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Vinayak S. Hegde[a]; Gundurao D. Kolavi[a]; Ravi S. Lamani[a]; Imtiyaz Ahmed M. Khazi[a]
[a] Department of Chemistry, Karnatak University, Dharwad, India

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RESEARCH ARTICLE

Mannich bases and novel benzothiazole derivatives of imidazo[2,1-*b*][1,3,4]thiadiazoles and their biological evaluation

VINAYAK S. HEGDE, GUNDURAO D. KOLAVI, RAVI S. LAMANI and IMTIYAZ AHMED M. KHAZI*

Department of Chemistry, Karnatak University, Dharwad – 580 003, India

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A series of 2,6-disubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles, their new Mannich bases and novel benzothiazole derivatives were synthesized. The structures of all the synthesized compounds were established by analytical and spectral data. All the compounds were screened for their antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ using the BACTEC 460 radiometric system and antibacterial activity against *E. coli* and *B. cirrhosis*, antifungal activity against *A. niger* and *P. worthmanni*. Among the tested compounds Mannich bases **3e**, **3f** and **4 g** and 5-carbaldehyde derivative **6d** have shown excellent inhibition (99, 99, 97 and 95%, respectively) against *M. tuberculosis*. Mannich bases in general have also shown impressive antifungal activity.

Keywords: Imidazo[2,1-*b*][1,3,4]thiadiazole; Mannich bases; Benzothiazole; Antitubercular activity; Antimicrobial activity

1. Introduction

Tuberculosis (TB), an infection caused by *Mycobacterium tuberculosis* (MTB), still remains the leading cause of world wide death among the infectious diseases [1]. The emergence of monodrug and multidrug resistant [2] strains of MTB has complicated treatment protocols and raises the concern with this prevalent disease. Imidazo[2,1-*b*][1,3,4]thiadiazole moiety attracted the organic chemists particularly after the discovery of novel broad spectrum anthelmintic tetramisole [3]. Imidazo[2,1-*b*][1,3,4]thiadiazole derivatives have shown interesting biological properties [4–6] and some of them are known for antitubercular activity [7–9]. In continuation of the work on antitubercular activity [9, 10] and with a hope of obtaining new and more potent antitubercular compounds, the authors have synthesized and evaluated new imidazothiadiazole derivatives. Recently the authors have reported [9] that Mannich bases of imidazo[2,1-*b*][1,3,4]thiadiazoles have shown considerable antitubercular and antimicrobial activity. It was thought that a slight modification in the structure would produce

*Corresponding author. Tel: 0836-2215286; Fax: 91-836-2771275. Email: drimkorgchem@gmail.com

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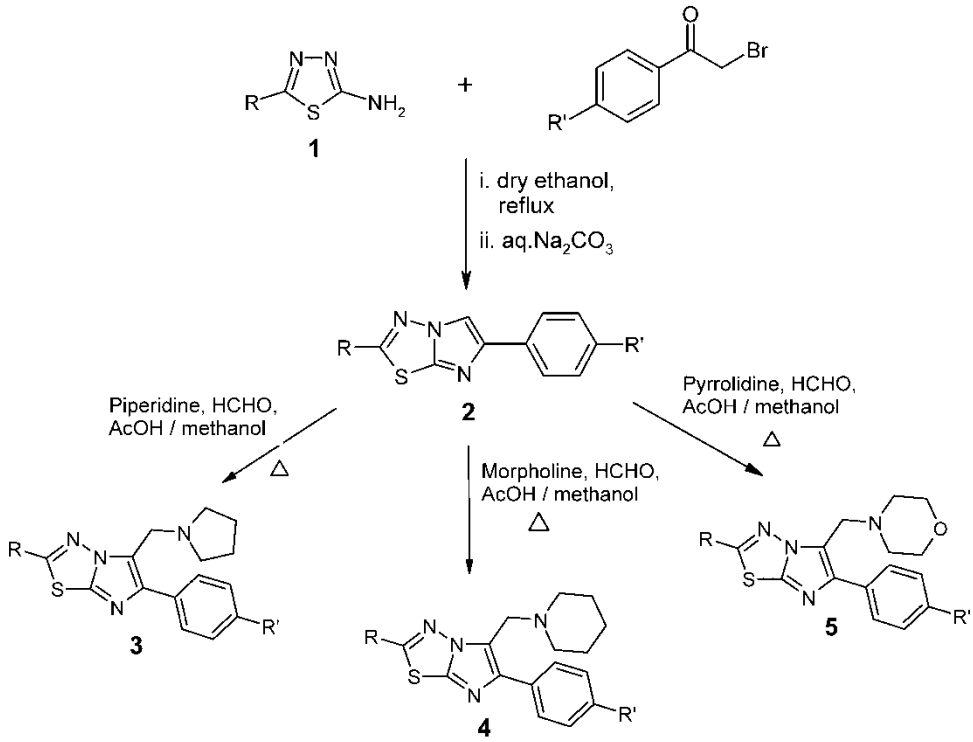
better activity. Apart from the new series of Mannich bases, novel benzothiazole derivatives of imidazo[2,1-*b*][1,3,4]thiadiazoles were synthesised and evaluated (TAACF, USA) for antitubercular activity. All the newly synthesized compounds were also screened for antibacterial and antifungal activity each against two strains.

2. Chemistry

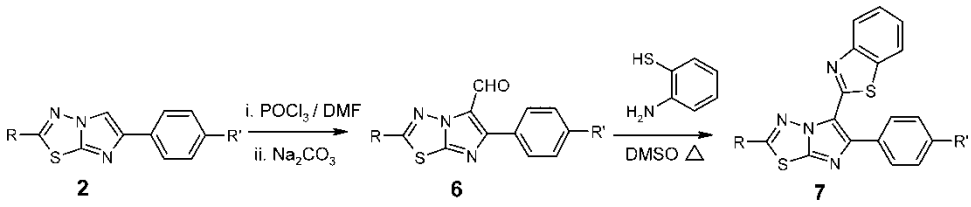
A library of Mannich bases (**3a–i, 4a–i, 5a–i**) were prepared by the reaction of different cyclic secondary amines *viz.* pyrrolidine, piperidine and morpholine with 2,6-disubstituted imidazo[2,1-*b*][1,3,4]thiadiazole and formaldehyde in methanol with catalytic amount of acetic acid. The required 2,6-disubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles were synthesized by the reaction of 2-amino-1,3,4-thiadiazole with α-bromoarylketone under reflux in dry ethanol (scheme 1). The Vilsmeier-Haack reaction of imidazo[2,1-*b*][1,3,4]thiadiazoles (**2a–i**) in DMF and $POCl_3$ provided 5-formyl derivatives (**6a–i**), which on reaction with 2-aminothiophenol yielded (scheme 2) novel imidazothiadiazole substituted benzothiazoles (**7a–i**).

The presence of imidazole (C_5-H) proton around δ 7.9 in ^{1}H NMR spectra and absence of $\nu_{N\text{-}H}$ band in IR spectra of the resulted compounds confirms the formation of imidazo[2,1-*b*][1,3,4]thiadiazole (**2a–i**). Imidazothiadiazoles were converted to Mannich bases (**3a–i, 4a–i, 5a–i**). The ^{1}H NMR spectra of pyrrolidine derivatives (**3a–i**) displayed two multiplets each for 4 protons at δ 1.7 (C_3, C_4-H *i.e.* -CH_2-CH_2-) and δ 2.6 (C_2, C_5-H; N-CH_2). For piperidine



R = propyl, cyclohexyl, 2-thienyl ; R' = Cl, CH_3, OCH_3.

SCHEME 1



R = propyl, cyclohexyl, 2-thienyl; R' = Cl, CH_3, OCH_3

SCHEME 2

derivatives (**4a–i**), N-CH_2 (C_2, C_6) protons resonated at δ 2.4 as triplet or broad singlet for 4 protons and C_3, C_4 and C_5 protons resonated in the region δ 1.4–1.7 as multiplets for 6 protons. For morpholine derivatives (**5a–i**), two triplets (each for 4 protons) are observed at δ 2.5 (C_3, C_5-H; N-CH_2) and δ 3.7 (C_2, C_6-H; O-CH_2). Formation of Mannich bases is further evidenced by the presence of a singlet around δ 4.0 in ^{1}H NMR for methylene proton and the carbon of which resonated at δ 54 in ^{13}C NMR spectra.

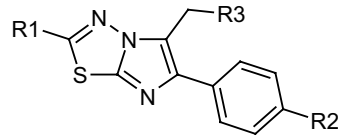
The formylated imidazo[2,1-*b*][1,3,4]thiadiazoles (**6a–i**) displayed the aldehydic carbonyl around 1680 cm^{-1} and $\nu_{C\text{-}H}$ around 2850 cm^{-1}. The structures are further confirmed by the presence of a singlet around δ 10.0 for aldehydic proton and absence of C_5-H of imidazole in the ^{1}H NMR spectra. Further ^{13}C NMR spectra exhibited carbonyl carbon around δ 177. Formylated imidazo[2,1-*b*][1,3,4]thiadiazoles (**6a–i**) were converted to corresponding benzothiazole derivatives (**7a–i**). The intermediates (**6a–i**) possessing one electrophilic carbon in the form of the formyl group has been reacted with 2-aminothiophenol utilizing its binucleophilicity leading to the formation of the five membered ring by a 4 + 1 approach. The formation of benzothiazoles is evidenced by the absence of carbonyl stretching frequency $\nu_{C=O}$ in IR and absence of the singlet due to aldehyde proton in ^{1}H NMR spectra. Further in ^{1}H NMR spectra the C_4-H and C_7-H of benzothiazole resonated around δ 8.1 and δ 7.9 as doublets, respectively, while C_5 and C_6-H of benzothiazoles appeared as triplets around δ 7.4 and δ 7.5, respectively.

