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Synthesis of *N*-alkyl-3- (1*H*-benzimidazolyl) -2-chloroquinoline derivatives potential candidates against infectious organisms

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In the search for new drugs possessing the activities we have sought to synthesize new quinoline derivatives which constitute a basic heterocyclic support of some drugs such as quinine, chloroquine marketed under the name Nivaquine®, Mefloquine®, used in the treatment of malaria. The objective of this work is to contribute to the synthesis of new derivatives of quinoline. It consists in introducing heterocycles such as benzimidazole in its 3-position. The introduction of heterocyclics, aryls or alkyls on the pyrrolic nitrogen of benzimidazole, allowed us to obtain compounds 3a-f. The chemical structures of all these compounds were determined by NMR (^{1}H, ^{13}C) and electron impact mass spectrometry.

Key words: Quinoline, benzimidazole, aryls, alkyls.

INTRODUCTION

Quinoline belongs to the family of alkaloids. It is a heterocyclic aromatic organic compound consisting of a pyridine ring and a benzene ring (Figure 1). Quinoline and its derivatives have various biological properties including anti-inflammatory (Daniel et al., 1998), antiasthmatic (Daniel et al., 1998), antibacterial (Yun et al., 2011), antifungal (Garudachari et al., 2012), antimicrobial (Garudachari et al., 2012), antioxidant (Massoud et al., 2014), anti-tumor (Bergh et al., 1997), anti-plasmodia (Andrew et al., 2005) etc… The quinoline nucleus constitutes a basic heterocyclic support for some drugs such as quinine, chloroquine marketed under the name Nivaquine®, Mefloquine® (Figure 1), used in the treatment of malaria (Jane et al., 2011). Structurally, studies have made it possible to identify different substitution sites. The main ones are positions -2, -3 and -4. The objective of this work is to contribute to the synthesis of new derivatives of quinoline. It consists in introducing heterocycles such as benzimidazole in its 3-position. To achieve our objective, we will try to introduce the heterocyclics, aryls or alkyls on to the pyrrolic nitrogen of benzimidazole, in order to obtain new quinoline derivatives.

MATERIALS AND METHODS

Nuclear Magnetic Resonance (NMR) spectra of the ^{1}H proton (300–

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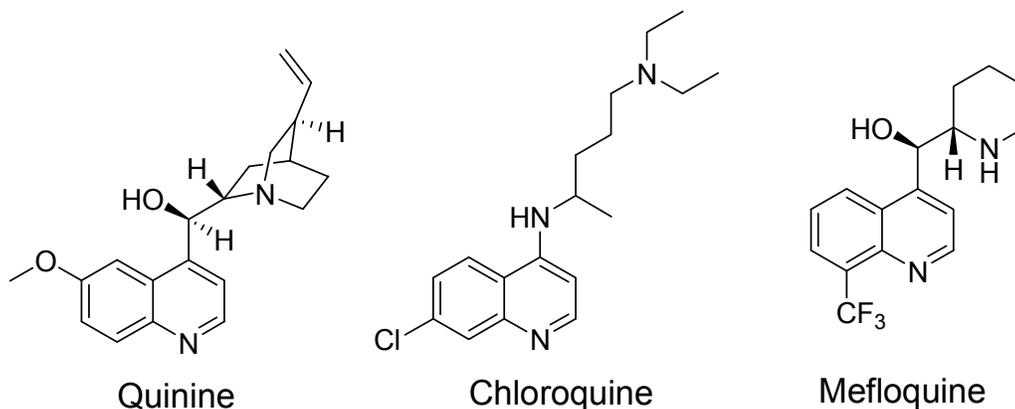
Figure 1. Structure of some quinoline derivatives.

400 MHz) and those of ^{13}C carbon (75-100 MHz) were recorded on a Brüker advance 300 device. Tetramethylsilane (TMS) is used as an internal reference for chemical shifts expressed in ppm. The Mass spectra (MS) were carried out on a quadrupole HP 5889A electron impact (EI) or chemical ionization (IC) spectrometer. Melting points were determined using a KÖFFLER bench with temperature graduation (40-260°C). Dichloromethane, toluene, ethanol, ethyl acetate and hexane are distilled off at atmospheric pressure. The purifications by column chromatography were carried out on silica gel of Kieselgel 60 type (230-400 mesh-Merck).

