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4H-Quinolizin-4-one Derivatives: A Review

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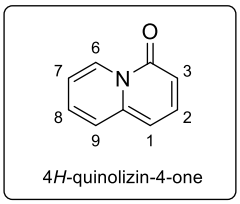
ABSTRACT

In this literature review, Synthesis and analysis of new 4H-quinolizin-4-one derivatives and structural determination using NMR spectroscopy, mass spectroscopy, also the purification of these products by chromatography and finally, bioactivity testing will be discussed.



4*H*-quinolizin-4-one

1. Introduction

Piperidine ring is widely used in chemistry, and it is the most common moiety in natural as well as synthetic compounds and it has various biological activities (Chou and Huang, 2013). On the top of that, piperidine compounds were formed and evaluated for their anti HIV infection, in addition, they have been found that these compounds have a good activity against four strains of bacteria including Staphylococcus aureus which is the most dangerous staph types, Bacillus subtilis, Pseudomonas aeruginosin and Escherichia coli (Pandey and Chawla, 2012). Hence their concentrations to inhibit these organisms (IC50) are too low from previous papers, a product with an (IC50) ranging from 1 to 30 μM has a low lethal dose of 30 mg/kg (Iwase and Tsutsui, 2007). Quinolizinone compounds have a piperidine ring and amide function group in addition to various substituted groups. Recently 2-Pyridone containing compounds showed very important biological activities such as cytotoxic activity against many cancer types and that is because the different functional groups that they have including the double bond and the hetero ring (Nofal *et al*., 2011). Bacteria and other microorganisms developed a resistant, so as a result there is an immense need to discover new types of compounds with new modes of action for the treatment of these infections. A lot of synthetic pathways for the formation of quinolizinone compounds have been recorded before, but the most famous method is the Suzuki Mayara coupling reaction between the building blocks and specific solvent in presence of a base and palladium source or nickel source (Satoh *et al*., 2010) Another reaction depends mainly on a series of steps and finally, reflux the product under high temperature. "Generally, heterocycles can be synthesized either by cyclization or by transformation of an existing ring"(Katritzky and Pozharski, 2000). As the number of heteroatoms that share in the ring increases the function of the compound increases consequently. Nowadays, research showed the relative importance of ring synthesis and its wonderful molecular structure provided us with opportunities to consider its synthesis and design sequences, use reactions and effective strategies for its construction. Also, aromatic heterocycles is a serious topic because almost around two-thirds of organic compounds classify under this class, and they are very important compounds for human beings for example in the sixteenth-century quinine compounds were used to treat malaria even though the chemical structure was not identified (Nicolaou and Chen, 2008). Moreover, the first synthetic drug was antipyrine for the treatment of fever and the first effective antibiotic was sulfapyridine (Clayden, *et al*., 2001).

The rapid collection of the complex big molecules is an important goal in organic chemistry as well as phytochemistry. Previously, the formation of nitrogen-containing heterocyclic was rare, however, nowadays this field is under investigation especially after the discovery of rhodium to catalyze the synthesis of these heterocycles (Friedman *et al*., 2010).

To add to this, heterocyclic are compounds of particular significant particularly for new bioactive agents in both the agrochemical and pharmaceutical industries. "Heterocyclic forms over 60% of the top retailing drugs" that contain at least one heterocyclic nucleus in their structure (Muir *et al*., 2013).

In the regard of the synthesis, heterocycles compounds are globally used as scaffolds because of their important nucleus this helps to bind efficiently to their biological targets. In addition to this, they are usually available by very simple synthetic methods and there are no difficulties due to stereoisomers formation (Kettle *et al*., 2012). Thus the goal of the new research is to identify new heteroaromatic rings that show improved characters, for example, good metabolic stability, better solubility, also develop new ways that help to access novel substitutions.

1.1. Quinolizinone and its derivative

Quinolizinones A are compounds that have several biological activities such as anticancer, anti-bacterial particularly Staphylococcus aureus, and have anti-viral activity. The latter because they have the ability to inhibit an integrase enzyme in the virus, which present in a retrovirus and enable it from integrating its genetic content into the DNA of the host cell.

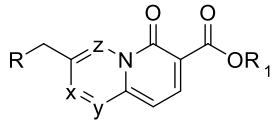


Fig. 1: Quinolizinone Compound (A)

Where: R is carbon atoms, and might be substituted by 1 to 5 substituents; in the heterocyclic a saturated or unsaturated ring group containing besides carbon atom(s), at least one hetero atom could be a nitrogen atom, an oxygen atom or a sulfur atom. R_1 is a hydrogen atom or a $C_{1\text{-}4}$ alkyl group (Satoh *et al.*, 2010).