3. Biological activity

The *in vitro* antimycobacterial activity was assayed by Tuberculosis Antimicrobial Acquisition and Coordinating facility (TAACF), antitubercular drug discovery programme.

Primary screening was conducted at the concentration of 6.25 μg/mL against *M. tuberculosis* H_{37}Rv (ATCC 27294) in BACTEC 12B [11, 12] medium using a broth microdilution assay [13, 14], the Microplate Alamar Blue Assay (MABA) [8]. Compounds exhibiting fluorescence were tested in the BACTEC 460 radiometric system. Compounds effecting <90% inhibition in the primary screen were not evaluated further. Compounds demonstrating at least 90% inhibition were tested at lower concentrations by serial dilution against *M. tuberculosis* H_{37}Rv to determine the minimum inhibitory concentration (MIC) using MABA. Rifampicin was used as a reference drug. Mannich bases **3e** (99%), **3f** (99%), **4g** (97%) and 5-carbaldehyde derivative **6a** (95%) were selected for further screening, where they exhibited promising inhibitory activity of 47, 54, 58 and 41%, respectively. They were also tested for their antibacterial activity [15, 16] against *Escherichia coli and Bacillus cirrhosis* and antifungal activity [17] against *Penicillium wortmannii and Aspergillus niger* by cup plate method at the concentration of 25–100 μg/mL using DMF as solvent. Norfloxacin and Greseofulvin were used as standards, respectively. In general, Mannich bases exhibited very good antifungal activity against both strains but not comparable with the standard Greseofulvin.

Table 1. The *in vitro* antitubercular activity of compounds against *M. tuberculosis* $H_{37}Rv$.

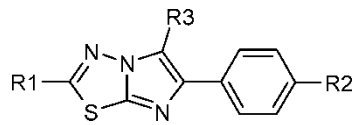


Comp. No.	R_1	R_2	R_3	% inhibition	Comp. No.	R_1	R_2	R_3	% inhibition
3a	propyl	Cl	1-pyrrolidinyl	63	4f	cyclohexyl	OMe	1-piperidinyl	66
3b	propyl	Me	1-pyrrolidinyl	76	**4g**	**2-thienyl l**	**Cl**	**1-piperidinyl**	**97**
3c	propyl	OMe	1-pyrrolidinyl	88	4h	2-thienyl	Me	1-piperidinyl	52
3d	cyclohexyl	Cl	1-pyrrolidinyl	70	4i	2-thienyl	OMe	1-pyrrolidinyl	76
3e	**cyclohexyl**	**Me**	**1-pyrrolidinyl**	**99**	5a	propyl	Cl	4-morpholinyl	72
3f	**cyclohexyl**	**OMe**	**1-pyrrolidinyl**	**99**	5b	propyl	Me	4-morpholinyl	79
3g	2-thienyl l	Cl	1-pyrrolidinyl	59	5c	propyl	OMe	4-morpholinyl	84
3h	2-thienyl	Me	1-pyrrolidinyl	67	5d	cyclohexyl	Cl	4-morpholinyl	75
3i	2-thienyl	OMe	1-pyrrolidinyl	78	5e	cyclohexyl	Me	4-morpholinyl	81
4a	propyl	Cl	1-piperidinyl	64	5f	cyclohexyl	OMe	4-morpholinyl	83
4b	propyl	Me	1-piperidinyl	72	5g	2-thienyl l	Cl	4-morpholinyl	67
4c	propyl	OMe	1-piperidinyl	84	5h	2-thienyl	Me	4-morpholinyl	79
4d	cyclohexyl	Cl	1-piperidinyl	59	5i	2-thienyl	OMe	4-morpholinyl	84
4e	cyclohexyl	Me	1-piperidinyl	67					

Standard: Rifampicin (100% inhibition); All compounds tested at concentration of 6.25 μg/mL

The preliminary *in vitro* antituberculosis screening results (tables 1 and 2) of novel imidazo[2,1-*b*][1,3,4]thiadiazole derivatives, reported in the present article evidenced that the imidazo[2,1-*b*][1,3,4]thiadiazole derivatives (**2a–i**) without substitution at position-5 did show moderate activity. Mannich bases of imidazothiadiazoles (**3–5a–i**) have consistently shown very good antitubercular activity than Mannich bases reported in our recent article [9]. The changes made in substitution position-6 have good impact on the activity profile. In most cases Mannich bases with *p*-chlorophenyl, *p*-methylphenyl and *p*-methoxyphenyl

Table 2. The *in vitro* antitubercular activity of compounds against *M. tuberculosis* $H_{37}Rv$.



Comp. No.	R_1	R_2	R_3	% inhibition	Comp. No.	R_1	R_2	R_3	% inhibition
2a	propyl	Cl	H	57	6f	cyclohexyl	OMe	CHO	86
2b	propyl	Me	H	80	6g	2-thienyl l	Cl	CHO	67
2c	propyl	OMe	H	83	6h	2-thienyl	Me	CHO	78
2d	cyclohexyl	Cl	H	54	6i	2-thienyl	OMe	CHO	84
2e	cyclohexyl	Me	H	81	7a	propyl	Cl	BTz	57
2f	cyclohexyl	OMe	H	83	7b	propyl	Me	BTz	54
2g	2-thienyl l	Cl	H	62	7c	propyl	OMe	BTz	62
2h	2-thienyl	Me	H	78	7d	cyclohexyl	Cl	BTz	35
2i	2-thienyl	OMe	H	71	7e	cyclohexyl	Me	BTz	48
6a	**propyl**	**Cl**	**CHO**	**95**	7f	cyclohexyl	OMe	BTz	56
6b	propyl	Me	CHO	66	7g	2-thienyl l	Cl	BTz	62
6c	propyl	OMe	CHO	79	7h	2-thienyl	Me	BTz	71
6d	cyclohexyl	Cl	CHO	34	7i	2-thienyl	OMe	BTz	64
6e	cyclohexyl	Me	CHO	82					

Standard: Rifampicin (100% inhibition); All compounds tested at concentration of 6.25 μg/mL

groups at position-6 have enhanced the activity in the preliminary test. In general, among the Mannich bases pyrrolidine derivatives (**3a–i**) have imparted excellent antitubercular activity. In most cases, imidazothiadiazoles (**2a–i**) retained their activity after conversion to their formyl derivatives (**6a–i**), which, in turn lost their activity after further conversion to corresponding benzothiazole derivatives (**7a–i**). The possible improvements in antitubercular activity can be further achieved by modifications in the basic imidazothiadiazole nucleus and Mannich bases using different cyclic and acyclic secondary amines. Antimicrobial screening results revealed that only Mannich bases are active than the rest of the derivatives. Our findings will have impact on chemists and pharmacists for further investigations in this field in search of potent antitubercular and antimicrobial agents.

4. Experimental

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on Nicolet Impact 410 FT IR spectrophotometer using KBr pellets or Nujol. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300-MHz FT NMR spectrometer in $CDCl_3$ and DMSO-d_6 with TMS as internal standard. Mass spectrum was recorded on Thermo-Finnigan-MAT, Bremen (Model MAT8200) spectrometer. Electrospray ionization mass spectrum (ESI-MS) was recorded on Quattro LCZ (Walters-Micromass, Manchester) and elemental analysis was carried out using Heraus CHN rapid analyzer.

4.1 *Preparation of 2-alkyl/aryl-6-arylimidazo[2,1-b][1,3,4]thiadiazoles (2a–i): General method*

A mixture of equimolar quantities of bromoacetyl compound *i.e.* phenacyl bromide (0.02 mol) and 2-amino-5-alkyl/aryl-1,3,4-thiadiazole (**1a–i,** 0.02 mol) was refluxed in dry ethanol for 8 hrs. The excess of solvent was distilled off under reduced pressure and the hydrobromide salt that separated was collected by filtration, suspended in water and neutralized by aqueous sodium carbonate solution to get free base (**2a–i**). It was filtered, washed with water, dried and recrystalised from suitable solvent.

4.1.1 6-(4-Chlorophenyl)-2-propylimidazo[2,1-*b*][1,3,4]thiadiazole (2a). Colorless granules (ethanol), yield 81%, m.p. 124–126 °C; IR (KBr) ν: 3035, 2942, 1605, 1557, 1516 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.08 (t, $J = 7.3$ Hz, 3H, $CH_2CH_2CH_3$), 1.87 (sextet, $J_{CH2CH3} = 7.5$ Hz, $J_{CH2CH2} = 3.3$ Hz, 2H, $CH_2CH_2CH_3$), 2.98 (t, $J = 3.0$ Hz, 2H, $CH_2CH_2CH_3$), 7.46 (d, $J = 7.8$ Hz, 2H, C_3, C_5-H, phenyl), 7.82 (d, $J = 7.9$ Hz, 2H, C_2, C_6-H, phenyl), 7.91 (s, 1H, C_5-H, imidazole). Anal. calcd. for $C_{13}H_{12}ClN_3S$: C, 56.21; H, 4.35; N, 15.13. Found: C, 56.43; H, 4.43; N, 14.98%.

4.1.2 6-(4-Methylphenyl)-2-propylimidazo[2,1-*b*][1,3,4]thiadiazole (2b). Colorless shiny flakes (ethanol), yield 70%, m.p. 122–124 °C; IR (KBr) ν: 2926, 1599, 1548 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.06 (t, $J = 7.3$ Hz, 3H, $CH_2CH_2CH_3$), 1.84 (sextet, $J_{CH2CH3} = 7.4$ Hz, $J_{CH2CH2} = 7.4$ Hz, 2H, $CH_2CH_2CH_3$), 2.38 (s, 3H, CH_3), 2.94 (t, $J = 7.4$ Hz, 2H, $CH_2CH_2CH_3$), 7.23 (d, $J = 7.8$ Hz, C_3, C_5-H, phenyl), 7.72 (d, $J = 7.8$ Hz, 2H, C_2, C_6-H, phenyl), 7.92 (s, 1H, C_5-H, imidazole). Anal. calcd. for $C_{14}H_{15}N_3S$: C, 65.34; H, 5.87; N, 16.33. Found: C, 65.58; H, 5.74; N, 16.21%.

