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Design, Synthesis of Pyrimidinothiazoles and Pyrimidinobenzimidazoles N-ethyl Carboxylic Acid Derivatives Analogs of 4-Quinolone

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Abstract: Heterocycles containing pyrimidine and pyridine moieties are of great interest because they represent an important class of natural products such as nucleic acid, cytosine, and thymine. In addition, structural thiazole and benzimidazole subunits are present in various synthetic compounds, many of them have beneficial biological activities. The combination of these structures could beneficial in the discovery of new bioactive molecules and drugs. In this article, the synthesis of two series of new molecules derived from both pyrimidinothiazole (7a, 7b) and pyrimidinobenzimidazole carboxylic acids (9a-c) was presented. Structurally, these compounds are 4-quinolone analogs, which also possess medicinal properties. These compounds were synthesized by first developing ethyl pyrimidinothiazoles carboxylate (6a, 6b) and pyrimidinobenzimidazoles N-ethyl carboxylate (8a-c). Ethyl pyrimidinothiazoles carboxylate (6a, 6b) were synthesized by condensing ethyl ethoxymethylenemalonate with 2-amino-1,3-thiazoles (2a-b) at ethanol reflux. Pyrimidinobenzimidazoles carboxylate N-ethyl (8a-c) were obtained by an interaction between 2-aminobenzimidazoles (4a-c) and ethyl ethoxymethylenemalonate (5) followed by N-alkylation by the action of ethyl iodide in the presence of potassium carbonate. Obtained esters (6a, 6b) and (8a-c) were converted to the corresponding acids (7a, 7b) and (9a-c) by saponification with sodium hydroxide followed by neutralization with acetic acid. The structure of the compounds was confirmed by spectroscopic analysis of ^{1}H, ^{13}C-NMR and mass spectrometry.

Keywords: 4-Quinolones, Pyrimidinobenzimidazole Carboxylic Acid, Pyrimidino-Benzimidazoles *N*-ethyl Carboxylate, *N*-alkylation

1. Introduction

Quinolones are a well-known class of synthetic antimicrobials that have proven effective in treating many types of infectious diseases, particularly those caused by bacteria [1]. Over the years, several quinolone antibacterial agents have become available to treat human urinary tract infections. The use of quinolones as antibacterial agents (a well-established antibiotic) is not new. It began in 1963, with the discovery of nalidixic acid (Figure 1), during the synthesis of the antimalarial agent drug chloroquine [2].

Nalidixic acid was the first synthetic quinolone antibacterial agent used to treat certain enteric bacteria in urinary tract infections. However, nalidixic acid has never

been a useful drug for the treatment of systemic infections due to its narrow spectrum of action, poor tissue penetration, rapid emergence of bacterial resistance, and common side effects on the central nervous system [3-5].

Therefore, the work on nalidixic acid has led to the synthesis of a wide variety of broad-spectrum quinolone derivatives and provides a chemical basis upon which modifications can improve pharmacokinetics profiles and limit side effects. This led to the discovery of fluoroquinolones [3, 6] and among them, the most commonly used drugs are Norfloxacin, Ciprofloxacin, and Levofloxacin (Figure 1).

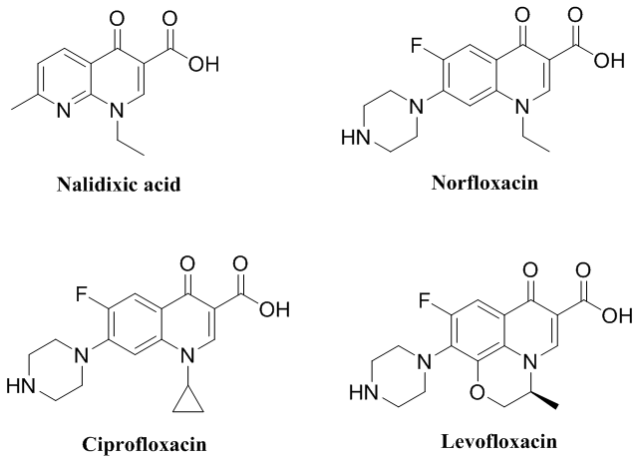

Figure 1. *Structure of drugs based on quinolones.*

The study of Stein, G.E showed that the N-1 alkyl group, the C-2 hydrogen atom, the C-3 carboxylic acid group, and the C-4 carbonyl group were beneficial for the quinolones with a better antibacterial activity [7]. C-6 and C-7 substitutions lead to increase the activity, especially of the C-6 fluorine atom, as well as additional ring structures with an average size of four to six chains containing a C-nitrogen atom. However, the therapeutic benefit of these drugs is hampered by side effects and the rapid development of resistance in microorganisms [8, 9]. Therefore, it is convenient to synthesize other more active compounds that avoid this resistance phenomenon.

