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Ruthenium(II)-catalyzed synthesis of 2-arylbenzimidazole and 2-arylbenzothiazole in water

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Abstract
Benzimidazoles/benzothiazoles are heterocyclic compounds which contain a five membered heteroatom and a benzene ring. They constitute a crucial structural unit of numerous bioactive compounds and natural products. Since the compounds containing benzimidazole/benzothiazole core and their derivatives possess interesting biological activity, steady efforts are being made on the development of an improved synthetic methodology for the synthesis of these biologically important class of compounds. Inspired by their biological properties, synthesis of 2-arylbenzimidazoles and 2-aryl benzothiazoles has been attempted using N^O chelate ruthenium(II)-catalyst in water. A series of 2-arylbenzimidazoles and 2-arylbenzothiazoles including a few new derivatives have been prepared by the reaction of *ortho*-phenylenediamine or *ortho*-aminothiophenol with aromatic aldehydes in the presence of 5 mol% of ruthenium(II)-catalyst under nitrogen without the use of additive in water. This reaction was extended to various heteroaromatic aldehydes obtaining up to 88% yield of the desired 2-arylbenzimidazoles/2-arylbenzothiazoles. In a few cases, a small amount of diarylated compounds was formed depending on the aldehydes used. Additionally, antibiotic properties of the synthesized compounds have been screened using the standard disc diffusion method.

Introduction

Benzimidazole and its derivatives constitute an important structural unit in biologically active compounds, natural products and pharmacophores [1]. Benzimidazoles possess diverse biological activity and clinical applications, including anticancer [2, 3], antitumor [4], antibacteria [5], antidiabetic [6], antiviral [7] and antioxidant [8, 9] properties. Moreover, compounds having benzimidazole scaffold such as HOECHST 33258 [10], FB642 [11] and nocodazole [12] possessed antitumor properties (Fig. 1). Further, benzimidazole core, particularly, the 2-aminoimidazole derivatives, are widely found in marine sponges of the genus *Agelasidae and Leucetta* sp.[13].

Owing to their wide application in therapeutics, the development of new synthetic methodology for benzimidazoles and its derivatives has been paid considerable attention [14–16]. In general, the synthesis of benzimidazoles was achieved by the reaction of *ortho*-phenylenediamine with aldehydes [17–19], acids and their derivatives such as acid chlorides 20–23], esters, amides [22] and even nitriles in the presence of transition metals or organic catalysts under appropriate conditions. It is noteworthy that the traditional method for the synthesis of benzimidazoles involves condensation of an *ortho*-diaminoarene with a carboxylic acid or its derivatives under harsh dehydrating conditions [24]. Over the past decades, numerous synthetic methods have been developed for the synthesis of 2-arylbenzimidazoles [14, 16–20]. In contrast, the synthesis of 1,2-diarylbenzimidazoles remained scarce, and the synthesis was achieved in the presence of certain catalysts such as $Bi(OTf)_3$ [25], L-proline [26] and silica sulfuric acid [27].

In 2003, Dudd and coworkers showed that the synthesis of benzimidazoles could be achieved in hot water by heating the reaction in a specially designed autoclave to sustain high temperature (300 °C) and pressure [28]. Later, in 2013, Samanta et al. described a transition-metal catalyst-free synthesis of 2-arylbenzimidazole and 2-arylbenzothiazole

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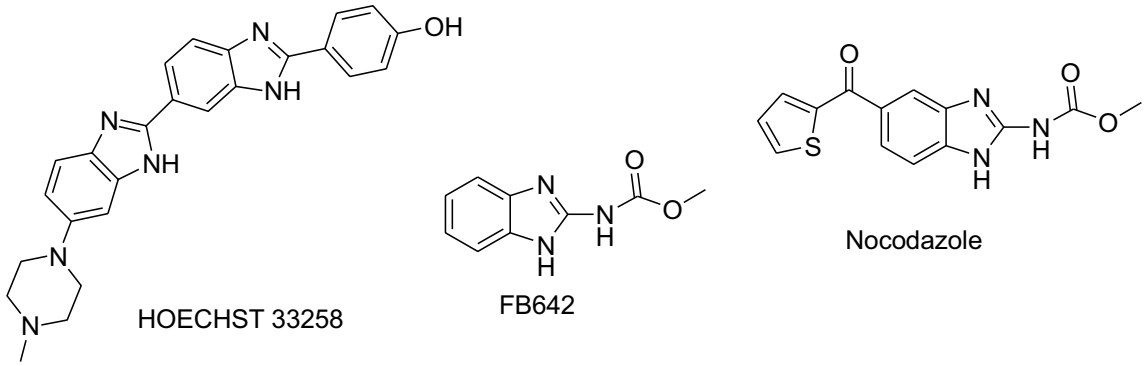


