CHAPTER – II

Synthesis & reactions of Imidazo[2,1-b] [1,3,4]thiadiazoles.


There are a number of reports in the literature on the synthesis and biological activities of condensed imidazo[2,1-b][1,3,4]thiazoles,\textsuperscript{1-4} appeared particularly after the discovery of novel broad spectrum anthelmintic Tetramisole.\textsuperscript{5}

\begin{center}
\includegraphics{tetramisole.png}
\end{center}

Tetramisole

But not a single drug worth the commercial use has been evaluated till now amongst the imidazo[2,1-b]thiadiazole analogues. With the hope of evolving a promising drug related to tetramisole and to prepare various other biologically important compounds, the trend has been shifted to explore the drugs containing bioisosteric thiadiazole ring in place of thiazole ring of tetramisole. Imidazo[2,1-b][1,3,4]thiadiazole nucleus is known for diverse biological properties through innumerable derivatives.\textsuperscript{6-10}

Numerous organic compounds have various bioactivities which render them as valuable active ingredients for medicines or plant protecting agents. The methoxy substituent can have a significant effect on the basicity or acidity of neighboring groups and on the electron distribution and can change the overall reactivity and stability of a molecule.\textsuperscript{11} In recent years it is reported that the incorporation of methoxy group could alter the course of the reaction as well as the biological properties. Introduction of \textit{p}-methoxyphenyl substituent into a molecule provides compound with enhanced biological activity. Accumulation of methoxyphenyl on carbon leads to increased oxidative and thermal stability. Further it leads to increased lipid solubility, thereby enhancing the rate of absorption and transport of drug in vivo.\textsuperscript{11} In view of the above facts we have synthesized methoxy substituted thiadiazoles, imidazothiadiazoles and their mannich bases hoping that this would enhance the biological activity of this ring system. We present herein few reports of thiadiazole, imidazothiadiazole derivatives and mannich bases of imidazothiadiazoles of biological interest.
Gadad et al.,\textsuperscript{12} have synthesized a series of 2-sulfonamido/trifluoromethyl-6-(4'-substituted aryl/heteroaryl)imidazo[2,1-b][1,3,4]thiadiazole derivatives and the selected compounds were screened for their preliminary \textit{in vitro} cyclooxygenase inhibitory activity against COX-2 and COX-1 enzymes using colorimetric method. The compounds tested showed selective inhibitory activity toward COX-2 over COX-1. These compounds also exhibited significant anti-inflammatory activity.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{structure1.png}
\caption{Structure of synthesized derivatives.}
\end{figure}

Khazi \textit{et al.},\textsuperscript{13} have synthesized the following series of imidazo[2,1-b][1,3,4]thiadiazole derivatives and the compounds were evaluated for their preliminary \textit{in vitro} antitubercular activity against \textit{M. tuberculosis} H\textsubscript{37}Rv strain using broth microdilution and microplate alamar blue assay methods. Further they have reported few of the compounds emerged with moderate to good antitubercular activity.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{structure2.png}
\caption{Structure of antitubercular derivatives.}
\end{figure}

A variety of new methylene bridged benzofuranyl imidazo[2,1-b][1,3,4]thiadiazoles and their mannich bases of morpholine derivative have been synthesized by Jadhav \textit{et al.},\textsuperscript{14} and they have reported them as potent anti-inflammatory agents.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{structure3.png}
\caption{Structure of anti-inflammatory agents.}
\end{figure}
Aldo Andreani et al.\textsuperscript{15} have reported the synthesis and antitumor activity of new guanylhydrazones from imidazo[2,1-b][1,3,4]thiazoles (I) and the new heterocyclic system thiazolo[2',3':2,3]imidazo[4,5-e]quinoline (II). The compounds were tested as antitumor agents. They are found to be active on cell lines HI29 and HL60.

\begin{figure}[h]
\includegraphics[width=\textwidth]{figure1.png}
\end{figure}

Nalan et al.\textsuperscript{16} have synthesized some novel 2,6-dimethyl-N'-substituted phenylmethylene imidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazides (II) from 2,6-dimethylimidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazide (I). The newly synthesized compounds were evaluated for anticancer activity. 2,6-dimethyl-N'-(2-hydroxyphenyl methylidene)imidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazide (II) showed the most favorable cytotoxicity on ovarian cancer cell line.

\begin{figure}[h]
\includegraphics[width=\textwidth]{figure2.png}
\end{figure}

Aldo Andreani et al.\textsuperscript{17} have synthesized new fused heterocyclic system 2,7-disubstituted diimidazo[2,1-b:1,2-d][1,3,4]thiadazole (I) and diimidazo[1,2-a:1,2-c]pyrimidine (II) and studied their antitumor activities on human tumor cell lines.
Li-Xue Zhang et al.\textsuperscript{18} have synthesized various 3-(2-furanyl)-6-aryl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles and reported that most of the compounds possess significant growth promoting effects on mug bean radicals.

\[ \text{R} = 4-\text{NH}_2, \ 3-\text{Cl}, \text{etc.} \]

Several new 1,3,4-thiadiazoles, imidazo[2,1-b][1,3,4]thiadiazoles and thiadiazolo- [3,2-a]pyrimidines derived from 1-ethyl or benzyl-2-(2-amino-1,3,4-thiadiazol-5-yl)thio- methyl benzimidazole were synthesized by Ashour et al.\textsuperscript{19} They found them as potential antimicrobial agents.