Based on the structural variations in the quinolone scaffold for better activity, we propose to design pyrimidine-like 4-quinolone analogs with incorporated benzimidazole and thiazole cores. Bicyclic pyrimidine derivatives are often reported to have various biological activities [10-14]. As for the benzimidazole core, it is an excellent pharmacophore found in several drugs such as thiabendazole and flubendazole (anthelminthic), omeprazole and lansoprazole (antiulcer), and astemizole (antihistamine). It has various biological activities including antioxidant [15], antimicrobial [16, 17], antiviral [18], anti-inflammatory [19] and anticancer [20]. Thiazole derivatives also have a wide range of pharmacological activities including antifungal [21], antimicrobial [22], anti-inflammatory [23, 24], anticancer [25, 26] and anti-HIV [27].

We found it convenient to design and synthesize compounds containing the pyrimidine cycle that are connected in one hand with a thiazole ring and with the benzimidazole ring on the other hand, and show structural analogy with 4-quinolones.

2. Experimental Part

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 proton ^{1}H and carbon ^{13}C were recorded on a Brucker 300 advance device with dimethyl sulfoxide (DMSO-d_6) as the solvent, tetramethylsilane (TMS) was used as a reference for chemical displacements (δ) expressed in ppm. The NMR spectra description uses the following symbols: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quadruplet), m (multiplet), br (broad). The mass spectra were recorded on a JEOL JMS DX300 spectrometer in ESI mode (electrospray/quadripolar ionization or ESI mass).

Synthesis of 2-Amino-4, 5-Dihydro-1, 3-Thiazole 2a

10 g of 2-bromoethane-1-amine hydrobromide (48.80 mmol, 1.1 eq) were dissolved in 250 mL of distilled water under magnetic agitation. Then 4.08 g thiourea 1 were added (44.37 mmol, 1 eq) to the mixture and heated to 70°C for 4 hours. After cooling, the reaction medium was neutralized with an aqueous 5% sodium carbonate solution. The supernatant oily phase was extracted with ethyl acetate. The organic layer was washed with water, dried on magnesium sulfate ($MgSO_4$), and the solvent removed by evaporation under reduced pressure. A crude was obtained in the form of a yellow powder (3.63 g, 35.50 mmol) with a yield of 80%.

Synthesis of 2-Amino-1, 3-Thiazole 2b

5.49g thiourea 1 (72.07 mmol, 1.1 eq) were added to 30 mL of a (50/50) water-ethanol mixture under magnetic agitation and then added drop by drop 9.6 mL of 2-chloro-1,1-diethoxyethane (65.52 mmol, 1 eq). The mixture stayed under reflux for 10 hours. Then the mixture was cooled down to about 75°C and a small portion potassium carbonate was added under magnetic agitation to reach pH = 10. While the mixture was still hot, it was filtered and the residue was washed with hot ethanol. The mixture was then concentrated by evaporation and the crystals formed after cooling in an ice bath were filtered under reduced pressure, washed in ice water and wringed out. At the end, the powder was dried in a desiccator overnight. A yellow powder (5.58 g) was obtained with a yield of 85%.

General Procedure for the Synthesis of 2-Aminobenzimidazoles 4a and 4c

5 g of orthophenylenediamine or 4-nitro-orthophenylenediamine was suspended in 50 mL of water,

then were added in small portions 1.2 eq of cyanogen bromide under magnetic agitation. The mixture was carried under reflux of water for 7 hours. After cooling, the mixture was neutralized with a 25% ammonium hydroxide solution up to reach pH = 10. The precipitate obtained was filtered, washed several times with water, and then dried in the open air overnight.

2-Amino-1H-Benzimidazole 4a

Light brown crystals, yield= 70% (4.3 g, 32 mmol), m.p = 228-230°C.

2-Amino-5-Nitro-1H-Benzimidazole 4c

Yellow-orange crystals, yield = 86% (5.06 g, 28 mmol), m.p = 243-245°C.

