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Synthesis and evaluation of antitubercular activity of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives

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Abstract—AbstractA series of 2,6-disubstituted and 2,5,6-trisubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles were synthesized, the structures of the compounds were elucidated and screened for antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ using the BACTEC 460 radiometric system, antibacterial activity against *Escherichia coli* and *Bacillus cirrhosis*, and antifungal activity against *Aspergillus niger* and *Penicillium wortmanni*. Among the tested compounds 2-(2-furyl)-6-phenylimidazo[2,1-*b*][1,3,4] thiadiazole-5-carbaldehyde (**6c**) and (2-cyclohexyl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl)methanol (**7a**) have shown the highest (100%) inhibitory activity. Compounds **6a**, **6b**, **7c**, and **8a** exhibited moderate antitubercular activity with percentage inhibition 36, 30, 15, and 20, respectively, at a MIC of >6.25 μg/ml.

1. Introduction

Tuberculosis is one of the serious health problems with a wide variety of manifestations caused by *Mycobacterium tuberculosis* and as per the recent report it has been estimated that approximately one-third of the world's population is infected with this microorganism. The treatment of mycobacterial infections especially the tuberculosis, has become an important problem due to the emergence of monodrug and multidrug-resistant strains of *M. tuberculosis*.[1] Therefore, there is a need for new drugs of new structural classes and with a novel mechanism of action other than isoniazid (INH), rifampicin (RIF), and pyridazinamide (PZA). In this regard, since the last decade search for new antitubercular substances has ranked among the priority areas of chemotherapeutic research.

During recent years, there have been intense investigations on thiadiazole and imidazo[2,1-*b*][1,3,4]thiadiazole compounds, many of which are known to possess interesting biological properties such as antimicrobial,[2–6] antitubercular,[7,8] anti-inflammatory,[9–11] anticonvulsant,[12,13] antihypertensive,[14,15] and anticancer[16–18] activities. Recently, these derivatives have attracted the interest of researchers as antituberculosis agents. Some members of the imidazo[2,1-*b*][1,3,4]thiadiazoles family displayed good activity against *M. tuberculosis* $H_{37}Rv$.

The purpose of the present work was to explore and develop the novel molecules with improved potential for treating tuberculosis. In this paper, we report the design, synthesis, and antimycobacterial and antimicrobial evaluation of various imidazo[2,1-*b*][1,3,4]thiadiazole derivatives.

2. Chemistry

Synthesis of the basic nucleus imidazo[2,1-*b*][1,3,4]thiadiazole is brought about by the condensation of 2-amino-1,3,4-thiadiazole with α-bromoarylketone under reflux in dry ethanol (Scheme 1). Mannich reaction of imidazo[2,1-*b*][1,3,4]thiadiazole (**2**) with different cyclic secondary amines (morpholine, piperidine, and pyrrolidine) and formaldehyde in methanol with catalytic amount of acetic acid yielded corresponding derivatives **3**, **4**, and **5**. Vilsmeier–Haack reaction of imidazothiadiazole **2** in DMF and $POCl_3$ provided 5-formyl derivative **6** (Scheme 2). The aldehyde functional group has been utilized to synthesize corresponding alcohols, nitriles, and thiazolidinone

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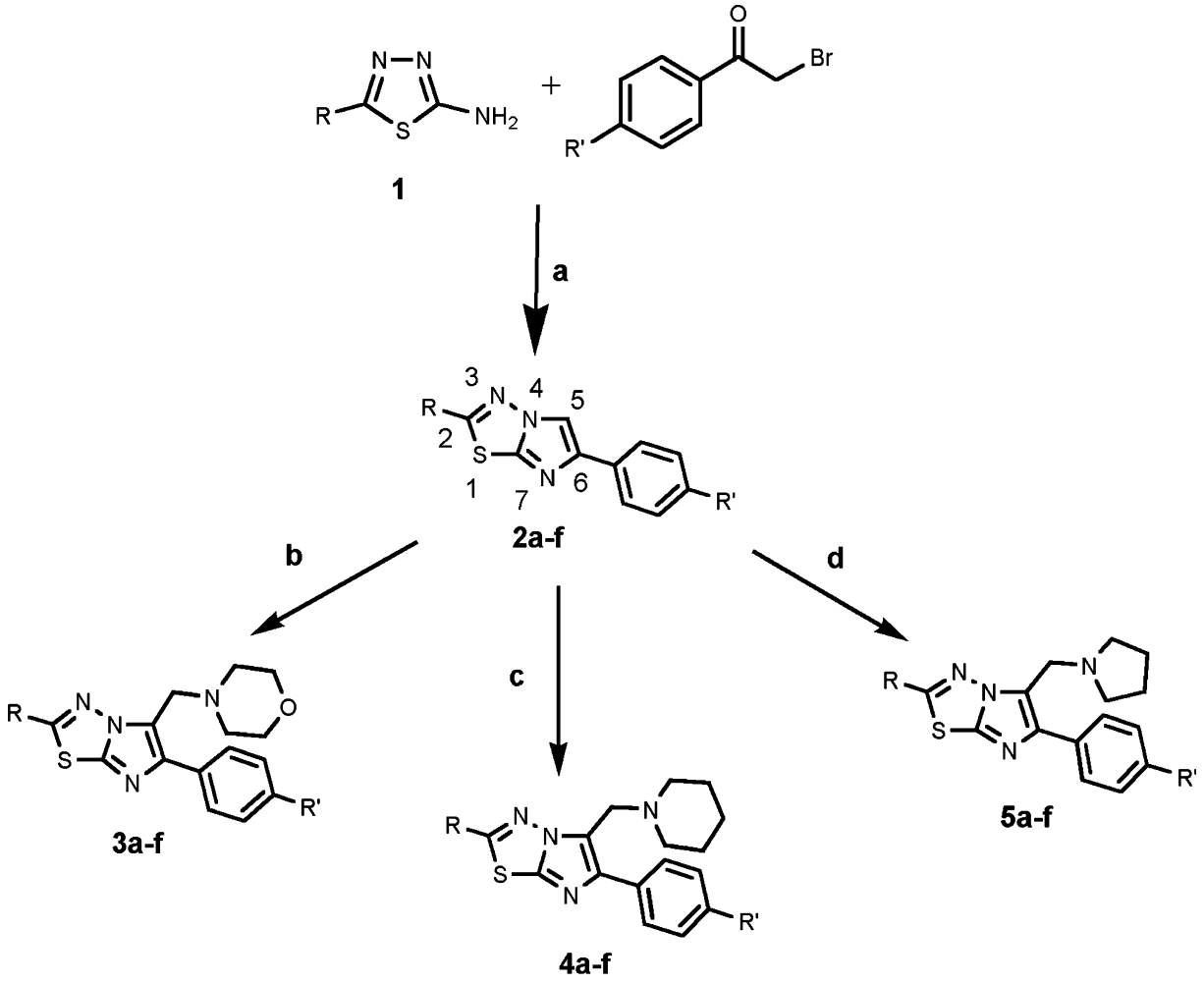


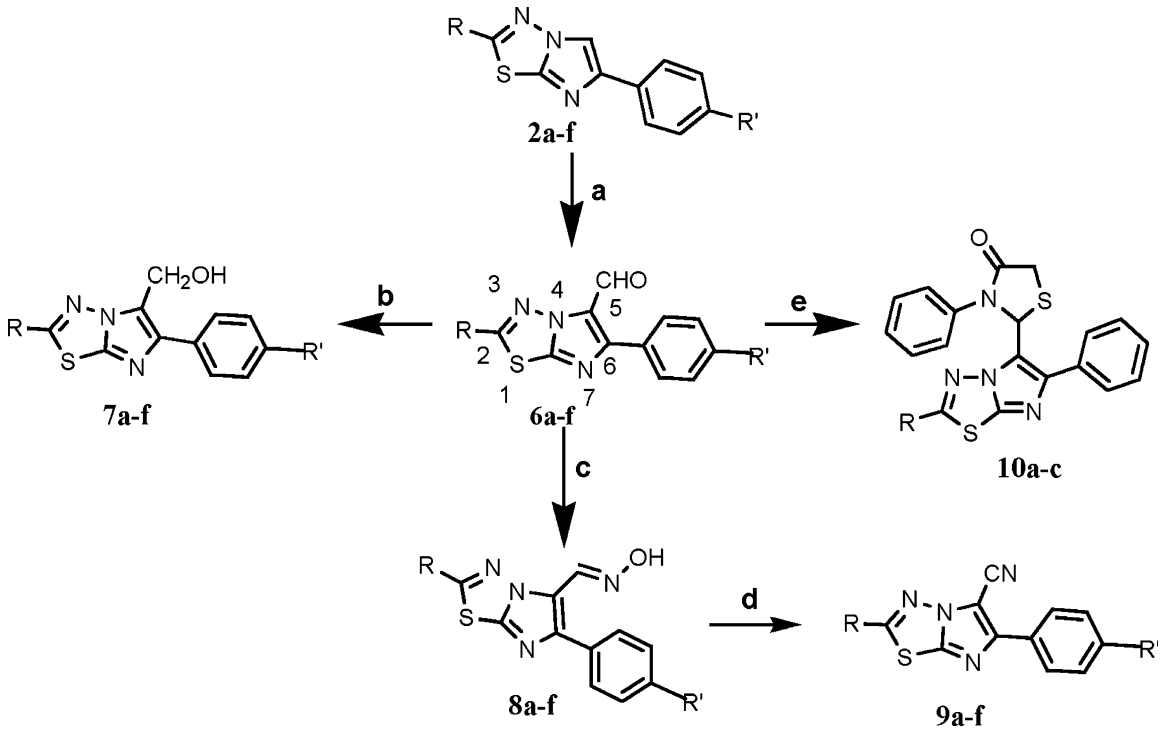
Scheme 1. Reagents and conditions: (a) dry ethanol, reflux, 12 h, Na_2CO_3; (b) morpholine, HCHO, AcOH, MeOH, reflux, 4 h; (c) piperidine, HCHO, AcOH, MeOH, reflux, 4 h; (d) pyrrolidine, HCHO, AcOH, MeOH, reflux, 4 h.

derivatives. The reduction of aldehyde **6** by $NaBH_4$ in methanol at room temperature yielded the respective carbinols **7** in good yields. The condensation of aldehyde **6** with hydroxylamine hydrochloride in pyridine gave corresponding oxime **8**, which on dehydration with thionylchloride produced the nitrile **9** in good yields. The aldehyde **6** when treated with aniline gave the corresponding Schiff bases, which on refluxing with thioglycolic acid in benzene underwent heterocyclization to yield thiazolidinone derivatives **10**.

