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Design, synthesis of bisbenzimidazole dithiol derivatives and analogs

Kouassi Yves Guillaume MOLOU [1, 2], Tchambaga Etienne CAMARA [2, *], Adeyolé TIMOTOU [2, 3], Souleymane COULIBALY [2, *], Aka Faustin KABRAN [2], Siomenan COULIBALI [2] and Drissa SISSOUMA [2]

[1] Department of Sciences and Technology, Section of Physics-Chemistry, Ecole Normale Superieure, Abidjan, Côte d'Ivoire, 08 BP 10 Abidjan 08.

[2] Department of Physics-Chemistry, UFR Sciences of the Structures of Matter and Technology, Félix Houphouët-Boigny University, Abidjan, Côte d'Ivoire, 22 BP 582 Abidjan 22.

[3] Department of Mathematics, Physics-Chemistry, UFR of Biological Sciences, Peleforo GON COULIBALY University, Korhogo, Côte d'Ivoire, BP 1328 Korhogo.

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Abstract

The benzimidazole scaffold is an important pharmacophore and one of the preferred structures in medicinal chemistry due to the wide range of biological activities of its derivatives. Here in this article, the synthesis of two series of compounds, namely bis(thiobenzimidazol-2-yl)methane derivatives and analogs (4a-e) and bis(benzimidazol-2-yl)dithiol derivatives and analogs (5a-e) are described. These compounds were synthesized by first designing 2-mercaptobenzimidazole derivatives and analogs (2a-e) by action of orthophenylenediamine and analogs (1a-e) with carbon disulfide. Reaction of thiols (2a-e) with diiodomethane leads to bis(thiobenzimidazol-2-yl)methane derivatives and analogs (4a-e). Their treatment in glacial acetic acid led to their oxidation to bis(benzimidazol-2-yl)dithiol derivatives and analogs (5a-e). The structures of the synthesized compounds were characterized by 1H, 13C Nuclear Magnetic Resonance (NMR), and High-Resolution Mass Spectrometry (HRMS) analyses.

Keywords: Benzimidazole; Dithiol; Oxidation; Diiodomethane; Analogs

1. Introduction

The benzimidazole scaffold is an important pharmacophore and a preferred structure in medicinal chemistry due to the wide range of biological activities of its derivatives. These compounds have shown several biological activities namely antioxidant [1,2], antimicrobial [3,8], antiviral including anti-HIV [9,11], anti-inflammatory [12,15] and anticancer [16,20]. Derivatives of 2-mercaptobenzimidazole, the most important benzimidazole derivatives, show a wide range of interesting biological activities including anti-HIV [21], antiprotozoal [22], antitumor [23] and antimicrobial [23,24]. This entity was used for the synthesis of a variety of bioactive compounds, some of which are used clinically with proven efficacy. The commonly used anti-ulcer drugs was derived from 2-mercaptobenzimidazole. These include omeprazole, lansoprazole, rabeprazole, ilaprazole and esomeprazole which inhibit the secretion of stomach acid. Considering the importance of 2-mercaptobenzimidazole derivatives, this work is focused on the design of new bis(benzimidazol-2yl)dithiol derivatives and analogs.

* Corresponding author: Tchambaga Etienne CAMARA

Laboratory of Constitution and Reaction of Matter, UFR Sciences of the Structures of Matter and Technology, Félix Houphouët-Boigny University, Abidjan, Côte d'Ivoire, 22 BP 582 Abidjan 22.

2. Material 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 (40-265 °C) Kofler bench.

For all compounds, the Nuclear Magnetic Resonance (NMR) spectra of ^{1}H and ^{13}C were recorded on a Brucker 300 advance device with dimethyl sulfoxide (DMSO-d_6) as the solvent, 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).

2.1. General method for synthesis of thiols 2a-e

To a solution of orthophenylenediamine derivatives (1 eq, 46.3 mmol) in 15 mL of dimethylformamide (DMF) cooled in an ice bath, carbon disulfide (5 eq, 231.2 mmol) was added dropwise. After 24 to 48 hours of stirring at room temperature, 200 mL of water were added to the reaction mixture. The precipitate formed 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).