General procedure for the synthesis of compound 1

The method used in the synthesis of compound 1 starts with aniline to access the acetanilide by adding acetic anhydride and sodium acetate, followed by a hydrolysis reaction with hydrochloric acid. The acetanilide obtained is subjected to the action of Vilsmeier's reagent (POCl$_3$ / DMF) in a 7/3 ratio, respectively, resulting in 2-chloro-3-formylquinoline (compound 1) with a yield of 40% (Scheme 1). Then the condensation of compound **1** with orthophenylenediamine in methanol under reflux makes it possible to obtain 3- (1H-benzimidazol-2-yl) -2-chloroquinoline (compound 2) with a yield of 52% (Scheme 1). This work consists in synthesizing N-alkylated derivatives by reacting the alkyl and aryl chlorides on compound 2 in the presence of K$_2$CO$_3$ in DMF to obtain compounds 3a-f with yields of between 46 and 64%. The mechanism for obtaining compounds 3a-f can be explained by the attack of the base (K$_2$CO$_3$) on the proton of the pyrrol nitrogen of compound **2** to create an amide ion. This ion will subsequently react with an appropriate electrophile to lead to the various derivatives (Scheme 1).

General procedure for the synthesis of acetanilide

In a Bicol, 50 ml of distilled water are added, then 3 ml (32.860 mmol, 1eq) of aniline and 0.5 ml (16.420 mmol; 0.5eq) of hydrochloric acid. Stir at room temperature until the mixture becomes homogeneous. Then 4 ml (42.720 mmol; 1.3eq) of acetic anhydride is added to the reaction medium. The mixture is heated to 50°C for about twenty minutes. At the end of the reaction, the reaction medium is neutralized with sodium acetate solution (4%). The precipitate obtained is filtered through a Buchner funnel and washed several times with water. The crude product obtained is purified by recrystallization from water.

Yield: 80%; Pf : 113 ° C; White solid

**Procedure of synthesis 1**

1.7 ml (22.95 mmol, 3eq) of anhydrous N, N-dimethylformamide (DMF) are introduced into a Bicol surmounted by a condenser and fitted with an addition funnel. The reaction medium is cooled to 0°C, then 4.8 ml (51.88 mmol, 7eq) of potassium oxychloride (POCl$_3$) are added dropwise, with magnetic stirring, using a funnel addition. Once the addition is complete, the temperature is allowed to rise and the reaction mixture is left with stirring for 30 min. Then 1 g (7.39 mmol, 1eq) of acetanilide is added and the reaction mixture is heated at 75°C for 4 h. When the reaction is complete, the reaction mixture is poured into an Erlenmeyer flask containing an ice-water mixture. The precipitate formed is filtered, dried in the open air, and then purified by chromatography on silica gel (eluent: hexane / ethyl acetate: 8/2).

General procedure of synthesis 2

In a 100 ml two-necked flask containing 5 ml of methanol, 0.3 g (1.571 mmol, 1eq) of 2-chloroquinoline-3-carbaldehyde and 0.16 g (1.571 mmol, 1eq) of o-phenylenediamine are added. Then the reaction mixture is refluxed at 90°C for 4 h, following the progress of the reaction by thin layer chromatography (TLC). Once the reaction is complete, the mixture is allowed to cool. The solution is poured slowly into ice-water, a yellow precipitate is obtained which is filtered, washed several times with water and dried.

