Chapter : 4
Synthesis and Characterization of Schiff bases derived from 2-Chloroquinoline-3-carbaldehyde and Its Derivatives

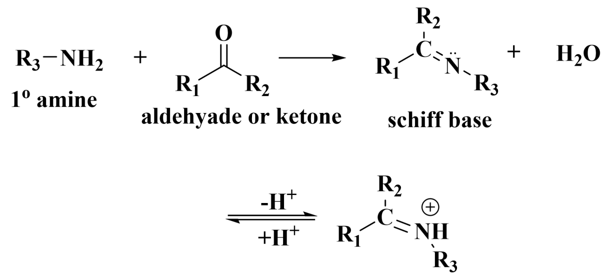
4. Study on Schiff base:

4.1 Introduction:

Schiff bases represent a significant group of compounds synthesized through the condensation reaction involving aromatic aldehydes or ketones and primary amines. This reaction leads to the formation of imine or azomethine moieties, adding to the structural diversity of these compounds. [196] Schiff bases are commonly found in various biological systems, including pyridoxal phosphate enzymes, indicating their widespread presence in nature. [197], [198] The study of Schiff bases in heterocyclic chemistry has proven to be a fruitful and actively researched area for a significant duration. [199], [200] In recent years, numerous studies have highlighted the diverse applications of Schiff bases in the field of biology. These applications encompass a wide range, including their effectiveness as antimicrobial [201], [202] , anticonvulsant [203] antituberculosis [204], anticancer [205], [206], antioxidant [207], anti-inflammatory[208], [209], [210], [211] antianalgesic[212], and anthelmintic[213] agents. Additionally, Schiff bases have been recognized for their catalytic roles in various chemical reactions. The nitrogen atom within the azomethine group can participate in the creation of hydrogen bonds with the active centers of cellular constituents, potentially disrupting normal cellular processes.

Advancements in bio-inorganic chemistry have sparked a growing fascination with Schiff base complexes. This interest stems from the realization that numerous complexes within this category can function as models for biologically significant species, further contributing to the understanding and exploration of their applications.

4.2 General Mechanism of Schiff base:



General scheme for formation of schiff base

A Schiff base is a compound with a specific functional group consisting of a carbon-nitrogen double bond (C=N) that is typically derived from the condensation reaction between a primary amine and a carbonyl compound, such as an aldehyde or a ketone. The general mechanism for the formation of a Schiff base involves a nucleophilic addition-elimination reaction.[214]

the resulting compound is the Schiff base, which contains the characteristic C=N double bond. Schiff bases are important in organic chemistry and biochemistry and are often involved in various reactions and coordination chemistry. They can be further reduced or hydrolyzed to produce a variety of products depending on the specific conditions and reactants involved in the reaction.

4.3 Schiff bases derived from 2-Chloroquinoline-3-Carbaldehyde:

Schiff bases derived from 2-chloroquinoline-3-carbaldehyde represent a class of organic compounds with unique chemical structures and versatile reactivity. [215]The synthesis of these Schiff bases involves the condensation reaction between 2-chloroquinoline-3-carbaldehyde and a primary amine. The resulting compounds are characterized by the presence of a carbon-nitrogen double bond (C=N), forming the core structure of a Schiff base. [216] The distinctive molecular framework of Schiff bases derived from 2-chloroquinoline-3-carbaldehyde makes them of interest in various fields of organic and coordination chemistry and these compounds can serve as valuable intermediates in the synthesis of complex organic molecules and can participate in diverse chemical transformations. The reactivity of Schiff bases allows for the modulation of their properties through appropriate chemical modifications, making them potentially useful in the design of novel materials and bioactive compounds. [217] Additionally, the presence of the quinoline moiety in the starting material introduces aromaticity, further influencing the electronic and structural properties of the resulting Schiff bases.[218]

Schiff bases derived from 2-chloroquinoline-3-carbaldehyde have garnered significant interest, primarily attributed to their potential utility as agents with antimicrobial, anti-malarial, and anti-inflammatory properties. [219], [220], [221] Quinolines represent aromatic compounds characterized by the fusion of a benzene ring with a pyridine heterocyclic system. Also referred to as benzo[b]pyridine and 1-azanaphthalene, quinolines feature one nitrogen atom in one benzene ring and none in the other ring or at the ring junction. Heterocycles containing nitrogen exhibit noteworthy medicinal and pharmaceutical properties, making them of significant interest.[222], [223], [224], [225] Moreover, quinolines serve as the central structural motif in various natural products [226] and pharmaceutical drugs [227], [228] . They are also integral components in numerous synthetic heterocyclic compounds, strategically employed to improve the biological and medicinal attributes of these substances.[229]

For instance, quinolines exhibit a broad spectrum of pharmacological activities, including anti-tuberculosis [230] , antiplasmodial [231] , antimicrobial [232], [233], [234], [235], [236], [237], [238], [239], [240], [241] , antihistamine [242] , antimalarial [243], [244], [245], [246], [247], anti-HIV, anticancer [248], [249], [250], [251] , anti-inflammatory [252], [253], [254], [255], [256], [257], [258] , anti-hypertensive [259] , and antioxidant [260] properties. Furthermore, quinolines find application as tyrosine kinase PDGF-RTK inhibitors [261] , inositol 5'-phosphatase (SH_2) inhibitors [262] , DNA gyrase B inhibitors against Mycobacterium tuberculosis[263], and DNA topoisomerase inhibitors[264].

Montelukast [265] serves as an antiasthma agent. Nadifloxacin [266] , introduced in Japan in 1993, is a racemic fluoroquinolone utilized topically to address acne and infections caused by methicillin-resistant staphylococci. Ozenoxacin [267] , a non-fluorinated quinolone, exhibits broad-spectrum activity against various Gram-positive bacteria, including resistant strains. Ciprofloxacin and Grepafloxacin [268] were acknowledged as highly effective drugs, with IC50 values less than $10mgmL^{-1}$. Sparfloxacin [269] is recognized as the antibiotic standard in antimicrobial tests. Camptothecin[270], an alkaloid extracted from the bark and stem of the Chinese plant

Camptotheca acuminate, is a natural substance known to inhibit the growth of tumor cells. Topotecan[271] has been identified for its anticancer properties.

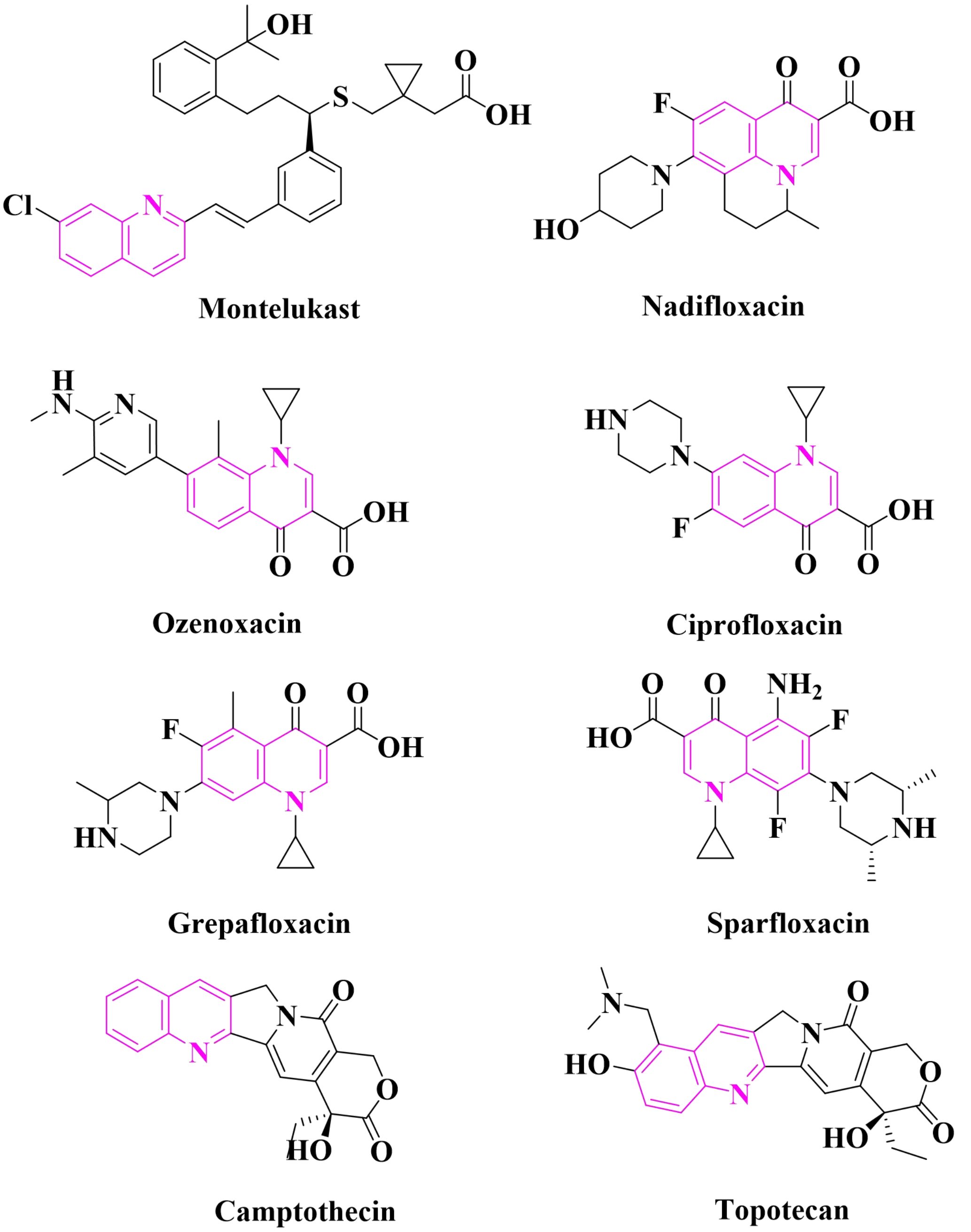


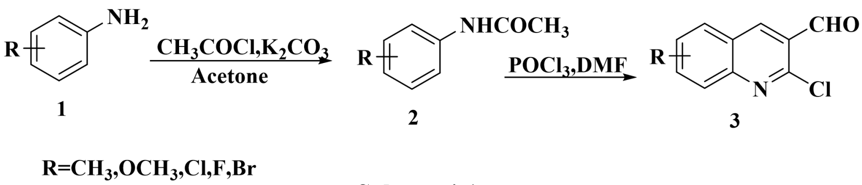
Fig.4.1: Commercially available quinoline based analogues

