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Short communication

Convenient one-pot synthesis of novel 2-substituted benzimidazoles, tetrahydrobenzimidazoles and imidazoles and evaluation of their in vitro antibacterial and antifungal activities

Shweta Sharma, Saloni Gangal, Abdul Rauf*

Department of Chemistry, Aligarh Muslim University, Aligarh 202002, Uttar Pradesh, India

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Abstract

A series of novel 2-substituted benzimidazoles and imidazoles have been synthesized from long-chain alkenoic acids. The reactions occurred under relatively mild conditions and afforded the desired product in good yields. The structures of these compounds have been elucidated by elemental and spectral (IR, ^{1}H NMR, ^{13}C NMR, mass) analyses. Furthermore, compounds were screened for in vitro antibacterial activity against the representative panel of two Gram-positive and two Gram-negative bacteria. All the synthesized compounds were also tested for their inhibitory action against five strains of fungus. The various compounds show potent inhibitory action against test organisms.
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Keywords: 2-Substituted benzimidazoles; Tetrahydrobenzimidazoles; Imidazoles; Antibacterial activity; Antifungal activity

1. Introduction

The benzimidazole has been an important pharmacophore and privileged structure in medicinal chemistry, encompassing a diverse range of biological activities including antiarrhythmic, antiulcer, anthelmintical, inotropic, antihistamine, antifungal, antiviral, and cytotoxicity displaying diverse range of biological activities [1]. Benzimidazoles exhibit significant activity as potential antitumor agents [2], antimicrobial agents [3], smooth muscle cell proliferation inhibitors [4], a treatment for intestinal cystitis [5], and in diverse area of chemistry [6]. The imidazole core is a common moiety in a large number of natural products and pharmacologically active compounds [7]. Recently, there has been considerable amount of progress in imidazole chemistry due to the recognition of importance of the imidazole structure in biological processes and the increasing application of imidazole containing compounds, such as asetomidate, cimetidine, omeprazole and lansoprazole, in drug therapy [8]. Therefore the development of facile synthetic routes to achieve access to these molecules is of prime interest. In view of the above mentioned pharmacological applications of benzimidazoles and imidazoles and in continuation of our research on the synthesis of biologically active molecules [9], we considered undertaking the design and synthesis of hitherto unknown benzimidazoles and imidazoles bearing long alkenyl chain.

Further, the increasing number of multidrug resistant pathogens has led us to screen the newly synthesized derivatives against the representative panel of Gram-positive (g+) and Gram-negative (g−) bacteria and fungi.

2. Chemistry

A typical one-pot procedure for the synthesis of **4aA–4dC** involves the addition of 1,2-phenylenediamine derivatives **2A–2C** to the acid chloride **1a–1d** (Scheme 1) at 0 °C in dry dioxane and stirring for 30 min at room temperature to furnish the corresponding *N*-acyl-1,2-phenylenediamine

* Corresponding author. Tel.: +91 9412545345.
E-mail address: abduloafchem@gmail.com (A. Rauf).

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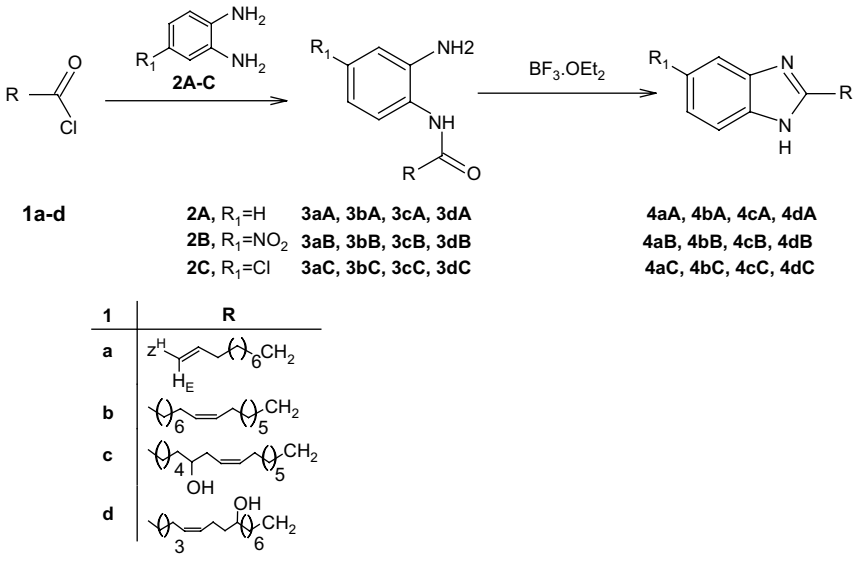


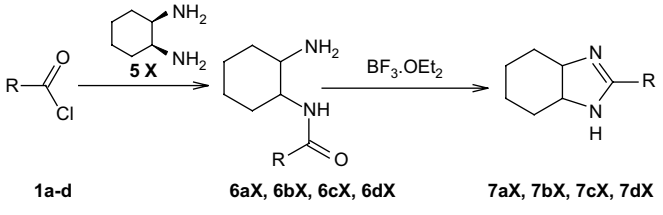
Scheme 1. Synthesis of 2-substituted-*1H*-benzimidazoles **4aA–4dC**.

derivatives **3**. To the prior, acid chloride **1a–1d** was synthesized from olefinic and hydroxy olefinic long-chain acids by in situ preparation. Since acid chlorides **1a–1d** are not commercially available the present method has greatly solved the problem by facile and efficient in situ preparation. We have used $BF_3 \cdot OEt_2$ for cyclization of **3**. $BF_3 \cdot OEt_2$ in dry dioxane was added to **3** without isolating the product and reaction mixture refluxed for 1–2 h at 130 °C. The yields of products **4aA–4dC** are excellent and independent of the substituents present in the precursor. The scope of the reaction using olefinic (internal and terminal) and hydroxy acids is found to be good. This strategy was also be used to increase the structural diversity of the member library through the synthesis of benzimidazole **7aX–7dX** (Scheme 2). Similarly **10aY–10dY** (Scheme 3) have been prepared by the reaction of ethylenediamine **8Y** to the acid chloride **1a–1d** at 0 °C in dry dioxane and stirring for 30 min at room temperature to furnish the corresponding **9** which undergo cyclization in presence of $BF_3 \cdot OEt_2$ to form **10aY–10dY**. The yield of products was found to be appreciable. The preliminary study of **4aA**, **4bA**, **10bY** has been reported earlier [10]. The newly synthesized compounds were analyzed for C, H and N content and structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

