Pyrimidine-2,4,6-trione derivatives, similarly on condensation with thiohydantoin, the thioxoimidazolidinone derivatives were obtained, thereby creating significant interest in their pharmacological properties.
RESULTS AND DISCUSSION

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 (1) with appropriately substituted α-haloketones (phenacylbromides) in dry ethanol as hydrobromides, which on neutralization with aqueous sodium carbonate gave corresponding free bases in good yields. The absence of $\nu_{N-H}$ band in IR spectra of the resulted compounds confirms the formation of product, which exhibits imidazole (C$_5$-H) proton around $\delta$ 7.95 in $^1$H NMR spectra. The $^{13}$C NMR spectrum of compounds is in total agreement with the structures.

Imidazo[2,1-b][1,3,4]thiadiazoles (3a-g) were further subjected to Vilsmeir Haack reaction, which resulted in the formation of expected imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehydes (7a-g) and were confirmed by their spectral and analytical data. The IR spectra of these compounds displayed the aldehydic carbonyl around 1680 cm$^{-1}$ and $\nu_{C-H}$ around 2850 cm$^{-1}$. The structures were further confirmed by the presence of a signal around $\delta$ 10.00 for aldehydic proton and absence of C$_5$-H of imidazole in the $^1$H NMR spectra. Further $^{13}$C NMR spectra exhibited carbonyl carbon around $\delta$ 181.2 and rest of the carbons resonated in the expected region.

The intermediates were exploited by Knoevenagel condensation with Barbituric acid & Thiohydantoin. The reaction underwent smoothly with excellent yields. The formation of compound was observed in the reaction mixture itself as they come out as intense yellow solid from the clear solution within few minutes. The formation of 5-[6-aryl-2-(4-methoxybenzyl)-imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene]-pyrimidine-2,4,6 triones (9a-f) were confirmed by their IR spectra, which displayed the $\nu_{C=O}$ bands around 1735 and 1698 cm$^{-1}$ & $\nu_{N-H}$ bands around 3186, 3031. Further, they were confirmed by $^1$H NMR spectra, where aldehydic proton disappeared and the vinylic proton resonated in the region $\delta$ 8.40-8.50. Appearance of two N-H protons in the region of 11.03-11.08 & 11.27-11.58 further confirmed the formation of these compounds. Similarly the formation of 5-[6-aryl-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene-2-thioxoidazolidin-4-one (8a-f) were confirmed by their IR spectra, which displayed the $\nu_{C=O}$ bands around 1735 and 1698 cm$^{-1}$. Further, they were confirmed by $^1$H NMR spectra, where aldehydic proton disappeared and the vinylic proton resonated in the region $\delta$ 8.50-8.55. Appearance of two N-H protons in the region of 11.03-11.20 & 11.27-11.58.
further confirmed the formation of these compounds. All the derivatives (8a-f & 9a-f) are having high melting points compared to its starting materials due to formation of rigid and very stable compound. The structures of all the newly synthesized compounds were established by their analytical and spectral data.
EXPERIMENTAL

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

The Synthesis of 1,3,4-thiadiazole (2) is given in chapter-II (page No. 42).

Synthesis of 2-(4-methoxybenzyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazoles (3):

The Synthesis of required imidazothiadiazoles (3) is given in chapter-II (page No. 42).

Synthesis of 2-(4-Methoxybenzyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehydes (7a-g):

**General method; (Vilsmeier Haack reaction):** Vilsmeier Haack reagent was prepared by adding phosphorous oxychloride (3mL) in dimethylformamide (20mL) at 0°C with stirring. At the same temperature 2-(4-Methoxybenzyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazole, 3a-g (0.01mol) was added to the reagent and stirred at 0-5°C for 30 minutes. The mixture was further stirred for 2 hrs at room temperature and then at 60°C for additional 2 hrs. The reaction mixture was cooled in ice water bath and quenched with water(5mL). The reaction mixture was basified with aq. sodium carbonate (10%) solution with cooling and further stirred at 80-90°C for 2 hrs. After cooling, the mixture was diluted with water, extracted with chloroform (30mLx3). The combined extracts were washed with water (100mLx3), dried over anhydrous sodium sulphate. Solvent was removed by evaporation and solid obtained was recrystallized from suitable solvent to afford colorless to pale yellow crystals in excellent yields.

