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SYNTHESIS AND BIOLOGICAL EVALUATION OF QUINOLINE DERIVATIVE FOR ANTI MICROBIAL ACTIVITY

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ABSTRACT

The present research is on synthesis of Quinoline derivative and evaluation of its anti-microbial activity. The synthesis is done by one pot synthesis method. In this step 4-hydroxy-2-methyl Quinoline is synthesized and this final product has been identified by TLC and FTIR spectroscopy. The compound was tested for anti-microbial activity by using streptomycin as standard drug against *B.subtilis* (gram positive bacteria), *E.coli*(gram negative bacteria).. The compound hassignificant anti-microbial activity.

Key words : Quinoline derivative, anti-microbial activity, *B.subtilis* , *E.coli* , streptomycin.

INTRODUCTION:

- Quinoline derivative is a heterocyclic aromatic organic compound with the chemical formula C9H7N.
- Quinoline derivative is the simplest member of the quinoline class of compounds, comprising a benzene ring ortho fused to C-2 and C-3 of a pyridine ring
- Quinoline derivative is slightly soluble in cold water but dissolves readily in hot water and most organic solvents.
- Quinoline derivative has pharmacological activities, including antimicrobial, antiprotozoal, antitubercular, anticancer, antipsychotics, antioxidants, anti-HIV. Quinoline derivative are a class of heterocyclic aromatic compounds characterized by a fused ring structure that combines a benzene ring and a pyridine ring. The general structure includes nitrogen at the 1-position of the pyridine ring. Quinoline derivative, a significant N-based heterocyclic aromatic compound, is widely researched due to its diverse applications. Its main sources include petroleum, coal processing, wood preservation, and shale oil. Quinoline derivatives are found in natural products, including alkaloids. First extracted from coal tar in 1834, it remains the primary commercial Source**.** Quinoline, a weak tertiary base extracted from coal tar in 1834, is a key structural component in various pharmaceuticals, agrochemicals, dyestuffs, and materials. It has diverse pharmacological activities, including antiprotozoal, antitubercular, anticancer, antipsychotics, anti-inflammatory, antioxidant, anti-HIV, antifungal, efflux pump inhibitors, neurodegenerative diseases and lupus treatment. Quinine and quinidine alkaloids from Cinchona bark also contain quinoline scaffold. Quinoline is a key component in several clinically used drugs, particularly antimalarial drugs.

PROPERTIES:

Chemical formula: C9H7N **Molecular weight:** 129.16 g/mol **Appearance:** Colourless oily liquid

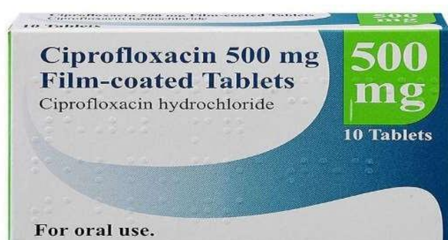
Boiling point: 237 ˚C

Solubility: Soluble in hot water, alcohol, ether, and carbon disulfide

Flash point: 105 °C

MARKETED DRUGS:

1. **Chloroquine (anti-malarial):** Chloroquine is a medication primarily used to prevent and treat malaria in areas where malaria remains sensitive to its effects.
2. **Ciprofloxacin (anti-bacterial):** It is used to treat different types of bacterial infections.
3. **Quinine (anti-malarial):** Quinine is used to treat malaria caused by Plasmodium falciparum. Quinine works by killing the parasite or preventing it from growing.