3. Biological activity

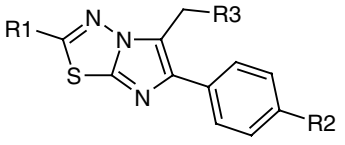
The in vitro antimycobacterial activity was assayed by Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF), antitubercular drug discovery program.

Primary screening was conducted at 6.25 μg/mL against *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B[19,20] medium using a broth microdilution assay,[21,22] 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. Compound **6c** was selected for further screening, where it exhibited promising inhibitory activity of 42%. The MIC is defined as the lowest concentration effecting a reduction in fluorescence of 90% relative to controls. Rifampicin was used as a reference drug. Biological significance of all the derivatives was also established by screening them against two bacterial strains *Bacillus cirrhosis* and *Escherichia coli* and two fungal species *Aspergillus niger* and *Penicillium wortmannii* by the cup plate method at a concentration of 25–100 μg/mL using DMF as the solvent. Norfloxacin and Greseofulvin were used as standards, respectively. The activity data are given in the following tables (Tables 1–4).



Scheme 2. Reagents and conditions: (a) DMF/$POCl_3$, Na_2CO_3; (b) $NaBH_4$, MeOH, rt; (c) $NH_2OH{\cdot}HCl$, pyridine reflux; (d) $SOCl_2$, digest, 10 min; (e) (i) $PhNH_2$, EtOH, reflux, (ii) thioglycolic acid, benzene, reflux.

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



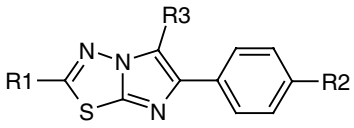
Compound	R_1	R_2	R_3	MIC (μg/mL)
3a	Cyclohexyl	H	4-Morpholinyl	>6.25
3b	**Cyclohexyl**	**Br**	**4-Morpholinyl**	**>6.25 (4)**
3c	2-Furyl	H	4-Morpholinyl	>6.25
3d	2-Furyl	Br	4-Morpholinyl	>6.25
3e	2-Thienyl	H	4-Morpholinyl	>6.25
3f	2-Thienyl	Br	4-Morpholinyl	>6.25
4a	Cyclohexyl	H	1-Piperidinyl	>6.25
4b	Cyclohexyl	Br	1-Piperidinyl	>6.25
4c	2-Furyl	H	1-Piperidinyl	>6.25
4d	2-Furyl	Br	1-Piperidinyl	>6.25
4e	2-Thienyl	H	1-Piperidinyl	>6.25
4f	2-Thienyl	Br	1-Piperidinyl	>6.25
5a	Cyclohexyl	H	1-Pyrrolidinyl	>6.25
5b	Cyclohexyl	Br	1-Pyrrolidinyl	>6.25
5c	2-Furyl	H	1-Pyrrolidinyl	>6.25
5d	2-Furyl	Br	1-Pyrrolidinyl	>6.25
5e	2-Thienyl	H	1-Pyrrolidinyl	>6.25
5f	2-Thienyl	Br	1-Pyrrolidinyl	>6.25

Rifampicin (standard) 6.25 μg/mL (100% inhibition). The active compounds and their activity is marked in bold letters.

4. Results and discussion

The formation of imidazothiadiazole derivatives **2** was confirmed by the absence of ν_{N-H} band in the IR spectra and presence of imidazole proton (C5-H) around δ 7.90 in ^1H NMR spectra. The ^1H NMR spectra of the products **3**, **4**, and **5** showed the absence of imidazole proton and a singlet was observed around δ 4.00, which was assigned to methylene protons and the other aliphatic protons of the amine substituent resonated in the expected region. For morpholine derivatives (**3**), two triplets were observed. Formation of Mannich bases was further confirmed by their ^{13}C NMR and mass spectra. IR spectra of **6** displayed the sharp band for carbonyl stretching frequency ($\nu_{C=O}$) around 1675 cm^{-1} and the singlet due to C_5-imidazole proton was absent and a signal for aldehyde proton was observed around δ 10.00 in the ^1H NMR spectrum, thus confirming the formation of imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehydes (**6a–f**). The products **7a–f** showed the absence of carbonyl stretching frequency $\nu_{C=O}$ and the presence of broad band in the region 3200 cm^{-1} for ν_{O-H} in IR spectra. The ^1H NMR showed the absence of signal due to aldehyde proton and the methylene protons resonated as singlet around δ 5.00 and –OH proton was observed as broad singlet. In a few cases, the doublet–triplet pattern was observed for $-CH_2OH$. The data confirmed the conversion of carbaldehydes **6** to imidazo[2,1-*b*]-[1,3,4]thiadiazole-5-carbinols (**7**). The absence of $\nu_{C=O}$ band and the presence of ν_{O-H} band in the IR spectrum of the product confirmed the formation of oximes **8**. Their ^1H NMR spectra also confirmed the aldoximes where the signal for aldehyde proton was absent, the azomethine and the –OH proton (D_2O exchangeable) resonated around δ 8.50 and 9.60, respectively. The product obtained after treatment of these aldoximes

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



Compound	R_1	R_2	R_3	MIC (μg/mL)
2a	Cyclohexyl	H	H	>6.25
2b	Cyclohexyl	Br	H	>6.25
2c	**2-Furyl**	**H**	**H**	**>6.25 (9)**
2d	2-Furyl	Br	H	>6.25
2e	2-Thienyl	H	H	>6.25
2f	2-Thienyl	Br	H	>6.25
6a	**Cyclohexyl**	H	**CHO**	**>6.25 (36)**
6b	**Cyclohexyl**	Br	**CHO**	**>6.25 (30)**
6c	**2-Furyl**	H	**CHO**	**>6.25 (100)**
6d	2-Furyl	Br	CHO	>6.25
6e	**2-Thienyl**	**H**	**CHO**	**>6.25 (10)**
6f	2-Thienyl	Br	CHO	>6.25
7a	**Cyclohexyl**	H	CH_2OH	**>6.25 (100)**
7b	Cyclohexyl	Br	CH_2OH	>6.25 (13)
7c	2-Furyl	H	CH_2OH	>6.25
7d	2-Furyl	Br	CH_2OH	>6.25
7e	2-Thienyl	H	CH_2OH	>6.25
7f	2-Thienyl	Br	CH_2OH	>6.25
8a	Cyclohexyl	H	CH=NOH	>6.25
8b	2-Furyl	H	CH=NOH	>6.25
8c	2-Thienyl	H	CH=NOH	>6.25
9a	Cyclohexyl	H	CN	>6.25
9b	2-Furyl	H	CN	>6.25
9c	2-Thienyl	H	CN	>6.25
10a	Cyclohexyl	H	2(3-Phenyl-1,3-thiazolidin-4-one)	>6.25
10b	2-Furyl	H	2(3-Phenyl-1,3-thiazolidin-4-one)	>6.25
10c	2-Thienyl	H	2(3-Phenyl-1,3-thiazolidin-4-one)	>6.25

Rifampicin (standard) 6.25 μg/mL (100% inhibition). The active compounds and their activity is marked in bold letters.

with thionylchloride exhibited the sharp band around 2200 cm^{-1} in the IR spectrum assigned for ν_{CN} and there was no band due to ν_{O-H}. The ^1H NMR of the compound showed the absence of both –OH proton and azomethine proton. This confirmed, the products obtained were the resultants of dehydrated aldoximes, that is, nitriles (**9**). The compound **10** showed the carbonyl stretching frequency $\nu_{C=O}$ around 1700 cm^{-1}, the ^1H NMR of the same exhibited two singlets around δ 6.00 and 7.50, respectively. These data confirmed the presence of thiazolidinone ring at 5-position.