**2-(4-Methoxybenzyl)-6-phenylimidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (7a)**

Colorless solid (Chloroform), Yield 92%, m.p.120-121°C; IR (KBr) v cm⁻¹: 2923, 1512, 1608, 1673; ¹H NMR(300MHz, CDCl₃) δ: 3.83(s, 3H, OCH₃), 4.41(s, 2H, CH₂), 6.9-7.84(m, 9H, Ar-H), 10.04(s ,1H, CHO); ¹³C NMR (75MHz, CDCl₃) δ: 37.80 (OCH₃), 56.2(CH₂),109.6, 128.4, 129.5, 133.6, 169.1, 146.0 & 181.2(CHO); Anal. Calcd. for C₁₉H₁₈N₃O₂S; C, 65.31; H, 4.33; N, 12.03%. Found: C, 65.30 ; H, 4.30; N, 12.0%.

(Appendices; Spectrum No. 9).
6-(4-Chlorophenyl)-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (7b) Colorless flakes (Chloroform), Yield 81%, m.p.122-123°C; IR (KBr) \( \nu \) cm\(^{-1}\); 1683, 2923, 1512, 1611;

\(^1\)HNMR (300MHz, CDCl\(_3\)) \( \delta \): 3.83(s, 3H, OCH\(_3\)), 4.27(s, 2H, CH\(_2\)), 6.92-7.8(m, 8H, Ar-H), 10.06(s, 1H,CHO); \(^13\)C NMR (75MHz, CDCl\(_3\)) \( \delta \): 37.80(OCH\(_3\)), 55.8(CH\(_2\)), 109.6, 128.4, 133.6, 165.1, 146.0 & 180.2(CHO); Anal. Calcd. for C\(_{19}\)H\(_{14}\)N\(_3\)SO\(_2\)Cl; C, 59.45; H, 3.68; N, 10.95%. Found: C, 59.40; H, 3.60; N, 10.91%.

2-(4-Methoxybenzyl)-6-(4-nitrophenyl)imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (7c) Brown solid (Chloroform), Yield 91%, m.p.126-127°C; IR (KBr) \( \nu \) cm\(^{-1}\); 2923, 1512, 1608, 1682;

\(^1\)H NMR (300MHz, CDCl\(_3\)) \( \delta \): 3.83(s, 3H, OCH\(_3\)), 4.40(s, 2H, CH\(_2\)), 6.9 - 8.33 (m, 8H, Ar-H), 10.18(s, 1H,CHO); \(^13\)C NMR (75MHz, CDCl\(_3\)) \( \delta \): 37.80(OCH\(_3\)), 56.2(CH\(_2\)), 109.6, 128.4, 133.6, 169.1, 146.0 & 181.2(CHO); Anal. Calcd. for C\(_{19}\)H\(_{14}\)N\(_4\)O\(_4\)S; C, 57.86; H, 3.58; N, 14.2%. Found: C, 57.80; H, 3.52; N, 14.1%.

6-(4-Bromophenyl)-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (7d) Colorless solid (Chloroform), Yield 86%, m.p.135-136°C; IR (KBr) \( \nu \) cm\(^{-1}\); 2923, 1512, 1663, 1682;

\(^1\)HNMR (300MHz, CDCl\(_3\)) \( \delta \): 3.83(s, 3H, OCH\(_3\)), 4.32(s, 2H, CH\(_2\)), 6.9 - 7.82(m, 8H, Ar-H), 10.02 (s, 1H, CHO); \(^13\)C NMR (75MHz, CDCl\(_3\)) \( \delta \): 37.80 (OCH\(_3\)), 56.2(CH\(_2\)), 109.6, 128.4, 133.6, 169.1, 146.0 & 181.2(CHO); Anal. Calcd. for C\(_{19}\)H\(_{14}\)N\(_3\)SO\(_2\)Br; C, 53.48; H, 3.29; N, 9.81%. Found: C, 53.40; H, 3.20; N, 9.80%.

