Med Chem Res (2013) 22:869–878
DOI 10.1007/s00044-012-0080-4

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and evaluation of antibacterial and antitubercular activities of some novel imidazo[2,1-*b*][1,3,4]thiadiazole derivatives

S. D. Joshi · K. Manish · Aravind Badiger

Received: 1 August 2011 / Accepted: 2 May 2012 / Published online: 19 May 2012

Abstract A series of 2,5,6-trisubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles were synthesized, structures of the compounds were elucidated and evaluated for antitubercular activity against *Mycobacterium tuberculosis* H37Rv using microplate alamar blue assay (MABA) method, antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Vibrio cholera*, and *Escherichia coli* by broth micro dilution assay method. Some compounds exhibited significant antibacterial and antitubercular activities. Compounds **10**, **14**, and **15** emerged as the most active molecules, showed significant antimicrobial activity and may serve as leads for further optimization.

Keywords Imidazo[2,1-*b*][1,3,4]thiadiazole · Antitubercular · Antibacterial activities

Introduction

Tuberculosis (TB) is a chronic necrotizing bacterial infection with a wide variety of manifestations caused by *Mycobacterium tuberculosis* and is responsible for over three million deaths annually worldwide (Valadas and Antunes, 2005). According to world health organization (WHO), it is estimated that one-third of the world's population is currently infected with the bacillus and about 30 million people will be infected within next 20 years if control is not further strengthened (Duncan, 1997). The worsening situation has prompted the WHO to declare tuberculosis a global public health crisis (Qian and Montellano, 2006).

In addition; HIV-1 and 2 infections, which impairs the immune system and allows large number of people already infected with the TB to progress to active disease. The pathogenic synergy of tuberculosis with HIV enhances the overall incidence of TB in HIV-positive patients by 50 times relative to the rate for HIV-negative individuals (Corbett *et al.*, 2003).

Therefore, there is an urgent need to develop new chemical entities with new structural classes and with a novel mechanism of action other than isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA). In this regard, since the last decade search for new antitubercular substances has ranked among the priority areas of chemotherapeutic research.

Imidazo[2,1-*b*][1,3,4]thiadiazoles are useful targets in the search for antimicrobials as they have been associated with a wide variety of interesting biological properties.

Among the numerous heterocyclic moieties of biological and pharmacological interest, the imidazo[2,1-*b*][1,3,4]thiadiazole ring is endowed with various activities, such as anticancer (Terzioglu and Gursoy, 2003), antitubercular (Kolavi *et al.*, 2006), antibacterial (Gadad *et al.*, 2000), anticancer (Karki *et al.*, 2011; Noolvi *et al.*, 2011), leishmanicidal (Foroumadi *et al.*, 2005), anticonvulsant-analgesic (Khazi *et al.*, 1996), anti-inflammatory (Jadhav *et al.*, 2008), and antisecretory (Andreani *et al.*, 2000)

This paper is dedicated to Professor G. S. Gadaginamath on the occasion of his 68th birthday.

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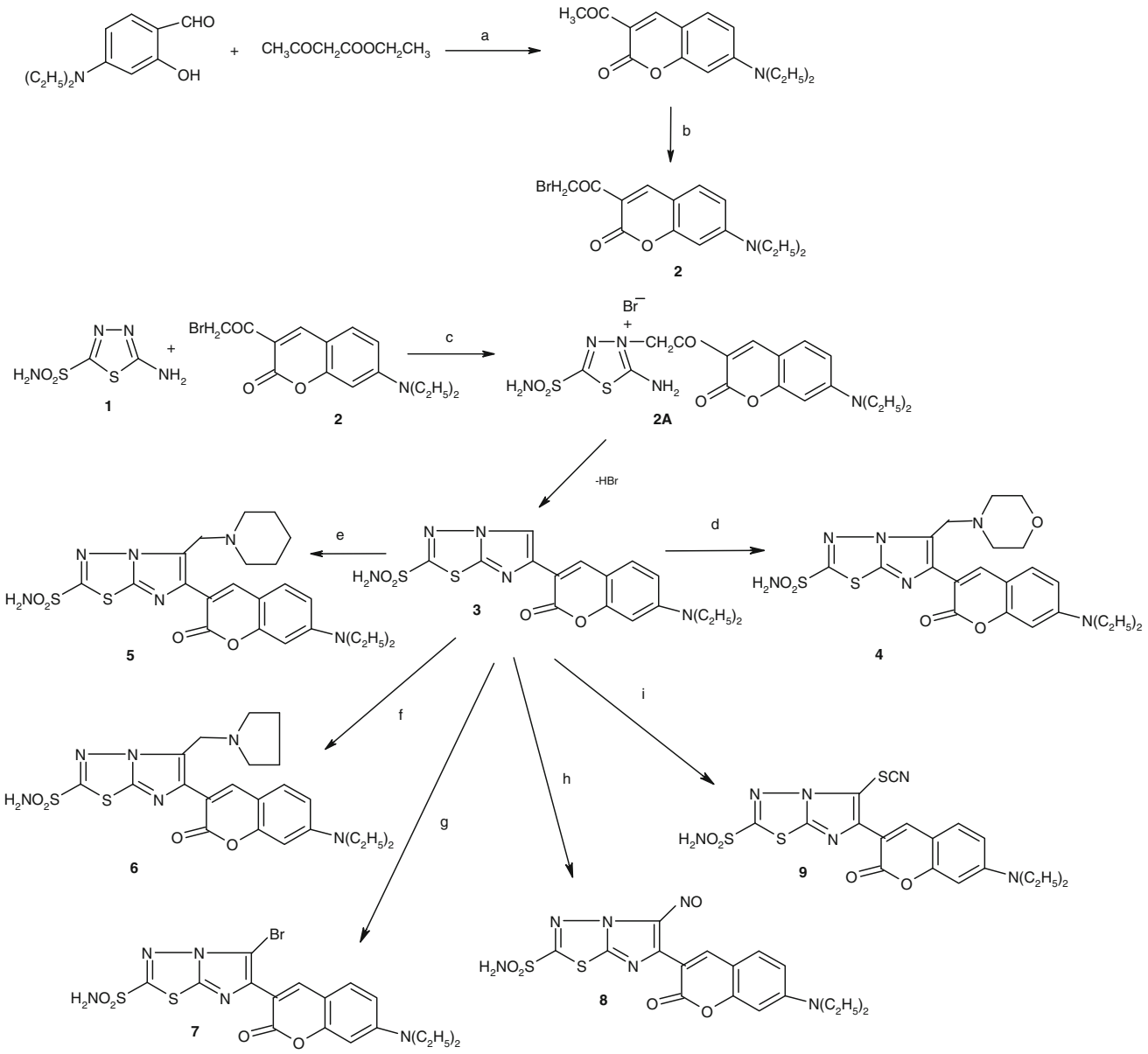
activities. Recently, these derivatives have attracted the interest of researchers as potential antitubercular agents. Some derivatives of the imidazo[2,1-*b*][1,3,4]thiadiazoles have exhibited good activity against *M. tuberculosis* $H_{37}Rv$ (Gadad *et al.*, 2004).

The purpose of the present study was to explore and develop the novel molecules with improved potential for treating tuberculosis. In this research paper, we have reported the design, synthesis and preliminary antimycobacterial and antibacterial evaluation of a novel class of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives.