Suzuki et al.\textsuperscript{20} have synthesized [1,3,4]-1,2,3-triazolo[4,5-d]pyrimidine-9(3H)-one derivatives as pharmacologically important molecules.

Mazzone et al.\textsuperscript{21} have reported a number of imidazo[2,1-b][1,3,4]thiadiazoles and screened them for their anti-inflammatory, antipyretic, analgesic and antimicrobial activities.

\[ \text{R} = \text{H, Me, Br, SCN, CHO.} \]

Abignentae et al.\textsuperscript{22} have reported the antipyretic, analgesic and ulcerogenic activities associated with imidazo[2,1-b][1,3,4]thiadiazoles of the following type.

\[ \text{R = H, Me, COOH, CH}_2\text{COOH.} \]

A series of 2-sulfamoyl-imidazo[2,1-b][1,3,4]thiadiazole derivatives were synthesized by Barnish et al.\textsuperscript{23} They have reported them as carbonic anhydrase inhibitors.
Many of these compounds showed the same degree of ionization as acetazolamide and methazolamide with higher lipophilic character. They tested them for anticonvulsant activities; compound I (R₁=t-butyl and R₂=H) had an anticonvulsant ED₅₀ of 2.6mg/kg when administered orally to mice. This compound selectively increased cerebral blood flow in animals without producing a high level of metabolic acidosis.

Kolavi, Hegde et al.²⁹-³² have reported the Mannich reaction of 2-alkyl/aryl-6-aryl imidazo[2,1-b][1,3,4]thiadiazoles with cyclic amines and formaldehyde in the presence of AcOH in refluxing methanol to give 2-alkyl/aryl-5-(substituted amino methyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazoles.

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{O=S} \\
\text{O} \\
\end{array}
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{S} \\
\end{array}
\begin{array}{c}
\text{R} \quad \text{1} \\
\text{R} \quad \text{2} \\
\text{R} \quad \text{1} \\
\text{R} \quad \text{2} \\
\end{array}
\]

\[
\begin{array}{c}
\text{HCHOamines HN\text{---}\text{R} \quad \text{1}} \\
\text{MeOH, AcOH reflux} \\
\end{array}
\]

R = H, Br, Cl, Me, OMe, R₂= Cy, 2-furyl, Pr, 2-thienyl
R₁ = 4-morpholinyl, 1-piperidinyl, 1-pyrrolidinyl

Trupti S. Chitre et al.³³ synthesized a novel series of mannich bases of 3-substituted 5-(pyridin-4-yl)-1,3, 4-oxadiazol-2-thione derivatives. The test compounds were screened for antimycobacterial activity using Middlebrook 7H9 medium against M. tuberculosis H37Rv (ATCC 27294) as well as Isoniazid (INH) resistant clinical strain. The SAR study reveals the importance of substitutions at para position for good activity.

\[
\begin{array}{c}
\text{N} \\
\text{O=S} \\
\text{S} \\
\end{array}
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{NH} \\
\text{N} \\
\text{Ar} \\
\end{array}
\]

In the light of above facts, it was planned to synthesize condensed methoxybenzyl imidazo[2,1-b][1,3,4]thiadiazoles and their Mannich bases and to screen some of the compounds for their enhanced pharmacological activities.
The work carried out in the present investigation in synthesizing Mannich bases of imidazothiadiazoles having \( p \)-methoxybenzyl substituent at 2-position is outlined in the following scheme.

**Reagents and Conditions:**
- i. \( \text{POCl}_3 \), reflux, 45 min, KOH.
- ii. dry ethanol, 18hr, \( \text{Na}_2\text{CO}_3 \).

**Scheme 1a**

The required 2-amino-5-(4-methoxybenzyl)-1,3,4-thiadiazole (1) was prepared by phosphorous oxychloride cyclisation of 4-methoxyphenyl acetic acid with thiosemicarbazide. Further imidazo[2,1-b][1,3,4]thiadiazoles 3 were prepared by the reaction of equimolar quantities of 2-amino-5-(4-methoxybenzyl)-1,3,4-thiadiazole (1) and appropriately substituted phenacyl bromides in dry alcohol. The respective free bases were obtained by neutralization of the hydrobromide salts with aqueous sodium carbonate solution in good yields (Scheme 1a). By this method the required substituents at 2 & 6 positions have been obtained by starting with suitably substituted synthons.