The synthesized compounds were evaluated for their in vitro anti-tuberculosis activity against *M. tuberculosis* strain $H_{37}Rv$ by using radiometric BACTEC and broth dilution assays. The data of the antitubercular activity screening reveal that the compounds **2a**–**f** having no substitution at position-5 did not show any considerable activity, in spite of the changes at the two variable at position-2 and position-6. However, when a formyl group was introduced at position-5 (compounds **6a**–**f**), it resulted in compounds having an enhanced antimycobacterial activity. 2-(2-Furyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde **6c** showed 100% inhibition at a concentration of 6.25 μg/mL. Encouraging activity profile was also found when the aldehydes (**6a**–**f**) were reduced to the corresponding carbinols (**7a**–**f**). In this series (2-cyclohexyl-6-phenylimidazo [2,1-*b*][1,3,4]thiadiazol-5-yl)methanol (**7a**) showed highest inhibition at the same concentration. It is interesting to note that the derivatization of aldehydes (**6a**–**f**) to oximes (**8a**–**f**), nitriles (**9a**–**f**), and thiazolidinones (**10a**–**c**) resulted in compounds with minimized activity potentials. Similarly, the Mannich bases of imidazothiadiazole at the 5th position derived from various secondary cyclic amines failed to produce any compound with improved antimycobacterial activity. We have noticed that even among the most active compounds (**6a**, **6c**, and **7a**) the 2-cyclohexyl/furyl and 6-phenyl contributed more to the antitubercular activity. The result of the antimycobacterial activity is presented in Tables 1 and 2.

The antibacterial screenings (Table 3) revealed that the Mannich bases are superior over imidazo[2,1-*b*]-[1,3,4]thiadiazoles. Among these the pyrrollidine derivatives were found to have more activity against *E. coli* and **5e** has shown complete inhibition of *B. cirrhosis*. The morpholine derivative **3a** and piperidinyl derivative **4a** showed significant activity against *E. coli* and *B. cirrhosis*. The aldehydes **6b** and **6c** showed good inhibition of *E. coli* and *B. cirrhosis*, respectively, at a concentration of 100 μg/mL.

Table 3. The in vitro antibacterial activity of compounds against *Escherichia coli* and *Bacillus cirrhosis*

Compound	Relative inhibition (%)					
	Escherichia coli			*Bacillus cirrhosis*		
	100 μg/mL	50 μg/mL	25 μg/mL	100 μg/mL	50 μg/mL	25 μg/mL
2a	10	—	—	24	10	—
2b	12	—	—	10	—	—
2c	21	—	—	34	20	—
2d	35	9	—	32	16	—
2e	9	—	—	20	—	—
2f	11	—	—	12	—	—
3a	90	60	30	40	22	—
3b	71	54	20	65	46	30
3c	60	51	34	50	38	10
3d	24	10	—	70	45	34
3e	40	24	—	58	36	12
3f	44	30	15	60	46	30
4a	91	50	18	24	10	—
4b	35	20	—	30	14	—
4c	75	50	39	66	42	26
4d	64	46	18	40	24	10
4e	75	50	36	14	—	—
4f	34	10	—	12	—	—
5a	100	80	47	30	12	—
5b	12	—	—	24	—	—
5c	100	89	43	12	—	—
5d	44	20	—	88	62	49
5e	84	69	23	100	80	68
5f	15	—	—	18	—	—
6a	10	—	—	12	—	—
6b	14	—	—	82	61	17
6c	93	78	51	46	24	10
6d	55	30	18	58	28	12
6e	60	44	30	30	12	—
6f	24	10	—	60	46	26
7a	12	—	—	24	—	—
7b	60	48	30	44	20	12
7c	40	28	10	20	—	—
7d	25	12	—	34	12	—
7e	18	—	—	60	50	30
7f	64	46	28	30	12	—
8a	20	12	—	10	—	—
8b	34	14	—	—	—	—
8c	80	66	40	81	60	48
9a	68	40	28	15	—	—
9b	12	—	—	—	—	—
9c	64	30	12	22	—	—
10a	24	14	—	10	—	—
10b	10	—	—	12	—	—
10c	34	22	—	80	55	30

Norfloxacin (standard) 100% inhibition at each concentration.

From the antifungal screening results it is clear that, the Mannich bases **3c**, **4a**, and **5a**, and **5a**, **7c**, and **7e** displayed better antifungal activity against *P. wortmannii* and *A. niger*, respectively. Compound **5a** is found to be the most potent antifungal agent against both the fungal strains.

5. Conclusion

The preliminary in vitro antituberculosis screening, antibacterial and antifungal screening results of novel imidazo[2,1-*b*][1,3,4]thiadiazole derivatives, reported in the present article, evidenced that many of the compounds from the series have emerged as potent antitubercular, antibacterial, and antifungal agents endowed with moderate to good activity. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic imidazo[2,1-*b*][1,3,4]thiadiazole nucleus. Our findings will have impact on chemists and pharmacists for further investigations in this field in search of potent antitubercular and antimicrobial agents.

Table 4. The in vitro antifungal activity of compounds against *Penicillium wortmannii* and *Aspergillus niger*

Compound	Relative inhibition (%)					
	Penicillium wortmannii			*Aspergillus niger*		
	100 μg/mL	50 μg/mL	25 μg/mL	100 μg/mL	50 μg/mL	25 μg/mL
2a	26	12	—	24	10	—
2b	20	—	—	18	—	—
2c	78	45	25	54	30	—
2d	56	30	20	22	—	—
2e	10	—	—	—	—	—
2f	12	—	—	—	—	—
3a	10	—	—	30	—	—
3b	64	30	12	44	20	—
3c	78	52	24	91	71	30
3d	50	30	20	30	10	—
3e	32	—	—	10	—	—
3f	44	36	14	40	18	10
4a	91	78	60	78	44	20
4b	24	10	—	18	—	—
4c	40	15	—	20	—	—
4d	12	—	—	25	10	—
4e	30	20	12	20	—	—
4f	14	—	—	18	—	—
5a	100	85	57	100	80	41
5b	32	12	—	34	12	—
5c	22	10	—	14	—	—
5d	12	—	—			
5e	78	42	20	46	20	—
5f	12	—	—	20	—	—
6a	—	—	—	—	—	—
6b	22	—	—	22	—	—
6c	38	15	—	20	10	—
6d	60	38	20	—	—	—
6e	22	—	—	12	—	—
6f	10	—	—	8	—	—
7a	34	20	—	28	10	—
7b	26	10	—	22	—	—
7c	68	42	26	75	51	25
7d	24	10	—	46	14	—
7e	66	52	30	75	49	22
7f	12	—	—	12	—	—
8a	10	—	—	10	—	—
8b	12	—	—	24	—	—
8c	20	—	—	—	—	—
9a	24	10	—	10	—	—
9b	40	24	—	—	—	—
9c	14	—	—	—	—	—
10a	68	46	20	—	—	—
10b	60	38	12	—	—	—
10c	46	20	—	20	—	—

Greseofulvin (standard) 100% inhibition at each concentration.

6. Experimental

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Nicolet Impact 410 FT IR spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR were recorded on a Bruker 300-MHz FT NMR spectrometer in $CDCl_3$ and DMSO-d_6 with TMS as internal standard. Mass spectra were recorded on a Quattro II Micromass Walter instrument (UK Ltd.) by electron impact technique and elemental analysis was carried out using Heraus CHN rapid analyzer.

6.1. Preparation of 2-alkyl/aryl-6-arylimidazo[2,1-*b*]-[1,3,4]thiadiazoles (2a–f): general method

A mixture of equimolar quantities of 2-amino-5-alkyl/aryl-1,3,4-thiadiazoles **1a**–**c**, (0.01 mol) and bromoacetyl compound (0.01 mol) was refluxed in dry ethanol for 8 h. The excess of solvent was distilled off and the solid hydrobromide that separated was collected by filtration, suspended in water, and neutralized by aqueous sodium carbonate solution to get free base (**2**). It was filtered, washed with water, dried, and recrystallized from suit-

able solvent. (Compounds **2a**, **2c**, and **2e** were prepared as per the literature method.[23])

6.1.1. 6-(4-Bromophenyl)-2-cyclohexylimidazo[2,1-*b*][1,3,4]-thiadiazole (2b). Yield 75%; colorless solid (ethanol); mp 188–190 °C IR (KBr) ν cm^{-1} 2928, 1623, 1580, 1457; ^{1}H NMR ($CDCl_3$) δ 1.34–3.01 (m, 11H, cyclohexyl), 7.55 (d, J = 9 Hz, 2H, C3, C5-H, phenyl), 7.71 (d, J = 9 Hz, 2H, C2, C6-H), 7.90 (s, 1H, C5-H, imidazole); ^{13}C NMR ($CDCl_3$) δ 25.9 (C4, cyclohexyl), 26.0 (C3, C5, cyclohexyl), 33.0 (C2, C6, cyclohexyl), 41.7 (C1, cyclohexyl), 109.5, 123.1, 126.9, 132.1, 133.4, 145.2, 145.7 and 170.5; Anal. Calcd for $C_{16}H_{16}BrN_3S$: C, 53.04; H, 4.45; N, 11.60. Found: C, 53.19; H, 4.61; N, 11.93.