Fig. 1 Structures of benzimidazole compounds with anticancer properties

via photocatalysis in the presence of 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (pytz) as catalyst [29, 30]. In the subsequent years, Deng and co-workers reported another metal free process involving the synthesis of 2-arylbenzoxalzoles from aryl amides and cyclohexanones in the presence of KI/TsOH and an oxidant. Previously, a palladium-catalyzed synthesis of *N*-arylbenzimidazoles by three-component cascade amination/amidation route was reported by Buchwald and co-workers obtaining the desired products up to 87% [31, 32]. Further, a novel copper catalyzed-synthesis of 1,2, disubstituted benzimidazoles has been described through an aerobic oxidative C-H functionalization of primary amines. It is noteworthy that the synthesis of benzimidazoles assisted by transition metals were performed mainly using the complexes of Fe [33, 34], Cu [35, 36], and Mo [37]. In some cases, the synthesis was catalyzed even by rare earth metal chlorides such as YCl_3 [38] and $LaCl_3$ [39]. However, to the best our knowledge, limited reports are available for the synthesis of 2-arylbenzimidazoles/2-arylbenzothiazoles with ruthenium catalysts [40]. Further, the majority of the synthesis of benzimidizoles catalyzed by the complexes of ruthenium [40, 41] and cobalt [42,43] proceeded through the dehydrogenative coupling of aromatic amines with primary alcohols or coupling of amine and alkyl group.

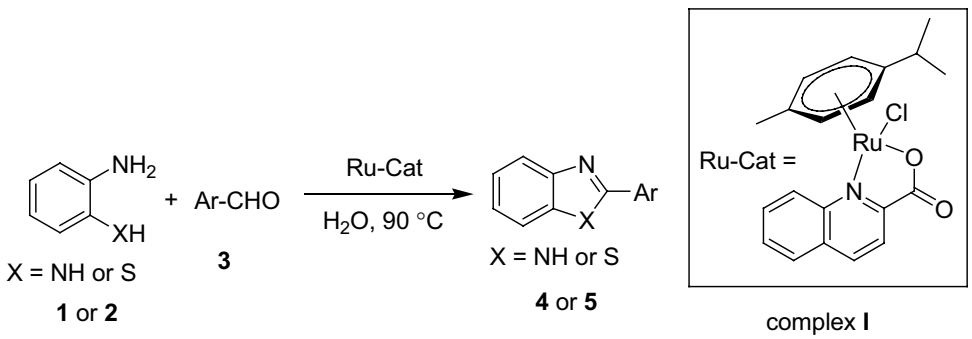
In continuation of our study on the synthesis of antimicrobial compounds, herein, we wish to disclose the synthesis of 2-aryl benzimidazoles/2-arylbenzothiazoles catalyzed by N^O chelate ruthenium(II) complex (I) in water. Additionally, the antimicrobial properties of the synthesized benzimidazoles/benzothiazoles compounds have been screened. The synthesis was achieved by the reaction of *ortho*-phenylenediamine/*ortho*-aminothiophenol with aromatic aldehydes in the presence of 5 mol% of ruthenium(II)-catalyst (**I**) under nitrogen using water as the sole solvent. This reaction was extended to various heteroaromatic aldehydes affording up to 88% yield of the desired 2-arylbenzimidazoles/2-arylbenzothiazoles. In a few cases, small amounts of diarylated benzimidazoles were formed depending on the aldehyde used (Scheme 1).

Experimental

Materials and method

Solvents used were of analytical grade and distilled prior to use. $RuCl_3.3H_2O$ was purchased from Arrora Matthey Pvt. Ltd. India, while all the other chemicals namely, *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde, *o*-chlorobenzaldehyde, 5-nitro-2-thiophenecarboxaldehyde, 5-nitrofurfural, 3-methyl-2-thiophenecarboxaldehyde, 5-methylthiophene-2-carboxaldehyde, 5-methylfurfural,

Scheme 1 Reaction pathways for the synthesis of 2-arylbenzimidaole and 2-arylbenzothiazole



pyrrole-2-carboxaldehyde, 5-bromoindole-3-carboxaldehyde, thiophene-2-carboxaldehyde, *o*-phenylenediamine, and 2-aminothiophenol were obtained either from Sigma-Aldrich Pvt. Ltd. or Avara chemicals, India, and used as received. Infrared spectra were recorded on a Shimadzu-IR affinity-1 spectrophotometer with sample prepared in KBr. The ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer at 300.13 (^{1}H), 75.47 MHz (^{13}C) with $SiMe_4$ as internal references and coupling constants are given in Hertz. The mass spectral analysis was performed on Waters UPLC-MSMS (Xevo TQD) mass spectrometer. The precursor complex [{(η^6-*p*-cymene)$RuCl_2$}$_2$] [44] was prepared by following a published procedure while the complex [RuCl(quinto)(*p*-cymene)] (**I**) [quinto = 2-quinaldinato) was prepared by a slight modification of the method reported earlier [45].