General synthesis procedure 3a-f

In a two-necked flask, 0.1 g (0.357mmol, 1eq) of 3- (1H-benzimidazolyl) -2-chloroquinoline is dissolved in 5ml of DMF with 0.14 g (1.072 mmol, 3 eq) of K$_2$CO$_3$ (Janardhana et al., 2011; Garuti et al., 2000; Kumar et al., 2015). The mixture is brought to stirring for 1 h. Excess alkyl or aryl chloride is then added and the reaction mixture is heated under reflux for 6 h. The reaction medium cooled in the presence of an ice-water mixture allows the products formed to precipitate. The purification of these various products is carried out by chromatography on silica gel in a mixture of hexane / ethyl acetate solvents respectively of ratio (4/1). The synthesis procedure is the same for these different 3a-f derivatives, only the
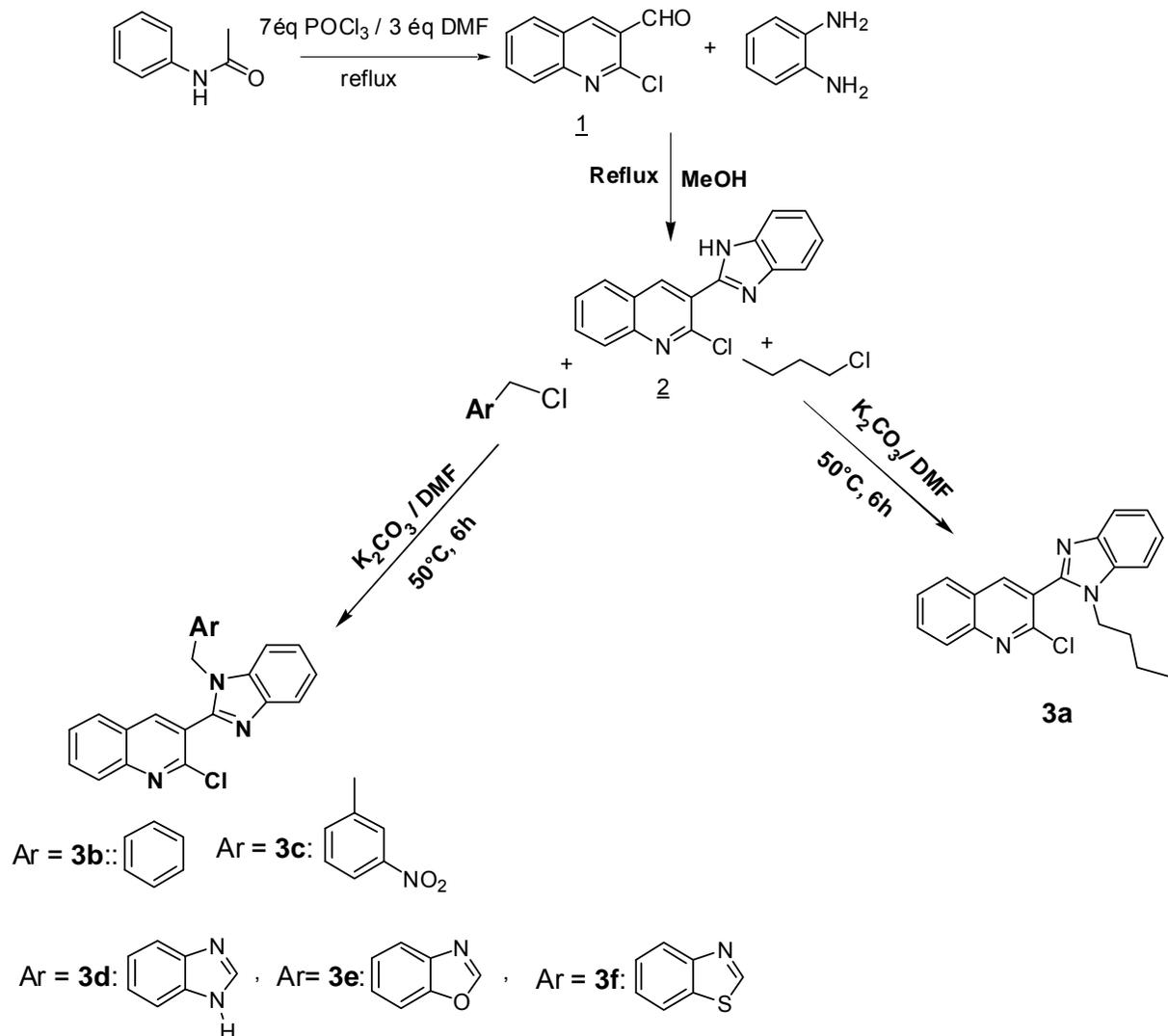
Scheme 1. Synthesis of *N*-alkyl derivatives of 3- (1*H*-benzimidazolyl)-2-chloroquinoline 3a-f.

alkyl or aryl chloride changes. 1-chlorobutane, benzyl chloride, benzyl 3-nitrochloride, 2-(chloromethyl) -benzimidazole, 2-(chloromethyl) -1,3-benzoxazole and 2- (chloromethyl) -benzothiazole are used respectively, to access the derivatives 3a, 3b, 3c, 3d, 3e and 3f respectively.

2-chloro-3-formylquinoline 1

Yield: 40%; Pf = 146 ° C., ^{1}H NMR (Acetone-d6, δ ppm): 10.52 (1H, s, CHO); 8.9-7.76 (5H, m, H$_{ar}$). ^{13}C NMR (DMSO-d6, δ ppm): 189.2 (CHO); 126.4-150.2 (9C$_{ar}$). Secondly, the condensation of compound 1 with o-phenylenediamine makes it possible to obtain 3- (1*H*-benzimidazolyl) -2-chloroquinoline (compound 2), a support for N-substitution.