6.1.2. 6-(4-Bromophenyl)-2-(2-furyl)imidazo[2,1-*b*][1,3,4]-thiadiazole (2d). Yield 42%; pale yellow solid (ethanol + DMF); mp 188–190 °C; IR (KBr) ν cm^{-1} 1593, 1533, 1500; ^{1}H NMR ($CDCl_3$) δ 6.64 (dd, J_{H3H4} = 3 Hz, J_{H4H5} = 3 Hz, 1H, C4-H, furan), 7.13 (d, J = 3 Hz, 1H, C3-H, furan), 7.57 (d, J = 9 Hz, 2H, C3, C5-H, phenyl), 7.64 (d, J = 3 Hz, 1H, C5-H, furan), 7.71 (d, J = 9 Hz, 2H, C2, C6-H, phenyl), 8.03 (s, 1H, C5-H, imidazole); Anal. Calcd for $C_{14}H_8BrN_3OS$: C, 48.57; H, 2.33; N, 12.14. Found C, 48.71; H, 2.48; N, 12.49.

6.1.3. 6-(4-Bromophenyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]-thiadiazole (2f). Yield 70%; light yellow solid (ethanol); mp 165–167 °C; IR (KBr) ν cm^{-1} 3015, 1605, 1543; ^{1}H NMR ($CDCl_3$) δ 7.05 (dd, J_{H3H4} = 3 Hz, J_{H4H5} = 3 Hz, 1H, C4-H, thiophene), 7.07 (d, J = 3 Hz, 1H, C3-H, thiophene), 7.40 (d, J = 3 Hz, 1H, C5-H, thiophene), 7.67 (d, J = 9 Hz, 2H, C3, C5-H, phenyl), 7.90 (d, J = 9 Hz, 2H, C2, C6-H, phenyl), 8.03 (s, 1H, C5-H, imidazole); Anal. Calcd for $C_{14}H_8BrN_3S_2$: C, 46.42; H, 2.23; N, 11.60. Found: C, 46.87; H, 2.35; N, 11.86.

6.2. Preparation of 2-alkyl/aryl-5-(morpholin-4-ylmethyl)-6-arylimidazo[2,1-*b*] [1,3,4]thiadiazoles (3a–f): general method

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 8 h (monitored by TLC). The solution was diluted with water, extracted with chloroform (3× 30 mL), the combined chloroform extract was washed with water (3× 30 mL) and dried over anhydrous sodium sulfate. The solution was evaporated to dryness in vacuum and the residue was recrystallized from appropriate solvent.

6.2.1. 2-Cyclohexyl-5-(morpholin-4-ylmethyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole (3a). Yield 75%; colorless needles (hexane); mp 104–106 °C; ^{1}H NMR ($CDCl_3$) δ 1.31–2.19 (m, 10H, cyclohexyl), 2.56 (t, J = 4.2 Hz, 4H, C3, C5-H, morpholine), 3.05 (m, 1H, C1-H, cyclohexyl), 3.72 (t, J = 3.9 Hz, 4H, C2, C6-H, morpholine), 3.91 (s, 2H, CH_2), 7.30–7.47 (m, 3H, C3, C4, C5-H, phenyl), 7.98 (m, 2H, C2, C6-H, phenyl); Anal. Calcd for $C_{21}H_{26}N_4OS$: C, 65.914; H, 6.85; N, 14.65. Found: C, 66.35; H, 6.78; N, 14.79. Mass (m/z) 376.

6.2.2. 6-(4-Bromophenyl)-2-cyclohexyl-5-(morpholin-4-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (3b). Yield 62%; colorless solid (chloroform + hexane); mp 164–166 °C; ^{1}H NMR ($CDCl_3$) δ 1.31–2.16 (m, 10H, cyclohexyl), 2.53 (t, J = 4.5 Hz, 4H, C3, C5-H, morpholine), 3.01 (m, 1H, C1-H, cyclohexyl), 3.69 (t, J = 4.5 Hz, 4H, C2, C6-H, morpholine) 3.84 (s, 2H, CH_2), 7.55 (d, J = 8.7 Hz, 2H, C3, C5-H, phenyl), 7.84 (d, J = 8.7 Hz, 2H, C2, C6-H, phenyl); ^{13}C NMR ($CDCl_3$) δ 25.9 (C4, cyclohexyl), 26.0 (C3, C5 cyclohexyl), 33.0 (C2, C6, cyclohexyl), 41.6 (C1 cyclohexyl), 51.7 (CH_2), 53.3 (NCH_2 morpholine), 67.3 (OCH_2 morpholine), 120.3, 121.5, 129.4, 131.8, 134.1, 143.6, 143.8 and 170.1; Anal. Calcd for $C_{21}H_{25}BrN_4OS$: C, 54.66; H, 5.46; N, 12.14. Found: C, 54.58; H, 5.89; N, 12.72. Mass, m/z(%), 461 (25), 463 (25), 374 (100), 376 (100).

6.2.3. 2-(2-Furyl)-5-(morpholin-4-ylmethyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole (3c). Yield 63%; pale yellow solid chloroform + hexane); mp 120–122 °C; ^{1}H NMR ($CDCl_3$) δ 2.54 (t, J = 4.5 Hz, 4H, C3, C5-H, morpholine), 3.68 (t, J = 4.5 Hz, 4H, C2, C6-H, morpholine), 3.90 (s, 2H, CH_2), 6.60 (dd, J_{H3H4} = 4.5 Hz, J_{H4H5} = 3.3 Hz, 1H, C4-H, furan), 7.14 (d, J = 4.5 Hz, 1H, C3-H, furan), 7.50–7.94 (m, 6H, phenyl, C5-H, furan). Anal. Calcd for $C_{19}H_{18}N_4O_2S1$: C, 62.28; H, 4.95; N, 15.29. Found: C, 62.42; H, 5.16; N, 15.62.

6.2.4. 6-(4-Bromophenyl)-2-(2-furyl)-5-(morpholin-4-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (3d). Yield 63%; pale yellow crystalline solid (benzene + pet ether); mp 176–178 °C; ^{1}H NMR ($CDCl_3$) δ 2.58 (t, 4.5 Hz, 4H, C3, C5-H, morpholine), 3.72 (t, J = 4.5 Hz, 4H, C2, C6-H, morpholine), 3.95 (s, 2H, CH_2), 6.63 (dd, J_{H3H4} = 3.3 Hz, J_{H4H5} = 3.3 Hz, 1H, C4-H, furan), 7.14 (d, J = 3.3 Hz, 1H, C3-H, furan), 7.52 (d, J = 9 Hz, 2H, C3, C5-H, phenyl), 7.63 (d, J = 3.3 Hz, 1H, C5-H, furan), 7.90 (d, J = 9 Hz, C2, C6-H, phenyl); Anal. Calcd for $C_{19}H_{17}BrN_4O_2S$: C, 51.24; H, 3.85, N, 12.58. Found: C, 51.62; H, 3.91; N, 12.88.

6.2.5. 5-(Morpholin-4-ylmethyl)-6-phenyl-2-thien-2-ylimidazo[2,1-*b*][1,3,4] thiadiazole (3e). Yield 70%; colorless needles (chloroform + hexane); mp 158–160 °C; ^{1}H NMR ($CDCl_3$) δ 2.61 (t, J = 6 Hz, 4H, C3, C5-H, morpholine), 3.73 (t, J = 6 Hz, 4H, C2, C6-H, morpholine), 3.97 (s, 2H, CH_2), 7.17 (dd, J = 3.6 Hz and 4.2 Hz, 1H, C3-H, thiophene), 7.32–7.58 (m, 5H, phenyl, C3, C5-H thiophene), 7.99 (m, 2H, C2, C6-H phenyl); ^{13}C NMR ($CDCl_3$) δ 51.6 (CH_2), 53.4 (NCH_2 morpholine), 67.4 (OCH_2 morpholine), 120.7, 127.8, 127.9, 128.4, 128.9, 129.3, 130.0, 133.1, 134.4, 143.3, 145.4 and 155.5; Anal. Calcd for $C_{19}H_{18}N_4OS_2$: C, 59.66; H, 4.74; N, 14.65. Found: C, 59.98; H, 4.89; N, 15.03.

6.2.6. 6-(4-Bromophenyl)-5-(morpholin-4-ylmethyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole (3f). Yield 60%; pale yellow solid (benzene + pet ether); mp 84–86 °C; ^{1}H NMR ($CDCl_3$) δ 2.50 (t, 4H, J = 6 Hz, C3, C5-H, morpholine), 3.71 (t, J = 6 Hz, 4H, C2, C6-H, morpholine), 4.14 (s, 2H, CH_2), 71.16 (dd, J_{H3H4} = 3.6 Hz, J_{H4H5} = 3.6 Hz, C4-H, thiophene), 7.23 (d, J = 3.6 Hz, 1H, C3-H, thiophene), 7.57 (d, J = 3.6 Hz, C5-H, thio-

phene), 7.71 (d, $J = 9$ Hz, 2H, C3, C5-H, phenyl), 7.89 (d, $J = 9$ Hz, 2H, C2, C6-H, phenyl); Anal. Calcd for $C_{19}H_{17}BrN_4OS_2$: C, 49.46; H, 3.71; N, 12.14. Found: C, 49.82; H, 3.76; N, 12.60.

6.3. Preparation of 2-alkyl/aryl-6-aryl-5-(piperidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazoles (4a–f): general method

Prepared by following the same procedure as for the preparation of **14**, piperidine was used as secondary amine.