Imidazo[2,1-b][1,3,4]thiadiazoles (3) were subjected to mannich reaction with three secondary cyclic amines (pyrrolidine, piperidine and morpholine) to yield corresponding Mannich bases 4, 5 and 6 (Scheme 1b).
Reagents and Conditions: i. pyrrolidine, HCHO, AcOH, MeOH, reflux. ii. piperidine, HCHO AcOH, MeOH, reflux. iii. morpholine, HCHO, AcOH, MeOH, reflux.

Scheme Ib
During the present investigation required imidazo[2,1-b][1,3,4]thiadiazoles were prepared (Scheme 1a) by the reaction of 2-amino-5-(4-methoxybenzyl)-1,3,4-thiadiazole (1) with appropriately substituted α-haloketones (phenacylbromides) in dry ethanol as hydrobromides, which on neutralization with aqueous sodium carbonate solution gave corresponding free bases 3a-e in good yields. The absence of νN-H band in IR spectra of the resulted compounds confirms the formation of product, which exhibits imidazole (C5-H) proton around δ 7.97 in 1H NMR spectra. The 13C NMR spectrum of compound (3d) is in total agreement with the structure.

Further imidazo[2,1-b][1,3,4]thiadiazoles 3a-e were subjected to Mannich reaction with three different cyclic secondary amines viz. pyrrolidine, piperidine and morpholine to afford corresponding Mannich bases (4a-e, 5a-e and 6a-e). In general the 1H NMR spectra of the products showed the absence of imidazole proton and a singlet is observed between δ 3.8-4.02 depending upon substitution, which is assigned to methylene protons bridged to cyclic amines and the aliphatic protons of the cyclic amine substituent resonated in the expected region along with rest of the protons.

In 1H NMR spectra of morpholine derivatives (6), two triplets (each for 4 protons) were observed at δ 2.58 (C3, C5-H; N-CH2) and δ 3.72 (C2, C6-H; O-CH2). For pyrrolidine derivatives (4), two multiplets (in few cases two broad singlets) each for 4 protons were observed at δ 1.7 (C3, C4-H i.e. -CH2-CH2-) and δ 2.6 (C2, C5-H; N-CH2). For piperidine derivatives (5), N-CH2 (C2, C6) protons resonated at δ 2.4 as triplet or broad singlet for 4 protons and C3, C4 and C5 protons resonated in the region δ 1.4-1.7 as multiplets for 6 protons.

Mannich products were analyzed for their C, H and N compositions and the values are within the limits. Analytical and spectral data for all the Mannich bases is given in experimental part of this chapter.
Required phenacyl bromides viz. p-chlorophenacyl bromide 24 (m.p. 95-96°C), p-bromophenacyl bromide 25 (m.p. 108-109°C), p-methoxy phenacyl bromide 25 (m.p. 68-70°C), phenacyl bromide 26 (m.p. 48-49°C), p-nitrophenacyl bromide 27 (m.p. 97-98°C) were prepared according to literature methods.

4-methoxyphenyl acetic acid was purchased (Sigma Aldrich) and directly used for the preparation of 2-amino-5-(4-methoxybenzyl)-1,3,4-thiadiazole.

1. Preparation of 2-amino-5-(4-methoxybenzyl)-1,3,4-thiadiazole (2):

A mixture of 4-methoxy phenyl acetic acid (16.7g, 0.1 mol) and thiosemicarbazide (9.3g, 0.1 mol) in phosphorous oxychloride (30 ml) was refluxed gently for 45 minutes. 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. Yield 83%, m.p 195-197°C (lit. 28 196°C).

2. Preparation of 2-(4-methoxybenzyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazoles (3a-g) General method:

A mixture of equimolar quantities of 2-amino-5-(4-methoxybenzyl)-1,3,4-thiadiazole (2) (2.21, 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 3a-g. It was filtered, washed with water, dried and recrystallized from suitable solvent.

The newly synthesized imidazothiadiazoles 3a-g were confirmed by spectral and analytical data. These were utilized as the intermediates for the synthesis of corresponding Mannich bases.
2-(4-methoxybenzyl)-6-phenylimidazo[2,1-b][1,3,4]thiadiazole (3a)

Brown crystalline solid (ethanol), yield 75%, m.p. 195-196°C; IR (KBr) v cm⁻¹: 3124, 2923, 2853, 1602, 1507; H NMR (300 MHz, CDCl₃) δ: 4.29 (s, 2H, CH₂), 3.83 (s, 3H, OCH₃), 7.06-7.44 (m, 7H, Ar-H), 7.83 (d, J=7.2Hz, 2H, Ar-H), 7.98 (s, 1H, C₅-H, imidazole). ¹³C NMR (75 MHz, CDCl₃) δ: 37.85 (OCH₃), 55.69 (CH₂), 109.38, 127.47, 129.6, 132.6, 164.8, 159.9 and 146.2; Anal. Calcd. for C₁₈H₁₃N₃OS; C, 67.27; H, 4.70; N, 13.07%. Found: C, 67.20; H, 4.46; N, 13.02%.