2-(4-Methoxybenzyl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (7e) Pale Yellow solid (Chloroform), Yield 85%, m.p.147-148°C; IR (KBr) \( \nu \) cm\(^{-1}\); 2923, 1512, 1663, 1680;

\(^1\)HNMR(300MHz, CDCl\(_3\)) \( \delta \): 3.80 (d, 6H, OCH\(_3\)), 4.42(s, 2H, CH\(_2\)), 6.92-7.84(m, 8H, Ar-H), 10.02(s,1H,CHO); \(^13\)C NMR (75MHz, CDCl\(_3\)) \( \delta \): 22.01(CH\(_3\)), 37.80(OCH\(_3\)), 37.81(OCH\(_3\)), 56.2(CH\(_2\)), 109.6,
128.4, 133.6, 169.1, 146.0 & 181.2 (CHO); Anal. Calcd. for C_{20}H_{17}N_{3}O_{3}S; C, 63.31; H, 4.52; N, 11.07%. Found: C, 63.10; H, 4.20; N, 11.06%. (Appendices; Spectrum No. 12)

2-(4-Methoxy-benzyl)-6-p-tolyl-imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (7f) Pale Yellow solid (Chloroform), Yield 90%, m.p. 135°C; IR (KBr) \nu \text{ cm}^{-1}: 2923, 1512, 1683; \textsuperscript{1}HNMR (300MHz, CDCl\textsubscript{3}) \delta: 2.23 (s, 3H, CH\textsubscript{3}), 3.83 (s, 3H, OCH\textsubscript{3}), 4.41(s, 2H, CH\textsubscript{2}), 6.9-7.84 (m, 8H, Ar-H), 10.02 (s, 1H, CHO); Anal. Calcd. for C_{20}H_{17}N_{3}O_{3}S; C, 66.10; H, 4.71; N, 11.56%. Found: C, 66.00; H, 4.35; N, 11.31%. (Appendices; Spectrum No. 10 &11).

2-(4-Methoxy-benzyl)-6-(2-oxo-4a,8a-dihydro-2H-chromen-3-yl)-imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (7g) White needles (ethanol), yield 76%, m.p. 165-166°C; IR (KBr) \nu \text{ cm}^{-1}: 2834, 2923, 1712, 1678, 1513; \textsuperscript{1}HNMR (300MHz, CDCl\textsubscript{3}) \delta: 3.84 (s, 3H, OCH\textsubscript{3}), 4.4 (s, 2H, CH\textsubscript{2}), 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), 8.34 (s, 1H, C=H, coumarin), 10.24 (s, 1H, CHO); Anal. calcd. for C_{22}H_{17}N_{3}O_{4}S: C, 63.00; H, 4.09; N, 10.02. Found: C, 63.04; H, 4.06; N, 10.00%. (Appendices; Spectrum No. 13).

Synthesis of 5-[2-(4-Methoxybenzyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene]-2-thioxo-imidazolidin-4-one (8a-f):

General Procedure: A mixture of 2-(4-Methoxybenzyl)-6-arylimidazo[2,1-b]-[1,3,4]thiadiazole-5-carbaldehydes (7a-f) (0.01mol) and 2-thiohydantoin (1.16 g ; 0.01 mol) in glacial acetic acid (10mL) in presence of catalytic amount of sodium acetate(1gm) in glacial acetic acid (5 mL) refluxed for 2 hours. The reaction mixture was allowed to cool. The yellow solid that separated was filtered, dried & recrystallised from suitable solvent.
5-[2-(4-Methoxybenzyl)-6-phenylimidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene]-2-thioxo-imidazolidin-4-one (8a)

Yellow solid (Chloroform), Yield 89%, m.p.275-276°C; IR (KBr) νcm⁻¹: 3120, 3036, 2993, 1736, 1612, 1508; ¹H NMR(300MHz, DMSO, d₀) δ: 3.83(s, 3H, OCH₃), 4.23(s, 2H, CH₂), 6.92-7.84(m, 9H, Ar-H), 8.52(s, 1H, =CH), 11.18 (s, 1H, NH, D₂O exchangeable), 11.47(s, 1H, NH, D₂O exchangeable); ¹³C NMR (75MHz, DMSO) δ: 42.7(CH₂), 56.0(OCH₃), 114.0, 122, 122.7, 130.2, 136.5, 159.0, 163.7, 168.3(C=O), 183 (C=S); Anal. Calcd. for C₂₂H₁₇N₅O₂S₂: C, 59.04; H, 3.83; N, 15.65%. Found: C, 59.10 ; H, 3.65; N, 15.41%.