6.3.1. 2-Cyclohexyl-6-phenyl-5-(piperidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4] thiadiazole (4a). Yield 58%; colorless granules (hexane); mp 100–102 °C; ^{1}H NMR ($CDCl_3$) δ 1.27–3.08 (m, 21H, cyclohexyl, piperidinyl), 3.86 (s, 2H, CH_2), 7.31–7.46 (m, 3H, C3, C4, C5-H, phenyl), 7.98 (m, 2H, C2, C6-H, phenyl);^{13}C NMR ($CDCl_3$) δ 24.6 (C4, piperidine), 25.9 (C4, cyclohexyl), 26.0 (C3, C5 cyclohexyl), 26.4 (C3, C5 piperidine), 33.1 (C2, C6 cyclohexyl), 41.7 (C1, cyclohexyl), 52.0 (CH_2), 54.3 (NCH_2, piperidine), 121.2, 127.3, 128.0, 128.7, 135.4, 143.5, 144.4 and 169.6; Anal. Calcd for $C_{22}H_{28}N_4S$: C, 69.44; H, 7.42; N, 14.72. Found: C, 69.82; H, 7.48; N, 14.91.

6.3.2. 6-(4-Bromophenyl)-2-cyclohexyl-(piperidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (4b). Yield 58%; pale yellow granules (benzene + pet ether); mp 138–140 °C; ^{1}H NMR ($CDCl_3$) δ 1.26–2.47 (m, 20H, cyclohexyl, piperidine), 3.02 (m, 1H, C1-H, cyclohexyl), 3.81 (s, 2H, CH_2), 7.57 (d, $J = 8.4$ Hz, 2H, C3, C5-H, phenyl), 7.90 (d, $J = 8.4$ Hz, 2H, C2, C6-H, phenyl); ^{13}C NMR ($CDCl_3$) δ 24.6 (C4, cyclohexyl), 25.9 (C4, piperidine), 26.0 (C3, C5, cyclohexyl), 26.3 (C2, C6 cyclohexyl), 33.1 (C3, C5 piperidine), 41.7 (C1, cyclohexyl), 52.0 (CH_2), 54.3 (C2, C6 piperidine), 121.4, 121.4, 129.6, 131.8, 134.3, 143.3, 143.6 and 169.9; Anal. Calcd for $C_{22}H_{27}BrN_4S$: C, 57.51; H, 5.92; N, 12.19. Found: C, 57.82; H, 5.88; N, 12.53.

6.3.3. 2-(2-Furyl)-6-phenyl-5-(piperidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (4c). Yield 67%; yellow granules (benzene + pet ether); mp 128–130 °C; ^{1}H NMR ($CDCl_3$) δ 1.24–1.53 (m, 6H, C3, C4, C5-H, piperidine), 2.44 (m, 4H, C2, C6-H, piperidine), 3.78 (s, 2H, CH_2), 6.62 (dd, $J_{H3H4} = 3$ Hz, $J_{H4H5} = 3$ Hz, 1H, C4-H, furan), 7.14 (d, $J = 3$ Hz, 1H, C3-H, furan), 7.53–7.90 (m, 6H, phenyl, C5-H, furan); Anal. Calcd for $C_{20}H_{20}N_4OS$: C, 65.91; H, 5.53; N, 15.37. Found: C, 66.26; H, 5.55; N, 15.99.

6.3.4. 6-(4-Bromophenyl)-2-(2-furyl)-5-(piperidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (4d). Yield 47%; pale yellow granules (benzene + pet ether); mp 101–103 °C; ^{1}H NMR ($CDCl_3$) δ 1.21–1.54 (m, 6H, C3, C4, C5-H, piperidine), 2.41 (m, 4H, C2, C6-H, piperidine), 3.81 (s, 2H, CH_2), 6.60 (dd, $J_{H3H4} = 3$ Hz, $J_{H4H5} = 3.3$ Hz, 1H, C4-H, furan), 7.13 (d, $J = 3$ Hz, 1H, C3-H, furan), 7.51–7.88 (m, 5H, phenyl, C5-H, furan); Anal. Calcd for $C_{20}H_{19}BrN_4OS$: C, 54.18; H, 4.32; N, 12.64. Found C, 54.41; H, 4.21; N, 12.55.

6.3.5. 6-Phenyl-5-(piperidin-1-ylmethyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole (4e). Yield 60%; yellow granules (chloroform + hexane); mp 144–146 °C; ^{1}H NMR ($CDCl_3$) δ 1.44–1.61 (m, 6H, C3, C4, C5-H, piperidine), 2.52 (m, 4H, C2, C6-H, piperidine), 3.92 (s, 2H, CH_2), 7.17 (dd, $J = 3.6$ Hz and 4.5 Hz, 1H, C4-H, thiophene), 7.31–7.57 (m, 5H, C3, C4, C5-H phenyl, C3, C5-H, thienyl), 8.04 (m, 2H, C2, C6-H, phenyl); ^{13}C NMR ($CDCl_3$) δ 24.6 (C4, piperidine), 26.4 (C3, C5 piperidine), 51.9 (C2, C6 piperidine), 54.3 (CH_2), 125.4, 127.6, 128.0, 128.3, 129.8, 129.1, 129.1, 129.8, 133.3, 135.2, 145.1 and 155.1; Anal. Calcd for $C_{20}H_{20}N_4S_2$: C, 63.13; H, 5.30; N, 14.72. Found: C, 63.38; H, 5.55; N, 15.31.

6.3.6. 6-(4-Bromophenyl)-5-(piperidin-1-ylmethyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole (4f). Yield 56%; pale yellow granules (chloroform + hexane); mp 138–140 °C; ^{1}H NMR ($CDCl_3$) δ 1.27–1.57 (m, 6H, C3, C4, C5-H, piperidine), 2.49 (m, 4H, C2, C6-H, piperidine), 3.76 (s, 2H, CH_2), 7.15 (dd, $J_{H3H4} = 3.6$ Hz, $J_{H4H5} = 3.6$ Hz, 1H, C4-H, thiophene), 7.22 (d, $J = 3.6$ Hz, 1H, C3-H, thiophene), 7.58 (d, $J = 3.6$ Hz, 1H, C5-H, thiophene), 7.91 (d, $J = 8.4$ Hz, 2H, C3, C5-H, phenyl), 7.96 (d, $J = 8.4$ Hz, 2H, C2, C6-H, phenyl); Anal. Calcd for $C_{20}H_{19}BrN_4S_2$: C, 52.29; H, 4.17; N, 12.19. Found: C, 52.63; H, 4.21; N, 12.73.

6.4. Preparation of 6-aryl-2-alkyl/aryl-(pyrrolidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazoles (5a–f)

Prepared by following the same procedure as for the preparation of **14**, pyrrolidine was used as secondary amine.

6.4.1. 2-Cyclohexyl-6-phenyl-5-(pyrrolidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (5a). Yield 59%; colorless crystalline solid (pet ether); mp 90–92 °C; ^{1}H NMR ($CDCl_3$) δ 1.27–3.34 (m, 19H, cyclohexyl, pyrrolidine), 4.04 (s, 2H, CH_2), 7.31–7.46 (m, 3H, C3, C4, C5-H, phenyl), 7.91 (m, 2H, C2, C6-H, phenyl); Anal. Calcd for $C_{21}H_{26}N_4S$: C, 68.82; H, 7.15; N, 15.29. Found: C, 68.65; H, 7.30; N, 15.41.

6.4.2. 6-(4-Bromophenyl)-2-cyclohexyl-5-(pyrrolidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (5b). Yield 55%; pale yellow solid (chloroform + pet ether); mp 128–130 °C; ^{1}H NMR ($CDCl_3$) δ 1.29–3.35 (m, 19H, cyclohexyl, pyrrolidine), 3.89 (s, 2H, CH_2), 7.63 (d, $J = 8.4$ Hz, 2H, C3, C5-H, phenyl), 7.88 (d, $J = 8.4$ Hz, 2H, C2, C6-H, phenyl); Anal. Calcd for $C_{21}H_{25}BrN_4$: C, 56.63; H, 5.66; N, 12.58. Found: C, 56.49; H, 5.51; N, 12.72.

6.4.3. 2-(2-Furyl)-6-phenyl-5-(pyrrolidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (5c). Yield 60%; colorless solid (benzene + pet ether); mp 110–112 °C; ^{1}H NMR ($CDCl_3$) δ 2.13–2.60 (m, 4H, C3, C4-H, pyrrolidine), 3.29–3.46 (m, 4H, C2, C5-H, pyrrolidine), 3.98 (s, 2H, CH_2), 6.69 (dd, $J_{H3H4} = 3.3$ Hz, $J_{H4H5} = 4.2$ Hz 1H, C4-H, furan), 7.16 (d, $J = 3.3$ Hz, 1H, C3-H, furan), 7.50–7.88 (m, 6H, phenyl, C5-H, furan); Anal. Calcd for $C_{19}H_{18}N_4OS$: C, 65.12; H, 5.18; N, 15.99. Found: C, 65.61; H, 5.39; N, 16.60.