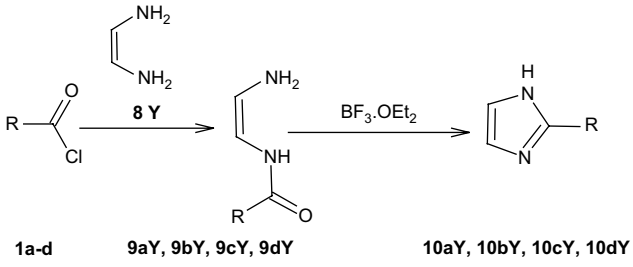
3. Biological activity

3.1. Antibacterial studies

The newly synthesized compounds were screened in vitro against an assortment of two Gram-positive bacteria *Staphylococcus aureus* MSSA 22 and *Bacillus subtilis* ATCC 6051 and two Gram-negative bacteria *Escherichia coli* K12 and *Salmonella typhimurium* MTCC 98. Screening results are summarized in Table 1. All the synthesized compounds were dissolved to prepare a stock solution of 1 mg/ml using DMSO. Stock solution was aseptically transferred and suitably diluted to have solutions of different concentrations ranging from 300 to 18.75 μg/ml by two-fold dilution. The antibacterial activity of test compounds and standard chloramphenicol was done by filter paper disc method [11]. Media with DMSO was set up as control. All cultures were routinely maintained on NA (nutrient agar) and incubated at 37 °C. The inoculums of bacteria were performed by growing the culture in NA broth at 37 °C for overnight. The culture was centrifuged at 1000 rpm and pellets was resuspended and diluted in sterile NSS to obtain viable count 10^5 cfu/ml. Approximately 0.1 ml of diluted bacterial culture suspension was spread with the help of spreader on NA plates uniformly.



Scheme 2. Synthesis of 2-substituted-tetrahydro-*1H*-benzimidazoles **7aX–7dX**.



Scheme 3. Synthesis of 2-substituted-*1H*-imidazoles **10aY–10dY**.

Table 1
In vitro antibacterial activity of compounds **4aA–10dY**

Compound	*E. coli*	Diameter of zone of inhibition (mm)		
		S. typhimurium	*B. subtilis*	*S. aureus*
4aA	18(150)	16(75)	22(75)	20(150)
4bA	16(150)	14(75)	21(75)	18(150)
4cA	17(150)	12(75)	21(75)	19(150)
4dA	17(150)	12(75)	19(75)	19(150)
4aB	20(75)	12(37.5)	19(37.5)	22(150)
4bB	20(75)	11(37.5)	20(37.5)	21(37.5)
4cB	16(37.5)	12(37.5)	21(37.5)	19(37.5)
4dB	18(37.5)	13(37.5)	22(37.5)	19(37.5)
4aC	20(75)	14(37.5)	19(75)	22(37.5)
4bC	18(75)	15(37.5)	18(75)	20(37.5)
4cC	18(75)	17(37.5)	19(75)	21(37.5)
4dC	19(37.5)	17(37.5)	20(75)	21(37.5)
7aX	17(37.5)	11(75)	18(75)	18(75)
7bX	17(150)	10(75)	19(75)	16(75)
7cX	15(150)	12(75)	19(75)	17(75)
7dX	16(150)	13(75)	23(75)	16(75)
10aY	15(150)	14(74)	22(37.5)	16(150)
10bY	11(150)	11(75)	19(37.5)	15(150)
10cY	12(150)	12(75)	18(37.5)	15(150)
10dY	12(150)	12(75)	19(37.5)	15(150)
Chloroamphenicol	25(12.5)	20(6)	24(6)	26(12.5)
Control DMSO	–	–	–	–

Values in brackets are MIC values (μg/ml).

Sterile 8 mm discs (Hi-media Pvt. Ltd.) were impregnated with the test compounds. Antibiotic disc, chloroamphenicol (30 μg/disc Hi-Media) was used as control. The disc was placed onto the plate. Each plate had one control disc impregnated with solvent. The plates were then incubated for 24 h at 37 °C, and the resulting zones of inhibition (in mm) were measured. The minimum inhibitory concentration at which no growth was observed was taken as the MIC values.

3.2. Antifungal studies

The newly synthesized compounds were also screened for *Aspergillus niger* (laboratory isolate), *Candida albicans* IOA-109, *Penicillium* sp. (laboratory isolate), *Trichoderma viridae* (lab isolate), *Helminthosporum oryzae* (2537 ICAR, Jaipur). The synthesized compounds were dissolved in DMSO. Media with DMSO was set up as control. All cultures were routinely maintained on SDA and incubated at 28 °C. Spore formation of filamentous fungi was prepared from 7-day old culture in sterile normal solution (8% NaCl) and approximately diluted to obtain 10^5 cfu/ml. The inoculums of non-sporing fungi, *C. albicans* was performed by growing the culture in SD broth at 37 °C for overnight. The culture was centrifuged at 1000 rpm and pellets was resuspended and diluted in sterile NSS to obtain viable count 10^5 cfu/ml. Approximately 0.1 ml of diluted fungal culture suspension was spread with the help of spreader on SDA plates uniformly. Sterile 8 mm discs (Hi-media Pvt. Ltd.) were impregnated with test compounds. Antibiotic disc, nystatin (30 μg/disc Hi-Media) was used as control. The disc was placed onto the plate. Each plate had one control disc impregnated with solvent. The plates were incubated at 28 °C for filamentous fungi for 72 h or more while for *C. albicans* plates were incubated at 37 °C for 18–48 h. Antifungal activity was determined by measuring the diameters of the inhibition zone (mm).

