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# Design, Synthesis of a Novel N-substituted Benzimidazole Derivatives

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## Abstract

**Heterocycles containing benzimidazole scaffold are of great interest because they represent an important class of various synthetic compounds which have beneficial biological activities. In this article, the synthesis of new N-substituted benzimidazole derivatives 4a-c, 5a-c, 6a-c, 7b-c, 8a-b and 9 are described. These compounds were synthesized by first designing the benzimidazole derivatives (3a-c). The derivative 3a was obtained from the condensation reaction between 4-nitroorthophenylenediamine and ethyl formate in the presence of hydrochloric acid. Products 3b and 3c were obtained by methylation of 2-mercaptobenzimidazole 2a and its 5-nitro derivative 2b by the action of methyl iodide in ethanol. Reaction of the derivatives (3a-c) with various functionalized halides in a basic medium led to the N-substituted benzimidazole derivatives. The use of dihalogenated compounds has led to the duplication of the molecule. The structures of the synthesized compounds were characterized by 1H, 13C Nuclear Magnetic Resonance (NMR) spectroscopy, and High-Resolution Mass Spectrometry (HRMS) analyses.**

***Keywords:* *Benzimidazole, Condensation, Functionalized halides, Basic medium, N-substituted benzimidazoles***

## Introduction

The benzimidazole scaffold is an important heterocycle used as a pharmacophore for several drugs. It has been a topic of particular interest in medicinal chemistry for the development of molecules with pharmaceutical or biological applications. In fact, there are several derivatives of it in the market. Thiabendazole, albendazole, mebendazole and flubendazole are used as anthelmintics, omeprazole and lansoprazole are used as proton pump inhibitors, and astemizole is an antihistaminic drug. Structural variations around this ring have led to many derivatives with several biological activities including antioxidant [1-2], antimicrobial [3-7], antiviral, including anti-HIV [6-10], anti-inflammatory [11-14], anticancer [15-19] and antihypertensive [20,21]. Of all the structural variants, those affecting the -1, -2 and -5 positions were the most significant. The appearance, orientation or optimization of biological properties depend on the nature of the substituents at these positions [22]. Considering the importance of substitution at these positions, this work shows new N-substituted benzimidazole derivatives with a thiomethyl group at the -2 position and/or a nitro group at the -5 position. Substitutions at the -1 position were inspired by the chemical class of 5-nitroimidazoles, antibiotics, with metronidazole being the leader **FIG.1**

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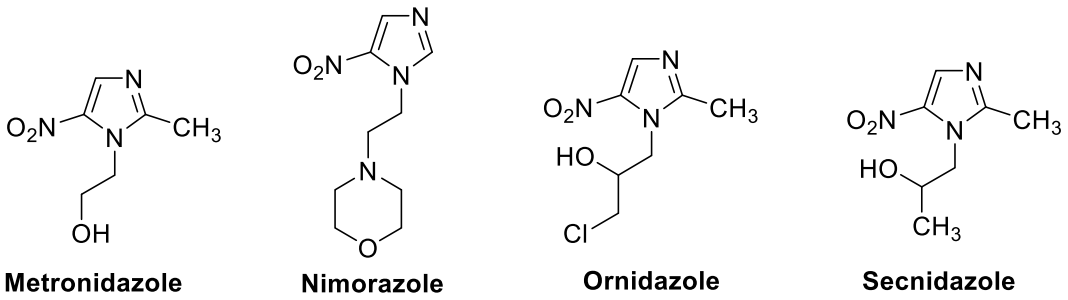


FIG.1. **Drugs developed around 5-nitroimidazole structures.**

## Materials and Methods

The solvents and reagents are of high quality and come from Aldrich Chemical or Fischer Scientific (France). The reactions were followed by TLC on pre-coated Merck 60 F254 silica gel plates and revealed using a UV lamp (6 W, 254 nm, and/or 365 nm). The purification of the products was carried out on a Merck G60 silica gel column. Melting points (m.p °C) were determined using a temperature gradient (40°C-265°C) Kofler bench.

