Med Chem Res (2012) 21:1550–1556
DOI 10.1007/s00044-011-9671-8

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Microwave-assisted synthesis and antimicrobial activity of some imidazo[2,1-b][1,3,4]thiadiazole derivatives

Sharad Dhepe · Sujeet Kumar · R. Vinayakumar · Sureshbabu A. Ramareddy · Subhas S. Karki

Received: 16 February 2011 / Accepted: 12 May 2011 / Published online: 27 May 2011

Abstract A simple and efficient method was developed for the synthesis of 2,6-disubstituted-imidazo[2,1-b][1,3,4] thiadiazoles under microwave (MW) activation using 2-amino-5-substituted-1,3,4-thiadiazoles and appropriate bromo ketones as materials. All reactions demonstrated the benefits of MW reactions: convenient operation, short reaction time, and good yields. All derivatives were characterized by IR, NMR, and Mass spectroscopy. Antibacterial and antifungal activity was performed using cup plate method against *Staphylococcus aureus*, *Klebsiella*, and *Candida albicans* microorganisms. 2-(4-nitro benzyl)-6-(4-bromo phenyl)imidazo[2,1-b][1,3,4]thiadiazole (**4Ce**) was the only derivative which showed activity against *Klebsiella* at low micromolar concentration (5 μg/ml) with moderate zone of inhibition. And 2-(4-nitro benzyl)-6-(4-fluoro phenyl)imidazo[2,1-b][1,3,4]thiadiazole (**4Cf**) as the most potent antifungal active derivative at 50 μg/ml against *C. albicans* on comparison to standard fluconazole.

Keywords Microwave · Imidazo[2,1-b][1,3,4]thiadiazole · Synthesis · Antibacterial activity · Antifungal activity

Introduction

The design of new compounds to lead with resistant bacteria has become one of the most important areas of antibacterial research today, that is because of resistance of pathogenic bacteria towards available antibiotics is rapidly becoming a major world wide problem. In addition to that, fungal infections continue to increase rapidly because of the increased number of immunocompromised patients. Levamisole, a well-known immunomodulator, (Amery *et al*., 1984) the possibility of reducing harmful effects of cytotoxic agents on immune system. Compounds closely related to levamisole have been investigated. Andreani et al. (1991a, b) reported that some imidazo[2,1-b]thiazole are more active than levamisole. Many derivatives containing the imidazo[2,1-b][1,3,4]thiadiazole ring system, which is bioisosteric with the imidazo[2,1-b]thiazole system of Levamisole, are being explored. Similarly, a large number of imidazo[2,1-b][1,3,4]thiadiazole have been reported to possess diverse pharmacological properties such as anticancer (Gadad *et al*., 1999; Karki *et al*., 2011), antitubercular (Gadad *et al*., 2004; Kolavi *et al*., 2006), antibacterial (Gadad *et al*., 2000; Lamani *et al*., 2009), antifungal (Andotra *et al*., 1997; Chen *et al*., 2007), anticonvulsant, analgesic (Khazi *et al*., 1996), antisecretory (Andreani et al., 2000), anti-inflammatory (Andreani *et al*., 1982; Jadhav *et al*., 2008; Gadad *et al*., 2008), cardiotonic (Andreani *et al*., 1986) diuretic (Andreani *et al*., 1987), and herbicidal activities (Andreani *et al*., 1991a, b).

The microwave (MW) radiation region is located between infrared radiation and radio waves. MWs have wavelengths of 1 mm–1 m. It has been known for a long time that MWs can be used for heating materials. In fact, the development of MW ovens for the heating of food has more than a 50-year history (Buffler, 1993).

MW technology has been used since the late 1970s, in inorganic chemistry, while it has been implemented in organic chemistry since the mid-1980s. The development of the technology for organic chemistry has been rather slow compared, to for example, combinatorial chemistry

S. Dhepe · S. Kumar · R. Vinayakumar · S. A. Ramareddy · S. S. Karki (✉)
Department of Pharmaceutical Chemistry, KLE University's College of Pharmacy, Bangalore 560 010, Karnataka, India
e-mail: subhasskarki@gmail.com

and computational chemistry. Since the mid-1990s, however the number of publications has increased significantly. The main reason for this increase includes the availability of commercial MW equipment intended for organic chemistry and the development of the solvent-free technique, which has improved the safety aspects, but are mostly due to an increased interest in shorter reaction times.