Synthesis of [RuCl(quinto)(*p*-cymene)] (I)

A round-bottom flask was charged with [$RuCl_2$(*p*-cymene)$_2$]$_2$ (0.1 g, 0.163 mmol), quinaldic acid (0.056 g, 0.326 mmol) and NaOMe (0.02 g, 0.37 mmol).The resulting mixture was stirred in methanol (40 ml) for 5 h at room temperature. The red solution becomes cloudy as the reaction progress and yellow solid appeared. The solid was collected and washed with cold methanol and then with diethyl ether (2 × 10 ml) and dried under vacuum. Yield 0.129 g (81%); Yellow solid; ^{1}HNMR ($CDCl_3$, δ): 8.59 (d, 1H, *J* = 8.7), 8.40 (d, 1H, *J* = 8.3), 8.23 (d, 1H, *J* = 8.4), 8.02–7.97 (m, 2H), 7.79 (d, 1H, *J* = 14.7), 5.74 (d, 1H, *J* = 5.8), 5.54 (d, 2H, *J* = 6), 5.42 (d, 1H, *J* = 6), 2.61 (m, 1H), 2.26 (s, 3H), 1.11 (d, 3H, *J* = 6.9), 1.00 (d, 3H, *J* = 6.9).

Representative procedure for the synthesis of 2-arylbenzimidazoles/2-arylbenzothiazoles with ruthenium(II)-catalyst (I) in water

A Schlenck tube was charged with 1, 2-phenylenediamine/2-aminothiophenol (0.5 mmol), aldehyde (0.5 mmol) and ruthenium(II) catalyst (**I**) (0.011 g, 0.025 mmol). Then 2 ml of distilled water was added to the tube and sealed. The reaction mixture was stirred at 100 °C under nitrogen atmosphere on a magnetic stirrer for about 16 h. The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 10 ml). The combined organic fractions was evaporated to dryness using a rotary evaporator and the residue thus obtained was purified by column chromatography over silica gel column using petroleum ether and ethyl acetate as eluents. The spectroscopic data of the known synthesized compounds were well-matched with the reported values [50] (see supplementary material).

Yield and spectroscopic data of the selected compounds:

(a) 1-(4-chlorobenzyl)-2-(4-chlorophenyl)-1H-benzo[d] imidazole (**4ab**): 0.014 g (8%); white solid;; FTIR (KBr, cm^{-1}): 2906, 1698, 1527, 1082; ^{1}H-NMR ($CDCl_3$, δ): 7.88 (d, 1H, *J* = 7.8), 7.60 (d, 2H, *J* = 8.1), 7.44 (m, 2H), 7.461–7.30 (m, 5H), 7.02 (d, 2H, *J* = 7.8), 5.40 (s, 2H); ^{13}C-NMR ($CDCl_3$, δ): 152.84, 143.05, 136.37, 135.90, 134.63, 133.88, 130.45, 129.36, 129.13, 128.35, 127.26, 123.47, 123.04, 120.18, 110.27, 47.76. ESI–MS: *m/z* 353.09 $[M+H]^+$.

(b) 2-(5-bromo-1H-indol-3-yl)-1H-benzo[d]imidazole (**4e**): 0.118 g (75%): brown solid; ^{1}H NMR (DMSO-d_6, δ): 11.83 (s, 1H), 8.66 (s, 1H), 8.15 (s, 1H), 7.50 (t, 2H, *J* = 8.4), 7.34 (d, 1H, *J* = 8.7), 7.16 (t, 2H, *J* = 5.7); ^{13}C-NMR (DMSO-d_6, δ): 172.67, 149.27, 135.71, 127.84, 127.24, 125.31, 123.81, 114.50, 113.56, 106.65.

(c) 2-(5-nitrothiophen-2-yl)-1H-benzo[d]imidazole (**4 g**): 0.108 g (88%); Yellowsolid; FTIR (KBr cm^{-1}): 3103, 2926, 1693, 1519, 1036, 744; ^{1}H-NMR (DMSO-d_6, δ): 13.44 (s, 1H), 8.19 (d, 1H, *J* = 4.5), 7.81 (d, 1H, *J* = 4.2), 7.62 (m, 2H), 7.26 (m, 2H); ^{13}C-NMR (DMSO-d_6, δ): 172.45, 151.46, 145.08, 143.80, 141.21, 135.41, 131.46, 126.20, 124.59, 123.16, 119.75, 112.26. ESI–MS: *m/z* 246.14 $[M+H]^+$.

(d) 2-(3-methylthiophen-2-yl)-1H-benzo[d]imidazole (**4 h**): 0.066 g (57%); Brown solid; FTIR (KBr cm^{-1}): 3047, 2924, 1720, 1562, 1068, 746; ^{1}H NMR (DMSO-d_6, δ): 12.41 (s, 1H), 7.56 (m, 3H), 7.18 (d, 2H, *J* = 4.2), 7.05 (d, 1H, *J* = 4.8), 2.58 (m, 3H); ^{13}C-NMR (DMSO-d_6, δ): 147.46, 138.12, 135.16, 132.30, 127.43, 122.78, 118.95, 111.80, 15.91; ESI–MS: *m/z* 215.16 $[M+H]^+$.