2.1.1. 2-mercaptobenzimidazole 2a

Reaction time: 24 h, beige crystals, yield = 82%, m.p > 265 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.54 (s, 1H, NH), 7.16-7.01 (m, 4H, H_{Ar}), 3.37 (s, 1H, SH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 167.23, 131.36, 121.44, 108.59. HRMS (ESI) Calc. for $C_7H_7N_2S$ (M + H^+) = 151.025 Found = 151.028.

2.1.2. 5-methyl-2-mercapto-1H-benzimidazole 2b

Reaction time: 24 h, brown crystals, yield = 84%, m.p > 265 °C. NMR ^{1}H (DMSO-d_6, 300 MHz) □ (ppm): 12.51 (s, 1H, NH), 7.23-7.12 (m, 3H, HAr), 3.23 (s, 1H, SH), 2.36 (s, 3H, CH3). NMR 13C (DMSO-d6, 75 MHz) □ (ppm): 147.11, 131.79, 128.02, 123.43, 109.38, 107.64, 20.02. HRMS (ESI) Calc. for C8H9N2S (M+H+) = 165.041 Found = 165.041.

2.1.3. 5-nitro-2-mercapto-1H-benzimidazole 2c

Reaction time: 48 h, orange crystals, yield = 92%, m.p = 262-264 °C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 12.54 (s, 1H, NH), 8.30-7.50 (m, 4H, H_{Ar}), 2.50 (s, 1H, SH). NMR ^{13}C (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 $C_7H_6N_3O_2S$ (M+H^+) = 196.010 Found = 196.013.

2.1.4. 2-mercaptobenzothiazole 2d

Reaction time: 24 h, beige crystals, yield = 99%, m.p = 180-182 °C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 7.25-7.70 (m, 4H, H_{Ar}), 3.39 (br s, 1H, SH). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 141.20, 129.30, 127.09, 124.14, 121.70, 112.38. HRMS (ESI) Calc. for $C_7H_6NS_2$ (M+H^+) = 167.986 Found = 167.989.

2.1.5. 6-methyl-2-mercaptobenzoxazole 2e

Reaction time: 24 h, beige crystals, yield = 77%, m.p = 210-212 °C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 7.10-7.32 (m, 3H, H_{Ar}), 3.30 (br s, 1H, SH), 2.36 (s, 3H, CH_3). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 148.33, 133.65, 128.84, 125.66, 110.19, 109.93, 20.86. HRMS (ESI) Calc. for C_8H_8NOS (M+H^+) = 166.025 Found = 166.027.

2.2. General method for synthesis of bis(thiobenzimidazol-2-yl)methane derivatives and analogs 3a-b, 4a-e

To compounds 2a-e (1 eq, 6.7 mmol) suspended in 10 mL of anhydrous ethanol, diiodomethane (1.2 eq, 8.04 mmol) was added. The reaction mixture was refluxed with ethanol from 4 hours to 24 hours. After cooling, the reaction mixture was neutralized with sodium hydrogen carbonate solution (10%) and extracted with dichloromethane (3 x 50 mL). The organic layer was washed with water, dried over magnesium sulfate and the solvent was removed under *vacuo*. The crude obtained was purified by silica gel column chromatography.

2.2.1. 2-iodothiomethyl-1H-benzimidazole 3a

Reaction time = 4h, orange crystals, yield = 14%, m.p = 208-210 °C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 12.77 (s, 1H, NH), 7.23-7.69 (m, 4H, H_{Ar}), 5.69 (s, 2H, CH_2). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 168.96, 136.82, 131.10, 124.06, 122.37, 110.67, 109.65, 36.12. HRMS (ESI) Calc. for $C_8H_9N_2SI$ ($M+H^+$) = 290.937 Found = 289.939.

2.2.2. Bis(thiobenzimidazol-2-yl)methane 4a

Reaction time = 4h, beige crystals, yield = 74%, m.p = 224-226 °C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm) : 7.2-7.67 (m, 8H, H_{Ar}), 5.71 (s, 2H, CH_2). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm) : 158.2, 131.55, 123.89, 123.67, 123.48, 123.16, 122.79, 114.62, 114.26, 110.91, 110.60, 39.36. HRMS (ESI) Calc. for $C_{15}H_{14}N_4S_2$ (M^+H^+) = 313.050 Found = 313.053.

