Available online at http://www.ifgdg.org

Int. J. Biol. Chem. Sci. 11(3): 1320-1335, June 2017

ISSN 1997-342X (Online), ISSN 1991-8631 (Print)

International Journal of Biological and Chemical Sciences

Original Paper http://ajol.info/index.php/ijbcs http://indexmedicus.afro.who.int

Synthesis of novel thiazolobenzimidazoles

Siomenan COULIBALI*, Roger Simplice Pépin ZOAKOUMA, Sagne Jacques AKPA, Venance Martial SAY, Fanté BAMBA, Drissa SISSOUMA and Ané ADJOU

Laboratoire de Chimie Organique et de Substances Naturelles, UFR SSMT, Université Félix Houphouët Boigny, 22 B.P 582 Abidjan 22, République de Côte d'Ivoire.
**Corresponding author, E-mail: bsiomenan@yahoo.fr, phone: (+225) 02 65 90 03*

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-1*H*-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 ^{1}H, ^{13}C 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.

Keywords: Thiazolo[3,2-*a*]benzimidazol-3-ones, thiazolo[3,2-*a*]benzimidazoles, hologenoesters, 2-mercaptobenzimidazoles, tetrahydrobenzo[*d*]benzo[4,5]imidazo[2,1-*b*]thiazoles, flourene.

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 B_{12} (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. lambia* (Cedillo-Rivera and Muñoz, 1992; Chavez et al., 1992; Sears and

DOI : https://dx.doi.org/10.4314/ijbcs.v11i3.32

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 1*H,*3*H*-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.*

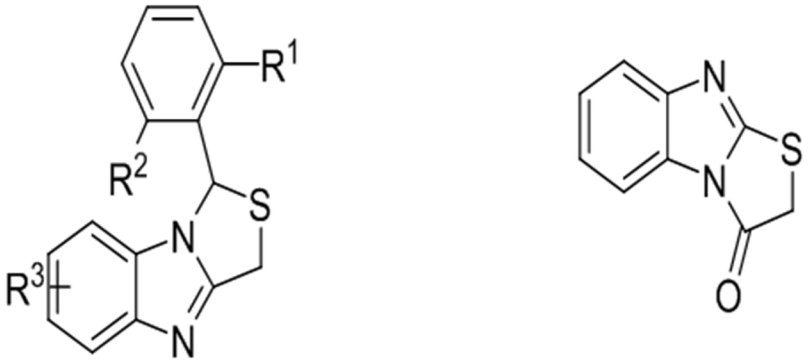


Figure 1: Structure of TBZs and 1,3-thiazolo [3,2-*a*] benzimidazol-3-ones.

MATERIALS AND METHODS

General procedures for analyses

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C 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 (0.04-0.06mm) (Merck AG Darmstadt, Germany).

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

Solution of 5-(un) substituted-1*H*-benzimidazole-2-thiols **2** (2 g) in dry ethanol (20 mL) and halogenoester compounds (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 1*H*-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 / ethyleacétate: 70/30), Rf = 0.69, mobile phase : ethylacetate / ethanol : 50/50.

^{1}H NMR (DMSO-*d6*,300 MHz), δ (ppm) : 4.32 (s, 2H, C<u>H</u>$_2$) ; 7.24-7.56 (m, 4H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm) : 34.09 (<u>C</u>H$_2$) ; 113.47-136.34 (C$_{ar}$) ; 149.70 (<u>C</u>=N) ; 169.28 (<u>C</u>=O).

Mass (m/z) = 190. M^+ = 190 (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-1*H*-benzimidazole-2-thiol (2.00 g, 1.02 10^{-2} mol) and ethyl 2-bromoacetate (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 / ethylacetate : 70/30.

^{1}H NMR (DMSO-*d6*, 300 MHz), δ (ppm): 4.31 (s, 2H, C<u>H</u>$_2$) ; 7.61-8.30 (m, 3H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm) : 33.86 (<u>C</u>H$_2$) ; 110.12-155.29 (C$_{ar}$) ; 168.03 (<u>C</u>=N) ; 169.15 (<u>C</u>=O).

Mass (m/z) = 235. M^+ = 235 (26), M+1 = 236.12 (25), 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 5c

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

^{1}H NMR (DMSO-*d6*, 300 MHz), δ (ppm) : 2.46 (s, 3H, C<u>H</u>$_3$) ; 4.51 (s, 2H, C<u>H</u>$_2$) ; 7.27-7.59 (m, 3H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm) : 21.04 (<u>C</u>H$_3$) ; 52.94 (C<u>H</u>$_2$) ; 112.91-135.01 (Car) ; 149.24 (<u>C</u>=N) ; 168.65 (<u>C</u>=O).

Mass (m/z) = 204. M^+ = 204 (100), M+1 = 205 (12), 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 1*H*-benzimidazole-2-thiol (2.00 g, 1.33 10^{-2} mol) and ethyl 2-bromopropanoate (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 (ethylacetate / hexane : 50/50), Rf = 0.66, mobile phase : ethylacetate / hexane : 50/50.

Diasteroisomere R(S) :

^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm) : 1.63 (d, 3H, C<u>H</u>$_3$, J = 7.5 Hz) ; 4.25 (q, 1H, C<u>H</u>, J = 7.5 Hz) ; 7.22-7.26 (m, 4H, Har).

^{13}C NMR (Acetone, 75 MHz), δ (ppm) : 19.44 (CH_3) ; 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).

Diasteroisomere S(R) :

^{1}H NMR (Acetone, 300 MHz), δ (ppm) : 1.64 (d, 3H, CH_3, J = 7.5 Hz) ; 4.68 (q, 1H, CH, J = 7.5 Hz) ; 7.15-7.18 (m, 4H, Har).

^{13}C NMR (Acetone, 75 MHz), δ (ppm) : 19.44 (CH_3) ; 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]imidazo[2,1-b] thiazol-3(2H)-one 5e

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

Diastereoisomer R(S):

^{1}H NMR (DMSO-*d6*, 300 MHz), δ (ppm): 1.6 (d, 3H, CH_3, J = 3 Hz); 4.7 (m, 1H, H-2) ; 7.61-8.32 (m, 3H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm) : 17.89 (CH_3) ; 43.41 (CH_2) ; 110.49-142.89 (Car) ; 153.96 (C=N) ; 171.39 (C=O).

Mass (m/z) = 249. M^+ = 249 (28), M+1 = 250 (15), m/z (%) : 222 (100), 195 (48), 176 (48), 149 (28), 148 (17), 121 (17), 105(16), 90 (38).