For all compounds, the Nuclear Magnetic Resonance (NMR) spectra of 1H and 13C were recorded on a Brucker 300 advance device with deuterated chloroform ($CDCl_3$), acetone (Acetone-$D_6$) and dimethyl sulfoxide (DMSO-$D_6$) as the solvents, while tetramethylsilane (TMS) was used as an internal standard for chemical displacements (δ) expressed in ppm. The NMR spectra description use the following symbols: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quadruplet), m (multiplet), br (broad). The mass spectra were recorded on a JEOL JMS DX300 spectrometer in ESI mode (electrospray/quadripolar ionization or ESI mass).

**Synthesis of 5-nitro-1H-benzimidazole (3a)**

A mixture of 4-nitro-orthophenylenediamine (equation **1a-b**) (1 eq, 33 mmol), 30 mL of ethyl formate and 6 mL of hydrochloric acid was refluxed under magnetic stirring for 48 hours. After cooling the reaction medium, the hydrochloric acid was neutralized with potassium carbonate ($K_2CO_3$). The precipitate obtained was filtered and then washed with hexane. Compound **3a** was obtained as a purple powder in 95 % yield, m.p = 217-219°C. 1H NMR (DMSO-$D_6$, 300 MHz), δ (ppm): 12.36 (s, 1H, NH), 8.29-7.76 (m, 4H, HAr). 13C NMR (DMSO-$D_6$, 75 MHz) δ (ppm): 145.15, 144.39, 136.49, 132.58, 120.08, 115.37, 111.6. HRMS (ESI) Calc. for $C_7H_5N_3O_2$ (M + H+) = 164.038 Found = 164.041.

**General method for the synthesis of compounds 2**

To a solution of o-phenylenediamine (1 eq, 46 mmol) in 15 mL of dimethylformamide (DMF) cooled in an ice bath, carbon disulfide ($CS_2$) (5 eq, 231 mmol) was added dropwise. The mixture was stirred at room temperature for 24 to 48 h and then 200 mL of water was added. The resulted precipitate was filtered, washed several times with water, and dried in an oven (80°C). The crude was recrystallized in a water/ethanol mixture (50/50).

**2-mercaptobenzimidazole (2a)**

Reaction time: 24 h. Beige crystals, yield = 82 %, m.p > 265 °C. 1H NMR (DMSO-$D_6$, 300 MHz)  (ppm): 12.54 (s, 1H, NH), 7.16-7.01 (m, 4H, HAr), 3.37 (s, 1H, SH). 13C NMR (DMSO-$D_6$, 75 MHz)  (ppm): 167.23, 131.36, 121.44, 108.59. HRMS (ESI) Calc. for $C_7H_6N_2S$ (M + H+) = 151.025 Found = 151.028.

**5-nitro-2-mercapto-1H-benzimidazole (2b)**

Reaction time: 48 h, orange crystals, yield = 92 %, m.p = 264°C-266°C. 1H NMR (DMSO-$D_6$, 300 MHz) δ (ppm): 12.54 (s, 1H, NH), 8.30-7.50 (m, 4H, HAr), 2.50 (s, 1H, SH). 13C NMR (DMSO-$D_6$, 75 MHz) δ (ppm): 171.49, 142.48, 137.29, 132.15, 118.82, 109.11, 104.56. HRMS (ESI) Calc. for $C_7H_5N_3O_2S$ (M + H+) = 196.010 Found = 196.0415.

**General method for the synthesis of 2-thiomethyl-1H-benzimidazole (3b and 3c)**

To **compound 2** (1 eq, 6.66 mmol) dissolved in 10 mL of anhydrous ethanol, was added iodomethane (1.1 eq, 7.33 mmol). The mixture was brought to reflux under magnetic stirring. The reaction was followed by thin layer chromatography (TLC) for 7 h. At the end of reaction, ethyl acetate was added to the mixture. Then a precipitate was obtained, filtered and dissolved in ethanol.

Addition of a 30% sodium hydrogen carbonate solution to the mixture led to a new precipitate which was filtered, washed with water, wrung out and dried in an oven.

