Res Chem Intermed
DOI 10.1007/s11164-017-2985-5

Microwave-assisted green synthesis of new imidazo [2,1-*b*]thiazole derivatives and their antimicrobial, antimalarial, and antitubercular activities

Rajesh H. Vekariya[1] · Kinjal D. Patel[1] · Mayur K. Vekariya[1] · Neelam P. Prajapati[1] · Dhanji P. Rajani[2] · Smita D. Rajani[2] · Hitesh D. Patel[1]

Received: 23 March 2017 / Accepted: 9 May 2017

Abstract We have synthesized some imidazo[2,1-*b*]thiazole derivatives by reaction of 1-(2-amino-4-methylthiazol-5-yl)ethanone or ethyl 2-amino-4-methylthiazole-5-carboxylate with α-bromo aralkyl ketones (phenacyl bromides) in presence of polyethylene glycol-400 (PEG-400) as efficient, inexpensive, biodegradable, and green reaction medium and catalyst (dual nature) under Microwave Irradiation (MWI) at 300 W as well as under thermal heating at 90 °C. Moreover, we also synthesized 1-(2-amino-4-methylthiazol-5-yl)ethanone and ethyl 2-amino-4-methylthiazole-5-carboxylate by one-pot reaction of acetyl acetone/ethyl acetoacetate with *N*-bromosuccinimide (NBS) and thiourea in presence of PEG-400 under microwave irradiation at 180 W. All synthesized compounds were screened for antimicrobial and antimalarial activities. All compounds were found to show good to excellent antibacterial activity, and some analogs exhibited good antimalarial activity.

Electronic supplementary material The online version of this article (doi:10.1007/s11164-017-2985-5) contains supplementary material, which is available to authorized users.

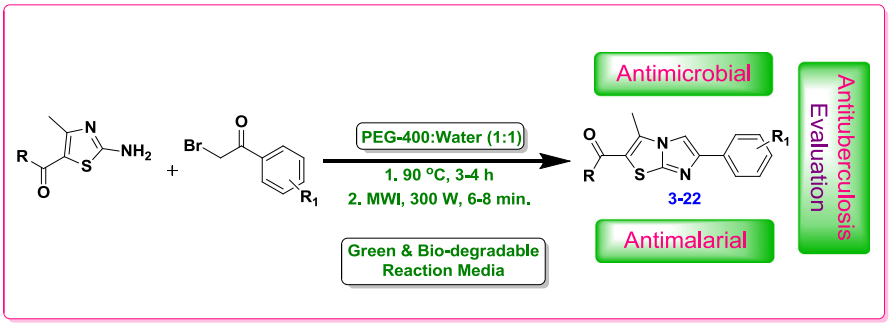
✉ Hitesh D. Patel
drhiteshpatel1@gmail.com

[1] Department of Chemistry, School of Sciences, Gujarat University, Ahmedabad, India

[2] Microcare Laboratory and TRC, Surat, Gujarat, India

Published online: 22 May 2017

Graphical Abstract



Keywords Imidazo[2,1-*b*]thiazoles · One-pot reaction · Homogeneous catalysis · PEG-400 · Aqueous-phase synthesis · Green synthesis · Antimicrobial activity · Antimalarial activity · Antitubercular activity

Introduction

Green synthesis of bioactive molecules and pharmaceutical intermediates in the field of bioorganic chemistry can be considered an attractive research opportunity, associated with advanced features such as waste reduction, energy savings, atom economy, easy workup processes, and avoidance of use of hazardous chemicals [1, 2]. Development of green, clean, and ecofriendly protocols for synthesis of highly potent bioactive molecules is an exciting area of medicinal chemistry with great potential for further discoveries [3, 4].

Compounds containing the imidazo[2,1-*b*]thiazole frame have been of interest to medicinal chemists for many years because of their wide range of therapeutic applications [5–7]. Imidazo[2,1-*b*]thiazole derivatives are important heterocyclic compounds and have drawn much attention because of their various biological and medicinal activities, including antibacterial [8–13], antiparasitic [14], antifungal [15–17], antiviral [18], anthelmintic [19, 20], antitumor [21–23], cardiotonic [24], chemopreventive, antioxidant [25], antiinflammatory [26], and antihypertensive properties [27]. It has been reported that they possess antitumor properties against a variety of human cancer cell lines [28–37]. In addition, imidazo[2,1-*b*]thiazole derivatives exhibit good antiproliferative activities against a variety of human cancer cell lines [38–43].

Despite much significant progress in antimicrobial therapy, infectious diseases caused by bacteria and fungi remain major worldwide health problems due to the rapid development of resistance to existing antibacterial and antifungal drugs, making this one of the most important areas of antibacterial research today [44]. Development of new antimicrobial agents is therefore urgently required to address this situation. It thus seems crucial to investigate novel antimicrobial molecules with new mechanisms of action, to overcome antimicrobial resistance [45].

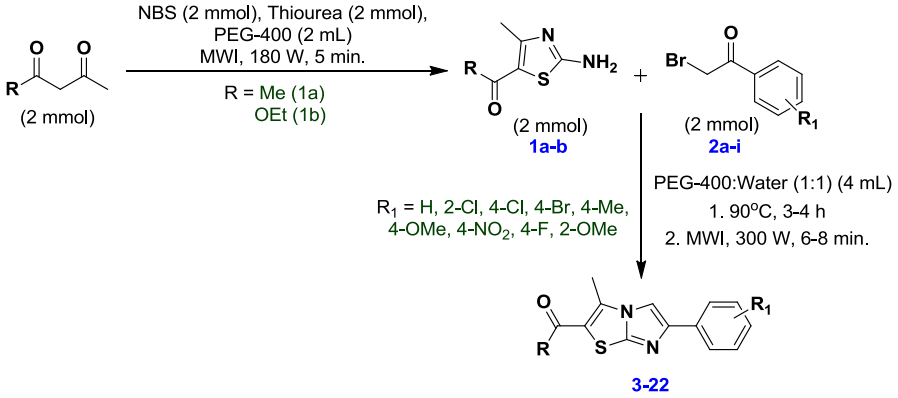
For this reason, development of imidazo[2,1-*b*]thiazole derivatives is currently receiving much attention. Various protocols have been established for synthesis of imidazo[2,1-*b*]thiazole derivatives through reaction between 2-aminothiazoles and various phenacyl bromides under reflux in propan-2-ol [46], methyl ethyl ketone [47], acetone and hydrochloric acid [48], acetone and hydrobromic acid [49], ethanol [50], benzene [51], and butanol [52]. However, these reactions are performed in organic solvents at reflux temperature, giving only moderate yield; such synthetic methodologies do not meet the requirements of green chemistry. Also, these methodologies do not enable synthesis of a wide range of imidazo[2,1-*b*]thiazole derivatives.

Regulatory pressure is increasingly focusing on the use, manufacture, and disposal of organic solvents, because their use in an industrial process can cause occupational health hazards as well as being harmful to the environment. The unique solvent properties, higher solubilizing power, and cation coordination ability of polyethylene glycol (PEG) solutions make them useful as green solvents and phase-transfer catalysts in organic synthesis [53]. PEGs are nonionic, nontoxic, inexpensive, and thermally stable reaction media that can be recovered by phase-separation methods. In addition, PEG-400 is nonvolatile, biodegradable, and has low flammability. PEGs have been found to be stable to acid, base, and high temperature [54, 55]. PEGs exhibit different solubility in organic solvents, enabling precipitation of PEGs from reaction mixtures in organic solvents for purification. Therefore, polyethylene glycol (PEG) has been found to be an exciting reaction medium for many organic syntheses in recent years [56–70]. The importance of green chemistry in organic synthesis has encouraged scientists to explore use of microwave irradiation. Over recent years, Microwave Irradiation (MWI) has emerged as a very useful energy source for a wide range of organic transformations with short reaction time and high yield of products with high purity [71]. Combined use of MWI with a PEG reaction medium can speed up organic reactions due to selective absorption of microwave energy by polar molecules.

In continuation of our studies towards development of cheap and environmentally benign methodologies for organic synthesis, we report herein aqueous PEG-400 as an extremely effective catalytic system for synthesis of imidazo[2,1-*b*]thiazole derivatives by reaction of 1-(2-amino-4-methylthiazol-5-yl)ethanone or ethyl 2-amino-4-methylthiazole-5-carboxylate with α-bromo aralkyl ketones (phenacyl bromides) at 90 °C or under MWI at 300 W (Scheme 1). Moreover, we also synthesized 1-(2-amino-4-methylthiazol-5-yl)ethanone/ethyl 2-amino-4-methylthiazole-5-carboxylate by one-pot reaction of acetyl acetone/ethyl acetoacetate with *N*-bromosuccinimide (NBS) and thiourea in presence of PEG-400 under microwave irradiation at 180 W (Scheme 1). The reaction proceeded smoothly, and succinimide was obtained as a byproduct that could be recycled to give NBS [71].

Results and discussion

Initially, it was planned to develop an efficient and green protocol for preparation of 2-aminothiazole derivatives **1a**, **b**. For this purpose, our initial work focused on optimization of the reaction conditions for synthesis of thiazole derivative **1a** using acetyl acetone, NBS, and thiourea in PEG-400 (2 mL) as model reaction.