Quinolizinone compound is a pharmaceutically acceptable drug, and an anti-AIDS agent contains the same as an active ingredient as its salt. This recent invention is used as an anti-HIV agent for both prophylaxis and treatment of AIDS. Furthermore, a combination with other anti-HIV drugs, for example, protease inhibitors, reverse transcriptase inhibitors quinolizinone compounds become more effective as an anti-HIV agent with fewer side effects. Currently, a multiple drug therapy is used and employed for a wide range of pharmaceutical agents. For an instant, a combination between two reverse transcriptase inhibitors (zidovudine and didanosine), and a combination of three agents of reverse transcriptase inhibitors (zidovudine and lamivudine) and a protease inhibitor (nelfinavir). However, some of these agents cause side effects such as liver failure, central nervous disorders for example vertigo. In addition, development of resistance to a drug causes a problem (Satoh *et al.*, 2010; Muir *et al.*, 2013).

In addition, Satoh et al. (Satoh *et al.*, 2010) depicts two types of quinolizinone, quinolizinone B below as antiviral agent especially for herpes viruses, and quinolizinone C below as an intermediate.

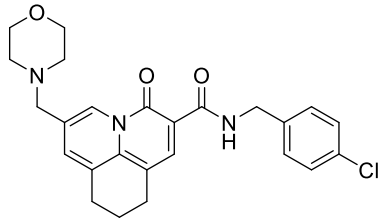


Fig. 2: Quinolizinone (antiviral agent) (B)

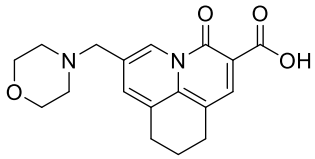


Fig. 3: Quinolizinone (C)

Quinolizinone compound E below according to Satoh et al. (Satoh *et al.*, 2010) shows also an antibacterial activity.

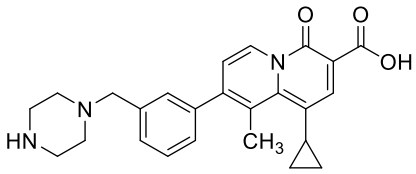


Fig. 4: Quinolizinone (antibacterial) (E)

In addition, quinolizinone compound F and compound G below show an inhibitory action against allergies and ulcers. (Satoh *et al.*, 2010; Muir *et al.*, 2013).

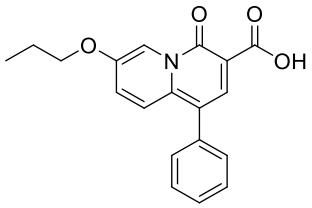


Fig. 5: Quinolizinone (anti-allergies) (F)

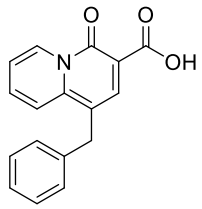


Fig. 6: Quinolizinone (anti ulcers) (G)

Moreover, quinolizinone compound H below according to Satoh reveals as an anticancer agent having an integrin inhibitory action, or vascular vessel regeneration inhibitors having an integrin inhibitory action (Satoh *et al.*, 2010; Muir *et al.*, 2013).

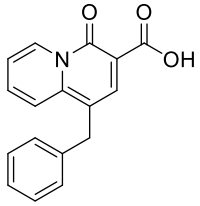


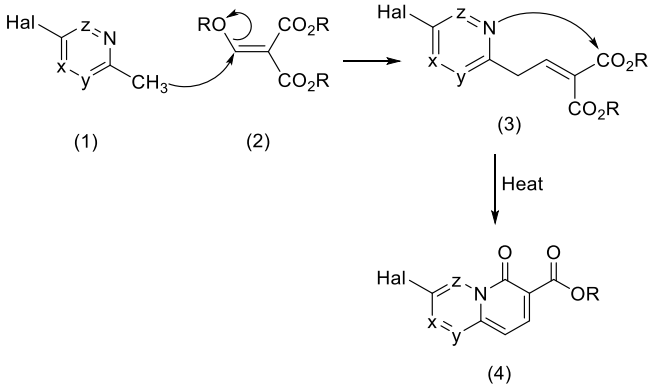
Fig. 7: Quinolizinone (anti-cancer) (H)

Based on previous papers and literature and clinical results obtained, quinolizinone compounds are drugs have a wide biological action and are very effective for both prophylaxis and therapy with a high safety margin; it is, therefore, an important to develop synthetic methods to prepare and optimize them. (Satoh *et al.*, 2010; Muir *et al.*, 2013).

