Synthesis of novel thiazolobenzimidazoles

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ABSTRACT

For the synthesis of novel thiazolo[3,2-a]benzimidazol-3-ones and thiazolo[3,2-a]benzimidazoles, two methods have been developed which afforded the target compounds in relatively good yields by a pot process. The reaction between 2-mercapto-1H-benzimidazoles, acetophenone derivatives and 4-methylcyclohexanone in acid medium gave the tricyclic and tetracyclic benzimidazole compounds. We have also studied the flexibility of the position-7 of the thiazolobenzimidazoles by introducing the nitro and the methyl group. All compounds were characterized by means of 1H, 13C NMR and mass spectroscopy. The structures of the isomers of the 3-(2-methoxyphenyl)-6-nitrobenzo[4,5]imidazo[2,1-b]thiazole 14a, separated by a selective crystallization from diethyl ether were confirmed by RX analysis.

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INTRODUCTION

Gastrointestinal infections are among the major public health problems in developing countries. Especially, the amoebiasis (Haque et al., 2003; Plorde et al., 2004; Leber and Novak-Weekley, 2007; Baxt and Singh, 2008) and the giardiasis (Krauss et al., 2003; Huang and White, 2006) have high morbidity and mortality indexes due to the severe diarrhoea and invasive infections. Some drugs have proved their effectiveness in the treatment of amoebiasis (Entamoeba histolytica) and giardiasis (Giardia lamblia); however their use is restricted because they have significant side effects (Bourée et al., 2011).

The Benzimidazole nucleus is one of the bioactive heterocyclic compounds that exhibits a range of biological activities (Akpa et al., 2016). Specifically, this nucleus is a constituent of the vitamin B12 (O’Neil et al., 2001). The pharmacological activities of the benzimidazole containing moiety have been well documented (Amari et al., 2002; Timotou et al., 2013).

Recent studies have established that the benzimidazole carbamate derivatives such as Albendazole, Mebendazole, Flubendazole and Fenbendazole widely used as anthelmintic drugs (Kohler, 2001) are also in vitro inhibitors of the trichomonas vaginalis and the giardia. lamblia (Cedillo-Rivera and Muñoz, 1992; Chavez et al., 1992; Sears and
O’Hare, 1998). Benzimidazole derivatives, well-known therapeutic agents used mainly as anthelmintics, have a broad antiparasitic spectrum activity, a low toxicity and have been successfully used to treat gastrointestinal helmintic infections (Mavrova et al., 2006).

Previous studies have also showed that some molecules like tricyclic benzimidazole derivatives had anti-HIV activity, which had led to the discovery of 1H,3H-thiazolo[3,4-a]benzimidazoles (TBZs, Figure 1). The latter are highly active on the NNRTIs (Al-Rashood and Abdel-Aziz, 2010) or effective anthelmintics against the trichinellosis (Mavrova et al., 2005).

The literature describes several methods of synthesis of thiazolobenzimidazoles and their potential biological activities (Chimiri et al., 2001; Grimaudo et al., 2001; Abdel-Aziz et al., 2010; Mavrova et al., 2016). Therefore, the development of more and novel effective anthelmintics against the activity of the trichinellosis is of a pharmacological interest. For these reasons, we decided to synthesize novel structural analogs of the thiazolobenzimidazole (Figure 1). The structure of thiazolo [3,2-a] benzimidazol-3-ones allows to realize changes in two ways:

• The introduction of some substituents either on the benzene cycle of the thiazolobenzimidazole or on the thiazole ring (Chen et al., 2003; Sissouma et al., 2005; Mavrova et al., 2006; Dianov, 2007; Gabillet et al., 2007). This alteration in the structure of the main model compounds could be used to determine the influence of different substituents over the antitrichinellosis and viral activity.

• The introduction of a condensed ring in the benzimidazole system, which may enhance the interaction of these molecules with biological targets (Sarhan, 2000; Sarhan et al., 2010).

On the basis of the facts above, we decided, as objective, to synthesize novel tricyclic and tetracyclic benzimidazoles in order to study their activity against the trichinellosis. This is a continuation of our previous study (Sissouma et al., 2015; Akpa et al., 2016a, 2016b) in which we reported the synthesis of some benzimidazole derivatives against *Haemonchus contortus* and *Candida albicans*.

![Figure 1: Structure of TBZs and 1,3-thiazolo [3,2-a] benzimidazol-3-ones.](image-url)
MATERIALS AND METHODS

General procedures for analyses

MELTING POINTS

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. 1H NMR and 13C NMR were recorded on a Bruker Avance 300 MHz spectrometer. Mass spectrometric measurements were performed using HP5989X instrument. Column chromatography was carried out over silica gel 60 (0.04-0.06 mm) (Merck AG Darmstadt, Germany).

General procedures for synthesis of benzo[4,5]imidazo[2,1-b]thiazol-3-ones (ols) derivatives 5, 9, 10, 11 and 12

Solution of 5-(un) substituted-1H-benzimidazole-2-thiols 2 (2 g) in dry ethanol (20 mL) and halogenoethanes (1.2 eq.) was refluxed for 2-3 hours (Scheme 2). After cooling at room temperature, the solvent was removed. The residue was purified by chromatography on silica gel or re-crystallized with appropriate solvent.