Scheme 1 General reaction scheme for preparation of imidazo[2,1-*b*]thiazole derivatives

Control experiments on the model reaction showed that it did not take place at room temperature, and unreacted starting materials were observed on Thin Layer Chromatography (TLC) after 2 h because of the low rate of the α-bromination process (A) at room temperature. After 4 h, **1a** was obtained in good yield (82%) (Table 1, entry 1). No significant change in the **1a** yield was observed after 24 h (Table 1, entry 2). In general, the reaction rate, solubility of reactants and products, and selectivity of catalyst are highly dependent on the operating temperature of the reaction. Thus, in the model reaction, the effect of temperature was investigated, and the results suggested that temperature had a dramatic effect on the reaction yield (Fig. 1). Increasing the temperature of the reaction from room temperature to 70 °C led to a reduction in the reaction time. The highest yield of **1a** was obtained at 70 °C within 4 h (92%) (Table 1, entry 6). From room temperature (r.t.) to 60 °C, product

Table 1 Optimization of reaction conditions for synthesis of **1a**

Entry	Solvent (2 mL)	Conditions	Time	Yield[a] (%)
1	PEG-400	R.t.	4 h	82
2	PEG-400	R.t.	16 h	83
3	PEG-400	40 °C	4 h	83
4	PEG-400	50 °C	4 h	85
5	PEG-400	60 °C	4 h	88
6	PEG-400	70 °C	4 h	94
7	PEG-400	80 °C	4 h	94
8	PEG-400	90 °C	4 h	93
9	PEG-400	100 °C	4 h	91
10	THF	Reflux	4 h	67
11	Ethanol	Reflux	4 h	76
12	Methanol	Reflux	4 h	69
13	PEG-400	180 W (MWI)	6 min	96
14	PEG-400	300 W (MWI)	6 min	92

[a] Isolated yields

yield increased significantly (Table 1, entries 3–5), whereas no significant improvement in rate of reaction or product yield was detected at higher temperature from 80 to 100 °C (Table 1, entries 7–9). Various solvents such as Tetrahydrofuran (THF), ethanol, and methanol were also tested for this one-pot synthesis, but afforded poor product yield compared with PEG-400 (Table 1, entries 10–12). After that, we performed this reaction under Microwave Irradiation (MWI) using similar reaction conditions. Unpredictably, we achieved the greatest yield (96%) of **1a** within 6 min when the reaction was carried out using PEG-400 under 180 W of microwave irradiation (Table 1, entry 14). In addition, it was also observed that high microwave irradiation power above 180 W resulted in lower product yield (Table 1, entry 15). Compared with conventional heating, reaction under microwave irradiation showed higher efficiency in terms of product yield and reaction time. When considering the heterocyclization step (B) alone, the α-bromination step (A) was also slightly influenced by the operating temperature of the reaction (Fig. 2).

To optimize the reaction conditions, the reaction was studied by employing bromination agents such as KBr, $KBrO_3$ and catalytic amount of acetic acid, HBr in acetic acid, bromine (Br_2), and NBS (Table 2, entries 1–4). Among these bromination reagents, it was observed that, when NBS reagent was used for bromination of the acetyl acetone under thermal heating at 70 °C in PEG-400, the bromination completed well followed by heterocyclization with thiourea within 4 h. The optimal conditions found for synthesis of **1a** were successfully applied to the reactions of ethyl acetoacetate with *N*-bromosuccinimide (NBS) and thiourea in presence of PEG-400 under microwave irradiation at 180 W, affording ethyl 2-amino-4-methylthiazole-5-carboxylate in excellent yield (97%) within 6 min. Based on our present study, we found reaction in PEG-400 at 180 W (MWI) to be the optimum condition for synthesis of 2-aminothiazoles **1a**, **b**. Furthermore, products **1a**, **b** were easily purified by recrystallization from ethanol, thus avoiding extraction steps or chromatographic separation. The purity of the synthesized compounds was confirmed by TLC and elemental analysis. The structures of the final products were well characterized by Infrared Spectroscopy (IR), mass, and ^{1}H and ^{13}C Nuclear Magnetic Resonance Spectroscopy (NMR) spectral analyses.

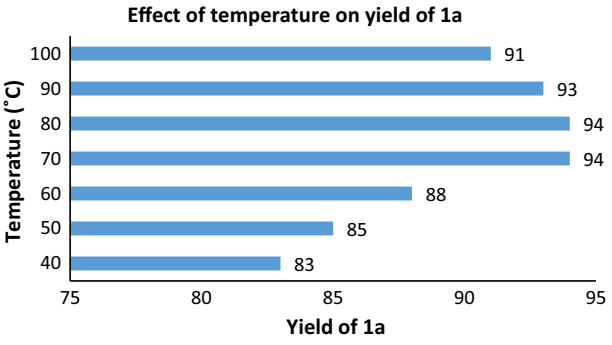


Fig. 1 Effect of temperature on yield of **1a**

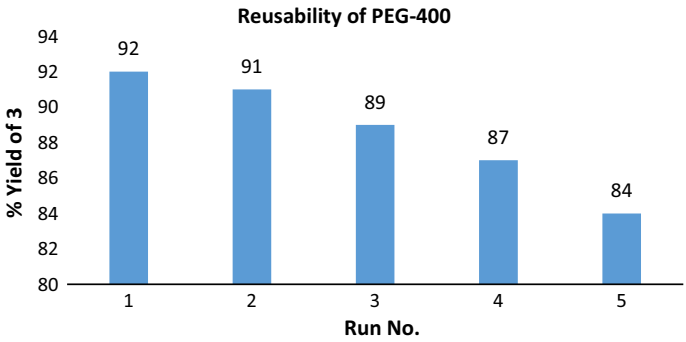


Fig. 2 Reusability profile of PEG-400

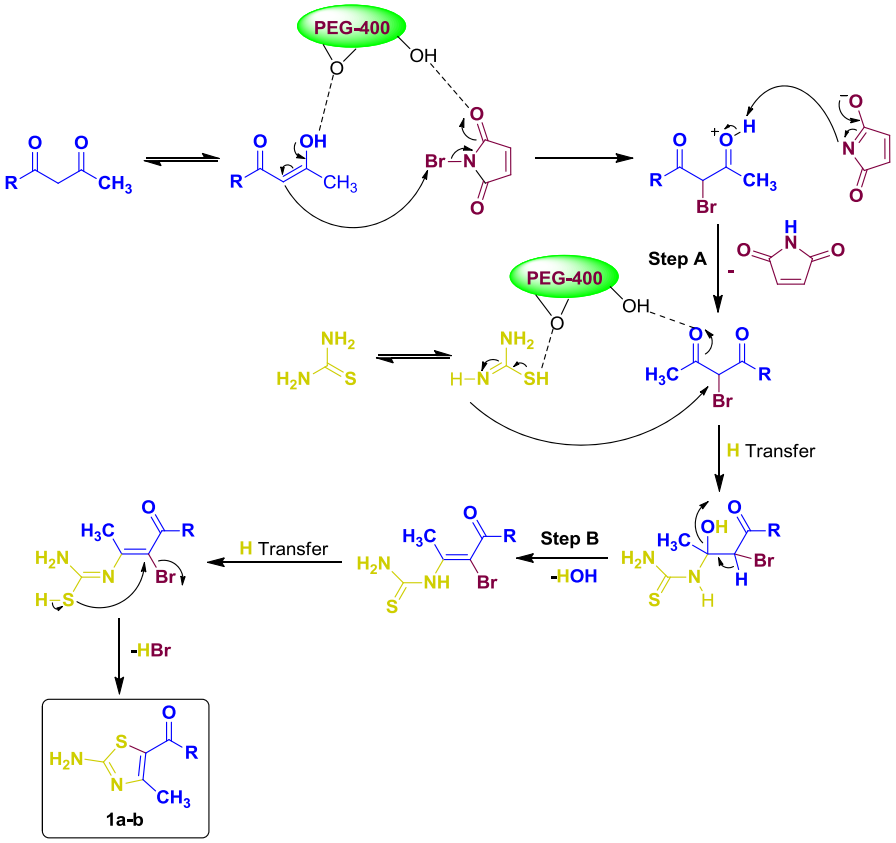
Table 2 Effect of various bromination agents on synthesis of **1a**

Entry	Bromination reagent	Solvent and temperature	Time (h)	Yield[a] (%)
1	KBr, $KBrO_3$, AcOH	PEG-400, 70 °C	4	53
2	HBr in acetic acid	PEG-400, 70 °C	4	60
2	Br_2	PEG-400, 70 °C	4	75
3	NBS	PEG-400, 70 °C	4	92

[a] Isolated yields

Scheme 2 presents a possible reaction mechanism for the formation of 2-aminothiazoles **1a**, **b**. According to this, initially, terminal –OH group of PEG-400 forms intermolecular H-bond with carbonyl oxygen of NBS. Simultaneously, ethereal oxygen of PEG-400 forms intermolecular H-bonding with –OH group of enol form of acetyl acetone/ethyl acetoacetate. This can activate substrates acetyl acetone/ethyl acetoacetate and even reagent NBS, for favorable interaction, leading to α-bromoketones in excellent yield with succinimide as byproduct. After that, ethereal oxygen of PEG-400 forms hydrogen bond with –SH group of thiourea (enolic form), which makes S–H bond weaker, enhancing the nucleophilicity of sulfur for nucleophilic addition to electron-deficient carbon of acetyl acetone/ethyl acetoacetate. Simultaneously, terminal –OH group of PEG-400 forms hydrogen bonding with the electron deficiency of carbonyl carbon of α-bromoketones. Finally, 2-aminothiazoles **1a**, **b** form via intramolecular cyclization and hydrogen transfer followed by removal of H_2O and HBr.

IR spectra of these derivatives showed two characteristic N–H stretching peaks at 3200–3400 cm^{-1} corresponding to primary NH_2 group, C=O stretching peak at 1709 cm^{-1} corresponding to $COCH_3$ group, and C=O stretching peak at 1674 cm^{-1} corresponding to $COOC_2H_5$ group. The ^1H NMR spectra of these derivatives exhibited a singlet near 7.8 ppm, attributed to primary NH_2 group. Furthermore, a singlet near 2.35 ppm indicated protons of CH_3 group of thiazole. In addition, a singlet near 3.41 ppm indicated protons of $COCH_3$ group of thiazole. Meanwhile, peaks at 1.23 ppm indicated triplets of CH_3 group of ester, and peaks at 4.15 ppm



Scheme 2 Proposed reaction mechanism

indicated quartet of CH_2 group of ester. The ^{13}C NMR spectrum exhibited a peak at 188.2 ppm, indicating C=O stretching of $COCH_3$ group, while a peak at 170.19 ppm indicated C=O stretching of $COOC_2H_5$. In addition, peaks between 13 and 18 ppm indicated CH stretching of CH_3 group of thiazole. Electrospray Ionisation (ESI) Mass Spectrometry (MS) of compounds **1a**, **b** showed corresponding $(M + 1)^+$ peak as well as $(M + 2)^+$ peak. In all spectra, $(M + 2)^+$ peak was observed due to presence of sulfur atom of thiazole.