1.2. Different Synthetic methods for quinolizinone derivatives

Several approaches have been studied to prepare different quinolizinone derivatives and they are summarized as following:

The first approach we are going to discuss in this review as shown in the following equation:

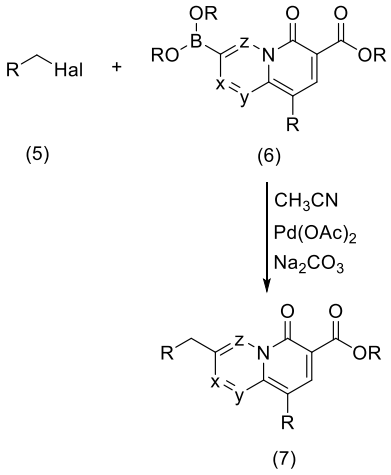


Scheme 1

Where Hal is a halogen atom such as fluorine atom, a chlorine atom, a bromine atom, an iodine atom, better one to use is a fluorine atom or a chlorine atom, R is a hydrogen atom or an alkyl group. (Satoh *et al.*, 2010)

The dicarboxylic intermediate (3) can be synthesized by adding the pyridine to a strong base such as n-butyl lithium or lithium diisopropylamide under an inert gas for example argon gas or nitrogen gas, then cool to room temperature followed by a reaction of the mixture with the malonate derivative (2) then cool to room temperature. Consequently, the quinolizinone compound can be prepared by heating the resulted compound in a solvent. It is recommended to use a solvent, which has a high boiling point, such as biphenyl ether, a mixture of biphenyl ether and biphenyl. (Satoh *et al.*, 2010). The resulted quinolizinone compound can also be synthesized by reaction of the intermediate compound with toluene under heat.

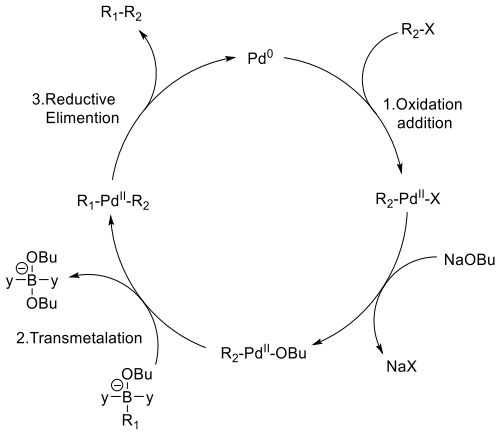
The second approach follows Suzuki Cross-Coupling reaction in the next equation (Satoh *et al.*, 2010; Muir *et al.*, 2013).



Scheme 2

Where quinolizinone compound can be prepared by subjecting halo methane and boronic acid derivative to Suzuki Mayara coupling reaction. Special solvents are used such as dimethyl formamide, acetonitrile, dimethyl Ethan amide, tetrahydrofuran in the presence of a palladium catalyst, for example, dichloro bistriphenyl phosphine palladium (II), palladium acetate-triphenylphosphine or a nickel catalyst such as nickel chloride, 1,3-bis(diphenylphosphino)propane nickel (II) chloride and a base to name but few sodium carbonate, potassium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, potassium phosphate, triethyl amine, potassium fluoride, cesium fluoride, sodium hydrogen phosphate, cesium carbonate under 25°C then under heat (Satoh *et al.*, 2010; Blangetti *et al.*, 2013).

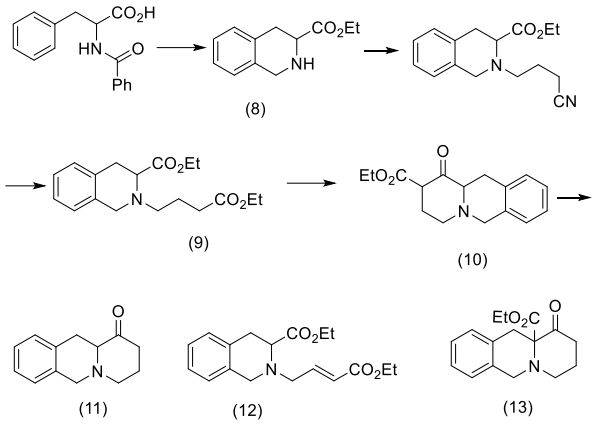
The safety and the mild reaction circumstance of Suzuki Cross-Coupling reaction makes it very distinguish not only this but also the accessibility of boronic acid is easier than other acids, for example from inorganic by-products, in addition, it is much less toxic than other procedures i.e. Suzuki Cross-Coupling reaction is environmentally safer and less toxic than Stille coupling that uses organo stannanes. To add to this, it is relatively cheap and easy to prepare (Kurokhtina and Schmidt, 2009). This scheme depicts the mechanism of action of Suzuki cross-coupling reaction.