(e) 2-(5-methylthiophen-2-yl)-1H-benzo[d]imidazole (**4ia**):0.061 g (53%), Brown solid; FTIR (KBr cm^{-1}): 3024, 2936, 1712, 1570, 746; ^{1}H NMR (DMSO-d_6, δ): 12.81 (s, 1H), 7.59 (m, 3H), 7.17 (d, 2H, *J* = 6.3), 6.90 (s, 1H), 2.50 (s, 3H); ^{13}C-NMR (DMSO-d_6, δ): 147.57, 144.03, 142.92, 135.09, 131.03, 127.34,127.10, 122.89, 122.09, 118.81, 111.38, 15.53.

(f) 2-(5-methylthiophen-2-yl)-1-((5-methylthiophen-2-yl) methyl)-1H-benzo[d]imidazole (**4ib**): 0.01 g (6%), light brown solid; FT-IR (KBr cm^{-1}): 2928, 1716, 1516, 1058, 742; ^{1}H NMR ($CDCl_3$, δ): 7.82 (d, 1H, *J* = 8.4), 7.38–7.29 (m, 4H), 6.81 (m, 1H), 6.70–6.59 (m, 2H), 5.82 (s, 2H), 2.56 (s, 3H), 2.42 (s, 3H); ^{13}C-NMR ($CDCl_3$, δ):147.82, 143.79, 143.08, 136.36, 135.92, 129.44, 128.30, 126.21, 125.36, 125.07, 122.96, 122.77, 119.76, 109.85, 44.16, 15.33, 15.25; ESI–MS: *m/z* 325.0495 $[M+H]^+$.

(g) 2-(5-methylfuran-2-yl)-1-((5-methylfuran-2-yl) methyl)-1H-benzo[d]imidazole (**4 kb**): yellow solid;0.025 g (17%); ^{1}H-NMR($CDCl_3$, δ): 7.79 (d, 2H, *J* = 5.1), 7.50 (d, 1H, *J* = 4.8), 7.29 (m, 2H), 7.11 (s, 1H), 6.21 (s, 1H), 6.14 (s, 1H), 5.88 (s, 1H), 5.55

(s, 2H), 2.47 (s, 3H), 2.23 (s, 3H); ^{13}C-NMR ($CDCl_3$, δ): 154.48, 152.40, 147.71, 144.28, 143.31, 142.82, 135.51, 122.91. 122.75, 119.55, 114.10, 109.96, 109.19, 108.25, 106.39, 41.82, 13.81, 13.47; ESI–MS: *m/z* 293.21 $[M+H]^+$.

(h) 2-(3-methylthiophen-2-yl)benzo[d]thiazole (**5f**): 0.1 g (86%); yellow solid; FTIR (KBr, cm^{-1}): 3074, 3057, 2968, 2920, 2856, 1435, 894; ^{1}H-NMR ($CDCl_3$, δ): 8.08 (d, 1H, *J* = 8.4), 7.90 (d, 1H, *J* = 8.1), 7.50 (t, 1H, *J* = 7.8), 7.39 (t, 2H, *J* = 5.7), 6.99(d, 1H, *J* = 4.8), 2.65 (s, 3H); ^{13}C-NMR ($CDCl_3$,δ): 163.89, 153.01, 138.90, 135.02, 132.06, 131.93, 127.70, 126.36, 124.79, 122.86, 121.25, 16.24; ESI–MS: *m/z* 232.97 $[M+H]^+$.

(i) 2-(5-methylfuran-2-yl)benzo[d]thiazole (**5 g**): 0.215 g (88%): brown solid; ^{1}H-NMR ($CDCl_3$, δ): 8.04 (d, 1H, *J* = 8.4), 7.88 (d, 1H, *J* = 4.05), 7.48 (t, 1H, *J* = 7.2), 7.36 (t, 1H, 7.8), 7.09 (d, 1H, *J* = 3.3), 6.21 (d, 1H, *J* = 3.3), 6.21 (d, 1H, *J* = 3.3), 2.46 (s, 3H); ^{13}C-NMR ($CDCl_3$, δ): 157.74, 155.51, 153.66, 147.12, 134.00, 126.34, 124.88, 122.91, 121.44, 113.04, 108.89, 13.90.

Antibiotic assay of 2-arylbenzimidazoles/2-arylbenzothiazoles.