Methods and materials

Chemistry

Synthesis of the basic nucleus imidazo[2,1-*b*][1,3,4]thiadiazole is brought about by the condensation of 5-amino-1,3,4-thiadiazole-2-sulphonamide **1** with 7-diethylamino-3-bromoacetyl-2*H*-chromen-2-one **2** under reflux in dry ethanol (Scheme 1). Mannich reaction of imidazo[2,1-*b*][1,3,4]thiadiazole **3** with different cyclic secondary amines (morpholine, piperidine, and pyrrolidine) and formaldehyde in methanol



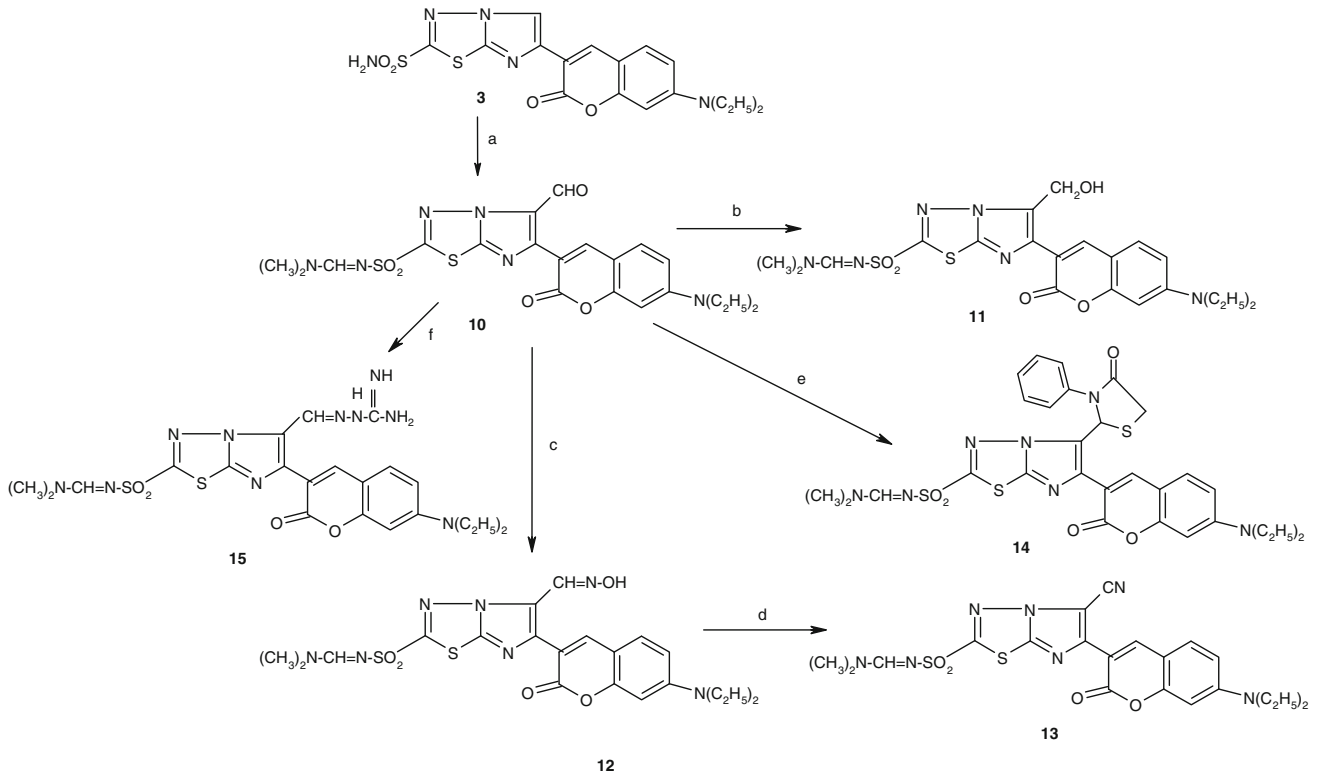
Scheme 1 Synthesis of imidazothiadiazole derivatives **3**–**9**. **a** Piperidine, stir, 30 min, **b** bromine, acetic acid, reflux, 2 h, **c** ethanol reflux, 24 h, Na_2CO_3, **d** morpholine, formaldehyde, methanol, reflux, 18 h, **e** piperidine, formaldehyde, methanol, reflux, 18 h, **f** pyrroldine, formaldehyde, methanol, reflux, 18 h, **g** bromine, acetic acid, CH_3COONa, stir, 1 h, **h** sodium nitrite, acetic acid, stir, rt, 1 h, reflux, 3 h, **i** potassium thiocyanate, acetic acid, stir, rt, 3 h

with catalytic amount of acetic acid yielded corresponding derivatives **4**, **5** and **6**. Imidazo[2,1-*b*][1,3,4]thiadiazole **3** was subjected to electrophilic substitution reaction at the fifth position with bromine in the presence of sodium acetate in acetic acid to obtain 5-bromo derivative **7**. Nitroso derivative **8** was obtained by refluxing the imidazothiadiazole **3** with sodium nitrite solution. While imidazothiadiazole **3** furnished thiocyanato derivative **9** on treating with bromine and potassium thiocyanate in glacial acetic acid.

Vilsmeier Haack reaction of imidazothiadiazole **3** in DMF and $POCl_3$ furnished formyl derivative **10**. During this reaction, the DMF also reacted with the NH_2 function of the 2-sulfonamido group converting it to *N*,*N*-(dimethylaminomethino)sulfonamide group. The formyl group has been utilized to synthesize corresponding alcohol, nitrile, thiazolidinone, and guanyl hydrazone derivatives. The reduction of aldehyde **10** by $NaBH_4$ in methanol at room temperature yielded the corresponding carbinol **11** in good yield. The condensation of aldehyde **10** with hydroxylamine hydrochloride in pyridine gave corresponding oxime **12**, which on dehydration with thionyl chloride produced the nitrile **13** in good yield. The aldehyde **10** when treated with aniline gave the corresponding Schiff base, which on refluxing with thioglycolic acid in benzene underwent heterocyclization to yield thiazolidinone derivative **14**. Reaction of **10** with aminoguanidine hydrochloride produced guanylhydrazone **15** (Scheme 2).

Experimental

Chemicals used in the synthesis of the titled compounds were purchased from Sigma-Aldrich, S.D. Fine-Chem Limited, and Spectrochem Pvt. Ltd. The melting points of synthesized compounds were determined on Shital scientific industries digital melting point apparatus and are uncorrected; infra-red spectra were recorded on a Bruker spectrophotometer by using KBr pellets. ^{1}H and ^{13}C-NMR spectra were recorded on Bruker 300 MHz and Bruker AVANCE III 500 MHz instruments using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard, chemical shifts are expressed as δ values (ppm). Mass spectra (MS) were taken in JEOL GCMATE II GC–mass spectrometer and Schimadzu QP 20105 GC–mass spectrometer. Microanalysis of compounds were also performed on Leco Tru Spec CHNS analyzer for the determination of percentage of C, H, and N. All new compounds exhibited spectral data consistent with the proposed structures and values of microanalysis are within ±0.4 % of the theoretical values. Analytical thin-layer chromatography



Scheme 2 Synthesis of imidazothiadiazole derivatives **10**–**15**. **a** phosphorous oxy chloride, DMF, stir, 0^0 C, 30 min, stir, rt, 2 h, stir, 60^0 C, 2 h, Na_2CO_3, **b** sodium borohydride, methanol, stir, 7 h, **c** hydroxylamine hydrochloride, pyridine, reflux 8 h, **d** thionyl chloride, reflux, 10 min, Na_2CO_3, **e** aniline, ethanol, acetic acid, reflux, 4 h, thioglycolic acid, benzene, reflux, 8 h, **f** ethanol, aminoguanidine hydrochloride, reflux, 1 h

(TLC) was performed on precoated TLC sheets of silica gel 60 F_{254} (Merck, Darmstadt, Germany), visualizing by long- and short-wavelength ultraviolet (UV) lamps.