4.4 Common Procedure for 2-Chloroquinoline-3-Carbaldehydes Schiff base:

The classical Vilsmeier-Haack reaction:

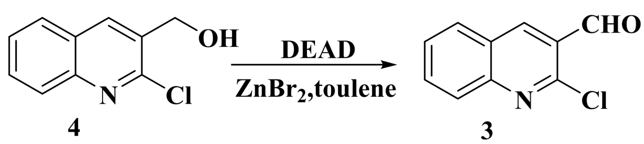
The synthesis of 2-chloroquinoline-3-carbaldehydes **3** is commonly achieved through a method that is both conventional and convenient. This traditional route is widely employed for the efficient production of these compounds**.**[272] Meth-Cohn synthesis of quinolines [273] derivatives 2-Chloroquinoline-3-carbaldehydes **3** were prepared from acetanilide **2** and acetoacetanilide via a Vilsmeier-Haack reaction. The utilization of Vilsmeier reagents in the synthesis of pyridines and condensed pyridines has emerged as a crucial synthetic methodology, particularly in the pharmaceutical sector.[274]This method has gained significance as a valuable tool for creating diverse pyridine-based compounds, addressing the specific needs and demands of the pharmaceutical industry.[275]

Optimal yields in the synthesis of quinolines hinge upon the judicious selection of methods, taking into consideration the specific characteristics of the substituents involved. The choice of a superior method is contingent upon the nature of these substituents, aiming to achieve the highest possible yields in the synthetic process.**(Scheme4.1)**



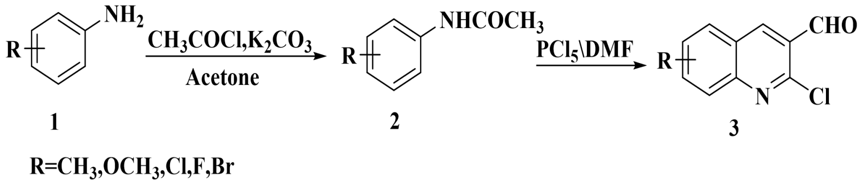
Scheme4.1

Cao et al., [276] reported the process, (2-Chloroquinolin-3-yl)methanol **4** underwent oxidation to form an aldehyde, employing a mixture of diethyldiazene-1,2-dicarboxylate (DEAD) and catalytic $ZnBr_2$ in toluene under reflux conditions to give 2-Chloroquinoline-3-carbaldehydes **3**. **(Scheme4.2)**



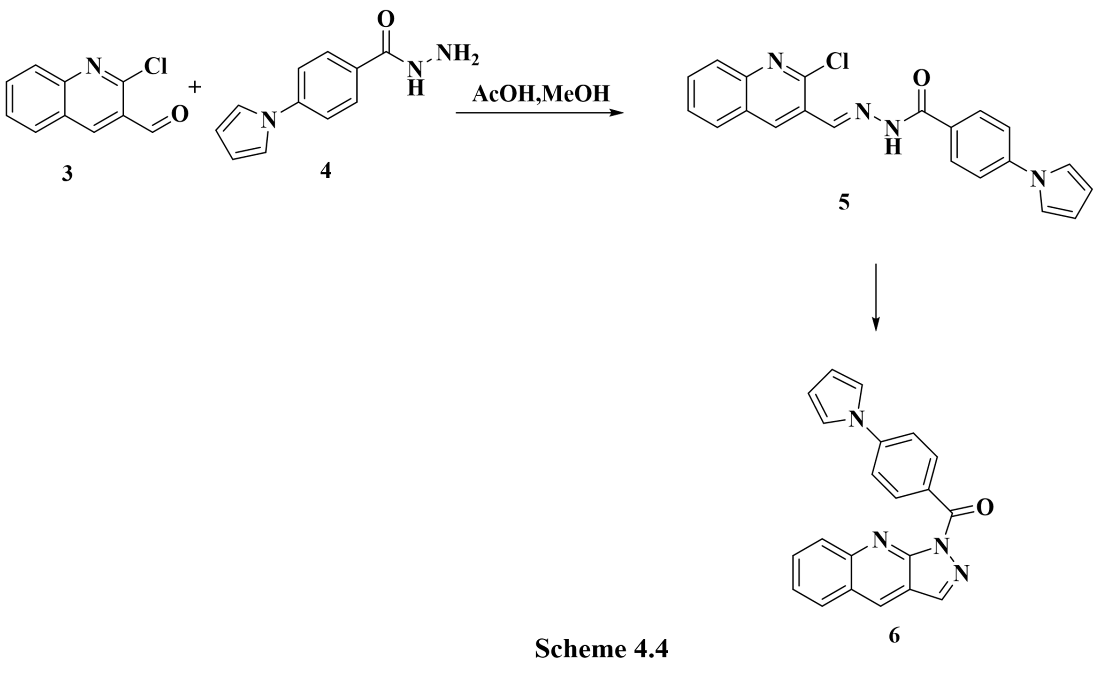
Scheme 4.2

Romero et al., [277] reported another more practical and effective method for producing 2-chloroquinoline-3-carbaldehyde **3** involved treating acetanilides **2** with Vilsmeier's reagent, substituting phosphorus pentachloride as the chlorinating agent instead of phosphoryl chloride. **(Scheme4.3)**



Scheme4.3

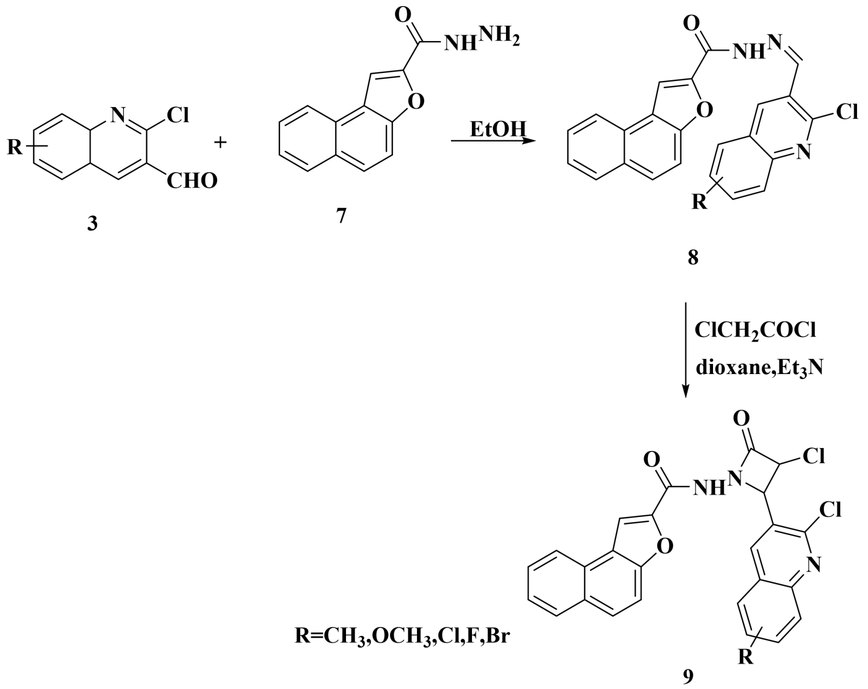
Joshi et al., [278] reported a novel series of (4-(1*H*-Pyrrol-1-yl)phenyl)(1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)methanone derivatives **6** was successfully synthesized through the microwave-assisted reaction of 2-chloroquinoline-3-carbaldehyde **3** with 4-(1*H*-pyrrol-1-yl)benzohydrazide **4**. This process led to the formation of *N*'-((2-chloroquinolin-3-yl)methylene)-4-(1*H*-pyrrol-1-yl)benzohydrazide **5**, followed by intramolecular cyclization. The application of microwave irradiation significantly improved yields, reducing the reaction time. The synthesized compounds **6** demonstrated moderate to good antibacterial and antitubercular activities. **(Scheme4.4)**



Scheme 4.4

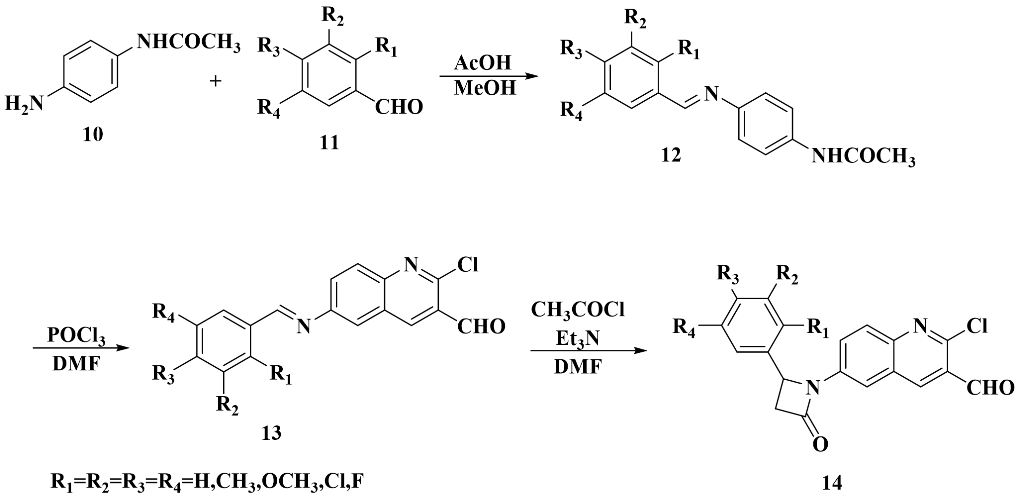
Nagaraja et al., [279] reported synthesis initiated with Naphtho[2,1-*b*]furan-2-carbohydrazide **7** underwent a reaction with substituted 2-chloroquinoline-3-carbaldehyde **3** in absolute ethanol, facilitated by a catalytic amount of acetic acid, resulting in the formation of the *N*'-((2-chloroquinolin-3-yl)methylene)naphtho[2,1-

b]furan-2-carbohydrazide **8**. Subsequent treatment of the hydrazone **7** with chloroacetyl chloride in the presence of triethylamine, conducted in dioxane, yielded substituted *N*-(3-chloro-2-(2-chloroquinolin-3-yl)-4-oxoazetidin-1-yl)naphtho[2,1-*b*]furan-2-carboxamide **9**. The synthesized compounds **9** were evaluated for antibacterial and antifungal activities. **(Scheme4.5)**