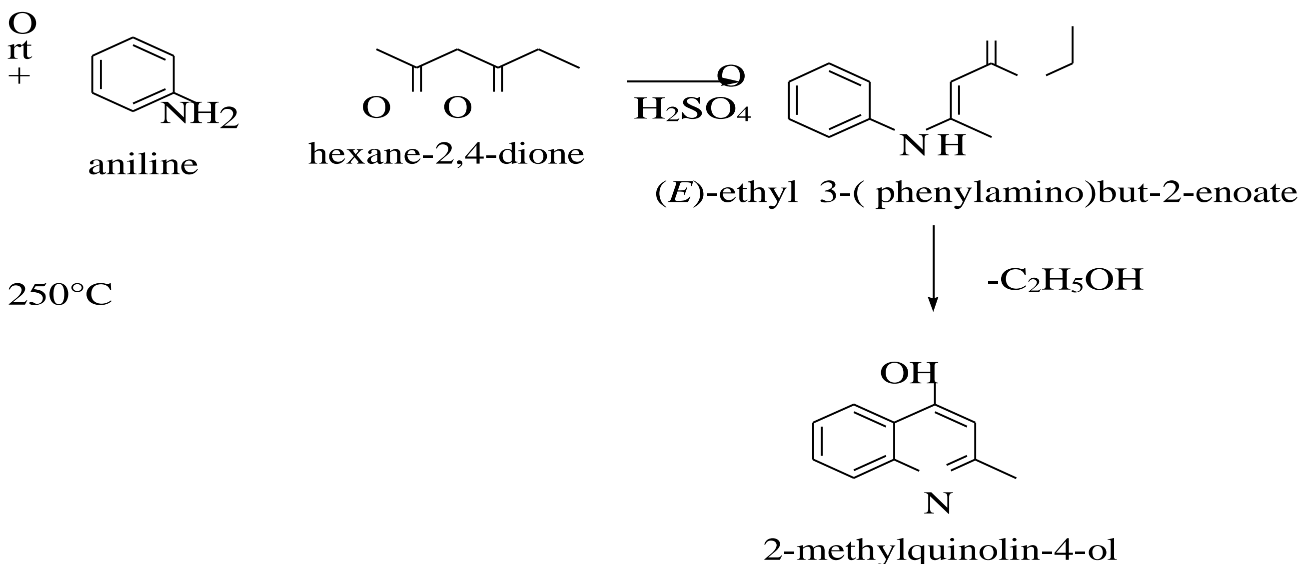
METHODOLOGY:

CONRAD-LIMPACH SYNTHESIS:

- The Conrad-Limpach synthesis is a chemical reaction used in organic chemistry for the synthesis of quinolines.
- Conrad-Limpach method involves synthesizing Quinoline derivative from the condensation of anilines (aromatic amines) with β-ketoesters (β-dicarbonyl compounds) in the presence of a strong acid, such as sulfuric acid or hydrochloric acid.
- Thus, the Conrad-Limpach synthesis has significant applications in pharmaceutical chemistry and the synthesis of complex organic molecules.

CHEMICALS REQUIRED: Aniline, ethyl acetoacetate, sulfuric acid, ethyl acetate, ethanol.

SCHEMATIC REPRESENTATION:



SYNTHETIC PROCEDURE:

- **Preparation of Reaction Mixture:** Mix the aniline or its derivative with the β-keto ester in a reaction vessel. The molar ratio of the starting materials can vary, but it's typically 1:1.
- **Addition of Acid Catalyst**: Add the acid catalyst to the mixture. The choice and amount of acid can affect the reaction rate and the yield of the desired quinoline product.
- **Heating**: Heat the reaction mixture to the required temperature.
- **Monitoring the Reaction:** Monitor the progress of the reaction using techniques like TLC (Thin Layer Chromatography). The reaction may take 4 to 5 hours to complete.
- **Completion and Cooling**: Once the reaction is complete, cool the reaction mixture to room temperature.
- **Product Isolation**: Depending on the solubility of the product, it can be isolated by adding water to the reaction mixture and extracting with an organic solvent, or by direct precipitation.
- **Purification:** Purified the crude quinoline product by recrystallization or column chromatography to obtain the pure compound.
- **Characterization:** Characterized the final product using Fourier-transform infrared spectroscopy.

IDENTIFICATION AND CHARACTERIZATION

The identification and characterization of the prepared compound were carried out by the following procedure.

1. Boiling point
2. Solubility
3. Thin layer chromatography
4. FT-IR

THIN LAYER CHROMATOGRAPHY:

- Cleaned and dried glass plates were taken.
- A uniform slurry of silica Gel-G in water was prepared in the ratio of 1:2.
- The slurry was then poured into the chamber of the TLC applicator, which was fixed and thickness was set to 0.5 mm.
- Glass plates were moved under the applicator smoothly to get an uniform coating of slurry on the plates.
- The plates were dried at room temperature and then kept for activation at 110˚c for 1 hour. Its derivatives were taken in a small bored capillary tube and spotted at 2 cm from the base end of the plate.
- Then the plate were allowed to dry at room temperature and plates were transferred to chromatographic chamber containing solvent system for development.
- The developed spots were detected by exposing them to iodine vapours. Then the R f values of compounds were calculated using the formula - Rf value = distance travelled by sample/ distance travelled by solvent.