MW-assisted organic synthesis is suited to the increased demand in industry because of short reaction times and expanded reaction range. In particular, there is a requirement in the pharmaceutical industry for a higher number of novel chemical entities to be produced.

In general, most organic reactions have been heated using traditional heat transfer equipment such as oil baths, sand baths, and heating jackets. These heating techniques are, however, rather slow, and a temperature gradient can develop within the sample. In addition, local overheating can lead to product, substrate, and reagent decomposition. In contrast, in MW dielectric heating, the MW energy is introduced into the chemical reactor remotely, and direct access by the energy source to the reaction vessel is obtained. The MW radiation passes through the walls of the vessel and heats only the reactants and solvent, not the reaction vessel. In view of the above and in continuation of our research on fused imidazo[2,1-b][1,3,4]thiadiazoles, we report here the MW and conventional-assisted synthesis, antibacterial, and antifungal activity of some 2-(4-substituted benzyl)-6-phenyl imidazo[2,1-b][1,3,4]thiadiazoles.

Experimental

Chemistry

The melting points are uncorrected. Silica gel plates were used for the TLC using $CHCl_3$:MeOH. The IR spectra were recorded in KBr on a Jasco 430+; the ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker (400 MHz), and *J* values are reported in hertz (Hz). Mass spectra were recorded in triple quadrapole LCMS-6410 from Agilent technologies.

*General procedure for preparation of **3A–3C***

The mixture of substituted/phenyl acetic acid (0.1 M) and thiosemicarbazide (0.15 M) was added slowly to the round bottom flask containing concentrated H_2SO_4 (30 ml) with constant stirring in ice bath. After complete addition, ice bath was replaced by water bath and slowly heated to 70–80°C and maintained at that temperature for 7 h. After cooling to room temperature, the contents of reaction were poured into ice water and made basic with ammonia, filtered the precipitate, washed with water, and recrystallized from ethanol.

*2-Amino-5-benzyl-1,3,4-thiadiazole (**3A**)*

MS *m/z* 192.00; FT IR (ν cm^{-1}) 3021, 2936, 1520, 1465, 1350, 1300, 1172, 1095, 1010. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.14 (s, 2H, –CH_2–), 7.12 (s, –NH_2, 2H), 7.23–7.34 (m, 5H).

*2-Amino-5-(4-chlorobenzyl)-1,3,4-thiadiazole (**3B**)*

MS *m/z* 226.10; FT IR (ν cm^{-1}) 3162, 3034, 2945, 2893, 1696, 1566, 1494, 1355, 1306, 1170, 1092, 1014. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.30 (s, 2H. –CH_2–), 7.06 (s, –NH_2, 2H), 7.55 (d, $J = 8$ Hz, 2H), 8.20 (d, $J = 8$ Hz, 2H).

*2-Amino-5-(4-nitrobenzyl)-1,3,4-thiadiazole (**3C**)*

MS *m/z* 237.00; FT IR (ν cm^{-1}) 3168, 3120, 3034, 2853, 2738, 1691, 1571, 1517, 1351, 1177. ^{1}H NMR (DMSO, 400 MHz) δ 4.32 (s, 2H. –CH_2–), 7.08 (s, –NH_2, 2H), 7.56 (d, $J = 8$ Hz, 2H), 8.19 (d, $J = 8$ Hz, 2H).

*Synthesis of imidazo[2,1-b][1,3,4]thiadiazoles (**4**)*

Conventional method The appropriate 2-amino-1,3,4-thiadiazole **3** (30 mmol) was treated with the appropriate α-bromo ketone (30 mmol) in ethanol (150 ml). The mixture was refluxed for 8–10 h. Excess of solvent was removed under reduced pressure, and the solid hydrobromide salt separated was filtered, washed with cold ethanol, and dried. Neutralization of hydrobromide salts with cold aqueous solution of sodium carbonate yielded the corresponding free base which was filtered and which were recrystallised with EtOH to yield products 40–60%.

MW method

The appropriate 2-amino-1,3,4-thiadiazole **3** (0.01 M) treated with the appropriate bromo ketone (0.01 M) in DMF (30 ml) was irradiated in a MW oven for 4–7 min at 640 W. Completion of the reaction was monitored by TLC using $CHCl_3$ and CH_3OH (9:1) as eluent. The resulting mixture was cooled to room temperature and neutralization of hydrobromide salts with cold aqueous solution of sodium carbonate yielded the corresponding free base in 75–84% yield.

