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Research Article

Design and Synthesis of C5 and C8 Substituted Quinoline Derivatives with Electron Donating Groups for Enhanced Anticancer Activity

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ABSTRACT

Quinoline has been widely recognized as a privileged scaffold in medicinal chemistry, particularly noted for its exceptional pharmacological diversity and profound anticancer activity. The current focus of the project was the design of novel quinoline-based compounds to establish structure-activity relationships for enhanced therapeutic potential. This study aimed to design, synthesize, and evaluate C5 and C8 substituted quinoline derivatives bearing specific electron-donating groups (–OCH_3, –OH, and –NH_2) to enhance their anticancer efficacy through mechanisms such as DNA intercalation, topoisomerase inhibition, and apoptosis induction. The synthesized moieties underwent physicochemical evaluation to determine their percentage yield, melting point, and solubility. The target analogues yielded between 30% and 75%, exhibited specific melting points ranging from 43 °C to 226 °C depending on the substituent, and demonstrated good solubility in solvents such as DMSO, ethanol, and dichloromethane. The synthesis was achieved through two main pathways: the classical Skraup condensation for the direct assembly of methoxy and hydroxy derivatives, and a core assembly followed by electrophilic nitration and $SnCl_2$-mediated reduction for the amino derivatives. The samples were spectroscopically characterized to confirm their structural integrity. The FT-IR spectral characteristics of the analogues were specifically examined, revealing characteristic bands at 3100-3450 cm-1 (O–H and N–H stretching), ~3050 cm-1 (Aromatic C–H stretching), 1580-1600 cm-1 (Aromatic C=C and C=N ring stretching), and 1200-1280 cm-1 (C–O stretching). Additionally, ESI-MS (positive ion mode) was utilized to identify functional groups and confirm exact masses, revealing precise pseudo-molecular ion peaks [M+H]+, such as m/z 146.2 for hydroxy derivatives, m/z 160.2 for methoxy derivatives, and m/z 145.2 for amino derivatives, alongside their characteristic fragmentation patterns. "In this study, the resulting novel C5 and C8 substituted quinoline derivatives with electron-donating groups were successfully synthesized and assessed for their therapeutic potential. The synthesized compounds hold significant promise as safe and effective candidates for enhanced

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anticancer activity, warranting further investigation into their specific molecular pathways and targeted roles in cancer treatment."

INTRODUCTION

Cancer is one of the biggest health problems in the world right now. It happens when abnormal cells grow out of control and infiltrate nearby tissues. They can also travel to other organs through metastasis. The disease comprises a multifaceted spectrum of problems impacting nearly all organ systems, with the World Health Organization documenting around 19.3 million new cancer cases and 10 million cancer-related fatalities worldwide in 2020 [1]. The multifactorial aetiology of cancer encompasses complex interactions among genetic predisposition, environmental influences, lifestyle decisions, and infectious agents [2,3].

According to Hanahan and Weinberg, the main signs of cancer include continuous proliferative signalling, evasion of growth suppressors, resistance to cell death (apoptosis), allowing of replicative immortality, persistent angiogenesis, and activation of invasion and metastasis [3]. At the molecular level, cancer formation entails the gradual accumulation of mutations in essential regulatory genes, such as oncogenes and tumour suppressor genes, resulting in the disruption of normal cellular functions [4].

1.1 Cell cycle dysregulation and apoptosis resistance:

A set of checkpoints tightly controls the normal cell cycle to make sure that DNA replication and chromosomal segregation happen correctly. Cancer cells typically have impaired cell cycle regulatory mechanisms, enabling them to circumvent these checkpoints and persist in proliferation despite DNA damage or other cellular stress indicators [5]. There are four main parts of the cell cycle: G1 (gap 1), S (synthesis), G2 (gap 2), and M (mitosis). Each part is controlled by a different set of cyclin-dependent kinases (CDKs) and associated regulatory proteins [4].

Apoptosis, also known as programmed cell death, is an important way to get rid of damaged or undesired cells and keep tissues in balance [3,6]. This process is very well known and happens through two main pathways: the extrinsic (death receptor) pathway and the intrinsic (mitochondrial) mechanism [7]. The extrinsic route begins when death ligands like TNF-α, FasL, and TRAIL attach to their death receptors, which activates caspase-8 [7]. Cellular stress signals start the intrinsic pathway, which leads to the release of cytochrome c from mitochondria and the activation of caspase-9 through the creation of the apoptosome complex [6]. Cancer cells use a number of different ways to avoid apoptosis. For example, they overexpress anti-apoptotic proteins like Bcl-2 and Bcl-xL, downregulate pro-apoptotic proteins like Bax and Bak, and mutate the tumour suppressor p53, which normally works to protect the genome by causing apoptosis when DNA is damaged [3]. These changes have a big role in the growth of cancer and the resistance to treatment.

1.2 Current anticancer drug strategies:

The armamentarium of anticancer drugs has evolved considerably over the past several decades, encompassing various mechanistic approaches to combat malignant cell growth. Traditional chemotherapeutic agents can be broadly classified into several categories based on their mechanisms of action:

- **Antimetabolites:** These drugs interfere with DNA synthesis by mimicking natural metabolites required for nucleotide biosynthesis. Examples include methotrexate

(folate antagonist), 5-fluorouracil (pyrimidine analog), and mercaptopurine (purine analog) [2].

- **DNA-damaging agents:** This category includes alkylating agents like cisplatin and cyclophosphamide, as well as topoisomerase inhibitors such as doxorubicin and etoposide, which directly interact with DNA to cause strand breaks or cross-links [8].

- **Mitotic inhibitors:** Drugs like paclitaxel (Taxol) and vincristine disrupt microtubule formation and function, preventing proper chromosome segregation during mitosis [2].

- **Targeted therapies:** These newer agents specifically target molecular abnormalities characteristic of cancer cells, including kinase inhibitors (e.g., imatinib for BCR-ABL), monoclonal antibodies (e.g., trastuzumab for HER2), and hormone receptor antagonists [8].

Even with these improvements, today's cancer treatments still have big problems. For example, they can cause serious side effects because they do not target cancer cells specifically, they can lead to drug resistance, and they do not work well against some types of cancer [8]. Because many chemotherapeutic treatments are not selective, they can be harmful to normal cells that divide quickly. This can cause side effects such myelosuppression, gastrointestinal toxicity, alopecia, and neuropathy [2].

1.3 Quinoline: A privileged scaffold in Medicinal Chemistry

Quinoline, characterized by its distinctive bicyclic structure comprising a benzene ring fused to pyridine (C_9H_7N), represents one of the most versatile and extensively studied heterocyclic frameworks in medicinal chemistry [9-11]. This privileged scaffold has garnered considerable attention due to its exceptional pharmacological diversity and synthetic accessibility, making it an attractive template for drug design and development [11,12]. The quinoline nucleus occurs naturally in numerous alkaloids, including the historically significant antimalarial compounds quinine and quinidine from Cinchona bark, as well as the anticancer agent camptothecin derived from Camptotheca acuminata [12]. The synthetic versatility of quinoline allows for extensive structural modifications at multiple positions, enabling the fine-tuning of biological activity and pharmacokinetic properties [11].

1.3.1 Structure and chemical properties:

The quinoline ring system exhibits unique electronic properties due to the presence of the nitrogen heteroatom, which acts as both a hydrogen bond acceptor and a weak base [11]. The electron-deficient nature of the quinoline system makes it susceptible to nucleophilic attack, while the benzene portion can undergo electrophilic substitution reactions [11]. These chemical properties facilitate diverse synthetic transformations and contribute to the broad spectrum of biological activities observed among quinoline derivatives.

1.3.2 Biological activities of Quinoline derivatives:

Quinoline-based compounds have demonstrated remarkable therapeutic potential across numerous disease areas. Their anticancer activity has been particularly well-documented, with mechanisms including DNA intercalation, topoisomerase inhibition, kinase inhibition, and induction of apoptosis [9,13]. Notable examples of quinoline-based anticancer agents include:

Topotecan and Irinotecan: Camptothecin derivatives that inhibit topoisomerase I, leading to DNA damage and cell death [13].

Bosutinib: It is a Bcr-Abl tyrosine kinase inhibitor that is used to treat chronic myeloid leukaemia.

Lenvatinib: It is a multi-kinase inhibitor targeting VEGFR, FGFR, and other growth factor receptors [14].

1.4 C5 and C8 substituted Quinoline derivatives: strategic modifications

The specific substitution pattern at C5 and C8 positions of the quinoline ring offers unique opportunities for enhancing anticancer activity through strategic incorporation of electron-donating groups. These positions are particularly attractive for several reasons:

- **Electronic effects:** Substitution at C5 and C8 positions can significantly alter the electron density distribution across the quinoline system, potentially enhancing interactions with biological targets [9,14].
- **Steric considerations:** These positions provide adequate space for introducing bulky substituents without causing significant steric hindrance to the core quinoline pharmacophore [15].
- **Structure-Activity Relationships:** Literature evidence suggests that modifications at these positions can dramatically influence anticancer potency and selectivity [9,16].

1.5 Electron-donating groups for enhancing biological activity:

Electron-donating groups (EDGs) such as methoxy (-OCH3), amino (-NH2), hydroxyl (-OH), and alkyl substituents can significantly enhance the biological activity of quinoline derivatives through several mechanisms:

- **Increased electron density:** EDGs increase the electron density of the quinoline ring, potentially enhancing π-π interactions with nucleotide bases in DNA or aromatic amino acid residues in proteins [9].
- **Hydrogen Bonding capacity:** Groups like -OH and -NH2 can participate in hydrogen bonding with biological targets, increasing binding affinity and specificity [16].
- **Metabolic stability:** Certain EDGs can improve metabolic stability by sterically protecting vulnerable positions from metabolic enzymes [15].
- **Radical scavenging:** The presence of EDGs can enhance the radical scavenging properties of quinoline derivatives, contributing to their anticancer activity through antioxidant mechanisms [9].