6.4.4. 6-(4-Bromophenyl)-2-(2-furyl)-5-(pyrrolidin-1-ylmethyl)imidazo[2,1-*b*][1,3,4]thiadiazole (5d). Yield 51%; Yellow solid (chloroform); mp 150–152 °C; ^{1}H NMR ($CDCl_3$) δ 2.15–2.62 (m, 4H, C3, C4-H, pyrrolidine), 3.32–3.55 (m, 4H, C2, C5-H, pyrrolidine), 6.68 (dd, J_{H3H4} = 3.3 Hz, J_{H4H5} = 3 Hz, 1H, C4-H, furan), 7.12 (d, J = 3.3 Hz, 1H, C3-H, furan), 7.50 (d, J = 9 Hz, 2H, C3, C5-H, phenyl), 7.61 (d, J = 3 Hz, 1H, C5-H, furan), 7.92 (d, J = 9 Hz, C2, C6-H, phenyl); Anal. Calcd for $C_{19}H_{17}BrN_4OS$: C, 53.15; H, 3.99; N, 13.05. Found: C, 53.47; H, 4.26; N, 13.37.

6.4.5. 6-Phenyl-5-(pyrrolidin-1-ylmethyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole (5e). Yield 61%; colorless solid (pet ether); mp 54–56 °C; ^{1}H NMR ($CDCl_3$) δ 2.22–2.66 (m, 4H, C3, C4-H, pyrrolidine), 3.28–3.47 (m, 4H, C2, C5-H, pyrrolidine), 4.10 (s, 2H, CH_2), 7.17 (dd, J = 3.6 Hz and 3.3 Hz, 1H, C4-H, thiophene), 7.30–7.86 (m, 7H, phenyl, C3, C5-H, thiophene); Anal. Calcd for $C_{19}H_{18}N_4S_2$: C, 62.26; H, 4.95; N, 15.29. Found: C, 62.45; H, 4.82; N, 15.76.

6.4.6. 6-(4-Bromophenyl)-5-(pyrrolidin-1-ylmethyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole (5f). Yield 58%; Yellow solid (chloroform + pet ether); mp 144–146 °C; ^{1}H NMR ($CDCl_3$) δ 2.18–2.63 (m, 4H, C3, C4-H, pyrrolidine), 3.33–3.51 (m, 4H, C2, C5-H, pyrrolidine), 4.15 (s, 2H, CH_2), 7.17 (dd, J_{H3H4} = 3.6 Hz, J_{H4H5} = 3.6 Hz, 1H, C4-H, thiophene), 7.30 (d, J = 3.6 Hz, 1H, C3-H, thiophene), 7.57 (d, J = 3.6 Hz, 1H, C5-H, thiophene), 7.69 (d, J = 8.4 Hz, 2H, C3, C5-H, phenyl), 7.91 (d, J = 8.4 Hz, 2H, C2, C6-H, phenyl); Anal. Calcd for $C_{19}H_{17}BrN_4S_2$: C, 51.24; H, 3.85; N, 12.58. Found: C, 51.10; H, 3.71; N, 12.71.

6.5. Preparation of 2-alkyl/aryl-6-arylimidazo[2,1-*b*]-[1,3,4]thiadiazole-5-carbaldehydes (6a–f)

Vilsmeier–Haack reagent was prepared by adding phosphoryl chloride (3 ml) in dimethylformamide (20 ml) at 0 °C with stirring. Then appropriately substituted 2-alkyl/aryl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole (**2a–f**, 0.01 mol) was added to the reagent and stirred at 0 °C for 30 min. The mixture was further stirred for 2 h at room temperature and at 60 °C for additional 2 h. The reaction mixture was then poured in sodium carbonate solution and stirred at 90 °C for 2 h. After cooling, the mixture was diluted with water, extracted with chloroform, and the collective extract was washed with water and dried over anhydrous sodium sulfate. The residue obtained after the removal of chloroform was recrystallized from a suitable solvent to get the crystalline solid.

6.5.1. 2-Cyclohexyl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (6a). Yield 68%; colorless cubes (chloroform + benzene); mp 114–116 °C; IR (KBr) ν cm^{-1}, 2851, 1674, 1597; ^{1}H NMR ($CDCl_3$) δ 1.30–3.27 (m, 11H, cyclohexyl), 7.51–7.86 (m, 5H, ArH), 10.04 (s, 1H, aldehyde); Anal. Calcd for $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.50; N, 13.49. Found: C, 65.92; H, 5.67; N, 13.68.

6.5.2. 6-(4-Bromophenyl)-2-cyclohexylimidazo[2,1-*b*][1,3,4]-thiadiazole-5-carbaldehyde (6b). Yield 67%; colorless cubes (chloroform + hexane); mp 144–146 °C; IR (KBr) ν cm^{-1}, 2848, 1676, 1588; ^{1}H NMR ($CDCl_3$) δ 1.30–3.15 (m, 11H, cyclohexyl), 7.60 (d, J = 9 Hz, 2H, C3, C5-H, phenyl), 7.77 (d, J = 9 Hz, 2H, C2, C6-H, phenyl), 10.03 (s, 1H, aldehyde) Anal. Calcd for $C_{17}H_{16}BrN_3OS$: C, 52.31; H, 4.13; N, 10.77. Found: C, 52.71; H, 4.27; N, 11.20.

6.5.3. 2-(2-Furyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (6c). Yield 76%; pale yellow solid (chloroform + hexane); mp 130–132 °C; IR (KBr) ν cm^{-1}, 2831, 1655, 1600, 1594; ^{1}H NMR ($CDCl_3$) δ 6.68 (dd, J_{H3H4} = 3 Hz, J_{H4H5} = 3 Hz, 1H, C4-H, furyl), 7.35 (d, J = 3 Hz, 1H, C3-H, furyl), 7.52–7.92 (m, 6H, C5-H, furyl, phenyl), 10.11 (s, 1H, aldehyde); Anal. Calcd for $C_{15}H_9N_3O_2S$: C, 61.01; H, 3.07; N, 14.23. Found: C, 61.10; H, 3.12; N, 14.29.

6.5.4. 6-(4-Bromophenyl)-2-(2-furyl)imidazo[2,1-*b*][1,3,4]-thiadiazole-5-carbaldehyde (6d). Yield 63%; pale yellow solid (chloroform); mp 172–174 °C; IR (KBr) ν cm^{-1} 2879, 1678, 1606; ^{1}H NMR ($CDCl_3$) δ 6.67 (dd, J_{H3H4} = 3 Hz, J_{H4H5} = 3 Hz, 1H, C4-H, furyl), 7.31 (d, J = 3 Hz, 1H, C3-H, furyl), 7.65 (d, J = 9 Hz, 2H, C3, C5-H, phenyl), 7.68 (d, J = 3 Hz, 1H, C5-H, furyl), 7.87 (d, J = 9 Hz, 2H, C2, C6-H, phenyl), 10.12 (s, 1H, aldehyde); Anal. Calcd for, $C_{15}H_8BrN_3O_2S$: C, 48.14; H, 2.15, N, 11.23. Found: C, 48.38; H, 2.26, N, 11.61.

6.5.5. 6-Phenyl-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (6e). Yield 70%; colorless needles (chloroform); mp 194–196 °C; IR (KBr) ν cm^{-1}, 2850, 1650, 1550; ^{1}H NMR ($CDCl_3$) δ 7.20 (dd, J = 3 Hz and 3.9 Hz, 1H, C4-H, thienyl), 7.22–7.95 (m, 7H, C3, C5-H, thienyl and phenyl), 10.13 (s, 1H, aldehyde); Anal. Calcd for $C_{15}H_9N_3OS_2$: C, 57.86, H, 2.91, N, 13.49. Found: C, 58.02, H, 3.10, N, 13.80.

6.5.6. 6-(4-Bromophenyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]-thiadiazole-5-carbaldehyde (6f). Yield 72%; colorless prisms (chloroform + hexane); mp 158–160 °C; IR (KBr) ν cm^{-1}, 2856, 1673, 1565; ^{1}H NMR ($CDCl_3$) δ 7.18 (dd, J = 3 Hz and 3.3 Hz, 1H, C4-H, thienyl), 7.25–7.98 (m, 6H, C3, C5-H, thiophene and phenyl), 10.10 (s, 1H, aldehyde); Anal. Calcd for $C_{15}H_8BrN_3OS_2$: C, 46.16; H, 2.07; N, 10.77. Found: C, 46.45; H, 2.26; N, 11.14.

6.6. Preparation of (2-alkyl/aryl-6-arylimidazo[2,1-*b*][1,3,4]-thiadiazol-5-yl) methanol (7a–f): general method

2-Alkyl/aryl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (0.001 mol) was added in small portions to a stirred and cooled solution of sodiumborohydride (0.36 g, 0.001 mol) in dry methanol (20 ml). The mixture was stirred at room temperature for 5 h (monitored by TLC) and poured over ice water. The solid separated was collected by filtration, washed with cold methanol, dried, and crystallized from benzene.

6.6.1. (2-Cyclohexyl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl)methanol (7a). Yield 80%; colorless needles (benzene); mp 176–178 °C; IR (KBr) ν cm^{-1}, 3201, 1603, 1557;^{1}H NMR ($CDCl_3$) δ 1.25–2.12 (m, 10H, cyclohexyl), 2.97 (m, 1H, C1-H, cyclohexyl), 3.18 (br s,

1H, OH, D_2O exchangeable), 5.03 (s, 2H, CH_2), 7.29–7.79 (m, 5H, phenyl), ^{13}C NMR ($CDCl_3$) δ 25.8 (C4, cyclohexyl), 26.0 (C3, C5, cyclohexyl), 33.1 (C2, C6, cyclohexyl), 41.7 (C1, cyclohexyl), 54.4 (CH_2), 122.6, 127.8, 127.9, 129.0, 134.5, 144.3, 144.4 and 170.7; Anal. Calcd for $C_{17}H_{19}N_3OS$: C, 65.15; H, 6.11, N, 13.41. Found: C, 65.53; H, 6.22, N, 13.74. Mass, *m*/*z* (%), 314.03 (M + 1, 100%).