INFRARED SPECTROSCOPY(FT-IR):

Infrared spectroscopy is an important analytical technique for determining the structure of both inorganic and organic compounds. It measures the vibrations of the atoms caused by the infrared light and from these measurements it is possible to identify functional group of the compound. Infrared spectroscopy (IR spectroscopy or vibrational spectroscopy) involves the interaction of infrared radiation with matter. It covers

a range of techniques, mostly based on absorption spectroscopy. As with all spectroscopic techniques, it can be used to identify and study chemical substances. Samples may be solid, liquid, or gas. The method or technique of infrared spectroscopy is conducted with an instrument called an infrared spectrometer (or spectrophotometer) to produce an infrared spectrum. An IR spectrum can be visualized in a graph of infrared light absorbance (or transmittance) on the vertical axis(y) vs. frequency or wavelength on the horizontal axis(x). Typical units of frequency used in IR spectra are reciprocal centimeters (sometimes called wave numbers), with the symbol /cm. Units of IR wavelength are commonly given in micrometers (formerly called "microns"), symbol pm, which are related to wave numbers in a reciprocal way. A common laboratory instrument that uses this technique is a Fourier transform infrared (FTIR) spectrometer.

PROCEDURE:

The infrared spectrum of a sample is recorded by passing a beam of infrared light through the sample. When the frequency of the IR is the same as the vibrational frequency of a bond or collection of bonds, absorption occurs. Examination of the transmitted light reveals how much energy was absorbed at each frequency (or wavelength). This measurement can be achieved by scanning the wavelength range using a monochromator. Alternatively, the entire wavelength range is measured using a Fourier transform instrument and then a transmittance or absorbance spectrum is generated using a dedicated procedure. This technique is commonly used for analyzing samples with covalent bonds. Simple spectra are obtained from samples with few IR active bonds and high levels of purity. More complex molecular structures lead to more absorption bands and more complex spectra.

BIOLOGICAL EVALUATION (ANTIMICROBIAL ACTIVITY)

Quinoline derivative possesses diverse variety of pharmacological activities. Due to this Quinoline derivative occupied unique place in field of medicinal chemistry. Quinoline derivative ring system is present occasionally in nature. Quinoline derivative finds use in research as a starting material for synthesis of larger, usually bioactive structure. It is structurally similar with nucleic bases as well as isosteres of naturally occurring cyclic nucleotide such as adenine and guanine that is why it probably interacts with biopolymers in living systems and show diverse biological activities like antimicrobial, anti-inflammatory, analgesic, antifungal, anticonvulsants, antitumor, anticancer, CNS activities, anti-tubercular, anti-HIV agents anthelmintic, and other anticipated activities

Principle:
Antimicrobial activity:

The number of life threatening infections caused by multidrug resistant gram positive pathogens has reached an alarming level in hospitals and the community. The infections caused by these organisms pose a serious challenge to serious challenge to the specific community and the need for an effective therapy has led to search for novel antimicrobial agents. Anti-microbial drugs are effective in treatment of infection because of their selective toxicity that is they have the ability to injure or kill an invading microorganism without harming the host. It is evident from literature that Furan are known to be associated with broad spectrum of biological activities like antibacterial, antifungal etc.

Types of media:

Media can be classified into 3 categories on the basis of chemical constituents

1. Synthetic media
2. Complex media
3. Natural media

1) Synthetic media: Media in which all the constituents are chemically defined. They are generally used to study the specific nutritional requirements of different microbes.
2) Complex media: Media in which the media components and composition is incompletely defined. Ex: beef extract used in the nutrient media chemically complex.
3) Natural media: Substrates of natural origin that favors microbial growth are employed in this media. Ex: milk.

Media can be classified based on their functional properties:-

1) **Simple media:** This media is used for cultivation of the most of the micro organisms. EX:- Nutrient agar.

