Chapter 6
Synthesis, Characterizations, and Biological Effects Study of Some Quinoline Family

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ABSTRACT

The objective of this work is the synthesis of new quinoline molecules which could have some biological activities. This chapter reported a new approach to the synthesis of some quinoline derivatives. The Baylis-Hillman reaction on 2-methoxy-3-formyl quinoléines derivatives have applied in order to obtain Baylis-Hillman adducts. The products are characterized by FTIR, NMR and X-ray single crystal diffraction .Also, a study of the antibacterial activity of the 3-(2-chloro quinoline)-3-hydroxy-2 methylene propanonitrile products synthesized have been explored. This assessment is made by using the disk diffusion method. The results showed that the 3-(2'-chloroquinoline)-3-hydroxy-2-methylenepropanonitril derivatives present a good antibacterial effectiveness against the strains tested Gram-positive and no antibacterial potency was observed against the stains Gram-negative used in the test.

INTRODUCTION

Nature is the source of a large number of molecules with major interest for humans. This reservoir is extremely rich in new organic compounds, with a high level of structural diversity, but also; a significant therapeutic potential, motivates the search for efficient routes for their synthesis and that of the like.

The quinoline ring system is a common structural component of a wide variety of natural or synthetically prepared products with highly desirable biological activity (Michael, 1997). It is a heterocyclic scaffold of paramount importance to human race. Indeed, quinoline derivatives are some of the oldest compounds which have been utilized for the treatment of a variety of diseases.

DOI: 10.4018/978-1-4666-9811-6.ch006

The bark of Cinchona plant (also known as Jesuit's or Cardinal's bark) containing quinine was utilized to treat palpitations (Levy & Azoulay, 1994) fevers and tertians since more than 200 years ago. Quinoline, a diastereoisomer of quinine was in the early 20th century acknowledged as the most potent of the antiarrhythmic compounds isolated from the Cinchona plant (Wenckebach, K.F., 1923).

Compounds containing quinoline motif are most widely used as antimalarials (Lutz, 1946; Surrey, 1950; Bilker, 1989; Roma, 2000), antibacterials (Desai, 1996; Fang, 2000; Phan,, 2004), antifungals (Vargas et al., 2003), anti VIH (Wilson, 1992; Strekowski, 1991) and antitumor agents (Dassonneville, 2000; Bailly, 2000). They have antiseptic, antipyretic and antiperiodic properties (Khan, 2007). Substituted quinolines play also an important role as receptor antagonists of endothelin (Cheng, 1996), 5HT3 (Anzini et al., 1995), NK-3 (Giardina et al., 1997) and leucotriens (Gauthier et al., 1990). Those compounds are used as inhibitors of tyrosine kinase PDGFRTK (Maguire et al., 1994), (H^+/K^+)-ATPase (Ife et al., 1992), dihydrorotate deshydrogenase (Chen, 1990; Zeevi, 1993) and 5- lipoxygenase (Musser et al., 1987).

Additionally, quinoline derivatives find use in the synthesis of fungicides, virucides, biocides, alkaloids, rubber chemicals and flavoring agents (Holla et al., 2006). They are also used as polymers, catalysts, corrosion inhibitors, preservatives, and as solvent for resins and terpenes (Fishbein, 1979). Furthermore, these compounds find applications in chemistry of transition-metal catalyst for uniform polymerization and luminescence chemistry (Calus, 2007). Quinoline derivatives also act as antifoaming agent in refineries (Caeiro, 2007). Owing to such as significance, the synthesis of substituted quinolines has been a subject of great focus in organic chemistry.

One of the developed research lines in recent years is devoted to the synthesis of new quinoline derivatives from the 2-chloro-3-formyl quinoline derivatives. These are of great interest synthetic in the organic chemistry field.

We focus on 3-formyl quinoline derivatives substituted in position two; either chlorine or a methoxy as starting precursors. The work performed is divided into two stages: first, we describe the preparation of 3-formyl-substituted quinolines derivatives by two chlorine position. The second step, involves the substitution of chlorine by methoxyl. The aldehyde function in position 3 will allow us, for further processing selected, access to structurally diverse derivatives.

The study that we are undertaking, purpose the preparation and structural identification of original quinoline compounds that will be subsequently submitted to an assessment of antibacterial activity.

Our strategy is to apply the Baylis-Hillman reaction of some derivatives of 2-chloro-3-formyl quinoline to prepare a new series of Baylis-Hillman adducts derived. This reaction is a catalytic coupling of activated olefins and carbon electrophiles leading to classes of highly functionalized molecules. Among some Baylis-Hillman adducts, have interesting biological activities and are also an important reservoir of intermediate reaction precursors countless classes of compounds as useful as each other.

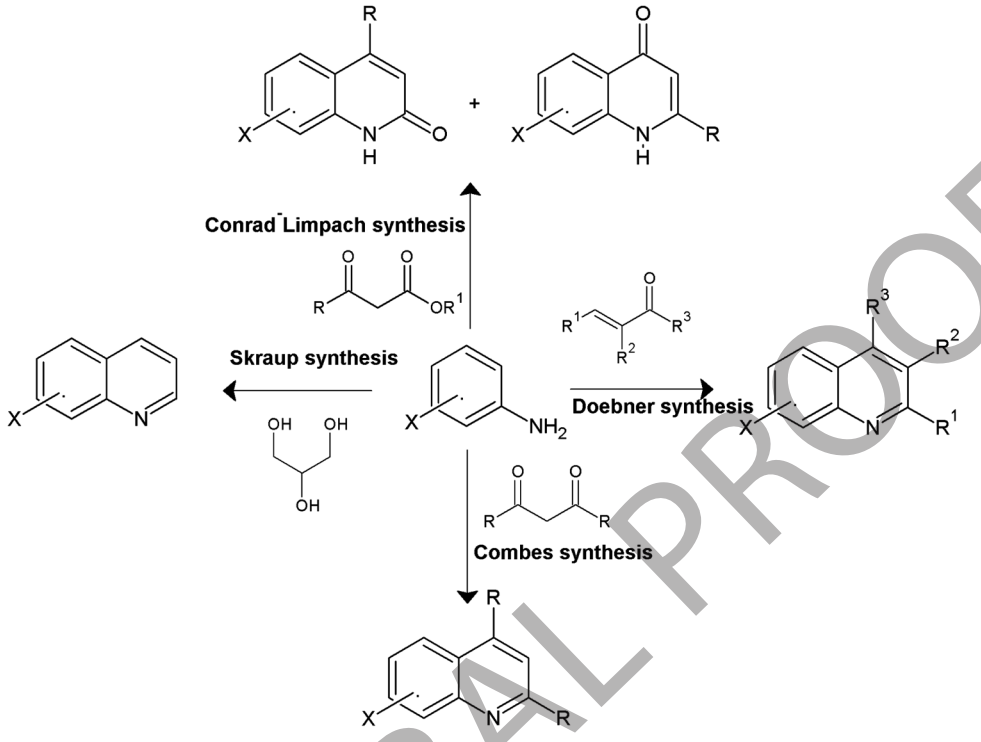
Given the phenomenon spread of the resistance and limited antibiotics in development number the discovery of new antibacterial agents, has become more indispensable. Joined in the general context, we will evaluate the antibacterial activated of some derivatives prepared.

1. BACKGROUND

1.1 The Quinolines Synthesis Methods

Considering the therapeutic value of quinoline derivatives, chemists can synthesize this hetero ring by several synthetic methods.

Figure 1. Conventional synthesis with primary aromatic amines



The first quinoline ring synthesis was implemented by Koeigs and Coll (Barton, et al., 1979); the synthesis comprises passing ethylamine vapors or other alkylamines on acrolein. We will now develop routes of access to conventional quinoline ring, and some recent developments.

1.1.1 Access Route to Quinolines

The quinolines access methods are diverse and numerous. In this part; we will be gathered as the most representative.

There are basically two major synthetic routes. The first involves the condensation of aniline and the second one of the ortho-substituted aniline.

1.1.1.1 From Aniline

There are four syntheses methods: Skraup method (Skraup, 1880), Conrad-Limpach method (Conrad, 1887), Combes method (Combes, 1888) and Doebner method (Doebner, 1881). When condensation must be in the presence of one or more reagents; which bring the three missing carbon in the formation condensed heterocyclic formation. (Figure 1).

Skraup and Coll (Skraup, 1880) were heated aniline, glycerol and the concentrated sulfuric acid in the presence of a mild oxidant to 170 ° C. The quinoline is then liberated by basifying the reaction mixture and isolated by distillation under reduced pressure.

Dobner-Von Miller (Doebner, 1881) synthesis is very similar to Skraup with some differences, the absence of an oxidizing agent and glycerol is replaced by a ketone α, β-unsaturated.

Using another method, Conrad Limpach (Conrad, 1887), and Knorr (Knorr, 1886) prepared the 2 or 4-quinolones, using aromatic amines with β-keto esters. At low temperatures, the amine condenses with the most reactive and gives the ketone anilinocrotonic ester which cyclizes to 250 ° C in 4-quinolone. It is the synthesis of Conrad Limpach. At higher temperatures (110-140 ° C), the initial product is the acetoacetic acid anilid derived from the condensation of the amine with the carbonyl group of the ester, cyclizing in an acidic medium yields the 2-quinolone. This is the method of Knorr.

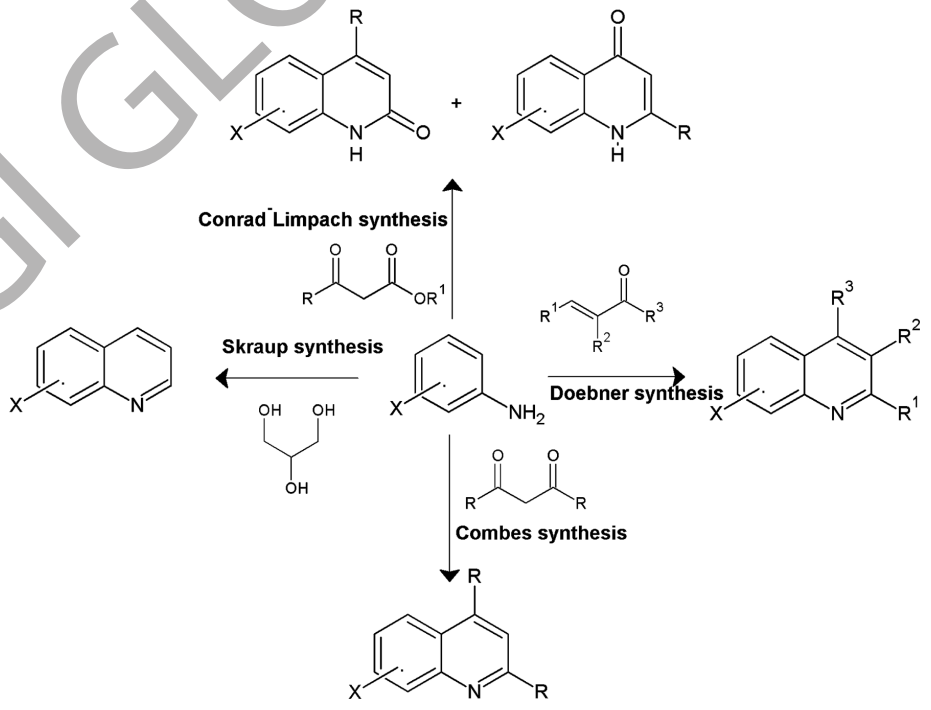
Combes (Combes, 1888) reacted aniline with a 1, 3-diketone in the presence of a strong acid, the result is a 2 and 4-substituted quinoline.