Benzo[4,5]imidazo[2,1-b]thiazol-3(2H)-one 5a

From 1H-benzimidazole-2-thiol (2.00 g, 1.33 10^-2 mol) and diethyl 2-chloromalonate (3.11 g, 1.60 10^-2 mol) 5a was obtained (2.00 g, 79%) as white powder. MP = 136 °C, purified by chromatography on silica gel (hexane / ethyleacetate: 70/30), Rf = 0.69, mobile phase : ethyleacetate / ethanol : 50/50.

1H NMR (DMSO-d6, 300 MHz), δ (ppm) : 4.32 (s, 2H, CH2); 7.24-7.56 (m, 4H, Har).

13C NMR (DMSO-d6, 75 MHz), δ (ppm) : 34.09 (CH3); 113.47-136.34 (C=O); 149.70 (C=N); 169.28 (C=O).

Mass (m/z) = 205. M+1 = 206 (100) M/z (%): 162 (42), 150 (4), 118 (72), 90 (16), 77 (7), 63 (16), 36 (19), 28 (4).

7-nitrobenzo [4,5] imidazo[2,1-b]thiazol-3(2H)-one 5b

From 5-nitro-1H-benzimidazole-2-thiol (2.00 g, 1.02 10^-2 mol) and ethyl 2-bromomalonate (2.05 g, 1.23 10^-2 mol) 5b was obtained (2.17 g, 90%) as green powder. MP = 202 °C, re-crystallized with dichloromethane / ethanol: 90/10, Rf = 0.53, mobile phase: hexane / ethyleacetate : 70/30.

1H NMR (DMSO-d6, 300 MHz), δ (ppm) : 4.31 (s, 2H, CH2); 7.61-8.30 (m, 3H, Har).

13C NMR (DMSO-d6, 75 MHz), δ (ppm) : 33.86 (CH3); 110.12-155.29 (C=O); 168.03 (C=N); 169.15 (C=O).

Mass (m/z) = 235. M+1 = 236 (26), M/z (%): 209 (34), 208 (100), 207 (79), 162 (68), 161(19), 121 (21), 118 (16), 117 (12), 91 (10), 90 (22).

7-methylbenzo[4,5]imidazo[2,1-b]thiazol-3(2H)-one 5e

From 5-methyl-1H-benzimidazole-2-thiol (2.00 g, 1.22 10^-2 mol) and ethyl 2-bromomalonate (2.44 g, 1.46 10^-2 mol) 5e was obtained (1.87 g, 75%) as beige crystals. MP = 170 °C, purified by chromatography on silica gel (hexane / ethyleacetate : 70/30), Rf = 0.60, mobile phase : hexane / ethyleacetate : 60/40.

1H NMR (DMSO-d6, 300 MHz), δ (ppm) : 2.46 (s, 3H, CH3); 4.51 (s, 2H, CH2); 7.27-7.59 (m, 3H, Har).

13C NMR (DMSO-d6, 75 MHz), δ (ppm) : 21.04 (CH3); 52.94 (CH2); 112.91-135.01 (Car); 149.24 (C=N); 168.65 (C=O).

Mass (m/z) = 204. M+1 = 205 (100), M/z (%): 175 (16), 163.19 (26), 142.88 (23), 131.97 (45), 130.97 (34), 121 (29), 90 (43), 45 (33), 41 (31).

2-methylbenzo[4,5]imidazo[2,1-b]thiazol-3(2H)-one 5d

From 1H-benzimidazole-2-thiol (2.00 g, 1.33 10^-2 mol) and ethyl 2-bromopropionate (2.89 g, 1.60 10^-2 mol) 5d was obtained (1.79 g, 66%) as white powder. MP = 127 °C, purified by chromatography on silica gel (ethyleacetate / hexane : 50/50), Rf = 0.66, mobile phase : ethyleacetate / hexane : 50/50.

Diasteroisomere R(S) :

1H NMR (CDCl3, 300 MHz), δ (ppm) : 1.63 (d, 3H, CH3, J = 7.5 Hz); 4.25 (q, 1H, CH2, J = 7.5 Hz); 7.22-7.26 (m, 4H, Har).
13C NMR (Acetone, 75 MHz), δ (ppm): 19.44 (CH3); 45.19 (CH); 115.76-141.27 (Car); 149.44 (C=N); 173.47 (C=O).

Mass (m/z) = 204, M+ = 204 (100), m/z (%): 175 (56), 161 (6), 143 (10), 132 (11), 118 (9), 90 (13), 63 (9), 45 (7), 39 (3), 27 (9). Diastereoisomer S(R):

1H NMR (Acetone, 300 MHz), δ (ppm): 1.64 (d, 3H, CH3, J = 7.5 Hz); 4.68 (q, 1H, CHJ = 7.5 Hz); 7.15-7.18 (m, 4H, Har).

13C NMR (Acetone, 75 MHz), δ (ppm): 19.44 (CH3); 45.19 (CH); 115.76-141.27 (Car); 149.44 (C=N); 173.47 (C=O).

Mass (m/z) = 204, M+ = 204 (100), m/z (%): 175 (56), 161 (6), 143 (10), 132 (11), 118 (9), 90 (13), 63 (9), 45 (7), 39 (3), 27 (9). 2-methyl-7-nitrobenzo[4,5]thiazol-3(2H)-one 5e

From 5-nitro-1H-benzimidazole-2-thiol (2.00 g, 1.02 \( \times \) 10⁻² mol) and ethyl 2-bromopropanoate (2.23 g, 1.23 \( \times \) 10⁻² mol) 5e was obtained (1.69 g, 75%) as beige crystals. MP = 184 °C, purified by chromatography on silica gel (dichloromethane / ethylacetate: 90/10), RF = 0.62, mobile phase: dichloromethane / ethylacetate: 90/10.