After this successful synthesis of 1-(2-amino-4-methylthiazol-5-yl)ethanone and ethyl 2-amino-4-methylthiazole-5-carboxylate, we planned to develop an efficient and green protocol for preparation of imidazo[2,1-*b*]thiazole derivatives **3**–**20**. To optimize the reaction conditions, the reaction was studied employing several solvents as well as under solvent-free conditions with the hope of maximizing the product yield in short reaction time (Table 3). In a model reaction, we used phenacyl bromide (2 mmol) with 1-(2-amino-4-methylthiazol-5-yl)ethanone (2 mmol) as reactants in presence of ethanol at 80 °C and found that imidazo[2,1-*b*]thiazole **3** could be produced in 54% yield in 16 h (Table 3, entry 1). To improve the yield and optimize

Table 3 Optimization of reaction conditions for synthesis of **3**

Entry	Solvent (4 mL)	Conditions	Time	Yield[a] (%)
1	Ethanol	80 °C	16 h	54
2	Butanol	100 °C	16 h	70
3	Propen-2-ol	100 °C	16 h	65
4	Water	90 °C	16 h	42
5	PEG-400	90 °C	3 h	82
6	PEG-400	100 °C	3 h	85
7	Water:PEG-400 (1:1)	90 °C	3 h	86
8	Water:PEG-400 (9:1)	90 °C	3 h	75
9	Water:PEG-400 (7:3)	90 °C	3 h	80
10	Water:PEG-400 (1:1)	300 W (MWI)	7 min	92
11	Water:PEG-400 (1:1)	450 W (MWI)	7 min	92

[a] Isolated yields

the reaction conditions, the same reaction was carried out in presence of solvents such as butanol and propane-2-ol at 100 °C for 16 h. However, this afforded the product in moderate yield. We also tested water for this reaction, but it gave poor results compared with other solvents. After that, the same reaction was performed utilizing PEG-400 as green and ecofriendly reaction medium. A surprisingly improved result was observed in terms of yield of **3** after stirring the mixture at 90 °C for 3 h (Table 3, entry 5). Increasing the temperature of the reaction from 90 to 100 °C led to no significant change in the reaction time or product yield (Table 3, entry 6). Finally, the optimized reaction conditions for this cyclocondensation were found to use a 1:1 mixture of water:PEG-400 as solvent system (Table 3, entry 7). We also applied the water:PEG-400 solvent system at 9:1 and 7:3 for this transformation, but better results were not afforded compared with the 1:1 solvent system (Table 3, entries 8, 9). After that, we performed this reaction under Microwave Irradiation (MWI) using similar reaction conditions. Unpredictably, we achieved the greatest yield (92%) of **3** within 7 min when the reaction was carried out utilizing water:PEG-400 (1:1) under microwave irradiation of 300 W (Table 3, entry 10). In addition, it was also observed that high microwave irradiation power up to 450 W did not result in any improvement (Table 3, entry 11). Compared with conventional heating, reaction under microwave irradiation showed higher efficiency in terms of product yield and reaction time.

The optimal conditions found for **3** were successfully applied for reaction of ethyl 2-amino-4-methylthiazole-5-carboxylate with phenacyl bromide in presence of water:PEG-400 (1:1) under microwave irradiation at 300 W, affording corresponding imidazo[2,1-*b*]thiazole derivative **12** in excellent yield (96%) within 7 min. We employed various phenacyl bromides to evaluate the generality of this protocol. The reaction progressed smoothly and provided excellent yields in all cases (Table 4). Phenacyl bromides bearing both electron-withdrawing and electron-donating substituents reacted smoothly with this protocol to afford products in excellent yields. Furthermore, all synthesized products were easily purified by recrystallization from ethanol, thus avoiding extraction steps or

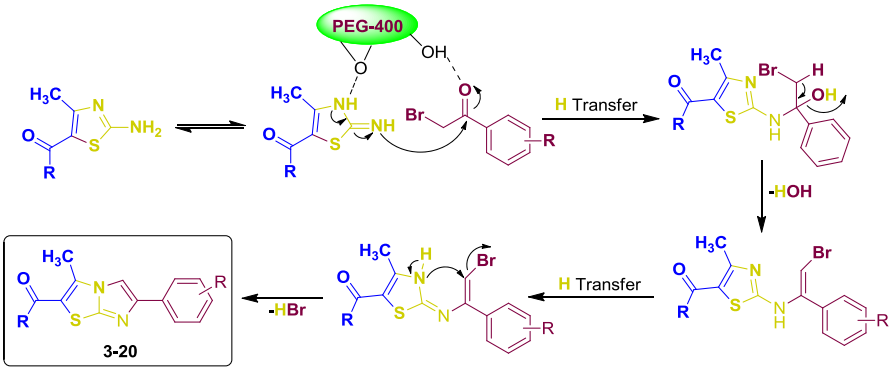
Table 4 Preparation of imidazo[2,1-*b*]thiazole derivatives using water:PEG-400 (1:1) as reaction medium

Compound	R	R_1	Thermal heating (90 °C)		Microwave irradiation (300 W)		M.p. (°C)
			Time (h)	Yield[a] (%)	Time (min)	Yield[a] (%)	
3	Me	C_6H_5	3	92	7	93	208–210
4	Me	2-Cl–C_6H_4	4	90	6	92	187–189
5	Me	4-Me–C_6H_4	4	88	7	91	236–237
6	Me	4-OMe–C_6H_4	3	92	7	95	275–277
7	Me	4-Br–C_6H_4	4	89	8	92	230–232
8	Me	4-Cl–C_6H_4	3	87	8	91	223–226
9	Me	2,4-diCl–C_6H_3	4	86	8	90	214–216
10	Me	4-F–C_6H_4	4	89	7	91	239–241
11	Me	2-OMe–C_6H_4	4	90	6	94	196–197
12	Me	4-NO_2–C_6H_4	4	89	8	92	244–246
13	OEt	C_6H_5	3	93	7	96	125–126
14	OEt	2-Cl–C_6H_4	4	88	7	92	226–227
15	OEt	4-Me–C_6H_4	4	86	8	88	120–122
16	OEt	4-OMe–C_6H_4	4	91	6	95	223–225
17	OEt	4-Br–C_6H_4	3	92	7	96	242–244
18	OEt	4-Cl–C_6H_4	3	89	7	90	232–234
19	OEt	2,4-diCl-C_6H_3	4	87	8	88	221–222
20	OEt	4-F–C_6H_4	4	88	7	91	200–201
21	OEt	2-OMe–C_6H_4	3	89	7	93	178–180
22	OEt	4-NO_2–C_6H_4	4	88	8	92	242–244

[a] Isolated yields

chromatographic separation. The purity of the synthesized compounds was confirmed by TLC and elemental analysis. The structures of the final products were well characterized by spectral (IR, mass, and ^{1}H and ^{13}C NMR) analyses.

IR spectra showed characteristic C=O stretching peak near 1710 cm^{-1} corresponding to $COCH_3$ group and C=O stretching peak near 1675 cm^{-1} corresponding to $COOC_2H_5$ group. The ^{1}H NMR spectrum exhibited a singlet near 8.45 ppm indicating proton of imidazo nucleus, while peaks between 7.20 and 8.20 ppm were observed for respective aromatic protons. Furthermore, a singlet near 2.55 ppm indicated protons of CH_3 group of thiazole. In addition, a singlet near 2.80 ppm indicated protons of $COCH_3$ group of thiazole. Moreover, peaks between 1.25 to 1.35 ppm indicated triplets of CH_3 group of ester, while peaks between 4.20–4.35 indicated quartet of CH_2 group of ester. The ^{13}C NMR spectrum exhibited a peak near 191 ppm indicating C=O stretching of $COCH_3$, while a peak near 161 ppm indicated C=O stretching of $COOC_2H_5$. In addition, peaks near 12–13 ppm indicated CH stretching of CH_3 group of thiazole. The ESI–MS spectra of compounds **3**–**22** showed corresponding $(M + 1)^+$ peak as well as $(M + 2)^+$



Scheme 3 Proposed reaction mechanism

peak. In all spectra, $(M + 2)^+$ peak was observed due to presence of sulfur atom in the imidazo[2,1-*b*]thiazoles.

To check the ecofriendliness of PEG-400, we recycled PEG-400 and reused it for five times, revealing slightly decreasing catalytic efficiency (Fig. 2).

Scheme 3 presents a possible reaction mechanism for formation of the imidazo[2,1-*b*]thiazole derivatives. According to this, initially, ethereal oxygen of PEG-400 forms hydrogen bond with –NH– group of 2-aminothiazoles (enolic form), which makes –N–H– bond weaker, enhancing the nucleophilicity of nitrogen for nucleophilic addition to electron-deficient carbon of phenacyl bromides. Simultaneously, terminal –OH group of PEG-400 forms hydrogen bonding with the electron deficiency of carbonyl carbon of phenacyl bromides. Finally, imidazo[2,1-*b*]thiazoles (**3**–**22**) form via intramolecular cyclization and hydrogen transfer followed by removal of H_2O and HBr.

Pharmacology

Antimicrobial activity

In vitro antibacterial activity

All novel synthesized scaffolds were investigated for their in vitro antibacterial activity (Table 5). The bioassay results demonstrated that imidazo[2,1-*b*]thiazole derivatives **3**–**22** showed remarkable activity against the tested microorganisms compared with standard drugs. In general, most of the tested compounds exhibited better activity against Gram-positive than Gram-negative bacteria. Among the Gram-positive bacterial strains, *Staphylococcus aureus* showed relatively higher sensitivity towards the tested compounds. In this regard, compound **21** bearing electron-donating –OMe group at 2-position of phenyl ring was found to be the most active in inhibiting Gram-positive *S. aureus* bacterial growth with the lowest minimum inhibitory concentration (MIC) value of 50 μg/mL, compared with the

Table 5 In vitro antibacterial activity of compounds **3–22**

Compound	*E. coli* MTCC 443 MIC (μg/mL)	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442
3	125	250	100	200
4	200	200	125	250
5	100	250	100	250
6	125	100	125	200
7	500	250	250	250
8	200	100	250	250
9	200	100	200	125
10	125	250	200	250
11	100	500	100	500
12	500	250	200	125
13	250	250	100	125
14	100	100	62.5	200
15	125	200	200	250
16	100	62.5	100	200
17	100	100	250	250
18	200	100	125	100
19	100	100	100	62.5
20	62.5	200	125	100
21	62.5	250	50	250
22	250	200	100	125
Ampicillin	100	100	250	100
Ciprofloxacin	25	25	50	50
Chloramphenicol	50	50	50	50

MIC of 250 μg/mL for ampicillin. In addition, compound **14** with chloro group on phenyl ring exhibited excellent activity with 62.5 μg/mL against *S. aureus* bacterium. Furthermore, compounds **3**, **5**, **11**, **13**, **16**, **19**, **22** showed excellent activity with MIC of 100 μg/mL against *S. aureus* compared with standard drug ampicillin, albeit 50% less active than chloramphenicol (MIC 50 μg/mL) or ciprofloxacin (MIC 50 μg/mL). Meanwhile, compounds **4**, **6**, **18**, **20** exhibited potent activity with MIC of 125 μg/mL against the same bacterium. Most of the tested compounds showed excellent activity. However, compounds **7**, **8**, **17** (MIC 250 μg/mL) showed equipotent activity against *S. aureus* compared with ampicillin, whereas analogs **9**, **10**, **12**, **15** (MIC 200 μg/mL) showed good activity compared with ampicillin. Against *S. pyogenes*, the best activity was exhibited by compound **19** (MIC 62.5 μg/mL) having two –Cl groups at 2- and 4-position of phenyl ring, being more potent then ampicillin (MIC 100 μg/mL). In addition, analogs **20**, **18** (MIC 100 μg/mL) displayed potency equivalent to ampicillin against the same species, but 50% less than chloramphenicol (MIC 50 μg/mL) or ciprofloxacin (MIC 50 μg/mL).