In recent years, various changes were made to improve the performance and reproducibility of these reactions. O. Meth-Cohn and B. Narine (Meth, 1979; Meth, 1981; Meth, 1993; Meth, 1995) were synthesized several quinolines derivatives, such as 2-chloro-3-formyl quinolines. They heated the acetanilide derivatives at 75 ° C in the presence of Vilsmeier reagent ($POCl_3$ / DMF) with the ratio 7/3. Recently, Satya Gupta and Paulet (Satya, 2000) redid the Meth-Cohn synthesis in microwave ovens at 170 ° C and silica gel as a carrier reactor, so they got the 2-chloro-3-formyl-quinoline derivatives after 2.5 min with good yields.

1.1.1.2 From Ortho-Aniline

We found Pfitzinger (Satya et al.; 2000), Friedlander (Pfitzinger, 1886), and Niementowski (Manske, 1942) Brosche (Borsche & Ried 1943) syntheses (Figure 2). In this case the aniline must react with the two missing carbon entity, to form the bicycle.

Figure 2. Conventional syntheses with ortho-substituted anilines



The first synthesis carried by the German chemist Paul Friedlander; involves 2-amino benzaldehyd and acetaldehyde (Friedlander, 1882). This reaction was then extended to other aldehyde derivatives to access all quinolines 2 and 3 substituted.

Friedländer reaction is the most widely method used in the actual quinoline motif synthesis (Marco-Contelles et al., 2009). However the first methods used are not advantageous because of drastic conditions, long reaction times for low yields. Various variations of the method have been applied (Das et al., 2007, Atechian et al., 2007). Some were directed to the development of acid catalysts. Further development conditions "green" with gold catalysts (Barbero et al., 2010).

Pfitzinger, Niementowski and Brosche reactions can be considered extensions of the Friedländer reaction. The difference between these lies in reactions of reagents. The Pfitzinger reaction an isatin used, that of Niementowski reacting anthranilic acid and Brosche involves reacting a substituted nitrobenzene in the ortho position.

1.2 Bayllis-Hillman Quinoline Adducts

The Bayllis-Hillman quinoline Adducts quinolines derivatives are widely used as insecticides (Balicki et al., 1986) and herbicides (Hagen et al., 1991), safeners. In the field of pharmaceutical research, these derivatives have proved effective as anti-microbial and anti-fungal (Rafat et al., 2008), anti-leishmania (Nakayama et al., 2007), and in the treatment of rheumatoid arthritis (Yonghan Hu et al., 2006) and cancer (William et al., 2008; Saleh et al., 2009).

Forming reactions of C-C bonds are among the most important tools in synthesis since these links are the backbone of all organic compounds. To achieve our goal, we chose the reaction of Morita-Baylis-Hillman (Morita et al 1968; Baylis et al., 1972) as a key step in our synthesis because it provides, in one step, highly functionalized products whose applications are varied (V. Singh & Batra., 2008).This reaction is condensation between an aldehyde and the system α, β-unsaturated in the presence of a catalyst. The most used is the 1, 4-diaza-bicyclo [2, 2, 2] octane (DABCO).

Inspired by the work done by P. Narender (Narender et al., 2005) team; novel adducts was synthesized, which is estimated to have an interesting biological properties. These compounds are synthesized using the Baylis-Hillman reaction between the derivatives 2-chloro-3-formyl quinolines, already prepared by the method of Meth Cohn and the methyl acrylate and as DABCO catalyst and the solid support as silica SiO_2.

1.2.1 Literature about Baylis-Hilman Reaction

The Baylis-Hillman reaction is basically a condensation reaction in which three components form the DC link. It involves the catalytic coupling of activated olefins and carbon electrophiles leading to highly functionalized molecules classes. This reaction was first discovered in 1968 by the Japanese Morita Kenici (Morita et al., 1968) he called "carbinol addition." He reported the reaction of methyl acrylate or acrylonitrile with an aldehyde in the presence of tricyclohexyl phosphine to form such adduct. The reaction yield remains quite low (23%).

In 1972, two German Anthony Baylis and Melville Hillman (Baylis & Hillmann, 1972) filed a patent; it describes the reaction between an activated olefin (ester, amide, nitrile or ketone α.β-unsaturated) and an aldehyde, substituting the phosphine with a tertiary amine (such as DABCO, or the indolizine quinuclidine). But it was not until ten years later that this reaction actually started to be used in organic synthesis with the work of Drewes (Drewes & Emslie, 1982) and Hoffman (Hoffmann & Rabe, 1983).

1.2.2 Components and Baylis-Hillman Reaction Mechanism

In general, the Baylis-Hillman reaction involves three components (Drewes & Roos, 1988; Basavaiah & Gowriswari, 1986; Basavaiah & Gowriswari, 1987; Market al., 1997): an activated olefin by which electron withdrawing group is a Michael acceptor, the basic catalyst which acts as a nucleophile or Michael donor and the electrophilic reagent.

The overall mechanism is an equilibrium reactions series (Basavaiah et al., 1996; Basavaiah et al., 2003; Basavaiah et al., 2007) whose key step is the aldol with the attack of the electrophile on the intermediary. Note whenever any of these intermediates has been isolated.

1.2.3 Baylis-Hillman Reaction Variants

We will give a brief overview of the alternatives that were considered during the development of the Baylis-Hillman reaction to improve its kinetics and expand its scope.

1.2.3.1 Pressure

The influence can exert pressure on such reactions is an interesting example of the potential performance of the Baylis-Hillman reaction based on the factors of reaction conditions.

In 1986, Isaacs and Hill (Hill & Isaacs, 1986) demonstrate that the use of a pressure of 2-5 Kbar affords a general acceleration of the Baylis-Hillman reaction conducted at atmospheric pressure with an increase in yield.

The classic Baylis-Hillman reaction is no result from β-substituted enone. However, through the use of high pressure (Van et al., 1993; Basavaiah et al., 1996), it could be effectively carried out on two crotonic derivatives: methyl crotonate and crotononitrile.

1.2.3.2 Polar Solvent

In 2002, the Aggarval group's (Aggarval et al., 2002) presents a new version of the Baylis-Hillman reaction carried out in polar solvents such as water. The high polarity of the solvent allows it to stabilize by means zwitterionic solvates, which improves some reactions initially little or not visible by the Baylis-Hillman method. The acceleration of Baylis-Hillman reactions carried out in water also provides access to some of the cyclohexenone derivatives adducts.

1.2.3.3 Adding a Co-Catalyst

After Morita and Coll publication (Morita et al., 1968), several studies have been reported in the literature using various derivatives of phosphine (Bu_3P, Ph_3P, ...) to carry out the Baylis-Hillman reaction (Toyo Rayon, 1969; Imagawa et al., 1984; Miyakoshi et al., 1983; Bertanshaaw et al., 1989; Roth et al., 1992) and usually the best results are obtained in the presence of an alcohol as co-catalyst.

Recent studies conducted by the Ikegami's group (Yamada & Ikegami;, 2000) regarding the use of phosphine (Bu_3P) as a catalyst, together with the addition of an alcohol in the reaction medium, allowed the coupling of cyclopentenone and aldehyde. Yields of this variant of the Baylis-Hillman reaction greatly change depending on the reactants. Thus, although this reaction is applicable to cyclohexenone, it requires several days and yields are generally quite average.

These examples highlight the use of phosphines relative to DABCO, and further illustrate the improvement provided by the addition of a co-catalyst.

It should be noted that the co-catalyst (methanol, or other alcohol Broensted acid) acts as a Broensted acid, causing the activation of enolate and aldehyde groups, which results in an acceleration of the reaction rate compared to reactions catalyzed by phosphines or amines alone.

Similarly, Shi and Coll (Shi & Jiang, 2002), have successfully used the L-proline as a co-catalyst with the imidazole in Baylis-Hillman reaction of various aromatic aldehydes and methyl vinyl ketone.

1.2.3.4 Temperature

In 2010, Cantillo and Kappe (Cantillo & Kappe, 2010) showed that the Baylis-Hillman reaction is reversible. Indeed, they reacted the Baylis-Hillman adduct with DABCO at 120 ° C in methanol and observed the formation of 68% of the corresponding aldehyde after one hour. Then they let the mixture at room temperature for 24 h, so then observed an increase amount of Baylis-Hillman product, present in 72%. These observations have not only shown the reversibility of this reaction, but also the strong dependence between equilibrium constant and temperature: the formation of the Baylis-Hillman adduct is favored at low temperatures, while the reactants are the species most abundant at elevated temperatures.

1.2.3.5 Hydrogen Bonds Influence

The experiments show that the hydrogen bonds accelerate reactions by stabilizing the substrate or activating the electrophilic reagent. This explains the influence of basic catalysts such as amino alcohols, or the use of water or methanol as solvents considerably accelerating the reactions. As an example, a recent study (Krishna et al., 2005) shows that aldehydes and activated olefins unresponsive such as hexanal and acrylamide can react and donate the Baylis-Hilman proceeds in good yields in the presence of standard catalyst (DABCO) and under the influence of polar aprotic solvents. These results are due to three reasons: 1) The elimination of the ester hydrolysis of functions (for ethyl acrylate / methyl), 2) The increase of the pKa of Lewis base (DABCO for this study) and, 3) The stabilization zwitterion by the effect of dipole interaction-dependent.

1.2.3.6 The Solid Phase Influence

Basaviah and Reddy (Basavaiah & Mallikarjuna, 2001) observed an acceleration Baylis-Hillman reaction in solid phase. Indeed, in the presence of silica gel or alumina, acrylate, tert-butyl, which is classified as less reactive alkenes activated, reacts with various aldehydes and gives very good yields (81%) and a rate relatively high reaction (36h).

1.2.3.7 Ionic Liquids Influence

It has been reported that the preparation of the Baylis-Hilman adduct is promoted using an ionic solvent (Wasserscheid & Keim, 2000; Dupont et al., 2002). This is due to the stability of the zwitterion intermediate ion (Dupont & *Braz*, 2004; Rosa et al., 2001; Kuma et al., 2003; Kim et al., 2003; Pegot et al., 2004; Mi et al., 2005). Indeed it has been shown that the use of highly ionic solvent accelerates the reaction (Rosa et al., 2001). Furthermore Aggarwal and Coll (Aggarwal et al.,2002), showed that the use of ionic liquid based on imidazolium gives a low yield due to the direct addition of the deprotonated imidazolium aldehyde against by the use of two salts methyl-1,3-dialkyl imidazole avoids this type of addition and thus improves performance.

1.2.4 Baylis-Hillman Adducts Application in Organic Synthesis

The presence of functional groups in the Baylis-Hillman adducts plays an important role in the construction and the molecular assembly. The Baylis-Hillman adducts obtained by reaction between the electrophilic and activated vinyl systems contain at least three functional groups specific. Who are the hydroxyl (or amino), alkene, and with drawing group. Since these functional groups are nearby. They should, in principle, be useful in various stereoselective either individually or both together and synthetic transformations.

In recent years, the application of the Baylis-Hillman reaction has been widely studied and the number of transformation methodologies and organic was developed. In Chromenes synthesis (Kaye & Nocanda., 2000; Kaye & Nocanda., 2002); Lactones synthesis (Basavaiah et al.,1996; Choudhury et al., 1998; Choudhury et al., 1999); Dihydrofurans and dihydropyrroles synthesis(Kim et al., 2004); Quinolines and quinolones synthesis(Familoni et al., 1998); Pyramidones synthesis (Basavaiah & Satyanarayana., 2002); Naphthalenes synthesis (Kim et al., 2001); Isoxazolines synthesis (Micuch et al ., 2000, Kaye & Nocanda., 2002; Musa & Nocanda., 2003); Indolizines synthesis (Bode & Kaye., 1990; Basavaiah & Rao., 2003; Basavaiah & Rao., 2003) and in Natural products synthesis (Sugahara & Ogasawara.,1999; Iura et al., 2001; Wang et al., 2001; Anand et al.,2002).