Diastereoisomer S(R):

1H NMR (DMSO-d6, 300 MHz), δ (ppm): 1.09 (t, 3H, CH3, J = 3 Hz); 2.43 (s, 3H, CH3); 3.72 (m, 2H, O-CH2); 4.06 (d, 1H, CH3, Jgem = 12 Hz); 4.5 (m, 1H, CH3); 6.55 (dd, 1H, CH, Jgem = 6 Hz, Jeis = 3 Hz); 7.25-8.04 (m, 3H, Har).

13C NMR (DMSO-d6, 75 MHz), δ (ppm): 14.95 (CH3-CH2); 20.98 (CH3); 43.57 (CH2-CH2); 64.44 (CH2); 85.44 (CH-O); 111.78-135.87 (Car); 158.04 (C=N).

Mass (m/z) = 234, M+ = 234 (53), M+1 = 235 (9), m/z (%): 190 (17), 188 (100), 177 (20), 164 (11), 133 (21), 131 (26), 104 (9), 89 (9). Diastereoisomer S(R):

1H NMR (DMSO-d6, 300 MHz), δ (ppm): 1.12 (t, 3H, CH3, Jeis = 3 Hz); 2.45 (s, 3H, CH3); 3.72 (m, 2H, O-CH2); 4.06 (d, 1H, CH3, Jgem = 12 Hz); 4.5 (m, 1H, CH3); 6.55 (dd, 1H, CH, Jgem = 6 Hz, Jeis = 3 Hz); 7.25-8.04 (m, 3H, Har).

13C NMR (DMSO-d6, 75 MHz), δ (ppm): 14.95 (CH3-CH2); 21.09 (CH3); 43.65 (CH2-CH2); 64.5 (CH2); 85.7 (CH-O); 111.78-137.87 (Car); 158.22 (C=N).

Mass (m/z) = 234, M+ = 234 (53), M+1 = 235 (9), m/z (%): 190 (17), 188 (100), 177 (20), 164 (11), 133 (21), 131 (26), 104 (9), 89 (9). 2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazol-3-ol 10a

From 1H-benzimidazole-2-thiol (2.00 g, 1.33 \( \times \) 10⁻² mol) and 2-bromo-1,1-diethoxyethane (3.15 g, 1.60 \( \times \) 10⁻² mol) 10a was obtained (2.25 g, 88%) as white crystals. MP = 202 °C, re-crystallized with ethanol, RF
= 0.31, mobile phase: dichloromethane / ethylacetate : 80/20.

_Diastereoisomere R(S) :_

\(^{1}\text{H} \) NMR (DMSO-d6, 300 MHz); \(\delta\) (ppm): 3.74 (dd, 1H, CH\(_2\), J\(_{gem}\) = 12.3 Hz, J\(_{cis}\) = 6 Hz); 4.33 (dd, 1H, CH\(_2\), J\(_{gem}\) = 12.3 Hz, J\(_{trans}\) = 1.8 Hz); 4.83 (s, 1H, OH); 6.38 (dd, 1H, CH\(_2\), J\(_{trans}\) = 1.8 Hz, J\(_{cis}\) = 6 Hz); 7.20-7.60 (m, 4H, Har).

\(^{13}\text{C} \) NMR (DMSO-d6, 75 MHz), \(\delta\) (ppm): 43.45 (CH\(_3\)); 78.53 (CH) 110.59-146.58 (Car); 157.60 (C=O).

Mass (m/z) = 192. M\(^{+}\) = 192 (84), m/z (%): 175 (9), 163 (48), 150 (100), 131 (56), 119 (38), 90 (22), 77 (10), 63 (19), 39 (11), 28 (8).

_Diastereoisomere S(R) :_

\(^{1}\text{H} \) NMR (DMSO-d6, 300 MHz); \(\delta\) (ppm): 3.85 (dd, 1H, CH\(_2\), J\(_{gem}\) = 12.3 Hz, J\(_{cis}\) = 6 Hz); 4.44 (dd, 1H, CH\(_2\), J\(_{gem}\) = 12.3, Hz, J\(_{trans}\) = 1.8 Hz); 4.35 (s, 1H, OH); 6.53 (dd, 1H, CH\(_2\), J\(_{trans}\) = 1.8 Hz, J\(_{cis}\) = 6 Hz); 7.34-7.77 (m, 4H, Har).

\(^{13}\text{C} \) NMR (DMSO-d6, 75 MHz), \(\delta\) (ppm): 44.56 (CH\(_3\)); 80.22 (CH) 111.87-139.68 (Car); 157.70 (C=O).

Mass (m/z) = 192. M\(^{+}\) = 192 (84), m/z (%): 175 (9), 163 (48), 150 (100), 131 (56), 119 (38), 90 (22), 77 (10), 63 (19), 39 (11), 28 (8).

**7-nitro-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazol-3-ol 10b**

From 5-nitro-1H-benzimidazole-2-thiol (2.00 g, 1.22 \(10^2\) mol) and 2-bromo-1,1-diethoxyethane (2.88 g, 1.46 \(10^2\) mol) 10b was obtained (2.02 g, 83%) as white crystals. MP = 208 ⋅C, purified by chromatography on silica gel (hexane / ethylacetate: 70/30), Rf = 0.40, mobile phase: hexane / ethylacetate: 70/30.