*Synthesis of 5-amino-1,3,4-thiadiazole-2-sulphonamide (**1**)*

N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide (0.03 mol, 6.60 g) in concentrated hydrochloric acid (30 mL) was refluxed for 6 h. The reaction mixture was cooled and basified with sodium bicarbonate solution. The solid that separated was filtered, washed with water, dried, and recrystallized from water (yield 65 %). mp 220–222 °C. IR (KBr) 3430, 3326, 1604, 678 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ; 7.78 (s, 2H, NH_2), 8.05 (s, 2H, SO_2NH_2). Anal.: $C_2H_4N_4O_2S_2$.

*Synthesis of 7-diethylamino-3-bromoacetyl-2H-chromen-2-one (**2**)*

A mixture of 4-*N*,*N*-diethyl amino salisaldehyde (0.015 mol, 2.88 g) and ethylacetoacetate (0.015 mol, 1.90 mL) in piperidine (1 mL) was stirred for 30 min. The solid that separated was filtered, washed with alcohol, and dried. The crude product was recrystallized from ethanol. To the yellow colored solid thus obtained (0.01 mol) in chloroform (10 mL) was added bromine (0.00095 mol, 0.13 g in 5 mL chloroform) drop wise at room temperature. After the addition, the mixture was refluxed for 2 h. The reaction mixture was poured into ice cold water; separated solid was collected, washed with water, dried, and recrystallized from ethanol (yield 65 %). mp 164–166 °C. IR (KBr) 1713, 1679, 1614, 1508, 622 cm^{-1}. Anal.: $C_{15}H_{16}BrNO_3$.

*Synthesis of 6-[7-(diethylamino)-2-oxo-2H-chromen-3-yl]imidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamide (**3**)*

A mixture of equimolar quantities of 5-amino-1,3,4-thiadiazole-2-sulphonamide (**1**) (0.03 mol, 5.40 g) and 7-diethylamino-3-bromoacetyl-2*H*-chromen-2-one (**2**) (0.03 mol, 10.14 g) was refluxed in dry ethanol for 24 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 **3**. It was filtered, washed with water, dried, and recrystallized from ethanol (yield 64.60 %). mp 192–194 °C. IR (KBr) 3315, 3293, 1711, 1603, 1496, 1353, 1180, 652 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ; 8.56 (s, 1H, imidazole-C_5–*H*), 7.55–7.58 (m, 2H, coumarin-C_4–*H*, C_5–*H*), 6.71 (d, J: 4.0 Hz, 1H, coumarin-C_6–*H*), 6.57 (s, 1H, coumarin-C_8–*H*), 3.22–3.45 (m, 4H, $2CH_2$), 2.50 (s, 2H, SO_2NH_2), 1.06–1.46 (m, 6H, $2CH_3$); ^{13}C-NMR (DMSO-d_6) δ; 172.11 (C=O), 153.29 (thiadiazole-C_{7a}), 151.15 (coumarin-C_9), 148.09 (imidazole-C_6), 145.70 (coumarin-C_7), 140.39 (coumarin-C_4), 130.40 (coumarin-C_3), 128.23 (coumarin-C_5), 119.82 (coumarin-C_{10}), 115.48 (coumarin-C_6), 113.08 (coumarin-C_8), 110.59 (imidazole-C_5), 106.09 (thiadiazole-C_2), 30.57 (coumarin-$2CH_2$), 12.84 (coumarin-$2CH_3$); MS (70 eV) *m/z* 420 (M + 1) 404, 340, 139, 101, 80, 62, 48. Anal. Calcd. For $C_{17}H_{17}N_5O_4S_2$: C, 48.67; H, 4.08; N, 16.70. Found: C, 48.49; H, 4.07; N, 16.65.

*Synthesis of 5-(morpholin-4-ylmethyl)-6-[7-(diethylamino)-2-oxo-2H-chromen-3-yl]imidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamide (**4**)*

A mixture of 6-[7-(diethylamino)-2-oxo-2*H*-chromen-3-yl] imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamide (**3**) (0.005 mol, 2.09 g), morpholine (0.006 mol, 0.52 g), formaldehyde (1 mL) and acetic acid (1 mL) in methanol (20 mL) was refluxed for 18 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 methanol (yield 62.30 %). mp 160–162 °C. IR (KBr) 3273, 2967, 1719, 1614, 1416, 1355, 1171, 641 cm^{-1}; ^{1}H-NMR (DMSO-d_6); 7.95–7.96 (m, 2H, coumarin-C_4–*H*, C_5–*H*), 7.19–7.20 (d, J: 4.0 Hz, 1H, coumarin-C_6–*H*), 6.76 (s, 1H, coumarin-C_8–*H*), 4.20 (s, 2H, CH_2), 3.85–4.00 (t, J: 4.0 Hz, 4H, morpholine-C_2–*H*, C_6–*H*), 3.22–3.45 (m, 4H, $2CH_2$), 2.82–2.96 (t, J: 4.0 Hz, 4H, morpholine-C_3–*H*, C_5–*H*), 2.47 (s, 2H, SO_2NH_2), 1.02–1.15 (m, 6H, $2CH_3$). ^{13}C-NMR; 171.82 (C=O), 156.92 (thiadiazole-C_{7a}), 150.66 (coumarin-C_9), 147.46 (imidazole-C_6), 146.44 (coumarin-C_7), 140.06 (coumarin-C_4), 131.55 (coumarin-C_3), 126.42 (coumarin-C_5), 117.12 (coumarin-C_{10}), 114.74 (coumarin-C_6), 113.88 (coumarin-C_8), 111.42 (imidazole-C_5), 106.78 (thiadiazole-C_2), 68.46 (morpholine-C_3 & C_5), 54.32 (morpholine-C_2 & C_6), 52.32 (N–CH_2), 39.22 (coumarin $2CH_3$), 31.56 (coumarin $2CH_2$); MS (70 eV) *m/z* 517 (M + 1), 516 (M^+), 445, 433, 419, 80, 62, 48; Anal. Calcd. For $C_{22}H_{26}O_5N_6S_2$: C, 50.95; H, 5.05; N, 16.20. Found: C, 50.90; H, 5.06; N, 16.16.