Diastereoisomere S(R) :

^{1}H NMR (DMSO-*d6*, 300 MHz), δ (ppm) : 1.62 (d, 3H, CH_3, J = 3 Hz) ; 4.7 (m, 1H, H-2) ; 7.61-8.32 (m, 3H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm) : 18.30 (CH_3) ; 43.91 (CH_2) ; 110.49-142.89 (Car) ; 154.53 (C=N) ; 172.22 (C=O).

Mass (m/z) = 249. M^+ = 249 (28), M+1 = 250 (15), m/z (%) : 222 (100), 195 (48), 176 (48), 149 (28), 148 (17), 121 (17), 105(16), 90 (38).

3-ethoxy-7-methy-2,3-dihydrobenzo[4,5] imidazo[2,1-b]thiazol 9c

From 5-methyl-1*H*-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) **9c** was obtained (5.99 g, 21%) as white crystals. MP = 200 °C, selective crystallization by diethyl ether, Rf = 0.60, mobile phase: hexane / ethylacetate: 50/50.

Diastereoisomere R(S) :

^{1}H NMR (DMSO-*d6*, 300 MHz), δ (ppm) : 1.09 (t, 3H, CH_3, J = 3 Hz) ; 2.43 (s, 3H, CH_3) ; 3.72 (m, 2H, O-CH_2) ; 4.06 (d, 1H, CH_2, J_{gem} = 12 Hz) ; 4.5 (m, 1H, CH_2) ; 6.55 (dd, 1H, CH, J_{trans} = 6 Hz, J_{cis} = 3 Hz) ; 7.25-8.04 (m, 3H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm) : 14.95 (CH_3-CH_2) ; 20.98 (CH_3) ; 43.57 (CH_3-CH_2) ; 64.44 (CH_2) ; 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).

Diastereoisomere S(R) :

^{1}H NMR (DMSO-*d6*, 300 MHz), δ (ppm) : 1.12 (t, 3H, CH_3, J_{Cis} = 3 Hz) ; 2.45 (s, 3H, CH_3) ; 3.72 (m, 2H, O-CH_2) ; 4.06 (d, 1H, CH_2, J_{gem} = 12 Hz) ; 4.5 (m, 1H, CH_2) ; 6.55 (dd, 1H, CH, J_{trans} = 6 Hz, J_{cis} = 3 Hz) ; 7.25-8.04 (m, 3H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm) : 14.95 (CH_3-CH_2); 21.09 (CH_3) ; 43.65 (CH_3-CH_2) ; 64.5 (CH_2) ; 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 1*H*-benzimidazole-2-thiol (2.00 g, 1.33 10^{-2} mol) and 2-bromo-1,1-diethoxyethane (3.15 g, 1.60 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}H NMR (DMSO-*d6,* 300 MHz); δ (ppm): 3.74 (dd, 1H, C$\underline{H}_2$, $J_{gém}$ = 12.3 Hz, J_{cis} = 6 Hz) ; 4.33 (dd, 1H, C$\underline{H}_2$, J_{gem} = 12.3 Hz, J_{trans} = 1.8 Hz) ; 4.83 (s, 1H, O$\underline{H}$) ; 6.38 (dd, 1H, C$\underline{H}$, J_{trans} = 1.8 Hz, J_{cis} = 6 Hz) ; 7.20-7.60 (m, 4H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm): 43.45 (C$\underline{H}_2$); 78.53 (C$\underline{H}$) 110.59-146.58 (Car) ;157.60 (C$\underline{=}$N).

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}H NMR (DMSO-*d6*, 300 MHz), δ (ppm) : 3.85 (dd, 1H, C$\underline{H}_2$, J_{gem} = 12.3 Hz, J_{cis} = 6 Hz) ; 4.44 (dd, 1H, C$\underline{H}_2$, J_{gem} = 12.3, Hz, J_{trans} = 1.8 Hz) ; 4.35 (s, 1H, O$\underline{H}$) ; 6.53 (dd, 1H, C$\underline{H}$, J_{trans} = 1.8 Hz, J_{cis} = 6 Hz) ; 7.34-7.77 (m, 4H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm): 44.56 (C$\underline{H}_2$) *;* 80.22 (C$\underline{H}$) *;* 111.87-139.68 (Car) *;* 157.70 (C$\underline{=}$N).

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-1*H*-benzimidazole-2-thiol (2.00 g, 1.02 10^{-2} mol) and 2-bromo-1,1-diethoxyethane (2.42 g, 1.23 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}H NMR (DMSO-*d6*, 300 MHz), δ (ppm) : 3.37 **(**dd, 1H, C$\underline{H}_2$, J_{gem} = 12 Hz, J_{cis} = 3 Hz) ; 4.38 (dd, 1H, C$\underline{H}_2$, J_{gem} = 12 Hz, J_{trans} = 6 Hz) ; 6.49 (dd, 1H, C$\underline{H}$, $J_{trans.}$ = 6Hz, J_{cis} = 3Hz) ; 6.65 (s, 1H, O$\underline{H}$) ; 7.65-8.56 (m, 3H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz) : δ (ppm) : 43.27 (C$\underline{H}_2$) ; 78.59 (C$\underline{H}$) ; 106.86-147.11 (Car) ; 162.06 (C$\underline{=}$N).

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}H NMR (DMSO-*d6*, 300 MHz), δ (ppm) : 3.37 **(**dd, 1H, C$\underline{H}_2$, J_{gem} = 12 Hz, J_{cis} = 3 Hz) ; 4.38 (dd, 1H, C$\underline{H}_2$, J_{gem} = 12 Hz, J_{trans} = 6 Hz) ; 6.49 (dd, 1H, C$\underline{H}$, $J_{trans.}$ = 6Hz, J_{cis} = 3Hz) ; 6.65 (s, 1H, O$\underline{H}$) ; 7.65-8.56 (m, 3H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz) : δ (ppm) : 43.27 (C$\underline{H}_2$) ; 78.80 (C$\underline{H}$) ; 110.55-152.35 (Car) ; 163.69 (C$\underline{=}$N).

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-1*H*-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 cristallization, Rf = 0.33, mobile phase : Hexane / ethylacetate : 50/50.

Diastereoisomere R(S) :

^{1}H NMR (DMSO-*d6*, 300 MHz) ; δ (ppm) : 2.43 (s, 3H, C$\underline{H}_3$) ; 3.9 (d, 1H, C$\underline{H}_2$, J = 12 Hz) ; 4.51 (dd, 1H, C$\underline{H}_2$, J_{gem} = 12 Hz, J_{trans} = 6 Hz) ; 5.26 (s, 1H, O$\underline{H}$) ; 6.58 (t, 1H, C$\underline{H}$, J_{trans} = 6 Hz) ; 7.25-7.73 (m, 3H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm) : 21.02 (C$\underline{H}_3$) ; 44.81 (C$\underline{H}_2$) ; 80.53 (C$\underline{H}$) ; 111.78-135.27 (Car) ; 156.93 (C$\underline{=}$N).