The synthesized 2−arylbenzimidazoles/2−arylbenzothiazoles were screened for their antibacterial activity against 10 fouling and 10 clinical bacteria using the standard paper−disc diffusion assay method [46–49]. The fouling bacteria used for the antifouling assay were isolated from fouled substrata collected from the coastal waters of Goa, whereas the clinical pathogens were obtained from the Goa Medical College. Briefly, sterile Whatman filter paper discs (GF/C) measuring 6 mm diameter were loaded with compounds under study (50 µg/disc). The impregnated discs were aseptically placed on Agar plates containing a lawn of test bacterial strains (spread plated with approx 1.2 x 10^8 CFU/ml of test organisms). Nutrient agar plates were used for growing fouling bacteria while Muller−Hinton agar plates were used for growing clinical bacteria. Standards streptomycin and penicillin (for clinical pathogens and fouling bacteria, respectively) served as positive control. Same concentrations of standard and synthesized compounds (**4b**,**4c, 4 g, 4 ka, 5d** and **5f)** were used during the assay for the purpose of comparison. Discs containing solvent (methanol/DMSO), used for dissolving the compounds served as negative control. After loading the compound/standards on the discs, they were placed aseptically on the agar plates and incubated at 37ºC for 24 h. At the end of the incubation period, the diameter of inhibition−zone formed around each disc was measured in millimetres using a vernier calliper to obtain a semiquantitative determination of the antibiotic nature of the synthetic compounds. The experiments were performed in triplicate and the results of the antibacterial screening of the compounds 4b, **4c, 4 g, 4 ka, 5d** and **5f** against the test bacteria (fouling and clinical) are summarized in Tables 3 and 4 respectively.

Results and discussion

A series of 2-arylbenzimidazoles/2-arylbenzothiazoles have been synthesized by the reaction of aromatic aldehydes and *ortho*-phenylenediamine or *ortho*-aminothiophenol in the presence of 5 mol% of N^O-chelate ruthenium(II)-catalyst(I) in water to give the desired products in high yields (Scheme 1). This protocol provides direct access to the various 2-arylbenzimidazoles/2-arylbenzothiazoles in a rapid manner under base-free reaction conditions. Initially, the reaction was evaluated using 1,2-phenylenediamine with 4-chlorobenzaldehyde in the presence of 5 mol% of ruthenium(II)-catalyst in water to give the monoarylated product **4aa** and diarylated product **4ab** in 60 and 8%, respectively (Table 1, entry 1). The products were readily isolated by column chromatography over silica gel using a gradient of petroleum ether and ethyl acetate as eluent. The isolated compounds were characterized based on spectroscopic data (^{1}H & ^{13}C-NMR and ESI–MS) as well as by comparison with reported data [36, 50]. The compound **4aa** was obtained as light yellow solid insoluble in $CHCl_3$ and acetone but soluble in DMSO whereas, the compound **4ab** was obtained as white solid soluble in most of the organic solvent. The formation of the compounds was readily confirmed by ^{1}H, ^{13}C-NMR and mass spectral data. The proton NMR spectrum of **4aa** showed a signal at δ 12.45 assignable to NH-proton and signal for the aromatic protons in the region of δ 8.18–7.25, while the ^{1}H-NMR spectrum of **4ab** displayed a singlet at δ 5.4 corresponding to the methylene group (-CH_2-) in addition to signals expected for aromatic proton. Similarly, 2-chlorobenzaldehyde, 4-nitrobenzaldehyde, and phterphthaldehyde reacted with *o*-phenylenediamine to give 72, 79 and 23% of **4b**, **4c** and **4d**, respectively (Table 1, entries 2–4). However, in these cases, no isolable diarylated products were obtained.[51–53

The reaction was extended to heteroaryl aldehydes such as 5-bromoindole-3-carboxaldehyde, 5-nitrothiophene-2-carboxaldehyde, 3-methylthiophene-2-carboxaldehyde, 5-methylthiophene-2-carboxaldehyde and 5-nitrofuran-2-carboxaldehyde to give the corresponding monoarylated benzimidazoles in good yields of 76, 88, 57, 52 and 86%, respectively (Table 1). In a few cases, a small amount of diarylated benzimidazole along with monoarylated products were observed. For instance, the reaction of *ortho*-phenylenediamine with pyrrole-2-carboxaldehyde gave the monoarylated benzimidazole (**4fa)** in 46%, while di-arylated benzimidazole (**4fb)** was obtained as minor product 15% (Table 1entry 6). Similarly, the reaction of

Table 1 Ruthenium(II)-catalyzed synthesis of 2-arylbenzimidazole in water[a]