4.1.3 6-(4-Methoxyphenyl)-2-propylimidazo[2,1-*b*][1,3,4]thiadiazole (2c). Colorless shiny flakes (ethanol), yield 63%, m.p. 118–120 °C; IR (KBr) ν: 2958, 1616, 1560, 1179 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.04 (t, $J = 6.7$ Hz, 3H, $CH_2CH_2CH_3$), 1.81 (m, 2H, $CH_2CH_2CH_3$), 2.91 (t, $J = 6.6$ Hz, 2H, $CH_2CH_2CH_3$), 3.82 (s, 3H, OCH_3), 6.94 (d, $J = 7.9$ Hz, 2H, C_3, C_5-H, phenyl), 7.74 (d, $J = 8.0$ Hz, 2H, C_2, C_6-H, phenyl), 7.85 (s, 1H, C_5-H, imidazole); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.8, 22.6, 34.2, 55.6, 108.5, 114.5, 126.7, 127.0, 145.5, 146.2, 159.6 and 164.5. Anal. calcd. for $C_{14}H_{15}N_3OS$: C, 61.51; H, 5.53; N, 15.37. Found: C, 61.36; H, 5.44; N, 15.61%.

4.1.4 6-(4-Chlorophenyl)-2-cyclohexylimidazo[2,1-*b*][1,3,4]thiadiazole (2d) [18]. Colorless shiny flakes (ethanol), yield 77%, m.p. 180–182 °C.

4.1.5 2-Cyclohexyl-6-(4-methylphenyl)imidazo[2,1-*b*][1,3,4]thiadiazole (2e) [18]. Colorless shiny needles (ethanol), yield 65%, m.p. 178–182 °C.

4.1.6 2-Cyclohexyl-6-(4-methoxyphenyl)imidazo[2,1-*b*][1,3,4]thiadiazole (2f) [18]. Shiny Colorless needles (ethanol), yield 64%, m.p. 176–178 °C.

4.1.7 6-(4-Chlorophenyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole (2g). Pale yellow granules (ethanol + dioxane), yield 71%, m.p. 152–154 °C; IR (KBr) ν: 3052, 1618, 1523 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.08 (s, dd, $J_{H3H4} = 3.3$ Hz, $J_{H4H5} = 3.3$ Hz, 1H, C_4-H, thiophene), 7.16 (d, $J = 3.2$ Hz, 1H, C_3-H), 7.42–7.59 (m, 3H, C_5-H, thiophene; C_3, C_5-H, phenyl), 7.87 (d, $J = 7.6$ Hz, 2H, C_2, C_6-H, phenyl), 7.96 (s, 1H, C_5-H, imidazole). Anal. calcd. for $C_{14}H_8ClN_3S_2$: C, 52.91; H, 2.54; N, 13.22. Found: C, 52.69; H, 2.62; N, 13.36%.

4.1.8 6-(4-Methylphenyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole (2h). Pale yellow granules (ethanol + dioxane), yield 62%, m.p. 160–162 °C; IR (KBr) ν: 3044, 2978, 1621, 1562, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.40 (s, 3H, CH_3), 7.11 (s, dd, $J_{H3H4} = 3.1$ Hz, $J_{H4H5} = 3.3$ Hz, 1H, C_4-H, thiophene), 7.19–7.27 (m, 3H, C_3-H, thiophene; C_3, C_5-H, phenyl), 7.56 (d, $J = 4.2$ Hz, 1H, C_5-H, thiophene), 7.75 (d, $J = 7.8$ Hz, 2H, C_2, C_6-H, phenyl), 7.99 (s, 1H, C_5-H, imidazole). Anal. calcd. for $C_{15}H_{11}N_3S_2$: C, 60.58; H, 3.73; N, 14.13. Found: C, 60.39; H, 3.64; N, 14.26%.

4.1.9 6-(4-Methoxyphenyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole (2i). Yellow granules (ethanol + dioxane), yield 65%, m.p. 138–140 °C; IR (KBr) ν: 3078, 1612, 1512, 1192 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.87 (s, 3H, OCH_3), 6.96–7.08 (m, 3H, C_4-H, thiophene; C_3, C_5-H, phenyl), 7.15 (d, $J = 3.3$ Hz, 1H, C_3-H, thiophene), 7.37 (d, $J = 3.1$ Hz, 1H, C_5-H, thiophene), 7.56 (d, $J = 7.6$ Hz, 2H, C_2, C_6-H, phenyl), 7.84 (s, 1H, C_5-H, imidazole). Anal. calcd. for $C_{15}H_{11}N_3OS_2$: C, 57.49; H, 3.54; N, 13.41. Found: C, 57.31; H, 3.61; N, 13.58%.

4.2 *Preparation of 6-aryl-2-alkyl/aryl-(pyrrolidin-1-ylmethyl)imidazo[2,1-b][1,3,4] thiadiazoles (3a–i): General procedure*

A mixture of 2-alkyl/aryl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole (0.005 mol), pyrrolidine (0.43 g, 0.006 mol), formalin (1 mL) and acetic acid (1 mL) in methanol (20 mL) was refluxed for 8 hrs (monitored by TLC). Reaction mixture was diluted with water and extracted with chloroform (3 × 30 mL). The combined chloroform extract was washed with water (3 × 30 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue was recrystallized from benzene and hexane mixture to yield colorless to yellow granules.

4.2.1 6-(4-Chlorophenyl)-2-propyl-5-(pyrrolidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4] thiadiazole (3a). Colorless granules (benzene + hexane), yield 68%, m.p. 96–98 °C; IR (KBr) υ: 3048, 2946, 2872, 1597, 1543 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.09 (t, $J = 7.2$ Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.78–1.87 (m, 6H, $CH_2\underline{CH_2}CH_3$; C_3, C_4-H, pyrrolidine), 2.62 (m, 4H, C_2, C_5-H, pyrrolidine), 2.98 (t, $J = 6.6$ Hz, 3H, $\underline{CH_2}CH_2CH_3$), 4.04 (s, 2H, CH_2), 7.41 (d, $J = 7.1$ Hz, 2H, C_3, C_5-H, phenyl), 7.88 (d, $J = 7.0$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{18}H_{21}ClN_4S$: C, 59.90; H, 5.86; N, 15.52. Found: C, 60.18; H, 5.95; N, 15.38%.

4.2.2 6-(4-Methylphenyl)-2-propyl-5-(pyrrolidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4] thiadiazole (3b). Colorless granules (benzene + hexane), yield 75%, m.p. 110–112 °C; IR (KBr) υ: 3061, 2935, 2870, 1605, 1552 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.06 (t, $J = 7.4$ Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.76–1.85 (m, 6H, $CH_2\underline{CH_2}CH_3$; C_3, C_4-H, pyrrolidine), 2.38 (s, 3H, CH_3), 2.63 (br s, 4H, C_2, C_5-H, pyrrolidine), 2.97 (t, $J = 7.1$ Hz, 2H, $\underline{CH_2}CH_2CH_3$), 4.01 (s, 2H, CH_2), 7.29 (d, $J = 7.9$ Hz, 2H, C_3, C_5-H, phenyl), 7.84 (d, $J = 7.8$ Hz, 2H, C_2, C_6-H, phenyl); MS m/z (%): 340.2 (14.9), 270.1 (100), 201.1 (8.6). Anal. calcd. for $C_{19}H_{24}N_4S$: C, 67.02; H, 7.10; N, 16.45. Found: C, 67.29; H, 7.12; N, 16.31%.

4.2.3 6-(4-Methoxyphenyl)-2-propyl-5-(pyrrolidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4] thiadiazole (3c). Colorless granules (benzene + hexane), yield 78%, m.p. 102–104 °C; IR (KBr) υ: 3045, 2854, 1599, 1540, 1186 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.08 (t, $J = 7.7$ Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.78–1.87 (m, 6H, $CH_2\underline{CH_2}CH_3$; C_3, C_4-H, pyrrolidine), 2.64 (m, 4H, C_2, C_5-H, pyrrolidine), 2.98 (t, $J = 6.6$ Hz, 3H, $\underline{CH_2}CH_2CH_3$), 3.84 (s, 3H, OCH_3), 3.97 (s, 2H, CH_2), 6.96 (d, $J = 8.7$ Hz, 2H, C_3, C_5-H, phenyl), 7.54 (d, $J = 8.6$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{19}H_{24}N_4OS$: C, 64.01; H, 6.79; N, 15.72. Found: C, 64.24; H, 6.74; N, 15.55%.

4.2.4 6-(4-Chlorophenyl)-2-cyclohexyl-5-(pyrrolidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4] thiadiazole (3d). Colorless granules (benzene + hexane), yield 75%, m.p. 130–132 °C; IR (KBr) υ: 3065, 2987, 1594, 1552 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.31–2.23 (m, 14H, cyclohexyl; C_3, C_4-H, pyrrolidine), 2.61 (m, 4H, C_2, C_5-H, pyrrolidine), 3.05 (m, 1H, C_1-H, cyclohexyl), 3.94 (s, 2H, CH_2), 7.46 (d, $J = 8.1$ Hz, 2H, C_3, C_5-H, phenyl), 7.94 (d, $J = 8.4$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{21}H_{25}ClN_4S$: C, 62.90; H, 6.28; N, 13.97. Found: C, 63.16; H, 6.39; N, 13.84%.