*2-Benzyl-6-(4-chlorophenyl)imidazo [2,1-b][1,3,4]thiadiazole (**4Aa**)*

MS *m/z* 324.10; FT IR (ν cm^{-1}) 3127, 3061, 3032, 2917, 2848, 1523, 1256, 1027. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.30

(s, 2H, –CH_2–), 7.32–7.39 (m, 7H), 7.74 (d, $J = 8$ Hz, 2H), 7.95 (s, 1H, im).

*2-Benzyl-6-(4-methylphenyl)imidazo [2,1-b][1,3,4]thiadiazole (**4Ab**)*

MS *m/z* 306.01; FT IR (v cm^{-1}) 3134, 3058, 3033, 2973, 2864, 1524, 1470, 1232, 1177, 1092.^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3H, CH_3), 4.43 (s, 2H, –CH_2–), 7.20 (d, $J = 8$ Hz, 2H), 7.29–7.41 (m, 5H), 7.73 (d, $J = 8$ Hz, 2H), 8.55 (s, 1H, im).

*2-Benzyl-6-(4-methoxyphenyl)imidazo [2,1-b][1,3,4]thiadiazole (**4Ac**)*

MS *m/z* 322.10; FT IR (v cm^{-1}) 3133, 3062, 2960, 2910, 1611, 1522, 1488, 1430, 1244. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.84 (s, 3H, –OCH_3), 4.33 (s, 2H, –CH_2–), 6.97 (d, $J = 8$ Hz, 2H), 7.31–7.41 (m, 5H), 7.74 (d, $J = 8$ Hz, 2H), 7.88 (s, 1H, im).

*2-Benzyl-6-(4-nitrophenyl)imidazo [2,1-b][1,3,4]thiadiazole (**4Ad**)*

MS *m/z* 337.00; FT IR (v cm^{-1}) 3132, 3074, 2931, 2830, 1600, 1504, 1469, 1339, 1029. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.46 (s, 2H, –CH_2–), 7.29–7.42 (m, 5H), 8.10 (d, $J = 8$ Hz, 2H), 8.27 (d, $J = 8$ Hz, 2H), 8.92 (s, 1H, im).

*2-Benzyl-6-(4-bromophenyl)imidazo [2,1-b][1,3,4]thiadiazole (**4Ae**)*

MS *m/z* 372.00; FT IR (v cm^{-1}) 3148, 3060, 3026, 2964, 2826, 1517, 1480, 1397, 1256, 1004. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.30 (s, 2H, –CH_2–), 7.31–7.41 (m, 5H), 7.52 (d, $J = 8$ Hz, 2H), 7.68 (d, $J = 8$ Hz, 2H), 7.96 (s, 1H, im).

*2-(4-Chlorobenzyl)-6-(4-chlorophenyl)imidazo [2,1-b][1,3,4]thiadiazole (**4Ba**)*

MS *m/z* 360.00; FT IR (v cm^{-1}) 3147, 3057, 2927, 2861, 1528, 1476, 1403, 1092. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.27 (s, 2H, –CH_2–), 7.27 (d, $J = 8$ Hz, 2H), 7.35–7.38 (dd, $J = 8$, 8 Hz, 4H), 7.72 (d, $J = 8$ Hz, 2H), 7.94 (s, 1H, im).

*2-(4-Chlorobenzyl)-6-(4-methylphenyl)imidazo [2,1-b][1,3,4]thiadiazole (**4Bb**)*

MS *m/z* 340.00; FT IR (v cm^{-1}) 3143, 3055, 3021, 2961, 2924, 2865, 1596, 1535, 1461, 1290, 1935. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H, –CH_3), 4.26 (s, 2H, –CH_2–), 7.22 (d, $J = 8$ Hz. 2H), 7.27 (d, $J = 8$ Hz, 2H), 7.36 (d, $J = 8$ Hz, 2H), 7.69 (d, $J = 8$ Hz, 2H), 7.92 (s, 1H, im).