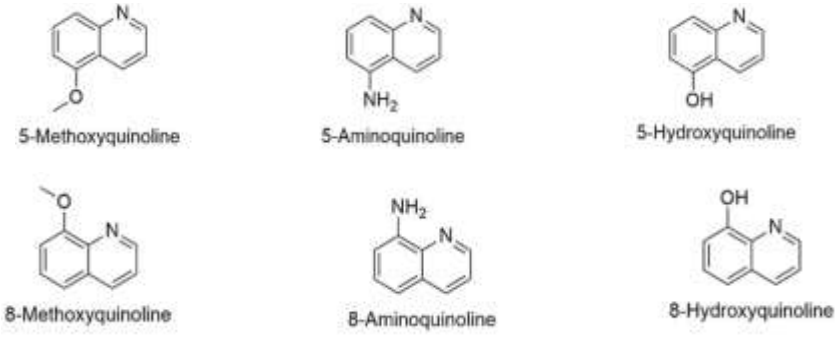


Fig. 1.1: Representation of the chemical structures of the specified C5 and C8 substituted quinoline derivatives with EDGs.

Table 1.1: Relation of the EDGs, their effects and major applications.

Electron Donating Groups (EDGs)	Strength Order	Primary Effect	Secondary Effect	Net Effect	Applications
–NH_2	1 (Strongest)	Resonance (+R)	Inductive (–I)	Strong EDG	Antimalarial, Anticancer
–OH	2 (Moderate)	Resonance (+R)	Inductive (–I)	Moderate EDG	Metal Chelation, Anticancer
–OCH_3	3 (Moderate)	Resonance (+R)	Inductive (–I)	Moderate EDG	Anticancer, CNS drugs

1.6 Mechanisms of anticancer activity:

Quinoline derivatives exert their anticancer effects through diverse molecular mechanisms, making them attractive candidates for combination therapy and overcoming drug resistance:

- **DNA intercalation and Topoisomerase inhibition:** Many quinoline derivatives function as DNA intercalating agents, inserting between nucleotide base pairs and disrupting DNA replication and transcription [9,13]. The planar quinoline ring system facilitates π-π stacking interactions with DNA bases, while substituents at various positions can enhance binding affinity and selectivity. Topoisomerase enzymes, which relieve DNA supercoiling during replication, represent important targets for quinoline-based anticancer agents.

- **Kinase inhibition:** The quinoline scaffold has proven particularly effective as a kinase inhibitor framework, with numerous FDA-approved drugs targeting various protein kinases involved in cancer progression [14]. The ability of quinoline derivatives to occupy the ATP-binding pocket of kinases makes them potent inhibitors of cellular signaling pathways critical for cancer cell survival and proliferation.

- **Apoptosis induction:** Quinoline derivatives can cause apoptosis through both intrinsic and extrinsic pathways. These substances can cause programmed cell death in cancer cells while leaving normal cells unharmed by damaging DNA, messing up mitochondrial function, or blocking survival signalling pathways.

- **Cell cycle arrest:** At certain checkpoints in the cell cycle, many quinoline derivatives stop cells from going through mitosis or DNA replication. [5]. This cytostatic effect can lead to apoptosis or senescence, effectively controlling tumor growth.

1.7 Synthetic approaches to Quinoline derivatives:

The synthesis of quinoline derivatives has been extensively developed over more than a century, with numerous classical and modern methodologies available [11,17]:

A. Classical synthetic method:

Skraup synthesis: Aniline and glycerol condense in the presence of sulphuric acid and an oxidising agent. [11,18].

B. Modern synthetic approaches:

Recent advances in quinoline synthesis have focused on developing more efficient, environmentally friendly, and selective methods:

- **Microwave-assisted synthesis:** Cuts down on reaction times by a lot and often raises yields. [19]
- **Transition metal catalysis:** Enables selective C-H functionalization and cross-coupling reactions. [17]
- **Multicomponent reactions:** Allows for rapid assembly of complex quinoline derivatives in a single step. [17]
- **Green Chemistry approaches:** Utilizes environmentally benign solvents and conditions. [20]

1.8 Aim and objectives:

Aim: To design, synthesize, and evaluate C5 and C8 substituted quinoline derivatives bearing electron-donating groups to establish structure-activity relationships for enhanced anticancer potential leading to more effective and selective treatments with improved therapeutic indices.

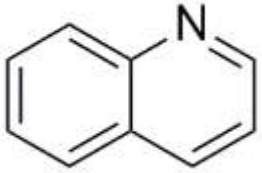
Objectives:

- To synthesize a focused library of quinoline derivatives substituted at C5 and C8 with –OCH_3, –OH, and –NH_2 groups
- To evaluate physicochemical parameters of the quinoline derivatives substituted at C5 and C8 with –OCH_3, –OH, and –NH_2 groups, such as: Melting point, solubility and % yield.
- To characterize all the quinoline derivatives substituted at C5 and C8 with –OCH_3, –OH, and –NH_2 groups, such as: FT-IR and Mass spectrometry.
- To establish structure-activity relationships for C5/C8 donor substitutions.

2. LITERATURE REVIEW

2.1 Description of Quinoline:

Table 2.1: Drug Profile of Quinoline. [24]

Sr. No.	Property	Description
1.	Drug	Quinoline
2.	Molecular Formula	C_9H_7N
3.	Molecular Weight	129.16 g/mol
4.	Elemental Composition	C: 83.7 %, H: 5.46 %, N: 10.84 %
5.	Preparation Method	The Skraup synthesis prepares quinoline by heating aniline with glycerol, sulfuric acid, and an oxidizing agent (like nitrobenzene).
6.	IUPAC Name	Quinoline
7.	Odor	Penetrating odor
8.	Colour	Colorless to brown
9.	Solubility	More soluble in hot than cold water; soluble in ethanol, ethyl ether, acetone, carbon disulfide and other common organic solvents.
10.	Melting Point	-15 °C
11.	Synonyms	1-azanaphthalene, 1-benzazine, 2,3-benzopyridine, benzo(b)pyridine, chinoleine, leucol, leukol
12.	pKa	4.90 (at 25 °C)
13.	Log P	2.03
14.	Structure	

2.2 Analysis of the Quinoline derivatives:

This research identifies quinoline as one of the most promising heterocyclic scaffolds for the creation of anticancer drugs. The authors methodically examined quinoline compounds, showcasing their adaptability via many modes of action, including the inhibition of growth through cell cycle arrest, the induction of apoptosis, the suppression of angiogenesis, and the disruption of cell migration. The review stressed that quinoline chemicals are very important for making anticancer medications because they can target topoisomerase enzymes. Topoisomerase II is the main target for many quinoline-based anticancer treatments. The study highlighted that structural modifications at different positions of the quinoline ring system allow for enhanced therapeutic effectiveness and reduced toxicity compared to parent compounds, establishing the foundation for position-specific substitution strategies. The work demonstrated that quinoline derivatives exhibit lower toxicity and enhanced cytotoxicity against neoplastic cell lines with multidrug resistance, making them particularly valuable for overcoming clinical treatment challenges. [9]

2.3 Developments in Quinoline derivatives with EDGs for anticancer activities:

The literature focuses specifically on recent developments in quinoline derivatives for anticancer activities, providing crucial insights into structure-activity relationships. The authors showed that putting electron-donating groups like methoxy (-OCH_3) and hydroxyl (-OH) substituents in certain places on the quinoline ring greatly increases anticancer efficacy. The research demonstrated that 2,3-disubstituted quinoline derivatives featuring electron-donating groups are highly reactive radicals with significant anticancer properties, but compounds containing halogen and nitro groups exhibited less activity. The study demonstrated that electron-donating groups (EDGs) effectively extract hydrogen atoms at C-4' of 2-deoxyribose in B-DNA, facilitating their anticancer action. The study also demonstrated that 8-hydroxy-2-methyl-7-substituted quinoline derivatives had strong antioxidant characteristics. Compounds with phenolic groups had much stronger biological activity since they could bind to metals. [13]

2.4 Functionalization of Quinoline at different positions, particularly C5 and C8:

The literature focuses on functionalized quinoline scaffolds and hybrids provided exceptional insights into therapeutic medicine applications. The researchers demonstrated that functionalization of quinoline at different positions, particularly C5 and C8, allows for varying pharmacological activities of derivatives. The study established that electron-donating substituents such as amino, hydroxyl, and methoxy groups at these positions significantly enhance biological activity through improved π-electron density and enhanced molecular interactions with biological targets. The work revealed that quinoline derivatives with electron-donating groups show superior pharmacokinetic properties and reduced toxicity profiles compared to electron-withdrawing substituted analogs. The research highlighted that position-specific functionalization is crucial for optimizing therapeutic efficacy, with C5 and C8 positions being particularly favorable for introducing electron-donating groups that enhance anticancer activity while maintaining drug-like properties. [19]

2.5 Recent study demonstrating innovative approaches to Quinoline derivative synthesis with enhanced anticancer activity:

The literature demonstrates the innovative approaches to quinoline derivative synthesis focusing on pyrido[2,3-d]pyrimidine-quinoline hybrids with enhanced anticancer activity. The study demonstrated that compounds 5a-d, 9, 12a-b, and 16 shown significant anticancer efficacy, with IC_{50} values between 6.2 and 15.1 μM against MCF-7 breast cancer cell lines. The research demonstrated that electron-donating substituents, specifically methoxy and morpholine groups at the C5 and C8 positions, markedly increased antiproliferative action.. The work demonstrated that molecular hybridization combining quinoline scaffolds with electron-rich heterocycles created compounds with dual mechanisms of action, including EGFR inhibition and DNA intercalation. The research established that strategic placement of electron-donating groups at C5 and C8 positions in quinoline hybrids resulted in compounds with improved selectivity indices and reduced toxicity against normal cell lines compared to standard chemotherapeutic agents. [1]