_Diastereoisomere R(S) :_

\(^{1}\text{H} \) NMR (DMSO-d6, 300 MHz); \(\delta\) (ppm): 3.37 (dd, 1H, CH\(_2\), J\(_{gem}\) = 12 Hz, J\(_{cis}\) = 3 Hz); 4.38 (dd, 1H, CH\(_2\), J\(_{gem}\) = 12 Hz, J\(_{trans}\) = 6 Hz); 6.49 (dd, 1H, CH, J\(_{trans}\) = 6Hz, J\(_{cis}\) = 3Hz); 6.65 (s, 1H, OH); 7.65-8.56 (m, 3H, Har).

\(^{13}\text{C} \) NMR (DMSO-d6, 75 MHz): \(\delta\) (ppm): 43.27 (CH\(_3\)); 78.59 (CH); 106.86-147.11 (Car); 162.06 (C=O).

Mass (m/z) = 237. M\(^{+}\) = 237 (100), m/z (%): 209 (22), 208 (20), 195 (63), 162 (22), 130 (19), 121 (12), 118 (16), 90 (28).

_Diastereoisomere S(R) :_

\(^{1}\text{H} \) NMR (DMSO-d6, 300 MHz), \(\delta\) (ppm): 3.37 (dd, 1H, CH\(_2\), J\(_{gem}\) = 12 Hz, J\(_{cis}\) = 3 Hz); 4.38 (dd, 1H, CH\(_2\), J\(_{gem}\) = 12 Hz, J\(_{trans}\) = 6 Hz); 6.49 (dd, 1H, CH, J\(_{trans}\) = 6Hz, J\(_{cis}\) = 3Hz); 6.65 (s, 1H, OH); 7.65-8.56 (m, 3H, Har).

\(^{13}\text{C} \) NMR (DMSO-d6, 75 MHz), \(\delta\) (ppm): 43.27 (CH\(_3\)); 78.80 (CH); 110.55-152.35 (Car); 163.69 (C=O).

Mass (m/z) = 237. M\(^{+}\) = 237 (100), m/z (%): 209 (22), 208 (20), 195 (63), 162 (22), 130 (19), 121 (12), 118 (16), 90 (28).

7-methyl-2,3-dihydrobenzo [4,5] imidazo [2,1-b]thiazol-3-ol 10c

From 5-methyl-1H-benzimidazole-2-thiol (2.00 g, 1.22 \(10^2\) mol) and 2-bromo-1,1-diethoxyethane (2.88 g, 1.46 \(10^2\) mol) 10c was obtained (1.71 g, 68%) as beige crystals. MP = 218 °C, selective crystallization, Rf = 0.33, mobile phase: Hexane / ethylacetate: 50/50.

_Diastereoisomere R(S) :_

\(^{1}\text{H} \) NMR (DMSO-d6, 300 MHz); \(\delta\) (ppm): 2.43 (s, 3H, CH\(_3\)); 3.9 (d, 1H, CH\(_2\), J = 12 Hz); 4.51 (dd, 1H, CH\(_2\), J\(_{gem}\) = 12 Hz, J\(_{trans}\) = 6 Hz); 5.26 (s, 1H, OH); 6.58 (t, 1H, CH, J\(_{trans}\) = 6 Hz); 7.25-7.73 (m, 3H, Har).

\(^{13}\text{C} \) NMR (DMSO-d6, 75 MHz), \(\delta\) (ppm): 21.02 (CH\(_3\)); 44.81 (CH\(_2\)); 80.53 (CH) 111.78-135.27 (Car); 156.93 (C=O).

Mass (m/z) = 206. M\(^{+}\) = 206 (100), M+1 = 207 (20), m/z (%): 205 (17), 189 (22), 177 (52), 164 (60), 163(20),145 (95), 133 (37), 131 (38), 104 (28), 103 (16), 91 (16), 89 (20), 78 (21), 77 (40), 51 (15), 31 (5).

_Diastereoisomere S(R) :_

\(^{1}\text{H} \) NMR (DMSO-d6, 300 MHz), \(\delta\) (ppm): 2.43 (s, 3H, CH\(_3\)); 3.9 (d, 1H, CH\(_2\), J = 12 Hz); 4.51 (dd, 1H, CH\(_2\), J\(_{gem}\) = 12 Hz, J\(_{trans}\) = 6 Hz); 5.26 (s, 1H, OH); 6.58 (t, 1H, CH, J\(_{trans}\) = 6 Hz); 7.25-7.73 (m, 3H, Har).
**Ethyl 3-oxo-2,3-dihydrobenzo[4,5]imidazo[2,1-b]thiazole-2-carboxylate 11a**

From 1H-benzimidazole-2-thiol (2.00 g, 1.33 \(10^2\) mol) and diethyl 2-chloromalonate (3.11 g, 1.60 \(10^2\) mol) 11a was obtained (3.18 \(10^4\) g, 24%) as yellow crystals. MP = 252 °C, purified by chromatography on silica gel (hexane / ethylacétate: 70/30), RF = 0.16, mobile phase: dichlorométhane / acétate d'éthyle: 90/10.

**1H NMR (DMSO-d6, 300 MHz), δ (ppm):** 1.1 (t, 3H, CH₃-J = 7.2 Hz); 1.18 (t, 3H, CH₃-J = 7.2 Hz); 2.10 (q, 2H, CH₂, J = 7.2 Hz); 2.33 (q, 2H, CH₂, J = 7.2 Hz); 2.66 (s, 1H, CH); 7.4-7.9 (m, 4H, Har).