Scheme 3: Mechanism of action of Suzuki Cross-Coupling reaction

The first step is the oxidation addition, where the addition of a reagent (R-X) to a metal atom (Pd), Pd oxidation state increases by 2 from Pd^0 to Pd^{II}. While in the second step (transmetalation) exchange reaction between B-R_1 and Pd^{II} and the Pd oxidation state and coordination number remain unchanged. Elimination is the last step where Pd oxidation state decreases by 2 from Pd^{II} to Pd^0. So oxidation and elimination are reverses of each other. However, this kind of coupling reactions have also disadvantages that if the aryl halides are used not aliphatic ones, in this case, the reaction will be so static because aryl usually react sluggishly (Jana *et al.*, 2011; Callam & Lowary, 2001).

Another approach discovered since years ago by Clemo and Swan, which is a synthesis of quinolizinone from an amino acid. They prepared a reasonable quantity of tetrahydroquinolizinone structure number (11) in the next scheme from DL-benzoyl phenylalanine according to this scheme. (Archer, 1951)



Scheme 4: Clemo and Swan synthesis

When the ester treated with ethyl bromo crotonate in the presence of small amount of benzene, it gave compound (12) in a reasonable yield in form of crystals but they did not actually define the structure of it. Adam catalyst was used to reduce the double bond in structure (12). Adams's catalyst is obtained from chloroplatinic acid H_2PtCl_6 or ammonium chloroplatinate, $(NH_4)_2PtCl_6$, by fusion with sodium nitrate. Although this method is safe, there were a lot of difficulties involved in this preparation but the most obvious was the low yield quantity (less than 3%). This problem encouraged them to develop a method to increase the yield to 24% by using Julian method which is mainly to convert DL-phenylalanine to 1,2,3,4- tetrahydroisoquinoline -3-carboxylic acid hydrochloride. (Archer, 1951)

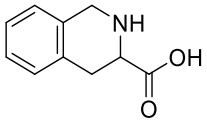
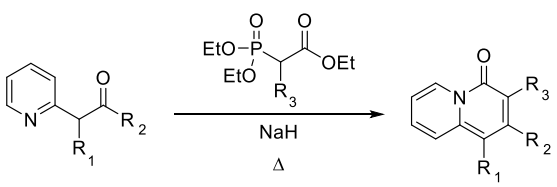


Fig. 8: 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

Synthesis of 2-substituted 4H-quinolizin- 4-ones derivatives was the focus of attention in the recent years because all the previous synthesis gave only mixtures of products such as 1,2-, 2,3-, or 1,2,3- substitutions. However, they found that 2-substitution of quinolizinone is the key to activity and selectivity. (Muir *et al.*, 2013; Čebašek *et al.*, 2006). Some scientists worked on this derivative and they initiated their preparation as in the following equation by β-keto pyridines synthesis where R_1 and R_3 = H and R_2 = alkyl or aryl, then direct acylation of the 2-picoline anion prepared from deprotonation using organolithium reagents such as n-BuLi. During the synthesis, the use of amides decreased the problem of over-alkylation. This method gives better yield compare with the ester-based acylation (Muir *et al.*, 2013; Čebašek *et al.*, 2006).



Scheme 5

Finally, nowadays the discovery of rhodium to catalyze the synthesis of heterocycles brought to light a new synthetic pathway. Development of a new approach to synthesize heterocyclic agents has a great sign in drug development, medicinal science, and natural drug synthesis (Takahashi *et al.*, 2014) Generally, the method depends on using a rhodium to catalyze a C–H bond followed by an intramolecular nucleophilic attack of a nitrogen atom. However,

such an approach to obtain heterocyclic compounds has not been reported and is still under investigation and evaluation (Takahashi *et al.*, 2014). Since the pyridine and 2-pyridone are essential building blocks for quinolizinone components and because they have a variety of biological activities, so it is important to consider the synthesis of both molecules.