4. Results and discussion

The antibacterial and antifungal screening revealed that all the tested compounds **4aA–4dA**, **7aX–7dX**, **10aY–10dY** showed moderate to good inhibition. The antibacterial screening indicated that among the tested bacterial strains, good inhibitory results were obtained against *S. typhimurium* and *E. coli*. The structural activity study showed that benzimidazoles and their substituted derivatives **4aA–4dC** have varying degrees of microbial inhibition. The antibacterial and antifungal activity seemed to be dependent on the heterocyclic moiety as well as on the nature of substituents. Although the benzimidazoles **4aA–4dA** itself are observed active the activity was further enhanced by the presence of nitro and chloro substituent on the benzimidazole moiety (Table 1). The nitro substituted derivatives **4aB**, **4bB** have shown good activity against *E. coli* and *S. aureus*. The maximum inhibition was observed in **4dB** against *B. subtilis*. The chloro substituted derivatives **4aC–4dC** have shown maximum inhibition against *S. aureus*. The tetrahydrobenzimidazoles **7aX–7dX** are moderately active against *S. typhimurium* and **7aX**, **7dX** are best active against *E. coli* and *B. subtilis* whereas the imidazoles **10aY–10dY** showed moderate activity results against test bacterial strains. In another set of experiments, the above mentioned compounds were also examined for antifungal activity (Table 2). Nystatin was used as standard drug for the

Table 2
In vitro antifungal activity of compounds **4aA–10dY**

Compound	Diameter of zone of inhibition (mm)				
	C. albicans	*H. oryzae*	*A. niger*	*T. viridae*	*Penicillium* sp.
4aA	19(75)	13(150)	14(150)	7(75)	18(75)
4bA	19(75)	12(150)	16(150)	6(75)	18(75)
4cA	19(75)	13(150)	16(150)	8(75)	19(75)
4dA	18(75)	11(150)	14(150)	8(75)	17(75)
4aB	18(37.5)	10(75)	15(37.5)	8(37.5)	18(37.5)
4bB	19(37.5)	12(75)	15(37.5)	8(37.5)	18(37.5)
4cB	19(37.5)	15(75)	16(37.5)	9(37.5)	19(37.5)
4dB	19(37.5)	14(75)	14(37.5)	9(37.5)	19(37.5)
4aC	18(37.5)	15(75)	15(37.5)	10(37.5)	19(37.5)
4bC	18(37.5)	16(75)	15(37.5)	9(37.5)	19(37.5)
4cC	18(37.5)	14(75)	14(37.5)	9(37.5)	19(37.5)
4dC	18(37.5)	14(75)	14(37.5)	8(37.5)	19(37.5)
7aX	18(75)	11(150)	12(37.5)	7(37.5)	18(75)
7bX	18(75)	12(150)	13(37.5)	6(37.5)	17(75)
7cX	17(75)	11(150)	12(37.5)	7(37.5)	16(75)
7dX	19(75)	11(150)	12(37.5)	8(37.5)	17(75)
10aY	19(75)	12(150)	11(150)	6(75)	16(150)
10bY	18(75)	12(150)	12(150)	4(75)	17(150)
10cY	18(75)	13(150)	13(150)	6(75)	18(150)
10dY	18(75)	12(150)	14(150)	6(75)	19(150)
Nystatin	20(6)	18(12.5)	18(12.5)	15(6)	20(6)
Control DMSO	–	–	–	–	–

Values in brackets are MIC values (μg/ml).

comparison of antifungal results. The nitro and chloro substituted compounds **4aB–4dB** and **4aC–4dC** showed same trend in case of fungal strains. The excellent inhibition results were obtained against *C. albicans* and *Penicillium* sp. by **4aB–4dB**. The moderate activity was obtained in *H. oryzae* and *A. niger*. The inhibitory activity against *T. viridae* was significantly lower than the other tested microorganisms. Hence we conclude that higher activity of compounds **4aB–4dB** and **4aC–4dC** may be attributed to the presence of nitro and chloro groups. The inhibition by **4aA–4dA**, **7aX–7dX**, **10aY–10dY** is due to the presence of benzimidazole, tetrahydrobenzimidazole and imidazole, respectively. Thus the nature of substituents and basic skeleton of molecule have strong influence on the extent of antibacterial and antifungal activities. Thus the data revealed that all compounds have produced the marked enhancement in the potency of these analogues as antibacterial and antifungal agents.

5. Conclusion

The fact that readily synthesized starting material, available reagents along with short reaction time, no additives and simple work-up and isolation of the product make the current method a feasible and attractive protocol for generation of benzimidazoles and imidazoles from long-chain olefinic and hydroxyl olefinic acids. The antibacterial and antifungal evaluation of compounds has proved them potent antibacterial and antifungal agents. The other biological evaluation may furnish some other important applications.

6. Experimental

(9*Z*,12*R*)-12-Hydroxyoctadec-9-enoic (ricinoleic) and (9*R*,12*Z*)-9-hydroxyoctadec-12-enoic (isoricinoleic) acids were isolated from the natural sources, i.e. from *Ricinus communis* and *Wrightia tinctoria* seed oils, respectively. The concentrate of pure hydroxy acids were obtained by Gunstone's partitioning [12] of freshly prepared acids and further purified by column chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 instrument. The chemical shifts (δ) were measured relative to TMS as an internal standard. Coupling constants (J) are expressed in Hz. Mass spectra were obtained on a Jeol SX-102 (FAB) spectrometer. IR spectra were obtained on Shimadzu 8201 PC FT-IR using KBr pellet with absorption given in cm^{-1}.