1.3 Biological Properties of Quinoline Derivatives

The literature revealed that Interest in family quinoline result of their numerous biological activities. The quinoline derivatives generally exhibit activities: anti malaria, analgesic, anti-inflammatory and anti-mitotic ... etc.

1.3.1 Anti-Malarial Quinoline Derivatives

Malaria is one of the most common infectious diseases in the world, each year between 1 to 3 million people die. Plasmodium falciparum is the parasite species responsible for malaria mortality. The latter has become resistant to many antimalarial drugs such as chloroquine (Allinger et al., 1984), mefloquine (WHO et al ., 1975; Trenholme et al., 1975) and others. Chemists and biologists have joined forces to combat this disease and they combine all their efforts to find molecules that are both effective and economically accessible to developing countries. For this Chibale and his team (Chibale et al., 2000) synthesized analogs Ferrochloroquine, resulting from the incorporation of a ferrocene unit in the basic skeleton of chloroquine, which have good anti malarial activity.

Also in the same axis, Modapa (Modapa et al., 2009) have synthesized and enhanced anti malarial effect of some quinoline derivatives . These compounds inhibit the chloroquine-sensitive Plasmodium falciparum clones with an MIC of 0.25 mg / ml.

1.3.2 Anti-Inflammatory Quinoline Derivatives

The anti-inflammatory power of quinoline derivatives was highlighted in many studies (Chen et al., 2006; Baba et al., 1996). Recently Gilbert et al (Gilbert et al., 2008) were able to synthesize amino acetamides quinoline that prove their efficiency in the treatment of osteoarthritis as aggrecanase-2 inhibitors .

1.3.3 Anti-Cancer Quinoline Derivatives (Antineoplastic)

Cancer is characterized by uncontrolled growth and multiplication of cells. This uncontrolled overgrowth can affect most body tissues. It drives up to 6 million deaths per year, or 12% of global deaths. The Camptothecin is isolated from the plant Camptotheca acuminate (Wall et al., 1966; Hsiang et al., 1985) which has remarkable anti-tumor properties (Muggia et al., 1972; Fan et al., 1998) by selective inhibition of topoisomerase I. Following severe adverse effects, its development was stopped in Phase II clinical trials. Due to their pharmacological interest, other compounds are obtained by semi-synthesis from camptothecin such as irinotecan (Fang et al., 1994; Dallavalle et al., 2001) and topotecan (Ettinger, 2002) .

1.3.4 Antibacterial Quinoline Derivatives

Many antibacterial agents quinoline have been cited in the literature, including Nibiol used in urinary infections (Dorvaults, 1982), quinolones having a carboxylic function in position 4 such as norfloxacin (Allen, 1984) and the Lomofloxacine (Spinorin, 1989). The latter has an excellent anti-pathogen efficacy even in cases where penicillin, cephalosporins and aminoglycosides are without action. The resistance developed by certain pathogens to existing drugs, requires the search for a new class of antibacterial agents.

In this context, the group of Upadhayaya (Upadhayaya et al., 2009) decried to synthesis the derivatives of 3-benzyl-6-bromo-2-methoxyquinoline through molecular modeling technique. These compounds are endowed with activity against Mycobacterium tuberculosis H37Rv. On the other hand, and to conquer the emergence again of tuberculosis, a series of quinoline derivatives derivatives synthesized by the group of Eswaran (Eswaran et al., 2010), using Mefloquine as the leader, prove his anti-tuberculosis activity.

1.3.5 Antifungal Quinoline Derivatives

The tetrahydroquinolines synthesized by the Gholap team (Gholap et Al., 2007) showed a good degree of inhibition against fungi Candida albicans, Fusarium oxysporum and Mucor sp. Recently, the group was able to synthesize Kumar (Kumar et al 2011) some secondary amines containing 2-chloroquinoline and evaluate their antifungal activity against Aspergillus Niger, A. flavus, Penicillium citrinum and Monascus purpureus.

1.3.6 Antiviral Quinoline Derivatives

To replicate, HIV (human immunodeficiency virus) badly needs the Tat protein and an element of the viral RNA: TAR. These two compounds form a complex for the integration of viral genome into that of the host cell, and especially expression of the viral genes.

This is why for many years the Tat-TAR complex is the new antiviral target. Examples of these antivirals, quinoline derivatives synthesized by the group and Chen et al (Chen et al., 2009) autrespréparés by Fakhfakh (Fakhfakh et al., 2003) showed an inhibitory effect of the very important Tat-TAR interaction.

1.3.7 Quinoline Derivatives and Cardiovascular Disease

Atherosclerosis is a cardiovascular disease that affects the arteries, their tissues become stiffer and loses their elasticity, with the formation of atherosclerotic plaques resulting from the excess of cholesterol. Bernotas's group (Bernotas et al., 2009) developed some quinolines that act as agonists liver X recep-

tors (regulating the metabolism of cholesterol and lipids) in the case of dyslipidemia and its agents have also reversed the condition of arteriosclerosis. Still in the same way, Rano et al (Rano et al., 2009) have synthesized the (figure. 9b) tetrahydroquinolines that inhibit protein transfer cholesterol esters.

The quinoline derivatives (Figure 9c-d) developed by the Ramos (Ramos et al., 2007) group showed their effectiveness as platelet inhibitors (To prevent the formation of blood clots and thrombosis).

1.3.8 Quinoline Compounds and their Effects on the Central Nervous System

The quinoline structures have shown their importance in the neuropathological field. Studies on hydroxyquinolines and their derivatives have shown that these compounds have antioxidant activity and properties of the iron chelator (Li et al., 2010). Such as Quinolobactine (Matthijs et al., 2004) derived from the bacterium Pseudomonas fluorescens ATCC 17400, and synthetic compound O-Trensox (Pierre et al., 2003) .

More recent studies have disclosed novel quinoline compounds characterized by several properties, compounds act as antagonists neurokines 3 receptors (NK3) (Smith el al., 2009) and other derivatives showed an interesting affinity, selective agonists for receptors cannabinoid (CB2)(Manera et al., 2007).

1.3.9 Other Biological Properties

The quinoline derivatives presented above show only a small part of the active quinolines, literature has shown us several properties. There are quinoline derivatives which are used for the treatment of renal failure, another act against cutaneous leishmaniasis, visceral and Chagas disease (Ma et al, 2009; Franck et al., 2004). They are also analgesics (Abadi et al., 2005; Manera et al., 2007) and of hyperglycemic (Edmont et al., 2000) Anthelmintics (Rossiter et al, 2005)... .. etc.

1.4 Reminder of Bacteria and Antibiotics

1.4.1 Bacteria

Bacteria are prokaryotic unicellular organisms, characterized by an absence of nucleus and organelles. Most bacteria have a carbohydrate wall peptidoglycan.

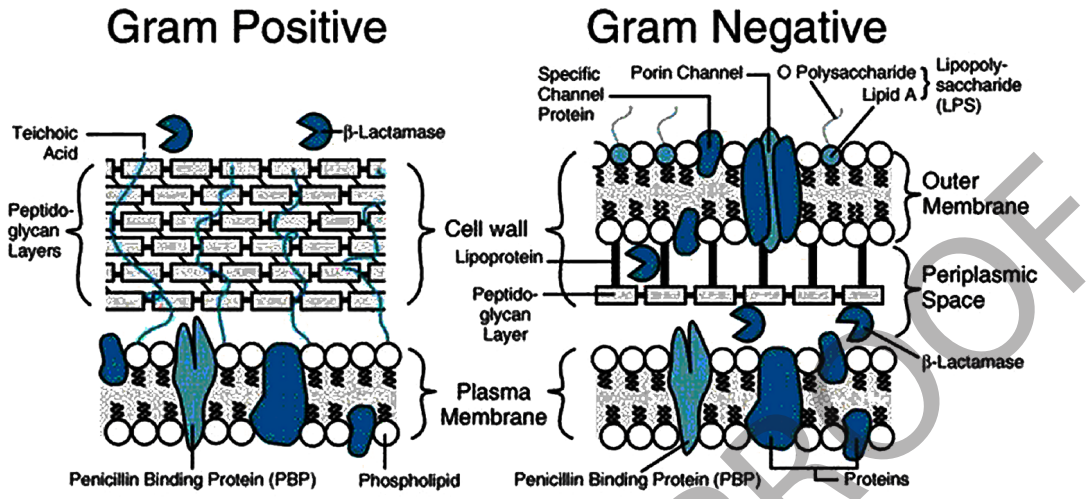
However, there are many pathogenic species responsible for many infectious diseases (Nauciel, 2000) such as cholera, syphilis, tuberculosis.

The bacteria can be divided into two groups (Gram positive and Gram negative) based on the difference in structure and chemical composition of the cell wall (Figure 3).

1.4.1.1 Gram Positive Bacteria

The Gram positive bacteria have a large peptidoglycan structure. As noted above, this accounts for the differential staining with Gram stain. Some Gram positive bacteria are also capable of forming spores under stressful environmental conditions such as when there is limited availability of carbon and nitrogen. Spores therefore allow bacteria to survive exposure to extreme conditions and can lead to reinfection (*e.g.,* pseudomembranous colitis).

Figure 3. Bacterial wall structure



1.4.1.2 Gram Negative Bacteria

The Gram negative bacteria have a small peptidoglycan layer but have an additional membrane, the outercytoplasmic membrane. This creates an additional permeability barrier and results in the need fortransport mechanisms across this membrane.

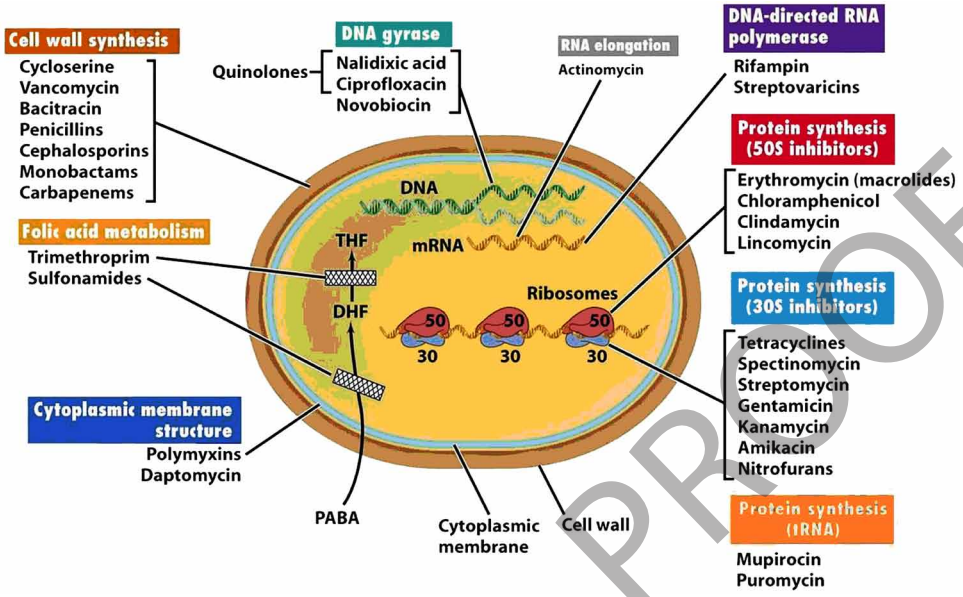
A major component of the cytoplasmic membrane that is unique to Gram negatives is endotoxin. This component is essential for bacterial survival. Endotoxin has three components: the lipid a moiety, the highly conserved core polysaccharide and the species specific O antigen (also polysaccharide). In contrast with the secreted exotoxins, endotoxin is cell associated but with bacterial division and death can be released. The Lipid a moiety of endotoxin is responsible for sepsis and this may be fatal. It is characterized clinically by confusion, fever, drop in blood pressure and ultimately multi-organ failure.