2-Amino-5-Fluoro-1H-Benzimidazole 4b

3 g of 4-fluoro-orthophenylenediamine (23.80 mmol) (3b) were added to 40 mL of water under magnetic agitation and then added in small portions 3.03 g of cyanogenic bromide (28.50 mmol, 1.2 eq). The mixture was carried to the reflux of water for 7 hours. After cooling, the mixture was neutralized with a 25% ammonium hydroxide solution up to pH = 10. The product was extracted with ethyl acetate (2 x 100 mL). The organic layer was washed with water, dried on magnesium sulfate ($MgSO_4$), and the solvent removed by evaporation under reduced pressure. A crude product in the form of black paste (2.52 g, 16.66 mmol) was obtained with a yield of 70%.

General Procedure for the Synthesis of Ethyl Pyrimidinothiazole Carboxylate 6a and 6b

2 g of the 2-aminothiazole 2a-b and ethyl ethoxymethylenemalonate derivatives (1.1 eq) were dissolved under magnetic agitation in 40 mL of anhydrous ethanol. The mixture was allowed to stay under ethanol reflux for 4 hours. The precipitate formed was isolated by filtration, washed with ethanol, and then dried in the oven.

Ethyl 7-Oxo-2, 3-Dihydro-7H-Thiazolo [3,2-a] Pyrimidine-6-Carboxylate 6a

Beige crystals, yield = 65% (2.8 g, 12.35 mmol), m.p = 174-176°C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 8.35 (s, 1H, H_{Ar}), 4.43 (t, 2H, CH_2N, J = 8,1 Hz), 4.20 (q, 2H, CH_2O), 3.57 (t, 2H, CH_2S, J = 8.1 Hz), 1.26 (t, 3H, CH_3). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 170.78, 163.00, 158.74, 156.40, 111.56, 60.12, 49.23, 26.36, 14.00. HRMS (ESI) Calc. for $C_9H_{11}N_2O_3S$ (M+H+) = 227.0412 Found = 227.0415.

Ethyl 7-Oxo-7H-Thiazolo [3,2-a] Pyrimidine-6-Carboxylate 6b

Clear yellow crystals, yield = 60% (2.7 g, 12 mmol), m.p > 260°C. NMR ^{1}H (DMSO-*d6*, 300 MHz) δ (ppm): 8.64 (s, 1H, H_{Ar} pyrimidine), 8.2 (d, 1H, H_{Ar}), 7.70 (d, 1H, H_{Ar}), 4.25 (q, 2H, CH_2), 1.28 (t, 3H, CH_3). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 163.78, 157.27, 157.05, 154. 33, 123.15, 115.42, 106.58, 60.19, 14.16. HRMS (ESI) Calc. for $C_9H_9N_2O_3S$ (M+H+) = 225.0256 Found = 225.0259.

General Procedure for the Synthesis of Pyrimidinobenzimidazole N-ethyl Carboxylate Acids 8a-c

2 g of 2-aminobenzimidazole derivatives (4a-c) and 1.1 eq of ethyl ethoxymethylenemalonate were dissolved under magnetic agitation in 40 mL of anhydrous ethanol. The mixture was refluxed in ethanol for 4 to 8 hours. The precipitate formed was isolated by filtration, washed with ethanol, and then dried in the oven. 1 g of the crude obtained and 2.5 eq of K_2CO_3 were added to 15 mL of DMF. The mixture was kept under magnetic agitation for 3 hours at room temperature and then added 5 eq of ethyl iodide. The medium was heated to 95°C for 24 hours under magnetic agitation. After cooling the reaction medium, 50 mL of water were added. The organic layer was extracted with DCM (2 x 100 mL) and washed with a saltwater solution (2 x 100 mL). The solvent was removed by evaporation under reduced pressure and the resulting crude was purified by silica gel chromatography.

Ethyl 6-Ethyl-4-Oxo-2H-Pyrimido [2,1-b] Benzimidazol-3-Carboxylate 8a

White foam, yield = 55% (605 mg, 2.12 mmol), m.p > 260°C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 8.92 (s, 1H, H_{Ar} pyrimidine), 8.40 (d, 1H, H_{Ar}), 7.71 (d, 1H, H_{Ar}), 7.40-7.56 (m, 2H, H_{Ar}), 4.60 (q, 2H, CH_2, J = 7.5 Hz), 4.29 (q, 2H, CH_2, J = 6 Hz), 1.45 (t, 3H, CH_3, J = 7.5 Hz), 1.31 (t, 3H, CH_3, J = 6 Hz). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 165.12, 150.01, 146.12, 141.08, 130.41, 126.63, 121.51, 119.62, 113.88, 101.35, 61.19, 47.13, 14.01, 13.87. HRMS (ESI) Calc. for $C_{15}H_{16}N_3O_3$ (M+H+) = 286.1113 Found = 286.1116.