6.1. Procedure for the preparation of 2-substituted benzimidazoles and imidazoles

Thionyl chloride (0.015 mol) was added to fatty acid (0.01 mol) at 80 °C for about 2 h to form the corresponding acid chloride **1a–1d**. The excess of thionyl chloride was distilled off. A typical reaction procedure involves the addition of 1,2-phenylenediamine derivatives (0.01 mmol) **2A–2C** and **5X** to the stirred solution of acid chloride at 0 °C in dry dioxane and stirring for 30 min at rt to furnish the corresponding **3aA–3dC** and **6aX–6dX**, respectively. Similarly **9aY–9dY** were synthesized by utilizing *cis* cyclohexanediamine and acid chlorides. $BF_3{\cdot}OEt_2$ (0.015 mol) in dry dioxane (10 ml) was added dropwise to the above stirred reaction mixtures in 10 min and reaction mixtures further refluxed for 1–2 h at 130 °C. The resulting solution was concentrated in vacuo, saturated NH_4Cl solution added until the pH becomes 6, extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the crude products **4aA–4dC**, **7aX–7dX**, **10aY–10dY** which were further purified by column chromatography.

6.1.1. 2-(Dec-9-enyl)-1H-benzimidazole (*4aA*)

Colorless oily liquid: yield: 89%; IR (KBr): ν_{max} cm^{-1} 3350, 1630, 1585. ^{1}H NMR δ (ppm): 9.01 (s, 1H, N–H), 6.73–6.71 (m, 4H, Ar–H), 5.82 (tdd, 1H, $J_{H-^8CH_2} = 6.6$ Hz, $J_{H-H_Z} = 10.2$ Hz, $J_{H-H_E} = 17.1$ Hz, CH_2=C*H*–), 5.02 (dd, 1H, $J_{H_Z-H} = 10.2$ Hz, $J_{H_Z-H_E} = 1.2$ Hz, H_ZC=CH), 4.90 (dd, 1H, $J_{H_E-H} = 17.1$ Hz, $J_{H_E-H_Z} = 1.2$ Hz, H_EC=CH–), 2.34 (t, 2H, $J = 7.12$ Hz, α to benzimidazole ring), 2.03 (m, 2H, –CH_2–CH=CH_2), 1.63 (m, 2H, β to benzimidazole ring), 1.30 (br s, 10H, chain CH_2). ^{13}C NMR δ (ppm): 143.44, 139.01, 133.56, 121.45, 118.17, 114.14, 34.25, 33.77, 29.20, 28.88, 24.73. MS (*m/z* %): 257 ($M^+ + 1$, 56), 256 (M^+, 45), 229 (34), 145 (40), 117 (100). Anal. calcd. for $C_{17}H_{24}N_2$: C, 79.65; H, 9.43; N, 10.92. Found: C, 79.06; H, 9.49; N, 10.87%.

6.1.2. 2-(Heptadec-8-enyl)-1H-benzimidazole (*4bA*)

Pale yellow oily liquid; yield: 89%; IR (KBr): ν_{max} cm^{-1} 3360, 1640, 1590. ^{1}H NMR δ (ppm): 9.12 (s, 1H, N–H), 6.73–6.70 (m, 4H, Ar–H), 5.38 (m, 2H, –CH=CH–), 2.35 (t, 2H, $J = 7.22$ Hz, α to benzimidazole ring), 2.02 (m, 4H, –CH_2–CH=CH–CH_2–), 1.61 (m, 2H, β to benzimidazole ring), 1.30 (br s, 20H, chain CH_2), 0.89 (dist. t, 3H, CH_3). ^{13}C NMR δ (ppm): 143.22, 133.66, 122.77, 118.41, 34.20, 31.81, 29.65, 29.49, 29.09, 27.05, 24.72, 22.56, 22.45, 14.92. MS (*m/z* %): 355 ($M^+ + 1$, 40), 354 (M^+, 34), 237 (25), 181 (25), 117 (100). Anal. calcd. for $C_{24}H_{38}N_2$: C, 81.31; H, 10.79; N, 7.90. Found: C, 81.88; H, 10.73; N, 7.94%.

6.1.3. 2-[(8Z, 11R)-11-Hydroxyheptadec-8-enyl]-1H-benzimidazole (*4cA*)

Yellow oily liquid; yield: 88%; IR (KBr): ν_{max} cm^{-1} 3390, 1650, 1580. ^{1}H NMR δ (ppm): 9.25 (s, 1H, N–H), 6.72–6.70 (m, 4H, Ar–H), 5.42 (m, 2H, –CH=CH–), 3.66 (m, 1H, C-11 methine proton), 2.32 (t, 2H, $J = 7.19$ Hz, α to benzimidazole ring), 2.27 (m, 1H, –OH), 2.02 (m, 4H, –CH_2–CH=CH–CH_2–), 1.57 (m, 2H, β to benzimidazole ring), 1.39 (br s, 18H, chain CH_2), 0.88 (dist. t, 3H, CH_3). ^{13}C NMR δ (ppm): 143.44, 134.09, 123.22, 117.81, 34.02, 31.81, 29.56, 29.94, 29.90, 27.51, 24.27, 22.65, 22.54, 14.17. MS (*m/z* %): 371 ($M^+ + 1$, 38), 370 (M^+, 34), 255 (20), 241 (100), 173 (15). Anal. calcd. for $C_{24}H_{38}N_2O$: C, 77.79; H, 10.33; N, 7.56. Found: C, 77.16; H, 10.39; N, 7.51%.

*6.1.4. 2-[(8R, 11Z)-8-Hydroxyheptadec-11-enyl]-1H-benzimidazole (**4dA**)*

Yellow oily liquid; yield: 88%; IR (KBr): ν_{max} cm^{-1} 3355, 1626, 1596. ^1H NMR δ (ppm): 9.04 (s, 1H, N–H), 6.78–6.76 (m, 4H, Ar–H), 5.44 (m, 2H, –CH=CH–), 3.66 (m, 1H, C-8 methine proton), 2.31 (t, 2H, $J = 7.20$ Hz, α to benzimidazole ring), 2.11 (m, 1H, –OH), 2.04 (m, 4H, $-CH_2-CH=CH-CH_2-$), 1.61 (m, 2H, β to benzimidazole ring), 1.40 (br s, 18H, chain CH_2), 0.88 (dist. t, 3H, CH_3). ^{13}C NMR δ (ppm): 143.66, 133.17, 123.22, 118.12, 34.25, 31.41, 29.58, 29.39, 29.23, 27.26, 24.72, 24.22, 14.91. MS (*m/z* %): 371 ($M^+ + 1$, 20), 370 (M^+, 45), 299 (10), 245 (100), 131 (15). Anal. calcd. for $C_{24}H_{38}N_2O$: C, 77.79; H, 10.33; N, 7.56. Found: C, 77.21; H, 10.27 N, 7.53%.