6.6.2. [6-(4-Bromophenyl)-2-cyclohexylimidazo[2,1-*b*][1,3,4]-thiadiazol-5-yl] methanol (7b). Yield 76%; colorless needles (chloroform + hexane); mp 190–192 °C; IR (KBr) ν cm^{-1}, 3244, 1597, 1538; ^1H NMR ($CDCl_3$) δ 1.25–2.16 (m,10H, cyclohexyl), 2.96 (m, 1H, C1-H, cyclohexyl), 3.01 (br s, 1H, OH, D_2O exchangeable), 4.99 (s, 2H, CH_2), 7.52 (d, J = 8.4 Hz, 2H, C3, C5-H, phenyl), 7.77 (d, J = 8.4 Hz, 2H, C2, C6-H, phenyl); Anal. Calcd for $C_{17}H_{18}BrN_3OS$: C, 52.05; H, 4.62; N, 10.71. Found: C, 52.29; H, 4.44; N, 11.32.

6.6.3. [2-(2-Furyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl]methanol (7c). Yield 85%; pale yellow granules (chloroform + hexane); mp 150–152 °C; IR (KBr) ν cm^{-1}, 3266, 1589; ^1H NMR ($CDCl_3$) δ 1.92 (br s, 1H, OH, D_2O exchangeable), 5.11 (s, 2H, CH_2), 6.63 (dd, J_{H3H4} = 3 Hz, J_{H4H5} = 3 Hz, 1H, C4-H, furyl), 7.14 (dd, J = 3 Hz, 1H, C3-H, furan), 7.37 (m, 1H, C4-H, phenyl), 7.47 (m, 2H, C3, C5-H, phenyl), 7.63 (d, J = 3 Hz, 1H, C5-H, furan), 7.83 (m 2H, C2, C6-H, phenyl); Anal. Calcd for $C_{15}H_{11}N_3O_2S$: C, 60.59; H, 3.73; N, 14.13. Found: C, 60.95; H, 3.83; N, 14.79.

6.6.4. [6-(4-Bromophenyl)-2-(2-furyl)imidazo[2,1-*b*][1,3,4]-thiadiazol-5-yl] methanol (7d). Yield 63%; pale yellow crystalline solid (benzene + pet ether); mp 192–194 °C; IR (KBr) ν cm^{-1} 3321, 1602, 1543; ^1H NMR ($CDCl_3$) δ 2.58 (br s, 1H, OH), 4.98 (s, 2H, CH_2), 6.67 (dd, J_{H3H4} = 3.3 Hz, J_{H4H5} = 3 Hz, 1H, C4-H, furan), 7.12 (d, J = 3.3 Hz, 1H, C3-H, furan), 7.49 (d, J = 9 Hz, 2H, C3, C5-H, phenyl), 7.67 (d, J = 3 Hz, 1H, C5-H, furan), 7.88 (d, J = 9 Hz, C2, C6-H, phenyl); Anal. Calcd for $C_{15}H_{10}BrN_3O_2S$: C, 47.89; H, 2.68; N, 11.17. Found: C, 47.78; H, 2.77; N, 11.31.

6.6.5. (6-Phenyl-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl)methanol (7e). Yield 83%; colorless granules (benzene); mp 202–204 °C; IR (KBr) ν cm^{-1} 3242, 1605, 1546; ^1H NMR ($CDCl_3$) δ 2.30 (t, 1H, OH, D_2O exchangeable), 5.14 (d, J = 5.7 Hz, 2H, CH_2), 7.18 (dd, J = 3 Hz and 3.3 Hz, 1H, C4-H, thienyl), 7.38–7.85 (m, 7H, phenyl, C3, C5-H, thienyl); Anal. Calcd for $C_{15}H_{11}N_3OS_2$: C, 57.49; H, 3.54; N, 13.41. Found: C, 57.86; H, 3.63; N, 13.55.

6.6.6. [6-(4-Bromophenyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]-thiadiazol-5-yl] methanol (7f). Yield 71%; colorless granules (benzene); mp 202–204 °C; IR (KBr) ν cm^{-1} 3312, 1621, 1539; ^1H NMR ($CDCl_3$) δ 2.54 (br s, 1H, OH, D_2O exchangeable), 5.08 (s, 2H, CH_2), 7.17 (dd, J = 3 Hz and 3.3 Hz, 1H, C4-H, thienyl), 7.38–7.85 (m, 6H, phenyl and C3, C5-H, thienyl); Anal. Calcd for $C_{15}H_{10}BrN_3OS_2$: C, 45.92; H, 2.57; N, 10.71. Found: C, 46.32; H, 2.79; N, 11.11.

6.7. Preparation of 2-alkyl/aryl-6-arylimidazo[2,1-*b*]-[1,3,4]thiadiazole-5-carbaldehydeoximes (8a–f): general method

A mixture of 2-alkyl/aryl-6-arylimidazo[2,1-*b*][1,3,4]-thiadiazol-5-carbaldehyde **3** (0.001 mol) and hydroxylamine hydrochloride (0.83 g, 0.0012 mol) was refluxed in pyridine (10mL) for 6 h (monitored by TLC), the cooled mixture was then poured over ice, and the precipitate was collected by filtration, washed with water, aq alcohol, dried, and recrystallized from appropriate solvent to yield the corresponding aldoximes.

6.7.1. 2-Cyclohexyl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde oxime (8a). Yield 83%; colorless crystalline solid(benzene + chloroform); mp 238–240 °C; IR (KBr) ν cm^{-1} 3250, 1623, 1537; ^1H NMR ($CDCl_3$) δ 1.30–2.22 (m, 10H, cyclohexyl), 3.17 (m, 1H, C1-H, cyclohexyl), 7.37–7.71 (m, 5H, phenyl), 8.46 (s, 1H, CH=N), 9.45 (s, b, 1H, OH, D_2O, exchangeable); Anal. Calcd for $C_{17}H_{18}N_4OS$: C, 62.55; H, 5.56; N, 17.16. Found: C, 62.49; H, 5.48; N, 17.31. Mass, *m*/*z* (%), 327.03 (M+1, 100).

6.7.2. 6-(4-Bromophenyl)-2-cyclohexylimidazo[2,1-*b*][1,3,4]-thiadiazole-5-carbaldehydeoxime (8b). Yield 82%; colorless solid (ethanol); mp 202–204 °C; IR (KBr) ν cm^{-1} 3250, 1623, 1537; ^1H NMR ($CDCl_3$) δ 1.30–3.15 (m, 11H, cyclohexyl), 7.60 (d, J = 9 Hz, 2H, C3, C5-H, phenyl), 7.77 (d, J = 9 Hz, 2H, C2, C6- H, phenyl), 8.63 (s, 1H, CH=N), 9.74 (br s, 1H, OH, D_2O exchange able); Anal. Calcd for $C_{17}H_{17}BrN_4OS$: C, 50.38; H, 4.23; N, 13.82. Found: C, 50.75; H, 4.43; N, 13.97.

6.7.3. 2-(2-Furyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehydeoxime (8c). Yield 83%; pale yellow solid (ethanol); mp 206–208 °C; IR (KBr) ν cm^{-1}, 2342, 1603, 1543; ^1H NMR ($CDCl_3$) δ 6.66 (dd, J_{H3H4} = 3.3 Hz, J_{H4H5} = 3 Hz, 1H, C4-H, furyl), 7.35 (d, J = 3.3 Hz, 1H, C3-H, furyl), 7.52–7.92 (m, 6H, C5-H, furyl, phenyl), 8.52 (s, 1H, CH=N), 9.83 (br s, 1H, OH, D_2O exchangeable); Anal. Calcd for $C_{15}H_{10}N_4O_2S$: C, 58.05; H, 3.25; N, 18.05. Found: C, 58.30; H, 3.32; N, 18.38.

6.7.4. 6-(4-Bromophenyl)-2-(2-furyl)imidazo[2,1-*b*][1,3,4]-thiadiazole-5-carbaldehydeoxime (8d). Yield 77%; pale yellow solid (ethanol); mp 212–214 °C; IR (KBr) ν cm^{-1} 3301, 1597, 1533; ^1H NMR ($CDCl_3$) δ 6.68 (dd, J_{H3H4} = 3.3 Hz, J_{H4H5} = 3 Hz, 1H, C4-H, furyl), 7.34 (d, J = 3.3 Hz, 1H, C3-H, furyl), 7.67 (d, J = 9 Hz, 2H, C3, C5-H, phenyl), 7.66 (d, J = 3 Hz, 1H, C5-H, furyl), 7.85 (d, J = 8.7 Hz, 2H, C2, C6-H, phenyl), 8.43 (s, 1H, CH=N), 10.08 (br s, 1H, OH, D_2O exchangeable); Anal. Calcd for $C_{15}H_9BrN_4O_2S$: C, 46.29; H, 2.33; N, 14.39. Found: C, 46.44; H, 2.21; N, 14.51.