1.4.2 Antibiotics

Antibiotics are "microbial products or their derivatives can kill sensitive or inhibiting their growth microorganisms." And their action being directed against the specific microorganisms, they are non-toxic to eukaryotic cells. More antibiotic acts on different bacterial species, the more action spectrum is wide. The action of antibiotics may have on structures or mechanisms required for growth or survival of the bacteria. So those that inhibit or prevent the growth of bacteria are called "*bacteriostatic*" while those that kill bacteria are called "*bactericidal*".

The antibiotic targets are involved in physiological functions or metabolic (Figure 4). The less antibiotics family includes a very variable number of molecules having a basic identical structure. Some molecules alter the structure of the bacteria by inhibiting their formation wall: For β-lactams, glycopeptides, fosfomycin and that block various stages of the synthesis pathway of peptidoglycan; or disrupting their membranes (despolymyxines case). Also ther are others, such as aminoglycosides, tetracyclines, chloramphenicol, lesmacrolides, lincosamides and streptogramin, which bind to the bacterial ribosome inhibiting various stages of protein synthesis.

Figure 4. Antibiotics mode action



1.4.2.1 Natural and Synthetic Antibiotics

Antibiotics are mainly represented by naturally occurring molecules and their derivatives. They may also be synthetic or semi-synthetic origin (Newman et al., 2003; Singh & Barrett, 2006). Synthetic antibiotics are obtained either from totally artificial derivatives, or recreating substances originally extracted from micro-organisms. Hemi-synthetic antibiotics are derived from the change in the laboratory of substances produced by microorganisms.

Antibiotics are grouped into classes or families based on their structural properties. Virtually all classes of antibiotics have been discovered in a "golden age", which ran from 1936 to 1962.

Penicillin, the first broad-spectrum antibiotic, isolated from fungi of the genus Penicillium sp, marks the beginning of the first antibiotic. It belongs to the class of β-lactams. His discovery paved the way for the identification of numerous other antibiotic classes of natural origin, including phenylpropanoids, tetracyclines, aminoglycosides, macrolides, glycopeptides, streptogramins and β-lactams second generation. A third generation of β-lactams has been marketed in the late 1970s, carbapenems.

There are only three classes of synthetic antibiotics (Laub, 1986). The first class is represented by sulfonamides, which are also the first antibiotic to be used clinically. The second class, quinolones (or fluoro-quinolones), was discovered in the synthesis of chloroquine in 1962 (Singh & Batra, 2008), an antimalarial. Oxazolidinones represent the third class of synthetic antibiotics. Discovered in 1979, it led to the development and commercialization of linezolid in 1999 with cyclic lipopeptides (daptomycin), oxazolidinones are one of the few classes of antibiotics on the market over the past ten years.

1.4.3 Quinolone and Quinoline Derived

The most important structures of quinoline acids are quinolones and fluoroquinolones. Indeed, in 1958 the researchers found the bactericidal activity of a secondary product, 7-chloroquinolin (Lescher et al, 1962) obtained during the synthesis of chloroquine.

Quinolones were introduced in therapy such as antibiotics, dice 1965 under the name Negram® or nalidixic acid discovered in 1962 by Lesher, indicated for the treatment of urinary tract infections with Gram (-) (Mannhold, 1986). Urotrate® or oxolinic acid, which is derived from nalidixic acid (Kaminsky & Meltzer, 1968; Mac Guirk et al., 1992), has an antibacterial effect on a few bacterial strains such as Escherichia coli, Proteus, Enterobacter, Citrobacter ... etc. Negram® and Urotrate® Both are antibiotics belong to the first generation of quinolones.

Structural modifications have improved the antibacterial spectrum and pharmacokinetic properties of the first generation of quinolones. The main modification is based on the substitution of a fluorine atom in position 6 of the quinoline ring. The resulting molecules, fluoro-quinolones of second generation quinolones have a better penetration through the cell wall thereby to widen their spectrum Gram positive bacteria. Norfloxacin prepared in 1986 (Schaad et al., 1995), Ciprofloxaxine in 1987 (Grohe & Heitzer, 1987), Ofloxacin (Egawa et al., 1986) and Pefloxacin (Koga et al.,**1980**; Allain, 2000; Gendrel & Moulin, 2001) in 1992 are indicated in the treatment of infections caused by aerobic gram-negative bacilli (Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter baumannii) or due to some Gram positive cocci (Staphylococcus), regardless of the location of the infection (bone, meninges, brain, lung, urinary tract, soft tissue ...) (Gendrel, 2002).

Sparfloxacin and levofloxacin (Allen, 1984) (third generation) developed in the USA in 1996, have activity against a wider range of Gram (+) (pneumococci, MICs of 0.25-0.5 mg / l). They also have a good activity against streptococci (S. pneumoniae. S. Viridams, S. Pyrogenes) including strains resistant to penicillin (Pinorin, 1989). They are indicated in the treatment of acute sinusitis and acute exacerbations of chronic bronchitis (Cheriq, 2000).

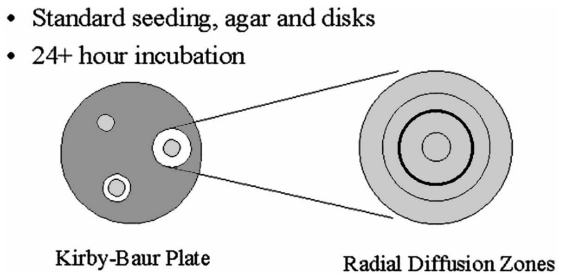
Gatifloxacin and Moxifloxacin are fluorinated quinoline acids of the fourth generation. They are very efficient compared to other agents since they inhibentles two target enzymes DNA gyrase and topoisomerase (II, IV) (Allain, 2000), and their activity against Mycobacterium tuberculosis (treatment-resistant TB) (Culey et al., 2001).

1.4.4 Methods for Determining the Antibacterial Activity

Review of reference data brings up the variety of methodologies used to highlight the antibacterial activity of a product. The choice of the method is determined by the insolubility of the test products in aqueous media, volatility, and the need to test at low concentrations.

- Disk diffusion method or agar (medical bacteriology called sensitivity).
- Well diffusion method; Proposed by COOPER and WOODMAN in 1946. It ensures radial diffusion of the test product by giving a clear zone easily measurable inhibition.
- Dilution method; in this method the test products may also be mixed directly in a known concentration to the culture medium, whether solid or liquid. The medium was then inoculated at a rate determined by microorganisms, after incubation, one notes the presence or absence of culture. The reading may be visually or using a spectrophotometer.

Figure 5. Disk diffusion method principles



1.4.4.1 Evaluation of Antibacterial Activity by Disc Diffusion Method

This method is used to evaluate the antibacterial activity of a product. Although recognized as a reliable and reproducible, it is mostly used for preliminary step further study because it provides access to essentially qualitative results. The technique used is a modification of the method of Hayes and Markovic. It involves depositing a sterile disk impregnated with the test product on a bacterial lawn at the very beginning of its growth and measure the area where the bacteria could not grow. The diameter of inhibition, which reflects the antibacterial activity of the tested product, is thus determined (Figure. 5).

2. SYNTHESIS AND CHARACTERISATION PART

2.1 Synthesis of Cyano Quinolines Derivatives

In our study, among these methods, we chose a developed method of Meth-Cohn (Meth. Cohn et al., 1979; Meth et al., 1981; Meth et al., 1993 ; Meth et al.,1995) for the preparation of our starting products 2-chloro-3-formyl-quinolines which are of great synthetic interest in the field of organic chemistry.

The Meth-Cohn method aim, is the Synthesis of the 2-chloro-3-formyl-quinolines derivatives, by heating the derivatives of acetanilide, in the presence of Vilsmeier reagent (POCl 3 / DMF) with a 7/3 ratio.

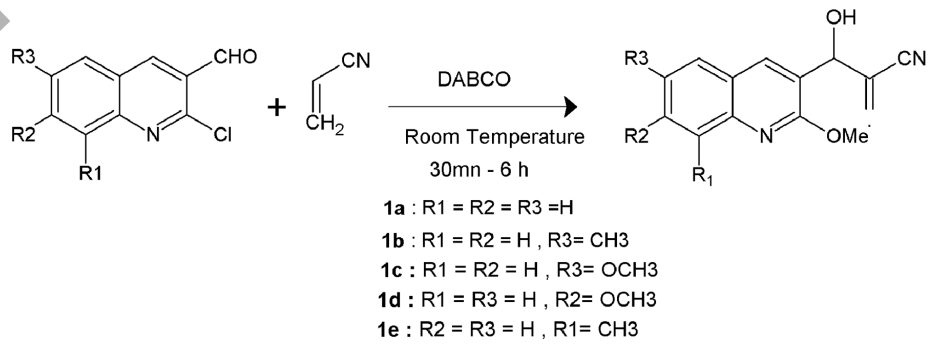
Baylis–Hillman adducts (1a–1e) were prepared from the reaction of 2-chloro-3-formyl quinoline derivatives (1), previously obtained from the Meth Cohn procedure, and acrylonitrile catalyzed by DABCO (Figure 6) and silicon oxide like solid support at room temperature. These compounds were obtained according to the literature methods published in the paper of Narender et al. (Narender et al., 2005).

- **(1a):** To a stirred solution of 2-chloro-3-Formyl-quinoline (0.5 g; 2.61 mmol) in acrylonitrile (2 ml; 30.40 mmol) was added DABCO (2.61 mmol; 0.292 g) at room temperature and the reaction was allowed to continue for 15 min. The final product was purified via silica gel column chromatography with Petroleum Ether/ethyl acetate (85:15, v/v) as eluent to furnish pure beige crystals in 80% yield (0.51 g; m.p = 116 _C). Rf = 0.37 (ethyl acetate/ Petroleum Ether (3/7)). I.R (KBr; m cm-1): 3,191(OH), 2,235 (CN), 1613 (C = C). 1H NMR (400 MHz, CDCl3): d 8.50 (t, 1H, J = 1.0 Hz, H–C3), 8.00 (ddt, 1H, J = 8.5, 1.1, 0.7 Hz, H–C9), 7.86 (ddt, 1H, J = 8.1, 1.4, 0.5 Hz, H– C6), 7.76 (ddd, 1H, J = 8.5, 7.0, 1.4 Hz, H–C8), 7.58 (ddd, 1H, J = 8.1, 7.0, 1.2 Hz, H–C7), 6.15 (d, 1H, J = 1.1 Hz, C = CH2), 6.11 (d, 1H, J = 0.7 Hz, C = CH2), 5.85 (dq, 1H, J = 4.3, 0.9

Hz, CHOH), 4.13 (d, 1H, J = 4.3 Hz, OH). 13C NMR (100 MHz, CDCl3): d 148.32 (Cquat, C1), 147.20 (Cquat, C5), 137.56 (CH, C3), 132.45 (C = CH2), 131.33 (CH, C8), 130.95 (Cquat, C2), 128.15 (CH, C6), 127.85 (CH, C9), 127.67 (CH, C7), 127.14 (Cquat, C4), 124.28 (Cquat, C = CH2), 116.39 (Cquat, CN), 70.4 (CHOH).