Ethyl 6-Ethyl-4-oxo-9-Fluoro-2H-Pyrimido [2,1-b] Benzimidazol-3-Carboxylate 8b and Ethyl 6-Ethyl-4-Oxo-8-Fluoro-2H-pyrimido [2,1-b] Benzimidazol-3-Carboxylate 8b'

Light yellow foam, yield = 57% (630 mg, 2.07 mmol), m.p > 260°C. NMR ^{1}H (DMSO-d_6, 400 MHz) δ (ppm): 8.85 (d, 1H, H_{Ar} pyrimidine), 8.68 (d, 1H, H_{Ar} pyrimidine), 7.14-8.19 (m, 6H, H_{Ar}), 4.19-4.43 (m, 8H, 4 x CH_2), 1.24-1.48 (m, 12H, 4 x CH_3). NMR ^{13}C (DMSO-d_6, 100 MHz) δ (ppm): 164.23, 163.02, 159.85, 159.39, 156.58, 155.44, 150.13, 146.18, 142.42, 137.27, 129.48, 126.47, 119.18, 117.57, 115.83, 114.20, 113.07, 110.56, 104.67, 103.29, 60.34, 60.31, 47.07, and 37.70, 14.30, 14.19, 13.90 and 13.92. HRMS (ESI) Calc. for $C_{15}H_{15}FN_3O_3$ (M+H+) = 305.1019 Found = 305.1021.

Ethyl 6-Ethyl-4-Oxo-9-Nitro-2H-Pyrimido [2,1-b] Benzimidazol-3-Carboxylate 8c and 6-Ethyl-4-Oxo-8-Nitro-2H-Pyrimido [2,1-b] Benzimidazol-3-Carboxylate ethyl 8c'

Orange crystals, yield = 55 % (100 mg, 0.3 mmol), m.p > 260°C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 9.17 (d, 1H, H_{Ar}), 9.05 (d, 1H, H_{Ar}), 8.95 (s, 1H, H_{Ar} pyrimidine), 8.75 (s, 1H, H_{Ar} pyrimidine), 8.45 (dd, 1H, H_{Ar}), 8.3 (dd, 1H, H_{Ar}), 8.05 (d, 1H, HAr), 7.85 (d, 1H, H_{Ar}), 4.2-4.5 (m, 8H, 4 x CH_2), 1.25-1.5 (m, 12H, 4 x CH_3). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 163.81, 162.59, 155.66, 155.25, 151.07, 150.35, 149.39, 146.39, 141.72, 135.27, 128.98, 125.06, 122.36, 121.04, 118.20, 117.37, 111.48, 110.83, 105.71, 102.33, 60.54, 60.05, 47.26, 38.03, 14.24, 14.21, 13.89 et 13.17. HRMS (ESI) Calc. for $C_{15}H_{15}N_4O_5$ (M+H+) = 331.0964 Found = 331.0967.

General Procedure for Converting Esters 6a-b and 8a-c into Acids 7a-b and 9a-c

0.5 g of ester (6a-b or 9a-c) were suspended in 10 mL of NaOH 2N and the mixture was refluxed under magnetic agitation for 2 hours. After cooling, the reaction medium was neutralized with 100% acetic acid up to pH = 5. The precipitate formed was filtered, washed with water, wringed out, and then dried in the oven (at 80°C).

7-Oxo-2, 3-Dihydro-7H-Thiazolo [3,2-a] Pyrimidine-6-Carboxylic Acid 7a

Beige crystals, yield= 70% (306 mg, 1.55 mmol), m.p = 240-242°C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 12.7 (br s, 1H, CO_2H), 8.32 (s, 1H, H_{Ar} pyrimidine), 4.39 (t, 2H, CH_2N, J = 8,1 Hz), 3.52 (t, 2H, CH_2S, J = 8.1 Hz). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 171.16, 162.08, 157.65, 155.30, 110.42, 49.02, 25.94. HRMS (ESI) Calc. for $C_7H_7N_2O3S$ (M+H+) = 198.0099 Found = 198.0102.