Table 6 In vitro antifungal activity of compounds **3**–**22**

Compound	*C. albicans* MTCC 227 MIC (μg/mL)	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
3	>1000	1000	1000
4	250	500	1000
5	>1000	1000	1000
6	1000	1000	1000
7	1000	500	1000
8	1000	1000	1000
9	500	>1000	>1000
10	250	500	1000
11	100	1000	1000
12	>1000	>1000	>1000
13	500	>1000	>1000
14	500	1000	>1000
15	500	>1000	>1000
16	>1000	1000	>1000
17	>1000	500	500
18	250	1000	>1000
19	1000	>1000	500
20	500	1000	1000
21	>1000	1000	>1000
22	500	>1000	>1000
Nystatin	100	100	100
Griseofulvin	500	100	100

On the other hand, investigation of the antibacterial activity of all the newly synthesized analogs against the two tested Gram-negative strains revealed that analogs **20**, **21** (MIC 62.5 μg/mL) displayed excellent activity against *E. coli*. Furthermore, analogs **5**, **11**, **14**, **16**, **17**, **19** (MIC 100 μg/mL) were equipotent to ampicillin (MIC 100 μg/mL) against *E. coli*, but 50% less active than chloramphenicol (MIC 50 μg/mL). Moreover, compound **8** with electron-donating substituent of –OMe on phenyl ring inhibited Gram-negative *P. aeruginosa* bacterial growth at the lowest minimum inhibitory concentration (MIC) value of 62.5 μg/mL, compared with the MIC of 100 μg/mL for ampicillin. Furthermore, compounds **6**, **8**, **9**, **14**, **17**–**19** exhibited good activity against Gram-positive *S. pyogenes* bacterial growth at minimum inhibitory concentration (MIC) of 100 μg/mL, equivalent to ampicillin.

In vitro antifungal activity

Concerning the antifungal activity of the tested compounds, only one strain, i.e., *C. albicans*, showed certain sensitivity to some of the tested compounds, whereas the other two fungal strains were insensitive to the same compounds (Table 6). The

Table 7 In vitro antimalarial activity of compounds **3**–**22**

Compound	Mean IC_{50} (μg/mL)
3	0.79
4	1.08
5	0.92
6	1.14
7	0.38
8	0.75
9	0.20
10	0.72
11	1.11
12	0.95
13	0.69
14	1.00
15	0.69
16	1.07
17	1.14
18	0.52
19	0.22
20	0.44
21	0.90
22	0.66
Quinine	0.268
Chloroquine	0.02

antifungal activity data showed that, among analogs **3**–**22**, compounds **4**, **10**, **18** bearing electron-deactivating halo groups (–Cl and –F) on phenyl ring displayed excellent activity with MIC of 100 μg/mL against *C. albicans*, equipotent to nystatin (MIC 100 μg/mL) but more potent then griseofulvin (MIC 500 μg/mL). Furthermore, compounds **9**, **13**–**15**, **20**, **22** showed excellent activity with MIC of 250 μg/mL, better then the MIC of 500 μg/mL for griseofulvin, against *C. albicans*. Analogs **6**–**8**, **19** exhibited 50% less efficiency (MIC 1000 μg/mL) against *C. albicans* than griseofulvin (MIC 500 μg/mL). Moreover, compounds **3**–**22** exerted moderate inhibitory efficiency against *A. niger* and *A. clavatus*.

In vitro antimalarial activity

The synthesized compounds were also screened for their in vitro antimalarial activity against *Plasmodium falciparum* 3D7 chloroquine-sensitive strain (Microcare Laboratory and TRC, Surat, Gujarat, India). All experiments were performed in duplicate, and the mean 50% Half Maximal Inhibitory Concentration (IC_{50}) values are presented in Table 7. Compounds **9** ($IC_{50} = 0.2$ μg/mL) and **19** ($IC_{50} = 0.22$ - μg/mL) bearing two electron-deactivating groups (–Cl) at 2- and 4-position of phenyl ring displayed excellent activity against *P. falciparum* compared with quinine as standard drug ($IC_{50} = 0.268$ μg/mL). This promising antimalarial

Table 8 In vitro antimalarial activity of compounds **3**–**22**

Compound	MIC (μg/mL)
3	62.5
4	50
5	100
6	62.5
7	100
8	100
9	50
10	100
11	62.5
12	62.5
13	100
14	100
15	500
16	1000
17	1000
18	500
19	500
20	100
21	100
22	500
Isoniazid	0.20
Rifampicin	0.25

activity of compounds **9**, **19** may be due to the lowest lipophilicity (lowest Log *P*) showing highest antimalarial activity. Other compounds exhibited only moderate antimalarial activity (IC_{50} = 0.38–1.14 μg/mL).

In vitro antitubercular activity

Preliminary screening of the title compounds **3**–**22** for their in vitro antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ strain was carried out. The observed MIC values of these compounds are presented in Table 8. Among the screened analogs, **4** and **9** showed the best activity (50 mg/mL), followed by compounds **3**, **6**, **11**, **12** (62.5 mg/mL). Isoniazid and rifampicin were used as standard drugs.

Experimental

Chemicals and reagents

All chemicals were of highest purity available, purchased from commercial sources, and used as received. Reaction progress was monitored by Thin Layer

Chromatography (TLC) analysis on Merck precoated silica gel 60 F254 aluminum sheets, visualized by ultraviolet (UV) light. Various phenacyl bromides (**2a–i**) were synthesized as per protocol previously reported by us [71].

Instrumentation

The reactions were performed using a CEM Discover microwave system as well as modified Samsung microwave oven. Melting points were measured on an Optimelt MPA 100 melting point apparatus and are uncorrected. Fourier-transform infrared (FT-IR) spectra were recorded on a PerkinElmer FT-IR 377 spectrometer using KBr. ^{1}H NMR spectra were recorded on Bruker AV 400 MHz spectrometer using dimethyl sulfoxide (DMSO)-d_6 as solvent and tetramethylsilane (TMS) as internal reference. ^{13}C NMR spectra were recorded on a Bruker AV 100 MHz spectrometer using DMSO as solvent. Mass spectra were recorded at Advion Expression CMS, USA. Acetone was used as mobile phase, and electron spray ionization (ESI) was used as ion source. Elemental analysis was performed on a CHNS elemental analyzer.

*Procedure for synthesis of 1-(2-amino-4-methylthiazol-5-yl)ethanone (**1a**)*

To solution of acetyl acetone (2 mmol) in polyethylene glycol PEG-400 (2 mL) were added *N*-bromosuccinimide (NBS) (2.2 mmol) and thiourea (2 mmol), and the mixture was heated under microwave irradiation at 180 W until reaction completion as indicated by TLC (approximately 5 min). After consumption of starting materials as indicated by TLC, the reaction mixture was cooled at room temperature, poured into water, and basified with aqueous ammonia with continuous stirring. The resulting precipitate was filtered and washed with water, and recrystallized from ethanol to give pure product.

Off-white solid M.p. = 215–217 °C. IR ν_{max} (KBr) cm^{-1}: 3334, 3268, 3052, 2993, 2379, 1709, 1663, 1511, 1309, 1297, 1102, 972, 761. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.33 (s, 3H, CH_3), 2.41 (s, 3H, $COCH_3$), 7.85 (s, 2H, thiazole-2-NH_2). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 188.20, 170.45, 157.66, 121.23, 29.45, 18.27. MS (ESI) *m*/*z* for (156.21): 157.1 $(M + 1)^+$, 258.1 $(M + 2)^+$. Elemental analysis: Calculated for $C_6H_8N_2OS$ (156.04): C 46.13%, H 5.16%, N 17.93%, S 20.53%; Found: C 46.11%., H 5.19%, N 17.92%, S 20.51%.

*Procedure for synthesis of ethyl 2-amino-4-methylthiazole-5-carboxylate (**1b**)*

To solution of ethyl acetoacetate (2 mmol) in polyethylene glycol-400 (PEG-400) (2 mL) were added *N*-bromosuccinimide (NBS) (2.2 mmol) and thiourea (2 mmol), and the mixture was heated under microwave irradiation at 180 W until reaction completion as indicated by TLC (approximately 5 min). After consumption of starting materials as indicated by TLC, the reaction mixture was cooled at room temperature, poured into water, and basified with aqueous ammonia with continuous

stirring. The resulting precipitate was filtered and washed with water, and recrystallized from ethanol to give pure product.

White solid M.p. = 177–179 °C. IR ν_{max} (KBr) cm^{-1}: 3372, 3301, 3062, 2960, 1674, 1516, 1373, 1279, 1095, 756. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.22-125 (t, 3H, $J = 7.2$), 2.39 (s, 3H, CH_3), 4.13-4.18 (q, 2H, $J = 7.1$), 7.75 (s, 2H, thiazole-2-NH_2). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 170.19, 161.92, 159.32, 107.29, 59.69, 17.07, 14.27. MS (ESI) *m/z* for (186.23): 187.1 $(M + 1)^+$, 188.1 $(M + 2)^+$. Elemental analysis: Calculated for $C_7H_{10}N_2O_2S$ (186.05): C 45.15%, H 5.41%, N 15.04%, S 17.22%; Found: C 45.13%., H 5.39%, N 15.02%, S 17.20%.

General procedure for synthesis of imidazo[2,1-*b*]thiazoles 3–20

To stirred solution of polyethylene glycol (PEG-400) (2 mL) in water (2 mL) were added 1-(2-amino-4-methylthiazol-5-yl)ethanone (2 mmol)/ethyl 2-amino-4-methylthiazole-5-carboxylate (2 mmol) and α-bromo aralkyl ketones (phenacyl bromides) (2 mmol), and the mixture was heated at 90 °C or subject to microwave irradiation at 300 W, until reaction completion as indicated by TLC. After reaction completion, the reaction mixture was cooled at room temperature, and the solid product formed was collected by filtration, washed with water, and recrystallized from ethanol to give pure product. The recovered PEG with water was reused for five further cycles.