2) **Differential media**: This type of media is employed to distinguish bacteria that differ in their specific property. EX: starch agar, blood agar.

3) **Selective media:** This type of media selectively allows the growth of particular type of microbes and prevents the growth of other microbes. EX: nutrient agar with crystal violet.

4) **Selective differential media:** This type of media allows only a particular type of organism to grow that can he further distinguish based on their property. EX: Macconky agar.

PREPARATION OF AGAR PLATES:

Label the Petri plates and transfer agar medium in liquid form with right hand, Turn your left hand palm side up and clamp the cotton plug between the finger flame the mouth of the flask after removing the cotton plug -Use the hand holding cotton plug to lift the lid of Petri dish now pour about 20-25m) of sterilized nutrient agar medium then hold the lid so that it partially covers the bottom of dish as you pour -This helps to prevent microbes and air borne dust particles from dropping into your sterilized plate and contaminating it. Immediately replace the lid. If bubbles occur on the surface of medium, quickly break them aseptically by passing Bunsen flam over the surface.

Allow the plates to cool down at room temperature and store the plates. Observe all the liquid and solid media after 2 days properly sterilize medium will remain clear. The broth which was not properly sterilized would have developed turbidity use only media that has properly gerili7Æd for your work.

PREPARATION OF NUTRIENT AGAR MEDIUM:

It is an aqueous solution, obtained from beef called beef extract. Digesting protein substance Obtained by acid or enzyme hydrolysis is called peptone. Agar is used for solidifying and provides sufficient nutrients required for the growth of micro- organisms

PRINCIPLE:

Nutrient agar is used for making plates for the growth of micro- organisms. Agar plates provide maximum surface area and it is easy to study colony characteristics

LIMITATIONS OF AGAR:

1. Large surface area is exposed to contamination
2. Difficulty in handling
3. Media is not sterilized in the plates
4. Breaking cost of apparatus is high as Petri dishes are costly

PROCEDURE:

Nutrient broth-

- Peptone - 10gm, Beef extract – 10gms, Sodium chloride – 5gms, Water- 1000ml.

PRINCIPLE:

Follow the procedure as nutrient broth, but add 1- 2percent of agar powder to nutrient broth. Weigh allthe additives separately by physical balance and addall the additives in a suitable container. Dissolve with the help of stirrer and adjust the pH using sodium hydroxide, sterilize the media in autoclave at 15lb pressure at 120°c for 20 min.

Preparation of Antibiotic solution:

- Prepare different concentrations of antibiotic solution (i.e.)10 mg/ml, 20, 30, 40, solutions.
- Take 10 mg of antibiotic and dissolve in solvent and make up to 10 ml to get 1 mg/ml or 1000 µg/mlsolution.
- From the above solution take 0.1, 0.2, 0.3 and 0.4 and makeup to 10ml respectively to get 10, 20, 30,40µg/ml.

EXPERIMENTAL PROCEDURE BY CUP PLATEMETHOD

- Prepare nutrient media and transfer 20 ml into boiling tube, plug and sterile them.
- After cooling inoculate each boiling tube with 0.1ml of test organism (Bacillus subtilis)
- The inoculated agar media is poured into Petri plate and solidified.
- Make holes in the solidified media at the center by using sterile borer. Add 0.1ml of prepared antibioticsolution into the holes.
- Incubate the Petri plate at 37°C for 24hrs.

(zone of inhibition)

Synthetic -Procedure:

The present study was aimed at synthesis of quinoline derivative by a synthetic procedure using anilines with β-ketoesters forms as starting compounds. The resulting in generation of 4- hydroxy 2-methyl Quinoline. The final compounds were confirmed by TLC and FT-IR studies.