6-(4-chlorophenyl)-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4]thiadiazole (3b)

Shining white needles (ethanol), yield 70%, m.p. 141-142°C; IR (KBr) v cm⁻¹: 3016, 2859, 2817, 1603, 1504; H NMR (300 MHz, CDCl₃) δ: 3.83 (s, 3H, OCH₃), 4.29 (s, 2H, CH₂), 7.05-7.42 (m, 6H, Ar-H), 7.64 (d, J=7.3Hz, 2H, Ar-H), 7.96 (s, 1H, C₅-H, imidazole). ¹³C NMR (75 MHz, CDCl₃) δ: 37.80 (OCH₃), 55.71 (CH₂), 109.58, 127.47, 129.2, 133.5, 165.1, 159.7 and 146.4; Anal. Calcd. for C₁₈H₁₃N₃SCl; C, 60.76; H, 3.97; N, 11.81%. Found: C, 60.70; H, 3.91; N, 11.2%. (Appendices; Spectrum No. 1, 2 & 4).

2-(4-methoxybenzyl)-6-(4-nitrophenyl)imidazo[2,1-b][1,3,4]thiadiazole (3c)

Brown crystalline solid (ethanol), yield 66%, m.p. 212-214°C; IR (KBr) v cm⁻¹: 3107, 2924, 2854, 1603, 1524, 1501; H NMR (300 MHz, CDCl₃) δ: 3.83 (s, 3H, OCH₃), 4.31 (s, 2H, CH₂), 7.07-7.39 (m, 4H, Ar-H), 7.91 (d, J=8.4Hz, 2H, Ar-H), 7.91 (d, J=8.4Hz, 2H, Ar-H), 8.12 (s, 1H, C₅-H, imidazole). ¹³C NMR (75 MHz, CDCl₃) δ: 37.82 (OCH₃), 55.73(CH₂), 109.38, 127.47, 129.6, 132.5, 164.1, 159.7 and 146.8; Anal. Calcd. for C₁₈H₁₃N₄O₃S; C, 59.01; H, 3.85; N, 15.29%. Found: C, 59.01; H, 3.81; N, 15.20%.

6-(4-bromophenyl)-2-(4-methoxybenzyl)imidazo[2,1-b][1,3,4]thiadiazole (3d)

White needles (ethanol), yield 67%, m.p. 158-160°C; IR (KBr) v cm⁻¹: 3013, 2858, 2817, 1601, 1505; H NMR (300 MHz, CDCl₃) δ:
3.8(s, 3H, OCH3), 4.23(s, 2H, CH2), 7.24-7.78(m, 8H, Ar-H), 7.98(s, 1H, C5-H Imidazole); Anal. Calcd. for C18H14N3OBr; C, 54.01; H, 3.53; N, 10.50%. Found: C, 54.00; H, 3.46; N, 10.48%. (Appendices; Spectrum No. 3).

2-(4-methoxybenzyl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazole (3e)

Yellow crystalline solid (ethanol), yield 74%, m.p. 212-214°C; IR (KBr) νcm⁻¹: 3107, 2924, 2854, 1603, 1524, 1501; ¹H NMR (300MHz, CDCl₃) δ: 3.83(d, 6H, OCH₃), 4.31 (s, 2H, CH₂), 7.07-7.39 (m, 4H, Ar-H), 7.91(d, J=8.4Hz, 2H, Ar-H), 7.91(d, J=8.4Hz, 2H, Ar-H), 7.8 (s, 1H, C₅-H, imidazole). ¹³C NMR (75MHz, CDCl₃) δ: 21.02 (CH₃), 37.85 (OCH₃), 37.86 (OCH₃), 55.69 (CH₂), 109.38, 127.47, 129.6, 132.6, 164.8, 159.9 and 146.2; Anal. Calcd. for C₁₉H₁₇N₃O₃S; C, 64.94; H, 4.88; N, 11.96%. Found: C, 64.90; H, 4.80; N, 11.42%.

2-(4-methoxybenzyl)-6-para-tolylimidazo[2,1-b][1,3,4]thiadiazole (3f)

White needles (ethanol), yield 75%, m.p. 161-163°C; IR (KBr) νcm⁻¹: 3010, 2834, 2812, 1610, 1509; ¹H NMR (300MHz, CDCl₃) δ: 2.38(s, 3H, CH₃), 3.83 (s, 3H, OCH₃), 4.25(s, 2H, CH₂), 6.90-7.71(m, 8H, Ar-H), 7.93(s, 1H, C₅-H Imidazole); Anal. Calcd. for C₁₉H₁₇N₃O₃S; C, 68.03; H, 5.11; N, 12.53%. Found: C, 67.90; H, 5.06; N, 12.42%.