Ethyl 7-Oxo-7H-Thiazolo [3,2-a] Pyrimidine-6-Carboxylate 7b

Yellow crystals, yield = 65% (325 mg, 1.64 mmol), m.p > 260°C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 13.1 (br s, 1H, CO_2H), 8.57 (s, 1H, H_{Ar} pyrimidine), 8.05 (d, 1H, H_{Ar}), 7.51 (d, 1H, H_{Ar}). NMR ^{13}C (DMSO-*d6*, 75 MHz) δ (ppm): 169.95, 158.13, 156.61, 153.42, 123.05, 116.15, 106.47. HRMS (ESI) Calc. for $C_7H_5N_2O_3S$ (M+H+) = 196.9943 Found = 196.9945.

6-Ethyl-4-Oxo-2H-Pyrimido [2,1-b] Benzimidazol-3-Carboxylic Acid 9a

Beige crystals, yield= 55 % (275 mg, 1.40 mmol), m.p > 260°C. NMR ^{1}H (DMSO-*d6*, 300 MHz) δ (ppm): 12.5 (br s, 1H, CO_2H), 8.96 (s, 1H, H_{Ar} pyrimidine), 8.38 (d, 1H, H_{Ar}), 7.74 (d, 1H, H_{Ar}), 7.35-7.51 (m, 2H, H_{Ar}), 4.42 (q, 2H, CH_2), 1.46 (t, 3H, CH_3). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 164.08, 158.18, 149.93, 145.62, 141.52, 129.46, 125.57, 122.52, 118.26, 114.97, 100.45, 47.13, 13.87. HRMS (ESI) Calc. for $C_{13}H_{12}N_3O_3$ (M+H+) = 258.0800 Found = 258.0803.

6-Ethyl-4-Oxo-9-Fluoro-2H-Pyrimido [2,1-b] Benzimidazol-3-Carboxylic Acid 9b and 6-Ethyl-4-Oxo-8-Fluoro-2H-Pyrimido [2,1-b] Benzimidazol-3-Carboxylic Acid 9b'

Yellow crystals, yield = 64% (320 mg, 1.16 mmol), m.p > 260°C. NMR ^{1}H (DMSO-d_6, 400 MHz) δ (ppm): 12.7-13.1 (br s, 2H, CO_2H), 8.85 (d, 1H, H_{Ar} pyrimidine), 8.68 (d, 1H, H_{Ar}), 7.18-8.06 (m, 6H, H_{Ar}), 4.31-4.39 (m, 4H, 2 x CH_2), 1.41-1.46 (m, 6H, 2 x CH_3), NMR ^{13}C (DMSO-d_6, 100 MHz) δ (ppm): 168.55, 168.05, 160.93, 160.12, 156.41, 154.39, 150.98, 144.76, 142.02, 136.16, 130.26, 125.43, 121.03, 118.02, 115.21, 113.98, 113.22, 109.28, 104.67, 103.29, 48.47, 48.20, 14.43, 14.10. HRMS (ESI) Calc. for $C_{13}H_{11}FN_3O_3$ (M+H+) = 276.0706 Found = 276.0709.

6-Ethyl-4-Oxo-9-Nitro-2H-Pyrimido [2,1-b] Benzimidazol-3-Carboxylic Acid 9c and 6-Ethyl-4-Oxo-8-Nitro-2H-Pyrimido [2,1-b] Benzimidazol-3-Carboxylic Acid 9c'

Orange crystals, yield = 55% (275 mg, 0.91 mmol), m.p > 260°C. NMR ^{1}H (DMSO-d_6, 300 MHz) δ (ppm): 12.8-13.23 (br s, 2H, CO_2H), 9.22 (d, 1H, H_{Ar}), 9.15 (d, 1H, H_{Ar}), 8.98 (s, 1H, H_{Ar} pyrimidine), 8.87 (s, 1H, H_{Ar} pyrimidine), 7.26-8,14 (m, 4H, H_{Ar}), 4.39-4.65 (m, 8H, 4 x CH_2), 1.43-1.51 (m, 6H, 2 x CH_3). NMR ^{13}C (DMSO-d_6, 75 MHz) δ (ppm): 163.02, 162.86, 156.97, 156.25, 152.15, 150.28, 149.66, 147.05, 141.93, 135.91, 129.26, 126.01, 122.88, 121.21, 119.07, 117.88, 111.56, 111.13, 106.01, 102.45, 48.54, 48.32, 14.48, 14.26. HRMS (ESI) Calc. for $C_{13}H_{11}N_4O_5$ (M+H+) = 303.0651 Found = 303.0653.