4.2.5 2-Cyclohexyl-6-(4-methylphenyl)-5-(pyrrolidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4] thiadiazole (3e). Colorless granules (benzene + hexane), yield 75%, m.p. 130–132 °C; IR

(KBr) υ: 3049, 2962, 2875, 1602, 1548 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.26–2.18 (m, 14H, cyclohexyl; C_3, C_4-H, pyrrolidine), 2.38 (s, 3H, CH_3), 2.63 (br s, 4H, C_2, C_5-H, pyrrolidine), 2.98 (m, 1H, C_1-H, cyclohexyl), 3.96 (s, 2H, CH_2), 7.24 (d, $J = 7.8$ Hz, 2H, C_3, C_5-H, phenyl), 7.81 (d, $J = 7.8$ Hz, 2H, C_2, C_6-H, phenyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.6, 24.0, 25.9, 26.0, 33.1, 41.6, 48.5, 54.1, 121.4, 127.8, 129.5, 132.5, 137.0, 143.5, 144.0 and 169.4. Anal. calcd. for $C_{22}H_{28}N_4S$: C, 69.44; H, 7.42; N, 14.72. Found: C, 69.24; H, 7.60; N, 14.88%.

4.2.6 2-Cyclohexyl-6-(4-methoxyphenyl)-5-(pyrrolidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (3f). Colorless granules (benzene + hexane), yield 78%, m.p. 118–122 °C; IR (KBr) υ: 3058, 2874, 1606, 1559, 1196 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.41–2.15 (m, 14H, cyclohexyl; C_3, C_4-H, pyrrolidine), 2.60 (m, 4H, C_2, C_5-H, pyrrolidine), 2.98 (m, 1H, C_1-H, cyclohexyl), 3.85 (s, 3H, OCH_3), 4.01 (s, 2H, CH_2), 6.96 (d, $J = 7.8$ Hz, 2H, C_3, C_5-H, phenyl), 7.83 (d, $J = 7.8$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{22}H_{28}N_4OS$: C, 66.63; H, 7.12; N, 14.13. Found: C, 66.85; H, 7.01; N, 14.02%.

4.2.7 6-(4-Chlorophenyl)-5-(pyrrolidin-1-ylmethyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole (3g). Pale yellow granules (benzene + hexane), yield 67%, m.p. 156–158 °C; IR (KBr) υ: 3074, 2996, 2864, 1658, 1556 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.78 (m, 4H, C_3, C_4-H, pyrrolidine), 2.65 (m, C_2, C_5-H, pyrrolidine), 4.11 (s, 2H, CH_2), 7.14 (dd, $J = 3.5$ Hz, $J_{H4H5} = 3.5$ Hz, 1H, C_4-H, thiophene), 7.30 (d, $J = 3.6$ Hz, 1H, C_3-H, thiophene), 7.44 (d, $J = 8.4$ Hz, 2H, C_3, C_5-H, phenyl), 7.57 (d, $J = 3.6$ Hz, 1H, C_5-H, thiophene), 7.96 (d, $J = 8.4$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{19}H_{17}ClN_4S_2$: C, 56.92; H, 4.27; N, 13.97. Found: C, 57.05; H, 4.33; N, 13.92%.

4.2.8 6-(4-Methylphenyl)-5-(pyrrolidin-1-ylmethyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole (3h). Pale yellow granules (benzene + hexane), yield 68%, m.p. 126–130 °C; IR (KBr) υ: 3038, 2985, 2849, 1600, 1543 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.81 (m, $J = 3.3$ Hz, 4H, C_3, C_4-H, pyrrolidine), 2.39 (s, 3H, CH_3), 2.68 (m, 4H, C_2, C_5-H, pyrrolidine), 4.03 (s, 2H, CH_2), 7.17 (dd, $J_{H3H4} = 3.5$ Hz, $J_{H4H5} = 3.5$ Hz, 1H, C_4-H, thiophene), 7.25–7.31(m, 3H, C_3-H thiophene; C_3, C_5-H, phenyl), 7.52 (d, $J = 3.3$ Hz, 1H, C_5-H, thiophene), 7.82 (d, $J = 7.2$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{20}H_{20}N_4S_2$: C, 63.13; H, 5.30; N, 14.72. Found: C, 63.36; H, 5.42; N, 14.55%.

4.2.9 6-(4-Methoxyphenyl)-5-(pyrrolidin-1-ylmethyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole (3i). Pale yellow granules (benzene + hexane), yield 68%, m.p. 138–140 °C; IR (KBr) υ: 3038, 2892, 1602, 1551, 1179 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.78 (m, 4H, C_3, C_4-H, pyrrolidine), 2.64 (m, 4H, C_2, C_5-H, pyrrolidine), 3.92 (s, 3H, OCH_3), 4.05 (s, 2H, CH_2), 6.96 (d, $J = 7.8$ Hz, 2H, C_3, C_5-H, phenyl), 7.16 (dd, $J_{H3H4} = 3.1$ Hz, $J_{H4H5} = 3.3$ Hz, 1H, C_4-H, thiophene), 7.27 (d, $J = 3.3$ Hz, 1H, C_3-H, thiophene), 7.51 (d, $J = 7.6$ Hz, 2H, C_2, C_6-H, phenyl), 7.58 (d, $J = 3.7$ Hz, 1H, C_5-H, thiophene). Anal. calcd. for $C_{20}H_{20}N_4OS_2$: C, 60.58; H, 5.08, N, 14.13. Found: C, 60.46; H, 5.14, N, 13.96%.

4.3 *Preparation of 6-aryl-2-alkyl/aryl-(piperidin-1-ylmethyl)imidazo[2,1-b][1,3,4]thiadiazoles (4a–i): General procedure*

A mixture of 2-alkyl/aryl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole (0.005 mol), piperidine (0.51 g, 0.006 mol), formalin (1 mL) and acetic acid (1 mL) in methanol (20 mL) was refluxed

for 8 hrs (monitored by TLC). Reaction mixture was diluted with water and extracted with chloroform (3 × 30 mL). The combined chloroform extract was washed with water (3 × 30 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum residue was recrystallized from benzene and hexane mixture to afford colorless to yellow granules.

4.3.1 6-(4-Chlorophenyl)-5-(piperidin-1-ylmethyl)-2-propylimidazo[2,1-*b*][1,3,4]thiadiazole (4a). Colorless granules (benzene + hexane), yield 74%, m.p. 134–136 °C; IR (KBr) υ: 3065, 2934, 2875, 1609, 1547 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.06 (t, J = 7.2 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.43–1.56 (m, 6H, C_3, C_4, C_5-H, piperidine), 1.85 (sextet, J_{CH2CH3} = 7.2 Hz, J_{CH2CH2} = 7.5 Hz, 2H, $CH_2\underline{CH_2}CH_3$), 2.46 (t, J = 6.1 Hz, 4H, C_2, C_6-H, piperidine), 2.97 (t, J = 7.5 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 3.81 (s, 2H, CH_2), 7.40 (d, J = 8.1 Hz, 2H, C_3, C_5-H, phenyl), 7.97 (d, J = 7.3 Hz, 2H, C_2, C_6-H, phenyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.8, 22.7, 24.5, 26.3, 34.3, 52.0, 54.3, 121.4, 128.9, 129.1, 133.2, 133.8, 143.4, 143.9 and 164.6. Anal. calcd. for $C_{19}H_{23}ClN_4S$: C, 60.87; H, 6.18; N, 14.94. Found: C, 60.98; H, 6.23; N, 14.81%.

4.3.2 6-(4-Methylphenyl)-5-(piperidin-4-ylmethyl)-2-propylimidazo[2,1-*b*][1,3,4]thiadiazole (4b). Colorless granules (benzene + hexane), yield 72%, m.p. 114–116 °C; IR (KBr) υ: 3058, 2978, 2896, 1605, 1548 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.07 (t, J = 7.2 Hz, 3H, $CH_2CH_2CH_3$), 1.46–1.55 (m, 6H, C_3, C_4, C_5-H, piperidine), 1.84 (sextet, J_{CH2CH3} = 7.3 Hz, J_{CH2CH2} = 7.4 Hz, 2H, $CH_2\underline{CH_2}CH_3$), 2.38 (s, 3H, CH_3), 2.45 (t, J = 6.3 Hz, 4H, C_2, C_6-H, piperidine), 2.97 (t, J = 7.5 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 3.84 (s, 2H, CH_2), 7.26 (d, J = 7.9 Hz, 2H, C_3, C_5-H, phenyl), 7.88 (d, J = 8.0 Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{20}H_{26}N_4S$: C, 67.76; H, 7.39; N, 15.80. Found: C, 67.87; H, 7.44; N, 15.76%

4.3.3 6-(4-Metoxyphenyl)-5-(piperidin-4-ylmethyl)-2-propylimidazo[2,1-*b*][1,3,4]thiadiazole (4c). Colorless granules (benzene + hexane), yield 65%, m.p. 118–122 °C; IR (KBr) υ: 3049, 2862, 1602, 1548, 1204 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.07 (t, J = 7.2 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.48–1.56 (m, 6H, C_3, C_4, C_5-H, piperidine), 1.86 (sextet, J_{CH2CH3} = 7.1 Hz, J_{CH2CH2} = 7.5 Hz, 2H, $CH_2CH_2CH_3$), 2.45 (br s, 4H, C_2, C_6-H, piperidine), 2.97 (t, J = 7.5 Hz, 2H, $CH_2CH_2CH_3$), 3.82 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 7.06 (d, J = 8.1 Hz, 2H, C_3, C_5-H, phenyl), 7.52 (d, J = 8.1 Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{20}H_{26}N_4OS$: C, 64.83; H, 7.07; N, 15.12. Found: C, 64.76; H, 7.03; N, 15.05%.