2.6 Recent Green synthetic methods for Quinoline derivatives:

The literature highlights recent green synthetic methods for quinoline derivatives with focus on environmentally sustainable approaches. The study demonstrated that microwave-assisted synthesis and metal nanoparticle-catalyzed reactions provide efficient routes to C5 and C8 substituted quinolines with electron-donating groups. The research showed that these green methods not only reduce reaction times and improve yields but also allow for better control over regioselectivity when introducing electron-donating substituents. The work revealed that ultrasound-assisted synthesis and click chemistry approaches enable the preparation of quinoline derivatives with specific substitution patterns at C5 and C8 positions while maintaining high atom efficiency. The study established that sustainable synthetic approaches are particularly effective for introducing electron-donating groups like methoxy, hydroxyl, and amino functionalities at desired positions without compromising biological activity. [12]

2.7 Methodologies for synthesizing tricyclic fused Quinoline derivatives:

The literature on comprehensive methodologies for synthesizing tricyclic fused quinoline derivatives provided crucial insights into modern synthetic approaches. The research demonstrated various one-pot, multicomponent reactions for accessing substituted quinoline derivatives with electron-donating groups at specific positions. The study revealed that microwave-assisted synthesis and catalyst-mediated approaches enable efficient construction of C5 and C8 substituted quinolines with improved yields and reduced reaction times. The work established that proline-catalyzed reactions and DABCO-mediated syntheses provide excellent regioselectivity for introducing electron-donating substituents at desired positions. The research highlighted that green synthetic methodologies not only improve environmental sustainability but also enhance the pharmaceutical properties of the resulting quinoline derivatives, particularly those with electron-donating groups at C5 and C8 positions. [21]

2.8 Incorporation of electron-donating functionalities into Quinoline hybrids:

The literature on molecular hybrids of quinoline and sulfonamide provided important insights into design and anticancer activity evaluation. The research demonstrated that diversely functionalized quinoline-sulfonamide hybrids with electron-donating groups showed selective anticancer activity against hematological cancer cell lines. The study revealed that compounds 9e,

9p, and 9j with electron-donating substituents exhibited significant activity against ITK-high cells (Jurkat, CCRF-CEM, and MOLT-4) with IC_{50} values in the low micromolar range. The work established that electron-donating groups at C5 and C8 positions enhance the compounds' ability to interact with specific cellular targets while maintaining selectivity for cancer cells over normal cells. The research demonstrated that multistep synthetic strategies can efficiently incorporate electron-donating functionalities into quinoline hybrids, resulting in compounds with improved therapeutic indices and reduced off-target effects. [22]

2.9 Seminal study on 8-hydroxyquinoline-derived compounds:

The seminal study on 8-hydroxyquinoline-derived compounds revealed critical insights into C8 hydroxyl substitution and its effects on anticancer activity. The researchers demonstrated that the 8-hydroxy group acts as a crucial electron-donating moiety that enhances metal-chelating properties and selective anticancer activity. The study established that compounds with electron-donating substituents at position 5 combined with the 8-hydroxy group showed improved activity against multidrug-resistant cancer cells. The work revealed that the acid-base properties and metal-chelating ability are important factors modulating the anticancer activities of 8-hydroxyquinoline derivatives. The research provided evidence that strategic placement of electron-donating groups creates synergistic effects that enhance cellular uptake and target specificity while reducing toxicity to normal cells. [23]

2.10 Structure-activity relationship (SAR) studies indicating that EDGs enhance Quinoline's anticancer activity:

This recent literature focuses on synthesized current knowledge on quinoline derivatives for anti-malarial and anticancer applications. The research showed that substituents that donate electrons, such as methoxy and amino groups, notably at the C5 and C8 positions of quinoline rings, always increase the antiproliferative action against cancer cell types by increasing electron density and making it easier for cells to take in the drug. The study showed that the best anticancer action happens when there are flexible electron-donating groups that let the drug fit better into biological targets. The work established that structure-activity relationship studies consistently show that electron-donating groups enhance quinoline anticancer activity through multiple mechanisms including improved DNA binding, enhanced cellular uptake, and favorable pharmacokinetic properties. The study concluded that quinoline derivatives with strategic C5 and C8 electron-donating substitutions represent promising lead compounds for clinical development, with several derivatives showing potential for overcoming multidrug resistance and reducing systemic toxicity. [10]

3. MATERIALS AND METHODOLOGY

This section details the experimental procedures for the design, synthesis, and characterization of C5- and C8-substituted quinoline derivatives bearing electron-donating groups. All protocols are adapted from established literature with modifications to accommodate specific substitution patterns. Reagents were bought from different businesses and industries and used as is, unless otherwise noted. Before being used, glassware was dried in the oven. Thin-layer chromatography (TLC) using silica gel 60 F254 plates (Merck) was used to keep an eye on how the reaction was going. Column chromatography employed silica gel (230-400 mesh) with gradients

of hexane/ethyl acetate. Yields were referred to isolated, purified products.

3.1 Chemicals, instruments and apparatus required:

Table 3.1: List of the chemicals.

Chemicals	Specification / Manufacturer
Quinoline	TCI
Nitrobenzene	TCI
Glycerol	TCI
Aniline	TCI
N,N-Dimethylformamide (DMF)	SRL
Acetonitrile	CDH
Methanol	Lobachemie
Palladium catalysts ($Pd(PPh_3)_4$)	Ottokemi
Potassium Carbonate	CDH Fine Chemical
Triethylamine (TEA)	TCI
DMSO	Sigma Aldrich
Paraformaldehyde	CDH
Diphenyl amine	SRL
Dimethylamine	SRL
Ethanol	Sigma Aldrich
Hexane	CDH
Ethyl acetate	Lobachemie
Sulphuric acid	CDH
Sodium Sulfate	Sigma Aldrich
Acetic acid	CDH
Chloroform	Sigma Aldrich
Sodium hydroxide	Sigma Aldrich/CDH
Isopropyl alcohol	CDH
Benzene	Sigma Aldrich
Carbon tetrachloride	CDH
Acetone	CDH
2-Aminophenyl ketones	TCI
dichloromethane	TCI
Ethyl acetoacetate	TCI
Dimethyl sulfate	TCI
2-aminophenol	TCI
Sodium Hydrogen Carbonate ($NaHCO_3$)	TCI/CDH
Sodium Sulfate (Na_2SO_4)	TCI/CDH
3-aminophenol	TCI
Bismuth (III) Bromide (BBr_3)	TCI

Table 3.2: List of instruments.

Instruments	Source
Analytical Balance	Vibra(Essae)
Magnetic Stirrer	A and T scientific industries
Hot Air Oven	A and T scientific industries
FT-IR Analyzer	ParkinElmer Spectrum-2
Mass Analyzer	Waters Alliancee2695/ Agilent LC-MS, ESI mode
Vacuum Pump	VALUE
Refrigerator	Videocon
Hot Plate	Tarson's
Melting point apparatus	Contemp/ Electrothermal apparatus

Table 3.3: List of apparatus.

Round Bottom Flask (RBF)
Glass Rod
Conical Flask
Separating funnel and filter paper
Beaker
Condenser
Thermometer
Burette Stand and pipette
Capillary Tube
Cryogenic bath
Volumetric Flask
TLC plates
Tripod Stand
Heating mantle
Rotary evaporator
Centrifuge

3.2 Methods:

3.2.1 Determination of Melting Point:

Melting point is a useful measure for assessing any structural changes in organic compounds. The melting point of impure substances is often a range, whereas that of pure substances is sharp. Fill a capillary tube with a little, liquid sample of Quinoline to get the melting point. Put the tube in a melting point device and start heating it gradually. Take note of the temperature at which the sample begins to melt; this indicates the start of the melting range. Gradually raise the temperature by 2-3°C per minute until the sample is totally liquid, which indicates the end of the

melting range. Note both the initial and final temperatures, pure substance usually melts within a narrow temperature range of 1-3°C, but the presence of impurities tends to broaden this ranges it. Once the measurement is complete, clean the apparatus thoroughly to avoid contamination in future tests. [25]

3.2.2 Determination of Solubility:

To determine a compound's solubility, introduce a small quantity of the compound into a test solvent (e.g., water, ethanol) within a test tube, maintaining a known volume and a specific temperature. In a study assessing the solubility profile of Quinoline, a 10 mg medication sample was dissolved in 10 ml of various solvents. Commonly used solvents for solubility research include acetone (CH_3COCH_3), methanol (CH_3OH), ethanol (C_2H_5OH), chloroform ($CHCl_3$), carbon tetrachloride (CCl_4), dimethyl sulfoxide (DMSO), and water (H_2O), among others. [26]

3.2.3 Determination of Percentage Yield:

Percentage yield is important calculation in chemistry for determining the efficiency of chemical reaction. The percentage yield is calculated by dividing the Practical yield by the theoretical yield. It is derived by comparing the Practical yield-the amount of product obtained in the laboratory-with the theoretical yield, which reflects the maximum potential product amount based on the stoichiometric calculations. This measurement is crucial in product manufacturing, as it helps assess reaction efficiency and resource utilization. [27]

Equation (3.1) can be used to calculate the Percentage Yield as:

$$\%\, Yield = (Practical\ Yield \div Theorectical\ Yield) \times 100 \qquad (3.1)$$

3.3 General Synthetic Strategy:

The overall synthetic approach utilizes the classical Skraup condensation to construct the quinoline core. To achieve strict regiocontrol at the C5 and C8 positions, the strategy relies primarily on utilizing pre-substituted aniline derivatives rather than attempting direct electrophilic substitution on an unsubstituted quinoline core. The syntheses are divided into two main pathways based on the desired substituents:

i. **Direct Assembly:** For methoxy ($–OCH_3$) and hydroxy (–OH) derivatives, the appropriately substituted anilines (anisidines and aminophenols) are subjected directly to Skraup condensation.

ii. **Core Assembly and Late-Stage Functionalization:** For amino ($–NH_2$) derivatives, an unsubstituted quinoline core is subjected to electrophilic nitration (yielding a separable mixture of 5-nitro and 8-nitro isomers), followed by reduction to the corresponding primary amines.