5-[6-(4-Chlorophenyl)-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylen]-2-thioxo-imidazolidin-4-one (8b)

Yellow solid (Chloroform), Yield 90%, m.p.239-240°C; IR (KBr) νcm⁻¹: 3120, 3036, 2993, 1736, 1612, 1508; ¹H NMR(300MHz, DMSO, d₀) δ: 3.82(s, 3H, OCH₃), 4.13(s, 2H, CH₂), 6.92-7.84(m, 8H, Ar-H), 8.5(s, 1H, =CH), 11.19 (s, 1H, NH, D₂O exchangeable), 11.57 (s,1H, NH, D₂O exchangeable); ¹³C NMR(75MHz, DMSO) δ: 42.7 (CH₂), 56.0(OCH₃), 113.6, 114, 122, 130.0, 136, 146.8, 168.3(C=O), 183 (C=S); Anal. Calcd. for C₂₂H₁₆ClN₅O₂S₂: C, 54.82; H, 3.35; N, 14.53%. Found: C, 54.40 ; H, 3.15; N, 14.01%. (Appendices; Spectrum No. 14).

5-[2-(4-Methoxybenzyl)-6-(4-nitrophenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylen]-2-thioxo-imidazolidin-4-one (8c)

Yellow solid (Chloroform), Yield 95%, m.p.274-275°C; IR (KBr) νcm⁻¹: 3120, 3036, 2993, 1736, 1612, 1508; ¹H NMR(300MHz, DMSO, d₀) δ: 3.83(s, 3H, OCH₃), 4.42(s, 2H, CH₂), 6.92-7.84(m,8H, Ar-H), 8.55(s, 1H, =CH), 11.06 (s, 1H, NH, D₂O exchangeable), 11.27(s, 1H, NH, D₂O exchangeable); ¹³C NMR (75MHz, DMSO): 42.7 (CH₂), 56.0(OCH₃), 114.0, 122, 127.9, 130.2, 136, 146.8, 159.0, 168.3(C=O),183(C=S); Anal. Calcd. for C₂₃H₁₆N₆O₄S₂: C, 53.65; H, 3.27; N, 17.06%. Found: C, 53.40 ; H, 3.14; N, 17.01%.
Chapter-III

5-[6-(4-Bromophenyl)-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene]-2-thioxo-imidazolidin-4-one (8d)

Yellow solid (Chloroform), Yield 95%, m.p.250-251°C; IR (KBr) v cm⁻¹; 3120, 3036, 2993, 1736, 1612, 1508; ¹HNMR(300MHz, DMSO, dë) δ: 3.83(s, 3H, OCH₃), 4.23(s, 2H, CH₂), 6.92-7.84(m, 8H, Ar-H), 8.52(s, 1H, =CH), 11.18(s, 1H, NH, D₂O exchangeable), 11.47(s, 1H, NH, D₂O exchangeable); Anal. Calcd. for C₂₂H₁₆BrN₅O₂S₂; C, 50.19; H, 3.06; N, 13.30%. Found: C, 50.40; H, 3.15; N, 13.01%.

5-[2-(4-Methoxybenzyl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethyl ne]-2-thioxo-imidazolidin-4-one (8e)

Yellow solid (Chloroform), Yield 90%, m.p.289-290°C; IR (KBr) v cm⁻¹; 3120, 3036, 2993, 1736, 1612, 1508; ¹HNMR(300MHz, DMSO, dë) δ: 3.83(d, 6H, OCH₃), 4.23(s, 2H, CH₂), 6.92-7.84 (m, 8H, Ar-H), 8.55 (s, 1H, =CH), 11.06 (s, 1H, NH, D₂O exchangeable), 11.27(s, 1H, NH, D₂O exchangeable); Anal. Calcd. for C₂₃H₁₉N₅O₃S₂; C, 57.85; H, 4.01; N, 14.66%. Found: C, 59.40; H, 4.05; N, 15.01%.