*1-(3-Methyl-6-phenylimidazo[2,1-b]thiazol-2-yl)ethanone (**3**)*

Off-white solid IR ν_{max} (KBr) cm^{-1}: 3130.89, 1642.48, 1571.57, 1145.37, 1171.78, 1017.64. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.55 (s, 3H, CH_3), 2.80 (s, 3H, $COCH_3$), 7.28–7.31 (t, 1H, $J = 7.2$ Hz, ArH), 7.43–7.40 (t, $J = 7.4$ Hz, 2H, ArH), 7.86–7.88 (d, $J = 7.2$ Hz, 2H, ArH), 8.45 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 13.81, 29.36, 108.94, 125.47, 127.59, 128.69, 133.43, 135.60, 146.95, 147.44, 191.18. MS (ESI) *m/z* for (256.32): 257.2 $(M + 1)^+$, 258.2 $(M + 2)^+$. Elemental analysis: Calculated for $C_{11}H_9NO_2$ (256.07): C 65.60%, H 4.72%, N 10.93%, S 12.51%; Found: C 65.63%, H 4.70%, N 10.92%, S 12.54%.

*1-(6-(2-Chlorophenyl)-3-methylimidazo[2,1-b]thiazol-2-yl)ethanone (**4**)*

Pale-yellow solid IR ν_{max} (KBr) cm^{-1}: 3135.34, 1628.54, 1613.98, 1125.03, 1000.97, 745.96, 765.37. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.58 (s, 3H, CH_3), 2.85 (s, 3H, $COCH_3$), 7.42–7.44 (m, 2H, ArH), 7.49–7.51 (d, $J = 7.4$ Hz, 1H, ArH), 7.75–7.77 (d, $J = 7.4$ Hz, 1H, ArH), 8.52 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 13.82, 29.33, 108.95, 122.98, 123.28, 127.69, 130.64, 132.64, 133.57, 134.26, 135.66, 146.93, 147.41, 191.20. MS (ESI) *m/z* for (290.03): 291.03 $(M + 1)^+$, 292.03 $(M + 2)^+$. Elemental analysis: Calculated for $C_{14}H_{11}ClN_2OS$ (290.77): C 57.83%, H 3.81%, N 9.63%, S 11.0%; Found: C 57.82%, H 3.82%, N 9.61%, S 11.02%.

*1-(3-Methyl-6-(p-tolyl)imidazo[2,1-b]thiazol-2-yl)ethanone (**5**)*

Off-white solid IR ν_{max} (KBr) cm^{-1}: 3210.23, 3036.67, 1690.43, 1092.65, 998.37, 1178.36, 795.98. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.55 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 2.82 (s, 3H, $COCH_3$), 7.39–7.41 (d, $J = 8.2$ Hz, 2H, ArH), 7.72–7.74 (d, $J = 7.2$ Hz, 2H, ArH), 8.52 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 13.82, 20.78, 29.33, 108.95, 126.76, 127.68, 130.24, 130 58, 131.97, 135.60, 146.93, 147.41, 191.20. MS (ESI) *m/z* for (270.08): 271.09 $(M + 1)^+$, 272.08 $(M + 2)^+$. Elemental analysis: Calculated for $C_{15}H_{14}N_2OS$ (270.35): C 66.64%, H 5.22%, N 10.36%, S 11.86%; Found: C 66.62%, H 5.23%, N 10.36%, S 11.02%.

*1-(6-(4-Methoxyphenyl)-3-methylimidazo[2,1-b]thiazol-2-yl)ethanone (**6**)*

White solid IR ν_{max} (KBr) cm^{-1}: 3165.64, 1647.72, 1485.37, 1134.60, 1117.90, 817.69. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.56 (s, 3H, CH_3), 2.84 (s, 3H, $COCH_3$), 3.66 (s, 3H, OCH_3), 7.39–7.41 (d, $J = 8.8$ Hz, 2H, ArH), 7.87–7.89 (d, $J = 7.6$ Hz, 2H, ArH), 8.51 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 13.82, 29.33, 55.20, 108.95, 126.76, 127.68, 130.24, 130 58, 131.97, 135.60, 146.93, 147.41, 191.20. MS (ESI) *m/z* for (286.08): 287.08 $(M + 1)^+$, 288.08 $(M + 2)^+$. Elemental analysis: Calculated for $C_{15}H_{14}N_2O_2S$ (286.35): C 62.92%, H 4.93%, N 9.78%, S 11.20%; Found: C 62.94%, H 4.92%, N 9.80%, S 11.23%.

*1-(6-(4-Bromophenyl)-3-methylimidazo[2,1-b]thiazol-2-yl)ethanone (**7**)*

Yellow solid IR ν_{max} (KBr) cm^{-1}: 3190.39, 1593.99, 1593.74, 1114.48, 1203.18, 798.30, 553.19. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.56 (s, 3H, CH_3), 2.84 (s, 3H, $COCH_3$), 7.46–7.48 (d, $J = 9.4$ Hz, 2H, ArH), 7.91–7.93 (d, $J = 8.0$ Hz, 2H, ArH), 8.52 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 13.79, 20.77, 108.94, 124.67, 126.79, 127.69, 130.23, 130 61, 131.98, 135.62, 146.95, 147.45, 191.22. MS (ESI) *m/z* for (333.98): 334.98 $(M + 1)^+$, 335.98 $(M + 2)^+$. Elemental analysis: Calculated for $C_{14}H_{11}BrN_2OS$ (335.22): C 50.16%, H 3.31%, N 8.36%, S 9.5%; Found: C 50.15%, H 3.29%, N 8.38%, S 9.6%.

*1-(6-(4-Chlorophenyl)-3-methylimidazo[2,1-b]thiazol-2-yl)ethanone (**8**)*

Light-yellow solid IR ν_{max} (KBr) cm^{-1}: 3138.16, 1644.97, 1570.75, 1144.11, 1048.62, 1008.20, 841.59, 727.66. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.50 (s, 3H, CH_3), 2.79 (s, 3H, $COCH_3$), 7.47–7.49 (d, $J = 9.6$ Hz, 2H, ArH), 7.86–7.88 (d, $J = 7.2$ Hz, 2H, ArH), 8.49 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 13.78, 20.74, 108.90, 124.63, 126.78, 127.71, 130.26, 130 65, 131.97, 135.64, 146.98, 147.43, 191.22. MS (ESI) *m/z* for (290.03): 291.03 $(M + 1)^+$, 292.03 $(M + 2)^+$. Elemental analysis: Calculated for $C_{14}H_{11}ClN_2OS$ (290.77): C 57.83%, H 3.81%, N 9.63%, S 11.03; Found: C 57.85%, H 3.80%, N 9.65%, S 11.02%.

*1-(6-(2,4-Dichlorophenyl)-3-methylimidazo[2,1-b]thiazol-2-yl)ethanone (**9**)*

Pale-yellow solid IR ν_{max} (KBr) cm^{-1}: 3093.65, 1620.01, 1590.16, 1141.31, 1080.26, 998.87, 800.90, 543.91, 748.27. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.57 (s, 3H, CH_3), 2.81 (s, 3H, $COCH_3$), 7.50 (s, 1H, ArH), 7.56–7.58 (d, $J = 8.2$ Hz, 1H, ArH), 7.72 (s, 1H, ArH), 8.06–8.08 (d, $J = 7.6$ Hz, 1H, ArH), 8.52 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 13.78, 20.74, 108.90, 124.33, 126.56, 127.88, 127.71, 130.26, 131 98, 133.47, 135.65, 146.96, 147.42, 191.21. MS (ESI) *m/z* for (323.99): 325.1 $(M + 1)^+$, 326.0 $(M + 2)^+$. Elemental analysis: Calculated for $C_{14}H_{10}Cl_2N_2OS$ (325.21): C 51.70%, H 3.10%, N 8.61%, S, 9.86%; Found: C 51.71%, H 3.11%, N 8.60%, S 9.85%.

*1-(6-(4-Fluorophenyl)-3-methylimidazo[2,1-b]thiazol-2-yl)ethanone (**10**)*

White solid IR ν_{max} (KBr) cm^{-1}: 3132.35, 1675.61, 1582.39, 1217.44, 1163.47, 1021.38, 1025.98, 775.11. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.52 (s, 3H, CH_3), 2.80 (s, 3H, $COCH_3$), 7.49–7.51 (d, $J = 9.6$ Hz, 2H, ArH), 7.87–7.89 (d, $J = 7.6$ Hz, 2H, ArH), 8.51 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 13.78, 20.80, 108.91, 124.59, 126.82, 127.70, 130.22, 130 61, 131.97, 135.61, 146.94, 147.46, 191.21. MS (ESI) *m/z* for (274.06): 275.06 $(M + 1)^+$, 276.06 $(M + 2)^+$. Elemental analysis: Calculated for $C_{14}H_{11}FN_2OS$ (274.31): C 61.30%, H 4.04%, N 10.21%, S 11.69%; Found: C 61.31%, H 4.05%, N 10.22%, S 11.66%.

*1-(6-(2-Methoxyphenyl)-3-methylimidazo[2,1-b]thiazol-2-yl)ethanone (**11**)*

Off-white solid IR ν_{max} (KBr) cm^{-1}: 3168.95, 1642.15, 1561.88, 1181.21, 1115.51, 750.63. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.58 (s, 3H, CH_3), 2.85 (s, 3H, $COCH_3$), 3.65 (s, 3H, OCH_3), 7.44–7.46 (m, 2H, ArH), 7.58–7.60 (d, $J = 7.6$ Hz, 1H, ArH), 7.79–7.81 (d, $J = 7.2$ Hz, 1H, ArH), 8.50 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 13.83, 29.35, 55.23, 108.96, 122.97, 123.31, 127.62, 130.77, 132.32, 133.58, 134.28, 135.67, 146.92, 147.43, 191.21. MS (ESI) *m/z* for (286.08): 287.08 $(M + 1)^+$, 288.08 $(M + 2)^+$. Elemental analysis: Calculated for $C_{15}H_{14}N_2O_2S$ (286.35): C 62.92%, H 4.93%, N 9.78%, S 11.20%; Found: C 62.93%, H 4.90%, N 9.79%, S 11.21%.