*2-(4-Chlorobenzyl)-6-(4-methoxyphenyl)imidazo [2,1-b][1,3,4]thiadiazole (**4Bc**)*

MS *m/z* 356.01; FT IR (v cm^{-1}) 3146, 3040, 2939, 2842, 1609, 1537, 1482, 1252, 1025. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.84 (s, 3H, –OCH_3), 4.96 (s, 2H, –CH_2–), 6.96 (d, $J = 8$ Hz, 2H), 7.27 (d, $J = 8$ Hz, 2H), 7.36 (d, $J = 8$ Hz, 2H), 7.73 (d, $J = 8$ Hz, 2H), 7.88 (s, 1H, im).

*2-(4-Chlorobenzyl)-6-(4-nitrophenyl)imidazo [2,1-b][1,3,4]thiadiazole (**4Bd**)*

MS *m/z* 369.00; FT IR (v cm^{-1}) 3130, 2925, 2832, 1597, 1504, 1414, 1338, 1266, 1098. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.47 (s, 2H, –CH_2–), 7.44 (m, 4H), 8.09 (d, $J = 8$ Hz, 2H), 8.26 (d, $J = 8$ Hz, 2H), 8.91 (s, 1H, im).

*2-(4-Chlorobenzyl)-6-(4-bromophenyl)imidazo [2,1-b][1,3,4]thiadiazole (**4Be**)*

MS *m/z* 405.90; FT IR (v cm^{-1}) 3149, 3055, 2927, 2865, 1590, 1528, 1476, 1401, 1082. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.27 (s, 2H, –CH_2–), 7.27 (d, $J = 8$ Hz, 2H), 7.37 (d, $J = 8$ Hz, 2H), 7.53 (d, $J = 8$ Hz, 2H), 7.68 (d, $J = 8$ Hz, 2H), 7.96 (s, 1H, im).

*2-(4-Nitrobenzyl)-6-(4-chlorophenyl)imidazo [2,1-b][1,3,4]thiadiazole (**4Ca**)*

MS *m/z* 371.01; FT IR (v cm^{-1}) 3077, 3038, 2939, 2846, 1601, 1598, 1518, 1341, 1093. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.65 (s, 2H, –CH_2–), 7.47 (d, $J = 8$ Hz, 2H), 7.72 (d, $J = 8$ Hz, 2H), 7.87 (d, $J = 8$ Hz, 2H), 8.26 (d, $J = 8$ Hz, 2H), 8.71 (s, 1H, im).

*2-(4-Nitrobenzyl)-6-(4-methylphenyl)imidazo [2,1-b][1,3,4]thiadiazole (**4Cb**)*

MS *m/z* 350.01; FT IR (v cm^{-1}) 3140, 3073, 2962, 2861, 1522, 1460, 1347, 1178. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.31 (s, 3H, –CH_3), 4.64 (s, 2H, –CH_2–), 7.22 (d, $J = 8$ Hz, 2H), 7.71 (d, $J = 8$ Hz, 2H), 7.74 (d, $J = 8$ Hz, 2H), 8.26 (d, $J = 8$ Hz, 2H), 8.59 (s, 1H, im).

*2-(4-Nitrobenzyl)-6-(4-nitrophenyl)imidazo [2,1-b][1,3,4]thiadiazole (**4Cd**)*

MS *m/z* 382.00; FT IR (v cm^{-1}) 3126, 3087, 2938, 2845, 1601, 1517, 1341, 1101, 1009. ^{1}H NMR ($CDCl_3$,

400 MHz) δ 4.67 (s, 2H, –CH_2–), 7.72 (d, $J = 8$ Hz, 2H), 8.11 (d, $J = 8$ Hz, 2H), 8.25 (d, $J = 8$ Hz, 2H), 8.28 (d, $J = 8$ Hz, 2H), 8.94 (s, 1H, im).

*2-(4-Nitrobenzyl)-6-(4-bromophenyl)imidazo [2,1-b][1,3,4]thiadiazole (**4Ce**)*

MS *m/z* 414.90; FT IR (v cm^{-1}) 3073, 2936, 1598, 1342, 1177. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.65 (s, 2H, –CH_2–), 7.60 (d, $J = 8$ Hz, 2H), 7.72 (d, $J = 8$ Hz, 2H), 7.81 (d, $J = 8$ Hz, 2H), 8.26 (d, $J = 8$ Hz, 2H), 8.72 (s, 1H, im).