*6.1.5. 2-(Dec-9-enyl)-5-nitro-1H-benzimidazole (**4aB**)*

Light yellow oily liquid; yield: 85%; IR (KBr): ν_{max} cm^{-1} 3375, 1660, 1575. ^1H NMR δ (ppm): 9.22 (s, 1H, N–H), 7.12 (d, 1H, Ar–H), 7.04 (m, 1H, Ar–H), 6.91 (m, 1H, Ar–H), 5.82 (tdd, 1H, $J_{H-^8CH_2} = 6.6$ Hz, $J_{H-H_Z} = 10.2$ Hz, $J_{H-H_E} = 17.1$ Hz, CH_2=C*H*–), 5.02 (dd, 1H, $J_{H_Z-H} = 10.2$ Hz, $J_{H_Z-H_E} = 1.2$ Hz, H_ZC=CH), 4.90 (dd, 1H, $J_{H_E-H} = 17.1$ Hz, $J_{H_E-H_Z} = 1.2$ Hz, H_EC=CH–), 2.28 (t, 2H, $J = 7.17$ Hz, α to benzimidazole ring), 2.04 (m, 2H, $-CH_2-CH=CH_2$), 1.66 (m, 2H, β to benzimidazole ring), 1.31 (br s, 10H, chain CH_2). ^{13}C NMR δ (ppm): 143.12, 139.01, 136.22, 130.12, 131.65, 122.26, 117.31, 33.91, 31.61, 28.22, 27.19, 22.33. MS (*m/z* %): 302 ($M^+ + 1$, 10), 301 (M^+, 82), 274 (10), 176 (100), 162 (60). Anal. calcd. for $C_{17}H_{23}N_3O_2$: C, 67.76; H, 7.68; N, 13.94. Found: C, 67.30; H, 7.73; N, 13.99%.

*6.1.6. 2-(Heptadec-8-enyl)-5-nitro-1H-benzimidazole (**4bB**)*

Pale yellow oily liquid; yield: 84%; IR (KBr): ν_{max} cm^{-1} 3352, 1636, 1580. ^1H NMR δ (ppm): 9.21 (s, 1H, N–H), 7.13 (d, 1H, Ar–H), 7.04 (m, 1H, Ar–H), 6.90 (m, 1H, Ar–H), 5.38 (m, 2H, –CH=CH–), 2.34 (t, 2H, $J = 7.24$ Hz, α to benzimidazole ring), 2.02 (m, 4H, $-CH_2-CH=CH-CH_2-$), 1.63 (m, 2H, β to benzimidazole ring), 1.30 (br s, 20 H, chain CH_2), 0.89 (dist. t, 3H, CH_3). ^{13}C NMR δ (ppm): 143.62, 136.06, 131.33, 129.71, 123.44, 118.13, 34.19, 31.41, 29.53, 28.99, 27.41, 22.32, 22.45, 14.15. MS (*m/z* %): 400 ($M^+ + 1$, 20), 399 (M^+, 25), 286 (75), 190 (70), 162 (100). Anal. calcd. for $C_{24}H_{37}N_3O_2$: C, 72.15; H, 9.33; N, 10.51. Found: C, 72.70; H, 9.28; N, 10.56%.

*6.1.7. 2-[(8Z, 11R)-11-Hydroxyheptadec-8-enyl]-5-nitro-1H-benzimidazole (**4cB**)*

Yellow oily liquid; yield: 82%; IR (KBr): ν_{max} cm^{-1}3355, 1640, 1580. ^1H NMR δ (ppm): 9.25 (s, 1H, N–H), 7.13 (d, 1H, Ar–H), 7.04 (m, 1H, Ar–H), 6.91 (m, 1H, Ar–H), 5.45 (m, 2H, –CH=CH–), 3.68 (m, 1H, C-11 methine proton), 2.33 (t, 2H, $J = 7.31$ Hz, α to benzimidazole ring), 2.23 (m, 1H, –OH), 2.04 (m, 4H, $-CH_2-CH=CH-CH_2-$), 1.61 (m, 2H, β to benzimidazole ring), 1.36 (br s, 18H, chain CH_2), 0.88 (dist. t, 3H, CH_3). ^{13}C NMR δ (ppm): 144.13, 135.44, 131.19, 129.31, 123.33, 117.71, 37.11, 34.26, 31.83, 29.61, 27.10, 25.81, 23.11, 22.15, 15.06. MS (*m/z* %): 416 ($M^+ + 1$, 35), 415 (M^+, 70), 330 (100), 300 (70), 260 (20). Anal. calcd. for $C_{24}H_{37}N_3O_3$: C, 69.37; H, 8.97; N, 10.11. Found: C, 69.79; H, 8.92; N, 10.16%.

*6.1.8. 2-[(8R, 11Z)-8-Hydroxyheptadec-11-enyl]-5-nitro-1H-benzimidazole (**4dB**)*

Yellow oily liquid; yield: 80%; IR (KBr): ν_{max} cm^{-1} 3390, 1630, 1584. ^1H NMR δ (ppm): 9.20 (s, 1H, N–H), 7.16 (d, 1H, Ar–H), 7.04 (m, 1H, Ar–H), 6.93 (m, 1H, Ar–H), 5.43 (m, 2H, –CH=CH–), 3.67 (m, 1H, C-8 methine proton), 2.36 (t, 2H, $J = 7.29$ Hz, α to benzimidazole ring), 2.21 (m, 1H, –OH), 2.04 (m, 4H, $-CH_2-CH=CH-CH_2-$), 1.64 (m, 2H, β to benzimidazole ring), 1.42 (br s, 18H, chain CH_2), 0.87 (dist. t, 3H, CH_3). ^{13}C NMR 1 δ (ppm): 144.23, 135.64, 131.39, 129.41, 123.83, 117.71, 37.51, 34.66, 31.38, 29.51, 27.43, 25.44, 23.11, 22.15, 15.16. MS (*m/z* %): 416 ($M^+ + 1$, 10), 415 (M^+, 70), 344 (100), 290 (25), 246 (20). Anal. calcd. for $C_{24}H_{37}N_3O_3$: C, 69.37; H, 8.97; N, 10.11. Found: C, 69.84; H, 8.92; N, 10.13%.