**13C NMR (DMSO-d6, 75 MHz), δ (ppm):** 18.51 (CH₃); 45.50 (S-CH=); 55.97 (CH₂); 111.78-129.73 (Car); 149.28 (C=O); 159.17 (C=O); 165.95 (COO).

**Mass (m/z):** 262. M⁺ = 262 (100), m/z (%): 217 (7), 203 (13), 190 (72), 161 (42), 134 (28), 118 (31), 90 (32), 77 (5), 63 (15), 45 (15), 29 (52).

**Ethyl 7-nitro-3-oxo-2,3-dihydrobenzo [4,5] imidazo [2,1-b] thiazole-2-carboxylate 11b**

From 5-nitro-1H-benzimidazole-2-thiol (2.00 g, 1.02 \(10^2\) mol) and diethyl 2-chloromalonate (2.39 g, 1.23 \(10^2\) mol) 11b was obtained (2.52 g, 80%) as beige crystals. MP = 201 °C, purified by chromatography on silica gel (hexane / ethylacétate: 70/30), RF = 0.40, mobile phase: Hexane / ethylacetate: 70/30.

**1H NMR (DMSO-d6, 300 MHz), δ (ppm):** 1.16 (t, 3H, CH₃-J = 6 Hz); 4.13 (q, 4H, CH₂, J = 6 Hz); 4.33 (s, 1H, H-2); 7.61-8.31 (m, 3H, Har).

**13C NMR (DMSO-d6, 75 MHz), δ (ppm):** 13.92 (CH₃); 33.39 (S-CH=); 61.34 (CH₂); 110.12-142.68 (Car); 155.3 (C=O); 168.08 (COO).

**Mass (m/z):** 207. M⁺ = 207 (17), m/z (%): 189 (22), 177 (52), 164 (60, 163(20), 145 (95), 133 (37), 131 (38), 104 (28), 103 (16), 91 (16), 89 (20), 78 (21), 71 (40), 51 (15), 31 (5).
General procedures for synthesis of 3-substituted benzo [4,5] imidazo[2,1-b]thiazoles derivatives 14 and 16

A mixture of 5-(un)substituted-1H-benzimidazole-2-thiols 2 (3 g) and substituted acetophenones 13 (2 eq.) or 4-methyl cyclohexanone 15 (2 eq.) was refluxed in acetic acid (30 mL) containing 1 mL of concentrated H2SO4 for 24-48 hours. The reaction mixture was cooled and neutralized with NH4OH solution. The resulting precipitate was collected by filtration, washed several times with water, dried and re-crystallized from ethanol or methanol to give the corresponding 14a-h and 16a-b compounds (Scheme 3). The compound 14c were purified by chromatography on silica gel.

3-(2-methoxyphenyl)-7-nitrobenzo[4,5] imidazo[2,1-b]thiazole 14a

From 5-nitro-1H-benzimidazole-2-thiol (2.00 g, 1.02 \(10^{-2}\) mol) and 1-(2-methoxyphenyl)ethan-1-one (1.85 g, 1.23 \(10^{-2}\) mol) 14a was obtained (2.77 g, 83%) as yellow crystals. MP = 178 °C, re-crystallized with methanol, Rf = 0.60, mobile phase: hexane/ethylacetate: 70/30.

\(^{1}H\) NMR (TFA, 300 MHz), δ (ppm): 3.83 (s, 6H, 2 O-CH\(_{3}\)); 7.32-8.12 (m, 8H, Har); 8.32 (s, 2H, S-CH\(_{3}\)); 8.42-8.91 (m, 6H, Har).

\(^{13}C\) NMR (TFA, 75 MHz), δ (ppm): 54.41 (CH\(_{2}\)O), 54.68 (CH\(_{2}\)O); 108.63-144.25(Car); 111(CH\(_{2}\)); 111.17-157.8 (Car), 146.28 (2 C=O); 156.57 (2 N-CH=).

Mass (m/z) = 325. M+ = 325 (100), M+1 = 326 (20), m/z (%): 309 (3), 281 (3), 380 (8), 379 (28), 264 (18), 248 (11), 246 (7), 236 (6), 209 (4), 163 (5), 131 (26), 42 (13).

3-(2-methoxyphenyl)-7(6)-methylbenzo[4,5] imidazo[2,1-b]thiazole 14b

From 5-methyl-1H-benzimidazole-2-thiol (2.00 g, 1.22 \(10^{-2}\) mol) and 1-(2-methoxyphenyl)ethan-1-one (2.19 g, 1.46 \(10^{-2}\) mol) 14b was obtained (3.05 g, 85%) as oil, Rf = 0.45, mobile phase: hexane/ethylacetate: 80/20.

\(^{1}H\) NMR (DMSO, 300 MHz), δ (ppm): 2.38 (s, 3H, CH\(_{3}\)); 3.41 (s, 3H, CH\(_{3}\)); 6.6-7.52 (m, 8H, Har).

\(^{13}C\) NMR (DMSO, 75 MHz), δ (ppm): 21.22 (CH\(_{3}\)); 55.39 (CH\(_{3}\)); 108.5-146.04 (Car); 111.42 (2 CH\(_{3}\)); 117.71-157.51 (Car); 148.23 (2 C=O); 155.76 (2 N-CH=).

Mass (m/z) = 309, M+ = 294 (100), M+1 = 295 (25), m/z (%): 279 (4), 261 (14), 249 (3), 247 (9), 132 (5), 131 (36), 103(5), 89 (6).