*Synthesis of 5-(piperidin-1-ylmethyl)-6-[7-(diethylamino)-2-oxo-2H-chromen-3-yl]imidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamide (**5**)*

A mixture of 6-[7-(diethylamino)-2-oxo-2*H*-chromen-3-yl] imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamide (**3**) (0.005 mol, 2.09 g), piperdine (0.006 mol, 0.51 g), formaldehyde (1 mL), and acetic acid (1 mL) in methanol (20 mL) was refluxed for 18 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 methanol (yield 64.70 %). mp 162–164 °C. IR (KBr) 3223, 2960, 2981, 1716, 1614, 1456, 1354, 1173, 643 cm^{-1}; ^{1}H-NMR (DMSO-d_6); 7.95–7.96 (m, 2H, coumarin-C_4–*H*, C_5–*H*), 7.19–7.20 (d, J: 3.99 Hz, 1H, coumarin-C_6–*H*), 6.76 (s, 1H, coumarin-C_8–*H*), 4.00 (s, 2H, CH_2), 3.22–3.45 (m, 4H, $2CH_2$), 2.52 (m, 4H, piperidine-C_2–*H*, C_6–*H*), 2.47 (s, 2H, SO_2NH_2), 1.61–1.81 (m, 6H, piperidine-C_3–*H*, C_4–*H*, C_5–*H*), 1.02–1.15 (m, 6H, $2CH_3$). ^{13}C-NMR; 170.28 (C=O), 157.56 (thiadiazole-C_{7a}), 151.38 (coumarin-C_9), 148.24 (imidazole-C_6), 147.26 (coumarin-C_7), 140.28 (coumarin-C_4), 132.82 (coumarin-C_3), 127.76 (coumarin-C_5), 118.10 (coumarin-C_{10}), 115.82 (coumarin-C_6), 114.22 (coumarin-C_8), 110.20 (imidazole-C_5), 106.84 (thiadiazole-C_2), 54.22 (piperdine-C_2 & C_6), 51.72 (N–CH_2), 26.52 (piperdine-C_3 & C_5), 25.90 (piperdine-C_4), 39.48 (coumarin $2CH_3$), 30.46 (coumarin $2CH_2$); MS (70 eV) *m/z* 519 (M + 1), 518 (M^+), 445, 439, 419, 80, 62, 48; Anal. Calcd. For $C_{23}H_{28}N_6S_2O_4$: C, 53.47; H, 5.46; N, 16.27. Found: C, 53.38; H, 5.45; N, 16.21.

*Synthesis of 5-(pyrrolidin-1-ylmethyl)-6-[7-(diethylamino)-2-oxo-2H-chromen-3-yl]imidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamide (**6**)*

A mixture of 6-[7-(diethylamino)-2-oxo-2*H*-chromen-3-yl] imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamide (**3**) (0.005 mol, 2.09 g), pyrrolidine (0.006 mol, 0.42 g), formalin (1 mL) and acetic acid (1 mL) in methanol (20 mL) was refluxed for 18 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 methanol (yield 54.00 %). mp 182–184 °C. IR (KBr) 3266, 2985, 1722, 1610, 1418, 1352, 1178, 645 cm^{-1}; ^{1}H-NMR (DMSO-d_6); 7.90–7.94 (m, 2H, coumarin-C_4–*H*, C_5–*H*), 7.20–7.21 (d, J: 3.99 Hz, 1H, coumarin-C_6–*H*), 6.68 (s, 1H, coumarin-C_8–*H*), 4.04 (s, 2H, CH_2), 3.20–3.50 (m, 8H, $2CH_2$ & pyrrolidine-C_2 & C_5–*H*), 2.42 (s, 2H, SO_2NH_2), 2.13–2.60 (m, 4H, pyrrolidine-C_3 & C_4–*H*), 1.00–1.22 (m, 6H, $2CH_3$). ^{13}C-NMR; 171.56 (C=O), 156.22 (thiadiazole-C_{7a}), 152.25 (coumarin-C_9), 150.26 (imidazole-C_6), 148.54 (coumarin-C_7), 142.85 (coumarin-C_4), 134.78 (coumarin-C_3), 128.54 (coumarin-C_5), 117.29 (coumarin-C_{10}), 116.14 (coumarin-C_6), 113.78 (coumarin-C_8), 111.29 (imidazole-C_5), 105.22 (thiadiazole-C_2), 52.44 (pyrrolidine-C_2 & C_5), 48.72 (N–CH_2), 24.66 (pyrrolidine-C_3 & C_4), 39.54 (coumarin $2CH_3$), 31.52 (coumarin $2CH_2$); MS (70 eV) *m/z* 503 (M^+), 419, 404, 340, 139, 101, 80, 62, 48. Anal. Calcd. For $C_{22}H_{26}N_6S_2O_4$: C, 52.57; H, 5.21; N, 16.72. Found: C, 52.50; H, 5.20; N, 16.69.

*Synthesis of 5-bromo-6-[7-(diethylamino)-2-oxo-2H-chromen-3-yl]imidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamide (**7**)*

To a well stirred solution of *imidazo[*2,1-*b][*1,3,4*]thiadiazole*-2-*sulfonamide* (**3**) (0.01 mol, 4.19 g) in glacial acetic acid (10 mL) and anhydrous sodium acetate (0.02 mol) was added bromine (0.01 mol) drop wise with stirring at room temperature. After the addition, stirring was continued for 2 h. The reaction mixture was poured into ice cold water and basified with ammonia solution. The separated solid was collected, washed with water, dried, and recrystallized from ethanol (yield 61.00 %). mp 142–145 °C. IR (KBr) 3319, 3269, 2974, 1715, 1599, 1375, 1489, 1180, 643, 585 cm^{-1}; ^{1}H-NMR (DMSO-d_6); 7.60–7.62 (m, 2H, coumarin-C_4–*H*, C_5–*H*), 6.76–6.78 (d, J: 7.99 Hz, 1H, coumarin-C_6–*H*), 6.56 (s, 1H, coumarin-C_8–*H*), 3.22–3.45 (m, 4H, $2CH_2$), 2.47 (s, 2H, SO_2NH_2), 1.11–1.18 (m, 6H, $2CH_3$). ^{13}C-NMR; 168.15 (C=O), 158.44 (thiadiazole-C_{7a}), 150.22 (coumarin-C_9), 149.15 (imidazole-C_6), 146.30 (coumarin-C_7), 130.22 (coumarin-C_3), 141.44 (coumarin-C_4), 126.44 (coumarin-C_5), 118.44 (coumarin-C_{10}), 116.56 (coumarin-C_6), 114.12 (coumarin-C_8), 110.24 (imidazole-C_5), 107.46 (thiadiazole-C_2), 39.24 (coumarin $2CH_3$), 30.78 (coumarin $2CH_2$); MS (70 eV) *m/z* 499 (M + 1), 498 (M^+), 419, 101, 80, 62, 48; Anal. Calcd. For $C_{17}H_{16}O_4N_5S_2Br$: C, 40.97; H, 3.24; N, 14.05. Found: C, 40.88; H, 3.23; N, 14.01.