- **(1b):** White single crystals were grown from the mixture of 2-chloro-3-Formyl-6-methyl quinoline (0.5 g; 2.43 mmol), DABCO (0.272 g; 2.43 mmol) and acrylonitrile (1.9 ml; 28.94 mmol). Purification of the resulting product was performed via silica gel column chromatography with the eluent Petroleum Ether/ethyl acetate (85:15, v/v) to obtain finally 0.56 g of the compound 2b (89% yield). Rf = 0.41 (ethyl acetate/Petroleum Ether (3/7)). m.p = 154 _C. I.R (KBr; m cm-1): 3,494 (OH), 2,223 (CN), 1,582 (C = C). 1H NMR (400 MHz, CDCl3): d 8.39 (t, 1H, J = 1.0 Hz, H–C3), 7.91 (dt, 1H, J = 8.6, 0.9 Hz, H–C9), 7.66–7.62 (m, 1H, H–C6), 7.59 (dd, 1H, J = 8.6, 1.9 Hz, H–C8), 6.16 (d, 1H, J = 1.1 Hz, C = CH2), 6.13 (d, 1H, J = 0.7 Hz, C = CH2), 5.84 (d, 1H, J = 3.6 Hz, CHOH), 3.44 (d, 1H, J = 4.2 Hz, OH), 2.54 (d, 3H, CH3). 13C NMR (100 MHz, CDCl3): d 147.36 (Cquat, C1), 145.95 (Cquat, C5), 137.80 (Cquat, C7), 136.74 (CH, C3), 133.57 (CH, C8), 132.32 (C = CH2), 130.59 (Cquat, C2), 127.69 (CH, C9), 127.19 (Cquat, C4), 126.97 (CH, C6), 124.31 (Cquat, C = CH2), 116.34 (Cquat, CN), 70.65 (CHOH), 21.61 (CH3).
- **(1c):** The derivative 2c was prepared from the reaction of 2-chloro- 3-Formyl-6-methoxy quinoline (0.5 g; 2,25 mmol) and acrylonitrile (3 ml; 54 mmol) catalyzed byDABCO(0.252 g; 2.25 mmol). We have obtained 0,44 g (m.p = 126 _C; yield = 71%) of beige single cristals after purification via silica gel column chromatography with the eluent Petroleum Ether/ethyl acetate (85:15, v/v). Rf = 0.61 (ethyl acetate). I.R (KBr; m cm-1): 3162 (OH), 2144 (CN), 1,623 (C = C). 1H NMR(400 MHz,CDCl3): d 8.37 (td, 1H, J = 0.8, 0.3 Hz, H– C3), 7.89 (dt, 1H, J = 9.2, 0.5 Hz, H–C9), 7.40 (dd, 1H, J = 9.2, 2.8 Hz, H–C8), 7.10 (d, 1H, J = 2.8 Hz,H–C6), 6.17 (d, 1H, J = 1.1 Hz, C = CH2), 6.13 (d, 1H, J = 0.7 Hz, C = CH2), 5.84 (d, 1H, CHOH), 3.92 (s, 3H, OCH3), 3.61 (d, 1H, J = 4.1 Hz, OH). 13C NMR (100 MHz, CDCl3): d 158.49 (Cquat, C7), 145.56 (Cquat, C1), 143.33 (Cquat, C5), 136.06 (CH, C3), 132.32 (C = CH2), 130.91 (Cquat, C2), 129.35 (CH, C9), 128.35 (Cquat, C4), 124.29 (Cquat,C = CH2), 124.14 (CH, C8), 16.35 (Cquat, CN), 105.40 (CH, C6), 70.61 (CHOH), 55.67 (OCH3).
- **(1d):** A mixture of 2-chloro-3-Formyl-7-methoxy quinoline (0.5 g; 2.25 mmol), DABCO (0.252 g; 2.25 mmol) and acrylonitrile (5 ml; 90 mmol) has yielded coulorless single crystals of 2d (0.46 g; 74%; m. p = 96 _C) which have been recristallized from a dichloromethane, ethyle acetate and

Figure 6. Baylis–Hillman adducts prepared



petroleum ether mixture after being purified via silica gel column chromatography with the eluent Petroleum Ether/ethyl acetate (85:15, v/v). Rf = 0,44 (ethyl acetate/ Petroleum Ether (3/7)). I.R (KBr; m cm-1): 3,468 (OH), 2,255 (CN), 1,594 (C = C). 1H NMR (400 MHz, CDCl3): d 8.38 (s, 1H, H–C3), 7.74 (d, 1H, J = 9.0 Hz, H–C6), 7.32 (d, 1H, J = 2.5 Hz, H–C9), 7.23 (dd, 1H, J = 9.0, 2.5 Hz, H–C76), 6.15 (d, 1H, J = 1.1 Hz, C = CH2), 6.13 (d, 1H, J = 0.8 Hz, C = CH2), 5.85–5.80 (s, 1H, CHOH), 3.94 (s, 3H, OCH3), 3.63 (d, 1H, J = 2.8 Hz, OH). 13C NMR (100 MHz, CDCl3): d 162.16 (Cquat, C8), 149.32 (Cquat, C1), 148.68 (Cquat, C5), 136.94 (CH, C3), 132.07 (C = CH2), 129.09 (CH, C6), 128.16 (Cquat, C2), 124.46 (Cquat, C = CH2), 122.37 (Cquat, C4), 120.85 (CH, C7), 116.46 (Cquat, CN), 106.17 (CH, C9), 70.55 (CHOH), 55.71 (OCH3).

- **(1e):** To a 2-chloro-3-Formyl-8-methyl quinoline (0.5 g; 243 mmol) and acrylonitrile (1.9 ml; 28.94 mmol) solution was added DABCO (0.252 g; 2.43 mmol). The resulting compound was purified via silica gel column chromatography with the eluent Petroleum Ether/ethyl acetate (85:15, v/v) to give rise to 0.472 g of 2e white single crystals in 75% yield (m.p = 112 _C). Rf = 0.43 (ethyl acetate/ petroleum ether (3/7)). I.R (KBr; m cm-1): 3,170 (OH), 2,226 (CN), 1,617 (C = C). 1H NMR (400 MHz, CDCl3): d 8.40 (s, 1H, H–C3), 7.70 (ddt, 1H, J = 8.1, 1.2, 0.7 Hz, H–C6), 7.60 (ddq, 1H, J = 7.1, 3.5, 1.0 Hz, H–C8), 7.47 (dd, 1H, J = 8.1, 7.1 Hz, H–C7), 6.15 (d, 1H, J = 1.1 Hz, C = CH2), 6.14 (d, 1H, J = 0.8 Hz, C = CH2), 5.83 (d, 1H, J = 3.6 Hz, CHOH), 3.06 (d, 1H, J = 4.3 Hz, OH), 2.76 (t, 3H, J = 0.9 Hz, CH3); 13C NMR (100 MHz, CDCl3): d 147.22 (Cquat, C1), 146.71 (Cquat, C5), 137.44 (CH, C3), 136.46 (Cquat, C9), 132.39 (C = CH2), 131.27 (CH, C8), 130.19 (Cquat, C2), 127.37 (CH, C7), 127.19 (Cquat, C4), 125.99 (CH, C6), 124.23 (Cquat, C = CH2), 116.36 (Cquat, CN), 70.72 (CHOH), 17.80 (CH3).

2.2 Synthesis of Adducts Bayllis Quinoline-Hillman

Baylis–Hillman adducts (2a–2b) were prepared from the reaction of 2-chloro-3-formyl quinoline derivatives (1), previously obtained from the Meth Cohn procedure, and methyl acrylate catalyzed by DABCO (Figure 7) and silicon oxide like solid support at room temperature. These compounds were obtained according to the literature methods published in the paper of Narender et al. (Narender et al., 2005).

Acetylation of the Baylis-Hillman adduct is generally described as a simple reaction between OH and acetyl chloride in an anhydrous medium. In this case mentioned adducts are acetylated by acetyl chloride in pyridine. Reaction was carried our under the action of acetyl chloride in dichloromethane, pyridine at a temperature of 0 ° C; after disappearance of the starting material. We have separated the product as shown in (Figure 8) (Djemel et al., 2015).

Figure 7. Baylis–Hillman adducts prepared

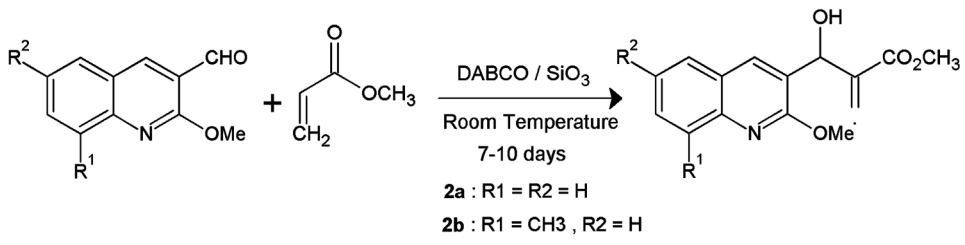


Figure 8. Acetylation of the Baylis-Hillman adduct

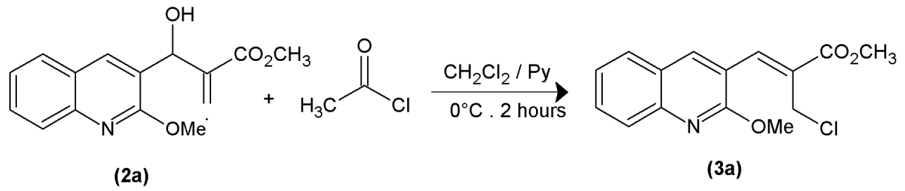
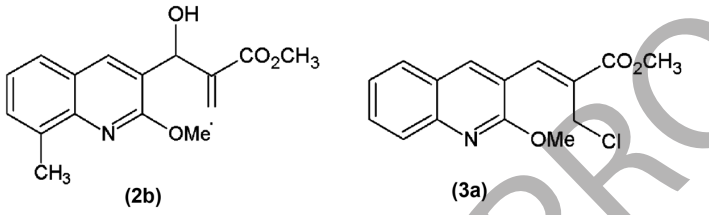


Figure 9. Schemes of (2b) and (3a)



The IR spectrum (3a) shows a band at 1714 cm^{-1} which was characterised as the carbonyl of the ester group vibrations, another vibrational band at 1602 cm-1 attributed to δ(C = C) and another peak at 774 cm^{-1} is assigned to the C-Cl stretching vibration . The ^{1}H NMR spectrum gave two singlets at δ 2.5 and another slightly downfield δ 3.7 integrating for three protons each attribuate to the methoxy protons CO-O-CH_3 and O-CH_3,, the singulet at δ 4.0 is due to the two protons (CH_2-Cl) while the signal at 5.2 ppm is split into the olefinic proton (C=CH).

The FTIR spectrum of (2b) gave a vibration at 3376 cm^{-1} which was the vibration of a free hydroxyl group, a band at 1734 cm^{-1} was also observed identified as that of an ester carbonyl CO group, and another band at 1625 cm^{-1} attributed to δ(C = C). ^{1}H NMR of the product (2b) shows two non-equivalent vinyl protons appear in mean field, Ha appears as a doublet at 6.36 ppm, against Hb appear as a doublet in the range 5.78-5.79 ppm; The protons of CHOH also resonates mean field between 5.86 and 5.89 ppm; while the proton of the hydroxyl function appears as a double wide on 1.4 ppm; Aromatic protons resonate in the usual region with different multiplicities of a product to another; the methyl group of the ester function resonates as a singlet at 3.84 ppm. While the signals of the quinoline ring substituents are either methyl groups which resonate as in a singluet 1.1 ppm or; the methoxyl groups appears as a singlet at 4.4 ppm.

2.2.1 Crystal Structure Analysis

The compound (3a) (Figure 9). Crystallizes in $Pna2_1$ space group. The molecular structure of this quinoline derivative (3a) and the atom-labeling scheme are shown in (Figure 10). The crystal and refinement data are given in (Table 1). However the compound (2b) (Figure 11), crystallizes in P^{-1} space group. The molecular structures of (3a) and (2b) derivative and the atom-labeling scheme are shown in (Figure 10) and (Figure 11). The crystal and refinement data are given in (Table 1).