6-nitro-3-(4-nitrophenyl)benzo[4,5]imidazo[2,1-b]thiazole 14d

From 5-nitro-1H-benzimidazole-2-thiol (2.00 g, 1.02 \(10^{-2}\) mol) and 1-(4-nitrophenyl)ethan-1-one (2.03 g, 1.23 \(10^{-2}\) mol) 14d was obtained (2.09 g, 60%) as red crystals. MP = 124 °C, purified by chromatography on silica gel (hexane / éthyle d’éthyle: 70/30), Rf = 0.50, mobile phase: hexane/ethylacetate: 60/40.

\(^{1}H\) NMR (TFA, 300 MHz), δ (ppm): 7.71-8.01 (m, 4H, Har); 8.04-8.8 (m, 4H, Har and S-CH\(_{3}\)).
13C NMR (TFA, 75 MHz), δ (ppm): 109.86-151.19 (Car); 115.8 (CH₂); 121.22; -193.62 (Car); 149.71 (N-CH); 155.29 (C=N).

Mass (m/z) = 340, M⁺ = 340 (20), M+1 = 341 (5), m/z (%): 310 (15), 294 (4), 264 (6), 248 (14), 203 (7), 196 (13), 195 (100), 165 (30), 149 (62), 137 (22), 120 (18), 105 (35), 90 (29), 63 (45).

7-methyl-3-(4-nitrophenyl)benzo[4,5]imidazo[2,1-b]thiazole 14c

From 5-methyl-1H-benzimidazole-2-thiol (2.00 g, 1.22 10⁻² mol) and 1-(4-nitrophenyl)ethan-1-one (2.41 g, 1.46 10⁻² mol) 14c was obtained (2.28 g, 63%) as yellow crystals. MP = 252 °C, re-crystallized with methanol, Rf = 0.70, mobile phase: hexane / ethylacetate: 70/30.

1H NMR (TFA, 300 MHz), δ (ppm): 7.54-7.66 (m, 4H, Har); 7.68 (s, 1H, S-CH⁺); 8.43-8.94 (m, 3H, Har).

13C NMR (TFA, 75 MHz), δ (ppm): 108.65-133.04 (Car); 112.4 (CH₃); 119.91-135.83 (Car); 146.47 (CH⁺); 157.16 (C=N).

Mass (m/z) = 374, M⁺ = 374 (31), M+1 = 375 (93), m/z (%): 373 (100), 329 (28), 327 (30), 249 (16), 248 (82), 247 (57), 246 (16), 177 (22), 147 (22), 133 (31), 101 (29), 89 (37), 75 (21), 63 (16), 28 (36).

13C NMR (TFA, 75 MHz), δ (ppm): 19.73 (CH₂); 108.65-132.05 (Car); 112.17 (S-CH⁺); 116.16-135.76 (Car); 140.11 (C=N); 152.64 (N-CH⁺).

Mass (m/z) = 343, M⁺ = 343 (40), M+1 = 344 (96), m/z (%): 342 (100), 341 (22), 263 (14), 162 (10), 161 (11), 131 (11), 101 (13), 89 (41), 77 (21), 76 (10), 63 (13).
3-(4-bromophenyl)benzo[4,5]imidazo[2,1-b]thiazole 14i

From 1H-benimidazole-2-thiol (2.00 g, 1.33 \(10^{-2}\) mol) and 1-(4-bromophenyl)ethan-1-one (1.90 g, 1.60 \(10^{-2}\) mol) 14i was obtained (3.77 g, 86%) as beige crystals. MP = 240 °C, re-crystallized with methanol, RF = 0.60, mobile phase: hexane / ethylacetate: 70/30.

\(^1\)H NMR (TFA, 300 MHz), \(\delta\) (ppm): 7.29 (s, 1H, S-CH\(^{=}\)); 7.33-7.82 (m, 8H, Har).

\(^13\)C NMR (TFA, 75 MHz), \(\delta\) (ppm): 108.56-135.17 (Car); 112.92 (S-CH\(^=\)); 116.07-126.82 (Car); 135.7 (C=\(\text{N}\)); 153.10 (N-C\(^=\)).

Mass (m/z) = 329. \(M^+ = 329\) (30), M+1 = 330 (98), m/z (%) = 328 (100), 327 (13), 249 (12), 248 (15), 247 (5), 191 (5), 190 (5), 164 (7), 124.6 (21), 124 (8), 102 (14), 101 (12), 90 (11), 89 (8), 76 (5).

2,9-dimethyl-1,2,3,4-tetrahydrobenzo[d] benzo[4,5]imidazo[2,1-b]thiazole 16a

From 5-nitro-1H-benimidazole-2-thiol (2.00 g, 1.02 \(10^{-2}\) mmol) and 4-methylcylohexan-1-one (1.38 g, 1.23 \(10^{-2}\) mmol) 16a was obtained (2.30 g, 78%) as pink crystals. MP = 206 °C, re-crystallized with methanol, RF = 0.45, mobile phase: hexane / ethylacetate: 80/20.

\(^1\)H NMR (TFA, 300 MHz), \(\delta\) (ppm): 1.29 (m, 3H, CH\(_3\)); 1.81-1.89 (m, 1H, CHCH\(_3\)); 2.21-2.30 (m, 2H, CH\(_2\)); 2.59-3.08 (m, 2H, CH\(_2\)); 3.34-3.50 (m, 2H, CH\(_2\)); 8.08-9.03 (m, 3H, Har).