4.3.4 6-(4-Chlorophenyl)-2-cyclohexyl-5-(piperidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (4d). Colorless granules (benzene + hexane), yield 69%, m.p. 144–146 °C; IR (KBr) υ: 3060, 2942, 2885, 1606, 1557 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.26–2.27 (m, 16H, cyclohexyl; C_3, C_4, C_5-H, piperidine), 2.47 (t, J = 6.5 Hz, 4H, C_2, C_6-H, piperidine), 3.02 (m, 1H, C_1-H, cyclohexyl), 3.85 (s, 2H, CH_2), 7.46 (d, J = 8.4 Hz, 2H, C_3, C_5-H, phenyl), 7.94 (d, J = 8.4 Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{22}H_{27}ClN_4S$: C, 63.67; H, 6.56; N, 13.50. Found: C, 63.91; H, 6.63; N, 13.62%

4.3.5 2-Cyclohexyl-6-(4-methylphenyl)-5-(piperidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (4e). Colorless granules (benzene + hexane), yield 70%, m.p. 134–136 °C; IR (KBr) υ: 3044, 2986, 2904, 1606, 1542 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.26–2.28 (m, 16H, cyclohexyl; C_3, C_4, C_5-H, piperidine), 2.34 (s, 3H, CH_3), 2.47 (t, 4H, C_2, C_6-H, piperidine), 3.03 (m, 1H, C_1- H, cyclohexyl), 3.84 (s, 2H, CH_2), 7.25 (d, J = 8.1 Hz, 2H, C_3, C_5-H,

phenyl), 7.79 (d, $J = 8.0$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{23}H_{30}N_4S$: C, 70.01; H, 7.66; N, 14.20. Found: C, 70.26; H, 7.72; N, 14.08%.

4.3.6 2-Cyclohexyl-6-(4-methoxyphenyl)-5-(piperidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4] thiadiazole (4f). Colorless granules (benzene + hexane), yield 76%, m.p. 136–140 °C; IR (KBr) υ: 3049, 2962, 2875, 1602, 1548, 1192 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24–2.26 (m, 16H, cyclohexyl; C_3, C_4, C_5-H, piperidine), 2.47 (t, $J = 5.8$ Hz, 4H, C_2, C_6-H, piperidine), 3.03 (m, 1H, C_1-H, cyclohexyl), 3.81 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 6.98 (d, $J = 7.6$ Hz, 2H, C_3, C_5-H, phenyl), 7.50 (d, $J = 7.5$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{23}H_{30}N_4OS$: C, 67.28; H, 7.36; N, 13.65. Found: C, 67.35; H, 7.39; N, 13.61%

4.3.7 6-(4-Chlorophenyl)-5-(piperidin-1-ylmethyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4] thiadiazole (4g). Pale yellow granules (benzene + hexane), yield 76%, m.p. 140–142 °C; IR (KBr) υ: 3028, 2892, 1597, 1548 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.42–1.56 (m, 6H, C_3, C_4, C_5-H, piperidine), 2.48 (t, $J = 4.5$ Hz, 4H, C_2, C_6-H, piperidine), 4.06 (s, 2H, CH_2), 7.14 (dd, $J_{H3H4} = 3.6$ Hz, $J_{H4H5} = 3.6$ Hz, 1H, C_4-H, thiophene), 7.22 (d, $J = 3.6$ Hz, 1H, C_3-H, thiophene), 7.47 (d, $J = 8.4$ Hz, 2H, C_3, C_5-H, phenyl), 7.58 (d, $J = 3.6$ Hz, 1H, C_5-H, thiophene), 7.96 (d, $J = 8.4$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{20}H_{19}ClN_4S_2$: C, 57.89; H, 4.61; N, 13.50. Found: C, 58.04; H, 4.64; N, 13.42%.

4.3.8 6-(4-Methylphenyl)-5-(piperidin-1-ylmethyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4] thiadiazole (4h). Pale yellow granules (benzene + hexane), yield 76%, m.p. 144–146 °C; IR (KBr) υ: 3038, 2958, 2875, 1602, 1553 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.44–1.57 (m, 6H, C_3, C_4, C_5-H, piperidine), 2.37 (s, 3H, CH_3), 2.48 (t, $J = 4.2$ Hz, 4H, C_2, C_6-H, piperidine), 4.04 (s, 2H, CH_2), 7.17 (dd, $J_{H3H4} = 3.6$ Hz, $J_{H4H5} = 3.6$ Hz, 1H, C_4-H, thiophene), 7.21–7.30 (m, 1H, C_3-H, thiophene; C_3, C_5-H, phenyl), 7.60 (d, $J = 3.6$ Hz, 1H, C_5-H, thiophene), 7.85 (d, $J = 7.5$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{21}H_{22}N_4S_2$: C, 63.93; H, 5.62; N, 14.20. Found: C, 64.06; H, 5.69; N, 14.09%.

4.3.9 6-(4-Methoxyphenyl)-5-(piperidin-1-ylmethyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4] thiadiazole (4i). Pale yellow granules(benzene + hexane), yield 76%, m.p. 144–146 °C; IR (KBr) υ: 3045, 2962, 2880, 1601, 1544, 1180 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.43–1.55 (m, 6H, C_3, C_4, C_5-H, piperidine), 2.48 (br s, 4H, C_2, C_6-H, piperidine), 3.92 (s, 3H, OCH_3), 4.01 (s, 2H, CH_2), 7.04 (d, $J = 7.5$ Hz, C_3, C_5-H, phenyl), 7.16 (dd, $J_{H3H4} = 3.6$ Hz, $J_{H4H5} = 3.6$ Hz, 1H, C_4-H, thiophene), 7.24 (d, $J = 3.3$ Hz, 1H, C_3-H, thiophene), 7.49 (d, $J = 7.8$ Hz, 2H, C_2, C_6-H, phenyl), 7.56 (d, $J = 3.6$ Hz, 1H, C_5-H, thiophene). Anal. calcd. for $C_{21}H_{22}N_4OS_2$: C, 61.43; H, 5.40; N, 13.65. Found: C, 61.62; H, 5.48; N, 13.42%.

4.4 *Preparation of 6-aryl-2-alkyl/aryl-(morpholin-1-ylmethyl)imidazo[2,1-b][1,3,4] thiadiazoles (5a–i): General procedure*

A mixture of 2-alkyl/aryl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole (0.005 mol), morpholine (0.52 g, 0.006 mol), formalin (1 mL) and acetic acid (1 mL) in methanol (20 mL) was refluxed for 6–8 hrs (monitored by TLC). The reaction mixture was diluted with water and extracted with chloroform (3 × 30 mL). The combined chloroform extract was washed with water (3 × 30 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated to dryness

under vacuum and the residue was recrystallized from suitable solvent to afford colorless to pale yellow granules.

4.4.1 6-(4-Chlorophenyl)-5-(morpholin-4-ylmethyl)-2-propylimidazo[2,1-*b*][1,3,4]thiadiazole (5a). Colorless needles (benzene + hexane), yield 74%, m.p. 116–118 °C; IR (KBr) υ: 3054, 2981, 1592, 1538 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.08 (t, $J = 7.2$ Hz, 3H, $CH_2CH_2CH_3$), 1.85 (sextet, $J_{CH2CH3} = 7.2$ Hz, $J_{CH2CH2} = 7.5$ Hz, 2H, $CH_2CH_2CH_3$), 2.55 (t, $J = 4.2$ Hz, 4H, C_3, C_5-H, morpholine), 2.99 (t, $J = 7.5$ Hz, 2H, $CH_2CH_2CH_3$), 3.71 (t, $J = 3.9$ Hz, 4H, C_2, C_6-H, morpholine), 3.87 (s, 2H, CH_2), 7.40 (d, $J = 8.4$ Hz, 2H, C_3, C_5-H, phenyl), 7.92 (d, $J = 8.4$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{18}H_{21}ClN_4OS$: C, 57.36; H, 5.62; N, 14.87. Found: C, 57.51; H, 5.68; N, 14.75%.

4.4.2 6-(4-Methylphenyl)-5-(morpholin-4-ylmethyl)-2-propylimidazo[2,1-*b*][1,3,4]thiadiazole (5b). Colorless needles (benzene + hexane), yield 76%, m.p. 118–122 °C; IR (KBr) υ: 3046, 2974, 2891, 1612, 1555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.04 (t, $J = 3.3$ Hz, 3H, $CH_2CH_2CH_3$), 1.85 (sextet, $J_{CH2CH3} = 3.3$ Hz, $J_{CH2CH2} = 3.9$ Hz, 2H, $CH_2CH_2CH_3$), 2.36 (s, 2H, CH_3), 2.55 (t, $J = 4.5$ Hz, 4H, C_3, C_5-H, morpholine), 2.97 (t, $J = 4.1$ Hz, 2H, $CH_2CH_2CH_3$), 3.69 (t, $J = 4.3$ Hz, 4H, C_2, C_6-H, morpholine), 3.84 (s, 2H, CH_2), 7.28 (d, $J = 7.5$ Hz, 2H, C_3, C_5-H, phenyl), 7.84 (d, $J = 7.5$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{19}H_{24}N_4OS$: C, 64.01; H, 6.79; N, 15.72. Found: C, 64.24; H, 6.73; N, 15.79%.