*2-(4-Nitrobenzyl)-6-(4-fluorophenyl)imidazo [2,1-b][1,3,4]thiadiazole (**4Cf**)*

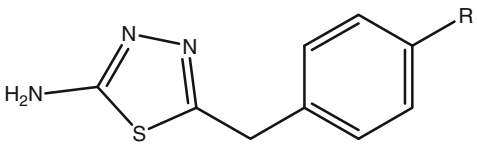
MS *m/z* 355.03; FT IR (v cm^{-1}) 3122, 3077, 2914, 2855, 1601, 1522, 1348, 1227, 1099. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.63 (s, 2H, –CH_2–), 7.19–7.25 (m, ar, 2H), 7.71 (d, $J = 8$ Hz, 2H), 7.84–7.89 (m, 2H), 8.25 (d, $J = 8$ Hz, 2H), 8.63 (s, 1H, im).

Results and discussion

Chemistry

2-Amino-5-substituted-1,3,4-thiadiazoles **3** were prepared from aryl acetic acid **1** and thiosemicarbazide **2** in H_2SO_4 heating at 70°C for 7 h (Table 1). The various α-bromo ketones were prepared by bromination of the corresponding ketones using the Friedel–Crafts reaction (Blatt 1943). The 2-(4-substituted phenyl)-6-(4-substituted aryl)-imidazo[2,1-b][1,3,4]thiadiazole derivatives **4** have been reported in Scheme 1 and Tables 2 3, and 4 were prepared by condensation of **3** with the appropriate α-bromo ketone, under reflux (8–10 h) and neutralization with cold aqueous sodium carbonate to get the free base in 40–60% yield. Using MW technique in DMF, and remaining contents are other wise same, desired products are obtained in good yield in less time (4–7 min). It is well estimated that these reactions proceed via the intermediate iminothiadiazole (Gadad *et al.*, 2000) which further undergoes dehydrocyclization to form the

Table 1 Physicochemical data for the derivatives (**3A–3C**)



Code no	R	Yield (%)	MP (°C)	Molecular formula	R_f	Molecular weight
3A	H	55–60	201–203	$C_9H_9N_3S$	0.71	192.15
3B	Cl	55–60	180–182	$C_9H_8N_3SCl$	0.69	225.70
3C	NO_2	50–55	181–183	$C_9H_8O_2N_4S$	0.60	237.14

Scheme 1 R = benzyl (A), 4-chloro benzyl (B), 4-nitro benzyl (C). R′ = Cl (a), CH_3 (b), OCH_3 (c), NO_2 (d), Br (e), F (f)