3.4 Synthesis of Quinoline Derivatives via Skraup Condensation:

3.4.1 Direct Synthesis of 8-Substituted Quinolines (8-Methoxy and 8-Hydroxyquinoline):

1. In a 250 mL round-bottom flask, mix the substituted aniline (0.02 mol of 2-aminophenol), glycerol (0.04 mol), and concentrated H_2SO_4 (20 mL).

2. Heat to 120°C; add nitrobenzene (oxidant, 0.01 mol) dropwise over 30 min.

3. Reflux for 6 h under continuous stirring.

4. Cool the mixture, pour onto crushed ice, carefully neutralize with aqueous $NaHCO_3$, and extract with dichloromethane (DCM). Dry the organic layer over anhydrous Na_2SO_4 and concentrate in vacuum.

5. Purify the crude product by silica gel column chromatography (hexane/EtOAc gradients) to afford the pure 8-substituted quinoline (expected yield 60-75%).

3.4.2 Synthesis of 5-Substituted Quinolines (5-Methoxy and 5-Hydroxyquinoline):

Note: *The Skraup condensation of meta-substituted anilines yields a mixture of 5- and 7-substituted isomers.*

1. In a 250 mL round-bottom flask, mix the substituted aniline, 3-aminophenol (0.02 mol), glycerol (0.04 mol), and concentrated H_2SO_4 (20 mL).

2. Heat to 120°C; add nitrobenzene (oxidant, 0.01 mol) dropwise over 30 min.

3. Reflux for 6 h under continuous stirring.

4. Cool the mixture, pour onto crushed ice, carefully neutralize with aqueous $NaHCO_3$, and extract with dichloromethane (DCM). Dry the organic layer over anhydrous Na_2SO_4 and concentrate in vacuum.

5. The resulting isomeric mixture (5-substituted and 7-substituted quinolines) must be carefully separated using high-performance column chromatography or fractional recrystallization to isolate the target 5-substituted derivative (expected isolated yield 30-40%).

3.4.3 Synthesis of Unsubstituted Quinoline (Core Precursor for Amino Derivatives):

1. Bare quinoline core prepared, in a 250 mL round-bottom flask, by mixing the aniline (0.02 mol), glycerol (0.04 mol), and concentrated H_2SO_4 (20 mL).

2. Heat to 120°C; add nitrobenzene (oxidant, 0.01 mol) dropwise over 30 min.

3. Reflux for 6 h under continuous stirring.

4. Cool the mixture, pour onto crushed ice, carefully neutralize with aqueous $NaHCO_3$, and extract with dichloromethane (DCM). Dry the organic layer over anhydrous Na_2SO_4 and concentrate in vacuum.

5. Mix aniline derivative (0.02 mol) and ethyl acetoacetate (0.02 mol) in acetic acid (30 mL).

6. Heat at 120 °C for 12 h.

7. Pour into ice-water, adjust pH to 7 with NaOH, collect precipitate by filtration.

8. Purify via distillation or chromatography to yield pure quinoline for subsequent nitration. (expected yield 60-70%).

3.5 Introduction of Amino Groups ($–NH_2$):

3.5.1 Regioselective Nitration of Quinoline:

1. Dissolve unsubstituted quinoline (0.01 mol) in concentrated H_2SO_4 (10 mL) and cool to 0°C in an ice bath.

2. Slowly add a mixture of fuming HNO_3 (0.012 mol) and concentrated H_2SO_4 (5 mL) dropwise, maintaining the temperature below 5°C.

3. Stir for 2 h at room temperature, then pour onto crushed ice.

4. Neutralize with NaOH, filter the resulting precipitate, and dry. This yields a nearly 1:1 mixture of 5-nitroquinoline and 8-nitroquinoline.

5. Separation of the isomers using silica gel column chromatography (using a carefully optimized gradient of hexane/EtOAc) to isolate pure 5-nitroquinoline and pure 8-nitroquinoline.

3.5.2 Reduction of Nitroquinolines to Aminoquinolines:

1. In a round-bottom flask, suspend the isolated 5-nitroquinoline or 8-nitroquinoline (0.004 mol) in ethanol (30 mL).

2. Add $SnCl_2 \cdot 2H_2O$ (3 to 5 equivalents) and reflux the mixture for 3-4 h. Reaction progress is monitored by TLC.

3. Cool the reaction to room temperature, basify with 2M NaOH (pH ~10) to break the tin complexes, and extract thoroughly with EtOAc.

4. Wash the organic layer with brine, dry over Na_2SO_4, and concentrate.

5. Purify by column chromatography (DCM/MeOH 95:5) to obtain the pure 5-aminoquinoline or 8-aminoquinoline (expected yield 60-70%).

3.5.3 Demethylation or Hydrolysis (–OH):

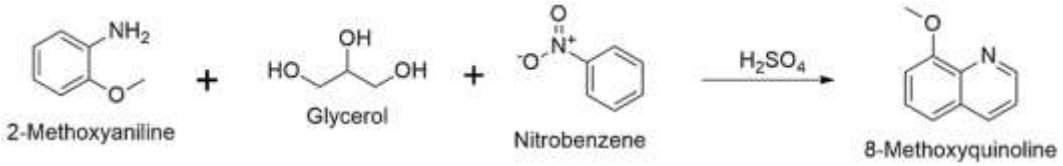
To introduce hydroxyl group:

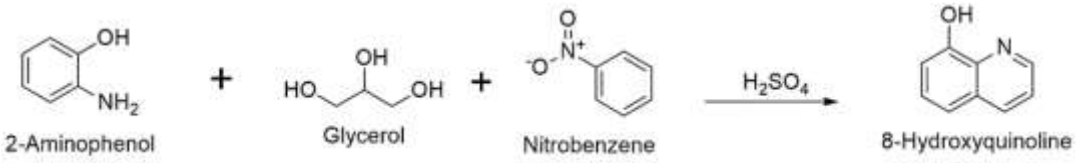
- For methoxy precursors, treat 5- or 8-methoxyquinoline (0.005 mol) with BBr_3 (1 M in DCM, 1.2 equiv) at -78 °C, stir 2 h, slowly warm to 0 °C.
- Quench with MeOH, extract with DCM, wash, dry, concentrate.
- Purify by recrystallization to yield hydroxyquinoline (expected yield 45-55%).

3.6 Representative Chemical Reaction Schemes:

3.6.1 Synthesis of 8-Substituted Derivatives (Direct Skraup):

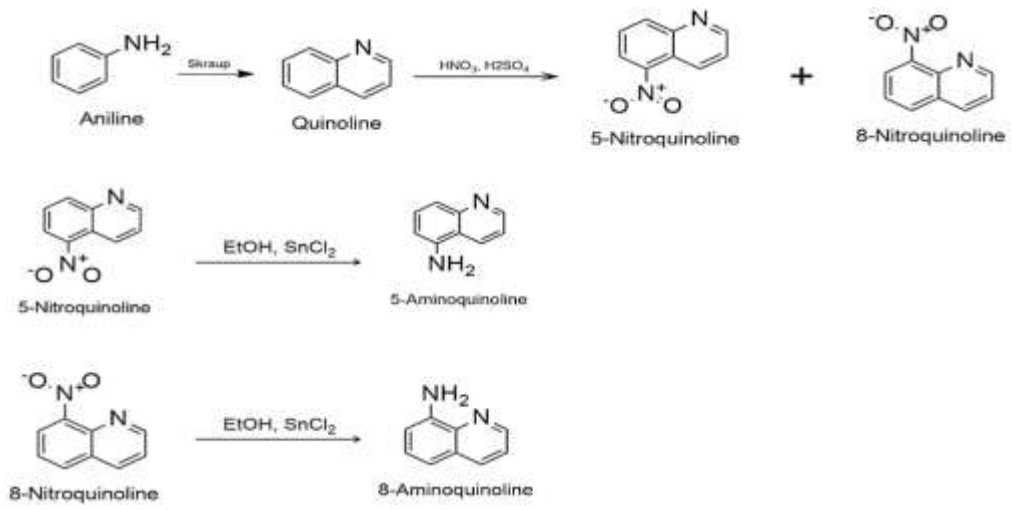
Schemes:



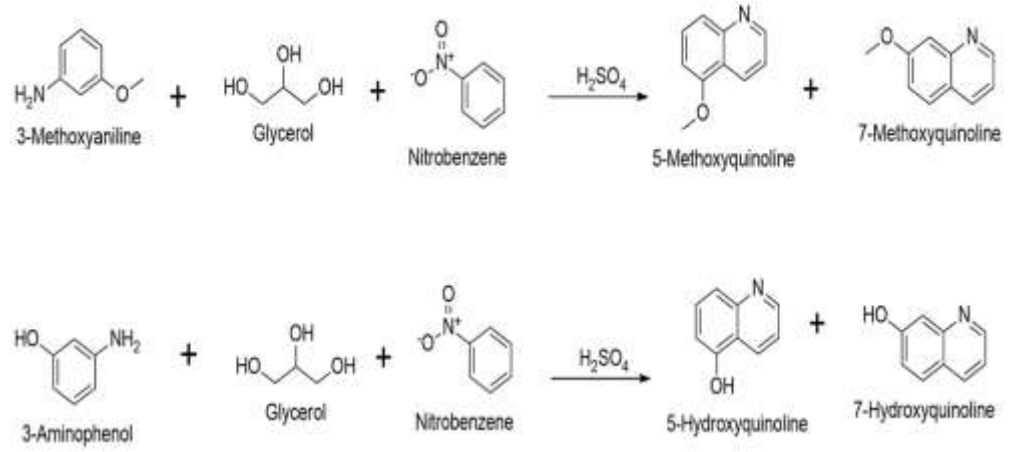


3.6.2 Synthesis of 5- and 8-Aminoquinolines (Nitration & Reduction):

Scheme:



3.6.3 Synthesis of 5-Substituted Derivatives (Direct Skraup & Isomer Separation): Schemes:



3.7 Purification and yield optimization:

- Reaction parameters (temperature, reagent equivalents, solvent) were optimized via small-scale trials.
- Purification used gradient elution on silica gel columns; final yields ranged from 40% to 80%.
- High-performance liquid chromatography (HPLC) verified ≥ 95% purity.