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}H NMR (DMSO-*d6*, 300 MHz), δ (ppm) : 2.43 (s, 3H, C$\underline{H}_3$) ; 3.9 (d, 1H, C$\underline{H}_2$, J = 12 Hz) ; 4.51 (dd, 1H, C$\underline{H}_2$, J_{gem} = 12 Hz, J_{trans} = 6 Hz) ; 5.26 (s, 1H, O$\underline{H}$) ; 6.58 (t, 1H, C$\underline{H}$, J_{trans} = 6 Hz) ; 7.25-7.73 (m, 3H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm) : 21.08 (CH_3) ; 44.81 (CH_2) ; 80.73 (CH) ; 111.95-137.27 (Car) ; 156.93 (C=N).

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).

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

From 1*H*-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^{-1} g, 24%) as yellow crystals. MP = 252 °C, purified by chromatography on silica gel (hexane / ethyleacétate : 70/30), Rf = 0.16, mobile phase : dichlorométhane / acétate d'éthyle : 90 / 10.

^{1}H NMR (DMSO-*d6*, 300 MHz), δ (ppm) : 1.1 (t, 3H, CH_3, J = 7.2 Hz) ; 1.18 (t, 3H, CH_3, J = 7.2 Hz) ; 3.10 (q, 2H, CH_2, J = 7.2 Hz) ; 3.44 (q, 2H, CH_2, J = 7.2 Hz) ; 4.65 (s, 1H, CH) ; 7.4-7.9 (m, 4H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm) : 18.51 (CH_3) ; 45.50 (S-CH-) ; 55.97 (CH_2) ; 111.78-129.73 (Car) ; 149.28 (C=N) ; 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-3oxo-2,3-dihydrobenzo [4,5] imidazo [2,1-b] thiazole-2-carboxylate 11b

From 5-nitro-1*H*-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 / ethylacetate : 70/30), Rf = 0.40, mobile phase : Hexane / ethylacetate : 70/30.

^{1}H NMR (DMSO-*d6*, 300 MHz), δ (ppm) : 1.16 (t, 3H, CH_3, J = 6 Hz) ; 4.13 (q, 4H, CH_2 , J = 6 Hz) ; 4.33 (s, 1H, H-2) ; 7.61-8.31 (m, 3H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm) : 13.92 (CH_3) ; 33.39 (S-CH-) ; 61.34 (CH_2) ; 110.12-142.68 (Car) ; 155.3 (C=N) ; 168.08 (COO).

Mass (m/z) = 307. M^+ = 307 (48), M+1 = 308 (64), m/z (%) : 281 (37), 121 (30), 118 (45), 91 (27), 90 (44).

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

From 5-methyl-1*H*-benzimidazole-2-thiol (2.00 g, 1.22 10^{-2} mol) and diethyl 2-chloromalonate (2.84 g, 1.46 10^{-2} mol) **11c** was obtained (1.35 g, 40%) as beige crystals. MP = 98 °C, purified by chromatography on silica gel (dichlomethane / ethylacetate : 90/10), Rf = 0.70, mobile phase : dichloromethane / ethylacetate : 90/10.

^{1}H NMR (DMSO-*d6*, 300 MHz) δ (ppm) : 1.17 (t, 3H, CH_3, J = 6 Hz) ; 2.38 (s, 3H, CH_3) ; 4.2 (q, 2H, CH_2, J = 6 Hz) ; 5.56 (s, 1H, H-2) ; 6.96-7.37 (m, 3H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm) : 13.69 (CH_3-CH_2) ; 21.12 (CH_3) ; 52.46 (S-CH-) ; 62.35 (CH_2) ; 113.57-138.42 (Car) ; 145.75 (C=N) ; 165.52 (COO).

Mass (m/z) = 276. M^+ = 276 (12), M+1 = 277 (15), m/z (%) : 249 (66), 204 (38), 176 (32), 175 (89), 164 (52), 162 (100), 136 (51), 131 (23), 104 (28), 91 (49), 78 (37), 77 (82), 57 (28), 45 (23).

2,3-dihydro-4H-benzo[4,5]imidazo[2,1-b] [1,3] thiazin-4-one 12a

From 1*H*-benzimidazole-2-thiol (2.00 g, 1.33 10^{-2} mol) and methyl 3-bromopropanoate (2.67 g, 1.60 10^{-2} mol) **12a** was obtained (2.42 g, 89%) as white crystals. MP = 140 °C, re-crystallized with dichlorometane, Rf = 0.71, mobile phase : dichloromethane / ethylacetate : 90/10.

^{1}H NMR (DMSO-*d6*, 300 MHz), δ (ppm) : 2.79 (t, 2H, CH_2, J = 6.9 Hz) ; 3.54 (t, 2H, CH_2S, J = 6.9 Hz) ; 7.28-7.61 (m, 4H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm) : 27.22 (CH_2) ; 34.04 (CH_2) ; 113.40-135.7 (Car) ; 150.20 (C=N) ; 172.52 (C=O).

Mass (m/z) = 204. M^+ = 204 (86), m/z (%) : 175 (53), 150 (31), 90 (26), 77 (9), 63 (22), 55 (100), 39 (14), 27 (28).

General procedures for synthesis of 3-substituedbenzo [4,5] imidazo[2,1-*b*]thiazoles derivates 14 and 16

A mixture of 5-(un)substituted-1*H*-benzimidazole-2-thiols **2** (3 g) and substitued acetophenones **13** (2 eq.) or 4-methyl cyclohexanone **15** (2 eq.) was refluxed in acetic acid (30 mL) containing 1 mL of concentrated H_2SO_4 for 24-48 hours. The reaction mixture was cooled and neutralized with NH_4OH 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-1*H*-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-C<u>H</u>$_3$) ; 7.32-8.12 (m, 8H, Har) ; 8.32 (s, 2H, S-C<u>H</u>=) ; 8.42-8,91 (m, 6H, Har).

^{13}C NMR (TFA, 75 MHz), δ (ppm) : 54.41 (<u>C</u>H$_3$O) , 54.68 (<u>C</u>H$_3$O) ; 108.63-144.25(Car) ; 111(<u>C</u>H$_2$) ; 111.17-157.8 (Car) , 146.28 (2 <u>C</u>=N) ; 156.57 (2 N-<u>C</u>H-).