**2-thiomethyl-1H-benzimidazole (3b)**

Brown powder, yield = 67 %, m.p = 210-212°C. 1H NMR (DMSO-$D_6$, 300 MHz) δ (ppm): 13.5 (s, 1H, NH), 7.67-7.64 (m, 2H, HAr), 7.46-7.43 (m, 2H, HAr), 2.91 (s, 3H, $SCH_3$). 13C NMR (DMSO-$D_6$, 75 MHz) δ (ppm): 152.72, 132.12, 125.11, 112.85, 14.91. HRMS (ESI) Calc. for $C_8H_8N_2S$ (M + H+) = 165.041 Found = 165.045.

**2-thiomethyl-5-nitro-1H-benzimidazole (3c)**

Yellow powder, yield = 83 %, m.p = 218-220°C. 1H NMR (DMSO-$D_6$, 300 MHz) δ (ppm): 10.5 (s, 1H, NH), 7.3-8.5 (m, 3H, HAr), 2.70 (s, 3H, $CH_3$). 13C NMR (DMSO-$D_6$, 75 MHz) δ (ppm): 144.25, 141.70, 139.75, 117.55, 112.98, 109.92, 13.68. HRMS (ESI) Calc. for $C_8H_7N_3O_2S$ (M + H+) = 210.026 Found = 210.028.

**General procedure for the synthesis of N-substituted benzimidazole**

To benzimidazole derivatives **(3a-c)** (1 eq, 6 mmol) dissolved in 10 mL of DMSO, were added potassium carbonate (2 eq, 12 mmol) and functionalized 2-chloroethanol halides (4 eq, 24 mmol). The mixture was heated to 50°C with magnetic stirring and the reaction was monitored by TLC. At the end of the reaction, the mixture was then diluted with 50 mL of water. The mixture was extracted with dichloromethane (2 x 50 mL), dried over magnesium sulfate and the solvent was evaporated. The residue was purified by column chromatography with silica gel.

**2-(5-nitro-1H-benzimidazol-1-yl) ethanol (4a)**

Reaction time: 4 h, orange crystals, yield = 52 %, m.p = 98°C-100°C. 1H NMR (Acetone-$D_6$, 300 MHz) δ (ppm): 8.62-7.80 (m, 4H, HAr), 4.56 (s, 1H, OH), 4.52 (t, J = 5.10 Hz, 2H, $CH_2N$), 3.99 (t, J = 5.10 Hz, 2H, $CH_2OH$). 13C NMR (Acetone-$D_6$, 75MHz) δ (ppm): 149.06, 120.50, 118.61, 117.80, 116.63, 111.79, 108.57, 61.47, 48.69. HRMS (ESI) Calc. for $C_7H_5N_3O_2S$ (M + H+) = 208.064 Found = 208.061.

**2-(2-thiomethyl-1H-benzimidazol-1-yl) ethanol (4b)**

Reaction time: 24 h, orange crystals, yield = 75 %, m.p = 136°C-138°C. 1H NMR (DMSO-$D_6$, 300 MHz) δ (ppm): 7.46-7.55 (m, 2H, HAr), 7.13-7.17 (m, 2H, HAr), 5.00 (t, J = 5.40 Hz, 1H, OH), 4.17 (t, J = 5.70 Hz, 2H, $CH_2N$), 3.68-3.73 (m, 2H, $CH_2O$), 2.71 (s, 3H, $CH_3$). 13C NMR (DMSO-$D_6$, 75 MHz) δ (ppm): 152.48, 142.92, 136.75, 121.21, 121.14, 117.31, 109.75, 59.14, 46.25, 14.35. HRMS (ESI) Calc. for $C_{10}H_{12}N_2OS$ (M + H+) = 209.067 Found = 209.071.

**2-(2-thiomethyl-5-nitro-1H-benzimidazol-1-yl) ethanol (4c)**

Reaction time: 24 h, yellow crystals, yield = 72 %, m.p = 152°C-154°C. 1H NMR (DMSO-$D_6$, 300 MHz) δ (ppm): 7.5-8.5 (m, 3H, HAr), 5.00 (t, J = 5.40 Hz, 1H, OH), 4.3 (m, 2H, $CH_2N$), 3.7 (m, 2H, $CH_2O$), 2.70 (s, 3H, $CH_3$). 13C NMR (DMSO-$D_6$, 75 MHz) δ (ppm): 162.23, 155.52, 147.37, 136.38, 117.13, 112.87, 110.03, 106.56, 59.00, 47.00, 14.28. HRMS (ESI) Calc. for $C_{10}H_{11}N_3O_3S$ (M + H+) = 254.052 Found = 254.049.