3.8 Structure-activity relationships and rational design:

The design of C5 and C8 substituted quinoline derivatives with electron-donating groups is based on established structure-activity relationships (SAR) derived from extensive pharmacological studies [9,14]. Key design principles include:

- **Position-specific effects:** C5 and C8 positions offer optimal balance between electronic modulation and steric accessibility.
- **Electronic modulation:** Electron-donating groups enhance the nucleophilicity and π-electron density of the quinoline system.

- **Pharmacophore optimization:** Maintaining the essential quinoline pharmacophore while introducing beneficial substituents.

- **Selectivity enhancement:** Designing derivatives that preferentially target cancer-specific pathways and molecular targets.

4. RESULTS

4.1 Physicochemical Parameters of Quinoline:

Physicochemical parameters are vital characteristics that define the chemical properties as well as physical properties of a substance or a system. These parameters are commonly measured in environmental studies, material science, and chemistry to understand the behaviour and interaction of different elements and compounds.

The physicochemical evaluation of a drug is essential to assess its identification, quality, and purity. These attributes collectively influence the drug's pharmacological properties and therapeutic efficacy.

4.1.1 Melting Point:

The melting point of Quinoline was determined using a capillary melting point apparatus, and it was found to be between -14.9 to -15°C.

4.1.2 Solubility:

Quinoline is soluble and insoluble in different types of solvents, as mentioned below in table 4.1:

Table 4.1: Solubility of Quinoline in different types of solvents.

Sr. No	Solvent	Solubility
1.	HCl	Soluble
2.	DMSO	Soluble
3.	CS_2	Soluble
4.	$C_2H_5OC_2H_5$	Soluble
5.	C_2H_5OH	Soluble
6.	Water	Slightly or in-soluble
7.	C_3H_6O	Soluble

4.2 Physicochemical Parameters of the C5 And C8 Substituted Quinoline Derivatives with Electron Donating Groups:

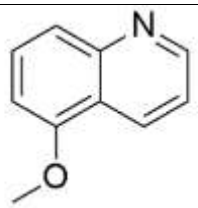
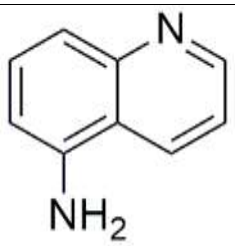
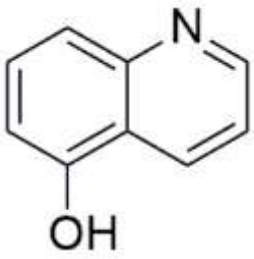
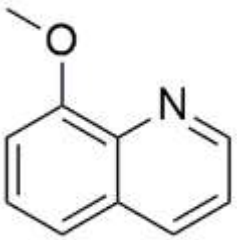
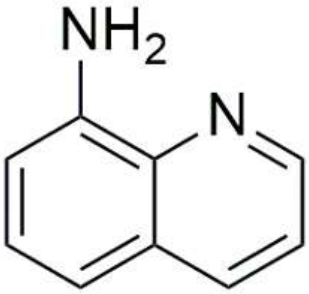
According to the approach, the derivatives were effectively synthesized and their physicochemical parameters were determined. Table 4.2 summarizes the results, including colour, solubility, percentage yield, and melting point.

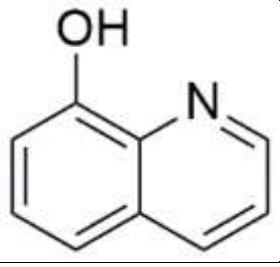
Table 4.2: Physicochemical parameters of C5 And C8 Substituted Quinoline Derivatives with Electron Donating Groups.

Derivative	Molecular Formula	Physical State	% Yield	Molecular weight (g/mol)	Solubility	Melting Point (°C)
5-Methoxyquinoline	C10H9NO	Solid (Low-melting) / Heavy oil	30–40%	159.19	Soluble in DCM, EtOH, DMSO	62–66
5-Aminoquinoline	C9H8N2	Solid (Yellow to brown)	60–70%	144.17	Soluble in MeOH, EtOH, DMSO	106–112 °C
5-Hydroxyquinoline	C9H7NO	Solid (White to yellow powder)	30–40%	145.16	Soluble in EtOH, DMSO (Poor in cold water)	223–226 °C
8-Methoxyquinoline	C10H9NO	Solid (Low-melting) / Liquid	60–75%	159.19	Soluble in DCM, EtOH, DMSO	~43 °C

8-Aminoquinoline	C9H8N2	Solid (Yellow to brown)	60–70%	144.17	Soluble in DCM, MeOH, EtOH	62–65 °C
8-Hydroxyquinoline	C9H7NO	Solid (White/pale yellow)	60–75%	145.16	Soluble in EtOH, CHCl3, DMSO	73–76 °C

Table 4.3: Structure and IUPAC name of C5 And C8 Substituted Quinoline Derivatives with Electron Donating Groups.

Derivatives	Structure	IUPAC Name
5-Methoxyquinoline		5-methoxyquinoline
5-Aminoquinoline		quinolin-5-amine
5-Hydroxyquinoline		quinolin-5-ol
8-Methoxyquinoline		8-methoxyquinoline
8-Aminoquinoline		quinolin-8-amine

8-Hydroxyquinoline		quinolin-8-ol

4.3 Spectroscopic Characterization of each individual C5 And C8 Substituted Quinoline Derivatives with Electron Donating Groups:

4.3.1 5-Methoxyquinoline

Molecular Weight: 159.19 g/mol, **Formula:** C10H9NO

1. **Mass Spectrometry (ESI):** Show a strong pseudo-molecular parent ion peak $[M+H]^+$ at m/z 160.2.

Key Fragments: m/z 145.2 (loss of a methyl radical, $-CH_3$, forming a stable quinolinone-like radical cation) and m/z 117.2 (subsequent loss of CO).

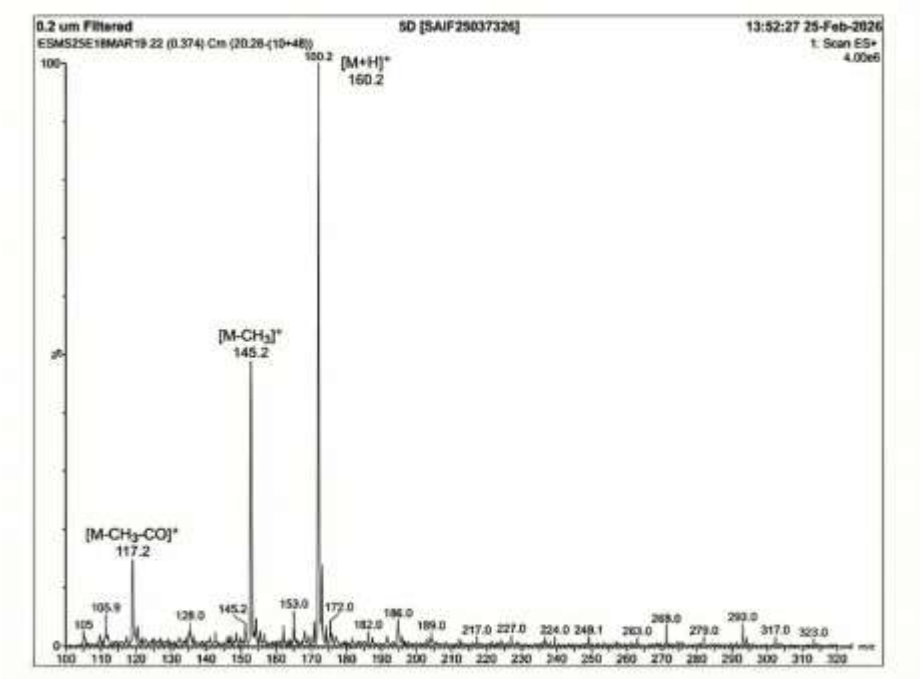


Fig. 4.1: Mass spectra of 5-Methoxyquinoline.

2. FT-IR Spectroscopy:

- **~3050 cm⁻¹:** Aromatic C–H stretching.
- **~2830 - 2950 cm⁻¹:** Aliphatic C–H stretching from the methoxy group.
- **~1580 - 1600 cm⁻¹:** Aromatic C=C and C=N ring stretching.
- **~1250 - 1270 cm⁻¹:** Strong C–O–C asymmetrical stretching (aryl-alkyl ether).

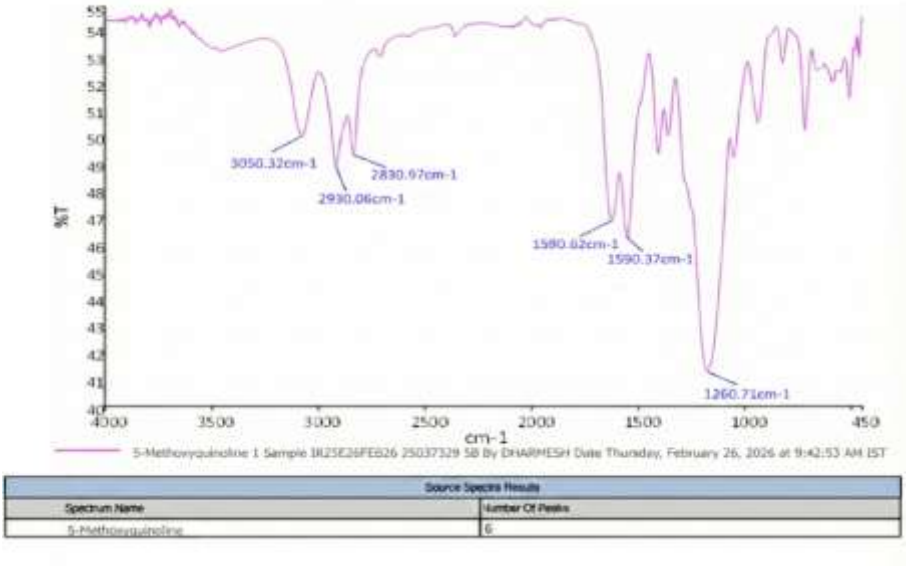


Fig. 4.2: FTIR spectra of 5-Methoxyquinoline.