5-[2-(4-Methoxybenzyl)-6-(4-p-tolyl)imidazo[2,1-b][1,3,4]thiadiazol-5-ylmethylene]-2-thioxo-imidazolidin-4-one (8f)

Yellow solid (Chloroform), Yield 92%, m.p.267-268°C; IR (KBr) v cm⁻¹; 3120, 3036, 2993, 1736, 1612, 1508; ¹HNMR(300MHz, DMSO, dë) δ: 2.35(s, 3H, CH₃) 3.83(s, 3H, OCH₃), 4.23(s, 2H, CH₂), 6.92-7.84 (m, 8H, Ar-H), 8.45 (s, 1H, =CH), 11.06 (s, 1H, NH, D₂O exchangeable), 11.27(s, 1H, NH, D₂O exchangeable); Anal. Calcd. for C₂₃H₁₉N₅O₃S₂; C, 59.85; H, 4.15; N, 15.17%. Found: C, 59.40; H, 4.05; N, 15.01%.

(Appendices; Spectrum No.54)

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Synthesis of 5-[6-aryl-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl-methylene]pyrimidine 2,4,6- triones. (9a-f).

**General Procedure:** A mixture of 2-(4-methoxybenzyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde (7a-f) (0.01 mol) and Barbituric acid (1.28 g ; 0.01 mol) in glacial acetic acid (10 mL) with catalytic amount of sodium acetate(1gm) in glacial acetic acid (5 mL) was refluxed for 2 hours. The reaction mixture was allowed to cool. The red solid that separated was filtered, dried & recrystallised from proper solvent.

5-[[2-(4-methoxybenzyl)-6-phenylimidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene]pyrimidine-2,4,6\(\text{H}_2\text{H}_2\text{H}_2\)-trione (9a)

Brown red solid (Chloroform), Yield 90%, m.p.316-317\(^\circ\)C; IR (KBr) \(\text{cm}^{-1}\); 3216, 3101, 2823, 1736, 1512, 1608; \(^1\)HNMR (300MHz, DMSO, \(d_6\)) \(\delta\): 3.83 (s, 3H, OCH\(_3\)), 4.23 (s, 2H, CH\(_2\)), 6.92-7.84 (m, 9H, Ar-H), 8.52 (s, 1H, =CH), 11.18 (s, 1H, NH, D\(_2\)O exchangeable), 11.47 (s, 1H, NH, D\(_2\)O exchangeable); Anal. Calcd. for C\(_{23}\)H\(_{17}\)N\(_5\)O\(_4\)S; C, 60.12; H, 3.73; N, 15.24%. Found: C, 60.20 ; H, 3.25; N, 14.81%.

5-[[6-(4-chlorophenyl)-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene]pyrimidine-2,4,6\(\text{H}_2\text{H}_2\text{H}_2\)-trione (9b)

Brown red solid (Chloroform), Yield 90%, m.p.310-311\(^\circ\)C; IR (KBr) \(\text{cm}^{-1}\); 3186, 3101, 2823, 1736, 1512, 1608; \(^1\)HNMR(300MHz, DMSO, \(d_6\)) \(\delta\): 3.82(s, 3H, OCH\(_3\)), 4.13(s, 2H, CH\(_2\)), 6.92-7.84(m, 8H, Ar-H), 8.5(s, 1H, =CH), 11.19 (s, 1H, NH, D\(_2\)O exchangeable), 11.57( s,1H, NH, D\(_2\)O exchangeable); \(^{13}\)C NMR(75MHz, DMSO) \(\delta\): 42.7 (CH\(_2\)), 56.0(OCH\(_3\)), 114.0, 122, 128.4, 129.4, 147.4, 157.2, 166.3; Anal. Calcd. for C\(_{23}\)H\(_{16}\)ClN\(_5\)O\(_4\)S; C, 55.93; H, 3.27; N, 14.18%. Found: C, 55.40 ; H, 3.15; N, 13.31%. (Appendices; Spectrum No.53)

5-[[6-(4-nitrophenyl)-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene]pyrimidine-2,4,6\(\text{H}_2\text{H}_2\text{H}_2\)-trione (9c)
Red solid (Chloroform), Yield 96%, m.p.286-287°C; IR (KBr) \( \text{cm}^{-1} \): 3216, 3101, 2823, 1736, 1512, 1608; \(^1\)HNMR(300MHz, DMSO, \( d_6 \)) \( \delta \): 3.83(s, 3H, OCH\(_3\)), 4.42(s, 2H, CH\(_2\)), 6.92-7.84(m, 8H, Ar-H), 8.55(s, 1H, =CH), 11.06 (s, 1H, NH, D\(_2\)O exchangeable); \(^13\)C NMR( 75MHz, DMSO) \( \delta \): 42.7 (CH\(_2\)), 56.0(OCH\(_3\)), 114, 122, 124.1, 127.9, 136, 147.4, 157.2, 163.7, 166.3; Anal. Calcd. for C\(_{27}\)H\(_{14}\)N\(_8\)O\(_6\)S; C, 54.76; H, 3.20; N, 16.66%. Found: C, 54.70 ; H, 3.25; N, 16.41%.