3- (1*H*-benzimidazolyl) -2-chloroquinoline 2

Yield: 52%; Pf = 220°C.

^{1}H NMR (Acetone-d6, δ ppm): 8.76 (1H, s, H$_{ar}$); 8.12 (H, dd, H$_{ar}$); 7.33 (2H, m, H$_{ar}$); 8.79 (3H, m, H$_{ar}$); 7.98 (^{1}H, t, H$_{ar}$); ^{13}C NMR (DMSO-d6, δ ppm): 119.2 (2C$_{ar}$); 123.1 (2C$_{ar}$); 127.2 (C$_{ar}$); 127.9 (C$_{ar}$); 131.1 (C$_{ar}$); 131.4 (3C$_{ar}$); 136.7 (C$_{ar}$); 137.8 (C$_{ar}$); 142.3 (-CH = C-N); 145.6 (-CH = C-N); 153.2 (N-C = N).

Finally, the suitably chosen alkyl or aryl chlorides provide access to the 6 expected 3a-f derivatives with yields varying between 46 and 60%.

3- (1-butylbenzimidazolyl) -2-chloroquinoline 3a

Yield: 64%. Mp = 242°C., ^{1}H NMR (DMSO-d6, δ ppm): 8.76 (1H, s, H$_{ar}$); 8.12 (H, dd, H$_{ar}$); 7.33 (2H, m, H$_{ar}$); 8.79 (3H, m, H$_{ar}$); 7.98 (1H, t, Har); 4.26 (2H, t, -CH$_2$-CH$_2$-N); 1.75 (4H, m, CH$_3$-CH$_2$-CH$_2$-CH$_2$-); 0.75 (3H, t, CH$_3$-CH$_2$-).^{13}C NMR (DMSO-d6, δ ppm): 14.3 (CH$_3$-CH$_2$-); 20.7 (CH$_3$-CH$_2$-); 33.8 (-CH$_2$-CH$_2$-N); 49.6 (-CH$_2$-CH$_2$-N); 110.1 (C$_{ar}$), 119.5 (C$_{ar}$); 123.2 (2C$_{ar}$); 126.3 (C$_{ar}$); 127.1 (3C$_{ar}$); 128.1 (C$_{ar}$); 131.2 (C$_{ar}$); 134.2 (C$_{ar}$); 134.5 (2Car); 142.7 (-CH = C-N); 149.9 (Cl-C = N) 153.2 (N-C = N). ES$^+$ MS: 336 [M+H$^+$].

3- (1-benzylbenzimidazoyl) -2-chloroquinoline 3b

Yield: 46%; Appearance: Oil, ^{1}H NMR (DMSO-d$_6$, δ ppm): 8.71 (1H, s, H$_{ar}$); 8.30 (2H, dd, Har); 7.90 (1H, t, H$_{ar}$); 7.70 (3H, m, H$_{ar}$); 7.33 (5H, m, H$_{ar}$); 7.31 (2H, m, H$_{ar}$); 5.65 (2H, s, CH$_2$-N).^{13}C NMR (DMSO-d6, δ ppm): 52.2 (-CH$_2$-N); 119.0 (2C$_{ar}$); 123.0 (2C$_{ar}$); 125.7 (C$_{ar}$); 127.2 (C$_{ar}$); 127.6 (3C$_{ar}$); 128.6 (2C$_{ar}$); 131.0 (Car); 131.4 (3C$_{ar}$); 136.8 (C$_{ar}$); 137.3 (C$_{ar}$); 137.8 (C$_{ar}$); 142.4 (C$_{ar}$); 145.7 (-CH = C-N); 149.9 (Cl-C = N); 153.3 (N-C = N). ES$^+$ SM: 370 [M+H$^+$].