*Synthesis of 5-nitroso-6-[7-(diethylamino)-2-oxo-2H-chromen-3-yl]imidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamide (**8**)*

To a well stirred solution of imidazothiadiazole (**3**) (0.01 mol, 4.19 g) in acetic acid (20 mL) was added sodium nitrite solution (0.021 mol, in 4 mL water) drop wise at room temperature. After the addition, stirring was continued for 30 min and the mixture was refluxed for 3 h. The reaction mixture was poured into ice cold water, separated solid was collected, washed with water dried and recrystallized from methanol (yield 80.70 %). mp 200–202 °C. IR (KBr) 3275, 1746, 1638, 1566, 1420, 1336, 1158, 648 cm^{-1}; ^{1}H-NMR (DMSO-d_6); 7.96–7.98 (m, 2H, coumarin-C_4–*H*, C_5–*H*), 7.19- 7.20 (d, J: 3.99 Hz, 1H, coumarin-C_6–*H*), 6.76 (s, 1H, coumarin-C_8–*H*), 3.22–3.45 (m, 4H, $2CH_2$), 2.48 (s, 2H, SO_2NH_2), 1.11–1.18 (m, 6H, $2CH_3$). ^{13}C-NMR; 169.22 (C=O), 156.24 (thiadiazole-C_{7a}), 150.78 (coumarin-C_9), 149.26 (imidazole-C_6), 147.10 (coumarin-C_7), 141.40 (coumarin-C_4), 133.16 (coumarin-C_3), 127.20 (coumarin-C_5), 119.46 (coumarin-C_{10}), 116.22 (coumarin-C_6), 115.20 (coumarin-C_8), 111.20 (imidazole-C_5), 107.60 (thiadiazole-C_2), 39.22 (coumarin $2CH_3$), 30.16 (coumarin $2CH_2$); MS (70 eV) *m/z* 449

(M + 1), 448 (M^+), 419, 369, 101, 80, 62, 48; Anal. Calcd. For $C_{17}H_{16}N_6O_5S_2$: C, 45.53; H, 3.60; N, 18.74. Found: C, 45.46; H, 3.61; N, 18.70.

*Synthesis of 5-thiocyanato-6-[7-(diethylamino)-2-oxo-2H-chromen-3-yl]imidazo[2,1-b][1,3,4]thiadiazole-2-sulphonamide (**9**)*

To a well stirred solution of imidazothiadiazole (**3**) (0.01 mol, 4.19 g) in glacial acetic acid (30 mL) and potassium thiocyanate (0.02 mol) was added bromine (0.01 mol) in glacial acetic acid (5 mL) drop wise with stirring at room temperature. The stirring was further continued for 3 h at room temperature. The reaction mixture was poured into ice water, the separated solid was collected, washed with water, dried, and recrystallized from methanol (yield 68.00 %). mp 124–126 °C. IR (KBr) 3313, 2968, 2153, 1716, 1569, 1487, 1345, 1182, 650 cm^{-1}; ^{1}H-NMR (DMSO-d_6); 7.60–7.62 (m, 2H, coumarin-C_4–*H*, C_5–*H*), 6.76–6.78 (d, J: 8.79 Hz, 1H, coumarin-C_6–*H*), 6.36 (s, 1H, coumarin-C_8–*H*), 3.22–3.45 (m, 4H, $2CH_2$), 2.47 (s, 2H, SO_2NH_2), 1.04–1.16 (m, 6H, $2CH_3$). ^{13}C-NMR; 170.44 (C=O), 155.12 (thiadiazole-C_{7a}), 151.22 (coumarin-C_9), 149.12 (SCN) 148.42 (imidazole-C_6), 146.20 (coumarin-C_7), 141.22 (coumarin-C_4), 132.10 (coumarin-C_3), 126.12 (coumarin-C_5), 119.12 (coumarin-C_{10}), 115.46 (coumarin-C_6), 114.14 (coumarin-C_8), 112.12 (imidazole-C_5), 106.12 (thiadiazole-C_2), 39.14 (coumarin $2CH_3$), 31.16 (coumarin $2CH_2$); MS (70 eV) *m/z* 477 (M + 1), 476 (M^+), 419, 101, 80, 62, 48; Anal. Calcd. For $C_{18}H_{16}O_4N_6S_3$: C, 45.37; H, 3.38; N, 17.63. Found: C, 45.30; H, 3.39; N, 17.58.

*Synthesis of 5-formyl-6-[7-(diethylamino)-2-oxo -2H-chromen-3-yl]imidazo[2,1-b][1,3,4]thiadiazole-2-[N-(dimethylaminomethino)] sulfonamide (**10**)*

Vilsmeier–Haack reagent was prepared by adding phosphoryl chloride (3 mL) in dimethylformamide (20 mL) at 0 °C with stirring. Then, imidazothiadiazole (**3**) (0.01 mol, 4.1 g) was added to the reagent and stirred 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 ethanol (yield 78.00 %). mp 198–200 °C. IR (KBr) 2926, 2853, 2742, 1714, 1681, 1622, 1489, 1336, 1156, 652 cm^{-1}; ^{1}H-NMR (DMSO-d_6); 10.06 (s, 1H, CHO), 8.69 (s, 1H, CH=N), 7.64–7.80 (m, 2H, coumarin-C_4–*H*, C_5–*H*), 6.78 (d, J: 8.79 Hz, 1H, coumarin-C_6–*H*), 6.63 (s, 1H, coumarin-C_8–*H*), 3.26–3.35 (m, 4H, $2CH_2$), 3.04 (m, 6H, $2CH_3$), 1.06–1.15 (m, 6H, $2CH_3$); ^{13}C-NMR; 182.15 (CHO), 172.10 (C=O), 160.10 (NH=CH), 153.21 (thiadiazole-C_{7a}), 151.15 (coumarin-C_9), 148.09 (imidazole-C_6), 145.70 (coumarin-C_7), 140.59 (coumarin-C_4), 131.40 (coumarin-C_3), 126.53 (coumarin-C_5), 119.82 (coumarin-C_{10}), 115.48 (coumarin-C_6), 113.08 (coumarin-C_8), 111.55 (imidazole-C_5), 106.59 (thiadiazole-C_2), 39.51 (coumarin $2CH_3$), 30.57 (coumarin $2CH_2$), 12.84 (formamide $2CH_3$); MS (70 eV) *m/z* 502 (M^+), 474, 459, 431, 101, 62, 48. Anal. Calcd. For $C_{21}H_{22}O_5N_6S_2$: C, 50.19; H, 4.41; N, 16.72. Found: C, 50.02; H, 4.42; N, 16.68.

*Synthesis of [6-[7-(diethylamino)-2-oxo-2H-chromen-3-yl] imidazo[2,1-b][1,3,4]thiadiazole-2-[N-(dimethylamino-methino)] sulfonamido-5-yl]methanol (**11**)*