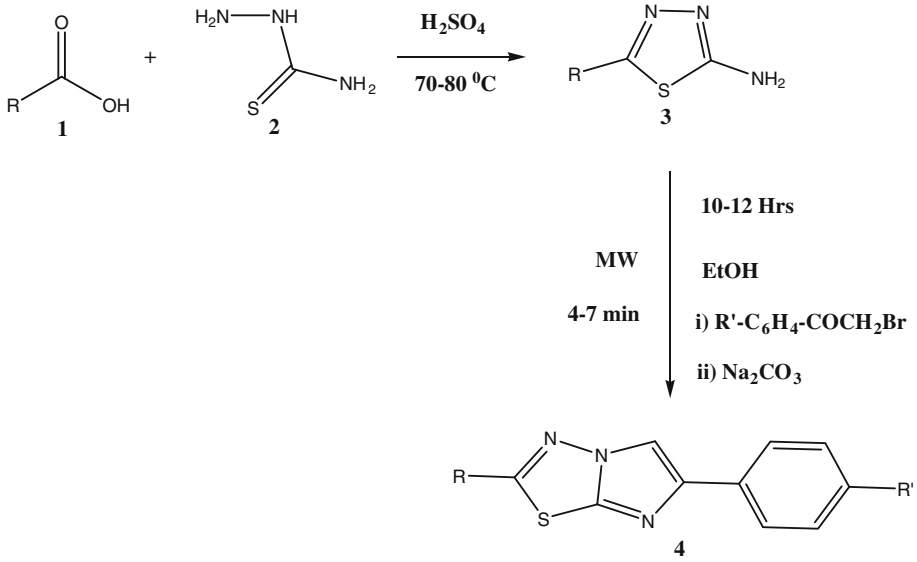


Table 2 Physicochemical parameters of synthesized derivatives

Code no	R	R′	Molecular formula	R_f	Molecular weight
4Aa	H	Cl	$C_{17}H_{12}N_3SCl$	0.78	325.82
4Ab	H	CH_3	$C_{18}H_{15}N_3S$	0.76	305.40
4Ac	H	OCH_3	$C_{18}H_{15}ON_3S$	0.69	321.40
4Ad	H	NO_2	$C_{17}H_{12}N_4SO_2$	0.63	336.37
4Ae	H	Br	$C_{17}H_{12}N_3SBr$	0.86	370.27
4Ba	Cl	Cl	$C_{17}H_{11}N_3SCl_2$	0.74	360.27
4Bb	Cl	CH_3	$C_{18}H_{14}N_3SCl$	0.35	339.85
4Bc	Cl	OCH_3	$C_{18}H_{14}ON_3SCl$	0.78	355.85
4Bd	Cl	NO_2	$C_{17}H_{11}O_2N_4SCl$	0.67	370.82
4Be	Cl	Br	$C_{17}H_{11}N_3SClBr$	0.53	404.72
4Ca	NO_2	Cl	$C_{17}H_{11}O_2N_4SCl$	0.72	370.82
4Cb	NO_2	CH_3	$C_{18}H_{14}O_2N_4S$	0.30	350.40
4Cd	NO_2	NO_2	$C_{17}H_{11}O_4N_5S$	0.65	381.37
4Ce	NO_2	Br	$C_{17}H_{11}O_2N_4SBr$	0.64	415.27
4Cf	NO_2	F	$C_{17}H_{11}FN_4O_2S$	0.48	354.36

Table 3 Comparative reaction time and melting points of the synthesized compounds

Code no	MW (min)	Conv (h)	Yields (%)		MP (°C)	
			MW	Conv	MW	Conv
4Aa	4		85	45	159–162	165–168
4Ab	5		75	48	140–142	142–144
4Ac	7		84	51	158–161	160–163
4Ad	5		83	55	233–235	231–233
4Ae	5		80	48	162–163	160–162
4Ba	4		84	52	174–176	178–179
4Bb	6	8–10	80	50	180–183	178–181
4Bc	4		75	60	171–173	174–176
4Bd	5		83	55	192–194	195–198
4Be	5		78	57	160–162	164–165
4Ca	4		75	60	178–180	178–181
4Cb	5		75	55	175–177	173–175
4Cd	5		82	52	216–218	215–218
4Ce	4		80	60	180–181	186–188
4Cf	4		82	55	181–184	179–182

MW microwave method; *Conv* conventional method

MP melting point; *min* minutes; *h* hours

desired fused heterocyclic (Scheme 1) derivative (**4Aa–4Cf**). The IR and ^{1}H NMR spectra of the synthesized compounds are in agreement with the assigned structures.

The formation of 2-amino thiadiazole **3** by the reaction was confirmed by its IR spectrum, which showed the presence of ν_{N-H} band and the absence of the carbonyl stretching band of carboxylic acid. Further, ^{1}H NMR spectra displayed a D_2O exchangeable peak due to NH_2 at δ 7.08–7.12 ppm. Structures of imidazothiadiazole derivatives were established by the absence of ν_{N-H} band in the IR spectra and appearance of imidazole proton (C_5-H) around δ 7.94–8.94 ppm in the ^{1}H NMR spectra. The mass spectra of these compounds further confirmed the assigned structures.

Table 4 Antibacterial and antifungal activities of the compounds (**4Ba–4Be** and **4Ca–4Ce**)

Comp. code	*S. aureus*	*Klebsiella*	*C. albicans*
4Ba	–	50(12)	50(12)
4Bb	–	–	–
4Bc	75(15)	–	75(12)
4Bd	75(12)	50(14)	–
4Be	–	50(12)	50(14)
4Ca	–	50(12)	–
4Cb	–	50(12)	–
4Cd	–	50(16)	–
4Ce	–	5(14)	–
4Cf	–	–	50(22)
Ciprofloxacin	10(28)	10(28)	–
Fluconazole	–	–	30(22)
Control	DMSO	DMSO	DMSO

Zone of inhibition in millimeters and MIC values (mean of triplicates)

MIC values are given in brackets

– not active

Antimicrobial activity

The newly synthesized compounds were screened for their antibacterial and antifungal activity using cup plate method (Revol-Junelles *et al*., 1996). The antibacterial activity of test compounds was evaluated against *Staphylococcus aureus* and *Klebsiella*, and ciprofloxacin was used as standard drug. Antifungal activity was screened against *Candida albicans* using fluconazole as standard drug, and dimethyl formamide was used as solvent control.