2.2.3. 2-iodothiomethyl-5-methyl-1H-benzimidazole 3b

Reaction time = 4h, brown crystals, yield = 11%, m.p = 230-232 °C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 7.67-8.33 (m, 3H, H_{Ar}), 5.33 (s, 2H, ICH_2), 2.5 (s, 3H, CH_3). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 154.76 (C=N), 140.24, 129.72, 118.19, 113.70, 110.71, 110.61, 38.90, 34.70. HRMS (ESI) Calc. for $C_9H_{10}N_2SI$ ($M+H^+$) = 304.953 Found = 304.956.

2.2.4. Bis(5-thiomethylbenzimidazol-2-yl)-methane 4b

Reaction time = 4h, brown crystals, yield = 68%, m.p = 244-246 °C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 7.02-7.38 (m, 6H, H_{Ar}), 5.31 (d, 2H, CH_2), 2.54 and 2.38 (2s, 6H, 2 $C\underline{H}_3$). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 149.3, 135.91, 131.64, 131.54, 123.65, 123.47, 113.88, 113.41, 117.54, 117.31, 110.20, 109.84, 36.12, 21.39 and 21.23. HRMS (ESI) Calc. for $C_{17}H_{17}N_4S_2$ ($M+H^+$) = 341.082 Found = 341.080.

2.2.5. Bis(5-nitro-thiobenzimidazol-2-yl)methane 4c

Reaction time: 8h, yellow crystals, yield = 72%, m.p > 265 °C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 12.69 (s, 2H, NH), 7.03-7.51 (m, 6H, H_{Ar}), 5.69 (s, 2H, CH_2). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 169.23, 147.83, 147.25, 134.83, 134.32, 131.28, 130.97, 123.89, 123.62, 113.39, 113.21, 110.10, 109.80, 37.05. HRMS (ESI) Calc. for $C_{15}H_{11}N_6O_4S_2$ ($M+H^+$) = 403.020 Found = 403.023.

2.2.6. Bis(thiobenzothiazol-2-yl)methane 4d

Reaction time: 24h, orange crystals, yield = 82%, m.p = 223-225 °C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 7.15-7.62 (m, 8H, H_{Ar}), 4.31 (s, 2H, CH_2). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 169.97, 136.30, 126.66, 126.38, 123.26, 123.06, 122.67, 122.56, 111.72, 111.45, 33.91. HRMS (ESI) Calc. for $C_{15}H_{11}N_2S_4$ ($M+H^+$) = 346.973 Found = 343.975.

2.2.7. Bis(6-methylthiobenzothiazol-2-yl)methane 4e

Reaction time: 24 h, red crystals, yield = 78%, m.p = 252-254 °C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 6.95-7.10 (m, 6H, H_{Ar}), 3.36 (s, 2H, CH_2), 2.33 (s, 6 H, 2 CH_3). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 154.56, 143.49, 131.35, 127.87, 127.71, 124.04, 110.27, 110.00, 109.33, 20.91. HRMS (ESI) Calc. for $C_{17}H_{15}N_2O_2S_2$ ($M+H^+$) = 343.050 Found = 343.053.

2.3. General method for synthesis of bisbenzimidazole dithiols and analogs 5a-e

To compounds 2a-e (1 eq, 10 mmol) suspended in 20 mL of glacial acetic acid, were added few drops of concentrated sulfuric acid. The reaction mixture was stirred at room temperature for 10 minutes. Then it was allowed to reflux on acetic acid for 4 to 7 hours. After cooling, the mixture was neutralized with a concentrated ammonium hydroxide solution. The precipitate formed was filtered, wrung out, washed several times with water and dried in an oven (70°C). The crude obtained was recrystallised with ethanol.