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-1*H*-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, C<u>H</u>$_3$) ; 3.41 (s, 3H, C<u>H</u>$_3$) ; 6.6-7.52 (m, 8H, Har).

^{13}C NMR (DMSO, 75 MHz), δ (ppm) : δ (ppm) : 21.22 (<u>C</u>H$_3$) ; 55.39 (<u>C</u>H$_3$) ; 108.5-146.04 (Car) ; 111.42 (2 <u>C</u>H$_2$) ; 117.71-157.51 (Car) ; 148.23 (2 <u>C</u>=N) ; 155.76 (2 N-<u>C</u>H-).

Mass (m/z) = 294. 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).

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

From 1*H*-benzimidazole-2-thiol (2.00 g, 1.33 10^{-2} mol) and 1-(2-methoxyphenyl)ethan-1-one (2.40 g, 1.60 10^{-2} mol) **14c** was obtained (3.13 g, 89%) as oil, Rf = 0.56, mobile phase : Hexane/ ethylacetate : 70/30.

^{1}H NMR (DMSO-*d6*, 300 MHz), δ (ppm) : 2.41 (s, 3H, C<u>H</u>$_3$) ; 6.85-7.29 (m, 5H, Har and S-C<u>H</u>=) ; 7.50-7.70 (m, 4H, Har).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm) : 55.85 (C<u>H</u>$_3$) ; 108.76-132.21 (Car) ; 112.26-157.55 (Car) ; 147.84 (<u>C</u>=N) ; 155.9 (N-<u>C</u>H-).

Mass (m/z) = 380. M^+ = 380 (100), M+1 = 381 (37), m/z (%) : 279 (25), 265 (5), 247 (15), 237 (7), 140 (16), 134 (7), 132 (9), 131 (75), 119 (4), 103 (6), 90 (10), 89 (7), 77 (8), 63 (6).

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

From 5-nitro-1*H*-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 / acétate 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-C<u>H</u>=).

^{13}C NMR (TFA, 75 MHz), δ (ppm) : 109.66-151.19 (Car) ; 115.5 (CH_2) ; 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 14e

From 5-methyl-1*H*-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) **14e** was obtained (2.28 g, 63%) as yellow crystals. MP = 252 °C, re-crystallized with methanol, Rf = 0.55, mobile phase : hexane / ethylacetate : 80/20.

^{1}H NMR (DMSO-*d6*, 300 MHz), δ (ppm) : 2.43 (s, 3H, CH_3) ; 7.16-7.53 (m, 4H, Har and S-CH=) ; 8.04 (d, 2H, H in ortho) ; 8.46 (dd, 2H, H in meta, J_{ortho} = 9 Hz, J_{meta} = 3 Hz).

^{13}C NMR (DMSO-*d6*, 75 MHz), δ (ppm) : 21.30 (CH_3) ; 55. 39 (CH_3) ; 111.44-135.08 (Car) ; 111.2 (2 CH_2) ; 118.47-146.3 (Car) ; 148.09 (2 C=N) ; 148.52 (2 N-CH-).

Mass (m/z) = 309. M^+ = 309 (100), M+1 = 310 (15), m/z (%) : 279 (8), 264 (7), 263 (30), 262 (13), 261 (12), 249 (4), 248 (15), 205 (6), 204 (5), 190 (6), 89 (11).

3-(4-nitro-phenyl)benzo[4,5]imidazo[2,1-b] thiazole 14f

From 1*H*-benzimidazole-2-thiol (2.00 g, 1.33 10^{-2} mol) and 1-(4-nitrophenyl)ethan-1-one (2.64 g, 1.60 10^{-2} mol) **14f** was obtained (3.38 g, 86%) as yellow crystals. MP = 210 °C, re-crystallized with methanol, Rf = 0.60, mobile phase : hexane / ethylacetate : 70/30.

^{1}H NMR (TFA, 300 MHz), δ (ppm) : 7.54 (s, 1H, S-CH=) ; 7.63-8.08 (m, 4H, Har) ; 8.20 (d, 2H, H in ortho, J_{ortho} = 9 Hz) ; 8.78 (d, 2H, H in meta, J_{ortho} = 9 Hz).

Mass (m/z) = 295. M^+ = 295 (100), M+1 = 296 (31), m/z (%) : 250 (17), 249 (41), 248 (24), 205 (16), 90 (22), 86 (16), 84 (24), 77 (18), 76 (17), 75 (32), 74 (20), 69 (25), 64 (20), 63 (32), 55 (52), 51 (46), 50 (17).

3-(4-bromophenyl)-6-nitrobenzo[4,5]imidazo [2,1-b]thiazole 14g

From 5-nitro-1*H*-benzimidazole-2-thiol (2.00 g, 1.02 10^{-2} mol) and 1-(4-bromophenyl)ethan-1-one (1.46 g, 1.23 10^{-2} mol) **14g** was obtained (2.76 g, 72%) as orange crystals. MP = 268 °C, re-crystallized with methanol, Rf = 0.70, mobile phase : hexane / ethylacetate : 70/30.

^{1}H 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).

^{13}C NMR (TFA, 75 MHz), δ (ppm) : 108.65-133.04 (Car) ; 112.4 (CH_2) ; 119.91-135. 83 (Car) ; 146.47 (CH_2) ; 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).

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

From 5-methyl-1*H*-benzimidazole-2-thiol (2.00 g, 1.22 10^{-2} mol) and 1-(4-bromophenyl)ethan-1-one (1.74 g, 1.46 10^{-2} mol) **14h** was obtained (3.14 g, 75%) as beige crystals. MP = 248 °C, re-crystallized with methanol, Rf = 0.60, mobile phase : hexane / ethylacetate : 80/20.

^{1}H NMR (TFA, 300 MHz), δ (ppm) : 2.62 (s, 3H, CH_3) ; 7.65-7.62 (m, 3H, Har) ; 7.67 (d, 2H, H in ortho, J_{ortho} = 9 Hz) ; 7.75 (s, 1H, S-CH=) ; 7.90 (dd, 2H, H in meta, J_{ortho} = 9 Hz, J_{meta} = 3 Hz).

^{13}C NMR (TFA, 75 MHz), δ (ppm) : 19.73 (CH_3) ; 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 1*H*-benzimidazole-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), δ (ppm) : 7.29 (s, 1H, S-C<u>H</u>=) ; 7.33-7.82 (m, 8H, Har).

^{13}C NMR (TFA, 75 MHz), δ (ppm) : 108.56-135.17 (Car) ; 112.92 (S-<u>C</u>H=) ; 116.07-126.82 (Car) ; 135.7 (<u>C</u>=N) ; 153.10 (N-<u>C</u>=).