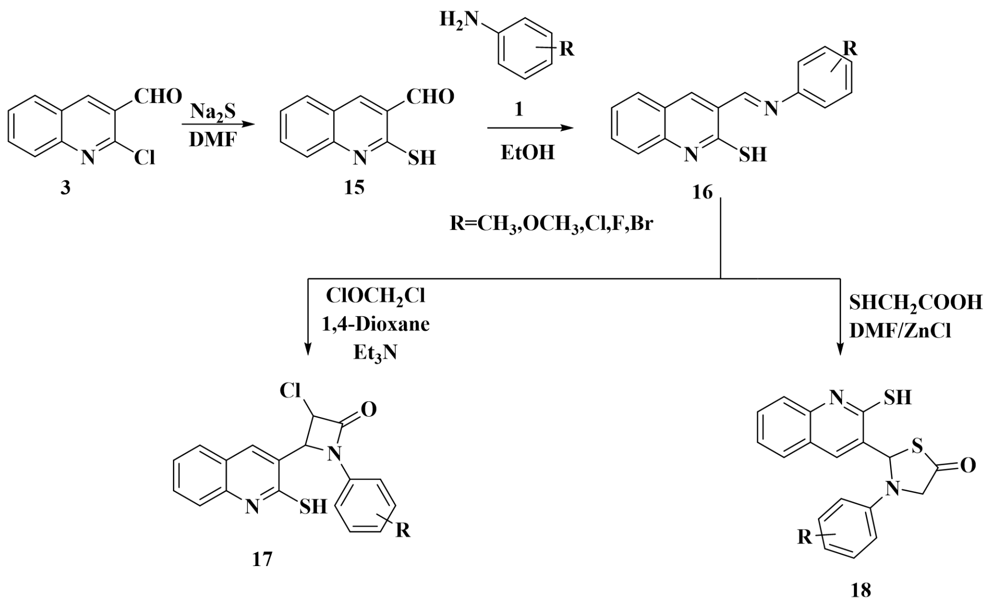
Scheme 4.5

Gaidhane et al.,[280] an investigation into the structural activity led to the synthesis of a series of oxa-azetidin-1-yl quinoline 3-carbaldehyde derivatives **14**, commencing from 4-Amino acetanilide **10**. The condensation of 4-Amino acetanilide **10** with substituted benzaldehyde **11** produced *N*-(4-(4-methoxybenzylideneamino) phenyl) acetamide **12**, which, upon reaction with dimethylformamide in the presence of $POCl_3$, resulted in 6-(4-methoxybenzylideneamino) 2-chloroquinoline-3-carbaldehyde **13**. Subsequent treatment of this Schiff base-derived substituted 2-chloroquinoline-3-carbaldehyde **13** with acetyl chloride and triethylamine in DMF yielded the corresponding 2-chloro-6-(2-(4-methoxyphenyl) 4-oxaazetidin-1-yl) quinoline-3-carbaldehyde **14**. The distinctive chemotherapeutic properties of β–lactam antibiotics continue to captivate the interest of the chemical community. **(Scheme4.6)**



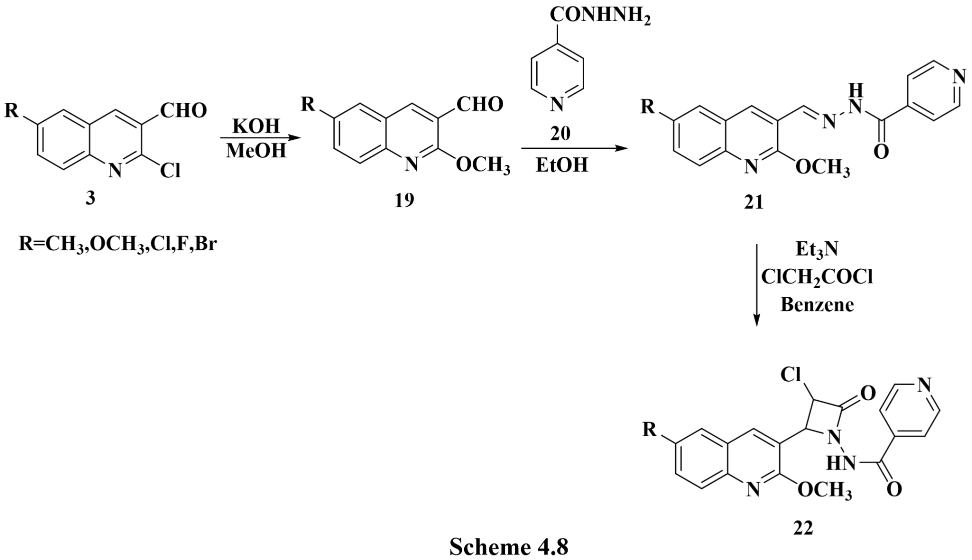
Scheme 4.6

Mistry et al., [281] reported a novel series of azetidinones **17** and thiazolidinone **18** analogs based on quinoline **3** was successfully developed through a straightforward and efficient synthetic methodology. The thione nucleus 2-mercaptoquinoline-3-carbaldehyde **15** was derived from 2-chloroquinoline-3-carbaldehyde **3** by employing sodium sulphite in DMF, followed by reaction with various substituted amines **1** to generate the Schiff base intermediates 3-((phenylimino)methyl)quinoline-2-thiol **16**. The final 3-chloro-4-(2-mercaptoquinolin-3-yl)-1-phenylazetidin-2-one **17** and 2-(2-mercaptoquinolin-3-yl)-3-phenylthiazolidin-5-one derivatives **18** were obtained from these Schiff bases **16** by chloroacetyl chloride and 2-mercaptoacetic acid, respectively. The antibacterial and antifungal activities of the synthesized derivatives **17** and **18** were subsequently assessed.**(Scheme4.7)**



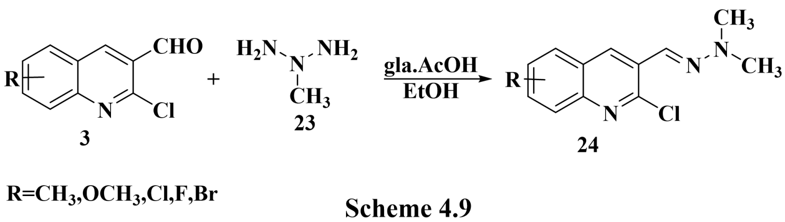
Scheme 4.7

Joshi et al., [282] reported the synthesis of a novel series of quinolinyl Schiff's bases **21** and azetidinones **22**. In the study, substituted 2-chloroquinoline-3-carbaldehyde **3** was reacted with potassium hydroxide in methanol to yield 2-methoxyquinoline-3-carbaldehyde **19**. This compound **19** was then reacted with isoniazid **20** in ethanol, with glacial acetic acid as a catalyst, to produce substituted *N*'-((2-methoxyquinolin-3-yl)methylene)isonicotinohydrazide **21**. The final derivatives, *N*-(3-chloro-2-(2-methoxyquinolin-3-yl)-4-oxoazetidin-1-yl)isonicotinamides **22**, were synthesized by treating intermediate **21** with chloroacetyl chloride in the presence of triethylamine in dry benzene. **(Scheme4.8)**



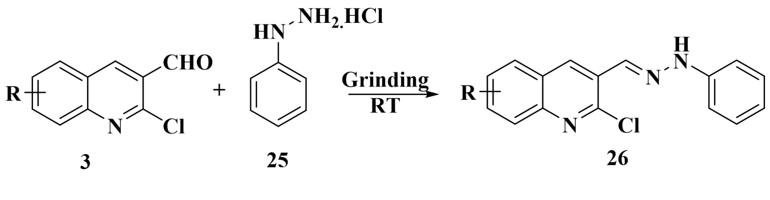
Scheme 4.8

Ghanei et al., [283] reported a novel set of quinoline derivatives was synthesized through a reflux process involving a mixture of substituted 2-chloroquinoline-3-carbaldehydes **3**, 1,1-dimethylhydrazine **23**, and a few drops of glacial acetic acid in ethanol for a duration of 4-5 hours to formed 2-chloro-3-((2,2-dimethylhydrazineylidene)methyl)quinoline derivatives **24**. **(Scheme4.9)**



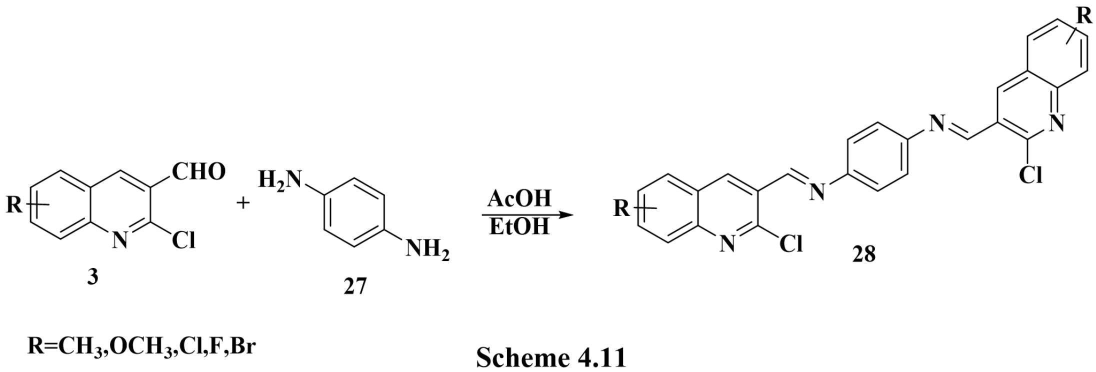
Scheme 4.9

Chandrashekharappa et al., [284] establish mild and environmentally friendly conditions for 2-chloro-3-((2-phenylhydrazineylidene)methyl)quinoline **26** synthesis. Initially, substituted 2-chloroquinoline-3-carbaldehyde **3** and phenylhydrazine hydrochloride **25** were thoroughly ground together in a clean, dry mortar for approximately 15 minutes. compounds **26** were subsequently subjected to DNA cleavage studies. **(Scheme4.10)**