3-[2-(4-methoxy-benzyl)-imidazo[2,1-b][1,3,4]thiadiazol-6-yl]-4a,8a-dihydro-chromen-2-one (3g)

White needles (ethanol), yield 70%, m.p. 151-153°C; IR (KBr) νcm⁻¹: 3010, 2834, 2812, 1718, 1610, 1509; ¹H NMR (300MHz, CDCl₃) δ: 3.84 (s, 3H, OCH₃), 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 C₂₁H₁₈N₃O₄S: C, 64.43; H, 4.38; N, 10.73. Found: C, 64.40; H, 4.36; N, 10.73%. (Appendices; Spectrum No. 5 & 6).
3. Preparation of 2-(4-methoxybenzyl)-6-aryl-5-pyrrolidin-1-ylmethylimidazo[2,1-b][1,3,4]thiadiazole (4a-e):

**General method:** A mixture of 2-(4-methoxybenzyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazoles (3) (0.005 mol), pyrrolidine (0.71 g, 0.01 mol), formalin (1 mL) and acetic acid (1 mL) in methanol (20 mL) was refluxed for 10 hrs (monitored by TLC). Reaction mixture was diluted with water and extracted with chloroform (3x30 mL). The combined chloroform extract was washed with water (3x30 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue was recrystallized from chloroform and hexane mixture.

2-(4-methoxybenzyl)-6-phenyl-5-pyrrolidin-1-ylmethylimidazo[2,1-b][1,3,4]thiadiazole (4a) Pale yellow solid (chloroform + hexane), yield 70%, m.p. 100-102°C; IR (KBr) cm⁻¹: 3055, 2956, 2814, 1604, 1509; ¹H NMR (300 MHz, CDCl₃) δ: 1.79 (m, 4H, C₃, C₄-H, pyrrolidine), 2.63 (m, 4H, C₂, C₅-H, pyrrolidine), 3.84 (s, 3H, OCH₃), 4.07 (s, 2H, CH₂N), 4.3 (s, 2H, CH₂), 7.05-7.46 (m, 7H, Ar-H), 7.91 (d, J=7.49Hz, 2H, Ar-H). Anal. calcd. for C₂₃H₂₄N₄OS: C, 68.29; H, 5.98; N, 13.85. Found: C, 68.27; H, 5.96; N, 13.81%.

6-(4-chlorophenyl)-2-(4-methoxybenzyl)-5-pyrrolidin-1-ylmethylimidazo[2,1-b][1,3,4]thiadiazole (4b) Pale yellow solid (chloroform + hexane), yield 63%, m.p. 132-134°C; IR (KBr) cm⁻¹: 3050, 2948, 2830, 1610, 1503; ¹H NMR (300 MHz, CDCl₃) δ: 1.80 (m, 4H, C₃, C₄-H, pyrrolidine), 2.63 (m, 4H, C₂, C₅-H, pyrrolidine), 3.84 (s, 3H, OCH₃), 4.06 (s, 2H, CH₂N), 4.30 (s, 2H, CH₂), 7.91 (d, J=8.4Hz, 2H, Ar-H), 7.05-7.41 (m, 6H, Ar-H). Anal. calcd. for C₂₃H₂₃ClN₄OS: C, 62.93; H, 5.28; N, 12.76. Found: C, 62.91; H, 5.23; N, 12.74%. (Appendices; Spectrum No. 7).
2-(4-methoxybenzyl)-6-(4-nitrophenyl)-5-pyrrolidin-1-ylmethylimidazo[2,1-b]-[1,3,4]thiadiazole (4c)  
Yellow crystalline solid (chloroform + hexane), yield 72%, m.p. 156-157°C; IR (KBr) vcm\(^{-1}\): 3060, 2944, 2818, 1615, 1505; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 1.82 (m, 4H, C\(_3\), C\(_4\)-H, pyrrolidine), 2.60 (m, 4H, C\(_2\), C\(_5\)-H, pyrrolidine), 3.84 (s, 3H, OCH\(_3\)), 3.91 (s, 2H, CH\(_2\)N), 4.31 (s, 2H, CH\(_2\)), 8.1 (d, \(J=8.2\)Hz, 2H, Ar-H), 7.07-8.06 (m, 6H, Ar-H), Anal. calcd. for C\(_{23}\)H\(_{23}\)N\(_5\)O\(_3\)S: C, 61.45; H, 5.16; N, 15.58. Found: C, 61.44; H, 5.11; N, 15.56%.