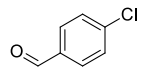
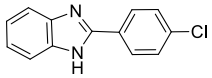
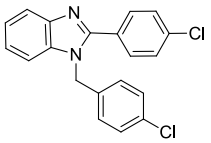
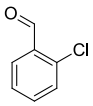
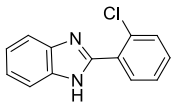
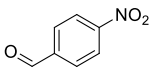
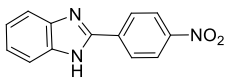
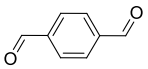
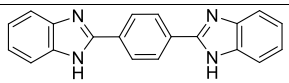
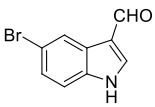
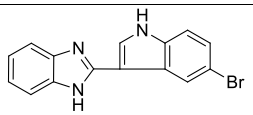
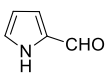
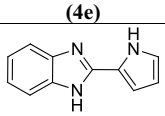
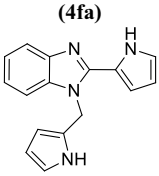
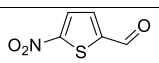
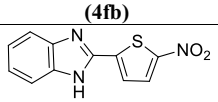
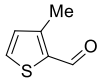
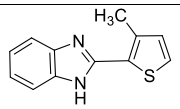
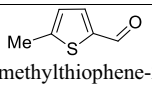
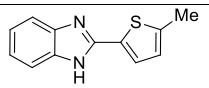
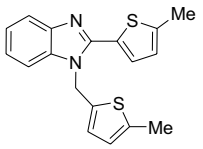
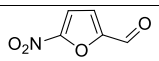
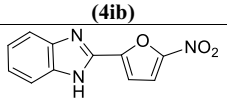
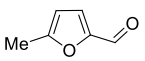
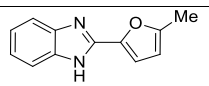
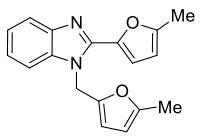
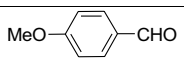
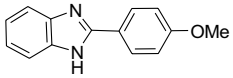
Sr. No.	Aldehyde	Product	Yield (%)[b]
1	 4-chlorobenzaldehyde **(3a)**	 2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazole **(4aa)**  1-(4-chlorobenzyl)-2-(4-chlorophenyl)-1*H*-benzo[*d*]imidazole **4ab**	60 8
2	 2-chlorobenzaldehyde **(3b)**	 2-(2-chlorophenyl)-1*H*-benzo[*d*]imidazole **(4b)**	72
3	 4-nitrobenzaldehyde **(3c)**	 2-(4-nitrophenyl)-1*H*-benzo[*d*]imidazole **(4c)**	79
4	 terephthalaldehyde 3d	 1,4-bis(1*H*-benzo[*d*]imidazol-2-yl)benzene **(4d)**	23
5	 5-bromo-1*H*-indole-3-carbaldehyde **3e**	 2-(5-bromo-1*H*-indol-3-yl)-1*H*-benzo[*d*]imidazole **(4e)**	76
6	 1*H*-pyrrole-2-carbaldehyde **3f**	 2-(1*H*-pyrrol-2-yl)-1*H*-benzo[*d*]imidazole **(4fa)**  1-((1*H*-pyrrol-2-yl)methyl)-2-(1*H*-pyrrol-2-yl)-1*H*-benzo[*d*]imidazole **(4fb)**	46 15
7	 5-nitrothiophene-2-carbaldehyde 3g	 2-(5-nitrothiophen-2-yl)-1*H*-benzo[*d*]imidazole **(4g)**	88

Table 1 (continued)

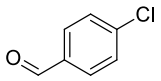
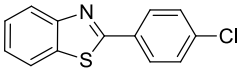
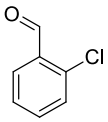
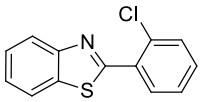
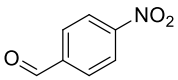
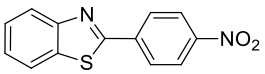
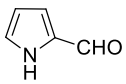
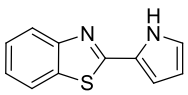
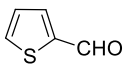
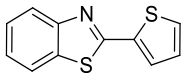
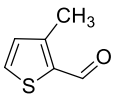
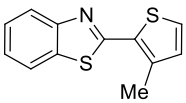
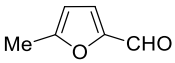
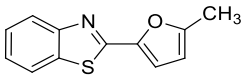
8	 3-methylthiophene-2-carbaldehyde **3h**	 2-(3-methylthiophen-2-yl)-1*H*-benzo[*d*]imidazole **(4h)**	57
9	 5-methylthiophene-2-carbaldehyde **3i**	 2-(5-methylthiophen-2-yl)-1H-benzo[d]imidazole **(4ia)**  2-(5-methylthiophen-2-yl)-1-((5-methylthiophen-2-yl)methyl)-1H-benzo[d]imidazole **(4ib)**	52 8
10	 5-nitrofuran-2-carbaldehyde **3j**	 2-(5-nitrofuran-2-yl)-1*H*-benzo[*d*]imidazole **(4j)**	86
11	 5-methylfuran-2-carbaldehyde **3k**	 2-(5-methylfuran-2-yl)-1H-benzo[d]imidazole **(4ka)**  2-(5-methylfuran-2-yl)-1-((5-methylfuran-2-yl)methyl)-1H-benzo[d]imidazole **(4kb)**	58 17
12	 **3l**	 2-(4-methoxyphenyl)-1H-benzo[d]imidazole **4l**	NR

[a]Reaction conditions: Amine (0.5 mmol), aldehyde (0.5 mmol), catalyst (5 mol%), water (3 mL), Temp = 90 °C, Time = 16h; [b]Isolated yield Oafter column chromatography

ortho-phenylenediamine with 5-methylthiophene-2-carboxaldehyde as well as 5-methylfurfural gave monoarylated product (**4ia**) and (**4 ka**) in 52 and 58%, while the dairylated products (**4ib**) and (**4 kb**) were obtained in 8 and 17%, respectively (Table 1, entries 9 and 11).