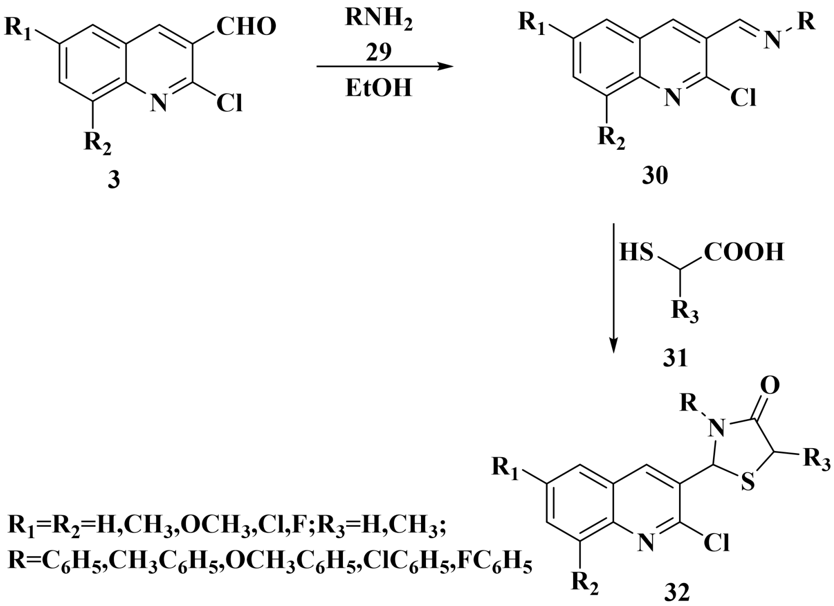
Scheme 4.10

Ghanei et al., [285] reported the synthesis of di Schiff's bases, specifically *N*,*N'*-(1,4-phenylene)bis(1-(2-chloroquinolin-3-yl)methanimine) derivatives **28**, was achieved by reacting 2-chloroquinoline-3-carbaldehyde **3** with benzene-1,4-diamine **27** in ethanol under reflux conditions, using acetic acid as a catalyst.**(Scheme4.11)**



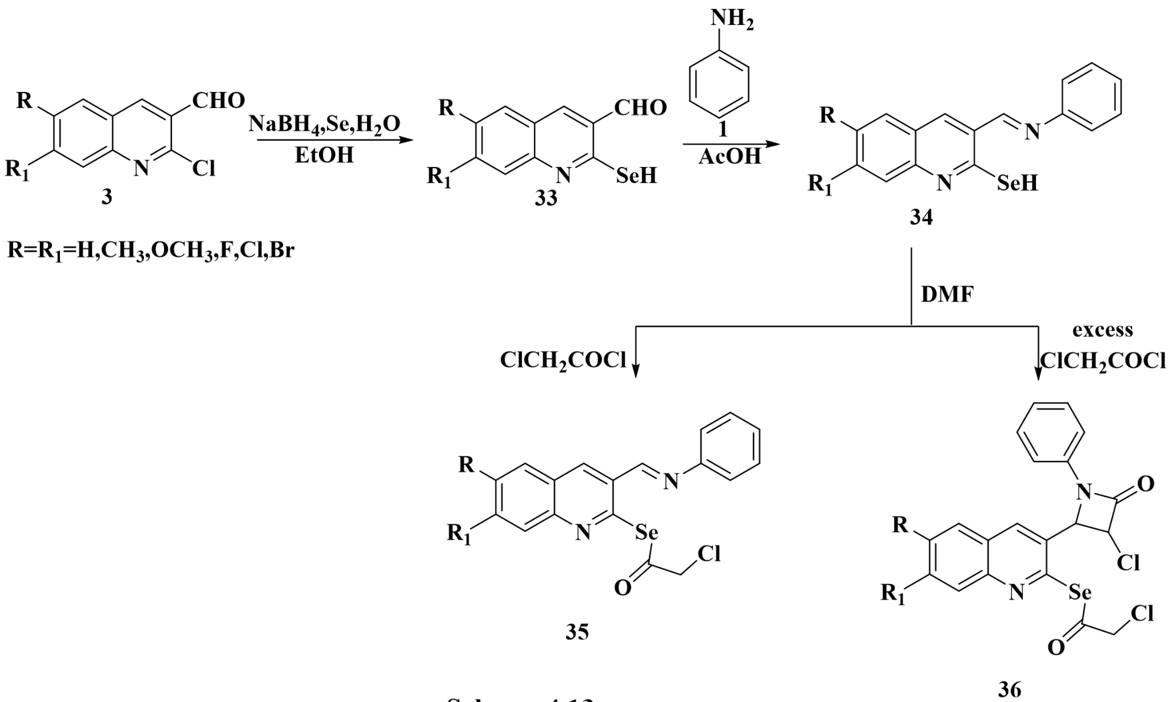
Scheme 4.11

Shelke et al., [286] synthesized compounds **32** were thoroughly evaluated for their interactions with calf thymus DNA using electronic spectra, viscosity measurements, and thermal denaturation studies. Additionally, their antimicrobial activity against various microbes was assessed through screening. Initially, substituted -2-chloroquinoline-3-carbaldehyde **3** reacts with substituted aromatic amines **29** to form Schiff bases of substituted 1-(2-chloroquinolin-3-yl)-*N*-phenylmethanimine **30**. These Schiff bases **30** are then reacted with 2-mercaptopropanoic acid derivatives **31** to produce 2-(2-chloroquinolin-3-yl)-3,5-substituted thiazolidin-4-one derivatives **32**.**(Scheme4.12)**



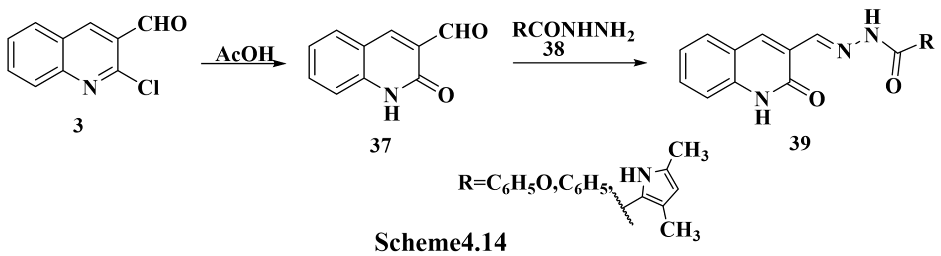
Scheme 4.12

Nandeshwarappa et al.,[287] reported the 2-hydroselenoquinoline-3-carbaldehydes **33** were successfully synthesized in a quantitative yield through the reaction of Substituted 2-chloroquinoline-3-carbaldehyde **3** with sodium hydrogen selenide in ethanol. After this, the 2-hydroselenoquinoline-3-carbaldehydes **33** were subjected to a reaction with aniline **1** in glacial acetic acid, leading to the formation of 3-[(phenylimino)methyl]quinoline-2-selenol **34**. The resulting compound **34** was then refluxed with chloroacetyl chloride in dimethylformamide (DMF), employing both stoichiometric and nonstoichiometric amounts, resulting in the synthesis of 3-[[(phenylimino)methyl]quinolin-2-yl] chloroethaneselenates **35** and [3-(3-chloro-4-oxo-1-phenylazetidin-2-yl)quinolin-2-yl] chloroethaneselenates **36**.**(Scheme4.13)**



Scheme 4.13

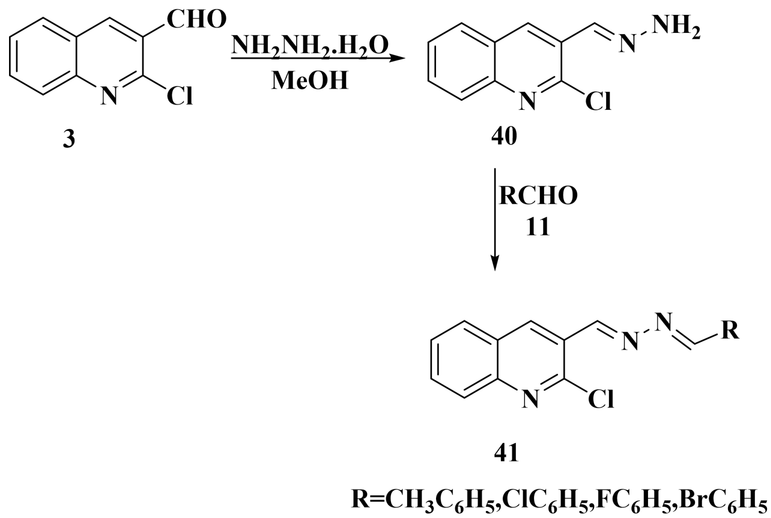
Liu et al., [288] reported synthesis initiated Upon refluxing the Substituted 2-chloroquinoline-3-carbaldehyde **3** in 70% acetic acid, it underwent conversion into 2-oxoquinoline-3-carbaldehyde **37**. After this transformation, compound **37** was subjected to a reaction with substituted hydrazides **38**, leading to the formation of the corresponding schiff bases *N'*-((2-oxo-1,2-dihydroquinolin-3-yl)methylene)substitutedhydrazide derivatives **39**. Crystal structures of compound **39** shows DNA-binding and cytotoxic activities.**(Scheme4.14)**