Figure 10. Ortep 3 view of the asymmetric unit (3a), Ellipsoids are drawn at the 30% probability level, Hydrogen atoms are shows as spheres of arbitrary radii

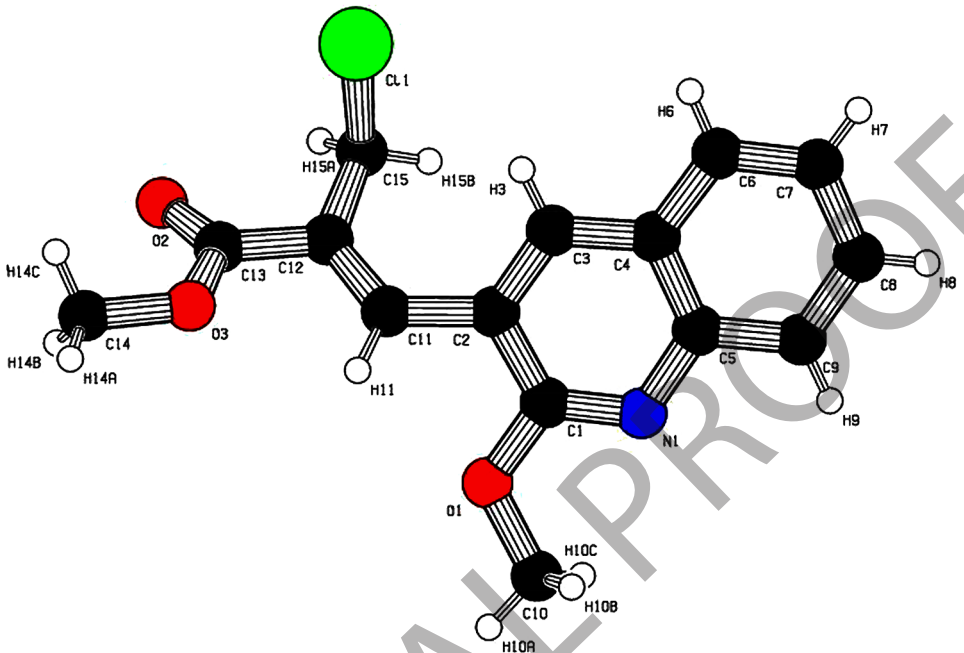
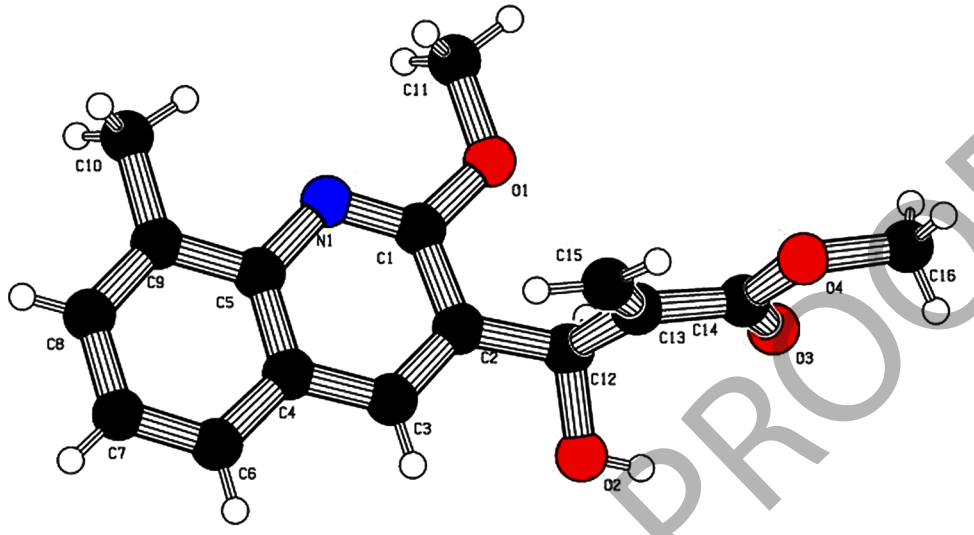


Table 1. Experimental detail of the data collections (2b), (3a)

Compound	***3a***	***2b***
Formula	$C_{15}H_{14}O_3NCl$	$C_{10}H_{37}O_4N$
Fw	*291.7*	*287.3*
Colour	*Colourless*	*Colourless*
cryst. syst.	*Orthorhombic*	*Triclinic*
space group	$Pna2_1$	P^{-1}
a (A)	*7.7237(12)*	*7.9145 (12)*
b (A)	*20.2539(28)*	*9.1412 (11)*
c (A)	*8.7164(12)*	*10.7286 (16)*
α (deg)	*90*	*94.760 (11)*
β (deg)	*90*	*105.988 (13)*
γ (deg)	*90*	*101.818 (11)*
V (Å^3)	*1363.55(3)*	*722.29*
Z	*4*	*2*
ρcalcd (g/cm3)	*1.42*	*1.32*
μ (mm−1)	*0.286*	*0.095*
T (K)	*150*	*150*
F(000)	*608*	*304.0*
Data collection instrument	*Mo Ka(0.71069)*	
Radiation graphite monochromator k (A°)		
R[a]	*0.0553*	*0.0689*
Rw [b]	*0.0772*	*0.0819*

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $R_{w2} = \{\Sigma[w(F_o^2 - F_c^2)2]/[w(F_o^2)2]\}1/2$ *and* $[I > 2\sigma(I)]$.

Figure 11. Ortep 3 view of the asymmetric unit (2b), Ellipsoids are drawn at the 30% probability level, Hydrogen atoms are shows as spheres of arbitrary radii



The quinoline rings (C1-C9/N1) are almost planar, with a maximum deviation of 0.038 (5) A° for C2 (3a) and 0.014(5) A° for C1 (2b). The methoxy group is in the plane of the quinoline ring (C10/O1/C1/C2 = -175.9(3) °) for 3a and (C11/O1/C1/C2 = 179.5(2) °) for 2b; the methyl group on 2b is also in the plane of the quinoline ring with (C10/C9/C5/N1 = 0.4(3) °.

The bond distances within the quinoline portion of the molecules show evidence for significant bond fixation; ; the N1-C1 bands (1.310(5) A°) 3a ; (1.294(3) A°) 2b were significantly shorter than N1-C5 (1.368(5) A°) 3a; (1.375(3) A°) 2b, while the C2-C3 (1.367(5) A°) 3a; (1.363(3) A°) 2b, C6-C7 (1.370(5) A°) 3a; (1.371(4) A°) 2b, and C8-C9 (1.377(6) A°) 2a; (1.380 (4)A°) 1a bands are all significantly shorter than the other aromatic C-C bonds. These distances compare well with the results observed in similar derivatives (Kalkhambkar et al., 2008; Benzerka et al., 2008). Selected bond lengths and angles of the structures are given in Table 2.

Figure 12. Hydrogen bond interaction (3a) assuring the crystal structure cohesion

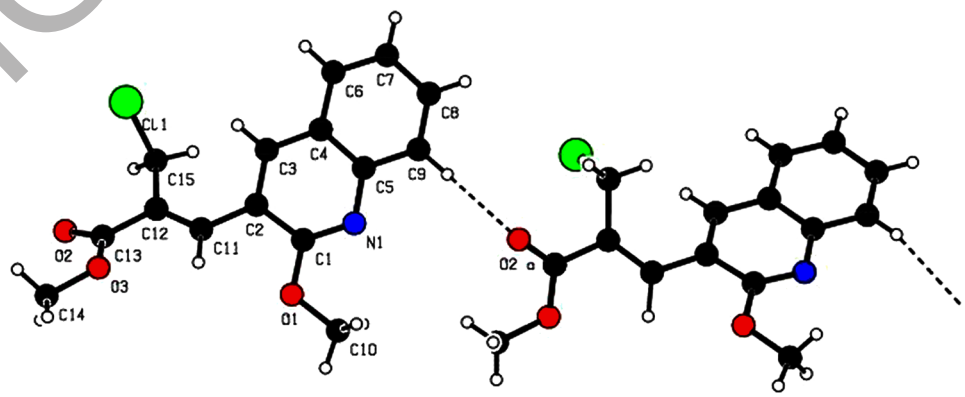


Table 2. Selected geometric parameters (A°, °)

3a				2b			
Bond Distances							
Cl1-C15	1.819(4)	C3-C4	1.402(5)	O1-C1	1.355(2)	C3-C4	1.417(3)
O1-C1	1.355(4)	C4 -C5	1.406(5)	O1-C11	1.433(3)	C4-C6	1.415(3)
O1-C10	1.428(4)	C4-C6	1.426(5)	O2-C12	1.425(2)	C4-C5	1.415(3)
O2-C13	1.217(5)	C5-C9	1.406(6)	O3-C14	1.215(3)	C5-C9	1.420(3)
O3-C13	1.335(4)	C6-C7	1.370(5)	O4-C14	1.329(3)	C6-C7	1.371(4)
O3-C14	1.447(5)	C7-C8	1.387(6)	O4-C16	1.437(3)	C7-C8	1.400(4)
N1-C1	1.310(5)	C8-C9	1.377(6)	N1-C1	1.294(3)	C8-C9	1.380(4)
N1-C5	1.368(5)	C11-C12	1.347(5)	N1-C5	1.375(3)	C9-C10	1.499(3)
C1-C2	1.421(5)	C12-C13	1.479(5)	C1-C2	1.432(3)	C12-C13	1.519(3)
C2-C3	1.367(5)	C12-C15	1.483(5)	C2-C12	1.506(3)	C13-C14	1.479(3)
C2-C11	1.462(5)			C2-C3	1.363(3)	C13-C15	1.327(3)
Bond Angles							
C1-O1-C10	116.3(3)	C4-C6-C7	120.0(4)	C1-O1-C11	116.33(18)	C4-C6-C7	119.3(2)
C13-O3-C14	115.6(3)	C6-C7-C8	120.0(4)	C14-O4-C16	116.0(2)	C6-C7-C8	120.8(2)
C1-N1-C5	117.6(3)	C7-C8-C9	121.8(4)	C1-N1-C5	117.55(17)	C7-C8-C9	122.1(2)
O1-C1-N1	119.5(3)	C5-C9-C8	119.4(4)	O1-C1-C2	114.11(17)	C5-C9-C8	117.73(19)
O1-C1-C2	115.1(3)	C2-C11-C12	126.6(3)	N1-C1-C2	125.82(18)	C5-C9-C10	119.7(2)
N1-C1-C2	125.4(3)	C11-C12-C13	120.4(3)	O1-C1-N1	120.07(17)	C8-C9-C10	122.6(2)
C1-C2-C3	116.0(3)	C11-C12-C15	125.3(3)	C1-C2-C12	119.69(17)	O2-C12-C2	108.83(15)
C1-C2 -C11	119.6(3)	C13-C12-C15	114.3(3)	C3-C2-C12	123.75(17)	O2-C12-C13	110.29(16)
C3 -C2 -C11	124.4(3)	O2-C13-O3	122.7(3)	C1-C2-C3	116.55(18)	C2-C12-C13	112.91(19)
C2-C3-C4	121.3(3)	O2-C13-C12	123.2(3)	C2-C3-C4	120.34(18)	C12-C13-C15	124.77(18)
C3-C4 -C5	117.7(3)	O3-C13-C12	114.1(3)	C3-C4-C6	122.49(19)	C14-C13-C15	121.52(18)
C3-C4-C6	123.1(3)	Cl1-C15-C12	109.3(3)	C5-C4-C6	119.60(19)	C12-C13-C14	113.7(2)
C5-C4-C6	119.2(3)			C3-C4-C5	117.91(18)	O3-C14-C13	122.74(19)
N1-C5-C4	121.9(3)			N1-C5-C9	117.69(18)	O4-C14-C13	114.3(2)
N1-C5-C9	118.5(3)			C4-C5-C9	120.50(18)	O3-C14-O4	122.91(19)
C4-C5-C9	119.6(3)			N1-C5-C4	121.81(18)		
Torsion Angles							
C10-O1-C1-N1	4.7(4)	C4-C6-C7-C8	0.0(6)	C4-C6-C7-C8	0.5(4)	C16-O4-C14-O3	1.3(3)
C10-O1-C1-C2	-175.9(3)	C3 -C4-C5-C9	178.1(4)	C4-C5-C9-C8	0.9(4)	C16-O4-C14-C13	-177.7(1)
C3-C4-C5-N1	-1.3(6)	C6 -C4-C5-N1	178.6(3)	N1-C5-C9-C8	-179.1(2)	N1-C1-C2-C12	177.9(2)
C6 -C4-C5-C9	-1.9(6)	N1-C1-C2 -C11	-178.3(3)	C5-N1-C1-O1	-179.6(2)	C12-C2-C3-C4	-178.8(2)
C5-N1-C1-O1	179.5(3)	C3-C4-C6-C7	-178.5(4)	C5-N1-C1-C2	0.9(3)	C1-C2-C12-O2	-161.6(2)