5-Formyl-6-[7-(diethylamino)-2-oxo-2*H*-chromen-3-yl]imidazo[2,1-*b*][1,3,4]thiadiazole-2-[*N*-(dimethylaminomethino)] sulfonamide **10** (0.001 mol, 0.50 g) was added in small portions to a stirred and cooled solution of sodium borohydride (0.001 mol, 0.36 g) in dry methanol (25 mL). The mixture was stirred at room temperature for 7 h (monitored by TLC) and poured over ice water. The solid separated was collected by filtration, washed with cold methanol, dried, and crystallized from DMF. (yield 67.00 %). mp 210–212 °C. IR (KBr) 3354, 2942, 2866, 2766, 1718, 1618, 1495, 1360, 1166, 658 cm^{-1}; ^{1}H-NMR (DMSO-d_6); 8.25 (s, 1H, CH=N), 7.58–7.92 (m, 2H, coumarin-C_4–*H*, C_5–*H*), 6.44 (d, 1H, J: 8.99 Hz, coumarin-C_6–*H*), 6.24 (s, 1H, coumarin-C_8–*H*), 5.02 (s, 2H, CH_2), 3.16–3.34 (m, 4H, $2CH_2$), 3.08 (m, 6H, $2CH_3$), 2.58 (br s, 1H, OH, D_2O exchangeable), 1.15–1.45 (m, 6H, $2CH_3$); ^{13}C-NMR; 171.54 (C=O), 162.44 (NH=CH), 152.24 (thiadiazole-C_{7a}), 152.56 (coumarin-C_9), 149.22 (imidazole-C_6), 146.48 (coumarin-C_7), 142.28 (coumarin-C_4), 130.88 (coumarin-C_3), 125.78 (coumarin-C_5), 120.54 (coumarin-C_{10}), 116.54 (coumarin-C_6), 114.20 (coumarin-C_8), 112.26 (imidazole-C_5), 107.58 (thiadiazole-C_2), 46.98 (CH_2OH), 38.54 (coumarin $2CH_3$), 31.48 (coumarin $2CH_2$), 13.78 (formamide $2CH_3$); MS (70 eV) *m/z* 505 (M^+), 475, 462, 434, 101, 62, 48. Anal. Calcd. For $C_{21}H_{24}O_5N_6S_2$: C, 49.99; H, 4.79; N, 16.66. Found: C, 49.90; H, 4.78; N, 16.68.

*Synthesis of 6-[7-(diethylamino)-2-oxo-2H-chromen-3-yl]imidazo[2,1-b][1,3,4]thiadiazole-2-[N-(dimethylaminomethino)] sulfonamido-5-carbaldehydeoxime (**12**)*

A mixture of 5-formyl-6-[7-(diethylamino)-2-oxo-2*H*-chromen-3-yl]imidazo[2,1-*b*][1,3,4] thiadiazole-2-[*N*-(dimethylaminomethino)]sulfonamide **10** (0.001 mol, 0.50 g)

and hydroxylamine hydrochloride (0.0012 mol, 0.83 g) was refluxed in pyridine (15 mL) for 8 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 DMF. (yield 65.00 %). mp 228–230 °C. IR (KBr) 3282, 2948, 2852, 2771, 1720, 1628, 1488, 1366, 1160, 652 cm^{-1}; ^{1}H-NMR (DMSO-d_6); 9.86 (br s, 1H, OH, D_2O exchangeable), 8.69 (s, 1H, CH=N), 8.46 (s, 1H, CH=N), 7.44–7.84 (m, 2H, coumarin-C_4–*H*, C_5–*H*), 6.45 (d, J: 8.90 Hz, 1H, coumarin-C_6–*H*), 6.20 (s, 1H, coumarin-C_8–*H*), 3.02–3.45 (m, 4H, $2CH_2$), 2.98 (m, 6H, $2CH_3$), 1.10–1.22 (m, 6H, $2CH_3$); ^{13}C-NMR; 170.24 (C=O), 161.28 (NH=CH), 154.30 (CH=N), 153.87 (thiadiazole-C_{7a}), 151.46 (coumarin-C_9), 148.56 (imidazole-C_6), 145.92 (coumarin-C_7), 141.54 (coumarin-C_4), 131.54 (coumarin-C_3), 124.46 (coumarin-C_5), 121.46 (coumarin-C_{10}), 117.22 (coumarin-C_6), 115.24 (coumarin-C_8), 111.46 (imidazole-C_5), 107.41 (thiadiazole-C_2), 37.21 (coumarin $2CH_3$), 31.85 (coumarin $2CH_2$), 12.54 (formamide $2CH_3$); MS (70 eV) *m/z* 518 (M^+), 475, 474, 447, 101, 62, 48. Anal. Calcd. For $C_{21}H_{23}O_5N_7S_2$: C, 48.73; H, 4.48; N, 18.94. Found: C, 48.69; H, 4.47; N, 18.89.

*Synthesis of 6-[7-(diethylamino)-2-oxo-2H-chromen-3-yl]imidazo[2,1-b][1,3,4]thiadiazole-2-[N-(dimethylaminomethino)] sulfonamido-5-carbonitrile (**13**)*

The 6-[7-(diethylamino)-2-oxo-2*H*-chromen-3-yl]imidazo-[2,1-*b*][1,3,4]thiadiazole-2-[*N*-(dimethylaminomethino)] sulfonamido-5-carbaldehydeoxime **12** (0.001 mol, 0.51 g) was suspended in thionyl chloride (8 mL) and refluxed for 10 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 benzene. (yield 58.00 %). mp 238–240 °C. IR (KBr) 2990, 2856, 2746, 2210, 1722, 1612, 1492, 1368, 1155, 656 cm^{-1}; ^{1}H-NMR (DMSO-d_6); 8.44 (s, 1H, CH=N), 7.76–8.10 (m, 2H, coumarin-C_4–*H*, C_5–*H*), 6.95 (d, J: 8.99 Hz, 1H, coumarin-C_6–*H*), 6.26 (s, 1H, coumarin-C_8–*H*), 3.12–3.52 (m, 4H, $2CH_2$), 2.96 (m, 6H, $2CH_3$), 1.16–1.26 (m, 6H, $2CH_3$); ^{13}C-NMR; 172.63 (C=O), 162.32 (NH=CH), 152.54 (thiadiazole-C_{7a}), 150.26 (coumarin-C_9), 149.34 (imidazole-C_6), 145.24 (coumarin-C_7), 142.64 (coumarin-C_4), 130.24 (coumarin-C_3), 125.56 (coumarin-C_5), 121.88 (coumarin-C_{10}), 118.92 (CN), 118.34 (coumarin-C_6), 116.44 (coumarin-C_8), 112.87 (imidazole-C_5), 108.62 (thiadiazole-C_2), 36.56 (coumarin $2CH_3$), 32.76 (coumarin $2CH_2$), 12.36 (formamide $2CH_3$); MS (70 eV) *m/z* 500 (M^+), 474, 457, 429, 101, 62, 48. Anal. Calcd. For $C_{21}H_{21}O_4N_7S_2$: C, 50.49; H, 4.24; N, 19.63. Found: C, 50.40; H, 4.23; N, 19.68.

*Synthesis of 2-[-6-[7-(diethylamino)-2-oxo-2H-chromen-3-yl]imidazo[2,1-b][1,3,4]thiadiazole-2-[N-(dimethylaminomethino)] sulfonamido]-3-phenyl-1, 3-thiazolidin-4-one (**14**)*