6-(4-bromophenyl)-2-(4-methoxybenzyl)-5-pyrrolidin-1-ylmethylimidazo[2,1-b]-[1,3,4]thiadiazole (4d)  
Yellow crystalline solid (chloroform + hexane), yield 75%, m.p. 141-142°C; IR (KBr) vcm\(^{-1}\): 3055, 2956, 2814, 1604, 1510, 1509; \(^1\)H NMR (300MHz, CDCl\(_3\)) \(\delta\): 1.80 (m, 4H, C\(_3\), C\(_4\)-H, pyrrolidine), 2.62 (m, 4H, C\(_2\), C\(_5\)-H, pyrrolidine), 3.84 (s, 3H, OCH\(_3\)), 4.02 (s, 2H, CH\(_2\)N), 4.30 (s, 2H, CH\(_2\)), 7.05-7.33 (m, 4H, Ar-H), 7.57(d, \(J=8.3\)Hz, 2H, Ar-H), 7.83 (d, \(J=8.39\)Hz, 2H, Ar-H). Anal. calcd. for C\(_{23}\)H\(_{23}\)BrN\(_4\)O\(_2\)S: C, 57.14; H, 4.80; N, 11.59. Found: C, 57.11; H, 4.78; N, 11.52%.

2-(4-methoxybenzyl)-6-(4-methoxyphenyl)-5-pyrrolidin-1-ylmethylimidazo [2,1-b][1,3,4]thiadiazole (4e)  
Pale yellow solid (chloroform + hexane), yield 78%, m.p. 133-135°C; IR (KBr) vcm\(^{-1}\): 3047, 2928, 2821, 1624, 1509; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 1.80 (m, 4H, C\(_3\), C\(_4\)-H, pyrrolidine), 2.64 (m, 4H, C\(_2\), C\(_5\)-H, pyrrolidine), 3.85 (d, 6H, OCH\(_3\)), 4.08 (s, 2H, CH\(_2\)N), 4.29 (s, 2H, CH\(_2\)), 6.98 (d, \(J = 6.76\) Hz, 2H, Ar-H), 7.04-7.30 (m, 4H, Ar-H), 7.83 (d, \(J = 8.35\) Hz, 2H, Ar-H). Anal. calcd. for C\(_{24}\)H\(_{26}\)N\(_4\)O\(_2\)S: C, 66.33; H, 6.03; N, 12.89. Found: C, 66.31; H, 6.01; N, 12.86%.
4. Preparation of 2-(4-methoxybenzyl)-6-aryl-5-piperidin-1-ylmethyl-imidazo-[2,1-b][1,3,4] thia diazole (5a-e):

**General method:** A mixture of 2-(4-methoxybenzyl)-6-arylimidazo[2,1-b]-[1,3,4]thiadiazoles (3) (0.005 mol), piperidine (0.85g, 0.01 mol), formalin (1mL) and acetic acid (1 mL) in methanol (20 mL) was refluxed for 10 hrs (monitored by TLC). Reaction mixture was diluted with water and extracted with chloroform (3x30 mL). The combined chloroform extract was washed with water (3x30 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue was recrystallized from chloroform and hexane mixture.

2-(4-methoxybenzyl)-6-phenyl-5-piperidin-1-ylmethylimidazo[2,1-b][1,3,4]-thiadiazole (5a) Pale yellow solid (chloroform + hexane), yield 70%, m.p. 115-117°C; IR (KBr) \text{cm}^{-1}: 3062, 2926, 2854, 1608, 1507, 1244; \text{H NMR (300 MHz, CDCl}_3): \delta: 1.26-1.58 (m, 6H, C3, C4, C5-H, piperidine), 2.48 (br, s, 4H, C2, C6-H, piperidine), 3.80 (s, 3H, OCH3), 3.88 (s, 2H, CH2N), 4.29 (s, 2H, CH2), 7.09 (d, \text{J}=8.31Hz, 2H, Ar-H), 7.26-7.44 (m, 5H, Ar-H), 7.97 (d, \text{J}=7.46Hz, 2H, Ar-H). Anal. calcd. for C24H26N4OS: C, 68.87; H, 6.26; N, 13.39. Found: C, 68.84; H, 6.23; N, 13.38%.

6-(4-chlorophenyl)-2-(4-methoxy benzyl)-5-piperidin-1-ylmethylimidazo[2,1-b][1,3,4]thiadiazole (5b) Pale yellow solid (chloroform + hexane), yield 65%, m.p. 130-131°C; IR (KBr) \text{cm}^{-1}: 3064, 2956, 2930, 2843, 1610, 1502, 1250; \text{H NMR (300 MHz, CDCl}_3): \delta: 1.45-1.59 (m, 6H, C3, C4, C5-H, piperidine), 2.49 (s, 4H, C2, C6-H, piperidine), 3.87 (s, 2H, CH2N), 3.80 (s, 3H, OCH3), 4.30 (s, 2H, CH2), 7.05-7.41 (m, 6H, Ar-H), 7.96 (d, \text{J}=8.3Hz, 2H, Ar-H). Anal. calcd. for C24H25ClN4OS: C, 63.63; H, 5.56; N, 12.37. Found: C, 63.60; H, 5.55; N, 12.37%.
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2-(4-methoxybenzyl)-6-(4-nitrophenyl)-5-piperidin-1-ylmethylimidazo[2,1-b]-[1,3,4]thiadiazole (5c)