Scheme4.14

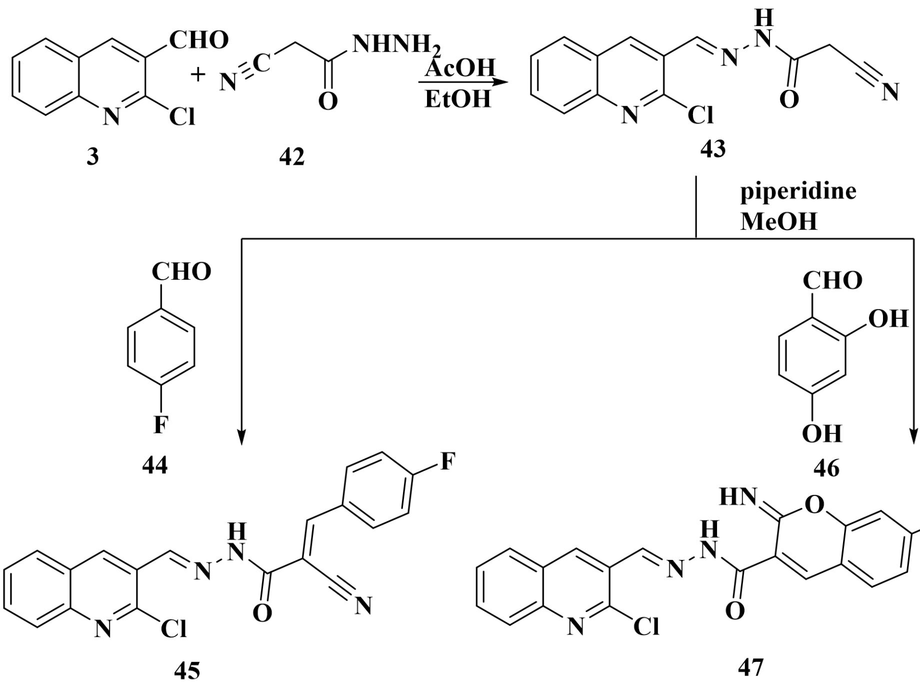
Lamani et al., [289] reported the synthesis of 2-chloro-3-(4-substituted benzylidene)hydrazineylidene)methyl)quinoline derivatives **41** began with the reaction of 2-chloroquinoline-3-carbaldehyde **3** and hydrazine hydrate in methanol, yielding 2-chloro-3-(hydrazineylidenemethyl)quinoline hydrazone **40**. This hydrazone **40** was then further reacted with substituted aldehydes **11**. The resulting derivatives

41 were screened for antibacterial and antifungal activities.**(Scheme4.15)**



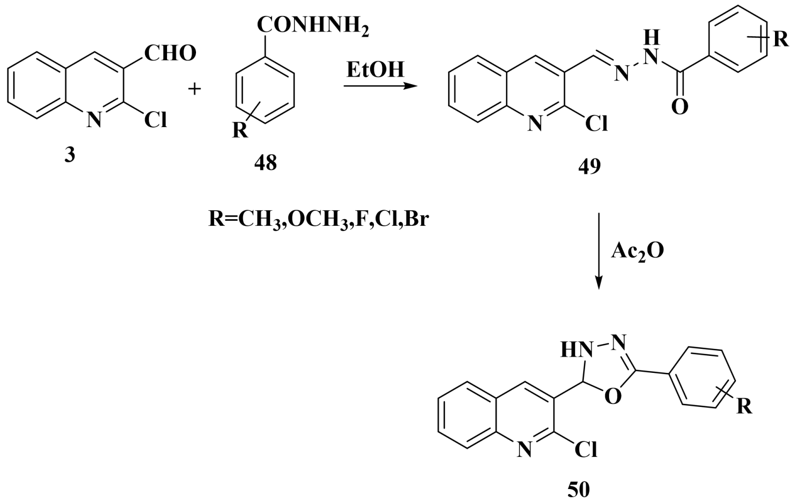
Scheme 4.15

Elsayed Khidre et al., [290] reported the synthesis of *N'*-[(2-chloroquinolin-3-yl)methylene]-2-cyanoacetohydrazide **43** was achieved through the reaction of 2-chloroquinoline-3-carbaldehyde **3** with 2-cyanoacetohydrazide **42** in boiling ethanol, supplemented with a few drops of acetic acid. Condensation of this compound with 4-fluorobenzaldehyde **44** and 2,4-dihydroxybenzaldehyde **46** in methanol, in the presence of a small amount of piperidine yielded *N'*-((2-chloroquinolin-3-yl)methylene)-2-cyano-3-(4-fluorophenyl)acrylohydrazide **45** and *N'*-[(2-chloroquinolin-3-yl)methylene]-7-hydroxy-2-imino-2*H*-chromene-3-carbohydrazide **47**, respectively. The anti-inflammatory and analgesic activities of the synthesized compounds **45** and **47** were subsequently evaluated.**(Scheme4.16)**



Scheme 4.16

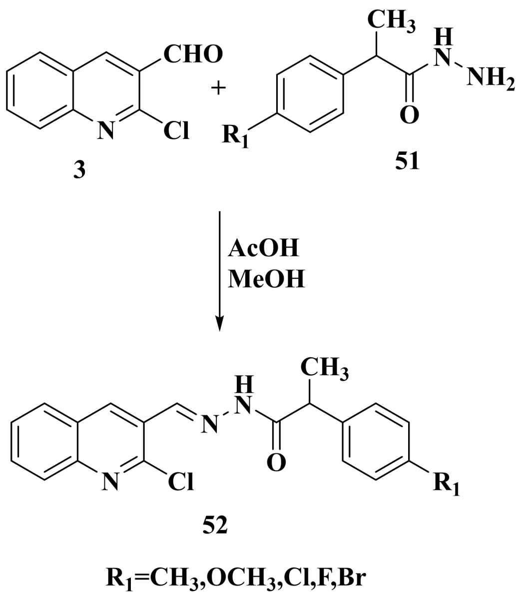
Dubey et al., [291] reported the synthesis of quinoline hydrazones was accomplished by treating the 2-Chloroquinoline-3-carbaldehyde **3** reacts with substituted benzohydrazide **48** to form the Schiff base *N'*-((2-chloroquinolin-3-yl)methylene)-4-substituted benzohydrazide **49**. This Schiff base **49** is then treated with acetic anhydride under reflux conditions to yield 2-(2-chloroquinolin-3-yl)-5-(p-tolyl)-2,3-dihydro-1,3,4-oxadiazole **50**.**(Scheme4.17)**



Scheme 4.17

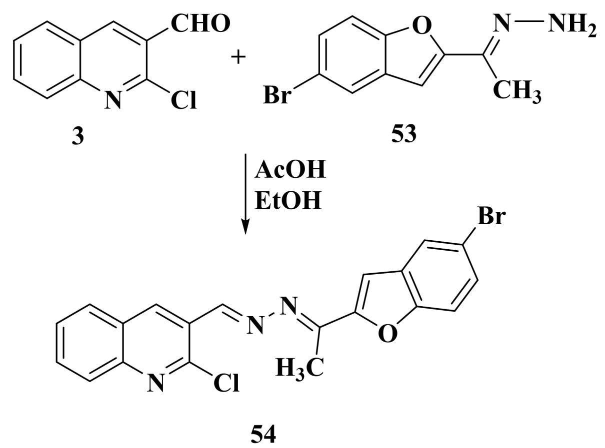
Abdel-Wahab et al., [292] reported the synthesis of *N'*-((2-chloroquinolin-3-

yl)methylene)-2-(substituted)propanehydrazide **52** was carried out, and its anti-inflammatory activity was subsequently evaluated. This compound **52** was obtained through the reaction of 2-Chloroquinoline-3-carbaldehyde **3** reacts with 2-substituted propanehydrazide **51** in ethanol with a few drops of glacial acetic acid to yield *N'*-((2-chloroquinolin-3-yl)methylene)-2-(substituted)propanehydrazide derivatives **52**. **(Scheme4.18)**



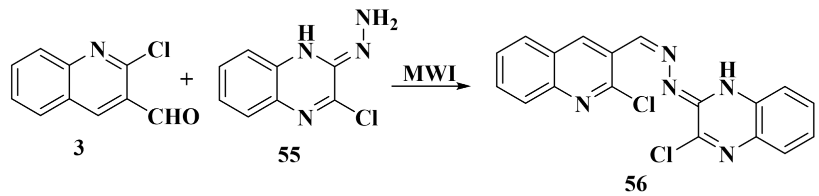
Scheme 4.18

Bhovi et al., [293] reported the corresponding Schiff base 1-(5-bromobenzofuran-2-yl)ethylidene)hydrazineylidene)methyl)-2-chloroquinoline derivatives **54** was synthesized by reacting (1-(5-bromobenzofuran-2-yl)ethylidene)hydrazine **53** with 2-chloroquinoline-3-carbaldehyde **3**. This reaction was conducted in refluxed ethanol with a few drops of acetic acid as a catalyst. The newly synthesized compounds **54** were then screened for antimicrobial activity. **(Scheme4.19)**



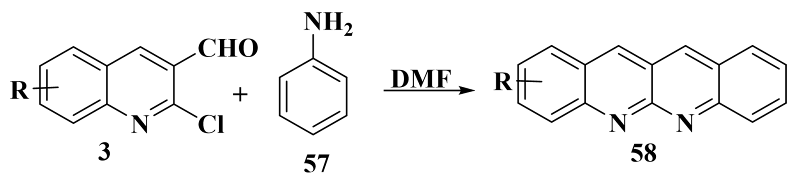
Scheme 4.19

Pramod Kumar et al.,[294] reported the synthesis of 3-chloro-2-((2-chloroquinolin-3-yl)methylene)hydrazono)-1,2-dihydroquinoxaline **56** was accomplished through the reaction of 3-chloro-2-hydrazono-1,2-dihydroquinoxaline **55** with 2-chloroquinoline-3-carbaldehyde **3**. This reaction was conducted under microwave irradiation conditions. **(Scheme4.20)**



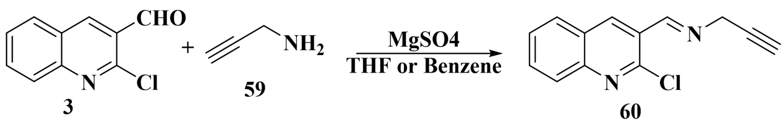
Scheme 4.20

N. Samath Kumar et al., [295] documented series initiated with substituted 2-Chloroquinoline-3-carbaldehyde **3** reacts with aniline **57** in DMF under reflux for 2 hours, resulting in the formation of substituted dibenzo[b,g][1,8]naphthyridine derivative **58**. **(Scheme4.21)**