3- (3-nitrobenzyl-1-benzimidazolyl) -2-chloroquinoline 3c

Yield: 52%. Appearance: Oil ,^{1}H NMR (DMSO-d6, δ ppm): 8.27-7.27 (13H, m, Har); 5.78 (-CH$_2$-N). ^{13}C NMR (DMSO-d6, δ ppm): 51.2 (-CH$_2$-N); 119.2 (2C$_{ar}$); 120.9 (C$_{ar}$); 125.7 (C$_{ar}$); 127.2 (C$_{ar}$); 127.8 (C$_{ar}$); 129.5 (C$_{ar}$); 131 (C$_{ar}$); 131.4 (3C$_{ar}$); 133.7 (C$_{ar}$); 136.8 (C$_{ar}$); 137.1 (C$_{ar}$), 137.8 (C$_{ar}$), 145.7 (CH = C-N); 147.8 (CH = C-NO$_2$); 149.9 (Cl-C = N); 153.3 (N-C = N). ES$^+$ SM: 415 [M+H$^+$].

3- (1-methylbenzimidazol-1-benzimidazolyl) -2-chloroquinoline 3d

Yield: 60%; Pf > 260°C,^{1}H NMR (DMSO-d$_6$, δ ppm): 12.22 (1H, s, NH); 8.76 (1H, s, H$_{ar}$); 8.10 (2H, dd, H$_{ar}$); 7.90 (1H, t, H$_{ar}$); 7.41 (4H, m, H$_{ar}$); 5.02 (2H, s, CH$_2$-N). ^{13}C NMR (DMSO-d$_6$, δ ppm): 52.8 (-CH$_2$-N); 115.2 (2Car); 119.1 (2Car); 123.2 (4C$_{ar}$); 127.1 (2C$_{ar}$); 131.0 (C$_{ar}$); 131.4 (3C$_{ar}$); 132.4 (C$_{ar}$); 136.8 (C$_{ar}$); 137.8 (C$_{ar}$); 138.9 (2C$_{ar}$); 141.5 (N-C = C); 145.7 (CH = C-N); 149.9 (Cl-C = N); 153.3 (N-C = N). ES$^+$ SM: 779 [M+H$^+$].

3- (1-methylbenzoxazolbenzimidazolyl) -2-chloroquinoline 3e

Yield: 50%; Pf> 260°C, ^{1}H NMR (DMSO-d$_6$, δ ppm): 8.25-7.27 (13H, m, HAr); 5.02 (2H, s, -CH$_2$-N); 13C NMR (DMSO-d$_6$, δ ppm): 52.9 (-CH$_2$-N); 111.3 (C$_{ar}$); 119.1 (3C$_{ar}$); 123.2 (2C$_{ar}$); 123.9 (2C$_{ar}$); 127.1 (2C$_{ar}$); 131.1 (C$_{ar}$); 131.5 (3C$_{ar}$); 132.4 (C$_{ar}$); 136.9 (C$_{ar}$); 137.8 (C$_{ar}$); 141.5 (N-C = C); 145.7 (CH = C-N); 149.9 (Cl-C = N); 150.2 (CH = C-O); 152.6 (O-C = N); 153.4 (N-C = N). ES$^+$ SM: 780 [M+H$^+$].

3- (1-methylbenzothiazolbenzimidazolyl) -2-chloroquinoline 3f

Yield: 52%. Pf> 260°C;^{1}H NMR (DMSO-d$_6$, δ ppm): 8.26-7.26 (13H, m, H$_{ar}$); 4.98 (-CH$_2$-N). ^{13}C NMR (DMSO-d6, δ ppm): 54.9 (-CH$_2$-N); 119.3 (2C$_{ar}$); 121.7 (2C$_{ar}$); 123.1 (2C$_{ar}$); 125.3 (2C$_{ar}$); 127.1 (C$_{ar}$); 131.1 (C$_{ar}$); 131.5 (3C$_{ar}$); 132.5 (C$_{ar}$); 135.2 (C$_{ar}$); 136.8 (C$_{ar}$); 137.8 (C$_{ar}$); 145.7 (CH = C-N); 149.8 (Cl-C = N); 152.7 (-C = C-N = C-S); 153.4 (-N = C-N); 163.4 (N = C-S). ES$^+$ SM: 796 [M+H$^+$].

RESULTS AND DISCUSSION

For the preparation of 3- (1*H*-benzimidazolyl) -2-chloroquinoline support for N-substitutions (Scheme 1), we first have to synthesize 2-chloro-3-formylquinoline using the Meth-Cohn et al. (1981) method. We started from the aniline molecule to access acetanilide by adding acetic anhydride and sodium acetate, followed by a hydrolysis reaction with hydrochloric acid. The N-phenylacetamide derivative obtained is subjected to the

action of Vilsmeier's reagent (7POCl$_3$ / 3DMF) and results in 2-chloro-3-formylquinoline (compound 1).