**Bis (5-nitro-benzimidazol-1-yl) methane (5a)**

Reaction time: 4 h, yellow crystals, yield = 71 %, m.p > 266°C. 1H NMR (Acetone-$D_6$, 300 MHz) δ (ppm): 8.62-7.80 (m, 8H, HAr), 6.74 (s, 2H, $CH_2$). 13C NMR (Acetone-$D_6$, 75 MHz) δ (ppm): 149.25, 147.70, 143.54, 132.14, 120.26, 115.98, 107.77, 148.06, 142.74, 137.01; 118.85, 118.12, 111.32, 52.87. HRMS (ESI) Calc. for $C_{15}H_{10}N_6O_4$ (M + H+) = 339.076 Found = 339.074.

**Bis(2-thiomethyl-1H-benzimidazol-1-yl) methane (5b)**

Reaction time: 2 h, brown powder, yield = 76 %, m.p = 262°C-264°C. 1H NMR (DMSO-$D_6$, 300 MHz) δ (ppm): 7.64-7.61 (m, 2H, HAr), 7.45-7.42 (m, 2H, HAr), 7.22-7.18 (m, 4H, HAr), 6.61 (s, 2H, $CH_2$), 2.77 (s, 6H, 2 $CH_3$). 13C NMR (DMSO-$D_6$, 75 MHz) δ (ppm): 152.60, 142.66, 135.53, 121.94, 121.85, 117.74, 109.37, 52.36, 14.36. HRMS (ESI) Calc. for $C_{17}H_{14}N_6O_4S_2$ (M + H+) = 341.052 Found = 341.055.

**Bis(2-thiomethyl-5nitro-1H-benzimidazol-1-yl) methane (5c)**

Reaction time: 3 h, yellow crystals, yield = 68 %, m.p = 258°C-260°C. 1H NMR (DMSO-$D_6$, 300 MHz) δ (ppm): 8.48-7.08 (m, 6H, HAr), 6.64 (s, 2H, $CH_2$), 2.73 (s, 6H, 2 $CH_3$). 13C NMR (DMSO-$D_6$, 300 MHz) δ (ppm): 150.13, 148.65, 142.49, 133.02, 122.13, 117.08, 107.01, 148.29, 143.61, 138.05, 119.03, 119.89, 113.07, 53.96, 14.26. HRMS (ESI) Calc. for $C_{17}H_{16}N_4S_2$ (M + H+) = 430.052 Found = 430.056.

**1-(2-chloroethyl)-5-nitro-benzimidazole (6a)**

Reaction time: 5 h, beige powder, yield = 62 %, m.p = 132°C-134°C. 1H NMR (Acetone-$D_6$, 300 MHz) δ (ppm): 8.50 (s, 1H, CH=N),

8.64-7.89 (m, 3H, HAr), 4.94 (t, J = 5.7 Hz, 1H, $CH_2$aN), 4.87 (t, J = 5.7 Hz, 1H, $CH_2$bN,), 4.20 (m, 2H, $CH_2$Cl). 13C NMR (Acetone-$D_6$, 75 MHz) δ (ppm): 148.86, 120.93, 118.96, 118.20, 116.92, 111.62, 108.33, 44.00. HRMS (ESI) Calc. for $C_9H_8N_3O_3Cl$ (M + H+) = 226.031 Found = 226.034.

**1-(2-chloroethyl)-2-thiomethyl-1H-benzimidazole (6b)**

Reaction time: 5 h, yellow oil, yield = 51 %, 1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.63-7.60 (m, 2H, HAr), 7.22-7.13 (m, 2H, HAr), 4.30 (t, 2H, J = 6,61 Hz, $CH_2$N), 3.72 (t, 2H, J = 6,61 Hz, $CH_2$Cl), 2.73 (s, 3H, $CH_3$). 13C NMR ($CDCl_3$, 75 MHz) δ (ppm): 152.83, 143.13, 135.99, 122.21, 118.10, 45.32, 41.1, 14.78. HRMS (ESI) Calc. for $C_{10}H_{11}N_2SCl$ (M + H+) = 227.033 Found = 227.036.