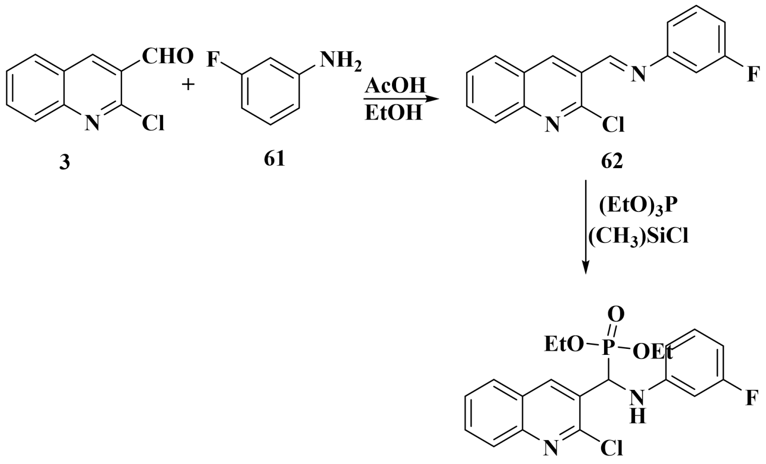
Scheme 4.21

Jia et al., [296] reported *N*-[(2-chloroquinolin-3-yl)methylene]prop-2-yn-1-amine **60** was successfully synthesized with excellent yield through the condensation of 2-Chloroquinoline-3-carbaldehyde **3** with prop-2-yn-1-amine **59**. This reaction was carried out in either benzene or tetrahydrofuran (THF), and magnesium sulphate was employed as a catalyst. **(Scheme4.22)**



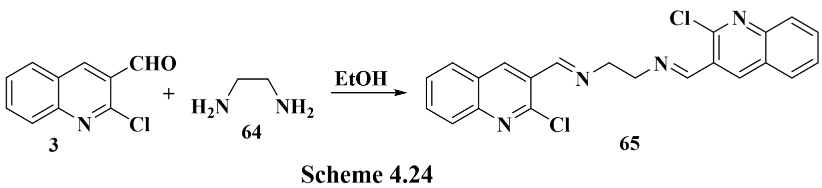
Scheme 4.22

Pokalwar et al., [297] reported series initiated through 2-Chloroquinoline-3-carbaldehyde **3** reacts with 3-fluoroaniline **61** in ethanol with a catalytic amount of acetic acid to produce 1-(2-chloroquinolin-3-yl)-*N*-(3-fluorophenyl)methanimine **62** in excellent yields. This intermediate **62** is then treated with triethylphosphite and acetonitrile under reflux, followed by the addition of TMSCl, resulting in the formation of diethyl ((2-chloroquinolin-3-yl)((3-fluorophenyl)amino)methyl)phosphonate **63**. **(Scheme4.23)**



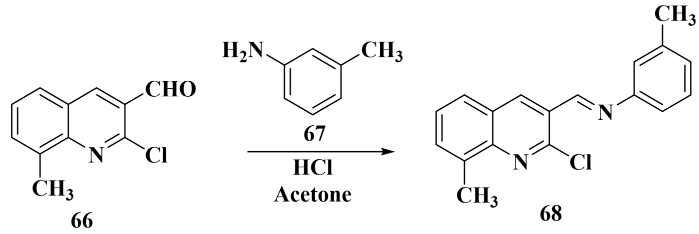
Scheme 4.23

Naik et al.,[298] reported the stereoselective synthesis of N^1,N^2-bis[(2-chloroquinolin-3-yl)methylene]ethane-1,2-diamine **65** was conducted through the reaction of 2-Chloroquinoline-3-carbaldehyde **3** with ethylenediamine **64**. This synthesis occurred in ethanol under reflux conditions. **(Scheme4.24)**



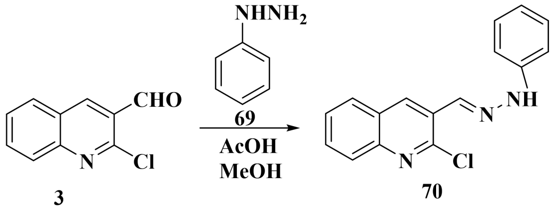
Scheme 4.24

Tekale and As et al., [299-300] reported an efficient and straightforward method for synthesizing 2-chloro-3-formyl-8-methylquinoline **66** has been developed using the Vilsmeier-Haack reagent, achieving high yields with minimal raw material usage and a shortened reaction time. This compound is then reacted with m-toluidine **67** in an acidic medium with acetone as the solvent to produce 1-(2-chloro-8-methylquinolin-3-yl)-*N*-(m-tolyl)methanimine **68**. **(Scheme4.25)**



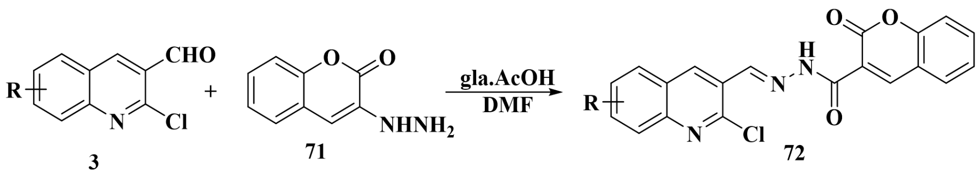
Scheme 4.25

Akhramez et al., [301] reported the synthesis of 2-chloro-3-((2-phenylhydrazineylidene)methyl)quinoline **70** involved the condensation reaction between 2-Chloroquinoline-3-carbaldehyde **3** and phenylhydrazine **69** in presence of methanol and few drops of acetic acid. **(Scheme4.26)**



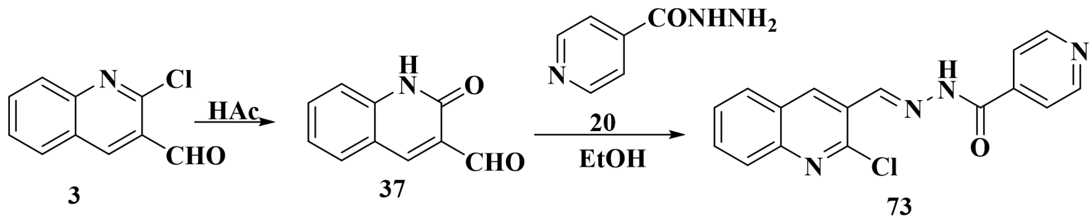
Scheme 4.26

Sheeja et al., [302] reported a novel series of compounds, termed *N'*-((2-chloroquinolin-3-yl)methylene)-2-oxo-2*H*-chromene-3-carbohydrazide **72**, was synthesized by reacting 3-hydrazinyl-2*H*-chromen-2-one **71** with various 2-chloroquinoline-3-carbaldehyde derivatives **3** in the presence of a catalytic amount of glacial acetic acid in *N*,*N*-dimethylformamide. The resulting compounds **72** exhibited antimicrobial activities. **(Scheme4.27)**



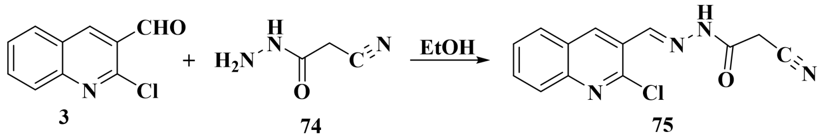
Scheme 4.27

Li et al.,[303] reported the quinolin-2-one derivative **37** was synthesized by refluxing 2-chloroquinoline-3-carbaldehyde **3** in acetic acid. This was followed by condensation with isonicotinohydrazide **20** in ethanol under reflux conditions, leading to the formation of *N*'-((2-chloroquinolin-3-yl)methylene)isonicotinohydrazide **73**. **(Scheme4.28)**



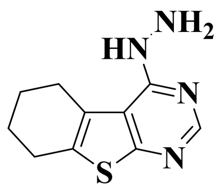
Scheme 4.28

Bondock et al., [304] reported the acetohydrazide derivative **75** was synthesized by condensing 2-chloroquinoline-3-carbaldehyde **3** with 2-cyanoacetohydrazide **74** in ethanol under reflux conditions. The resulting compound was identified as *N*'-((2-chloroquinolin-3-yl)methylene)-2-cyanoacetohydrazide **75**. **(Scheme4.29)**



Scheme 4.29

4.5 Study on 4-hydrazineyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine:



4.6 Introduction:

4-hydrazinyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine holds significant importance in various scientific and pharmaceutical contexts due to its unique structural and chemical properties. Understanding its relevance is crucial for appreciating its potential applications. The compound features a complex heterocyclic scaffold, which is known for its versatility in medicinal chemistry. Such scaffolds often serve as a foundation for designing novel molecules with diverse biological activities.[305]

Compounds with similar structural motifs have demonstrated promising biological activities, including antimicrobial, anti-inflammatory, and anticancer properties.[306], [307], [308] Researchers are exploring derivatives of 4-hydrazinyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine to harness its pharmacological potential. The unique structure of 4-hydrazinyl-5,6,7,8 tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine makes it a valuable building block in medicinal chemistry. [309] Scientists can modify its chemical structure to develop new drug candidates with improved efficacy and reduced side effects. The compound's structural characteristics may make it suitable for use in targeted drug delivery systems and by functionalizing the molecule, researchers can enhance its specificity towards cells or tissues, potentially minimizing off-target effects. [310] The compound's synthesis and study contribute to the broader field of biomedical research. Investigating its interactions with biological systems can provide insights into molecular mechanisms, aiding the development of new therapeutic strategies. [311] The molecular features of 4-hydrazinyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine may serve as a pharmacophore, guiding the design of new molecules with desired biological activities. This can expedite the drug discovery process.[312]

In conclusion, the compound's distinctive structure and potential pharmacological activities make it a valuable entity in the realms of medicinal chemistry and drug development. Researchers are actively exploring its properties to unlock new possibilities for therapeutic interventions.