\(^13\)C NMR (TFA, 75 MHz), \(\delta\) (ppm): 18.67 (CH\(_3\)); 22.34 (CH\(_3\)); 28.24 (CH=CH\(_2\)); 28.78 (CH\(_3\)); 30.95 (CH\(_3\)); 108.66-130.18 (Car); 146.18 (C=\(\text{N}\)); 130.72 (C-C\(^=\)); 155.17 (C-C\(^=\)).

Mass (m/z) = 256. \(M^+ = 256\) (100), M+1 = 257 (21), m/z (%) = 255 (10), 254 (3), 239 (2), 216 (3), 214 (51), 213 (19), 128 (5), 116 (4), 104 (3).

RESULTS AND DISCUSSION

We previously described the synthesize of 1,3-thiazolo[3,2-\(\alpha\)]benzimidazol-3-ones by condensation with 4-unsubstituted-1,2-diaminobenzene and halogenoester compounds. (Sissouma et al., 2005). The present work is an extension of our ongoing efforts to the development of new benzimidazole derivatives. The synthesis of the 1,3-thiazolo[3,2-\(\alpha\)]benzimidazol-3-ones 5 is illustrated in Scheme 1.

Synthesis of 1H-benimidazole-2-thiols (2-mecapto benimidazoles) was described by Van Allan and co-workers by refluxing sodium hydroxide, carbon disulfide, and 4-(un)substituted-1,2-diaminobenzene in ethanol-water solution (Van Allan and Deacon, 1963). In this work, 1H-benimidazole-2-thiols were prepared using the procedure described by Sorba et al. (1986) by condensing carbon disulfide and 4- (un)substituted-1,2-diaminobenzene 1 in

2-methyl-9-nitro-1,2,3,4-tetrahydrobenzo[d]benzo[4,5]imidazo[2,1-b]thiazole 16b

From 5-methyl-1H-benimidazole-2-thiol (2.00 g, 1.22 \(10^{-2}\) mol) and 4-methylcylohexan-1-one (1.64 g, 1.46 \(10^{-2}\) mol) 16b was obtained (2.65 g, 85%) as yellow crystals. MP = 154 °C, re-crystallized with ethanol, RF = 0.74, mobile phase: hexane / ethylacetate: 80/20.

\(^1\)H NMR (TFA, 300 MHz), \(\delta\) (ppm): 1.29 (m, 3H, CH\(_3\)); 1.81-1.89 (m, 1H, CHCH\(_3\)); 2.21-2.30 (m, 2H, CH\(_2\)); 2.59-3.08 (m, 2H, CH\(_2\)); 3.34-3.50 (m, 2H, CH\(_2\)); 8.08-9.03 (m, 3H, Har).

\(^13\)C NMR (TFA, 75 MHz), \(\delta\) (ppm): 18.78 (CH\(_3\)); 19.75 (CH\(_3\)); 22.5 (CH\(_3\)); 28.48 (CH-CH\(_3\)); 28.85 (CH\(_3\)); 30.92 (CH\(_3\)); 108.66-130.18 (Car); 139.52 (C=\(\text{N}\)); 149 (C-C\(^=\)); 150.78 (C-C\(^=\)).

Mass (m/z) = 287. \(M^+ = 287\) (100), M+1 = 288 (23), m/z (%) = 286 (10), 245 (39), 244 (14), 241 (6), 215 (12), 199 (12), 147 (6), 141 (13), 140 (7), 114 (3), 91 (3).
dimethyl formamide (DMF). The reaction mixture was stirred at room temperature for 24 hours and then treated with water to precipitate 1H-benzimidazole-2-thiols 2. The reaction between halogenoester compounds 3 and 5-(un)substituted-1H-benzimidazole-2-thiol 2 in the presence of triethylamine in dry ethanol at room temperature led to compounds 4 in good yields (71-75%). 1,3-thiazolo[3,2-a]benzimidazol-3-(2H)-ones 5 were obtained by heating (benzimidazol-2-ylthio)acetic acid ethyl ester 4 in dry ethanol in the presence of a few drops of hydrochloric acid.

The second way, a one-pot reaction is needed to synthesize 1,3-thiazolo[3,2-a]benzimidazol-3-(2H)-ones 5. The substituted target compounds 5 (Scheme 2) were obtained in good yields (66-90%) by cyclocondensation reaction of 5-(un)substituted-1H-benzimidazole-2-thiol 2 and (ethyl 2-bromoacetate or ethyl 2-bromopropanoate) 3 under reflux in ethanol. On the other hand, by refluxing in dry ethanol 1H-benzimidazole-2-thiol or 5-nitro-1H-benzimidazol-2-thiol 2 with 2-bromo-1,1-(diethoxy) ethane 6, gave the corresponding thiazolobenzimidazoles 10a and 10b in good yield respectively. But the reaction of 5-methyl-1H-benzimidazol-2-thiol with 2-bromo-1,1-(diethoxy) ethane 6 gave two products (Scheme 2) 9c (21%) and 10c (68%). Compound 10c is obtained by hydrolyzing of compound 9c under acidic conditions. The yields of these compounds depended on the 2-mercaptopbenzimidazole used.

Diethyl 2-chloromalonate reacted in a similar way with 1H-benzimidazole-2-thiol 2 to give compounds 5a and 11a. After chromatography, compounds 5a and 11a were isolated in moderate yield. Compound 11a was hydrolyzed under acid conditions to give an intermediate acid compound which was then decarboxylated to give compound 5a (Scheme 2). Also, diethyl 2-chloromalonate reacted with 5-nitro-1H-benzimidazol-2-thiol or 5-methyl-1H-benzimidazol-2-thiol to give the compounds 11b (80%) and 11c (40%) respectively (Scheme 2).