5-Formyl-6-[7-(diethylamino)-2-oxo-2H-chromen-3-yl]imidazo[2,1-*b*][1,3,4]thiadiazole-2-[*N*-(dimethylaminomethino)] sulfonamide **10** (0.001 mol, 0.50 g) and aniline (1.1 g, 0.012 mol) were refluxed in dry ethanol (40 mL) with catalytic amount of acetic acid for 4 h. The solid that separated was filtered, washed with alcohol, and dried. The crude product was recrystallized from DMF, the yellow colored solid thus obtained (0.01 mol) was refluxed with thioglycolic acid (0.012 mol), in dry benzene (25 mL) for 8 h. The colorless solid that separated was collected by filtration, dried, and recrystallized from aq DMF. (yield 49.00 %). mp 252–254 °C. IR (KBr) 2990, 2888, 2752, 1726, 1710, 1612, 1495, 1374, 1162, 658 cm^{-1}; ^{1}H-NMR (DMSO-d_6); 8.72 (s, 1H, CH=N), 7.64–7.89 (m, 2H, coumarin-C_4–*H*, C_5–*H*) 7.96 (s, 1H, thiazolidine-*CH*), 6.78 (d, J: 8.99 Hz, 1H, coumarin-C_6–*H*), 6.59 (s, 1H, coumarin-C_8–*H*), 5.88 (s, 2H, CH_2), 3.33–3.55 (m, 4H, $2CH_2$), 3.22 (m, 6H, $2CH_3$), 1.08–1.22 (m, 6H, $2CH_3$); ^{13}C-NMR; 171.22 (C=O), 166.84 (thiazolidine-C=O), 161.65 (NH=CH), 152.54 (thiadiazole-C_{7a}), 151.62 (coumarin-C_9), 150.12 (imidazole-C_6), 144.54 (coumarin-C_7), 141.32 (coumarin-C_4), 131.58 (coumarin-C_3), 126.94 (coumarin-C_5), 120.44 (coumarin-C_{10}), 119.23 (coumarin-C_6), 117.75 (coumarin-C_8), 111.46 (imidazole-C_5), 109.79 (thiadiazole-C_2), 40.26 (thiazolidine-C_2), 37.68 (thiazolidine-C_5), 36.26 (coumarin $2CH_3$), 31.82 (coumarin $2CH_2$), 11.89 (formamide $2CH_3$); MS (70 eV) *m/z* 652 (M^+), 609, 581, 474, 101, 62, 48. Anal. Calcd. For $C_{29}H_{29}O_5N_7S_3$: C, 53.44; H, 4.48; N, 15.04. Found: C, 53.40; H, 4.47; N, 15.00.

*Synthesis of 5-guanylhydrazone-6-[7-(diethylamino)-2-oxo-2H-chromen-3-yl]imidazo[2,1-b][1,3,4]thiadiazole-2-[N-(dimethylaminomethino)] sulfonamide (**15**)*

5-formyl-6-[7-(diethylamino)-2-oxo-2H-chromen-3-yl]imidazo[2,1-*b*][1,3,4]thiadiazole-2-[*N*-(dimethylaminomethino)] sulfonamide **10** (0.001 mol, 0.50 g) was dissolved in 100 mL of ethanol and treated with (0.01 mol) of aminoguanidine hydrochloride prepared from treating the suspension of aminoguanidine bicarbonate in ethanol with excess of 37 % hydrochloric acid. The reaction mixture was refluxed for 1 h and the resulting precipitate was collected by filtration and dried. The HCl salt thus obtained was suspended in ice cold water and basified with aqueous ammonia solution. The free base **15** thus formed was filtered, dried, and recrystallised from ethanol. (yield

61.00 %). mp 263–265 °C. IR (KBr) 3425 (b), 3122, 2948, 2844, 2736, 1714, 1615, 1484, 1340, 1162, 650 cm^{-1}; ^{1}H-NMR (DMSO-d_6); 12.20 (s, 1H, =N–NH), 8.78 (s, 1H, 5-CH=N), 8.58 (s, 1H, CH=N–SO_2), 7.55–7.99 (m, 2H, coumarin-C_4–*H*, C_5–*H*), 6.71 (d, t: 8.90 Hz, 1H, coumarin-C_6–*H*), 6.52 (s, 1H, coumarin-C_8–*H*), 3.18–3.41 (m, 4H, $2CH_2$), 3.09 (m, 6H, $2CH_3$), 2.02 (s, 2H, NH_2), 1.09–1.20 (m, 6H, $2CH_3$); ^{13}C-NMR; 172.56 (C=O), 163.81 (NH-C=NH), 162.44 (NH=CH), 154.94 (CH=N), 151.32 (thiadiazole-C_{7a}), 150.75 (coumarin-C_9), 149.71 (imidazole-C_6), 144.28 (coumarin-C_7), 142.69 (coumarin-C_4), 130.47 (coumarin-C_3), 127.29 (coumarin-C_5), 121.85 (coumarin-C_{10}), 118.54 (coumarin-C_6), 117.22 (coumarin-C_8), 110.29 (imidazole-C_5), 108.82 (thiadiazole-C_2), 36.42 (coumarin $2CH_3$), 31.26 (coumarin $2CH_2$), 11.24 (formamide $2CH_3$); MS (70 eV) *m/z* 559 (M^+), 516, 488, 474, 101, 62, 48. Anal. Calcd. For $C_{22}H_{26}O_4N_{10}S_2$: C, 47.30; H, 4.69; N, 25.07. Found: C, 47.26; H, 4.68; N, 25.02.

Biological activities

Minimum Inhibitory Concentration (MIC) values were determined for newly synthesized compounds against *M. tuberculosis* strain H_{37}Rv using the Micro plate Alamar Blue assay (MABA) (Franzblau *et al.* 1998. Pyrazinamide and streptomycin were used as standard drugs. The 96-wells plate received 100 µl of the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate. The final drug concentrations tested were 0.2, 0.4, 0.8, 1.6, 3.125, 6.25, 12.5, 25, 50, and 100 µg mL^{-1}. Plates were covered and sealed with parafilm and incubated at 37 °C for five days. After this, 25 µl of freshly prepared 1:1 mixture of almar blue reagent and 10 % tween 80 was added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth and pink color was scored as growth. The MIC was defined as lowest drug concentration which prevented the color change from blue to pink. Table 1 reveals the antitubercular activity (MIC) of compounds **3**–**15**.

The MIC determination of the tested compounds was investigated in side-by-side comparison with norfloxacin against Gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*) and Gram-negative bacteria (*Vibrio cholera*, *Escherichia coli*) by broth microdilution method (Yajko *et al.*, 1995). Serial dilutions of the test compounds and reference drugs were prepared in Mueller–Hinton agar. Drugs (10 mg) were dissolved in dimethylsulfoxide (DMSO, 1 mL). Further progressive dilutions with melted Mueller–Hinton agar were performed to obtain the required concentrations of 1, 2, 4, 8, 16, 31.25, 62.5, 125, 250, and 500 µg mL^{-1}. The tubes were inoculated with 10^5 cfu mL^{-1} (colony forming unit/mL) and incubated at 37°C for 18 h. The MIC was the lowest concentration of the tested compound that yield no visible growth on the plate. To insure that the solvent had no effect on the bacterial growth, a control was performed with the test medium supplemented with DMSO at the same dilutions as used in the experiments and DMSO had no effect on the microorganisms in the concentrations studied. Table 2 reveals the antibacterial activity (MIC values) of compounds **3**–**15**.

Table 1 *In vitro* antitubercular activities (MIC, µg/mL) of imidazo[2,1-*b*][1,3,4]thiadiazoles **3**–**15**

Compound	*Mycobacterium tuberculosis* H_{37}Rv[a]
3	3.125
4	25
5	25
6	25
7	6.25
8	50
9	12.5
10	1.6
11	3.125
12	25
13	25
14	0.8
15	0.8
Pyrazinamide	3.125
Streptomycin	6.25

[a] MIC was evaluated by the alamar blue dye using microplate alamar blue assay method

Results and discussion

Structure of imidazothiadiazole **3** was established by the absence of υ_{N-H} band in the IR spectra and appearance of imidazole proton (C_5–H) at δ 8.56 in ^{1}H-NMR spectra. The ^{1}H-NMR spectra of the compounds **4**, **5**, and **6** showed the absence of imidazole proton and a singlet was observed around δ 4.00, which was assigned to methylene protons and other aliphatic and aromatic protons resonated in the expected region. For morpholine derivatives **4**, two triplets were observed. Formation of Mannich bases was further confirmed by their ^{13}C NMR and mass spectra.