6.7.5. 6-Phenyl-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehydeoxime (8e). Yield 83%; colorless crystalline solid (ethanol); mp 212–214 °C; IR (KBr) ν cm^{-1} 3246, 1615, 1530; ^1H NMR ($CDCl_3$) δ 7.18 (dd, J = 3.3 Hz and 3.3 Hz, 1H, C4-H, thienyl), 7.22–7.95

(m, 7H, C3, C5-H, thienyl and phenyl), 8.47 (s, 1H, CH=N), 9.65 (br s, 1H, OH, D_2O exchangeable); Anal. Calcd for $C_{15}H_{10}N_4OS_2$: C, 55.20; H, 3.09; N, 17.17. Found: C, 55.55; H, 3.38; N, 17.34.

6.7.6. 6-(4-Bromophenyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]-thiadiazole-5-carbaldehydeoxime (8f). Yield 76%; colorless granules (ethanol); mp 202–204 °C; IR (KBr) ν cm^{-1} 3229, 1618, 1526; ^1H NMR ($CDCl_3$) δ, 7.15 (dd, J = 3.6 Hz and 3.3 Hz, 1H, C4-H, thienyl), 7.32–7.84 (m, 6H, ArH), 8.56 (s, 1H, CH=N), 9.34 (br s, 1H, OH, D_2O exchangeable); Anal. Calcd for $C_{15}H_9BrN_4$ OS_2: C, 44.45; H, 2.24; N, 13.82. Found: C, 44.34; H, 2.17; N, 13.93.

6.8. Preparation of 2-alkyl/aryl-6-arylimidazo[2,1-*b*]-[1,3,4]thiadiazole-5-carbonitriles (9a–f): general method

The 2-alkyl/aryl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehydeoxime (0.001 mol) was suspended in thionylchloride (7mL) and refluxed for 5 min. Poured over cold water, neutralized by sodium carbonate solution, the solid that separated was collected by filtration was washed repeatedly with water, dried, and recrystallized from appropriate solvent.

6.8.1. 2-Cyclohexyl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbonitrile (9a). Yield 90%; colorless granules (benzene); mp 145–147 °C; IR (KBr) ν cm^{-1} 2219, 1600; ^1H NMR ($CDCl_3$) δ 1.45–1.91 (m, 10H, cyclohexyl), 3.12 (m, 1H, C1-H, cyclohexyl), 7.49–8.09 (m, 5H, phenyl); Anal. Calcd for $C_{17}H_{16}N_4S$: C, 66.21; H, 5.23; N, 18.17. Found: C, 66.30; H, 5.17; N, 18.54.

6.8.2. 6-(4-Bromophenyl)-2-cyclohexylimidazo[2,1-*b*][1,3,4]-thiadiazole-5-carbonitrile (9b). Yield 81%; colorless granules (benzene); mp 175–177 °C; IR (KBr) ν cm^{-1} 2223, 1608, 1546; ^1H NMR ($CDCl_3$) δ 1.42–1.93 (m, 10H, cyclohexyl), 3.13 (m, 1H, C1-H, cyclohexyl); 7.62 (d, J = 9 Hz, 2H, C3, C5-H, phenyl), 7.75 (d, J = 9 Hz, 2H, C2, C6-H, phenyl); Anal. Calcd for $C_{17}H_{15}BrN_4S$: C, 52.72; H, 3.90; N, 14.47. Found: C, 52.61; H, 3.71; N, 14.63.

6.8.3. 2-(2-Furyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbonitrile (9c). Yield 69%; pale yellow solid (benzene); mp 206–208 °C; IR (KBr) ν cm^{-1}, 2215, 1600, 1543; ^1H NMR ($CDCl_3$) δ 6.69 (dd, J_{H3H4} = 3.3 Hz, J_{H4H5} = 3.3 Hz, 1H, C4-H, furyl), 7.29 (d, J = 3 Hz, 1H, C3-H, furyl), 7.48–7.98 (m, 6H, C5-H, furyl, phenyl); Anal. Calcd for $C_{15}H_8N_4OS$: C, 61.63; H, 2.76; N, 19.17. Found: C, 61.55; H, 2.88; N, 19.31.

6.8.4. 6-(4-Bromophenyl)-2-(2-furyl)imidazo[2,1-*b*][1,3,4]-thiadiazole-5-carbonitrile (9d). Yield 71%; pale yellow solid (chloroform); mp 177–179 °C; IR (KBr) ν cm^{-1} 2220, 1605, 1546; ^1H NMR ($CDCl_3$) δ 6.67 (dd, J_{H3H4} = 3.3 Hz, J_{H4H5} = 3 Hz, 1H, C4-H, furyl), 7.32 (d, J = 3.3 Hz, 1H, C3-H, furyl), 7.65 (d, J = 8.7 Hz, 2H, C3, C5-H, phenyl), 7.66 (d, J = 3 Hz, 1H, C5-H, furyl), 7.82 (d, J = 8.7 Hz, 2H, C2, C6-H, phenyl); Anal. Calcd for $C_{15}H_7BrN_4OS$: C, 48.53; H, 1.90; N, 15.09. Found: C, 48.67; H, 2.01; N, 15.35.

6.8.5. 6-Phenyl-2-thien-2-ylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbonitrile (9e). Yield 73%; colorless solid (benzene + chloroform); mp 166–168 °C; IR (KBr) ν cm^{-1} 2219, 1634, 1545; ^1H NMR ($CDCl_3$) δ 7.17 (d, J = 3 Hz and 4.2 Hz, 1H, C4-H, thienyl), 7.25–7.99 (m, 7H, C3, C5-H, thienyl and phenyl); Anal. Calcd for $C_{15}H_8N_4S_2$: C, 58.42; H, 2.61; N, 18.17. Found: C, 58.68; H, 2.92; N, 18.45.

6.8.6. 6-(4-Bromophenyl)-2-thien-2-ylimidazo[2,1-*b*][1,3,4]-thiadiazole-5-carbonitrile (9f). Yield 68%; pale yellow solid (chloroform); mp 152–154 °C; IR (KBr) ν cm^{-1} 2222, 1632, 1544; ^1H NMR ($CDCl_3$) δ 7.17 (dd, J = 3.3 Hz and 3.9 Hz, 1H, C4-H, thienyl), 7.22–7.96 (m, 6H, C3, C5-H, thiophene, phenyl); Anal. Calcd for $C_{15}H_7BrN_4S_2$: C, 46.52; H, 1.82; N, 14.47. Found: C, 46.63; H, 1.98; N, 14.77.

6.9. Preparation of 2-(2-alkyl/aryl-6-phenylimidazo[2,1-*b*]-[1,3,4]thiadiazol-5-yl)-3-phenyl-1,3-thiazolidin-4-ones (10a–c): general method

2-Alkyl/aryl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde (0.01 mol) and aniline (1.1 g, 0.012 mol) were refluxed in rectified spirit (30mL) with catalytic amount of acetic acid for 3 h. The solid that separated was filtered, washed with alcohol and dried. The crude product was recrystallized from alcohol, the yellow colored solid thus obtained (0.01 mol) was refluxed with thioglycolic acid (0.012 mol), in dry benzene (25 mL) for 5 h. The colorless solid that separated was collected by filtration, dried, and recrystallized from appropriate solvent.

6.9.1. 2-(2-Cyclohexyl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl)-3-phenyl-1,3-thiazolidin-4-one (10a). Yield 66%; colorless granules (ethanol); mp 212–214 °C; IR (KBr) ν cm^{-1} 2927, 1710, 1600, 1492; ^1H NMR (DMSO-d_6) δ 1.29–2.10 (m, 10H, cyclohexyl), 3.17 (m, 1H, C1-H, cyclohexyl), 5.90 (s, 2H, CH_2), 7.32–7.74 (m, 11H, Ar-H and CH, thiazolidinone); Anal. Calcd for $C_{25}H_{24}N_4OS_2$: C, 65.19; H, 5.25; N, 12.16. Found: C, 65.26; H, 5.39; N, 12.63.

6.9.2. 2-[2-(2-Furyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl]-3-phenyl-1,3-thiazolidin-4-one (10b). Yield 64%; pale yellow granules (ethanol); mp 218–220 °C; IR (KBr) ν cm^{-1} 1716, 1546, 1498, 1463; ^1H NMR (DMSO-d_6) δ 5.95 (s, 2H, CH_2), 6.67 (dd, J = 3.9 Hz and 3 Hz, 1H, C4-H, furan), 7.26–7.94 (m, 13H, ArH and CH, thiazolidinone); Anal. Calcd for $C_{23}H_{16}N_4O_2S_2$: C, 62.14; H, 3.63; N, 12.60. Found: C, 62.27; H, 3.55; N, 12.88.

6.9.3. 3-Phenyl-2-(6-phenyl-2-thien-2-ylimidazo[2,1-*b*][1,3,4]-thiadiazol-5-yl)-1,3-thiazolidin-4-one (10c). Yield 64%; pale yellow granules (ethanol); mp 218–220 °C; IR (KBr) ν cm^{-1} 1716, 1546, 1498, 1463; ^1H NMR (DMSO-d_6) δ, 5.95 (s, 2H, CH_2), 7.26–7.94 (m, 14H, ArH and CH, thiazolidinone); Anal. Calcd for $C_{23}H_{16}N_4OS_3$: C, 59.98; H, 3.50; N, 12.16. Found: C, 60.10; H, 3.87; N, 12.21%; Mass, *m/z* (%), 460 (100).

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