*6.1.9. 2-(Dec-9-enyl)-5-chloro-1H-benzimidazole (**4aC**)*

Colorless oily liquid; yield: 88%; IR (KBr): ν_{max} cm^{-1} 3368, 1640, 1578. ^1H NMR ($CDCl_3$) (δ): 9.01 (s, 1H, N–H), 7.43–7.31 (m, 3H, Ar–H), 5.82 (tdd, 1H, $J_{H-^8CH_2} = 6.6$ Hz, $J_{H-H_Z} = 10.2$ Hz, $J_{H-H_E} = 17.1$ Hz, CH_2=C*H*–), 5.02 (dd, 1H, $J_{H_Z-H} = 10.2$ Hz, $J_{H_Z-H_E} = 1.2$ Hz, H_ZC=CH), 4.90 (dd, 1H, $J_{H_E-H} = 17.1$ Hz, $J_{H_E-H_Z} = 1.2$ Hz, H_EC=CH–), 2.31 (t, 2H, $J = 7.33$ Hz, α to benzimidazole ring), 2.04 (m, 2H, $-CH_2-CH=CH_2$), 1.63 (m, 2H, β to benzimidazole ring), 1.33 (br s, 10H, chain CH_2). ^{13}C NMR ($CDCl_3$) (δ): 142.81, 141.31, 132.91, 131.61, 129.71, 128.91, 124.71, 123.46, 29.71, 28.36, 27.91, 23.91, 22.45, 14.81. MS (*m/z* %): 291 ($M^+ + 1$, 10), 290 (M^+, 85), 263 (100), 179 (25), 151 (40). Anal. calcd. for $C_{17}H_{23}ClN_2$: C, 70.22; H, 7.96; N, 9.63. Found: 70.80; H, 7.92; N, 9.58%.

*6.1.10. 2-(Heptadec-8-enyl)-5-chloro-1H-benzimidazole (**4bC**)*

Light yellow oily liquid; yield: 87%; IR (KBr): ν_{max} cm^{-1} 3370, 1655, 1589. ^1H NMR δ (ppm): 9.12 (s, 1H, N–H), 7.55–7.20 (m, 3H, Ar–H), 5.44 (m, 2H, –CH=CH–), 2.24 (t, 2H, $J = 7.44$ Hz, α to benzimidazole ring), 2.04 (m, 4H, $-CH_2-CH=CH-CH_2-$), 1.56 (m, 2H, β to benzimidazole ring), 1.29 (br s, 20 H, chain CH_2), 0.87 (dist. t, 3H, CH_3). ^{13}C NMR δ (ppm): 143.48, 133.85, 131.24, 129.57, 127.71, 121.61, 117.81, 37.41, 34.21, 33.92, 29.56, 29.13, 25.84, 23.13, 22.35, 14.12. MS (*m/z* %): 389 ($M^+ + 1$, 30), 388 (M^+, 75), 275 (15), 165 (100), 151 (80). Anal. calcd. for $C_{24}H_{37}ClN_2$: C, 74.11; H, 9.58; N, 7.20. Found: C, 74.68; H, 9.63; N, 7.16%.

*6.1.11. 2-[(8Z, 11R)-11-Hydroxyheptadec-8-enyl]-5-chloro-1H-benzimidazole (**4cC**)*

Yellow oily liquid; yield: 87%; IR (KBr): ν_{max} cm^{-1} 3412, 1648, 1572. ^1H NMR δ (ppm): 9.25 (s, 1H, N–H), 7.43–7.31 (m, 3H, Ar–H), 5.46 (m, 2H, –CH=CH–), 3.67 (m, 1H, C-11 methine proton), 2.33 (t, 2H, $J = 7.12$ Hz, α to

benzimidazole ring), 2.27 (m, 1H, −OH), 2.02 (m, 4H, CH_2−CH=CH−CH_2), 1.57 (m, 2H, β to benzimidazole ring), 1.39 (br s, 18H, chain CH_2), 0.88 (dist. t, 3H, CH_3). ^{13}C NMR δ (ppm): 142.98, 133.76, 130.99, 129.76, 127.80, 121.53, 119.01, 37.03, 34.12, 33.57, 29.34, 28.37, 25.71, 23.91, 22.11, 15.17. MS (*m/z* %): 405 ($M^+ + 1$, 15), 404 (M^+, 70), 319 (100), 249 (85), 207 (90). Anal. calcd. for $C_{24}H_{37}ClN_2O$: C, 71.18; H, 9.20; N, 6.91. Found: C, 71.66; H, 9.23; N, 6.87%.

*6.1.12. 2-[(8R, 11Z)-8-Hydroxyheptadec-11-enyl]-5-chloro-1H-benzimidazole (**4dC**)*

Yellow oily liquid; yield: 86%; IR (KBr): ν_{max} cm^{-1} 3349, 1629, 1590. ^{1}H NMR δ (ppm): 9.29 (s, 1H, N−H), 7.46−7.33 (m, 3H, Ar−H), 5.45 (m, 2H, −CH=CH−), 3.68 (m, 1H, C-8 methine proton), 2.36 (t, 2H, $J = 7.23$ Hz, α to benzimidazole ring), 2.29 (m, 1H, −OH), 2.04 (m, 4H, $-CH_2-CH=CH-CH_2-$), 1.62 (m, 2H, β to benzimidazole ring), 1.28 (br s, 18H, chain CH_2), 0.88 (dist. t, 3H, CH_3). ^{13}C NMR δ (ppm): 142.68, 133.67, 130.89, 129.67, 127.82, 121.43, 119.01, 37.53, 34.41, 33.51, 29.43, 28.32, 25.17, 23.22, 22.13, 15.19. MS (*m/z* %): 405 ($M^+ + 1$, 10), 404 (M^+, 80), 333 (40), 279 (85), 179 (65). Anal. calcd. for $C_{24}H_{37}ClN_2O$: C, 71.18; H, 9.20; N, 6.91. Found: C, 71.71; H, 9.16; N, 6.94% .