3. Results and Discussion

The synthesis of pyrimidinonecarboxylic acids (7a-b) and (9a-c) was achieved by first synthesizing the ethyl pyrimidinones (6a-b) and (8a-c) carboxylate followed by their transformation into a carboxylic acid. The precursors of these compounds, amino-1,3-thiazoles (2a-b) and 2-aminobenzimidazoles (4a-c), have been previously synthesized [28-30]. Thus, 2-amino-4,5-dihydro-1,3-thiazole (2a) was obtained in 80% yield by reacting thiourea (1) with 2-bromoethane-1-amine hydrobromide salt in water at 70°C for 4 hours. The interaction of thiourea (1) with 2-chloro-1,1-diethoxyethane in a water/reflux ethanol mixture for 10 hours led to 2-amino-1,3-thiazole (2b) with an 85% yield (Figure 2).

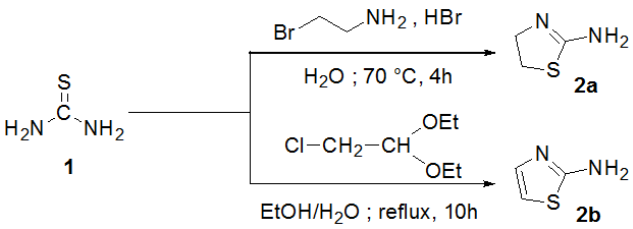

Figure 2. *Synthesis of 2-amino-1,3-thiazines.*

The 2-aminobenzimidazole derivatives (4a-c) were obtained with yields ranging from 70% to 86% by the action of cyanogen bromide on the orthophenylenediamine (3a-c) derivatives under water reflux for 7 hours (Figure 3).

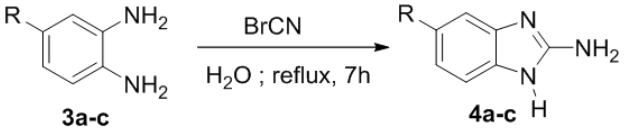

Figure 3. *Synthesis of 2-amino-1H-benzimidazole derivatives.*

The reaction of 2-amino-1,3-thiazoles (2a, 2b) with ethyl ethoxymethylenemalonate (5) to ethanol reflux for 4 hours allowed access to pymidinonecarboxylate derivatives (6a) and (6b) with respective yields of 65 and 60%. Pyrimidinobenzimidazoles N-ethylcarboxylate (8a-c) were obtained by reacting ethyl ethoxymethylenemalonate (5) with 2-aminobenzimidazole derivatives (4a-c) followed by N-alkylation reaction *via* the action of ethyl iodide (EtI) in the presence of potassium carbonate (K_2CO_3). The introduction of an ethyl group to the nitrogen of the intermediates aims to improve the solubility and possibly improve the biological properties of the target molecules (Figure 4).