This synthetic approach was used to prepare heterocyclic analog containing six numbers. Fluorene analog 12a were prepared by the reacting methyl 3-bromopropanoate 8 with 1H-benzimidazol-2-thiol 2 (Scheme 2). Compound 2 and compound 8 were heated under reflux in dry ethanol to afford 2,3-dihydro-1-thia-4a,9-diaza-fluoren-4-one 12a in good yield. All the compounds were characterized by means 1H, 13C NMR and mass spectroscopy. Physico-chemical data for the synthesized compounds are summarized in Table 1.

The thiazolo[3,2-a]benzimidazoles 14 were obtained in very good yields by reacting a 2-mercaptopbenzimidazole 2 with aromatic ketones 13 in boiling acetic acid containing 1 mL of concentrated H2SO4 (Scheme 3).

When R = o-OC6H4 and R7 = NO2 (compound 14a), the analysis of the 1H NMR spectra showed that 14a present a mixture of two compounds which are separated by crystallization in diethyl ether. Their structures were further confirmed by RX analysis (Figure 2).

The tetracyclic compounds 16 were obtained in good yield using alicyclic ketones 15 (cyclohexanone, 4-methylcyclohexanone) and 2-mercaptopbenzimidazole 2 in the same reaction conditions (Scheme 3).

The mechanism of the reaction is still under investigation. It may be proceeded via formation of dimeric disulfide 17 followed by nucleophilic attack by α-aryl/alkyl α-hydroxymethylene carboxylate 18 (formed by esterification of the enol form) as shown in Scheme 4. The less stable intermediate 18 cyclized directly to thiazolo[3,2-a]benzimidazoles 14. The yields and the physico-chemical data for the synthesised compounds are summarized in Table 2.
Scheme 1: Synthesis of the 1,3-thiazolo[3,2-a]benzimidazol-3-ones.

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Scheme 2: Synthesis of thiazolo[3,2-a]benzimidazol-3-ones (ols).
### Table 1: Physico-chemical data for the synthesised compounds 5, 9, 10, 11 and 12.

| Compounds | R^7 | R^2 | R^3 (Function) | Yield | MP °C |
|-----------|-----|-----|----------------|-------|-------|
| 5a        | H   | H   | =O             | 79    | 136   |
| 5b        | NO₂ | H   | =O             | 90    | 202   |
| 5c        | CH₃ | H   | =O             | 75    | 170   |
| 5d        | H   | CH₃ | =O             | 66    | 127   |
| 5e        | NO₂ | CH₃ | =O             | 75    | 184   |
| 9c        | CH₃ | H   | -OEt           | 21    | 200   |
| 10a       | H   | H   | -OH            | 88    | 202   |
| 10b       | NO₂ | H   | -OH            | 83    | 208   |
| 10c       | CH₃ | H   | -OH            | 68    | 218   |
| 11a       | H   | Et-COO | =O         | 24    | 252   |
| 11b       | NO₂ | Et-COO | =O         | 80    | 201   |
| 11c       | CH₃ | Et-COO | =O         | 40    | 98    |
| 12a       | H   | -   | =O             | 89    | 140   |

**Scheme 3**: Synthesis of thiazolo[3,2-a]benzimidazoles.

- **i**: R'-acetophenone 13, AcOH / H₂SO₄, Δ
- **ii**: 4-methyl-cyclohexanone 15, AcOH / H₂SO₄, Δ
Table 2: Physico-chemical data for the synthesised compounds 14 and 16.

| Compounds | R^7  | R'    | Yields | MP (°C) |
|-----------|------|-------|--------|---------|
| 14a       | NO₂  | o-MeO | 83     | 178     |
| 14b       | CH₃  | o-MeO | 85     | Oil     |
| 14c       | H    | o-MeO | 89     | Oil     |
| 14d       | NO₂  | p-NO₂ | 60     | 124     |
| 14e       | CH₃  | p-NO₂ | 63     | 252     |
| 14f       | H    | p-NO₂ | 86     | 210     |
| 14g       | NO₂  | p-Br  | 72     | 268     |
| 14h       | CH₃  | p-Br  | 75     | 248     |
| 14i       | H    | p-Br  | 86     | 240     |
| 16a       | NO₂  |      | 78     | 206     |
| 16b       | CH₃  |      | 85     | 154     |
Conclusion

In this work, some new thiazolobenzimidazole derivatives have been synthesized using two different synthetic methods. All the compounds were characterized by nuclear magnetic resonance and mass spectroscopy. The analyzes have shown that the 3-(2-methoxyphenyl)-6-nitrobenzo[4,5]imidazo[2,1-b]thiazole 14a was a mixture of two isomers which were separated by a selective crystallization from diethyl ether, their structures were further confirmed by RX analysis.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

SC carried out the synthesis of compounds 5b-e, 9, 10, 12a, 14a-h and 16a-b; Spectroscopic analysis of the synthesized compounds; Writing of the manuscript (French); RSPZ carried out the synthesis of compounds 4, 5a and 11; Spectroscopic analysis of the synthesized compounds; SJA corrected the manuscript (French version); VMS: Translated the manuscript into English; FB Corrected of the manuscript (English version); DS carried out the Second correction of the manuscript (French version); AA Produced of spectra (NMR, MS and X-rays)

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