*1-(3-Methyl-6-(4-nitrophenyl)imidazo[2,1-b]thiazol-2-yl)ethanone (**12**)*

Dark-yellow solid IR ν_{max} (KBr) cm^{-1}: 3150.95, 1703.47, 1559.65, 1543.36, 1367.59, 1098.17, 821.85. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.52 (s, 3H, CH_3), 2.82 (s, 3H, $COCH_3$), 7.40–7.42 (d, $J = 8.8$ Hz, 2H, ArH), 7.88–7.90 (d, $J = 7.6$ Hz, 2H, ArH), 8.49 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 13.76, 20.82, 108.99, 124.19, 126.62, 127.39, 130.12, 130 68, 131.77, 135.62, 146.93, 147.45, 191.20. MS (ESI) *m/z* for (301.05): 302.05 $(M + 1)^+$, 303.05 $(M + 2)^+$. Elemental analysis: Calculated for $C_{14}H_{11}N_3O_3S$ (301.32): C 55.80%, H 3.68%, N 13.95%, S 10.64%; Found: C 55.83%, H 3.67%, N 13.94%, S 10.63%.

*Ethyl 3-methyl-6-phenylimidazo[2,1-b]thiazole-2-carboxylate (**13**)*

Off-white solid IR ν_{max} (KBr) cm^{-1}: 3132.58, 1748.13, 1644.84, 1586.15, 1231.18, 1141.89, 1178.15, 1017.15. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.28–1.32 (t, $J = 7.0$ Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.25–4.31 (q, $J = 7.1$ Hz, 2H, CH_2), 7.29–7.32 (t, 1H, $J = 7.4$ Hz, ArH), 7.42–7.45 (t, $J = 7.6$ Hz, 2H, ArH), 7.78–7.80 (d, $J = 8.2$ Hz, 2H, ArH), 8.31 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 12.81, 20.77, 61.43, 108.11, 112.89, 125.44, 129.25, 130.61, 133.38, 137.17, 146.51, 147.41, 161.48. MS (ESI) *m/z* for (286.08): 287.08 $(M + 1)^+$, 288.08 $(M + 2)^+$. Elemental analysis: Calculated for $C_{15}H_{14}N_2O_2S$ (286.35): C 62.92%, H 4.93%, N 9.78%, S 11.20%; Found: C 62.93%, H 4.94%, N 9.79%, S 11.17%.

*Ethyl 6-(2-chlorophenyl)-3-methylimidazo[2,1-b]thiazole-2-carboxylate (**14**)*

Pale-yellow solid IR ν_{max} (KBr) cm^{-1}: 3137.90, 1715.25, 1634.25, 1567.98, 1231.18, 1113.03, 1005.68, 744.16, 768.48. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.32–1.36 (t, $J = 7.2$ Hz, 3H, CH_3), 2.33 (s, 3H, CH_3), 4.35–4.39 (q, $J = 7.4$ Hz, 2H, CH_2), 7.30–7.35 (m, 2H, ArH), 7.46–7.48 (d, $J = 8.4$ Hz, 1H, ArH), 7.75–7.77 (d, $J = 7.6$ Hz, 1H, ArH), 8.34 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 12.82, 20.76, 61.44, 108.11, 113.29, 127.24, 128.45, 130.12, 130.88, 132.72, 133.45, 137.18, 146.53, 147.45, 161.49. MS (ESI) *m/z* for (320.04): 321.04 $(M + 1)^+$, 322.04 $(M + 2)^+$. Elemental analysis: Calculated for $C_{15}H_{13}ClN_2O_2S$ (320.79): C 56.16%, H 4.08%, N 8.73%, S 10.00%; Found: C 56.17%, H 4.09%, N 8.70%, S 10.01%.

*Ethyl 3-methyl-6-(p-tolyl)imidazo[2,1-b]thiazole-2-carboxylate (**15**)*

Pale-yellow solid IR ν_{max} (KBr) cm^{-1}: 3218.25, 1718.17, 3035.91, 1689.47, 1240.54, 1090.23, 1000.15, 1176.34, 791.32. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.28–1.32 (t, $J = 7.0$ Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 4.25–4.31 (q, $J = 7.1$ Hz, 2H, CH_2), 7.19–7.21 (d, 1H, $J = 8.0$ Hz, ArH), 7.73–7.75 (d, $J = 7.6$ Hz, 2H, ArH), 8.32 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 12.80, 14.01, 20.78, 61.41, 108.09, 112.69, 124.74, 129.15, 130.62, 136.77, 137.17, 146.51, 147.41, 161.48. MS (ESI) *m/z* for (300.09): 301.09 $(M + 1)^+$, 302.09 $(M + 2)^+$. Elemental analysis: Calculated for $C_{16}H_{16}N_2O_2S$ (300.38): C 63.98%, H 5.37%, N 9.33%, S 10.67%; Found: C 63.99%, H 5.34%, N 9.34%, S 10.68%.

*Ethyl 6-(4-methoxyphenyl)-3-methylimidazo[2,1-b]thiazole-2-carboxylate (**16**)*

White solid IR ν_{max} (KBr) cm^{-1}: 3243.33, 1719.70, 1615.31, 1465.78, 1258.01, 1178.54, 1117.90, 807.90. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.30–1.34 (t, $J = 7$ Hz, 3H, CH_3), 2.76 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 4.29–4.34 (q, $J = 7.06$ Hz, 2H, CH_2), 7.01–7.03 (d, $J = 8.4$ Hz, 2H, ArH), 7.73–7.75 (d, $J = 6.0$ Hz, 2H, ArH), 8.55 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm)

12.80, 14.01, 20.78, 55.20, 61.41, 108.09, 114.59, 124.18, 134.28, 137.17, 143.51, 145.41, 159.12, 161.48. MS (ESI) *m/z* for (316.09): 317.09 $(M + 1)^+$, 318.09 $(M + 2)^+$. Elemental analysis: Calculated for $C_{16}H_{16}N_2O_3S$ (316.37): C 60.74%, H 5.10%, N 8.85%, S 10.14%; Found: C 60.77%, H 5.09%, N 8.84%, S 10.13%.

*Ethyl 6-(4-bromophenyl)-3-methylimidazo[2,1-b]thiazole-2-carboxylate (**17**)*

White solid IR ν_{max} (KBr) cm^{-1}: 3191.93, 1744.48, 1598.03, 1113.46, 1232.18, 1206.27, 1051.81, 1009.31, 799.04, 556.75. ^1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.30–1.34 (t, $J = 7.6$ Hz, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.29–4.35 (q, $J = 7.1$ Hz, 2H, CH_2), 7.28–7.30 (d, 1H, $J = 8.8$ Hz, ArH), 7.76–7.78 (d, $J = 8.0$ Hz, 2H, ArH), 8.35 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 12.82, 14.06, 20.76, 61.43, 108.11, 113.89, 126.18, 134.78, 138.09, 144.53, 146.51, 159.14, 161.68. MS (ESI) *m/z* for (363.99): 364.99 $(M + 1)^+$, 366.0 $(M + 2)^+$. Elemental analysis: Calculated for $C_{15}H_{13}BrN_2O_2S$ (365.24): C 49.33%, H 3.59%, N, 7.67%, S 8.78%; Found: C 49.32%, H 3.57%, N 7.71%, S 8.77%.

*Ethyl 6-(4-chlorophenyl)-3-methylimidazo[2,1-b]thiazole-2-carboxylate (**18**)*

Off-white solid IR ν_{max} (KBr) cm^{-1}: 3164.16, 1715.31, 1637.97, 1573.51, 1243.46, 1149.84, 1044.96, 1007.64, 840.37, 727.38. ^1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.29–1.33 (t, $J = 7.8$ Hz, 3H, CH_3), 2.69 (s, 3H, CH_3), 4.28–4.34 (q, $J = 7.2$ Hz, 2H, CH_2), 7.27–7.29 (d, 1H, $J = 8.8$ Hz, ArH), 7.78–7.80 (d, $J = 8.0$ Hz, 2H, ArH), 8.38 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 12.81, 14.10, 20.74, 61.48, 108.15, 113.85, 126.17, 134.79, 138.08, 144.51, 146.64, 159.13, 161.67. MS (ESI) *m/z* for (320.04): 321.04 $(M + 1)^+$, 322.04 $(M + 2)^+$. Elemental analysis: Calculated for $C_{15}H_{13}ClN_2O_2S$ (320.79): C 56.16%, H 4.08%, N 8.73%, S 10.00%; Found: C 56.19%, H 4.07%, N 8.72%, S 9.99%.

*Ethyl 6-(2,4-dichlorophenyl)-3-methylimidazo[2,1-b]thiazole-2-carboxylate (**19**)*

Off-white solid IR ν_{max} (KBr) cm^{-1}: 3098.46, 1717.23, 1619.17, 1593.17, 1240.97, 1144.47, 1050.18, 1009.87, 803.18, 547.29, 746.55. ^1H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.32–1.36 (t, $J = 7.2$ Hz, 3H, CH_3), 2.33 (s, 3H, CH_3), 4.35–4.39 (q, $J = 7.4$ Hz, 2H, CH_2), 7.36–7.38 (d, $J = 8.2$ Hz, 1H, ArH), 7.54 (s, 1H, ArH), 8.76–8.78 (d, $J = 7.6$ Hz, 1H, ArH), 8.36 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 12.81, 20.77, 61.45, 108.12, 113.31, 127.23, 128.42, 130.07, 130.92, 132.61, 134.40, 137.20, 146.51, 147.42, 161.48. MS (ESI) *m/z* for (354.00): 355.0 $(M + 1)^+$, 356.0 $(M + 2)^+$. Elemental analysis: Calculated for $C_{15}H_{12}Cl_2N_2O_2S$ (355.24): C 50.72%, H 3.40%, N 7.89%, S 9.03%; Found: C 50.71%, H 3.43%, N 7.88%, S 9.02%.

*Ethyl 6-(4-fluorophenyl)-3-methylimidazo[2,1-b]thiazole-2-carboxylate (**20**)*

White solid IR ν_{max} (KBr) cm^{-1}: 3131.39, 1716.56, 1677.84, 1588.51, 1258.35, 1215.05, 1160.92, 1020.34, 1027.26, 778.66. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.28–1.32 (t, $J = 7.6$ Hz, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.29–4.33 (q, $J = 7.1$ Hz, 2H, CH_2), 7.29–7.31 (d, 1H, $J = 8.6$ Hz, ArH), 7.80–7.82 (d, $J = 8.0$ Hz, 2H, ArH), 8.36 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 12.83, 14.09, 20.73, 61.45, 108.16, 113.88, 126.19, 134.81, 138.10, 144.49, 146.54, 159.12, 161.66. MS (ESI) *m/z* for (304.07): 305.07 $(M + 1)^+$, 306.07 $(M + 2)^+$. Elemental analysis: Calculated for $C_{15}H_{13}FN_2O_2S$ (304.34): C 59.20%, H 4.31%, N 9.20%, S, 10.54%; Found: C 59.22%, H 4.30%, N 9.18%%, S 10.55%.