Analysis of the ^{1}H NMR spectra for compound 1 reveals the presence of a peak at 10.52 ppm attributed to the proton of the aldehyde function. We also observe the presence of four signals between 7.76 ppm and 8.90 ppm corresponding to the five aromatic protons of quinoline. As for the ^{13}C spectrum of the same compound, we observe peaks comprised between 126.4 ppm and 150.6 ppm corresponding to the sp^2 aromatic carbons of the quinoline nucleus. This major information confirms the formation of compound 1. Analysis of the ^{1}H NMR spectrum of compound 2 reveals five signals between 7.33 ppm and 8.79 ppm corresponding to aromatic protons. Likewise, it should be noted the disappearance of the peak at 10.52 ppm corresponding to the proton of the aldehyde function shows the absence of the aldehyde function in compound 2. The presence of the peak at 12 ppm corresponding to the proton of pyrrol nitrogen is a major peak. Also the ^{13}C NMR analysis of compound 2 reveals only aromatic carbons because the peaks are between 126 ppm and 154 ppm. This information confirms the formation of compound 2. As regards the N-substitutions derivatives, analysis of the ^{1}H NMR spectrum of compound 3a reveals a set of peaks between 7.73 ppm and 8.76 ppm on the one hand and other peaks between 4.26 ppm and 0.75 ppm. Also the ^{13}C NMR spectrum of compound 3a shows two sets of peaks. The sp^2 carbons having peaks between 110 ppm and 153 ppm and the sp^3 carbons with peaks between 14 ppm and 50 ppm. This information confirms the formation of derivative 3a. Analysis of the ^{1}H NMR spectrum of compound 3b reveals peaks between 8.70 ppm and 7.30 ppm. It should be noted the presence of the peak at 5.62 ppm corresponding to the two protons methylene group bound to pyrrolic nitrogen (-CH$_2$-N). Likewise, the ^{13}C NMR spectrum shows peaks between 119 ppm and 153 ppm characterizing the sp^2 carbons. We also have a peak at 52.2 ppm which highlights the presence of a sp^3 carbon of the methylene group (-CH$_2$-N). This information makes it possible to confirm the formation of compound 3b. Analysis of the ^{1}H NMR spectrum of compound 3c reveals peaks of 8.26 ppm and 7.27 ppm characteristic of aromatic protons. We also have a peak at 5.78 ppm corresponding to the two protons of the methylene group (-CH$_2$-N). Likewise, the ^{13}C NMR spectrum reveals peaks between 119 ppm and 153 ppm characteristic of the carbons of aromatic rings. The large peak at 51.2 ppm reveals the presence of the carbon of the methylene group bound to pyrrolic nitrogen (-CH$_2$-N). All this information makes it possible to confirm the formation of derivative 3c. Analysis of the ^{1}H NMR spectrum of the 3d derivative reveals a large peak at 12.22 ppm corresponding to the pyrrolic proton. We also have a set of peaks between 8.76 ppm and 7.40 ppm corresponding to the protons of the aromatic rings. The peak at 5.02 ppm corresponds to the two protons of the methylene

group bound to pyrrol nitrogen. The ^{13}C NMR spectrum reveals peaks between 115 ppm and 153 ppm corresponding to the carbons of the aromatic rings. A significant peak is observed at 52.8 ppm corresponding to the carbon of the methylene group bound to pyrrol nitrogen. This information confirms the formation of 3d compound. Analysis of the ^{1}H NMR spectra of the 3e and 3f derivatives reveals peaks between 8.25 ppm and 7.27 ppm correspond to the protons of the aromatic rings. The large peak observed around 5.00 ppm corresponds to the two protons of the methylene group bound to pyrrol nitrogen. Likewise, the ^{13}C NMR spectra of compounds 3e and 3f reveal peaks between 119 ppm and 154 ppm corresponding to the aromatic rings. The large peak around 53 ppm corresponds to the sp^3 carbon of the methylene group linked to pyrrol nitrogen. All this information clearly shows the formation of derivatives 3e and 3f.

Conclusion

This work has allowed us to access chemical synthesis new derivatives of 3-(1*H*-benzimidazol-2-yl) -2-chloroquinoline through N-substitutions. This could open up avenues of investigation towards the development of a chemical class of antifungal and antimalarial. The resulting compounds will be subjected to biological analysis. The chlorine in position-2 of the different compounds obtained (3a-f) gives a reaction flexibility that can be exploited later.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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