4.7 Result and Discussion:

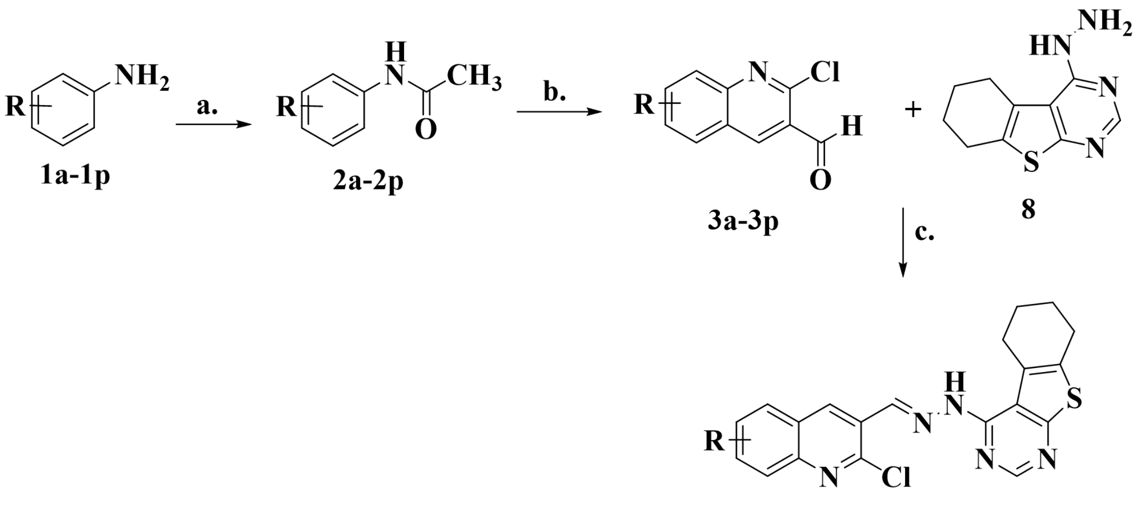
The synthesis of 2-chloroquinoline-3-carbaldehyde (3) was achieved through a two-step procedure starting from aniline (1). The transformation involved an initial acylation step, followed by a Vilsmeier–Haack formylation to introduce the formyl group at the desired position. In a parallel synthetic route, 4-hydrazinyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine (8) was obtained through a sequential four-step process. The initial compound, ethyl-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (5), was synthesized by condensing cyclohexanone (4), ethyl cyanoacetate, and elemental sulfur in methanol under basic conditions. This intermediate (5) was then cyclized with formamide under reflux to yield the pyrimidinone derivative (6), which was subsequently chlorinated using phosphorus oxychloride under anhydrous conditions to give compound (7). Further treatment with hydrazine hydrate afforded the desired hydrazinyl derivative (8), which was finally condensed with various substituted 2-chloroquinoline-3-carbaldehydes (3) to furnish a series of novel Schiff bases, designated as (9a–9p).

The synthesized compounds were thoroughly characterized using a combination of IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry, and elemental analysis to confirm their structures. In the IR spectra, broad bands observed between 3360–3364 cm^{-1} were attributed to N–H stretching vibrations, while the C–H stretching bands appeared in the 3047–3063 cm^{-1} (aromatic) and 2845–2854 cm^{-1} (aliphatic) regions. The characteristic azomethine (C=N) stretching vibration was identified in the region of 1612–1620 cm^{-1}, confirming the formation of Schiff bases. ^{1}H NMR spectra (recorded in DMSO-d^{6} with TMS as internal standard) revealed aliphatic protons of the tetrahydrobenzo ring system in the δ 1.06–3.06 ppm range, typically as singlets, doublets, or multiplets. The aromatic protons of the quinoline and thienopyrimidine rings were observed in the δ 7.29–8.66 ppm region. The azomethine proton (–CH=N–) appeared consistently as a singlet between δ 9.16–9.26 ppm, while the hydrazone N–H proton was detected as a broad singlet near δ 12.00–12.12 ppm, indicative of possible intramolecular hydrogen bonding.

The ^{13}C NMR spectra supported these assignments, displaying aliphatic carbon signals in the δ 17.7–27.0 ppm range, while aromatic and heteroaromatic carbon atoms resonated broadly from δ 106.1 to 158.7 ppm. These chemical shift patterns were consistent across the series and confirmed the incorporation of desired substituents in each derivative. Mass spectrometric data further supported the structural integrity of the synthesized compounds, with observed [M^{+}] peaks corresponding precisely to their calculated molecular weights. Elemental analysis values were in good agreement with theoretical values for carbon, hydrogen, and nitrogen, affirming the purity and composition of each compound.

All final products were isolated as yellow solids with excellent yields ranging from 60% to 95%. The compounds exhibited sharp melting points in the range of 204–243 °C. These findings collectively indicate that the synthetic methodology was highly effective, yielding structurally and analytically well-defined Schiff base derivatives. The comprehensive characterization confirms the success of the synthetic strategy and provides a solid foundation for the potential application of these compounds in further biological or pharmaceutical evaluations.

4.8 Reaction Scheme:



a) K_2CO_3, CH_3COCl, Dry Acetone; b) DMF, $POCl_3$ 80°-90°C; c) MeOH, gla.AcOH, reflux 4-5 hr

4.9 Physical Characterization:

Table 4.1: Characteristics physical data of Schiff base derivatives(9a-9p)

Entry	Compound Code	R	Molecular Formula	Molecular Weight	M.P. In (⁰C)	Yield (%)
1	9a	H	$C_{20}H_{16}ClN_5S$	393.89	204-206	95

2	9b	7-CH_3	$C_{21}H_{18}ClN_5S$	407.92	207-209	90
3	9c	7-OCH_3	$C_{21}H_{18}OClN_5S$	423.92	214-216	62
4	9d	6,8-CH_3	$C_{22}H_{20}ClN_5S$	421.11	212-214	60
5	9e	6-Cl	$C_{20}H_{15}Cl_2N_5S$	428.33	221-223	88
6	9f	7-Cl	$C_{20}H_{15}Cl_2N_5S$	428.33	219-221	71
7	9g	7-F	$C_{20}H_{15}FClN_5S$	411.88	234-236	62
8	9h	7-Br	$C_{20}H_{15}BrClN_5S$	472.79	241-243	78
9	9i	8-OCH_3	$C_{21}H_{18}OClN_5S$	423.92	210-212	67
10	9j	8-CH_3	$C_{21}H_{18}ClN_5S$	407.92	209-211	68
11	9k	6-CH_3	$C_{21}H_{18}ClN_5S$	407.92	198-200	69
12	9l	6-OCH_3	$C_{21}H_{18}OClN_5S$	423.92	201-203	61
13	9m	7-OCH_2CH_3	$C_{22}H_{20}OClN_5S$	437.95	196-198	70
14	9n	6-Cl 7-F	$C_{20}H_{14}Cl_2FN_5S$	446.33	213-215	64
15	9o	7,8-F	$C_{20}H_{14}ClF_2N_5S$	429.87	217-219	63
16	9p	6,7-Cl	$C_{20}H_{14}Cl_3N_5S$	462.78	200-202	72

All compounds are either crystalline or amorphous yellow solid

4.10 Conclusion:

In this study, we successfully synthesized and characterized a series of Schiff bases derived from 2-chloroquinoline-3-carbaldehyde and its derivatives. The synthetic pathway was efficient, resulting in high yields of the target compounds. The condensation reactions between 2-chloroquinoline-3-carbaldehyde and various amine derivatives proceeded smoothly, demonstrating the robustness of the methodology. Comprehensive spectral analysis, including ^{1}H NMR, ^{13}C NMR, and mass spectrometry, confirmed the structural integrity and composition of the synthesized Schiff bases. The characteristic imine (C=N) bond formation was verified, ensuring the successful synthesis of the desired compounds. the incorporation of different substituents on the quinoline ring allowed for the exploration of structural diversity and its impact on the potential pharmacological properties of the Schiff bases. The presence of the chloro and quinoline moieties is anticipated to enhance the biological activity of these compounds.

Overall, the successful synthesis and detailed characterization of these Schiff bases derived from 2-chloroquinoline-3-carbaldehyde and its derivatives underscore their potential as valuable candidates for further studies in medicinal chemistry. Future research should focus on investigating their biological activities and exploring their therapeutic applications to fully realize their potential in drug discovery and development.

4.11 Experimental Section:

4.11.1 Material and Methods:

Commercial-grade solvents and reagents were employed without further purification. The melting points of various substances were determined using open capillary tubes in a melting point apparatus. To assess the purity of the compounds, thin-layer chromatography (TLC) was conducted on silica F254-coated aluminium plates (Merck) as an adsorbent, with visualization under UV light and in an iodine chamber. Solvent evaporation was performed using a rotary evaporator. The Shimadzu Model FTIR-435 recorded infrared (IR) spectra in KBr, measured in cm^{-1}. For nuclear magnetic resonance (NMR) analysis, a Bruker Advance spectrometer at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, using DMSO-d^{6} as the solvent, was utilized. TMS (tetramethylsilane) served as the internal reference standard, with chemical shift values expressed in parts per million (ppm). Mass spectra were acquired using a mass spectrometer.