*Ethyl 6-(2-methoxyphenyl)-3-methylimidazo[2,1-b]thiazole-2-carboxylate (**21**)*

Off-white solid IR ν_{max} (KBr) cm^{-1}: 3169.25, 1723.25, 1641.75, 1567.95, 1245.37, 1186.45, 1118.47, 752.21. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.32–1.36 (t, $J = 7.2$ Hz, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 4.34–4.38 (q, $J = 7.4$ Hz, 2H, CH_2), 7.28–7.33 (m, 2H, ArH), 7.45–7.47 (d, $J = 8.4$ Hz, 1H, ArH), 7.76–7.78 (d, $J = 7.6$ Hz, 1H, ArH), 8.35 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 12.82, 20.76, 55.22, 61.44, 108.11, 113.29, 127.24, 128.45, 130.12, 130.88, 132.72, 133.45, 137.18, 146.53, 147.45, 161.49. MS (ESI) *m/z* for (316.09): 317.09 $(M + 1)^+$, 318.09 $(M + 2)^+$. Elemental analysis: Calculated for $C_{16}H_{16}N_2O_3S$ (316.37): C 60.74%, H 5.10%, N 8.85%, S 10.14%; Found: C 60.77%, H 5.09%, N 8.84%, S 10.13%.

*Ethyl 3-methyl-6-(4-nitrophenyl)imidazo[2,1-b]thiazole-2-carboxylate (**22**)*

Dark-yellow solid IR ν_{max} (KBr) cm^{-1}: 3148.91, 1725.82, 1700.71, 1557.55, 1546.15, 1368.86, 1259.25, 1091.08, 828.45. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 1.25–1.28 (t, $J = 7.4$ Hz, 3H, CH_3), 2.67 (s, 3H, CH_3), 4.27–4.31 (q, $J = 7.2$ Hz, 2H, CH_2), 7.28–7.30 (d, 1H, $J = 8.4$ Hz, ArH), 7.82–7.84 (d, $J = 8.0$ Hz, 2H, ArH), 8.32 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO): δ_C (ppm) 12.79, 14.08, 20.75, 61.76, 108.17, 113.89, 125.24, 133.83, 137.99, 144.15, 146.94, 159.12, 161.64. MS (ESI) *m/z* for (331.06): 332.06 $(M + 1)^+$, 333.06 $(M + 2)^+$. Elemental analysis: Calculated for $C_{15}H_{13}N_3O_4S$ (331.35): C 54.37%, H 3.95%, N 12.68%, S 9.68%; Found: C 54.40, H 3.94%, N 12.67%, S 9.67%.

Microbiology

Antibacterial and antifungal activity

Mueller–Hinton broth and Sabouraud broth were used as nutrient medium to grow bacteria and fungi, respectively. Inoculum size for the test strain was adjusted to 10^6 colony-forming units (CFU) per milliliter by comparing turbidity. Serial dilutions were prepared for primary and secondary screening. Control tube containing no

antibiotic was immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter plate of medium suitable for growth of the test organism and incubated at 37 °C for bacteria or 22 °C for fungi overnight. The MIC of the control organism was read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism was recorded as the MIC. Each test compound was diluted, obtaining 2000 μg/mL concentration, as stock solution. In primary screening, 1000, 500, 250, and 125 μg/mL concentrations of the test compounds were taken. The active synthesized compounds found in this primary screening were further tested in a second dilution set against all organisms. The drugs found active in primary screening were similarly diluted to obtain 100, 50, 62.5, 25, 12.5, and 6.25 μg/mL concentrations. The highest dilution showing at least 99% inhibition was taken as the MIC.

All newly synthesized imidazo[2,1-*b*]thiazole derivatives (**3**–**22**) were examined for antimicrobial activity against two Gram-positive bacterial strains (*Staphylococcus aureus* MTCC 96, *Streptococcus pyogenes* MTCC 442), two Gram-negative bacterial strains (*Escherichia coli* MTCC 443, *Pseudomonas aeruginosa* MTCC 1688), as well as three fungal strains (*Aspergillus clavatus* MTCC 1323, *Candida albicans* MTCC 227, and *Aspergillus niger* MTCC 282) by agar dilution method [72]. Ampicillin, ciprofloxacin, and chloramphenicol were used as standard control drugs for antibacterial activity, whereas nystatin and griseofulvin were used as standard control drugs for antifungal activity.

Antimalarial activity

Stock solution of 5 mg/mL of each test sample as well as standards was prepared in DMSO, and subsequent dilutions were prepared with culture medium. The diluted samples in 20 μL volume were added to test wells to obtain final concentrations (at fivefold dilutions) ranging between 0.4 and 100 μg/mL in duplicate wells containing parasitized cell preparation. In vitro antimalarial assay was carried out in 96-well plates according to the microassay protocol of Reickmann and coworkers with minor modifications [73]. Cultures of *P. falciparum* strain were maintained in Roswell Park Memorial Institute (RPMI) 1640 medium supplemented with 25 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), 1% D-glucose, 0.23% sodium bicarbonate, and 10% heat-inactivated human serum. Asynchronous parasites of *P. falciparum* were synchronized after 5% D-sorbitol treatment to obtain only ring-stage parasitized cells. To carry out the assay, initial ring-stage parasitemia of 0.8–1.5% at 3% hematocrit in total volume of 200 μL of RPMI 1640 medium was determined by Jaswant–Singh–Bhattacharya (JSB) staining [74] to assess percent parasitemia (rings) and uniformly maintained with 50% red blood cells (RBCs) (O^{+ve}). The culture plates were incubated at 37 °C in a candle jar. After 36–40 h of incubation, thin blood smears from each well were prepared and stained with JSB stain. The slides were microscopically observed to record maturation of the ring-stage parasites into trophozoites and schizonts in presence of different concentrations of test agents. The test concentration which inhibited complete maturation into schizonts was recorded as the minimum inhibitory concentration (MIC). Chloroquine and quinine were used as reference drugs.

Antitubercular activity

The MIC of the test compounds against *M. tuberculosis* $H_{37}Rv$ was determined by Löwenstein–Jensen (L–J) agar (MIC) method [75, 76]. Primary 1000, 500, and 250 μg/mL and secondary 200, 100, 50, 25, 12.5, 6.250, and 3.125 μg/mL dilutions of each test compound were added to liquid L–J medium, which was then sterilized by inspissation method. Culture of *M. tuberculosis* $H_{37}Rv$ growing on L–J medium was harvested in 0.85% saline in bijou bottles. For all test compounds, stock solution of 2000 μg/mL concentration was first prepared in DMSO. These tubes were then incubated at 37 °C for 24 h, followed by streaking of *M. tuberculosis* $H_{37}Rv$ (5×10^4 bacilli per mL). These tubes were then incubated at 37 ± 1 °C. Growth of bacilli was observed after 12, 22, and finally 28 days of incubation. Tubes containing compounds were compared with control tubes in which medium alone was incubated with *M. tuberculosis* $H_{37}Rv$. The concentration at which no development of (or fewer than 20) colonies occurred was taken as the MIC of the test compound. The standard strain *M. tuberculosis* $H_{37}Rv$ was tested with known drug rifampicin.

Conclusions

One-pot tandem preparation of 2-aminothiazole derivatives **1a**, **b** was achieved by reaction of acetyl acetone or ethyl acetoacetate with *N*-bromosuccinimide (NBS) and thiourea in presence of green and biodegradable PEG-400 as alternative reaction medium under microwave irradiation at 180 W. After that, aqueous PEG-400 was utilized as an extremely effective catalytic system for synthesis of imidazo[2,1-*b*]thiazole derivatives **3**–**22** by reaction of **1a**, **b** with α-bromo aralkyl ketones (phenacyl bromides) at 90 °C or under MWI at 300 W. The major advantages of the presented protocol are the use of nonvolatile and biodegradable PEG-400 as substitute reaction medium, the potential for process scale-up, excellent product yield, short reaction time, and simple work-up procedure. Moreover, using this methodology, highly pure products were obtained with no need for column purification. It is therefore determined that the current protocol is a useful addition to green chemical procedures. From the bioassays, it is clear that the imidazo[2,1-*b*]thiazole derivatives showed greater antimicrobial as well as antimalarial activity. In the present study, compounds **7**–**9**, **18**–**20** exhibited highly potent activity against most of the tested bacteria.

Acknowledgements The authors are grateful to the Department of Chemistry, Gujarat University, Ahmedabad, for providing the necessary facilities. UGC-Info net and INFLIBNET Gujarat University are acknowledged for providing the e-resource facilities, the NFDD Centre for proton NMR and carbon NMR, and the Synzeal Research Laboratory for mass spectroscopy. R.H.V. is grateful to UGC-BSR [F.7-74/2007 (BSR)] for financial assistance.