4.4.3 6-(4-Methoxyphenyl)-5-(morpholin-4-ylmethyl)-2-propylimidazo[2,1-*b*][1,3,4]thiadiazole (5c). Colorless needles (chloroform + hexane), yield 70%, m.p. 116–118 °C; IR (KBr) υ: 2983, 1604, 1548, 1188 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.07 (t, $J = 4.5$ Hz, 3H, $CH_2CH_2CH_3$), 1.85 (sextet, $J_{CH2CH3} = 4.5$ Hz, $J_{CH2CH2} = 4.3$ Hz, 2H, $CH_2CH_2CH_3$), 2.55 (t, $J = 4.5$ Hz, 4H, C_3, C_5-H, morpholine), 2.97 (t, $J = 4.2$ Hz, 2H, $CH_2CH_2CH_3$), 3.69 (t, $J = 4.3$ Hz, 4H, C_2, C_6-H, morpholine), 3.82 (s, 2H, CH_2), 3.88 (s, 3H, OCH_3), 6.98 (d, $J = 7.2$ Hz, 2H, C_3, C_5-H, phenyl), 7.54 (d, $J = 7.2$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{19}H_{24}N_4O_2$ S: C, 61.26; H, 6.49; N, 15.04. Found: C, 61.22; H, 6.54; N, 15.12%.

4.4.4 6-(4-Chlorophenyl)-2-cyclohexyl-5-(morpholin-4-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (5d). Colorless needles (benzene + hexane), yield 71%, m.p. 140–142 °C; IR (KBr) υ: 3042, 2884, 1597, 1559 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.31–2.16 (m, 10H, cyclohexyl), 2.54 (t, $J = 4.5$ Hz, 4H, C_3, C_5-H, morpholine), 3.01 (m, 1H, C_1-H, cyclohexyl), 3.70 (t, $J = 4.2$ Hz, 4H, C_2, C_6-H, morpholine), 3.86 (s, 2H, CH_2), 7.49 (d, $J = 8.1$ Hz, 2H, C_3, C_5-H, phenyl), 7.95 (d, $J = 8.2$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{21}H_{25}ClN_4OS$: C, 60.49; H, 6.04; N, 13.44. Found: C, 60.54; H, 6.09; N, 13.33%.

4.4.5 2-Cyclohexyl-6-(4-methylphenyl)-5-(morpholin-4-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (5e). Colorless needles (benzene + hexane), yield 69%, m.p. 146–150 °C; IR (KBr) υ: 3036, 2982, 2856, 1589, 1554 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.29–2.17 (m, 10H, cyclohexyl), 2.39 (s, 3H, CH_3), 2.56 (t, $J = 3.9$ Hz, 4H, C_3, C_5-H, morpholine), 3.01 (m, 1H, C_1-H, cyclohexyl), 3.71 (t, $J = 4.2$ Hz, 4H, C_2, C_6-H, morpholine), 3.84 (s, 2H, CH_2), 7.26 (d, $J = 7.8$ Hz, 2H, C_3, C_5-H, phenyl), 7.86 (d, $J = 8.1$ Hz, 2H, C_2, C_6-H, phenyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.6, 25.9, 26.0, 33.1, 41.6, 51.7, 53.4, 67.4, 119.7, 127.8, 129.5, 132.3, 137.2, 143.7, 144.8 and 169.7. Anal. calcd. for $C_{22}H_{28}N_4OS$: C, 66.63; H, 7.12; N, 14.13. Found: C, 66.84; H, 7.16; N, 14.04%.

4.4.6 2-Cyclohexyl-6-(4-methoxyphenyl)-5-(morpholin-4-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (5f). Colorless needles (benzene + hexane), yield 69%, m.p. 140–142 °C; IR (KBr) υ: 3043, 2847, 1598, 1556, 1184 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34–2.14 (m, 10H, cyclohexyl), 2.54 (t, $J = 4.2$ Hz, 4H, C_3, C_5-H, morpholine), 3.03 (m, 1H, C_1-H, cyclohexyl), 3.71–3.86 (m, 9H, C_2, C_6-H, morpholine; CH_2 and OCH_3), 6.97 (d, $J = 7.9$ Hz, 2H, C_3, C_5-H, phenyl), 7.88 (d, $J = 8.1$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{22}H_{28}N_4O_2S$: C, 64.05; H, 6.84; N, 13.58. Found: C, 64.14; H, 6.87; N, 13.52%.

4.4.7 6-(4-Chlorophenyl)-5-(morpholin-4-ylmethyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole (5g). Pale yellow granules (chloroform + hexane), yield: 69%, m.p. 160–162 °C; IR (KBr) υ: 3059, 2872, 1605, 1551 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.58 (t, $J = 6.3$ Hz, 4H, C_3, C_5-H, morpholine), 3.71 (t, $J = 6.3$ Hz, 4H, C_2, C_6-H, morpholine), 4.03 (s, 2H, CH_2), 7.15 (dd, $J_{H3H4} = 3.6$ Hz, $J_{H4H5} = 3.5$ Hz, C_4-H, thiophene), 7.22 (d, $J = 3.6$ Hz, 1H, C_3-H, thiophene), 7.48 (d, $J = 9.1$ Hz, 2H, C_3, C_5-H, phenyl), 7.57 (d, $J = 3.6$ Hz, C_5-H, thiophene), 7.96 (d, $J = 8.7$ Hz, 2H, C_2, C_6-H, phenyl). Anal. calcd. for $C_{19}H_{17}ClN_4OS_2$: C, 54.73; H, 4.11; N, 13.44. Found: C, 54.88; H, 4.16; N, 13.32%.

4.4.8 6-(4-Methylphenyl)-5-(morpholin-4-ylmethyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole (5h). Pale yellow granules (chloroform + hexane), yield 64%, m.p. 156–158 °C; IR (KBr) υ: 3072, 2992, 2922, 1602, 1562 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.58 (t, $J = 6.0$ Hz, 4H, C_3, C_5-H, morpholine), 2.36 (s, 3H, CH_3), 3.71 (t, $J = 5.8$ Hz, 4H, C_2, C_6-H, morpholine), 3.98 (s, 2H, CH_2), 7.15 (dd, $J_{H3H4} = 3.6$ Hz, $J_{H4H5} = 3.6$ Hz, C_4-H, thiophene), 7.22 (d, $J = 3.6$ Hz, 1H, C_3-H, thiophene), 7.48 (d, $J = 8.9$ Hz, 2H, C_3, C_5-H, phenyl), 7.57 (d, $J = 3.6$ Hz, C_5-H, thiophene), 7.96 (d, $J = 8.7$ Hz, 2H, C_2, C_6-H, phenyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.6, 51.6, 53.4, 67.4, 120.8, 127.7, 128.4, 129.4, 129.7, 130.0, 132.2, 133.0, 133.2, 137.9, 143.2 and 155.3. Anal. calcd. for $C_{20}H_{20}N_4OS_2$: C, 60.58; H, 5.08; N, 14.13%. Found: C, 60.70; H, 5.18; N, 14.02%.

4.4.9 6-(4-Methoxyphenyl)-5-(morpholin-4-ylmethyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole (5i). Pale yellow granules (chloroform + hexane), yield 66%, m.p. 144–146 °C; IR (KBr) υ: 3058, 2985, 2849, 1596, 1546, 1208 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.56 (t, $J = 6.3$ Hz, 4H, C_3, C_5-H, morpholine), 3.71 (t, $J = 6.3$ Hz, 4H, C_2, C_6-H, morpholine), 3.88 (s, 3H, OCH_3), 4.01 (s, 2H, CH_2), 7.18 (dd, $J_{H3H4} = 4.2$ Hz, $J_{H4H5} = 3.9$ Hz, C_4-H, thiophene), 7.25 (d, $J = 3.6$ Hz, 1H, C_3-H, thiophene), 7.02 (d, $J = 8.6$ Hz, 2H, C_3, C_5-H, phenyl), 7.49 (d, $J = 8.4$ Hz, 2H, C_2, C_6-H, phenyl), 7.57 (d, $J = 3.6$ Hz, C_5-H, thiophene). Anal. calcd. for $C_{20}H_{20}N_4O_2S_2$: C, 58.23; H, 4.89; N, 13.58. Found: C, 58.36; H, 4.92; N, 13.52%.

4.5 *Preparation of 2-alkyl/aryl-6-arylimidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehydes (6a–i): General method (Vilsmeier Haack reaction)*

Vilsmeier Haack reagent was prepared by adding phosphorous oxychloride (3 mL) in dimethylformamide (20 mL) at 0 °C with stirring. At the same temperature appropriately substituted 2-alkyl/aryl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole **26a–i** (0.01 mol) 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 5 mL water. The reaction mixture was basified with aqueous 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 (30 mL × 3). The combined

extracts were washed with water (100 mL × 3), dried over anhydrous sodium sulfate. Solvent was removed by evaporation and solid obtained was recrystallised from suitable solvent to afford colorless to pale yellow crystals in excellent yields.

4.5.1 6-(4-Chlorophenyl)-2-propylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (6a). Colorless cubes (chloroform + hexane), yield 85%, m.p. 88–90 °C; IR (KBr) υ: 3058, 2856, 1678, 1588, 1542 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.09 (t, $J = 7.3$ Hz, 3H, $CH_2\underline{CH_3}$), 1.86 (sextet, $J_{CH2CH3} = 7.4$ Hz, $J_{CH2CH2} = 7.3$ Hz, 2H, $CH_2\underline{CH_2}CH_3$), 3.10 (q, $J = 7.3$ Hz, 2H, $\underline{CH_2}CH_2CH_3$), 7.49 (d, $J = 8.4$ Hz, 2H, C_3, C_5-H, phenyl), 7.86 (d, $J = 8.3$ Hz, 2H, C_2, C_6-H, phenyl), 10.04 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.8, 23.0, 34.3, 124.3, 129.4, 130.6, 131.2, 136.3, 151.2, 154.6, 167.9 and 177.5. Anal. calcd. for $C_{14}H_{12}ClN_3OS$: C, 54.99; H, 3.96; N, 13.74. Found: C, 54.88; H, 4.05; N, 13.56%.