The bacterial cultures were inoculated on Mueller–Hinton Agar (Merck), fungal culture was inoculated on Potato Dextrose Agar, and Media (20 ml) were poured into each sterilized Petri dish (99 mm). Media plates were inoculated with liquid cultures homogenously by spread plate method.

All compounds were dissolved in DMSO to get a desired concentration. Each sample was loaded into the wells of agar plates directly. Plates inoculated with bacteria were incubated at 37°C for 24 h, and fungal culture was incubated at 25°C for 72 h. All determinations were done in triplicates. The standard antibiotic ciprofloxacin (10 μg/ml) for

bacteria and fluconazole (30 μg/ml) for fungal were used as positive controls, DMSO was used as a negative control, and zone of inhibition was recorded in millimeter.

The investigation of antibacterial screening revealed that compounds **4Bc**, **4Bd** had showed mild activity against *S. aureus* by 15 and 12 mm at 75 μg/ml, respectively, on comparing to standard ciprofloxacin 28 mm at 10 μg/ml. Where as **4Ce** showed antibacterial activity against *Klebsiella* at 5 μg/ml, and zone of inhibition was 14 mm. While for other compounds, namely, **4Ba**, **4Bd**, **4Be**, **4Ca**, **4Cb**, **4Cd**, and **4Ce** were showed mild to moderate activity against *Klebsiella* microorganism at $\geq$50 μg/ml.

Antifungal result indicated that compound **4Ba**, **4Be**, and **4Cf** had showed activity at 50 μg/ml, and zone of inhibitions were 12, 14, and 22 mm, respectively. Where as **4Bc** showed 12 mm zone of inhibition at 75 μg/ml on comparison to standard fluconazole (22 mm). Among the tested compounds, **4Cf** was only compound showed good antifungal activity comparable to that of standard fluconazole.

Conclusion

We have synthesized 15 derivatives of 2,6-disubstituted imidazo[2,1-b][1,3,4]thiadiazoles by conventional and MW technique. MW technique demonstrated the benefits like convenient operation, short reaction time, and good yields. **4Cf** was the lonely compound which showed good antifungal activity comparable to that of standard fluconazole at 50 μg/ml. The results of antibacterial screening reveal that among all the compounds screened **4Ba**, **4Be**, **4Ca**, **4Cd**, and **4Cb** showed mild activity at 50 μg/ml against *S. aureus* microorganism. Only **4Ce** had showed mild antibacterial activity at low micromolar concentration (5 μg/ml) against *S. aureus*. Most of these compounds were sensitive towards *Klebsiella* microorganism.

Acknowledgment Authors are thankful to Dr. B. G. Desai, Principal, KLE University's College of Pharmacy, Bangalore for providing necessary facilities. We gratefully acknowledge the support for this research effort from All India Council for Technical Education (AICTE), New Delhi (Ref. No. 8023/BOR/RID/RPS-169/2008-09). The authors are also grateful to NMR research centre, Indian Institute of Science, Bangalore, India for recording NMR spectra for our compounds.

References

Amery WK, Hoerig CH, Fenichel RI, Chirigos MA (eds) (1984) Immune modulation agents and their mechanism. Marcel Dekker, New York, pp 383–408

Andotra CS, Langer TC, Kotha A (1997) Synthesis and antifungal activity of some substituted 1,3,4-thiadiazolo[3,2-a]triazine-5-phenyl-7-thiones and imidazo[2,1-b]1,3,4-thiadiazol-5-ones. J Indian Chem Soc 74(2):125–127

Andreani A, Bonazzi D, Rambaldi M, Fabbri G, Rainsford KD (1982) 5,6-Disubstituted imidazo[2,1-b]thiazoles as potential antiinflammatory agents. Eur J Med Chem 17:271–274

Andreani A, Rambaldi M, Mascellani G, Bossa R, Galatulas I (1986) Synthesis and cardiotonic activity of 5,5-disubstituted imidazo[2,1-b]thiazoles. Eur J Med Chem 21:451–453

Andreani A, Rambaldi M, Mascellani G, Rugarli P (1987) Synthesis and diuretic activity of imidazo[2,1-b]thiazole acetohydrazones. Eur J Med Chem 22:19–22