Yellow crystalline solid (chloroform + hexane), yield 72%, m.p. 168-169°C; IR (KBr) ν/cm⁻¹: 3054, 2943, 2816, 1610, 1511; ¹H NMR (300 MHz, CDCl₃) δ: 1.26-2.01 (m, 6H, C₃, C₄, C₅-H, piperidine), 3.3 (s, 4H, C₂, C₆-H, piperidine), 3.80 (s, 3H, OCH₃), 3.87 (s, 2H, CH₂N), 4.30 (s, 2H, CH₂), 7.09-7.32 (m, 4H, Ar-H), 7.96 (d, J=8.5Hz, 2H, Ar-H), 8.28 (d, J=6.5Hz, 2H, Ar-H). Anal. calcd. for C₂₄H₂₅N₅O₃S: C, 62.18; H, 5.44; N, 15.11. Found: C, 62.14; H, 5.41; N, 15.8%.

6-(4-bromophenyl)-2-(4-methoxybenzyl)-5-piperidin-1-ylmethylimidazo[2,1-b]-[1,3,4]thiadiazole (5d)

Yellow solid (chloroform + hexane), yield 71%, m.p. 142-144°C; IR (KBr) ν/cm⁻¹: 3053, 2928, 2852, 1610, 1507; ¹H NMR (300 MHz, CDCl₃) δ: 1.26-1.57 (m, 6H, C₃, C₄, C₅-H, piperidine), 2.48 (s, 4H, C₂, C₆-H, piperidine), 3.80 (s, 3H, OCH₃), 3.86 (s, 2H, CH₂N), 4.29 (s, 2H, CH₂), 7.04-7.32 (m, 4H, Ar-H), 7.56 (d, J=8.2, 2H, Ar-H), 7.91(d, J=8.2Hz, 2H, Ar-H), MS (m/z): 497.45. Anal. calcd. for C₂₄H₂₅BrN₄O₃S: C, 57.95; H, 5.07; N, 11.26. Found: C, 57.92; H, 5.02; N, 11.24%.

2-(4-methoxybenzyl)-6-(4-methoxyphenyl)-5-piperidin-1-ylmethylimidazo[2,1-b]-[1,3,4]thiadiazole (5e)

Yellow solid (chloroform + hexane), yield 72%, m.p. 131-133°C; IR (KBr) ν/cm⁻¹: 3053, 2928, 2852, 1610, 1507; ¹H NMR (300 MHz, CDCl₃) δ: 1.52-1.79 (m, 6H, C₃, C₄, C₅-H, piperidine), 2.64 (s, 4H, C₂, C₆-H, piperidine), 3.87 (d, 6H, OCH₃), 3.92 (s, 2H, CH₂N), 4.31 (s, 2H, CH₂), 6.94 (d, J=7.2Hz, 2H, Ar-H), 6.97-7.89 (m, 6H, Ar-H), Anal. calcd. for C₂₅H₂₈N₄O₃S: C, 66.94; H, 6.29; N, 12.49. Found: C, 66.91; H, 6.22; N, 12.48%.

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5. Preparation of 2-(4-methoxybenzyl)-6-aryl-5-morpholin-1-ylmethylimidazo[2,1-b][1,3,4]thiadiazole (6a-e):

**General method:** A mixture of 2-(4-methoxybenzyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazoles (3) (0.005 mol), morpholine (0.85 g, 0.01 mol), formalin (1 mL) and acetic acid (1 mL) in methanol (20 mL) was refluxed for 10 hrs (monitored by TLC). Reaction mixture was diluted with water and extracted with chloroform (3x30 mL). The combined chloroform extract was washed with water (3x30 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue was recrystallized from chloroform and hexane mixture.

**2-(4-methoxybenzyl)-6-phenyl-5-morpholin-1-ylmethylimidazo[2,1-b][1,3,4]thiadiazole (6a)**

Pale yellow solid (chloroform + hexane), yield 68%, m.p. 118-120°C; IR (KBr) $\nu$ cm$^{-1}$: 3056, 2854, 2822, 1610, 1514; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.58 (t, $J$=3.6 Hz, 4H, C$_3$, C$_5$-H, morpholine), 3.72 (t, 4H, C$_2$, C$_6$-H, morpholine), 3.80 (s, 3H, OCH$_3$), 3.93 (s, 2H, CH$_2$N), 4.31 (s, 2H, CH$_2$), 7.05-7.46 (m, 7H, Ar-H), 7.95 (d, $J$=7.4 Hz, 2H, Ar-H). Anal. calcd. for C$_{23}$H$_{24}$N$_4$O$_2$S: C, 65.69; H, 5.75; N, 13.32. Found: C, 65.63; H, 5.71; N, 13.31%.