*6.1.13. 2-(Dec-9-enyl)-4,5,6,7-tetrahydro-1H-benzimidazole (**7aX**)*

Pale yellow oily liquid; yield: 90%; IR (KBr): ν_{max} cm^{-1} 3338, 1632, 1580. ^{1}H NMR δ (ppm): 9.01(s, 1H, N−H), 5.82 (tdd, 1H, $J_{H-^8CH_2} = 6.6$ Hz, $J_{H-H_Z} = 10.2$ Hz, $J_{H-H_E} = 17.1$ Hz, CH_2=C*H*−), 5.02 (dd, 1H, $J_{H_Z-H} = 10.2$ Hz, $J_{H_Z-H_E} = 1.2$ Hz, H_ZC=CH), 4.90 (dd, 1H, $J_{H_E-H} = 17.1$ Hz, $J_{H_E-H_Z} = 1.2$ Hz, H_EC=CH−), 2.34 (t, 2H, $J = 7.36$ Hz, α to benzimidazole ring), 2.03 (m, 2H, $-CH_2-CH=CH_2$), 1.87 (m, 2H, −CH− ring), 1.69 (m, 2H, β to imidazole ring), 1.50 (m, 8H, $-CH_2-$ ring), 1.30 (br s, 10H, chain CH_2). ^{13}C NMR δ (ppm): 170.33, 139.81, 117.61, 64.01, 37.62, 31.91, 29.88, 28.35, 24.57, 22.50, 22.21. MS (*m/z* %): 263 ($M^+ + 1$, 30), 262 (M^+, 70), 235 (100), 179 (70), 123 (60). Anal. calcd. for $C_{17}H_{30}N_2$: C, 77.82; H, 11.51; N, 10.67. Found: C, 77.30; H, 11.47; N, 10.70%.

*6.1.14. 2-(Heptadec-8-enyl)-4,5,6,7-tetrahydro-1H-benzimidazole (**7bX**)*

Light yellow oily liquid; yield: 89%; IR (KBr): ν_{max} cm^{-1} 3356, 1641, 1593. ^{1}H NMR δ (ppm): 9.12 (s, 1H, N−H), 5.38 (m, 2H, −CH=CH−), 2.34 (t, 2H, $J = 7.30$ Hz, α to benzimidazole ring), 2.02 (m, 4H, $-CH_2-CH=CH-CH_2-$), 1.86 (m, 2H, −CH− ring), 1.66 (m, 2H, β to imidazole ring), 1.50 (m, 8H, $-CH_2-$ ring), 1.32 (br s, 20 H, chain CH_2), 0.88 (dist. t, 3H, CH_3). ^{13}C NMR δ (ppm): 169.97, 63.91, 36.92, 31.88, 28.22, 27.36, 24.63, 22.49, 22.12, 21.90, 14.91. MS (*m/z* %): 361 ($M^+ + 1$, 40), 360 (M^+, 85), 247 (45), 207 (50), 193 (67). Anal. calcd. for $C_{24}H_{44}N_2$: C, 79.95; H, 12.29; N, 7.76. Found: C, 79.40; H, 12.36; N, 7.72%.

*6.1.15. 2-[(8Z, 11R)-11-Hydroxyheptadec-8-enyl]-4,5,6,7-tetrahydro-1H-benzimidazole (**7cX**)*

Yellow oily liquid; yield: 88%; IR (KBr): ν_{max} cm^{-1} 3350, 1620, 1592. ^{1}H NMR δ (ppm): 9.25 (s, 1H, N−H), 5.42 (m, 2H, −CH=CH−), 3.66 (m, 1H, C-11 methine proton), 2.32 (t, 2H, $J = 7.28$ Hz, α to benzimidazole ring), 2.27 (m, 1H, −OH), 2.02 (m, 4H, $-CH_2-CH=CH-CH_2-$), 1.88 (m, 2H, −CH− ring), 1.67 (m, 2H, β to imidazole ring), 1.50 (m, 8H, $-CH_2-$ ring), 1.39 (br s, 18H, chain CH_2), 0.88 (dist. t, 3H, CH_3). ^{13}C NMR δ (ppm): 169.99, 71.72, 63.89, 36.98, 34.22, 33.63, 31.66, 28.61, 27.63, 24.56, 22.91, 22.11, 21.81, 14.73. MS (*m/z* %): 377 ($M^+ + 1$, 15), 376 (M^+, 70), 291(10), 247 (85), 123 (100). Anal. calcd. for $C_{24}H_{44}N_2O$: C, 76.55; H, 11.77; N, 7.43. Found: C, 76.01; H, 11.82; N, 7.40%.

*6.1.16. 2-[(8R, 11Z)-8-Hydroxyheptadec-11-enyl]-4,5,6,7-tetrahydro-1H-benzimidazole (**7dX**)*

Yellow oily liquid; yield: 87%; IR (KBr): ν_{max} cm^{-1} 3358, 1658, 1577. ^{1}H NMR δ (ppm): 9.72 (s, 1H, N−H), 5.44 (m, 2H, −CH=CH−), 3.68 (m, 1H, C-8 methine proton), 2.28 (t, 2H, $J = 7.39$ Hz, α to benzimidazole ring), 2.21 (m, 1H, −OH), 2.03 (m, 4H, $-CH_2-CH=CH-CH_2-$), 1.87 (m, 2H, −CH− ring), 1.69 (m, 2H, β to imidazole ring), 1.52 (m, 2H, $-CH_2-$ ring), 1.36 (br s, 18H, chain CH_2), 0.88 (dist. t, 3H, CH_3). ^{13}C NMR δ (ppm): 169.87, 71.73, 64.01, 36.89, 34.32, 33.36, 31.66, 28.64, 27.53, 24.65, 22.98, 22.11, 21.81, 14.69. MS (*m/z* %): 377 ($M^+ + 1$, 30), 376 (M^+, 50), 305 (10), 251 (75), 123 (100). Anal. calcd. for $C_{24}H_{44}N_2O$: C, 76.55; H, 11.77; N, 7.43. Found: C, 76.98; H, 11.72; N, 7.47%.