2.3.1. 1,2-(1H-benzimidazol-2-yl)dithiol 5a

Reaction time: 4 h, beige foam, yield = 68%, m.p > 265 °C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 13.11 (s, 1H, NH), 7.28-7.72 (m, 8H, H_{Ar}). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 168.55, 142.32, 140.84, 132.90, 132.10, 131.24, 124.58, 123.27, 123.05, 122.08, 118.90, 112.26, 110.10. HRMS (ESI) Calc. for $C_{14}H_{11}N_4S_2$ ($M+H^+$) = 298.035 Found = 298.037.

2.3.2. 1,2-(5-methyl-1H-benzimidazol-2-yl)dithiol 5b

Reaction time: 4 h, brown crystals, yield = 75%, m.p = 238-240 °C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): δ (ppm): 12.39 (s, 2H, 2 NH), 7.39-7.56 (m, 6H, H_{Ar}), 2.28 (s, 2H, 2 $C\underline{H}_3$). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 167.76, 132.46, 131.64,

130.20, 129.81, 129.33, 127.41, 123.18, 120.87, 109.60, 109.10, 108.98, 108.14, 21.06 and 20.93. HRMS (ESI) Calc. for $C_{16}H_{15}N_2S_2$ ($M+H^+$) = 326.066 Found = 326.068.

2.3.3. 1,2-(5-nitro-1H-benzimidazol-2-yl)dithiol 5c

Reaction time: 7h, yellow crystals, yield = 71% (706 mg, 1.82 mmol) m.p > 265 °C. NMR ^1H (DMSO-d_6, 300 MHz) δ (ppm): 7.10-7.94 (m, 6H, H_{Ar}), 11.39 and 11.14 (2s, 2H, 2 NH). NMR ^{13}C (DMSO-d_6, 75 MHz). δ (ppm) : 155.56, 146.67, 142.22, 136.11, 118.89, 107.78, 103.88. HRMS (ESI) Calc. for $C_{14}H_9N_6O_4S_2$ ($M+H^+$) = 388.005 Found = 388.008.

2.3.4. 1,2-(benzothiazol-2-yl)dithiol 5d

Reaction time : 4h, beige crystals, yield = 87%, m.p > 265 °C. NMR ^1H (DMSO-d_6, 300 MHz) δ (ppm): 7.09-7.29 (m, 6H, H_{Ar}), 2.41 (s, 6H, 2 CH_3). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 170.02, 141.25, 136.32, 126.85, 126.39, 123.92, 123.51, 122.83, 122.57, 112.43, 112.09. HRMS (ESI) Calc. for $C_{14}H_9N_2S_4$ ($M+H^+$) = 331.957 Found = 331.959.

2.3.5. 1,2-(6-methylbenzoxazol-2-yl)dithiol 5e

Reaction time: 24 h, beige crystals, yield = 76% (755 mg, 2.30 mmol), m.p = 128-130 °C. NMR ^1H (DMSO-d_6, 300 MHz) δ (ppm): 7.09-7.29 (m, 6H, H_{Ar}), 2.41 (s, 6H, 2 CH_3). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 179.89, 148.37, 133.69, 133.39, 128.86, 125.70, 125.96, 125.40, 110.23, 109.97, 109.60, 21.13 and 20.92. HRMS (ESI) Calc. for $C_{16}H_{13}N_2O_2S_2$ ($M+H^+$) = 328.034 Found = 328.036.

3. Results and discussion

Bis(benzimidazol-2-yl)dithiol and their analogs 4a-e and 5a-e were synthetized by first preparing 2-mercaptobenzimidazole and its analogs 2a-e. It was done by the Van Allan method [25]. This consisted on a condensation reaction between orthophenylenediamine derivatives and analogs (1a-e) with carbon disulfide in dimethylformamide (DMF). The yields of compounds 2a-e were obtained in range of 82 to 99%. The 2-mercaptobenzimidazole and its analogs 2a-e react with diiodomethane and lead to the bis(thiobenzimidazol-2-yl)methane derivatives and analogs 4a-e. This reaction involves the formation of a monosubstituted iodomethylene compound that undergoes a cross or duplication reaction in the presence of another thiol. In the case of 2-mercaptobenzimidazole and its 5-methyl derivative, monosubstituted compound can be isolated in low yield. Bisbenzimidazole dithiols and analogs 5a-e were obtained by oxidation of 2-mercaptobenzimidazole and analogs 2a-e in glacial acetic acid in the presence of catalytic amount of concentrated sulfuric acid (Figure 1).