**1-(2-chloroethyl)-2-thiomethyl-5-nitro-1H-benzimidazole (6c)**

Reaction time: 24 h, yellow crystals, yield = 48 %, m.p = 128°C-130°C. 1H NMR (DMSO-$D_6$, 300 MHz) δ (ppm): 8.6-7.5 (m, 3H, HAr), 4.65 (t, J = 5.9 Hz, 1H, ($CH_2$aN), 4.55 (t, J = 5.9 Hz, 1H, $CH_2$bN), 4.1 (t, J = 6.7 Hz, 2H, $CH_2$Cl), 2.7 (s, 3H, $SCH_3$). 13C NMR (DMSO-$D_6$, 75 MHz) δ (ppm): 159.40, 147.32, 142.55, 142.00, 113.10, 110.11, 106.63, 46.00, 14.46. HRMS (ESI) Calc. for $C_{10}H_{10}N_3O_4SCl$ (M + H+) = 272.018 Found = 272.021.

**1,2-Bis(2-thiomethyl-1H-benzimidazol-1-yl) ethane (7b)**

Reaction time: 5 h, orange crystals, yield = 27 %, m.p = 200°C-202°C. 1H NMR (DMSO-$D_6$, 300 MHz) δ (ppm): 7.16-7.08 (m, 8H, HAr), 3.4 (s, 4H, 2 $NCH_2$), 2.72 (s, 6H, 2 $SCH_3$). 13C NMR (DMSO-$D_6$, 75 MHz) δ (ppm): 168.05, 132.18, 122.25, 109.41, 35.73, 30.72, 14.78. HRMS (ESI) Calc. for $C_{18}H_{18}N_4S_2$ (M + H+) = 355.097 Found = 355.101.

**1,2-bis (2-thiomethyl-5-nitro-1H-benzimidazol-1-yl) ethane (7c)**

Reaction time: 24 h, green crystals, yield = 20 %, m.p = 128°C-130°C. 1H NMR (DMSO-$D_6$, 300 MHz) δ (ppm): 8.51-7.12 (m, 6H, HAr), 5.76 (d, J = 7.1 Hz, 2H, $CH_2$N), 5.50 (d, 6.9 Hz, 2H, $CH_2$Cl), 2.71 (s, 6H, 2 $SCH_3$). 13C NMR (DMSO-$D_6$, 75 MHz) δ (ppm): 147.33, 142.30, 139.01, 134.24, 127.33, 118.35, 117.91, 117.58, 113.16, 110.58, 106.52, 110.33, 110.24, 14.49, 14.43. HRMS (ESI) Calc. for $C_{18}H_{16}N_6O_4S_2$ (M + H+) = 445.067 Found = 445.070.

**5-nitro-1-oxiranylmethyl-1H-benzimidazole (8a)**

Reaction time: 20 h, orange crystals, yield = 55 %, m.p = 231°C-233°C. 1H NMR (DMSO-$D_6$, 300 MHz) δ (ppm): 8.13 (s, 1H, N=CH), 8.12-7.86 (m, 6H, HAr), 5.20 (m, 4H, 2 $CH_2$N), 4.80 (m, 4H, $CH_2$N), 4.7 (m, 2H, CHO), 4.67 (m, 2H, CHO), 4.36 (d, 2H, J = 8.1 Hz, $CH_2$O), 4.30 (d, J = 8.1 Hz, 2H, $CH_2$O). 13C NMR (DMSO-$D_6$, 75 MHz) δ (ppm): 154.17, 149.39, 148.28, 147.57, 142.95, 142.33, 138.45, 133.39, 119.83, 118.24, 117.42, 115.69, 111.46, 108.19, 75.28, 66.71, 46.64. HRMS (ESI) Calc. for $C_{10}H_9N_3O_3$ (M + H+) = 220.064 Found = 220.062.