*6.1.17. 2-(Dec-9-enyl)-1H-imidazole (**10aY**)*

Colorless oily liquid: yield: 89%; IR (KBr): ν_{max} cm^{-1} 3354, 1642, 1598. ^{1}H NMR δ (ppm): 9.81(s, 1H, N−*H*), 5.82 (tdd, 1H, $J_{H-^8CH_2} = 6.6$ Hz, $J_{H-H_Z} = 10.2$ Hz, $J_{H-H_E} = 17.1$ Hz, CH_2=C*H*−), 5.60 (m, 2H, −CH=CH−), 5.02 (dd, 1H, $J_{H_Z-H} = 10.2$ Hz, $J_{H_Z-H_E} = 1.2$ Hz, H_ZC=CH), 4.90 (dd, 1H, $J_{H_E-H} = 17.1$ Hz, $J_{H_E-H_Z} = 1.2$ Hz, H_EC=CH−), 2.31 (t, 2H, $J = 7.16$ Hz, α to imidazole ring), 2.04 (m, 2H, $-CH_2-CH=CH_2$), 1.66 (m, β to imidazole ring), 1.36 (br s, 10H, chain CH_2). ^{13}C NMR δ (ppm): 152.3, 130.9, 125.9, 33.6, 32.8, 30.1, 23.2, 14.3. MS (*m/z* %): 207 ($M^+ + 1$, 20), 206 (M^+, 22), 176 (36), 109 (100), 81 (100). Anal. calcd. for $C_{13}H_{22}N_2$: C, 75.69; H, 10.74; N, 13.57. C, 75.22; H, 10.70; N, 13.63%.

*6.1.18. 2-(Heptadec-8-enyl)-1H-imidazole (**10bY**)*

Pale yellow oily liquid: yield: 88%; IR (KBr): ν_{max} cm^{-1} 3367, 1644, 1590. ^{1}H NMR δ (ppm): 9.77 (s, 1H, N−H), 5.62 (m, 4H, −CH=CH−), 2.33 (t, 2H, $J = 7.35$ Hz, α to imidazole ring), 2.05 (m, 4H, $-CH_2-CH=CH-CH_2-$), 1.62 (m, 2H, β to imidazole ring), 1.29 (br s, 20H, chain CH_2), 0.87 (dist. t, 3H, CH_3). ^{13}C NMR δ (ppm): 152.7, 131.7, 126.8, 33.3, 32.2, 30.4, 23.6, 14.3 MS (*m/z* %): 305 ($M^+ + 1$, 40), 304 (M^+, 22), 191 (31), 165 (31), 67 (100).

Anal. calcd. for $C_{20}H_{36}N_2$: C, 78.89; H, 11.91; N, 9.20. C, 78.35; H, 11.86; N, 9.15%.

*6.1.19. 2-[(8Z, 11R)-11-Hydroxyheptadec-8-enyl]-1H-imidazole (**10cY**)*

Yellow oily liquid: yield: 86%; IR (KBr): ν_{max} cm^{-1} 3378, 1655, 1597. ^1H NMR δ (ppm): 9.81 (s, 1H, N–H), 5.66 (m, 4H, –CH=CH–), 3.59 (m, 1H, C-11 methine proton), 2.36 (t, 2H, $J = 7.39$ Hz, α to imidazole ring), 2.32 (m, 1H, –OH), 2.03 (m, 4H, $-CH_2-CH=CH-CH_2-$), 1.62 (m, 2H, β to imidazole ring), 1.29 (br s, 18H, chain CH_2), 0.88 (dist. t, 3H, CH_3). ^{13}C NMR δ (ppm): 152.94, 131.41, 126.53, 71.91, 36.98, 34.22, 33.63, 31.66, 28.54, 27.36, 24.65, 22.19, 22.11, 21.81, 14.34. MS (*m/z* %): 321 ($M^+ + 1$, 40), 320 (M^+, 22), 235 (100), 191 (31), 165 (100). Anal. calcd. for $C_{20}H_{36}N_2O$: C, 74.96; H, 11.31; N, 8.74. C, 74.61; H, 11.37; N, 8.70%.

*6.1.20. 2-[(8R, 11Z)-8-Hydroxyheptadec-11-enyl]-1H-imidazole (**10dY**)*

Yellow oily liquid: yield: 86%; IR (KBr): ν_{max} cm^{-1} 3354, 1628, 1578. ^1H NMR δ (ppm): 9.81 (s, 1H, N–H), 5.59 (m, 4H, –CH=CH–), 3.61 (m, 1H, C-8 methine proton), 2.41 (t, 2H, $J = 7.44$ Hz, α to imidazole ring), 2.33 (m, 1H, –OH), 2.05 (m, 4H, $-CH_2-CH=CH-CH_2-$), 1.65 (m, 2H, β to imidazole ring), 1.30 (br s, 18H, chain CH_2), 0.89 (dist. t, 3H, CH_3). ^{13}C NMR δ (ppm): 152.88, 131.39, 126.35, 71.68, 36.89, 34.56, 33.34, 31.48, 28.45, 27.63, 24.56, 22.91, 22.18, 21.71, 14.37. MS (*m/z* %): 321 ($M^+ + 1$, 38), 320 (M^+, 46), 249 (100), 195 (18), 165 (73). Anal. calcd. for $C_{20}H_{36}N_2O$: C, 74.96; H, 11.31; N, 8.74. C, 74.48; H, 11.26; N, 8.69%.

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