1.3. Chemistry and background of pyridine and 2-pyridone

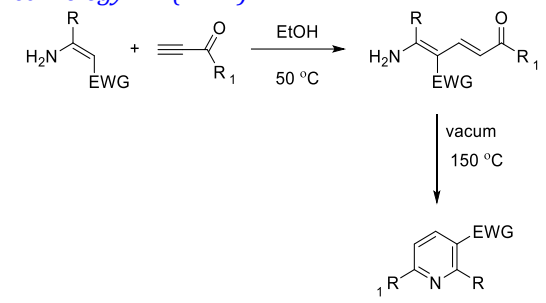
Undoubtedly a lot of research approved that benzene ring is aromatic. However, now most of the research focuses on insertion of a heteroatom into the benzene ring with retaining aromaticity. Also, they studied the type of atoms that have the same arrangement in the space, for example, to keep the flat hexagonal ring and to keep the delocalization of electrons. They have found that nitrogen is a good example and this gives a compound called pyridine. Obviously, nitrogen is trivalent so there is no NH bond because they all share into the ring but benzene instead has C–H bond (Prezhdo, *et al.*, 1998). The different between benzene and pyridine mainly appears in proton NMR spectrum because clearly benzene ring is symmetric and pyridine is not i.e. the six protons of benzene resonate at 7.27 ppm but the three types of protons in pyridine all resonate in the same region. However, nowadays 2-pyridone core, which is pyridine ring and a carbonyl group, is more important and more common heterocycle than only pyridine ring in many natural as well as synthetic compounds, which have widespread biological characteristics. The 2-pyridone core is also present in registered pharmaceuticals such as Corotrop® and Primacor®, both uses in the treatment of heart disorder. Sebiprox® uses in the treatment of dandruff and it also contains a 2-pyridone moiety called ciclopirox (Kibou *et al.*, 2011).

1.4. Approaches for the synthesis of pyridine and 2-pyridone

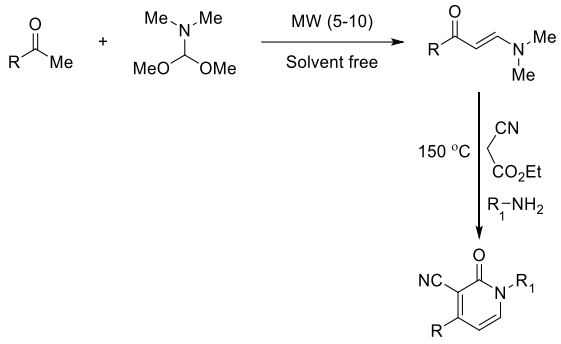
Pyridine ring is widely used in medicinal chemistry and it is easy to synthesize compare with other structures. For example, The Bohlmann-Rahtz pyridine synthesis acts by two steps. The first step is the condensation step of enamines with ethynyl ketones leads to an aminodiene intermediate and then after heating of this product, it induces isomer formation, the second step is the reaction with cyclodehydration to yield tri substituted pyridines as in the following scheme (Bagley and Glover, 2010).

2-pyridones derivatives have special attention because this moiety is present in many compounds that have been extracted from natural sources, with various activities, such as antibacterial and antifungal agents. (Pemberton, Åberg et al. 2004) Several methods have been studied in previous literature for the synthesis of this structure and here are some approaches to prepare this active moiety: The first approach for 2-pyridone preparation depends on the synthesis of a series of 2-pyridones derivatives by new multicomponent reaction (MCR) in good yields. The first step of this method is the reaction of methyl acetone with N,N-dimethylformamide dimethyl acetal under the effect of the microwave that gives the enaminone, which is the key to this synthetic method. Then react the resulted enaminone with ethyl 2-cyanoacetate in the presence of basic Al_2O_3 as catalyst without solvent (Kibou *et al.*, 2011).

Recently, this synthesis describes a new effective and convenient method for the synthesis of 2-pyridone derivatives from enaminones with solvent-free conditions. Solvent-free conditions mean they do not only decrease the load of organic solvent throwing, but also increase the rate of many organic reactions and this is useful in saving the time of the experiments. The general procedure that they followed to Synthesis 2-Pyridones derivative under solvent-free reaction is mainly, heating of primary amine, ethyl 2-cyanoacetate and a catalytic amount of Al_2O_3 for a few hours then they cooled down the mixture, the solid obtained was washed out many times with diethyl ether to give 2-pyridone derivatives (Kibou *et al.*, 2011).