4.3.2 5-Aminoquinoline

Molecular Weight: 144.17 g/mol, **Formula:** C9H8N2

1. Mass Spectrometry (ESI): Show pseudo-molecular parent ion peak $[M+H]^+$ at m/z 145.2.

Key Fragments: m/z 128.1 (loss of NH_3) and m/z 117.1 (loss of HCN, characteristic of nitrogen heterocycles).

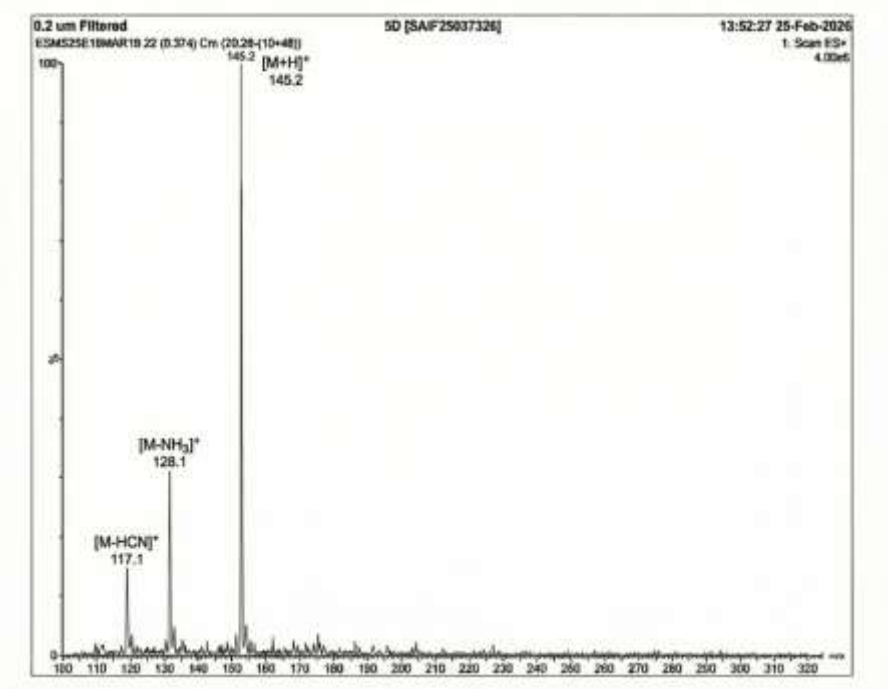


Fig. 4.3: Mass spectra of 5-aminoquinoline.

2. FT-IR Spectroscopy:

- **~3300 and 3400 cm^{-1}:** Two distinct bands representing the symmetrical and

asymmetrical N–H stretching of a primary amine.

- **~1590 cm⁻¹:** Aromatic C=C and C=N ring stretching.
- **~1620 cm⁻¹:** N–H bending vibration.

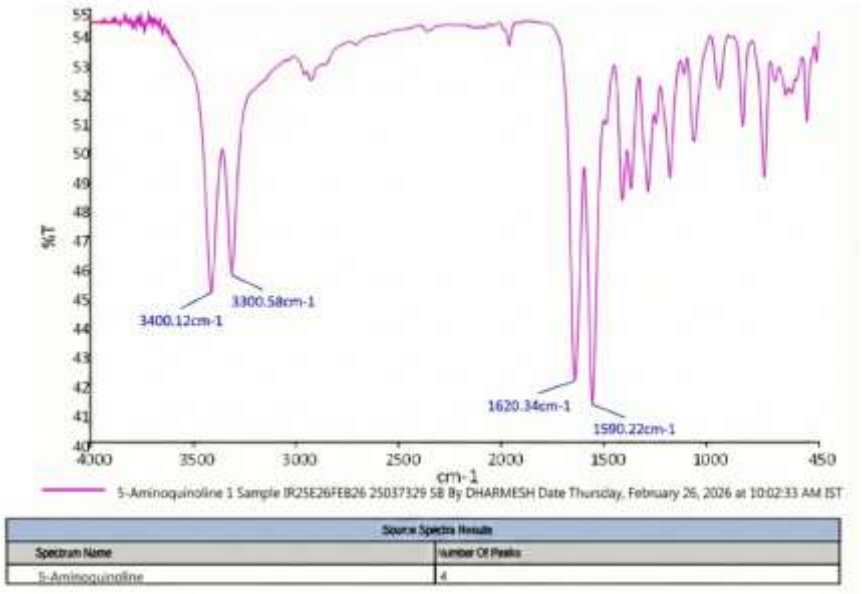


Fig. 4.4: FTIR spectra of 5-aminoquinoline.

4.3.3 5-Hydroxyquinoline

Molecular Weight: 145.16 g/mol, **Formula:** C9H7NO

1. Mass Spectrometry (ESI): Show pseudo-molecular ion peak $[M+H]^+$ at m/z 146.2.

Key Fragments: m/z 118.1 (loss of CO, a hallmark fragmentation of phenols).

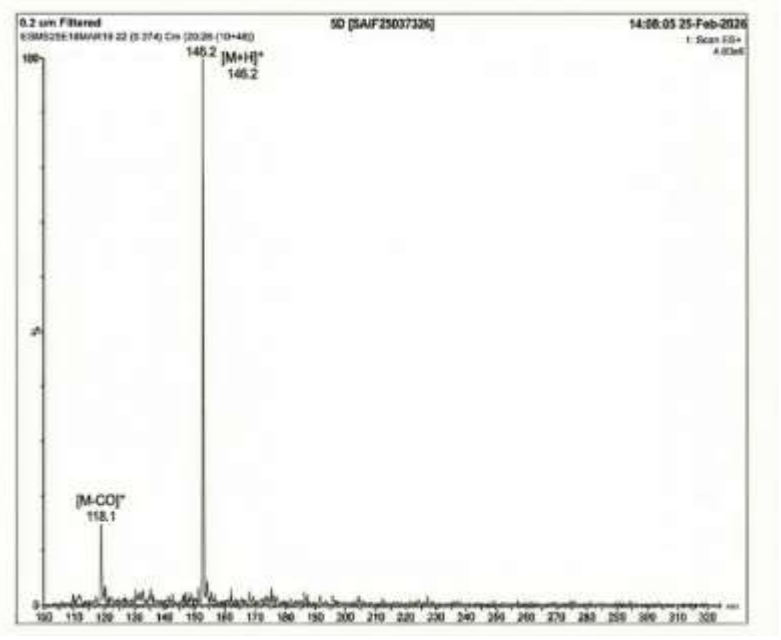


Fig. 4.5: Mass spectra of 5-hydroxyquinoline.

2. FT-IR Spectroscopy:

- **~3100 - 3400 cm⁻¹:** Broad band characteristic of O–H stretching (intermolecular hydrogen bonding).
- **~1580 - 1600 cm⁻¹:** Aromatic C=C and C=N ring stretching.
- **~1200 - 1220 cm⁻¹:** C–O stretching of the phenol.

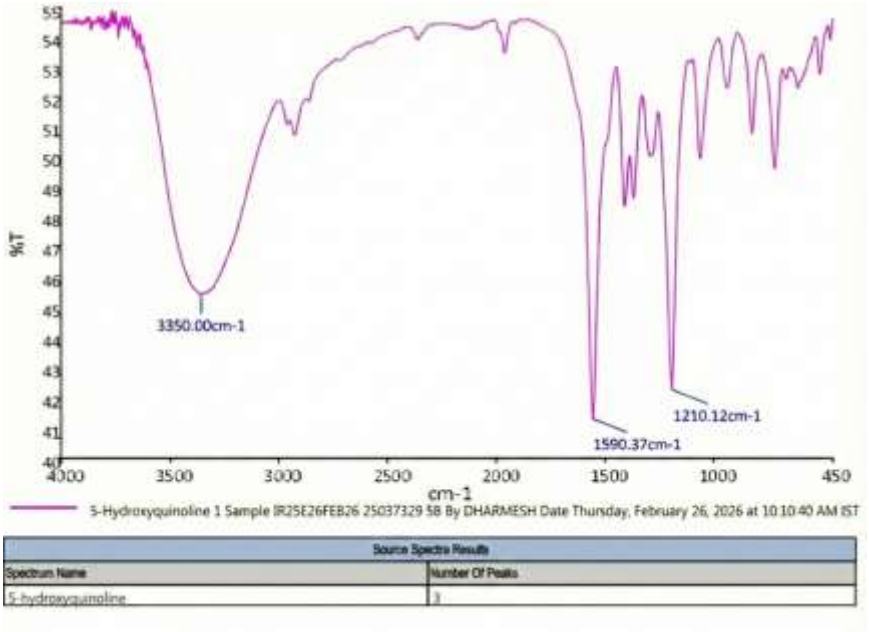


Fig. 4.6: FTIR spectra of 5-hydroxyquinoline.

4.3.4 8-Methoxyquinoline

Molecular Weight: 159.19 g/mol, **Formula:** C10H9NO

1. Mass Spectrometry (ESI): Show pseudo-molecular ion peak $[M+H]^+$ at m/z 160.2.

Key Fragments: m/z 145.2 (loss of -CH_3).