**1-oxiranylmethyl-2-thiomethyl-1H-benzimidazole (8b)**

Reaction time: 24 h, yellow oil, yield = 52 %. 1H NMR (DMSO-$D_6$, 300 MHz) δ (ppm): 7.62-7.56 (m, 4H, HAr), 7.21-7.17 (m, 4H, HAr), 5.16-5.13 (m, 2H, 2 CHO), 4.57-4.54 (m, 4H, 2 $CH_2$O), 4.70-4.64 (m, 2H, $CH_2$N), 4.34-4.39 (m, 2H, $CH_2$N), 2.73 (s, 6H, 2$CH_3$). 13C NMR (DMSO-$D_6$, 300 MHz) δ (ppm): 154.16, 152.69, 142.87, 136.47, 121.69, 117.54, 109.84, 74.99, 66.73, 45.66, 14.53. HRMS (ESI) Calc. for $C_{11}H_{22}N_2OS$ (M + H+) = 221.067 Found = 221.071.

**2,3-[bis(2-thiomethyl -1H-benzimidazol-1-yl)]propan-2-ol 9**

Reaction time: 24 h, brown crystals, yield = 16 %, m.p = 199°C-201°C. 1H NMR (DMSO-$D_6$, 300 MHz) δ (ppm): 7.56 -7.49 (m, 4H, HAr), 7.18-7.14 (m, 4H, HAr), 5.55 (s, 1H, OH), 4.24; (s, 4H, 2$CH_2$), 3.37 (s, 1H, CH), 2.73 (s, 3H, $SC_3$), 2 .70 (s, 3H, $SCH_3$). 13C NMR (DMSO-$D_6$, 75 MHz) δ (ppm): 152.61, 142.88, 136.84, 121.33, 117.42, 109.84, 68.09, 47.65, 14.48. HRMS (ESI) Calc. for $C_{20}H_{23}N_4OS_2$ (M + H+) = 399.131 Found = 399.134.

## Results and Discussion

The synthesis of N-substituted benzimidazole derivatives was carried out by first preparing the three derivatives compounds **(3a-c).** Compound **3a** was obtained by the procedure described by Wagner and Millett [23]. This consisted of the condensation of 4-nitroorthophenylenediamine**(1a-b)** with ethyl formate in the presence of hydrochloric acid under reflux. Compound **3a** was obtained in 95% yield. Compounds **3b** and **3c** were each derived from 2-mercaptobenzimidazole **2a** and its previously synthesized 5-nitro derivative **2b**. Derivatives **2a** and **2b** were both obtained according to the Van Allan method [24] by the reaction of orthophenylenediamine and its nitro derivative with carbon disulfide ($CS_2$) in 82 and 92% yield respectively. They were then methylated with methyl iodide ($ICH_3$) under the reflux of ethanol **FIG.2** [25].

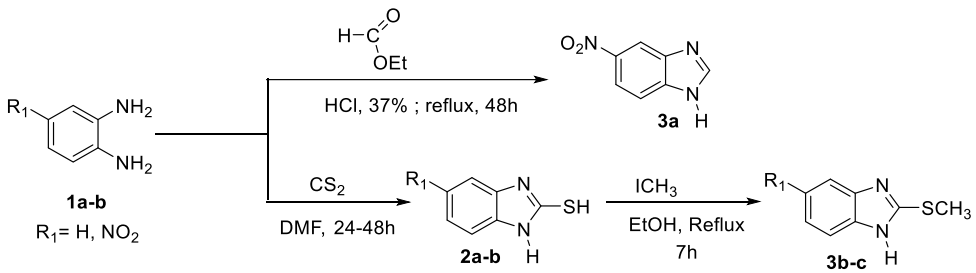


FIG.2. **Synthesis of benzimidazole precursors.**

Derivatives **(3a-c)** were subjected to N-deprotonation reactions in basic medium. Then N-alkylated derivatives of benzimidazole were obtained in a substitution reaction on the nitrogen via benzimidazolyl anion and various halogenated functional compounds with one to three carbon atoms ($(CH_2)$ n=1-3) in their chains **FIG.3**