Further, we have tested this reaction protocol for the synthesis of 2-arylbenzothiazoles by the condensation of *ortho*-aminothiophenol with aldehydes. We were delighted that under the similar reaction condition, *ortho*-aminothiophenol reacted with various aldehydes in the presence of [RuCl(quinto)(*p*-cymene)] (**I**) to give a series

Table 2 Ruthenium (II)-catalyzed synthesis of 2-arylbenzothizole in water[a]

Entry	Aldehyde	Product	Yield (%)[b]
1.	 4-chlorobenzaldehyde **(3a)**	 2-(4-chlorophenyl)benzo[*d*]thiazole **(5a)**	72
2.	 2-chlorobenzaldehyde **(3b)**	 2-(2-chlorophenyl)benzo[*d*]thiazole **(5b)**	88
3.	 4-nitrobenzaldehyde **(3c)**	 2-(4-nitrophenyl)benzo[*d*]thiazole **(5c)**	43
5.	 1*H*-pyrrole-2-carbaldehyde **3d**	 2-(1*H*-pyrrol-2-yl)benzo[*d*]thiazole **(5d)**	46
6	 thiophene-2-carbaldehyde 3e	 2-(thiophen-2-yl)benzo[d]thiazole **(5e)**	64
6.	 3-methylthiophene-2-carbaldehyde 3f	 2-(3-methylthiophen-2-yl)benzo[*d*]thiazole 5f	86
8.	 5-methylfuran-2-carbaldehyde **3g**	 2-(5-methylfuran-2-yl)benzo[d]thiazole **5g**	88

[a]Reaction conditions: Amine (0.5 mmol), aldehyde (0.5 mmol), catalyst (5 mol%), water (3 mL), 90 °C, 12h; [b]Isolated yield after column chromatography.

of 2-arylbenzothiazoles (Scheme 1, Table 2). The lowest yield of 43% was obtained for 2-(4-nitrophenyl)benzo[d] thiazole (**5c**) in the reaction of *ortho*-aminothiophenol and 4-nitrobenzaldehyde (Table 2, entry 3), while, the highest yield of 88% was obtained in the reaction of *ortho*-aminothiophenol with 5-methylfurfural (**5 g**) (Table 2, entry 8).

Interestingly, the reaction of 1, 2-phenylendiamine/2-aminothiophenol and aldehyde without ruthenium(II)-catalyst did not give the desired product 2-arylbenzimidazoles/2-arylbenzothiazoles indicating the presence of ruthenium(II)-catalyst (I) is essential in the reaction. Previously, a catalyst-free direct synthesis of benzimidazoles in water was reported by the reaction of aromatic acid and 1,2-phenylenediamine [28]. However, this protocol required the reaction to conduct at high temperature, (300 °C) and pressure using a specially design autoclave. Our synthetic method which employed a water-soluble ruthenium(II)-catalyst provided a greener method for ready access to 2-arylbenzimidazoles/2-arylbenzothiazoles from the corresponding amines and readily available aldehydes at a lower temperature under base free condition. However, this method did not give satisfactory results in the attempt to synthesis the corresponding 2-arylbenzoxazoles by the reaction of *ortho*-aminophenol and aldehydes. Further, it is found that the productivity of this reaction depends on the type of aldehyde used. Thus, the aldehydes with electron-withdrawing group such as nitrobenzaldehyde, and chloro-benzaldehyde gave good yields (Table 1, entries 2, 3, 7 and 10), whereas, no desired product was obtained in the case of aldehyde containing an electron-donating substituent such as anisaldehyde (Table 1entry 12). However, in the case of heteroaldehydes, the nature of the substituent group of the aldehyde ring did not give significant effect on the productivity of the reaction.

Antibacterial properties of the synthesized benzimidazole and benzothiazole compounds against 10 each of marine fouling bacteria and clinical bacterial pathogens have been investigated employing the disc diffusion method using penicillin and streptomycin as the standards (Tables 3 and 4). The 2-arylbenzimidazole/2-arylbenzothiazole compounds **4b,4c, 4 g, 4 ka, 5d** and **5f** exhibited antifouling activity against one or more fouling bacteria while the rest of the compounds did not show significant activity against the bacteria tested. The growth of fouling bacteria *Alcanivorax sp*. *Planococcus donghaensis* and *Aeromonas hydrophila* was not affected by compounds **4b**, **4c** and **5f,** however, they showed moderate to high sensitivity to the compounds **4 g**, **4 ka** and **5d**. Further, the compounds **4 g**, **4 ka** and **5d** exhibited significant activity against all the fouling bacteria tested, while **5f** showed weak activity against *Aeromonas salmonicida*, *Erythrobacter litoralis*, *Pseudomonas mendocina, Alivibrio salmonicida,* and *Vibrio furnisi* but was inactive against the rest of the bacteria tested (Table 3).[54, 55].