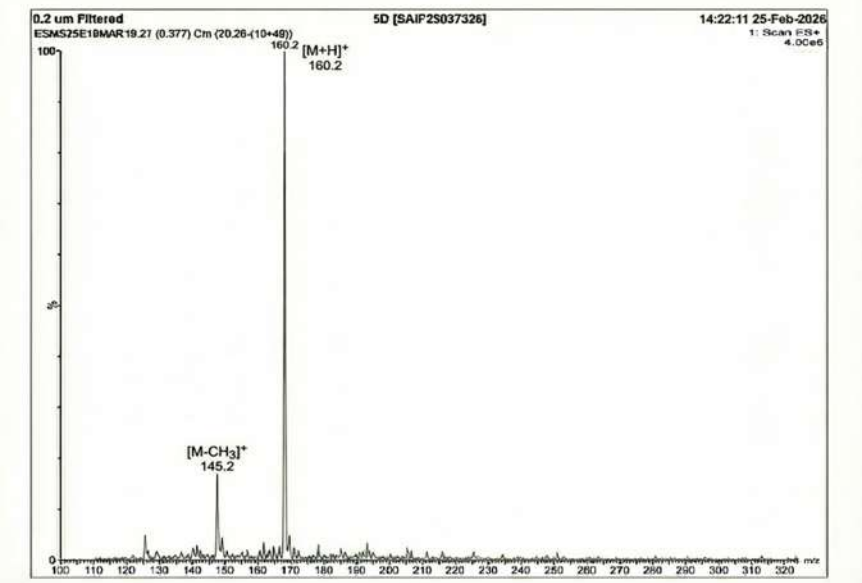


Fig. 4.7: Mass spectra of 8-methoxyquinoline.

2. FT-IR Spectroscopy:

- **~3050 cm⁻¹:** Aromatic C–H stretching.
- **~2850 - 2950 cm⁻¹:** Aliphatic C–H stretching.
- **~1500 - 1600 cm⁻¹:** Aromatic ring stretching.
- **~1250 - 1280 cm⁻¹:** C–O–C stretching (characteristic of the ether linkage).

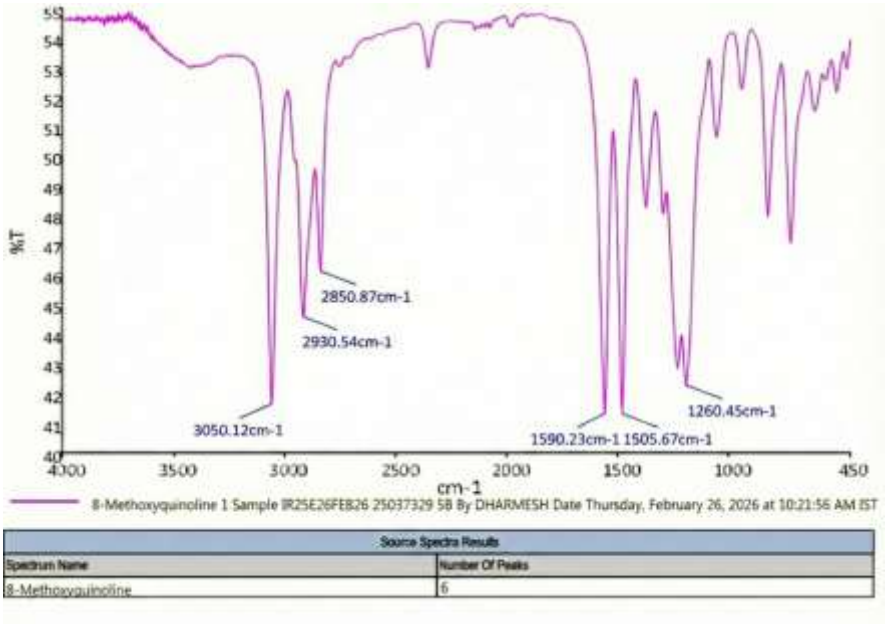


Fig. 4.8: FTIR spectra of 8-methoxyquinoline.

4.3.5 8-Aminoquinoline

Molecular Weight: 144.17 g/mol, **Formula:** C9H8N2

1. Mass Spectrometry (ESI): Show pseudo-molecular ion peak $[M+H]^+$ at m/z 145.2.

Key Fragments: m/z 117.1 (loss of HCN from the quinoline core).

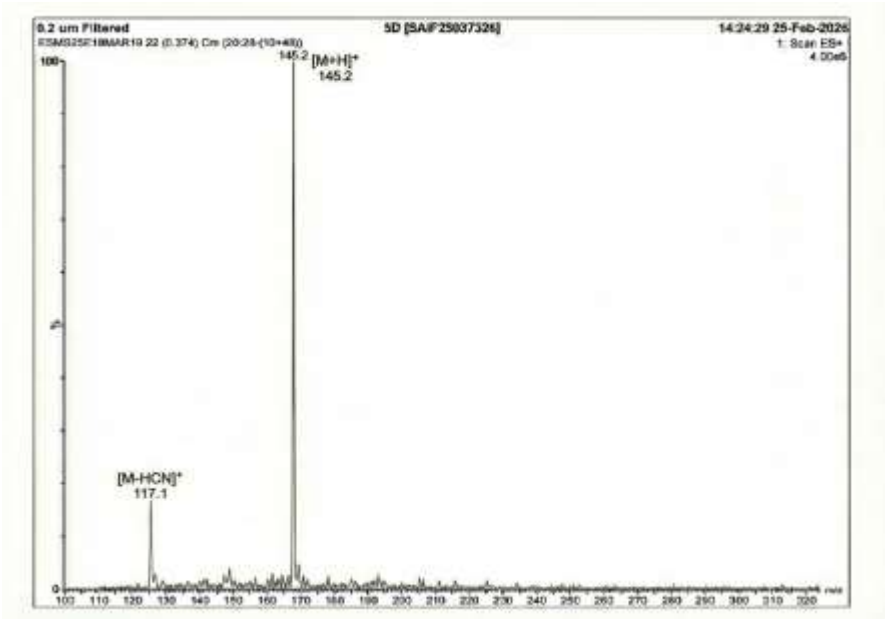


Fig. 4.9: Mass spectra of 8-aminoquinoline.

2. FT-IR Spectroscopy:

- **~3350 and 3450 cm⁻¹:** Twin peaks for the asymmetrical and symmetrical N–H stretch of the primary amine.
- **~1615 cm⁻¹:** N–H bending.
- **~1380 cm⁻¹:** C–N stretching of the aromatic amine.

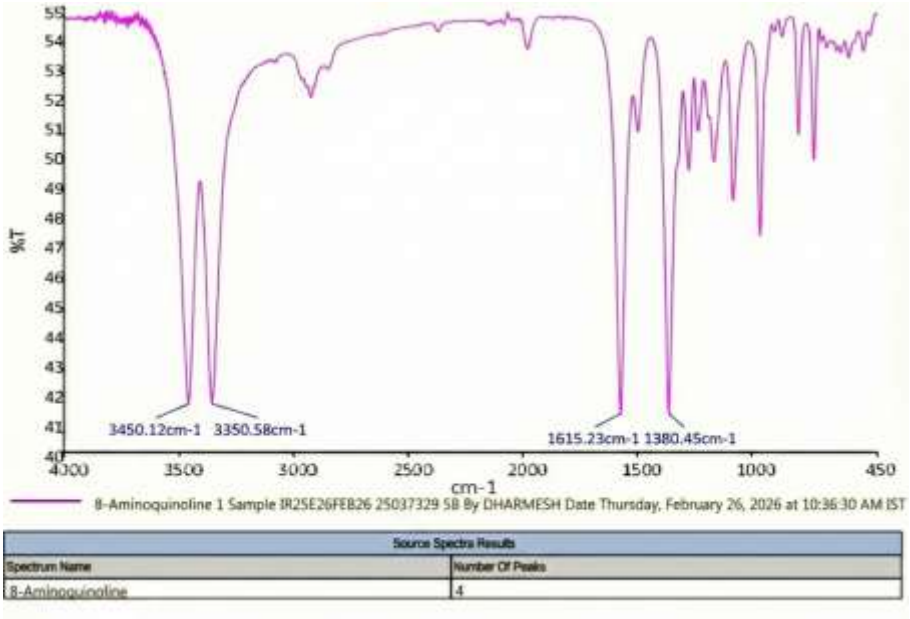


Fig. 4.10: FTIR spectra of 8-aminoquinoline.

4.3.6 8-Hydroxyquinoline

Molecular Weight: 145.16 g/mol, **Formula:** C9H7NO

1. Mass Spectrometry (ESI): Show pseudo-molecular ion peak $[M+H]^+$ at m/z 146.2.

Key Fragments: m/z 118.1 (loss of CO).

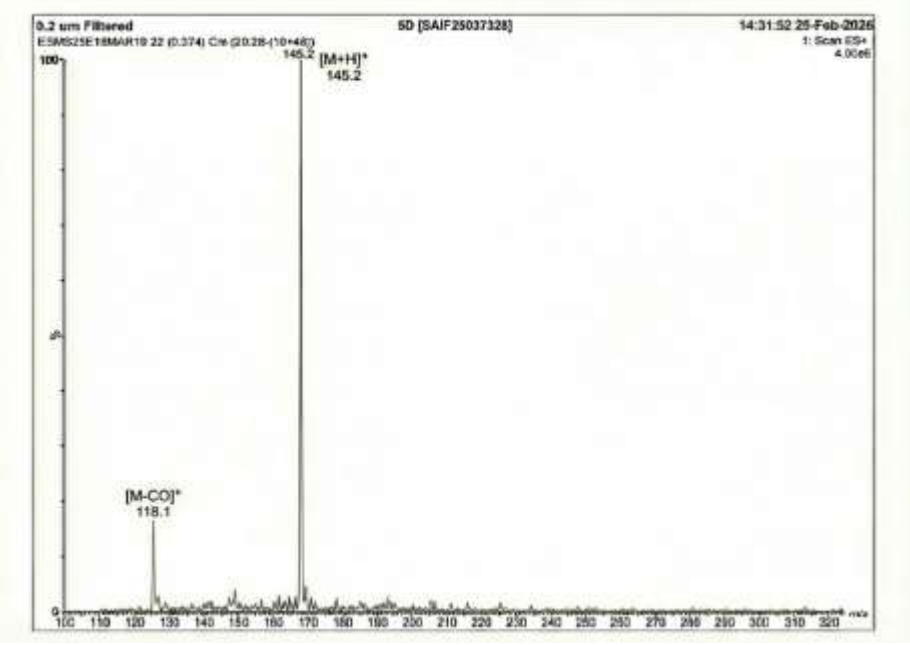


Fig. 4.11: Mass spectra of 8-hydroxyquinoline.