References

1. A. Kumar, M.K. Gupta, M. Kumar, Green Chem. **14**, 290 (2012)
2. P.T. Anastas, M.M. Kirchhoff, Acc. Chem. Res. **35**, 686 (2002)

3. R.H. Vekariya, H.D. Patel, Arkivoc **1**, 136 (2015)
4. R.H. Vekariya, H.D. Patel, Arkivoc **1**, 70 (2015)
5. A. Andreani, M. Rambaldi, A. Locatelli, R. Bossa, A. Fraccari, I. Galatulas, J. Med. Chem. **35**, 4634 (1992)
6. S. Jaguelin, A. Robert, P. Gayral, J. Med. Chem. **26**, 51 (1991)
7. T. Metaye, C. Millet, J.L. Kraimps, B. Saunier, J. Barbier, F. Begon, Biochem. Pharmacol. **43**, 150 (1992)
8. J. Mohan, K. Kiran, Indian J. Chem. **30**, 898 (1991)
9. N.U. Guzeldemirci, O. Kucukbasmaci, Eur. J. Med. Chem. **45**, 63 (2010)
10. N.S. Shetty, R.S. Koti, R.S. Lamani, N.P. Badiger, I.A.M. Khazi, J. Sulfur Chem. **29**, 539 (2008)
11. R.S. Lamani, N.S. Shetty, R.R. Kamble, I.A.M. Khazi, Eur. J. Med. Chem. **44**, 2828 (2009)
12. J. Mohan, G.S.R. Anjaneyulu, K. Kiran, Indian J. Chem. **27**, 570 (1988)
13. J.P. Paolini, L.J. Lendvay, J. Med. Chem. **12**, 1031 (1969)
14. A. Scribner, S. Meitz, M. Fisher, M. Wyvratt, P. Leavitt, P. Liberator, A. Gurnett, C. Brown, J. Mathew, D. Thompson, D. Schmatz, T. Biftu, Bioorg. Med. Chem. Lett. **18**, 5263 (2008)
15. G.D. Gupta, K.K. Jain, R.P. Gupta, H.K. Pujari, Indian J. Chem. **22**, 268 (1983)
16. R.R. Dangi, N. Hussain, G.L. Talesara, Med. Chem. Res. **20**, 1490 (2011)
17. T. Juspin, M. Laget, T. Terme, N. Azas, P. Vanelle, Eur. J. Med. Chem. **45**, 840 (2010)
18. J.S. Barradas, M.I. Errea, N.B. D'Accorso, C.S. Sepúlveda, E.B. Damonte, Eur. J. Med. Chem. **46**, 259 (2011)
19. H. Amarouch, P.R. Loiseau, C. Bacha, R. Caujolle, M. Payard, P.M. Loiseau, C. Bories, P. Gayral, Eur. J. Med. Chem. **22**, 463 (1987)
20. J.F. Robert, S. Boukraa, J.J. Panouse, V. Loppinet, J.P. Chaumont, Eur. J. Med. Chem. **25**, 731 (1990)
21. A. Andreani, M. Rambaldi, A. Locatelli, R. Bossa, A. Fraccari, I. Galatulas, J. Pharm. Belg. **48**, 378 (1993)
22. E. Gursoy, N.U. Guzeldemirci, Eur. J. Med. Chem. **42**, 320 (2007)
23. J.H. Park, M.I. El-Gamal, Y.S. Lee, C.H. Oh, Eur. J. Med. Chem. **46**, 5769 (2011)
24. A. Andreani, M. Rambaldi, A. Locatelli, R. Bossa, I. Galatulas, M. Ninci, Eur. J. Med. Chem. **27**, 431 (1992)
25. A. Andreani, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, R. Cervellati, E. Greco, T.P. Kondratyuk, E.J. Park, K. Huang, R.B. van Breemen, J.M. Pezzuto, Eur. J. Med. Chem. **68**, 412 (2013)
26. V.B. Jadhav, M.V. Kulkarni, V.P. Rasal, S.S. Biradar, M.D. Vinay, Eur. J. Med. Chem. **43**, 1721 (2008)
27. R. Budriesi, P. Ioan, A. Locatelli, S. Cosconati, A. Leoni, M.P. Ugenti, A. Andreani, R. di Toro, A. Bedini, S. Spampinato, L. Marinelli, E. Novellino, A. Chiarini, J. Med. Chem. **51**, 1592 (2008)
28. A. Kamal, D. Dastagiri, M.J. Ramaiah, J.S. Reddy, E.V. Bharathi, C. Srinivas, S.N.C.V.L. Pushpavalli, D. Pal, M. Pal-Bhadra, Chem. Med. Chem. **5**, 1937 (2010)
29. A. Kamal, J.S. Reddy, M.J. Ramaiah, D. Dastagiri, E.V. Bharathi, M.V. Premsagar, S.N.C.V.L. Pushpavalli, D. Pal, P. Roy, M. Pal-Bhadra, Chem. Commun. **1**, 355 (2010)
30. A. Andreani, S. Burnelli, M. Granaiola, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, L. Varoli, N. Calonghi, C. Cappadone, M. Voltattorni, M. Zini, C. Stefanelli, L. Masotti, R.H. Shoemaker, J. Med. Chem. **51**, 7508 (2008)
31. A. Andreani, S. Burnelli, M. Granaiola, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, L. Varoli, N. Calonghi, C. Cappadone, G. Farruggia, M. Zini, C. Stefanelli, L. Masotti, N.S. Radin, R.H. Shoemaker, J. Med. Chem. **51**, 809 (2008)
32. A. Andreani, D. Bonazzi, M. Rambaldi, E. Farmaco II, Science **35**, 896 (1980)
33. A. Andreani, D. Bonazzi, M. Rambaldi, Arch. Pharm. **315**, 451 (1982)
34. A. Andreani, M. Rambaldi, A. Locatelli, R. Bossa, A. Fraccari, I. Galatulas, Pharm. Acta Helv. **68**, 21 (1993)
35. A. Andreani, M. Rambaldi, A. Locatelli, R. Bossa, A. Fraccari, I. Galatulas, J. Pharm. Belg. **48**, 378 (1993)
36. A. Andreani, M. Rambaldi, A. Locatelli, R. Bossa, A. Fraccari, I. Galatulas, J. Med. Chem. **39**, 2852 (1996)
37. A. Andreani, M. Rambaldi, F. Andreani, R. Bossa, I. Galatulas, Eur. J. Med. Chem. **23**, 385 (1988)
38. A. Andreani, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, M. Recanatini, V. Garaliene, Bioorg. Med. Chem. **8**, 2359 (2000)
39. H.I. El-Subbagh, I.E. Al-Khawad, R.R. El-Bendary, A.M. Al-Obaid, Saudi Pharm. J. **9**, 14 (2001)
40. K. Srimanth, V.R. Rao, D.R. Krishna, Arzneim. Forsch. **52**, 388 (2002)

41. A. Andreani, M. Granaiola, A. Leoni, A. Locatelli, R. Morigi, M. Rambaldi, G. Lenaz, R. Fato, C. Bergamini, G. Farruggia, J. Med. Chem. **48**, 3085 (2005)
42. E. Gursoy, N.U. Guzeldemirci, Eur. J. Med. Chem. **42**, 320 (2007)
43. J.H. Park, C.H. Oh, Bull. Korean Chem. Soc. **31**, 2854 (2010)
44. R.H. Vekariya, K.D. Patel, D.P. Rajani, S.D. Rajani, H.D. Patel, J. Asso, J. Assoc. Arab Univ. Basic Appl. Sci. (2016). doi:10.1016/j.jaubas.2016.04.002
45. K. Coleman, Drug Discov. Today Ther. Strateg. **37**, 455 (2004)
46. A. Kamal, M. Balakrishna, V.L. Nayak, T.B. Shaik, S. Faazil, V.D. Nimbarte, Chem. Med. Chem. **9**, 2766 (2014)
47. C.B. Vu, J.E. Bemis, J.S. Disch, P.Y. Ng, J.J. Nunes, J.C. Milne, D.P. Carney, A.V. Lynch, J.J. Smith, S. Lavu, J. Med. Chem. **52**, 1275 (2009)
48. C. Mukherjee, K.T. Watanabe, E.R. Biehl, Tetrahedron Lett. **53**, 6008 (2012)
49. C.B. Vu, J.E. Bemis, J.S. Disch, P.Y. Ng, J.J. Nunes, J.C. Milne, D.P. Carney, A.V. Lynch, J.J. Smith, S. Lavu, J. Med. Chem. **52**, 1275 (2009)
50. J.H. Park, M.I. El-Gamal, Y.S. Lee, C.H. Oh, Eur. J. Med. Chem. **46**, 5769 (2011)
51. R.F. Fandy, Arch. Pharm. Res. **23**, 446 (2000)
52. S.M. Sayed, M.A. Khalil, M.A. Ahmed, M.A. Raslan, Synth. Commun. **32**, 481 (2002)
53. J. Chen, S.K. Spear, J.G. Huddleston, R.D. Rogers, Green Chem. **7**, 64 (2005)
54. J. Chen, S.K. Spear, J.G. Huddleston, J.H. Holbrey, R.D. Rogers, Ind. Eng. Chem. Res. **43**, 5358 (2004)
55. Z. Gou, M. Li, H.D. Willauer, J.G. Huddleston, G.C. April, R.D. Rogers, Ind. Eng. Chem. Res. **41**, 2535 (2002)
56. J.M. Harris, *Poly(ethelene glycol) Chemistry* (Plenum, New York, 1992)
57. J.M. Harris, S. Zalipsky, *Chemistry and Biological Application of Polyethylene Glycol* (ACS Books, Washington, DC, 1997)
58. J. Mao, J. Guo, F. Fang, S.J. Ji, Tetrahedron **64**, 3905 (2008)
59. C. Mukhopadhyay, P.K. Tapaswi, Tetrahedron Lett. **49**, 6237 (2008)
60. V.V. Kouznetsov, D.R. Merchan Arenas, A.R.R. Bohorquez, Tetrahedron Lett. **49**, 3097 (2008)
61. J. Sindhu, H. Singh, J. Khurana, C. Sharma, K. Aneja, Chin. Chem. Lett. **26**, 50 (2015)
62. H. Zeng, Y. Li, H. Shao, Synth. Commun. **42**, 25 (2012)
63. E. Rajanarendar, K.G. Reddy, M.N. Reddy, S. Raju, K.R. Murthy, Green Chem. Lett. Rev. **4**, 257 (2011)
64. M. Kidwai, A. Jahan, D. Bhatnagar, J. Sulfur Chem. **31**, 161 (2010)
65. B.S. Dawane, B.M. Shaikh, N.T. Khandare, V.T. Kamble, S.S. Chobe, S.G. Konda, Green Chem. Lett. Rev. **3**, 205 (2010)
66. M. Kidwai, D. Bhatnagar, R.J. Chauhan, Heter. Chem. **50**, 234 (2013)
67. X. Zhong, G. Dou, D. Wang, Molecules **18**, 13139 (2013)
68. M. Rajeswari, J. Sindhu, H. Singh, J.M. Khurana, RSC Adv. **5**, 39686 (2015)
69. M. Kidwai, D. Bhatnagar, Chem. Pap. **64**, 825 (2010)
70. Z.G. Wang, M. Lu, RSC Adv. **4**, 1234 (2014)
71. R.H. Vekariya, S.N. Panchal, K.D. Patel, H.D. Patel, Curr. Microw. Chem. **2**, 61 (2015)
72. P. Hawkey, D. Lewis, *Medical Bacteriology* (OUP, Oxford, 2003), p. 265
73. K.H. Reickmann, G.H. Campbell, L.J. Sax, J.E. Mrema, Lancet **1**, 221 (1978)
74. J.J.S.B. Singh, Indian J. Malariol. **10**, 117 (1956)
75. N.C. Desai, H.K. Shukla, K.A. Tahker, J. Indian Chem. Soc. **61**, 239 (1984)
76. P. Anargyros, D.J.S. Astill, I.S.L. Lim, J. Clin. Microbiol. **28**, 1288 (1990)