Table.No1.1: IUPAC Name of Synthesized Compounds

Structure	IUPAC Name of SynthesizedCompounds
OH N CH3	2-methylquinolin-4-ol

TLC OF SYNTHESIZED COMPOUNDS:

Rf = Distance travelled by solute/Distance travelled by solvent

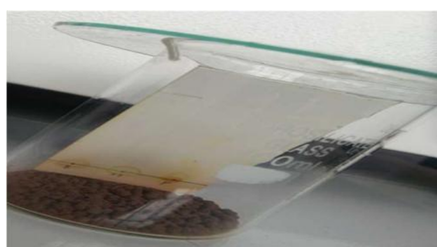


Table 1.2 TLC CALACULATIONS For synthesized Quinoline derivative compound

S.N O	COMPOUND	SOLVENT	COMPOSIT ION	Rf value
1	Aniline	Ethyl acetate: ethanol	1:5	O.32
2	Ethylacetoacetate	Ethyl acetate : ethanol	1:5	0.72
3	4-hydroxy-2-methyl-quinoline	Ethyl acetate: ethanol	1:5	0.22

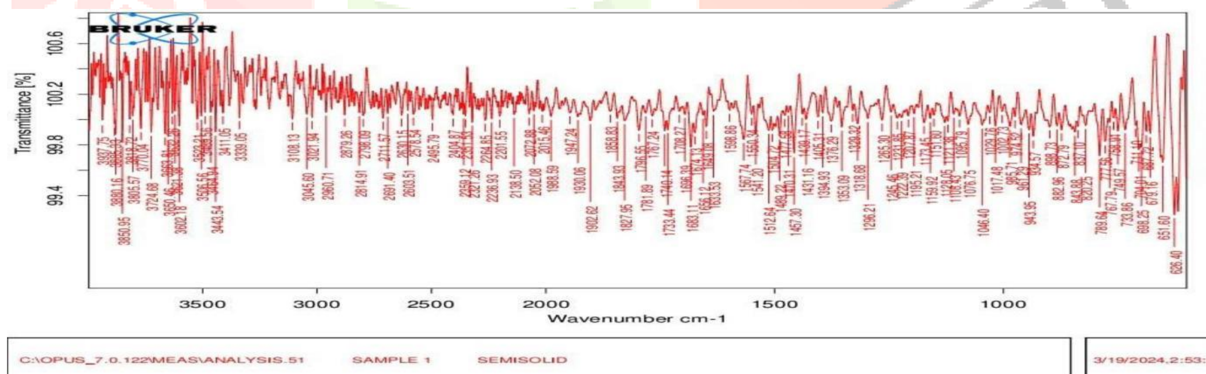
SOLUBILITY:

Solubility test for synthesized quinoline derivative compound are done individually.

Table 1.3

S.NO	COMPOUNDS	SOLUBLE IN	INSOLUBLE IN
1	Aniline	Soluble in HCL, ethanol	Insoluble in water
2	Ethylacetoacetate	Solubility in ethanol, ethylether	water
3	4-Hydroxy-2-methyl-quinoline	Soluble in ethanol	In soluble in cold water

FT-IR



Spectral Values Of Quinoline In FTIR

- **C = C : 1649.08 cm−1** **C−C : 2138.50 cm−1**
- **C = N : 1674. cm−1** **C−OH : 1121.3 cm−1**

Table No 1.4 Zone of inhibition of standard {Streptomycin} against *E.coli*

CONCENTRATIONS (µg/ml)	ZONE OF INHIBITION(cm)
20	2.5
40	3.0
60	3.3
80	4.0

Table No 1.5 Zone of inhibition of synthesized compound against E.coli

CONCENTRATIONS(µg/ml)	ZONE OF INHIBITION(cm)
20	2.7
40	3.3
60	3.9
80	4.3

Table No1.6 Zone of inhibition of standard {streptomycin} against B. *Subtillis*

CONCENTRATIONS(µ/ml)	ZONE OF INHIBITION(cm)
20	2.3
40	2.8
60	3.3
80	3.9

Table No1.6 Zone of inhibition of synthesized against B. *Subtillis*

CONCENTRATIONS(µ/ml)	ZONE OF INHIBITION(cm)
20	2.6
40	3.1
60	3.5
80	4.2

CONCLUSION:

The present study was aimed for the synthesis of quinoline derivative and evaluation of anti – microbial activity. Derivative of quinoline was synthesized and screened for Antimicrobial activity. In the study following steps were performed:

- Synthesis of quinoline derivative was carried out by a synthetic procedure in order to obtain a desired product in acceptable yield.
- Products formed were confirmed by TLC and characterized by FT-IR
- The compound was tested for antimicrobial activity and it is found to have significant antimicrobial activity when compared to standard.

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