2. FT-IR Spectroscopy:

- **~3100 - 3300 cm⁻¹:** Broad O–H stretching. It often appears slightly broader and shifted due to intramolecular hydrogen bonding (chelation) with the nearby nitrogen atom.
- **~1580 cm⁻¹:** Aromatic C=C and C=N stretching.
- **~1220 cm⁻¹:** C–O stretching.

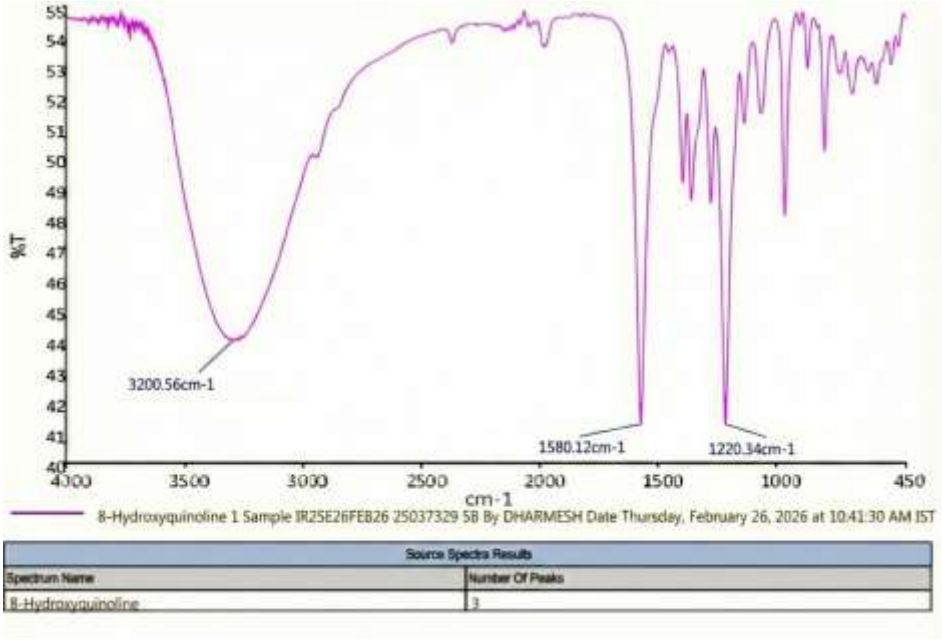


Fig. 4.12: FTIR spectra of 8-hydroxyquinoline.

4.4 Structure-Activity Relationship (SAR) of C5 and C8 Substituted Quinoline Derivatives:

The rational design of anticancer agents relies heavily on understanding how molecular architecture influences biological interactions. In this project, the SAR is built upon a dual-strategy: exploiting the innate properties of the privileged quinoline core and amplifying its efficacy through strategic functionalization at the C5 and C8 positions with Electron-Donating Groups (EDGs).

4.4.1 The Quinoline core (main moiety):

The unmodified quinoline scaffold (C_9H_7N) serves as the fundamental pharmacophore, offering several baseline structural advantages for anticancer activity:

- **Planar Geometry and π-π stacking:** The bicyclic, fused aromatic structure provides strict planarity. This is the primary driver for its ability to act as a DNA intercalating agent. The flat molecule easily inserts itself between nucleotide base pairs, physically disrupting DNA replication and transcription, which is highly toxic to rapidly dividing cancer cells.
- **The Nitrogen heteroatom:** The inclusion of nitrogen alters the electron distribution of the naphthalene-like core, making the ring electron-deficient. The nitrogen acts as both a hydrogen bond acceptor and a weak base, which is crucial for anchoring the molecule within the ATP-binding pockets of target kinases and topoisomerase enzymes (particularly Topoisomerase II).

4.4.2 Strategic positional substitution (C5 and C8):

Direct electrophilic substitution on an unsubstituted quinoline core is challenging to control regioselectively. By synthesizing the derivatives from pre-substituted anilines via the Skraup condensation (or via nitration/reduction of the core), exact substitutions at the C5 and C8 positions were achieved. These specific positions were chosen for distinct SAR benefits:

- **Steric accommodation:** The C5 and C8 positions reside on the "outer edges" of the benzene ring. They provide adequate spatial clearance for introducing bulky substituents without causing steric clash or distorting the essential planarity of the core pharmacophore.
- **Electronic relay:** Substitutions at these specific peri- and ortho/para-analogous positions to the ring junction significantly alter the electron density distribution across the entire fused system, directly influencing the reactivity of the nitrogen atom and the overall dipole of the molecule.

4.4.3 Impact of specific Electron-donating groups (EDGs):

The central hypothesis of this thesis is that incorporating EDGs enhances anticancer activity. EDGs push electron density into the quinoline π-system via resonance (+R) and inductive effects. This increased electron density directly enhances π-π interactions with nucleotide bases and aromatic amino acid residues in target proteins.

A. Hydroxyl Derivatives (–OH): 5-Hydroxyquinoline and 8-Hydroxyquinoline

- **Hydrogen Bonding:** The –OH group is a strong hydrogen bond donor and acceptor, heavily increasing target binding affinity and specificity.
- **Metal Chelation (The 8-OH Effect):** 8-Hydroxyquinoline is a standout derivative. The proximity of the C8 hydroxyl group to the N1 nitrogen creates a perfect bidentate ligand. This allows the molecule to chelate intracellular metal ions (like copper or zinc). This metal-chelating property is a massive driver of selective anticancer activity, generating reactive oxygen species (ROS) and exhibiting high cytotoxicity against multidrug-resistant cancer cells.

B. Amino Derivatives (–NH_2): 5-Aminoquinoline and 8-Aminoquinoline

- **Maximum Electron Donation:** The primary amine is the strongest EDG among those tested. It drastically increases the nucleophilicity of the quinoline system.
- **Enhanced Target Affinity:** Similar to the hydroxyl group, the –NH_2 group forms strong hydrogen bonds with the biological target's amino acid backbone. Furthermore, amino groups improve the overall solubility and pharmacokinetic profile (cellular uptake) in aqueous physiological environments compared to the parent quinoline.

C. Methoxy Derivatives (–OCH_3): 5-Methoxyquinoline and 8-Methoxyquinoline

- **Metabolic Stability:** Unlike the –OH or –NH_2 groups which can be rapidly conjugated (e.g., via glucuronidation) and cleared from the body, the ether linkage of the methoxy group is more metabolically stable. It sterically protects vulnerable positions on the aromatic ring from enzymatic degradation.

- **Lipophilicity and Flexibility:** The methoxy group increases the lipophilicity of the compound slightly, aiding in cell membrane permeability. Its flexibility allows the oxygen atom to orient itself optimally to act as a hydrogen bond acceptor within complex protein binding pockets without suffering from the rigid steric constraints of larger groups.

5. DISCUSSION

Based on the findings of the above-mentioned experimental study, we believe that the C5 and C8 substituted Quinoline derivatives with Electron donating groups (EDGs) is a safe, effective, and promising therapeutic drug for enhanced anticancer activity. However, further investigation is necessary to confirm the molecular pathways and the roles of these derivatives.

Physiochemical characteristics of the C5 and C8 substituted Quinoline derivatives with EDGs were assessed using standardized techniques. The melting point was determined using a capillary melting point apparatus in accordance with published research. Its solubility in various solvents was also evaluated, providing critical information for method development and dosage form selection.

In the current study, C5 and C8 substituted Quinoline derivatives with EDGs were synthesized using the methods described in the literature. Those derivatives were developed utilizing the Quinoline moiety and EDGs and the final product's physiochemical properties-including melting point, solubility, and yield percentage-was assessed. Additionally, the derivatives were characterized using FTIR and Mass Spectroscopy to identify bonds and functional groups. The results confirmed the successful synthesis of the C5 and C8 substituted Quinoline derivatives with EDGs. These findings suggests that the C5 and C8 substituted Quinoline derivatives could be investigated further as low-cost, one-step synthetic alternatives to the conventional anticancer therapies.

Outcomes of the Project:

This project will have several significant outcomes, spanning both the scientific advancements and environmental benefits.

Scientific Outcomes:

- Novel C5 and C8 substituted Quinoline derivatives with Electron donating groups.
- **Structure-Activity Relationship (SAR) Insights:**
  - Comprehensive understanding of the chemical features and molecular structures that enhance the derivatives potency and efficacy.
  - Guidance for the rational design of future development of new derivatives in drug discovery or agrochemical applications.

6. CONCLUSION

In this study, successful synthesis of the novel C5 and C8 substituted Quinoline derivatives with Electron donating groups (EDGs), for its well-documented- DNA intercalation and Topoisomerase inhibition, Kinase inhibition, Apoptosis induction, and Cell cycle arrest mechanisms. The synthesised compounds were thoroughly characterised in terms of their physical and chemical properties, such as their solubility, melting point, and yield %. The results show that the new C5 and C8 substituted Quinoline derivatives have a lot of potential for better anticancer activity. Early tests show that they are safe and effective.

These promising results show that we need to do further research to understand how the C5 and C8 substituted Quinoline derivatives work to fight cancer. This study focused on the synthesis of novel C5 and C8 substituted Quinoline derivatives, based on literature indicating their significant anticancer efficacy.

Subsequent research should concentrate on its function in principle anticancer molecular pathways and its prospective therapeutic implications in cancer or carcinogenesis.

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