continued on following page

Table 2. Continued

3a				2b			
C5-N1-C1-C2	0.1(5)	C3-C2-C11-C12	38.2(6)	C1-N1-C5-C9	-179.9(2)	C3-C2-C12-O2	17.2(3)
C1-N1-C5-C4	1.9(5)	N1-C5-C9-C8	-179.8(4)	O1-C1-C2-C3	179.5(2)	O1-C1-C2-C12	-1.6(3)
C1-N1-C5-C9	-177.6(3)	C1-C2 -C11-C12	-146.4(4)	C6-C4-C5-N1	179.0(2)	N1-C5-C9-C10	0.4(3)
O1-C1-C2-C3	178.1(3)	C14-O3-C13-O2	1.7(5)	N1-C1-C2-C3	-1.0(4)	C11-O1-C1-C2	179.5(2)
O1-C1-C2-C11	2.3(4)	C14-O3-C13-C12	-179.2(3)	C3-C4-C5-C9	179.1(2)	C4-C5-C9-C10	-179.6(2)
N1-C1-C2-C3	-2.6(5)			C6-C4-C5-C9	-1.0(4)	C7-C8-C9-C10	-179.7(2)
C6-C7-C8-C9	-1.2(6)			C3-C4-C6-C7	-179.8(2)	O2-C12-C13-C14	75.6(2)
C1 -C2-C3-C4	3.1(5)			C5-C4-C6-C7	0.3(4)	C2-C12-C13-C1	-162.4(1)
C11-C2-C3-C4	178.6(3)			C2-C3-C4-C5	0.8(3)	C2-C12-C13-C15	19.1(3)
C5-C4-C6-C7	1.5(6)			C2-C3-C4-C6	-179.1(2)	C12-C13-C14-O3	-3.3(3)
C4-C5-C9-C8	0.7(6)			C3-C4-C5-N1	-0.9(3)	C15-C13-C14-O3	175.2(2)
C2-C3-C4-C5	-1.3(6)			C6-C7-C8-C9	-0.5(4)	C1-C2-C12-C13	75.6(3)
C2-C3-C4-C6	178.7(4)			C7-C8-C9-C5	-0.2(4)	C16-O4-C14-O3	1.3(3)

The geometry withing (3a) and (2b) molecules are usual, the bond lengths and angles are in good agreement with those observed in similar compounds (Insuasty et al., 2006; Jasinski et al., 2010).

The crystal packing (3a) is stabilized by a hydrogen bonding interaction C9- H9… O2. (Figure 12, Table 3).

The intermolecular connection between (3a) molecules is stabilized by Intermolecular hydrogen bonds (Table 3). In the crystal structure, the molecules are stacked in alternating layers (Figure 13).

However the crystal packing (2b) is stabilized by variety of hydrogen bonding interactions O - H… O, C- H... O, and C- H...N (Figure 14, Table 4).

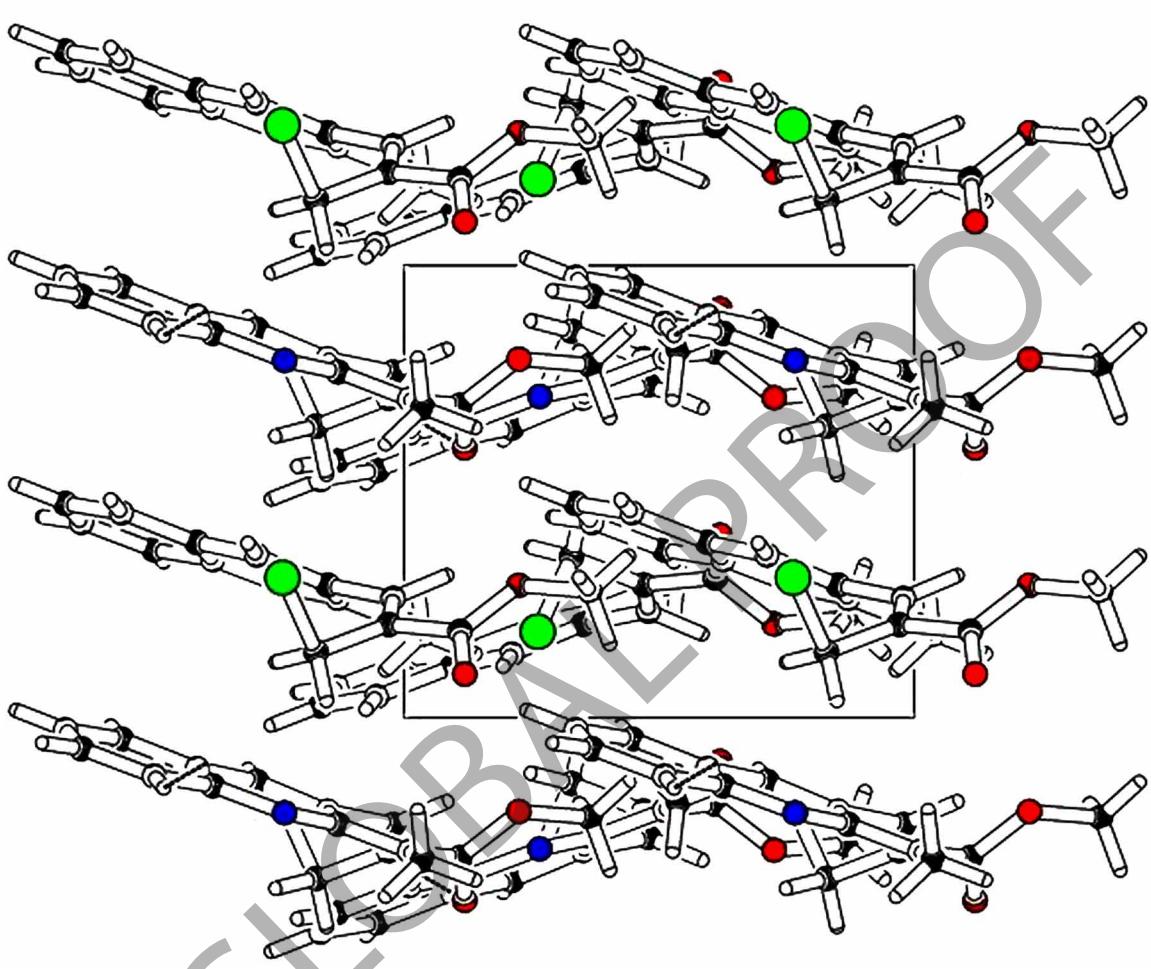
The intermolecular connection between (2b) molecules gives rise to consisting of running throng the a axis direction (Figure 15).

Table 3. Hydrogen bond interaction (3a)

D-H...A	D-H	H...A	D...A	*D-H...A*
C9 -- H9 .. O2 [i]	*0.9300*	*2.5500*	*3.418(5)*	*156.00*

Symmetry codes: (i)1/2-x,-1/2+y,-1/2+z

Figure 13. Packing for (3a) viewed down the a-axis (a), b-axis (b) and c axis (c)



3. BIOLOGICAL PROPERTIES

The main aim of the production and synthesis of any antimicrobial compound is to inhibit the causal microbe without any side effects on the patients. In addition, it is worthy to stress here on the basic idea of applying any chemotherapeutic agent which depends essentially on the specific control of only one biological function and not multiple ones. The chemotherapeutic agent affecting only one function has a highly sounding application in the field of treatment by anticancer, since most anticancer used in the present time affect both cancerous diseased cells and healthy ones which in turns affect the general health of the patients. Therefore, there is a real need for having a chemotherapeutic agent which controls only one function.

In testing the antibacterial activity of *cyano quinolines derivatives* (Table 5) and (Table 6) we used more than one test organism to increase the chance of detecting antibiotic principles in the tested materials. The sensitivity of a microorganism to antibiotics and other antimicrobial agents was determined by the assay plates which incubated at 37 °C for one day for bacteria.

Figure 14. Hydrogen bonds interactions (2b) assuring the crystal structure cohesion

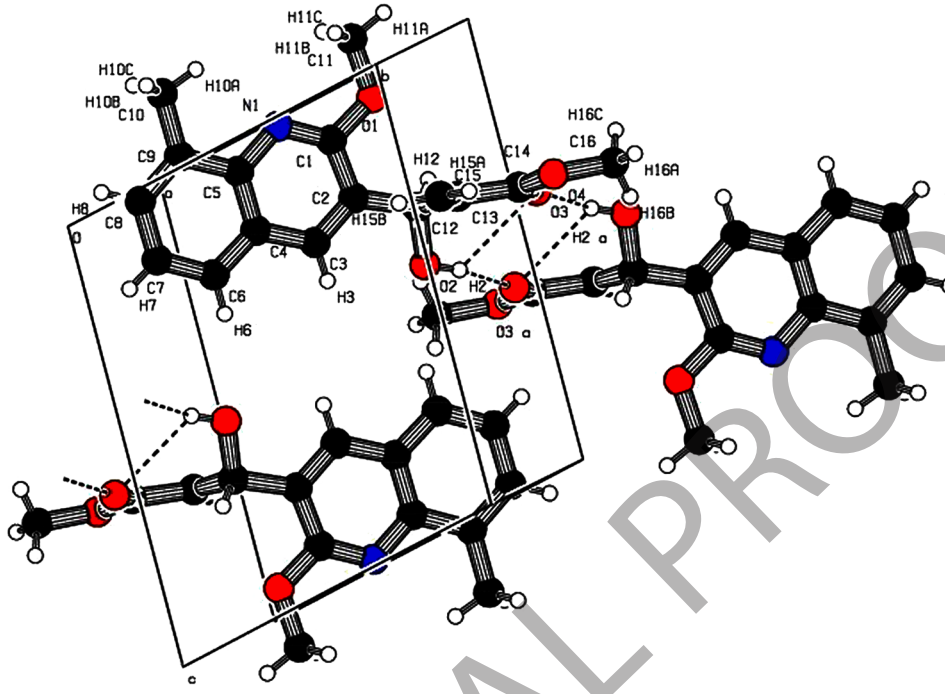


Figure 15. Packing for (2b) viewed down the a-axis (a), b-axis (b) and c axis (c)