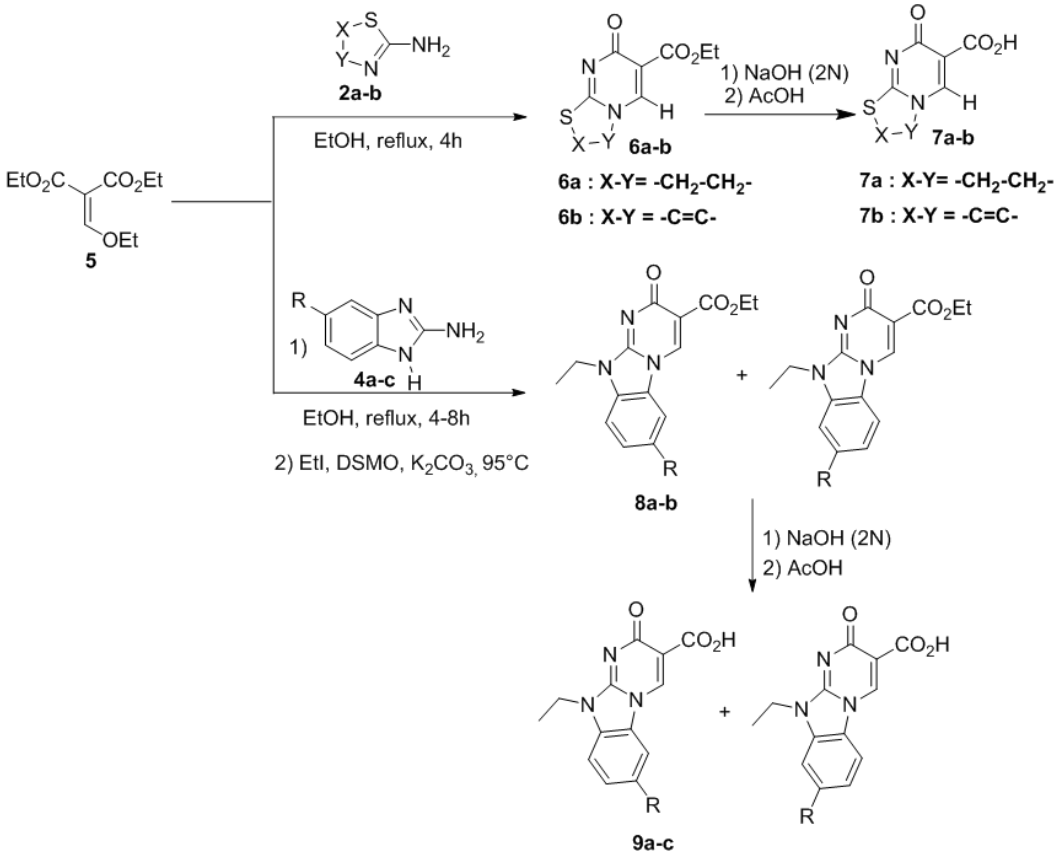

Figure 4. *Synthesis route of pyrimidine derivatives.*

The spectroscopic analyses ^{1}H, ^{13}C NMR and mass spectrometry are in accordance with the proposed structures. Indeed, the formation of these compounds were characterized in ^{1}H NMR by the presence of the pyrimidine ring proton signal which appears between 8.35 and 8.95 ppm for all compounds. The hydrogen ester function of compounds 6a, 6b, and 8a appear as two signals: a triplet between 1.26 and 1.28 ppm and a quadruplet between 4.20 and 4.29 ppm. In addition to these signals, compound 8a has a triplet at 1.45 ppm and a quadruplet at 4.60 ppm characteristic of the ethyl group located on the nitrogen atom of the benzimidazole scaffold.

If there is a substituent (R = F, NO_2) on the benzimidazole ring (compounds 8a and 8b), the reaction leads to a mixture of isomers. The presence of a substituent on the benzimidazole scaffold means that the two nitrogen atoms are not equivalent and lead to two possible substitutions. This is confirmed by ^{1}H, ^{13}C- spectroscopic analyses through peak duplication and/or overlap. Indeed, on the ^{1}H NMR spectra of compounds 8b and 8c, we observe a multiplet between 1.2 and 1.5 ppm and two triplets due to four methyl groups, two for the methyl of the ester group and two for the methyl of the N-ethyl group. The four methylene groups give two massifs between 4.2 and 4.5 ppm. Their ^{13}C spectrum also confirm the coexistence of the two products. There are four peaks between 13.1 and 14.3 ppm corresponding to the four methyl groups. The two methylene ester groups give two peaks between 60 and 62 ppm and those of the two amino methylene groups, one between 37 and 39 ppm and the other around 48 ppm.

Given the importance of the 3-position carboxyl group in 4-quinolone antimicrobials, we proceeded to convert esters 6a-b and 8a-c to the corresponding carboxylic acids. The esters were saponified in a 2N sodium hydroxide (NaOH) solution. After neutralizing the reaction medium with 100% acetic acid (AcOH), acids 7a-b and 9a-c were isolated by filtration to yield 55 to 70%.

4. Conclusion

In this work, pyrimidinothiazole and pyrimidinobenzimidazole carboxylic acids were developed from precursors, heterocyclic amines that were previously synthesized. All the compounds were obtained with yields greater than 50% and their structures were confirmed by spectroscopic analyses ^{1}H, ^{13}C-NMR and mass spectrometry. The presence of substituent (R = F, NO_2) on the benzimidazole scaffold results to a mixture of isomers which we detected in the ^{1}H and ^{13}C NMR spectra by the splitting of peaks.

Conflicts of Interest Statement

The authors declare no conflicts of interest regarding the

publication of this paper.

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