The result of antibacterial activity of the 2-arylbenzimidazole/2-arylbenzothiazole compounds against the clinical bacterial pathogens is summarized in Table 456–59. The compounds **4c, 4 g, 4 ka, 5d** and **5f** exhibited antibacterial activity against one or more clinical bacterial pathogen tested. As observed in Table 4, all the bacterial pathogens were sensitive to compounds **4 ka** and **5d** to a certain extent with inhibition zone varying between 2-5 mm**.** Compounds **4c** showed moderate activity against *Salmonella typhi*, and *Vibrio cholera* while, weak activity was observed against *E. Coli*, *Staphylococcus aureus* and *Mycobacterium smegmatis,* and no activity was evident against the rest of the tested bacterial pathogens. Interestingly, compound **5f** exhibited significant activity selectively only against clinical bacterium *Salmonella typhi causing typhoid in humans* while the rest of the bacteria were insensitive to compound **5f**. A moderate activity was displayed by compound **4 g** against *V. cholera*, *B. Subtili* and *Proteus* sp., while weak activity was shown by *E. coli*, *P. aeruginosa*, *S. aureus*, *S. flexineri, K. Pneumonia and M. smegmatis* [60–62].

Conclusion

This manuscript describes a straightforward method for the synthesis of 2-arylbenzimidazoles/2-arylbenzothiazoles with N^O chelate ruthenium(II)-catalyst (I). The protocol provides a rapid and base free condition for ready access to various 2-arylbenzimidazoles/2-arylbenzothiazoles in a greener manner using water as the sole solvent. The condensation of *ortho*-phenylenediamine/*ortho*-aminothiophenol with an aldehyde in water was best performed in the presence of ruthenium(II)-catalyst (**1**) (10 mol%) and the reaction was extended to heteroaldehydes affording compatible yields. We believed that the synthesis method described herein could be used for a convenient synthesis of 2-arylbenzimidazoles and 2-arylbenzothiazoles but not suitable for the synthesis of 2-arylbenzoxazoles. Antibiotic screening of the compounds indicated that compounds **4 g**, **4 ka** and **5d** possess significant antibacterial activities and hence could have application as potential antibiotic agents. Further, the study of the synthesis of these 2arylbenzimidazoles/2-arylbenzothiazoles compounds using less expensive and abundant transition metal complexes as well as synthesis employing metal-loaded chitosan under heterogeneous catalytic condition are under way in our laboratory.

Table 3 Results for the antibacterial screening of the compounds (**4b**, **4c**, **4 g 4 ka**, **5d** and **5f**) against fouling bacteria showing zones of growth inhibition values

Compound	*Alcanivorax sp.*	*Planococcus donghaensis*	*Aeromonas hydrophila*	*Aeromonas salmonicida*	*Erythrobacter litoralis*	*Pseudomonas mendocina*	*Alcanivorax borkumensis*	*Alivibrio salmonicida*	*Pseudoalteromonas sp.*	*Vibrio furnisi*
4b	−	−	−	+	+	+	−	+	_	+ +
4c	−	−	−	+	+	−	−	+	+	+
4 g	+	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ + +
4 ka	+	+ +	+	+	+ +	+ +	+	+ +	+ +	+ +
5d	+ +	+ +	+	+ +	+ +	+ +	+ +	+ +	+ +	+ +
5f	−	−	−	+	+	+	−	+	−	+
Penicillin	+ + +	+ + + + +	+ + + + +	+ + + + +	+ + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + +

The data expressed as a measure of the inhibition zones (mm) at concentration 50 µg/disc Toxicity grading: (−) no activity; (+) inhibition zone (1–2); (++) inhibition zone (3–5); (+++) inhibition zone (6–8); (++++) inhibition zone (9–15); (+++++) (>20)

Table 4 Results for the antibacterial screening of the compounds (4b, 4c, 4 g 4 ka, 5d and 5f) against pathogenic bacteria showing zones of growth inhibition values

Compounds	*Escherichia coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Shigella flexineri*	*Salmonella typhi*	*Vibrio cholera*	*Klebsiella pneumonia*	*Bacillus subtilis*	*Mycobacterium smegmatis*	*Proteus sp.*
4b	−	−	+	−	−	−	−	−	−	−
4c	+	−	+	−	+ +	+ +	−	−	+	−
4 g	+	+	+	+	−	+ +	+	+ +	+	+ +
4 ka	+ +	+ +	+ +	+ +	+ +	+	+ +	+ +	+	+ +
5d	+ +	+ +	+ +	+ +	+	+ +	+	+ +	+ +	+ +
5f	−	−	−	−	+ + +	−	−	−	−	−
Streptomycin	+ + + +	+ + + +	+ + +	+ + + +	+ +	+ + + +	+ + + +	+ + +	+ + + +	+ +

The data are expressed as a measure of the inhibition zones (mm) at concentration 50 µg/disc Activity grading (−) no activity; (+) inhibition zone (1–2); (++) inhibition zone (3–5); (+++) inhibition zone (6–8); (++++) inhibition zone (9–15)

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

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