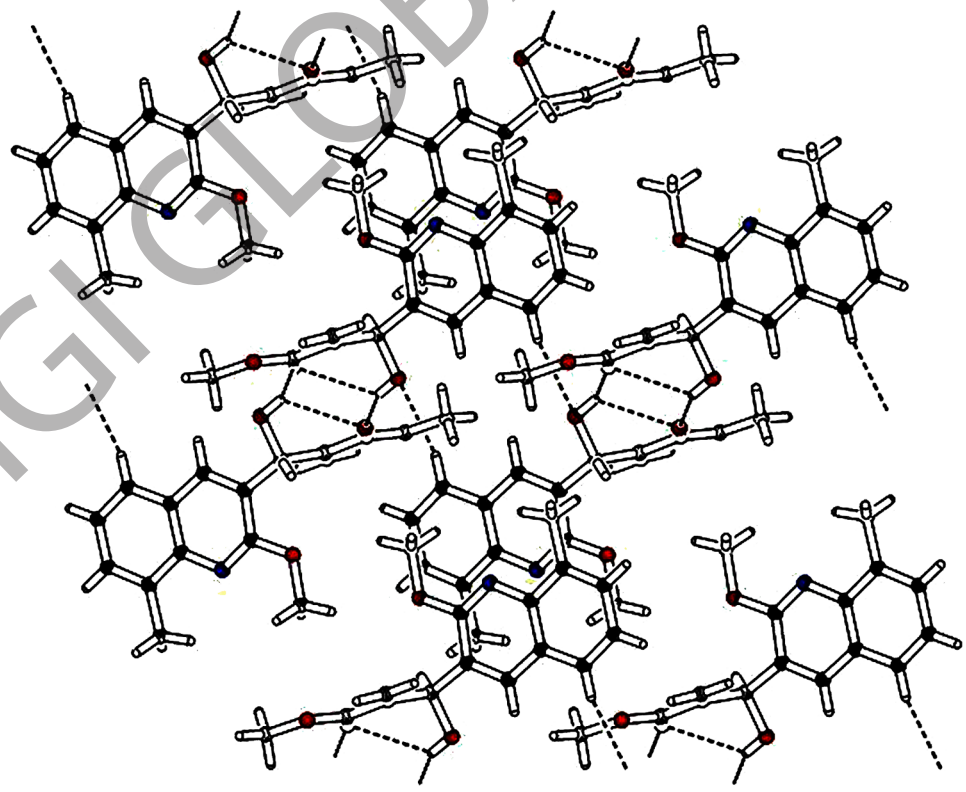


Table 4. Hydrogen bond geometry (A°,°) of the (2b) quinoline derivative

D-H...A	D-H	H...A	D...A	D-H...A
O2 -- H2 .. O3	0.8200	2.5500	3.068(2)	122.00
O2 -- H2 .. O3i	0.8200	2.1800	2.858(2)	140.00
C3 -- H3 .. O2	0.9300	2.4400	2.756(3)	100.00
C6 -- H6 .. O2 ii	0.9300	2.4600	3.369(3)	165.00
C10 -- H10A .. N1	0.9600	2.3200	2.802(3)	110.00

Symmetry codes: (i) 2-x,2-y,1-z ; (ii) 1-x,1-y,1-z

Table 5. Diameter (mm) of the zones of inhibition of the products 1a-1e stem Gram-negative

Products and Witnesses	**Bacterial Strains Gram- and Zones of Inhibition in mm ***						
	***Escherichia coli* ATCC 25922**	***Pseudomonas aeruginosa* ATCC27853**	***Klebsiella pneumoniae***	***Escherichia coli* (Low Level)**	***Enterobacter spp***	***Proteus mirabilis***	***Acinetobacter spp***
[mg/ml]	**4-1**	**4-1**	**4-1**	**4-1**	**4-1**	**4-1**	**4-1**
1a	7	˂6	˂6	˂6	7	˂6	˂6
1b	˂6	˂6	7	˂6	˂6	˂6	˂6
1c	˂6	˂6	7	˂6	˂6	7	˂6
1d	˂6	˂6	7	˂6	˂6	˂6	˂6
1e	˂6	˂6	7	7	7	˂6	˂6
OFX	32	19	20	28	27	21	˂7
CIP	37	33	Nd	34	Nd	Nd	Nd

*: The diameters of the disks (6 mm) are included in the measurements of the diameters of the inhibition zone.
Nd: Non determined

All tested compounds showed a remarkable biological activity against different types of Gram-negative (Escherichia coli ATCC 25922; *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella Pneumoniae, Escherichia coli (low level), Enterobacter spp, Proteus mirabilis and Acinetobacter spp*), Gram-positive (Staphylococcus aurous, Staphylococcus coagulase-negative SCNMR, *StaphylococcusAureus* SAMR, *Streptococcus spp and Enterococcus spp*) bacteria. The data obtained are listed in Table 5 and Table 6.

The Gram-negative strains studied have a high antibacterial activity against five **1a-1e** product strength potential. This resistance is due to the difference of the cell wall structures of the two types of bacteria (Table 5).

The reference strain of Staphylococcus aureusATCC 25923est sensibleaux 6a-6e five products tested (Figure 16) .Both products 6a and 6d show, with the concentration 4 mg / ml an inhibitory effect (21 and 20mm) better than the antibiotic nalidixic acid (NA), it has a natural resistance to this souche.Mais this effect is small when compared with the effect donnépar ofloxacin (26 mm) on the same souche.Le inhibition diameter decreases respectively from compound 6b, 6c to 6e as shown in and Table 6.

Staphylococcus coagulase-negative strain resistant to methicillin sensitive also to testés. Le products 6a compound showed significant activity against cettesouche with a diameter of 22 mm and the appearance of the synergy between the different concentrations. 1a gave the best diameter compared to compounds 1d and 1e (18 mm) but remains far diameters given by witnesses ciprofloxacin (CIP) and ofloxacin (OFX).

Table 6. Inhibition zones Diameter (mm) of 1a-1e products stem Gram positive

Product and Witnesses	The Bacterial Strains Gram + and Inhibition Zones in mm *																			
	Staphylococcus Aureus ATCC. 25923				*Staphylococcus coagulase négatif* SCNMR				*Staphylococcus Aureus* SAMR				*Streptococcus spp*				*Enterococcus spp*			
[mg/ml	4	3	2	1	4	3	2	1	4	3	2	1	4	3	2	1	4	3	2	1
1a	21	20	17	14	22	20	19	16	20	19	17	16	23	22	21	16	8	8	8	8
1b	17	16	16	12	15	15	14	13	13	12	12	09	20	19	19	16	10	9	8	8
1c	14	12	12	10	14	13	13	11	13	12	10	09	16	15	14	12	10	9	9	9
1d	20	19	18	16	18	17	15	15	21	15	14	13	19	18	17	16	10	10	9	9
1e	15	15	14	11	18	16	14	13	17	15	14	12	21	20	19	15	8	8	8	8
DMSO	˂6				˂6				˂6				˂6				˂6			
NA	-				-				-				-				-			
OFX	26				30				17				35				16			
CIP	29				32				Nd				Nd				25			

*: The diameters of the disks (6 mm) are included in the measurements of the diameters of the inhibition zone.
Nd: Non determined

The results of the positive control, S. aureus ATCC 25923 on and S.aureusclinique MRSA are bacteria of the same species, is observed that both strains react differently to controls tested (OFX), which shows the mutagenicity of these strains that allows them to acquire resistance to antibiotics.

The compounds 1a and 1d showed significant activity against Staphylococcus aureus strain aureus-résistante MRSA with inhibition respectively 20 and 21 mm diameter. The sixth compound inhibits the growth of MRSA a diameter of 17 mm same as Ofloxacin. The MRSA strain is resistant to the antibiotic Ofloxacin by against it is more sensitive to both products 6a and 6d.

The Sterptocoque spp strain was also sensitive révéléeelle vis-à-vis the products tested. 6a provides an inhibitory effect produced with a diameter of 23mm.

Enterococcus spp strain was more resistant products 1a-1e, the diameters of inhibition does not exceed 10 mm.

The results of the agar diffusion showed that among the five products tested, the compound 6c substituted six positions by a methoxy, is characterized by a weak antibacterial activity compared to other products. However the compound 6d, also substituted by methoxyl in position seven, revealed an interesting antibacterial activity. This brings up the structure-activity relationship.

4. MATERIALS AND METHODS

The FTIR has been carried out to analyse the chemical bonding and molecular structure of the compound. The FTIR spectrums of the crystals were recorded in frequency region from 400 to 4000 cm-1 with a FTIR NEXUS NICOLET Spectrometer in KBr pellets. The ^{1}H NMR was recorded on a Bruker 300 MHZ instrument at 23°C to confirm the molecular structure.

The unit cell determination and data reduction were performed using the CrysAlis program (Oxford Diffraction., 2006) on the full set of data.

Calculations were carried out using the WinGX software package (Farrugia, 1999).The crystal structure was solved by direct methods using SIR2004 (Burla et al., 2005) and refined by full-matrix least-squares against F^2 using all data (SHELX97) (Sheldrick,).

All non-H atoms were modelled with anisotropic displacement parameters. The H atoms attached to $–CH_3$ were located in difference Fourier maps refined as riding atoms (isotropically with a restrained bond distance) with distances constraints of methyl C-H = 0.96 A° and Uiso(H) = 1.5Ueq(C). Aromatic H atoms were positioned geometrically and were allowed to ride on their parent C atoms with C-H = 0.93 A° and and Uiso(H) = 1.2Ueq(C).

Crystal structure was visualized using ORTEP3 (Farrugia, 1997) and MERCURY (Bruno, 2002). Analyses were carried out using the program PLATON (Spek, A.L., 2003), as incorporated in the WinGX (Insuasty et al., 2006).

A filter paper sterilized disc saturated with measured quantity of the sample (10 µl, 4-1 mg/ml) is placed on plate containing solid bacterial medium (nutrient agar broth) which has been heavily seeded with spore suspension of the tested organism. The assay plates which incubated at 37 °C for one day for bacteria. After inoccupation, the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism (Grayer et al., 1994; Irob et al., 1996). The organisms used included five Gram-positive (Staphylococcus aurous, Staphylococcus coagulase-negative SCNMR, *StaphylococcusAureus* SAMR, *Streptococcus spp and Enterococcus spp*), and seven Gram-negative (Escherichia coli ATCC 25922; *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella Pneumoniae, Escherichia coli (low level), Enterobacter spp, Proteus mirabilis and Acinetobacter spp*) bacteria.

5. CONCLUSION

The quinoline derivatives, natural or synthetic, have interesting and varied biological properties. For this, the preparation of new products quinoline nucleus plays an important role in organic synthesis. Indeed, several methods of preparation of these derivatives have been reported in the literature.

First all were synthesized starting products; it is derived from 2-chloro-3-formyl quinoléines, following the method of Meth-Cohn. These compounds were then subjected to a series of reactions, to chlorine substituted in the two positions by a methoxy, leading to derivatives of 2-methoxy-3-formyl quinoléines.

In a second step, and in order to obtain highly functionalized products, we have prepared a new series of derivatives of 3-(2-chloroquinoline) -3-hydroxy-2-méthylene propanonitrile by applying condensation Baylis-Hillman acrylonitrile on some derivatives of 2-chloro-3-formylquinoline. The reactions proceed with generally excellent yields.

Condensation of [2-methoxy-3-formyl quinoléines derivatives] using Baylis-Hillman reaction. Then the acetylation of Baylis-Hillman adducts by acetyl chloride allowed us to obtain new unexpected chlorinated products.

The structures of all the compounds prepared were elucidated by conventional spectroscopic methods (IR, 1H NMR, 13C NMR), also the techniques single crystal X-ray diffraction for both compounds (3a and 2b); to study hydrogen bonds Intra-molecular cohesion.

At the end of reaching the goal of this work, antibacterial assessment was made on cyano-qunoléines derivatives. This assessment was made by the method of diffusion in solid medium on reference strains and clinical strains isolated from patients. The tested compounds have shown an interesting antibacterial

activity against most of the strains used in this test, except for strains Gram négatif. The compound 1a gave the best results of the antibacterial activity.

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