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-1*H*-benzimidazole-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), δ (ppm) : 1.29 (m, 3H, C<u>H</u>$_3$) ; 1.81-1.89 (m, 1H, C<u>H</u>-CH$_3$) ; 2.21-2.30 (m, 2H, C<u>H</u>$_2$) ; 2.59-3.08 (m, 2H, C<u>H</u>$_2$) ; 3.34-3.50 (m, 2H, C<u>H</u>$_2$) ; 8.08-9.03 (m, 3H, Har).

^{13}C NMR (TFA, 75 MHz), δ (ppm) : 18.67 (<u>C</u>H$_3$) ; 22.34 (<u>C</u>H$_2$) ; 28.24 (<u>C</u>H-CH$_3$) ; 28.78 (CH$_2$) ; 30.95 (<u>C</u>H$_2$) ; 108.66-130.18 (Car) ; 146.18 (<u>C</u>=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).

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

From 5-methyl-1*H*-benzimidazole-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), δ (ppm) : 1.29 (m, 3H, C<u>H</u>$_3$) ; 1.81-1.89 (m, 1H, C<u>H</u>-C<u>H</u>$_3$) ; 2.21-2.30 (m, 2H, C<u>H</u>$_2$) ; 2.59-3.08 (m, 2H, C<u>H</u>$_2$) ; 3.34-3.5 (m, 2H, C<u>H</u>$_2$) ; 8.08-9.03 (m, 3H, Har).

^{13}C NMR (TFA, 75 MHz), δ (ppm) : 18.78 (<u>C</u>H$_3$) ; 19.75 (<u>C</u>H$_3$) ; 22.5 (<u>C</u>H$_2$) ; 28.48 (<u>C</u>H-CH$_3$) ; 28.85 (CH$_2$) ; 30.92 (<u>C</u>H$_2$) ; 108.66-130.18 (Car) ; 139.52 (<u>C</u>=N) ;149 (C=<u>C</u>) ; 150.78 (C=<u>C</u>).

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).

RESULTS AND DISCUSSION

We previously described the synthesize of 1,3-thiazolo[3,2-*a*]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-*a*]benzimidazol-3-ones **5** is illustrated in Scheme 1.

Synthesis of 1*H*-benzimidazole-2-thiols (2-mecaptobenzimidazoles) **2** 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, 1*H*-benzimidazole-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

dimethylformamide (DMF). The reaction mixture was stirred at room temperature for 24 hours and then treated with water to precipitate 1*H*-benzimidazole-2-thiols **2**. The reaction between halogenoester compounds **3** and 5-(un)substituted-1*H*-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-(2*H*)-ones **5**. The substituted target compounds **5** (Scheme 2) were obtained in good yields (66-90%) by cyclocondensation reaction of 5-(un)substituted-1*H*-benzimidazole-2-thiol **2** and (ethyl 2-bromoacetate or ethyl 2-brompropanoate) **3** under reflux in ethanol. On the other hand, by refluxing in dry ethanol 1*H*-benzimidazole-2-thiol or 5-nitro-1*H*-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-1*H*-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-mercaptobenzimidazole used.

Diethyl 2-chloromalonate reacted in a similar way with 1*H*-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-1*H*-benzimidazol-2-thiol or 5-methyl-1*H*-benzimidazol-2-thiol to give the compounds **11b** (80%) and **11c** (40%) respectively (Scheme 2).

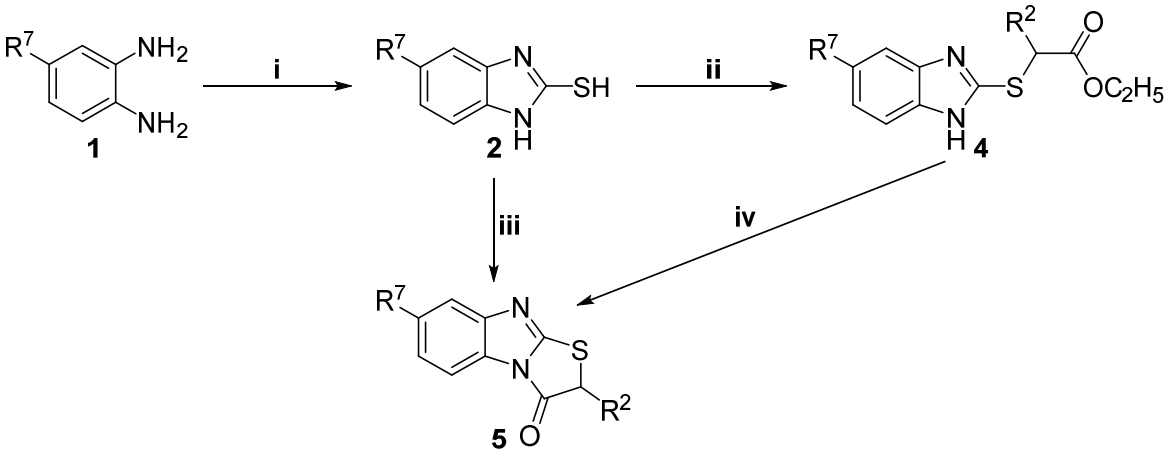
This synthetic approach was used to prepare heterocyclic analog containing six numbers. Fluorene analog **12a** were prepared by the reacting methyl 3-bromopropanoate **8** with 1*H*-benzimidazol-2-thiol **2** (Scheme 2). Compound **2** and compound **8** were heated under reflux in dry ethanol to afford 2,3-dihydro-1-thia-4*a*,9-diaza-fluoren-4-one **12a** in good yield. All the compounds were characterized by means ^{1}H, ^{13}C 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-mercaptobenzimidazole **2** with aromatic ketones **13** in boiling acetic acid containing 1 mL of concentrated H_2SO_4 (Scheme 3).

When $R^{'}$ = *o*-OCH_3 and R^{7} = NO_2 (compound **14a**), the analysis of the ^{1}H 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-mercaptobenzimidazole **2** in the same reaction conditions (Scheme 3).