**6-(4-chlorophenyl)-2-(4-methoxybenzyl)-5-morpholin-1-ylmethylimidazo[2,1-b][1,3,4]thiadiazole (6b)**

Pale yellow solid (chloroform + hexane), yield 58%, m.p. 151-153°C; IR (KBr) $\nu$ cm$^{-1}$: 3061, 2859, 2817, 1603, 1504; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.58 (t, $J$=4.0 Hz, 4H, C$_3$, C$_5$-H, morpholine), 3.73 (t, 4H, C$_2$, C$_6$-H, morpholine), 3.80 (s, 3H, OCH$_3$), 3.90 (s, 2H, CH$_2$N), 4.31 (s, 2H, CH$_2$), 7.06-7.42 (m, 6H, Ar-H), 7.95 (d, $J$=8.42 Hz, 2H, Ar-H). Anal. calcd. for C$_{23}$H$_{23}$ClN$_4$O$_2$S: C, 60.72; H, 5.10; N, 12.31. Found: C, 60.70; H, 5.09; N, 12.29%. (Appendices; Spectrum No. 8).
2-(4-methoxybenzyl)-6-(4-nitrophenyl)-5-morpholin-1-ylmethylimidazo[2,1-b][1,3,4]thiadiazole (6c)

Yellow solid (chloroform + hexane), yield 63%, m.p. 164-165°C; IR (KBr) \( \nu \text{cm}^{-1} \): 3061, 2842, 2819, 1604, 1507; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \): 2.57 (t, 4H, C\(_3\), C\(_5\)-H, morpholine), 3.75 (t, 4H, C\(_2\), C\(_6\)-H, morpholine), 3.80 (s, 3H, OCH\(_3\)), 3.93 (s, 2H, CH\(_2\)N), 4.31 (s, 2H, CH\(_2\)), 7.07-8.32 (m, 4H, Ar-H), 7.97 (d, \( J=8.6 \text{Hz} \), 2H, Ar-H), 8.29 (d, \( J=8.5 \text{Hz} \), 2H, Ar-H). Anal. calcd. for C\(_{23}\)H\(_{23}\)N\(_5\)O\(_4\)S: C, 59.34; H, 4.98; N, 15.04. Found: C, 59.31; H, 4.90; N, 15.04%.

6-(4-bromophenyl)-2-(4-methoxybenzyl)-5-morpholin-1-ylmethylimidazo-[2,1-b][1,3,4]thiadiazole (6d)

Yellow solid (chloroform + hexane), yield 68%, m.p. 140-141°C; IR (KBr) \( \nu \text{cm}^{-1} \): 3044, 2831, 2820, 1604, 1508; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \): 2.56 (t, 4H, C\(_3\), C\(_5\)-H, morpholine), 3.72 (t, 4H, C\(_2\), C\(_6\)-H, morpholine), 3.89 (s, 2H, CH\(_3\)N), 4.30 (s, 2H, CH\(_2\)), 7.04-7.33 (m, 4H, Ar-H), 7.57 (d, \( J=8.3 \text{Hz} \), 2H, Ar-H), 7.85 (d, \( J=8.3 \text{Hz} \), 2H, Ar-H). Anal. calcd. for C\(_{23}\)H\(_{23}\)BrN\(_4\)O\(_2\)S: C, 55.31; H, 4.64; N, 11.22. Found: C, 55.30; H, 4.61; N, 11.20%. (Appendices; Spectrum No.55)

2-(4-methoxybenzyl)-6-(4-methoxyphenyl)-5-morpholin-1-ylmethylimidazo-[2,1-b][1,3,4]thiadiazole (6e)

Yellow crystalline solid (chloroform + hexane), yield 68%, m.p. 135-137°C, IR (KBr) \( \nu \text{cm}^{-1} \): 3041, 2829, 2824, 1608, 1510; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \): 2.57 (t, 4H, C\(_3\), C\(_5\)-H, morpholine), 3.73 (t, 4H, C\(_2\), C\(_6\)-H, morpholine), 3.86 (d, 6H, OCH\(_3\)), 3.90 (s, 2H, CH\(_2\)N), 4.30 (s, 2H, CH\(_2\)), 6.97-7.31 (m, 6H, Ar-H), 7.89 (d, \( J=8.5 \text{Hz} \), 2H, Ar-H). Anal. calcd. for C\(_{24}\)H\(_{26}\)N\(_4\)O\(_3\)S: C, 63.98; H, 5.82; N, 12.44. Found: C, 63.96; H, 5.81; N, 12.41%.
REFERENCES