All the electrophillic substitution reactions carried out on imidazothiadiazole afforded the regioselectively expected 5-substituted derivatives **7**, **8**, **9**, and **10**. IR spectrum of compound **8** displayed the absorption band at 1566 cm^{-1} for NO, while compound **9** showed band at 2153 cm^{-1} for SCN. IR spectra of **10** displayed the sharp band for carbonyl stretching frequency $\upsilon_{C=O}$ at 1681 cm^{-1} and the singlet due to C_5-imidazole proton was absent and a signal for aldehyde proton was observed at δ 10.06 in the

Table 2 *In vitro* antibacterial activities (MIC, μg/mL) of imidazo[2,1-*b*][1,3,4]thiadiazoles **3–15**[a]

Compound	Gram-negative Organisms		Gram-positive Organisms	
	V. cholera	*E. coli*	*S. aureus*	*B. subtilis*
3	31.25	31.25	62.5	62.5
4	31.25	31.25	62.5	62.5
5	31.25	31.25	62.5	62.5
6	8	8	62.5	62.5
7	16	16	62.5	62.5
8	31.25	31.25	125	125
9	31.25	31.25	62.5	62.5
10	4	4	16	16
11	8	8	31.25	31.25
12	16	16	62.5	62.5
13	16	16	62.5	62.5
14	1	1	16	16
15	1	1	16	16
Norfloxacillin	1	16	2	2

[a] MIC was evaluated by the broth microdilution assay method

^{1}H-NMR spectrum, thus confirming the formation of imidazothiadiazole-5-carbaldehyde. All the 5-substituted derivatives showed the absence of C_5–H in their ^{1}H-NMR spectra confirming the substitution at 5th position. The structures of all the compounds were finally ascertained by the ^{13}C-NMR and mass spectra.

The compound **11** showed the absence of carbonyl stretching frequency $\upsilon_{C=O}$ and the presence of broad band at 3354 cm^{-1} for υ_{O-H} in IR spectrum. The ^{1}H-NMR displayed the absence of signal due to aldehyde proton and the methylene protons resonated as singlet at δ 5.02 and -OH proton was observed as broad singlet at δ 2.58. The absence of $\upsilon_{C=O}$ band and the presence of υ_{O-H} band in the IR spectrum of the product confirmed the formation of oxime **12** and signal due to aldehydic proton was absent and new signals for the azomethine and the –OH proton (D_2O exchangeable) resonated at δ 9.86 and δ 8.69, respectively in the ^{1}H-NMR spectrum, thus substantiating the formation of aldoxime **12**. The product obtained after treatment of this aldoxime with thionyl chloride showed a sharp band at 2210 cm^{-1} in the IR spectrum attributed for υ_{CN} and there was no band due to υ_{O-H}. The absence of both the -OH and azomethine protons in the ^{1}H-NMR spectrum confirmed the formation of nitrile **13**. The compound **14** showed the carbonyl stretching frequency $\upsilon_{C=O}$ at 1710 cm^{-1}, the ^{1}H-NMR of the same displayed two singlets at δ 7.96 and δ 5.88, respectively. These data confirmed the presence of thiazolidinone ring at 5-position. ^{1}H-NMR spectrum of **15** displayed a D_2O exchangeable peak due to NH_2 at δ 2.02. The presence of new resonances at δ 12.20 and δ 8.78 assigned to guanyl NH and 5-CH=N protons, respectively.

The synthesized compounds were evaluated for their in vitro antitubercular activity against *M. tuberculosis* H_{37}Rv by using microplate alamar blue assay method. The investigation of antimycobacterial screening data (Table 1) revealed that all the tested compounds showed good mycobacterial inhibition. The tested compounds showed activities against mycobacteria with MIC values ranging from 0.8 to 50 μg/mL. The activity is considerably affected by substitutents at position-5 on the imidazo[2,1-*b*][1,3,4]thiadiazole nucleus. Compounds **4**, **5**, **6**, **12**, and **13** exhibited moderate antitubercular activity at a MIC of 20 μg/mL. Compound **10** having formyl group at 5th position, showed improved activity at MIC value of 1.6 μg/mL. It has been observed that compounds **14** and **15** having a thiazolidinone and gaunylhydrazone groups respectively at 5th position, showed highest antimycobacterial activity at a MIC of 0.8 μg/mL.

In order to determine the antimicrobial activity of the synthesized compounds, two Gram-positive, two Gram-negative bacterial species were screened using the broth dilution technique. Results of antibacterial activity of the compounds are given in Table 2. The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial inhibition. All the compounds showed significant antibacterial activity against Gram-negative bacteria and moderate activity against Gram-positive bacteria. Compounds showed antimicrobial activity at MIC values of 1–125 μg/mL. Among the Mannich bases the pyrrolidine derivative **6** was found to have more activity against V. *cholera* and *E. coli* at a MIC of 8 μg/mL. Compound **10** has exhibited very good activity against all the bacterial strains; however, compounds **11** and **12** were highly active against V. *cholera* and *E. coli.* The thiazolidinone derivative **14** and gaunylhydrazone derivative **15** showed superior activity against V. *cholera* and *E. coli* at a MIC of 1 μg/mL.

Conclusion

The present research study reports the successful synthesis, antibacterial, and antitubercular studies of new series of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives carrying biologically active entities. Their screening results revealed that all the compounds showed moderate to very good activities against pathogenic strains. The preliminary in vitro antibacterial and antitubercular screening of these 5-substituted-6-[7-(diethylamino)-2-oxo-2*H*-chromen-3-yl] imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamides **4–15** has revealed that coumarin substitution at 6th position and different groups at 5th position, have emerged as potential

compounds endowed with moderate to good antibacterial and antitubercular activities. From first examination of the antimicrobial activity results, it is evident that compounds **10**, **14**, and **15** containing 5-formyl, 5-thiazolidinone, and 5-gaunylhydrazone groups, respectively showed increased activity. The possible improvement of antitubercular activity of basic imidazo[2,1-*b*][1,3,4]thiadiazole structure through modulation of ring substitutents and/or additional functional groups warrants further investigations. Due to the better activity against tested mycobacteria and microorganisms, compounds **10**, **14**, and **15** have been selected for further development and studies to acquire more information about structure–activity relationships are in progress in our laboratories. In summary we have identified a novel series of substituted imidazo[2,1-*b*][1,3,4]thiadiazole derivatives which may be developed into potential class of antitubercular and antimicrobial agents.

Acknowledgments We thank Dr. V. H. Kulkarni, Principal, Shri. H. V. Dambal, President, S. E. T's College of Pharmacy, Dharwad, India, for providing necessary facilities. We are thankful to Dr. G. S. Gadaginamath for his valuable suggestions. We are grateful to Dr. K. G. Bhat, Maratha Mandal's Dental College, Hospital and Research Centre, Belgaum, India for providing the facilities for antibacterial and antitubercular activity. We also wish to thank Director, SAIF, Indian Institute of Technology, Chennai, India and Director, USIC, Karnataka University Dharwad, India for providing NMR and Mass spectral data.

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