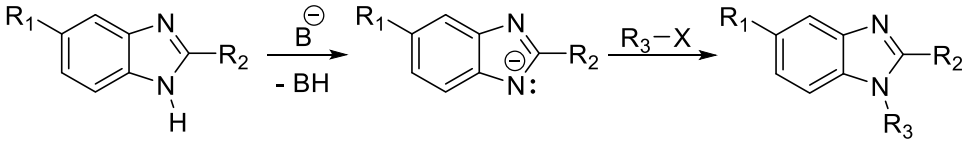


FIG.3. **N-alkylation mechanism.**

Reaction with 2-chloroethanol led to the N-substituted derivatives **(4a-c)** in yields between 52% and 75%. The reaction with diiodomethane under the same conditions leads to the duplication of the molecule. This result can be explained by the fact that, since iodine is a bulky and good initiator, the resulting N-alkylated products **(5a-c)** are transformed into an intermediate that undergoes a duplication reaction in the presence of a second benzimidazolyl anion. When diiodomethane was replaced by 1,2-chloroethane, the N-substituted compounds **(6a-c)** were obtained in higher yields compare to the duplicated compounds **(5a-c).** In this case, N-substituted compounds **(6a-c)** were less reactive because the number of carbon atoms increased and the C-Cl bond was less fragile or vulnerable than the C-I bond. A repeat coupling or duplication reaction was not obtained with compound **3a**. Reaction of 1,3-dichloropropan-2-ol with compounds **3b** and **3c** led to a chlorohydroxylated intermediate which was underwent a Williamson-type nucleophilic intramolecular substitution reaction to afford epoxides **8a** and **8b**. In the case of 2-thiomethyl-1H-benzimidazole, part of the epoxide formed was attacked by a corresponding second benzimidazolyl anion to form the duplicated compound 9.**FIG.4**

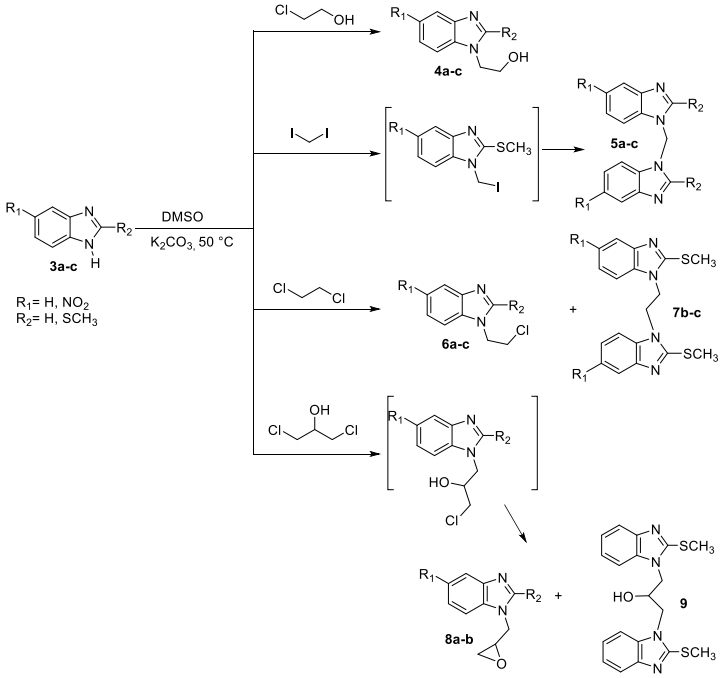


FIG.4. **Synthesis of N-alkylated benzimidazole derivatives.**

The structure of various compounds was confirmed by 1H, 13C NMR spectroscopic analysis and HRMS. Indeed, in the 1H NMR spectra of the different compounds, we clearly saw the substitution on the nitrogen atom by the absence of a peak between 11 and 12 ppm characteristic of the NH proton group and also the appearance of a novel peak between 4 and 6.6 ppm characteristic of the methylene protons bounded to the nitrogen.

## Conclusion

In this work, benzimidazole derivatives were prepared from previously synthesized precursors, 5-nitro-1H-benzimidazole **3a**, **2-**thimethylbenzimidazole **3b** and its nitro derivative **3c**. All compounds were obtained greater than 50% yield and their structures were confirmed by 1H, 13C NMR spectroscopic and mass spectrometry analyses. The use of dihalogenated compounds made possible the duplication of the benzimidazole derivatives.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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