4.5.2 6-(4-Methylphenyl)-2-propylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (6b). Colorless cubes (chloroform + hexane), yield 78%, m.p. 110–112 °C; IR (KBr) υ: 3053, 2918, 2852, 1682, 1581, 1552 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.06 (t, $J = 7.2$ Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.87 (sextet, $J_{CH2CH3} = 7.3$ Hz, $J_{CH2CH2} = 7.5$ Hz, 2H, $CH_2\underline{CH_2}CH_3$), 2.40 (s, 3H, CH_3), 3.07 (q, $J = 7.5$ Hz, 2H, $\underline{CH_2}CH_2CH_3$), 7.30 (d, $J = 7.4$ Hz, 2H, C_3, C_5-H, phenyl), 7.72 (d, $J = 7.7$ Hz, 2H, C_2, C_6-H, phenyl), 9.98 (s, 1H, CHO). Anal. calcd. for $C_{15}H_{15}N_3OS$: C, 63.13; H, 5.30; N, 14.73. Found: C, 63.34; H, 5.42; N, 14.63%.

4.5.3 6-(4-Methoxyphenyl)-2-propylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (6c). Colorless cubes (chloroform + hexane), yield 78%, m.p. 118–120 °C; IR (KBr) υ: 2964, 1679, 1580, 1557, 1178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.08 (t, $J = 7.3$ Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.87 (sextet, $J_{CH2CH3} = 7.6$ Hz and $J_{CH2CH2} = 7.5$ Hz, 2H, $CH_2\underline{CH_2}CH_3$), 3.09 (t, $J = 7.6$ Hz, 2H, $\underline{CH_2}CH_2CH_3$), 3.87 (s, 3H, OCH_3), 7.03 (d, $J = 8.5$ Hz, 2H, C_3, C_5-H, phenyl), 7.82 (d, $J = 8.5$ Hz, 2H, C_2, C_6-H, phenyl), 10.00 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.8, 22.9, 34.2, 55.7, 114.5, 123.9, 125.2, 130.8, 151.2, 156.3, 161.3, 167.2 and 177.6. Anal. calcd. for $C_{15}H_{15}N_3O_2S$: C, 59.78; H, 5.02; N, 13.94. Found: C, 59.96; H, 5.10; N, 13.82%.

4.5.4 6-(4-Chlorophenyl)-2-cyclohexylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (6d). Colorless crystalline solid (chloroform + hexane), yield 78%, m.p. 148–150 °C; IR (KBr) υ: 3053, 2927, 2856, 1675, 1589, 1546 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$,) δ: 1.30–2.19 (m, 10H, cyclohexyl), 3.18 (m, 1H, C_1-H, cyclohexyl), 7.43 (d, $J = 7.5$ Hz, 2H, C_3, C_5-H, phenyl), 7.76 (d, $J = 7.5$ Hz, 2H, C_2, C_6-H, phenyl), 10.01 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.0, 26.2, 33.6, 41.7, 113.6, 124.6, 129.3, 129.6, 130.4, 142.2, 152.6, 155.9 and 177.9. Anal. calcd. for $C_{17}H_{16}ClN_3OS$: C, 59.04; H, 4.66, N, 12.15. Found: C, 59.29; H, 4.71, N, 12.04%.

4.5.5 2-Cyclohexyl-6-(4-methylphenyl)imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (6e). Colorless cubes (chloroform + hexane), yield 73%, m.p. 154–156 °C; IR (KBr) υ: 3053, 2927, 1678, 1580, 1553 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.21–2.10 (m, 10H, cyclohexyl), 2.36 (s, 3H, CH_3), 3.12 (m, 1H, C_1-H, cyclohexyl), 7.25 (d, $J = 7.8$ Hz, 2H, C_3, C_5-H, phenyl), 7.70 (d, $J = 7.8$ Hz, 2H, C_2, C_6-H, phenyl), 9.95 (s, 1H, CHO); ^{13}C NMR(75 MHz, $CDCl_3$) δ: 21.7, 25.7, 26.0, 33.3, 41.7, 124.0, 129.5, 129.6, 129.9, 140.2,

151.0, 156.6, 172.1 and 178.7. Anal. calcd. for $C_{18}H_{19}N_3OS$: C, 66.43; H, 5.88; N, 12.91. Found: C, 66.61; H, 5.94; N, 12.75%.

4.5.6 2-Cyclohexyl-6-(4-methoxyphenyl)imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (6f). Colorless needles (chloroform + hexane), yield 68%, m.p. 140–142 °C; IR (KBr) υ: 3057, 2935, 1680, 1583, 1542, 1182 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.25–2.16 (m, 10H, cyclohexyl), 3.15 (m, 1H, C_1-H, cyclohexyl), 3.88 (s, 3H, OCH_3), 7.08 (d, $J = 8.1$ Hz, 2H, C_3, C_5-H, phenyl), 7.64 (d, $J = 8.1$ Hz, 2H, C_2, C_6-H, phenyl), 9.98 (s, 1H, CHO). Anal. calcd. for $C_{18}H_{19}N_3O_2S$: C, 63.32, H, 5.61; N, 12.31. Found: C, 63.58, H, 5.70; N, 12.23%.

4.5.7 6-(4-Chlorophenyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (6g). Pale yellow cubes (chloroform + hexane), yield 66%, m.p. 140–142 °C; IR (KBr) υ: 2855, 1682, 1610, 1553 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.16 (dd, $J_{H3H4} = 3.3$ Hz, $J_{H4H5} = 3.3$ Hz, 1H, C_4-H, thiophene), 7.26–7.86 (m, 6H, C_3, C_5-H, thiophene and phenyl protons), 10.08 (s, 1H, CHO). Anal. calcd. for $C_{15}H_8ClN_3OS_2$: C, 52.10; H, 2.33; N, 12.15. Found: C, 52.36; H, 2.37; N, 12.06%.

4.5.8 6-(4-Methylphenyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (6h). Pale yellow cubes (chloroform + hexane), yield 66%, m.p. 162–164 °C; IR (KBr) υ: 2857, 1680, 1606, 1552 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.43 (s, 3H, CH_3), 7.14 (dd, $J_{H3H4} = 3.3$ Hz, $J_{H4H5} = 3.5$ Hz, 1H, C_4-H, thiophene), 7.18–7.84 (m, 6H, C_3, C_5-H, thiophene and phenyl protons), 10.02 (s, 1H, CHO). Anal. calcd. for $C_{16}H_{11}N_3OS_2$: C, 59.06; H, 3.41; N, 12.91. Found: C, 59.23; H, 3.46; N, 12.85%.

4.5.9 6-(4-Methoxyphenyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (6i). Pale yellow needles (chloroform + hexane), yield 75%, m.p. 168–170 °C; IR (KBr) υ: 2857, 1678, 1614, 1552 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 3.86 (s, 3H, OCH_3), 7.04 (d, $J = 6.7$ Hz, 2H, C_3, C_5-H, phenyl), 7.17 (dd, $J_{H3H4} = 3.3$ Hz, $J_{H4H5} = 3.3$ Hz, 1H, C_4-H, thiophene), 7.28 (d, $J = 3.1$ Hz, 1H, C_3-H, thiophene), 7.56–7.69 (m, 3H, C_5-H, thiophene; C_2, C_6-H, phenyl), 10.03 (s, 1H, CHO). Anal. calcd. for $C_{16}H_{11}N_3O_2S_2$: C, 56.29; H, 3.25; N, 12.31. Found: C, 56.44; H, 3.31; N, 12.19%.

4.6 *Preparation of 2-(2-alkyl/aryl-6-arylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)-1,3-benzothiazoles (7a–i): General procedure*

A well stirred mixture of 2-alkyl/aryl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (**6**, 0.01 mol) and 2-aminothiophenol (1.2 g, 0.01 mol) in DMSO (12 mL) was heated on a oil bath at 120 °C for 4 hrs. The solid that separated on cooling was filtered, washed with aqueous alcohol and dried. The crude benzothiazoles were recrystallized from appropriate solvent.

4.6.1 2-[6-(4-Chlorophenyl)-2-propylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl]-1,3-benzothiazole (7a). Light green needles (ethanol), yield 81%, m.p. 144–146 °C; IR (Nujol) υ: 3046, 1596, 1546 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.13 (t, $J = 7.5$ Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.93 (sextet, $J_{CH2CH3} = 7.5$ Hz, $J_{CH2CH2} = 7.2$ Hz, 2H, $CH_2CH_2CH_3$), 3.11 (t, $J = 7.2$ Hz, 2H, $\underline{CH_2}CH_2CH_3$), 7.41–7.52 (m, 4H, C_3, C_5-H, phenyl; C_5, C_6-H, benzothiazole), 7.92–7.97 (m, 3H, C_2, C_6-H, phenyl; C_7-H, benzothiazole), 8.07 (d, $J = 6.3$ Hz,

1H, C_4-H, benzothiazole). Anal. calcd. for $C_{20}H_{15}ClN_4S_2$: C, 58.45; H, 3.68; N, 13.63. Found: C, 58.54; H, 3.72; N, 13.55%.