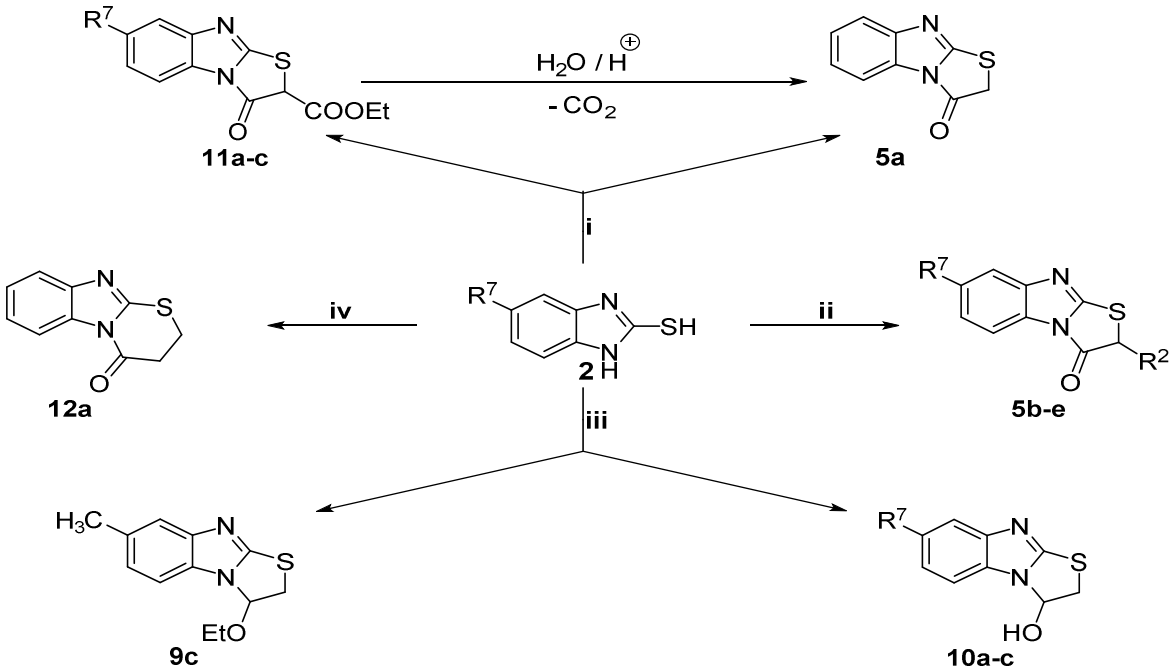
The mechanism of the reaction is still under investigation. It may be proceeded *via* formation of dimeric disulfide **17** followed by nucleophilic attack by α-aryl/alkyl α-hydroxymethylene carboxylate **18** (formed by esterification of the enol form) as shown in Scheme 4. The less stable intermediate **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.



i: CS_2, DMF, r.t
ii: ethyl-2-bromo-2-R^2-acetate **3**, NEt_3, EtOH, r.t
iii: ethyl-2-bromo-2-R^2-acetate **3**, EtOH, Δ
iv: EtOH, HCl, Δ

R^2 = H, CH_3; R^7 = H, NO_2, CH_3

Scheme 1: Synthesis of the 1,3-thiazolo[3,2-*a*]benzimidazol-3-ones.



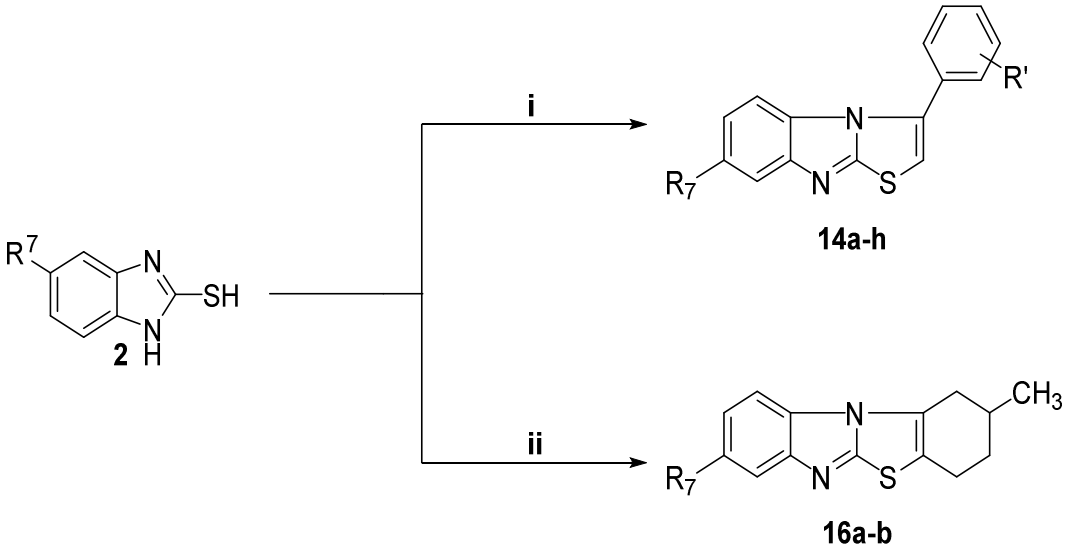
i: Diethyl 2-chloromalonate **7**, EtOH, Δ
ii: Ethyl 2-bromo-2-R^2-acetate **3**, EtOH, Δ
iii: 2-bromo-1,1-diethoxyethane **6**, EtOH, Δ
iv: Methyl 3-bromopropanoate **8**, EtOH, Δ

R^2 = H, CH_3, COOEt; R^7 = H, NO_2, CH_3

Scheme 2: Syntesis 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	NO_2	H	=O	90	202
5c	CH_3	H	=O	75	170
5d	H	CH_3	=O	66	127
5e	NO_2	CH_3	=O	75	184
9c	CH_3	H	-OEt	21	200
10a	H	H	-OH	88	202
10b	NO_2	H	-OH	83	208
10c	CH_3	H	-OH	68	218
11a	H	Et-COO	=O	24	252
11b	NO_2	Et-COO	=O	80	201
11c	CH_3	Et-COO	=O	40	98
12a	H	-	=O	89	140



i: R'-acetophenone **13**, AcOH / H_2SO_4, Δ
ii: 4-methyl-cyclohexanone **15**, AcOH / H_2SO_4, Δ