Andreani A, Rambaldi M, Locatelli A, Isetta AM (1991a) Synthesis and mitogenic activity of new imidazo[2,1-b]thiazoles. Eur J Med Chem 26:335–337

Andreani A, Rambaldi M, Locatelli A, Andreani F (1991b) 5-Formylimidazo[2,1-b]thiazoles and derivatives with herbicidal activity. Collect Czech Chem Commun 56:2436–2447

Andreani A, Leonia A, Locatelli A, Morigi R, Rambaldi M, Simon WAJ, Senn B (2000) Synthesis and antisecretory activity of 6-substituted 5-cyanomethylimidazo[2,1-b]thiazoles and 2,6-dimethyl-5-hydroxymethyl imidazo [2,1-b][1,3,4]thiadiazole. Arzneim-Forsch 50: 550–553

Blatt AH (1943) Organic synthesis collective, vol 2. Wiley, New York, p 480

Buffler CR (1993) Microwave cooking and processing. Van Nostrand Reinhold, New York, pp 1–68

Chen CJ, Song BA, Yang S, Xu GF, Bhadury PS, Jin LH et al (2007) Synthesis and antifungal activities of 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-thiadiazole and 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-oxadiazole derivatives. Bioorg Med Chem 15: 3981–3989

Gadad AK, Karki SS, Rajurkar VG, Bhongade BA (1999) Synthesis and biological evaluation of 5-formyl-6-arylimidazo(2,1-b)-1,3,4-thiadiazole-2-*N*-(dimethylaminomethino) sulfonamides as antitumor agents. Arzneim-Forsch 49:858–863

Gadad AK, Mahajanshetti CS, Nimbalkar S, Raichurkar A (2000) Synthesis and antibacterial activity of some 5-guanylhydrazone/thiocyanato-6-arylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide derivatives. Eur J Med Chem 35:853–857

Gadad AK, Noolvi MN, Karpoormath RV (2004) Synthesis and anti-tubercular activity of a series of 2-sulfonamido/trifluoromethyl-6-substituted imidazo[2,1-b]-1,3,4-thiadiazole derivatives. Bioorg Med Chem 12:5651–5659

Gadad AK, Palkar MB, Anand K, Noolvi MN, Boreddy TS, Wagwade J (2008) Synthesis and biological evaluation of 2-trifluoromethyl/sulfonamido-5,6-diaryl substituted imidazo[2,1-b]-1,3,4-thiadiazoles: a novel class of cyclooxygenase-2 inhibitors. Bioorg Med Chem 16(1):276–283

Jadhav VB, Kulkarni MV, Rasal VP, Biradar SS, Vinay MD (2008) Synthesis and anti-inflammatory evaluation of methylene bridged benzofuranyl imidazo[2,1-b][1,3,4]thiadiazoles. Eur J Med Chem 43:1721–1729

Karki SS, Panjamurthy K, Kumar S, Nambiar M, Ramareddy SA, Chiruvella KK, Raghavan SC (2011) Synthesis and biological evaluation of novel 2-aralkyl-5-substituted-6-(4′-fluorophenyl)-imidazo[2,1-b][1,3,4]thiadiazole derivatives as potent anticancer agents. Eur J Med Chem 46(6):2109–2116

Khazi IAM, Mahajanshetti CS, Gadad AK, Tarnalli AD, Sultanpur CM (1996) Synthesis, anticonvulsant and analgesic activities of some 6-substituted imidazo(2,1-b)-1,3,4-thiadiazole-2-sulfonamides and their 5-bromo derivatives. Arzneim-Forsch 46:949–952

Kolavi G, Hegde V, Khan IAM, Gadad P (2006) Synthesis and evaluation of antitubercular activity of imidazo[2,1-b][1,3,4] thiadiazole derivatives. Bioorg Med Chem 14:3069–3080

Lamani RS, Shetty NS, Kamble RR, Khazi IAM (2009) Synthesis and antimicrobial studies of novel methylene bridged benzisoxazolyl imidazo[2,1-b][1,3,4]thiadiazole derivatives. Eur J Med Chem 44:2828–2833

Revol-Junelles A-M, Mathis R, Krier F, Delfour A, Lefebvre G (1996) Leuconostoc mesenteroides subsp. mesenteroides FR52 synthesizes two distinct bacteriocins. Lett Appl Microbiol 23: 120–124