4.6.2 2-[6-(4-Methylphenyl)-2-propylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl]-1,3-benzothiazole (7b). Light green needles (ethanol), yield 82%, m.p. 144–146 °C; IR (Nujol) υ: 3072, 1588, 1562 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.12 (t, $J = 7.8$ Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.90 (sextet, $J_{CH2CH3} = 7.8$ Hz, $J_{CH2CH2} = 7.6$ Hz, 2H, $CH_2\underline{CH_2}CH_3$), 2.39 (s, 3H, CH_3), 3.08 (t, $J = 7.5$ Hz, 2H, $\underline{CH_2}CH_2CH_3$), 7.31–7.40 (m, 3H, C_3, C_5-H, phenyl; C_6-H, benzothiazole), 7.64 (t, $J = 6.8$ Hz, C_5-H, benzothiazole), 7.87 (d, $J = 7.5$ Hz, C_2, C_6-H, phenyl), 7.91(d, $J = 6.9$ Hz, 1H, C_7-H, benzothiazole), 8.10 (d, $J = 6.9$ Hz, 1H, C_4-H, benzothiazole). Anal. calcd. for $C_{21}H_{18}N_4S_2$: C, 64.59; H, 4.65; N, 14.35. Found: C, 64.72; H, 4.72; N, 14.26%.

4.6.3 2-[6-(4-Methoxyphenyl)-2-propylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl]-1,3-benzothiazole (7c). Light green needles (ethanol), yield 78%, m.p. 206–208 °C; IR (Nujol) υ: 3038, 1598, 1552, 1178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.10 (t, $J = 7.2$ Hz, 3H, $CH_2CH_2CH_3$), 1.88 (sextet, $J_{CH2CH3} = 7.2$ Hz, $J_{CH2CH2} = 7.3$ Hz, 2H, $CH_2CH_2CH_3$), 3.08 (t, $J = 7.2$ Hz, 2H, $CH_2CH_2CH_3$), 3.90 (s, 3H, OCH_3), 7.02 (d, $J = 7.2$ Hz, 2H, C_3, C_5-H, phenyl), 7.39 (t, $J = 6.6$ Hz, 1H, C_6-H, benzothiazole), 7.52 (t, $J = 6.6$ Hz, 1H, C_5-H, benzothiazole), 7.90–7.98 (m, 3H, C_7-H, benzothiazole; C_2, C_6-H, phenyl), 8.09 (d, $J = 6.8$ Hz, 1H, C_4-H, benzothiazole). Anal. calcd. for $C_{21}H_{18}N_4OS_2$: C, 62.04; H, 4.46; N, 13.78. Found: C, 62.16; H, 4.53; N, 13.70%.

4.6.4 2-[6-(4-Chlorophenyl)-2-cyclohexylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl]-1,3-benzothiazole (7d). Light green needles (ethanol), yield 79%, m.p. 184–186 °C; IR (Nujol) υ: 3058, 1604, 1548 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.33–2.27 (m, 10H, cyclohexyl), 3.16 (m, 1H, C_1-H, cyclohexyl), 7.38–7.44 (m, 3H, C_3, C_5-H, phenyl; C_6-H, benzothiazole), 7.51 (t, $J = 7.5$ Hz, 1H, C_5-H, benzothiazole), 7.93 (d, $J = 7.8$ Hz, 1H, C_7-H, benzothiazole), 8.04 (d, $J = 8.7$ Hz, 2H, C_2, C_6-H, phenyl), 8.08 (d, $J = 9.0$ Hz, C_4-H, benzothiazole); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.9, 26.0, 33.2, 41.8, 119.2, 121.6, 123.7, 125.5, 126.6, 128.6, 131.0, 132.6, 134.9, 135.4, 146.4, 146.9, 153.4, 155.5 and 171.4. Anal. calcd. for $C_{23}H_{19}ClN_2S_2$: C, 61.25; H, 4.25; N, 12.42. Found: C, 61.42; H, 4.29; N, 12.35%.

4.6.5 2-[2-Cyclohexyl-6-(4-methylphenyl)imidazo[2,1-*b*][1,3,4]thiadiazol-5-yl]-1,3-benzothiazole (7e). Light green needles (ethanol), yield 80%, m.p. 172–174 °C; IR (Nujol) υ: 3074, 1611, 1552 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.30–2.26 (m, 10H, cyclohexyl), 3.11 (m, 1H, C_1-H, cyclohexyl), 2.38 (s, 3H, CH_3), 7.30 (d, $J = 7.6$ Hz, 2H, C_3, C_5-H, phenyl), 7.39 (t, $J = 8.4$ Hz, 1H, C_6-H, benzothiazole), 7.48 (t, $J = 8.4$ Hz, 1H, C_5-H, benzothiazole), 7.86–7.92 (m, 3H, C_2, C_6-H, phenyl; C_7-H, benzothiazole), 8.08 (d, $J = 8.3$ Hz, C_4-H, benzothiazole). Anal. calcd. for $C_{24}H_{22}N_4S_2$: C, 66.94; H, 5.15; N, 13.01. Found: C, 67.08; H, 5.19; N, 12.94%.

4.6.6 2-[2-Cyclohexyl-6-(4-methoxyphenyl)imidazo[2,1-*b*][1,3,4]thiadiazol-5-yl]-1,3-benzothiazole (7f). Light green needles (ethanol), yield 77%, m.p. 210–212 °C; IR (Nujol) υ: 3069, 1603, 1547, 1186 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.27–2.26 (m, 10H, cyclohexyl), 3.09 (m, 1H, C_1-H, cyclohexyl), 3.88 (s, 3H, OCH_3), 7.00 (d, $J = 8.4$ Hz, 2H, C_3, C_5-H, phenyl), 7.40 (t, $J = 7.8$ Hz, 1H, C_6-H, benzothiazole), 7.49 (t, $J = 7.5$ Hz, 1H, C_5-H,

benzothiazole), 7.89 (d, $J = 7.8$ Hz, 1H, C_7-H, benzothiazole), 7.97 (d, $J = 8.4$ Hz, 2H, C_2, C_6-H, phenyl), 8.10 (d, $J = 8.1$ Hz, C_4-H, benzothiazole); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.9, 26.0, 33.2, 41.8, 55.7, 114.0, 118.6, 121.5, 123.6, 125.3, 126.4, 126.6, 131.1, 135.3, 146.9, 147.8, 153.5, 156.0, 160.5 and 171.0; MS m/z (%): 446 (100), 313.0 (11.7), 177.0 (26.8), 133.0 (51.2), 62.9 (21.3). Anal. calcd. for $C_{24}H_{22}N_4OS_2$: C, 64.55; H, 4.97; N, 12.55. Found: C, 64.67; H, 5.01; N, 12.52%.

4.6.7 2-[6-(4-Chlorophenyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl]-1,3-benzothiazole (7g). Light green needles (chloroform + hexane), yield 78%, m.p.174–176 °C; IR (Nujol) υ: 3057, 1610, 1556 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.14 (dd, $J = 2.8$ Hz and $J = 2.7$ Hz, 1H, C_4-H, thiophene), 7.44–7.62 (m, 5H, C_3, C_5-H, phenyl; C_5, C_6-H, benzothiazole, C_3-H, thiophene), 7.66 (d, $J = 5.7$ Hz, 1H, C_5-H, thiophene), 7.92–8.01 (m, 3H, C_7-H, benzothiazole; C_2, C_6-H, phenyl), 8.10 (d, $J = 7.5$ Hz, 1H, C_4-H, benzothiazole). Anal. calcd. for $C_{21}H_{11}ClN_4S_3$: C, 55.93; H, 2.46; N, 12.42. Found: C, 55.87; H, 2.52; N, 12.33%.

4.6.8 2-[6-(4-Methylphenyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl]-1,3-benzothiazole (7h). Light green needles (chloroform + hexane), yield 75%, m.p. 186–188 °C; IR (Nujol) υ: 3048, 1599, 1552 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.37 (s, 3H, CH_3), 7.15 (dd, $J = 3.3$ Hz and 3.1 Hz, 1H, C_4-H, thiophene), 7.32–7.41 (m, 3H, C_3, C_5-H, phenyl; C_6-H, benzothiazole), 7.51 (t, $J = 6.9$ Hz, 1H, C_5-H, benzothiazole), 7.59 (d, $J = 5.1$ Hz, 1H, C_3-H, thiophene), 7.67 (d, $J = 4.9$ Hz, C_5-H, thiophene), 7.88–7.95 (m, C_7-H, benzothiazole; C_2, C_6-H, phenyl), 8.11 (d, $J = 7.1$ Hz, 1H, C_4-H, benzothiazole). Anal. calcd. for $C_{21}H_{14}N_4S_3$: C, 61.37; H, 3.28; N, 13.01. Found: C, 61.46; H, 3.30; N, 12.97%.

4.6.9 2-[6-(4-Methoxyphenyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl]-1,3-benzothiazole (7i). Light green needles (chloroform + hexane), yield 71%, m.p. 192–194 °C; IR (Nujol) υ: 3036, 1592, 1546, 1185 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.90 (s, 3H, OCH_3), 7.01 (d, $J = 7.8$ Hz, 2H, C_3, C_5-H, phenyl), 7.20 (dd, $J = 4.5$ Hz and 4.8 Hz, 1H, C_4–H, thiophene), 7.44 (d, $J = 5.4$ Hz, 1H, C_3-H, thiophene), 7.52 (t, $J = 7.5$ Hz, 1H, C_6-H, benzothiazole), 7.61–7.67 (m, 2H, C_5-H, thiophene; C_5-H, benzothiazole), 7.95 (d, $J = 7.5$ Hz, 1H, C_7-H, benzothiazole), 8.02 (d, $J = 7.2$ Hz, 2H, C_2, C_6-H, phenyl), 8.12 (d, $J = 7.8$ Hz, 1H, C_4-H, benzothiazole); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.7, 114.0, 118.8, 121.6, 123.7, 125.5, 126.3, 126.5, 128.5, 129.8, 130.6, 131.0, 132.6, 135.4, 146.9, 148.1, 153.5, 156.3, 160.5 and 169.7. Anal. calcd. for $C_{22}H_{14}N_4OS_3$: C, 59.17; H, 3.16; N, 12.55. Found: C, 59.34; H, 3.22; N, 12.46%.

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