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

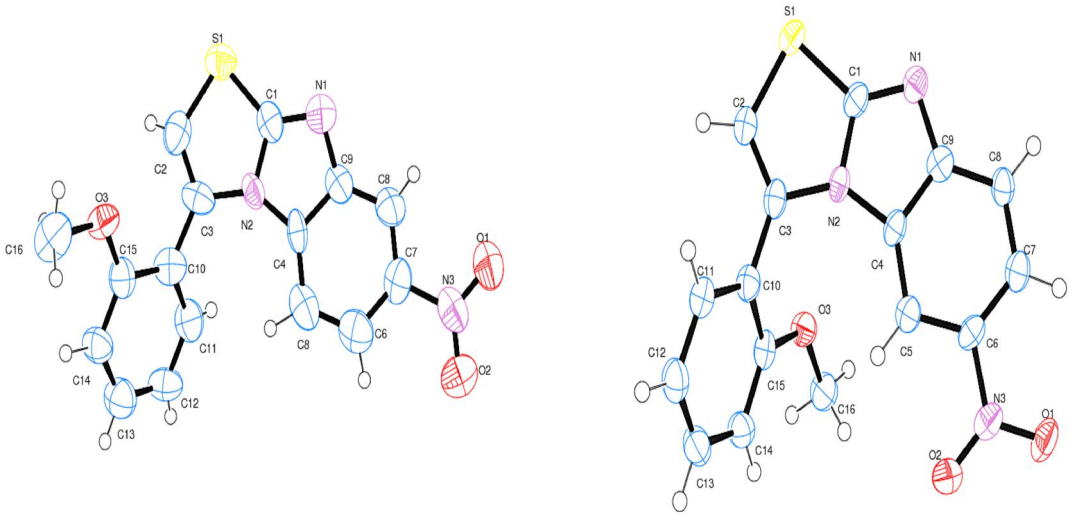
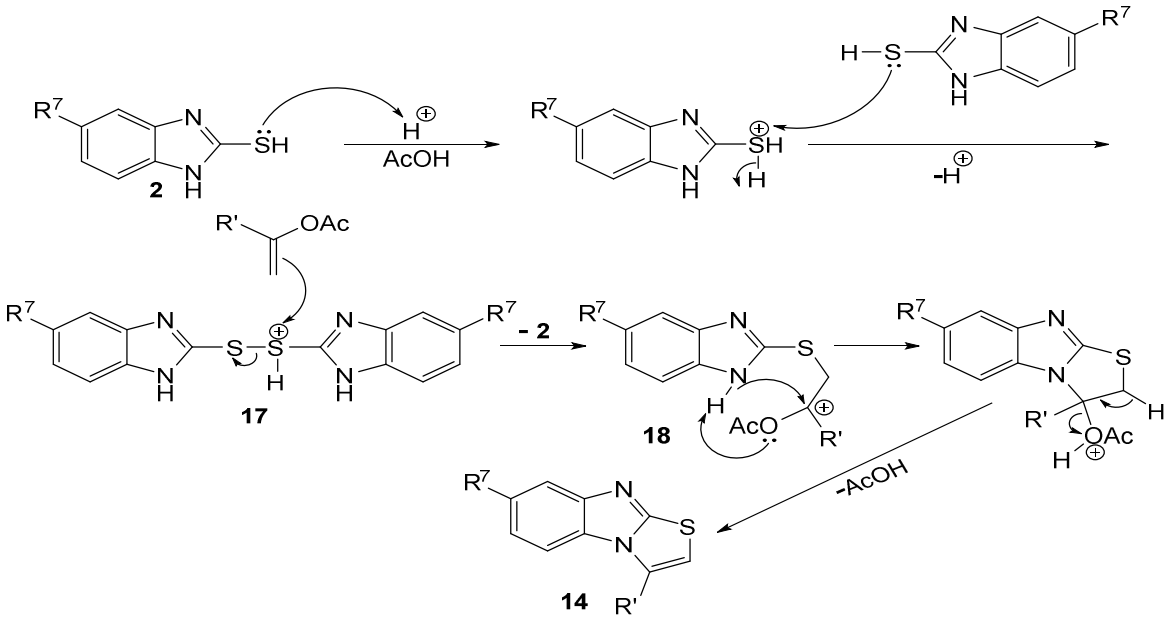


Figure 2: X-ray crystal structures of compound **14a.**

Table 2: Physico-chemical data for the synthesised compounds **14** and **16**.

Compounds	R^7	R'	Yields	MP (°C)
14a	NO_2	*o*-MeO	83	178
14b	CH_3	*o*-MeO	85	Oil
14c	H	*o*-MeO	89	Oil
14d	NO_2	*p*-NO_2	60	124
14e	CH_3	*p*-NO_2	63	252
14f	H	*p*-NO_2	86	210
14g	NO_2	*p*-Br	72	268
14h	CH_3	*p*-Br	75	248
14i	H	*p*-Br	86	240
16a	NO_2	-	78	206
16b	CH_3	-	85	154



Scheme 4: Mechanism of formation of compounds **14.**

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)

ACKNOWLEDGMENTS

We wish to thank the CEISAM laboratory (Chimie Et Interdisciplinarité, Synthèse, Analyse, Modélisation) of the University of Nantes (France) for providing us the chemical reagents and material for the spectroscopic analyzes. Our thanks go towards the Laboratory of Crystallography and Molecular Physical appearance, UFR SSMT University Félix Houphouët Boigny (République de Côte d'Ivoire) for the X-ray spectral data.

REFERENCES

Abdel-Aziz HA, Saleh TS, El-Zahabi HAS. 2010. Facile synthesis and *in-vitro* antitumor activity of some pyrazolo[3,4-*b*]pyridines and pyrazolo[1,5-*a*] pyrimidines linked to thiazolo[3,2-*a*]benzimidazole moiety. *Arch. Pharm.*,

343: 24-30. Doi: 10.1002/ardp. 200900082.

Akpa SJ, Say VM, Zoakouma RSP, Fanté B, Sissouma D, Ané Adjou A. 2016. Synthesis of 2-(benzylthio) benzimidazole, 2-[(benzimidazol-2-yl) methylthio] benzimidazole and structural analogues against *Haemoncus contortus*. *African Journal of Pharmacy and Pharmacology*, **10**(33): 670-680. http://dx.doi.org/ 10.5897/AJPP2016.4557.

Akpa SJ, Zoakouma RSP, Say VM, Ouattara M, Kone MW, Sissouma D, Adjou A. 2016. Synthesis and *in vitro* antifungal evaluation of 2-thioalkylaryl-benzimidazoles derivatives against *Candida albicans*. *Int. J. Biol. Chem. Sci*., **10**(3): 1403-1412. http://www.ifg-dg.org.

Al-Rashood KA, Abdel-Aziz HA. 2010. Thiazolo [3,2-*a*] benzimidazoles: Synthetic Strategies, Chemical Transformations and Biological Activities. *Molecules*, **15**: 3775-3815. Doi:10.3390/molecules15063775.

Amari M, Fodili M, Nedjar-kolli B. 2002. Reactivity studies on 4-aminopyrones: Access to benzimidazole and benzimidazolone derivatives. *J. Heterocycl. Chem*., **39**: 811-811.

Baxt LA, Singh U. 2008. New insights into *Entamoeba histolytica* pathogenesis. *Current Opinion in Infectious Diseases,* **21**(5): 489-494. Doi: 10.1097/QCO.0b013e32830ce75f.