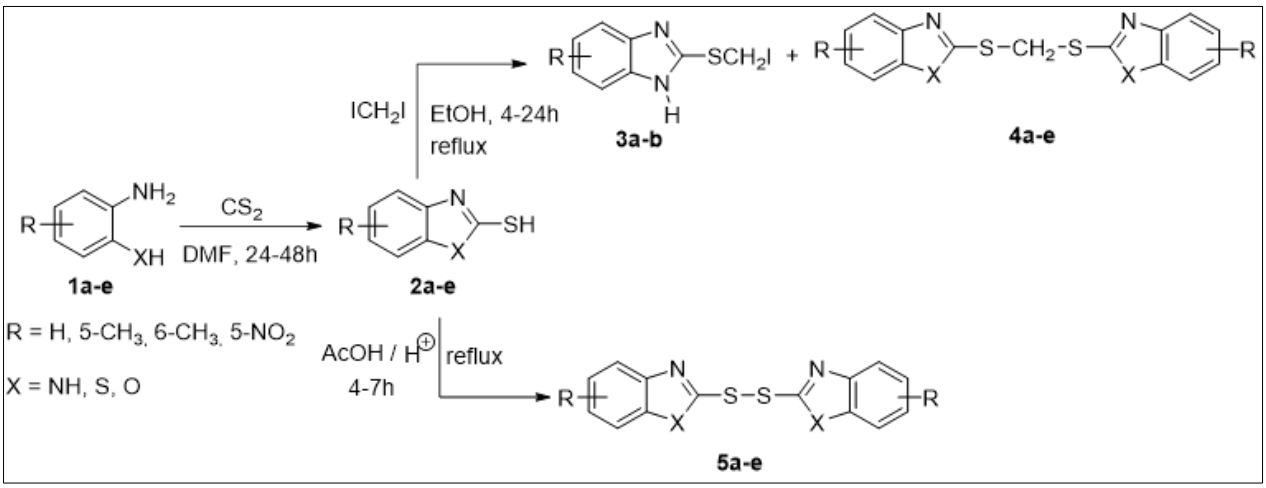

Figure 1 Synthesis of Bisbenzimidazole dithiols and analogs

The structure of the different compounds was confirmed by ^1H, ^{13}C NMR spectroscopy, and HRMS analyses. Indeed, on the ^1H NMR spectra of the various compounds, there are no distinct peaks for the SH group protons between 2.50 and 3.20 ppm characteristic, and there is an increase in signals in the aromatic region which clearly indicates compounds duplication. This can also be seen in the ^{13}C NMR spectra. Particularly for bis(thiobenzimidazol-2-yl)methane and analogs **4a-e**, the presence of a methylene group between the two sulfur atoms is characterized in ^1H NMR by the singlet between 4.30 and 5.80 ppm and in ^{13}C NMR by the peak between 33.90 and 39.40 ppm.

4. Conclusion

In this work, bisbenzimidazol-2-yl dithiols and analogs (4a-e and 5-e) were synthesized from the previously obtained precursors, 2-mercaptobenzimidazole and 2a-e analogs. The yields of all compounds were greater than 50% and their structures were confirmed by ^{1}H NMR, ^{13}C NMR and mass spectroscopic analyzes. In the case of 2-mercaptobenzimidazole and its 5-methyl derivatives, monosubstituted compound can be obtained during the reaction with diiodomethane. An ongoing study of their anthelmintic activities is currently underway with the collaboration of biologists and the first results are promising.

Compliance with ethical standards

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Disclosure of conflict of interest

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

Author contributions

K. Y. G. M. performed the syntheses, T.E.C participated in the purification of the compounds and write the paper. A. T. and S.C. participated in the spectroscopic analyses. A. F. K. , S.C and D.S. designed and conducted the project. All authors have read and agreed on the published version of the manuscript.

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