Scheme 6



Scheme 7

2. Purification of quinolizinone derivatives

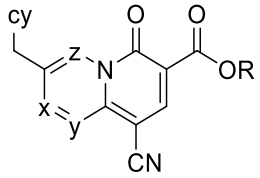
Nowadays, chromatography has wide applications including separation of gases, and volatile substances by Gas Chromatography (GC), non-volatile compounds and substances of high molecular weight such as polymers by Liquid Chromatography (LC), chiral compounds from each other by using suitable chiral stationary phase. (Núñez, Gallart-Ayala et al. 2013) Thin layer chromatography (TLC) is also available as a cheaper technique. (Kaale, Nyamweru et al. 2013) Generally, all these processes have the same principle of separation.

Quinolizinone can be purified by a chromatographic technique called silica gel electrophoresis (GE), which separate substances according to their size, shape, charge and isoelectric point (Satoh *et al.*, 2010) It can be used as an analytical technique or as a preparatory technique to purify molecules before they are used for other methods like mass spectrometry. Gel electrophoresis is based on placing the charged molecules in an electric field and then notes the migration either to the positive or the negative pole depending on their charge (Satoh *et al.*, 2010; Paunescu *et al.*, 2013).

Practically, quinolizinone can be separated by firstly, prepare a solution of lithium diisopropylamide mono tetrahydrofuran in tetrahydrofuran then added dropwise to a solution of 5-bromo-2-methylpyridine in tetrahydrofuran in an argon atmosphere at not more than −60°C. (Satoh, Aramaki et al. 2010) Then the mixture is stirred for one hour at the same temperature, next diethyl ethoxymethylenemalonate is added dropwise at −60°C, allow the mixture to warm to −20°C and stir for 60 mints, finally add brine and ethyl acetate to the mixture to partition the layers. Extract the aqueous layer with ethyl acetate and the organic layer with brine, and dry over sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure and the residue was roughly purified by silica gel chromatography (hexane:ethyl acetate=5:1) to give the object product as a yellow oil (Satoh *et al.*, 2010).

3. Analysis and structural determination of quinolizinone

Nuclear magnetic resonance (NMR), Infrared, and Mass spectroscopy are analytical chemistry techniques that are commonly used nowadays in research for determining the molecular structure of a compound. Practically, from previous papers, a lot of research has been done to determine and evaluate the structure of quinolizinone compounds, and the following structure is given as an example:



Scheme 8: Quinolizinone Derivative

This quinolizinone structure was mixed and dissolved in Dowtherm (3 ml), and then the mixture was mixed over heat (at 200°C) for 2 hours. Next, cool down then hexane was added to the mixture, and the mixture was mixed at room temperature for 20 min. Finally, the solid was filtered under reduced pressure using Buchner funnel to give the product as a brown solid (yield 18%). Then the following data was obtained 1H NMR 1.42 (3H, t, J=7.1 Hz), 4.42 (2H, q, J=7.1 Hz) adjacent to electronegative atom, 6.65 (1H, d, J=8.4 Hz) for alkene, 7.45 (1H, d, J=9.3 Hz) for the benzene ring, 7.61 (1H, dd, J=2.0, 9.2 Hz), 8.41 (1H, d, J=8.4 Hz), 9.50 (1H, s) for aldehyde (Satoh *et al*., 2010).

4. Evaluation of Biological Activity

The effect of quinolizinone compounds was tested and evaluated for their antiviral activity. For instance, in 2010, quinolizinone and others reverse transcriptase such as zidovudine were tested on a cell infected with HIV but before evaluation process, IC50 had to measure for safety reasons. The results obtained were analyzed using programs of Prichard and Shipman MacSyner (Prichard *et al.*, 1993), where a three-dimensional plot is drawn based on numerical values (Li *et al.* 1996). While in vivo antibacterial efficacy was tested in 40 mice at different strength with a single dose administered subcutaneously or orally. The ED_{50} should be calculated that results in protecting 50% of the treated animals. (Li *et al*., 1996). Gyrase inhibition is expressed by a CC50 value that is defined as the concentration of a drug which causes 50% of the maximal gyrase mediated DNA cleavage. This is done by using gyrase from E.coli (Li *et al.*, 1996).

5. Conclusion

Quinolizinone compounds are new drugs and they have promising anti-cancer, antibacterial such as Staphylococcus aureus, antiviral activity as they inhibit integrase enzyme in the virus, and this present in a retrovirus and enable it to integrate its genetic content into the DNA of the host cell. Scientists studied various ways to prepare and evaluate quinolizinone compounds and the most common one is from Suzuki Mayara coupling reaction, also they synthesized it from amino acid alanine. Most these methods showed a good yield.

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