Bourée P, Bisaro F, Nsimba B. 2011. Diagnostiquer et traiter une giardiose. *Option Bio*. **454**: 18-19.

Cedillo-Rivera R, Muñoz O. 1992. *In-vitro* susceptibility of *Giardia lamblia* to albendazole, mebendazole and other chemotherapeutic agents. *J. Med. Microbiol.*, **37**: 221-224. Doi :10.1099/00222615-37-3-221.

Chavez B, Cedillo-Rivera R, Martinez-Palomo A. 1992. *Gardia Lamblia* Ultra structural Study of in the *vitro* Effect of Benzimidazoles. *J. Protozool.*, **39**(4): 510-515. Doi: 10.1111/j.1550-7408.1992.tb04841.

Chen HL, Feng YQ, Li XF, Wang G. 2003. 4-(2-Chlorophenyl)-3-(2,6-dichlorophenyl) spiroisoxazoline-5,2'-benzo[4,5]imidazo[2,1-*b*]thiazol-3'-one dioxane hemisolvate. *Acta. Crystalographica, Sec. E*. **59**: 1128-1129.

Chimiri A, Monforte P, Musumeci L, Rao A, Zappala M, Monforte AM. 2001. Synthesis and antitumor activity of 1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole derivatives, *Arch. Pharm*., **334**(6): 203-208.

Dianov VM. 2007. Synthesis and antioxidant properties of 3-methyl substituted thiazolo[3,2-*a*]benzimidazole. *Pharm. Chem. J*., **41**: 308-309.

Gabillet S, Lecerclé D, Loreau O, Carboni M, Dézard S, Gomis J, Taran F. 2007. Phosphinecatalyzed construction of sulfur heterocycles. *Org. Lett*., **9**(20):

Grimaudo S, Raimondi MV, Capone F, Chimirri A, Poretto F, Monforte AM, Simoni D, Tolomeo M. 2001. Apoptotic effects of thiazolobenzimidazole derivatives on sensitive and multidrug resistant leukaemic cells. *Eur. J. Cancer*., **37**(1): 122-130. DOI: 10.3109/08923978509026471.

Haque R, Huston CD, Hughes M, Houpt E, Petri WAJr. 2003. Amebiasis. *New England Journal of Medicine.* **348**(16): 1565-1573. Doi: 10.1056/NEJMra 022710.

Huang DB, White AC. 2006. An Updated Review on Cryptosporidium and Giardia. *Gastroenterology Clinics of North America,* **35**(2): 291-314. Doi: 10.1016/j.gtc.2006.03.006.

Kohler P. 2001. The biochemical basis of anthelmintic action and resistance. *International Journal for Parasitology*, **31**(4): 336–345.

Krauss H, Schiefer HG, Weber A, Slenczka W, Appel M, von Graevenitz A, Enders B, Zahner H, Isenberg HD. 2003. *Parasitic Zoonoses: Infectious Diseases*

Transmissible from Animals to Humans (3rd edn). ASM Press: Washington D.C; 280-282.

Leber AL, Novak-Weekley S. 2007. Intestinal and urogenital amebae, flagellates, and ciliates. In *Manual of clinical microbiology,* Murray PR (edn), (9th edn). ASM Press: Washington, D.C.; 2092-2112.

Mavrova AT, Anichina KK, Vuchev DI, Tsenov JA, Denkova PS, Kondeva MS, Micheva MK. 2006. Antihelminthic activity of some newly synthesized 5(6)-(un) substituted-1*H*-benzimidazol-2-ylthioacetylpiperazine derivatives. *European Journal of Medicinal Chemistry*, **41**(12): 1412-1420. Doi: 10.1016/j.ejmech.2006.07.005.

Mavrova AT, Anichina KK, Vuchev DI, Tsenov JA, Kondeva MS, Micheva MK. 2005. Synthesis and antitrichinellosis activity of some 2-substituted-[1,3] thiazolo[3,2-*a*]benzimidazol-3(2H)-ones. *Bioorganic and Medicinal Chemistry*, **13**(19): 5550-5559. Doi: 10.1016/j.bmc.2005.06.046.

Mavrova AT, Wesselinova D, Anichina K. 2016. Synthesis Of Some Novel 2-Substituted-[1,3]Thiazolo[3,2-*a*] Benzimidazol-3(2H)-Ones As Potent Cytostatic Agents. *Journal of Chemical Technology and Metallurgy*, **51**(6): 660-666.

O'Neil MJ, Smith M, Heckelman. 2001. *The Merck Index* (13th edn). Merck & Co Inc.; 1785, 10074.

Plorde JJ, Ryan IKJ, Ray CG. 2004. *Sherris Medical Microbiology: An Introduction to Infectious Diseases* 4th edn. Rhizopods. McGraw Hill: Unites States; 733-740).

Sarhan AAO, Al-Dhfyan A, Al-Mozaini MA, Adra CN, Aboul-Fadl T. 2010. Cell cycle disruption and apoptotic activity of 3-aminothiazolo [3,2-*a*]benzimidazole-2-carbonitrile and its homologues. *Eur. J. Med. Chem*., **45**: 2689-2694.

Sarhan AAO. 2000. Synthesis, characterization and reactions of 4-hydrazino-2-methylpyrimidino [4',5':4,5]thiazolo[3,2-*a*]benzimidazole. *J. Chin. Chem. Soc*., **47**: 1279-1286.

Sears SD, O'Hare J. 1989. *In vitro* susceptibility of *Trichomonas vaginalis* to 50 antimicrobial agents. *Antimicrob. Agents Chemother*., **32**: 144-146.

Sissouma D, Adjou A, Toure SA, Zoakouma RSP, Gnon B, Téa GC. 2005. Reactivity of Amidinium Salts' Access to Benzo[4,5]imidazo[2,1-*b*]Thiazoles. *Phosphorus, Sulfur, and Silicon*, **180**: 1375-1378. Doi: 10.1080/ 10426500590910620.

Sorba G, Garronne A, Serafino A, Gasco A, Orsetti M. 1986. histamine H2-receptor antagonists: ranitidine analogues containing 2-amino-5(6)-substituted-benzimidazole moieties. *Eur. J. Med. Chim. Teur*., **21**: 391-395.

Timotou A, Adjou A, Say MV, Sissouma D, Touré SA, Téa GC, N'Guessan YT. 2013. Novel synthesis of benzimidazole by Ring Contraction Rearrangement of Benzodiazepine. *Int. J. Biol. Chem. Sci*., **7**(6): 2568-2580. http://ajol.info/ index.php/ijbcs.

Van Allan JA, Deagon BD. 1963. *Organic Syntheses Collect, Wiley: New York*; **4**: 569.