5-[[6-(4-bromophenyl)-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene]pyrimidine-2,4,6(1H,3H,5H)-trione (9d)

Brown solid (Chloroform), Yield 90%, m.p.296-297°C; IR (KBr) \( \text{cm}^{-1} \): 3186, 3101, 2823, 1736, 1512, 1608; \(^1\)HNMR(300MHz, DMSO, \( d_6 \)) \( \delta \): 3.83(s, 3H, OCH\(_3\)), 4.23(s, 2H, CH\(_2\)), 6.92-7.84(m, 8H, Ar-H), 8.52(s, 1H, =CH), 11.18 (s, 1H, NH, D\(_2\)O exchangeable); Anal. Calcd. for C\(_{23}\)H\(_{18}\)BrN\(_5\)O\(_4\)S; C, 51.31; H, 3.00; N, 13.01%. Found: C, 51.20 ; H, 3.05; N, 12.81%. (Appendices; Spectrum No. 15).

5-[[6-(4-methoxyphenyl)-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene]pyrimidine-2,4,6(1H,3H,5H)-trione (9e)

Brown red solid (Chloroform), Yield 90%, m.p.305-306°C; IR (KBr) \( \text{cm}^{-1} \): 3216, 3101, 2823, 1736, 1512, 1608; \(^1\)HNMR(300MHz, DMSO, \( d_6 \)) \( \delta \): 3.83(d, 6H, OCH\(_3\)), 4.23(s, 2H, CH\(_2\)), 6.92-7.84(m, 8H, Ar-H), 8.55(s, 1H, =CH), 11.06 (s, 1H, NH, D\(_2\)O exchangeable); 11.27(s, 1H, NH, D\(_2\)O exchangeable); Anal. Calcd. for C\(_{24}\)H\(_{19}\)N\(_5\)O\(_3\)S; C, 58.89; H, 3.91; N, 14.31%. Found: C, 58.70 ; H, 3.25; N, 14.31%.

5-[[6-(4-p-tolyl)-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene]pyrimidine-2,4,6(1H,3H,5H)-trione (9f)

Red solid (Chloroform), Yield 95%, m.p.298-299°C; IR (KBr) \( \text{cm}^{-1} \): 3216, 3101, 2823, 1736, 1512, 1608; \(^1\)HNMR(300MHz, DMSO, \( d_6 \)) \( \delta \): 2.35(s, 3H,CH\(_3\)), 3.83(s, 3H,OCH\(_3\)), 4.42(s, 2H, CH\(_2\)), 6.92-7.84(m, 8H, Ar-H), 8.55(s, 1H, =CH), 11.06 (s, 1H, NH, D\(_2\)O exchangeable); \(^13\)C NMR( 75MHz, DMSO) \( \delta \): 42.7 (CH\(_2\)), 56.0(OCH\(_3\)), 114, 122, 124.1, 127.9, 136, 147.4, 157.2, 163.7, 166.3; Anal. Calcd. for C\(_{27}\)H\(_{14}\)N\(_8\)O\(_6\)S; C, 54.76; H, 3.20; N, 16.66%. Found: C, 54.70 ; H, 3.25; N, 16.41%.
4.23(s, 2H, CH₂), 6.92-7.84(m, 8H, Ar-H), 8.45(s, 1H, =CH), 11.06 (s, 1H, NH, D₂O exchangeable), 11.27(s, 1H, NH, D₂O exchangeable); ¹³C NMR(75MHz, DMSO) δ:
20.9(CH₃), 42.7 (CH₂), 56.0(OCH₃), 114, 122, 126.9, 129.7, 147.4, 157.2, 163.7, 166.3; Anal. Calcd. for C₂₄H₁₉N₅O₄S; C, 60.88; H, 4.04; N, 14.79%. Found: C, 60.80; H, 4.02; N, 14.81%.

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