4.11.2 General Procedures:

General procedure for *N*-phenylacetamide(2a-2p):

Derivative of Aniline **(1a-1p)** (10 mmol) was dissolved in dry acetone, treated with $MgSO_4$ as a drying agent, and stirred for 10-15 minutes. Subsequently, K_2CO_3 (10 mmol) were added, and the entire mixture was stirred for an additional 10 minutes. A solution containing CH_3COCl (10 mmol) in dry acetone was then added dropwise. Following the addition, the reaction mixture was stirred for 30 minutes, Excess acetone was evaporated before the workup. The reaction mixture was poured into 200 ml of ice-cold water in a beaker with continuous stirring. The resulting product was filtered, washed with water, and then dried. The crude acetanilide obtained was subjected to recrystallization using methanol.[313] Yield: 96%

General procedure for 2-chloroquinoline-3-carbaldehyde(3a-3p):

The synthesis of 2-chloroquinoline-3-carbaldehyde from the initial substrate, aniline, involved a two-step process comprising acylation followed by a Vilsmeier-Hack reaction. *N*,*N*-dimethylformamide (DMF) (10 mmol) was cooled to temperatures ranging from 0°-5°C, and Phosphorus oxychloride ($POCl_3$) (10 mmol) was added dropwise with continuous stirring to maintain the temperature within the specified range. Upon complete addition of Phosphorus oxychloride($POCl_3$) in *N*,*N*-dimethylformamide, a white salt formed at room temperature. After 30 minutes, *N*-phenylacetamide **(2a-2p)** (10 mmol) was added portion-wise to the reaction mixture, which was then refluxed at 80-90°C for 15-16 hours. Following completion of the reaction, the mixture was poured into ice-cold water and stirred for 30-40 minutes. The resulting product was filtered and washed with saturated $NaHCO_3$, followed by a thorough water wash to remove excess Phosphorus oxychloride ($POCl_3$), and subsequently dried in an oven. The compounds were purified by recrystallization from either ethyl acetate or acetonitrile.[314] Yield:87%

General procedure for 4-hydrazineyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine 8:

The synthesis of 4-hydrazinyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine **8** has been successfully accomplished in four sequential steps, as documented in the literature.[315], [316], [317], [318], [319], [320]

Step:1

A solution comprising cyclohexanone **(4)** (10 mmol), triethylamine (10 mmol), and ethyl cyanoacetate (10 mmol) dissolved in methanol was prepared and placed in an ice bath. After 5 minutes, elemental Sulphur (10 mmol) was introduced, and the mixture was subjected to sonication at room temperature for 30 minutes. Following this, the reaction mixture was cooled in a fridge for 1 hour, resulting in the formation of a pale-yellow solid. The solid product was then filtered and washed with a cold methanol and water solution. Afterward, the obtained material was dried under vacuum overnight.

Step:2

A suspension was formed by combining ethyl-2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate **(5)** (10 mmol) with formamide (10 mmol), and the mixture was subjected to reflux for 6 hours. Upon cooling to room temperature, the resulting dark solution was transferred to a refrigerator and left overnight. The subsequent formation of dark brown needles was filtered, followed by washing with a cold methanol and water solution. The collected material was then dried under vacuum overnight.

Step:3

A suspension was formed by combining 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one **(6)** (10 mmol) with $POCl_3$ (10 mmol), and the mixture was refluxed for 3 hours. Following cooling to room temperature, excess $POCl_3$ was removed under reduced pressure, and then 300 mL of $CHCl_3$ was added. The resulting homogeneous solution was poured over iced deionized water (500 mL), forming a bilayer mixture. After separation, the aqueous layer was adjusted to pH=8 using NH_4OH and then extracted with $CHCl_3$. The organic fractions were combined and dried over anhydrous $MgSO_4$. Removal of $CHCl_3$ under reduced pressure left a yellow solid, which was re-dissolved in hot MeOH. The solution was allowed to cool to room temperature and placed in a fridge overnight. The resulting precipitated white crystals were filtered, washed with a cold methanol and water solution, and dried overnight under vacuum.

Step:4

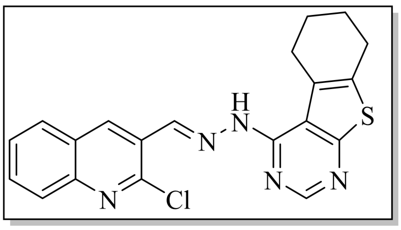
A suspension was created by combining 4-chloro-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine **(7)** (10 mmol) with MeOH (400 mL) and 80% hydrazine hydrate (10 mmol), and the mixture was refluxed for 1 hour. Subsequently, hydrazine was added to complete the reaction, and the mixture was allowed to reflux for an additional 1 hour. After cooling to room temperature, the reaction mixture was placed in a fridge overnight. The resulting yellow precipitate was then filtered and washed with a cold solution comprising 40% methanol in H_2O and dried it over to yield 4-hydrazinyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine **(8)** as off solid.

General procedure for Novel 4-(2-((2-chloroquinolin-3-yl)methylene)hydrazineyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine(9a-9p):

2-chloroquinoline-3-carbaldehyde (**3**, 1 gm, 0.005 mol, 1 eq) and 4-hydrazinyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine (**8**, 1.15 gm, 0.005 mol, 1 eq) was dissolved in MeOH with two to three drops of glacial acetic acid added. After then, the reaction mixture was treated to reflux for a duration of 3-6 hours to keep an eye on the progress of the reaction, thin-layer chromatography (TLC) was employed using a solvent mixture of ethyl acetate and hexane in a 2:1 ratio. Following completion, The resulting precipitate was filtered, purified with methanol and subsequently purified by recrystallization using an ethyl acetate solvent. This purification process yielded novel Schiff bases**(9a-9p)** in the form of yellow solids. All compounds **(9a-9p)** synthesised in similar manner and characteristic physical data are shown in Table:1

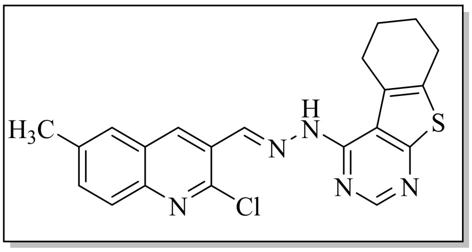
4.11.3 Spectral Characterization:

4-(2-((2-chloroquinolin-3-yl)methylene)hydrazineyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine(9a):



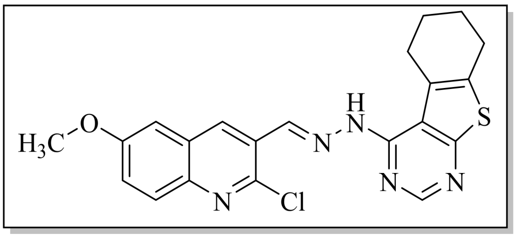
Yellow color; Yield: 95%; M.P.:204-206 ºC; IR(KBr,υ_{max},cm^{-1}): 3356, 3055, 2854, 1620, 1450, 740; ^{1}H NMR (400 MHz, DMSO-d^6) δ 1.77 (s, 4H), 2.72 (s, 2H), 2.97 (s, 2H), 7.68 (s, 1H), 7.82 (s, 1H), 7.89 – 7.94 (m, 2H), 8.01 (s, 1H), 8.62 (s, 1H), 9.26 (s, 1H), 12.07 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d^6)δ= 22.45, 22.82, 25.19, 27.01, 119.28, 127.44, 128.32, 128.86, 131.33, 147.42. Mass(*m/z*)=394.3(M^+). Anal. Calcd. For $C_{20}H_{16}ClN_5S$: C, 60.99; H, 4.09; N, 17.78; found: C, 60.93; H, 4.03; N, 17.75.

4-(2-((2-chloro-6-methylquinolin-3-yl)methylene)hydrazineyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine(9b):



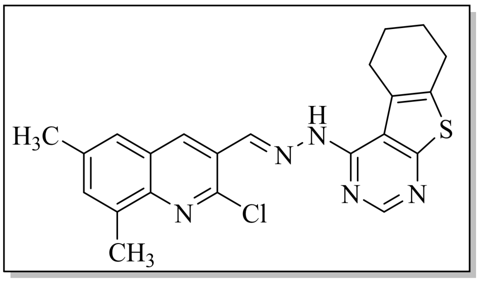
Yellow color; Yield: 90%; M.P.:207-209 °C; Mass(*m/z*)=408.2(M^+). Anal. Calcd. For $C_{21}H_{18}ClN_5S$: C, 61.83; H, 4.45; N, 17.17; found: C, 61.63; H, 4.09; N, 17.12.

4-(2-((2-chloro-6-methoxyquinolin-3-yl)methylene)hydrazineyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine(9c):



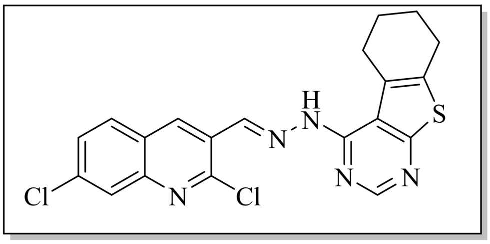
Yellow color; Yield: 62%; M.P.: 214-216 °C; IR(KBr,υ_{max},cm^{-1}): 3363, 3047, 2854, 1620, 1450, 1049, 740; ^{1}H NMR (400 MHz, DMSO-d^6) δ 1.77 (s, 4H), 2.74 (d, *J* = 5.0 Hz, 2H), 2.98 (d, *J* = 6.0 Hz, 2H), 3.93 (s, 3H), 7.29 (d, *J* = 2.9 Hz, 1H), 7.44 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.84 (d, *J* = 9.2 Hz, 1H), 7.90 (d, *J* = 3.4 Hz, 1H), 8.61 (s, 1H), 9.16 (s, 1H), 12.04 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d^6)δ= 22.45, 22.82, 25.17, 26.98, 56.09, 106.19, 119.27, 127.54, 124.31, 128.58, 128.76, 131.31, 133.24, 135.26, 143.49, 144.19, 146.61, 147.36, 150.63, 158.46, 158.74. Mass(*m/z*)=424.2(M^+). Anal. Calcd. For $C_{21}H_{18}ClN_5OS$: C, 59.50; H, 4.28; N, 16.52; found: C, 59.48; H, 4.25; N, 16.50.

4-(2-((2-chloro-6,8-dimethylquinolin-3-yl)methylene)hydrazineyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine(9d):



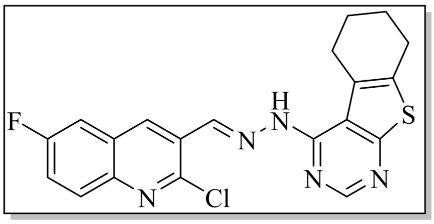
Yellow color; Yield: 60%; M.P.: 212-214 °C; IR(KBr,υ_{max},cm^{-1}): 3363.88, 3047.63, 2854.74, 1620, 1450, 1049, 740; ^{1}H NMR (400 MHz, DMSO-d^6) δ 1.06 (t, J = 7.0 Hz, 3H), 1.80 (s, 4H), 2.63 (d, J = 4.2 Hz, 3H), 2.76 (d, J = 7.1 Hz, 2H), 3.39 – 3.48 (m, 2H), 7.55 (s, 1H), 7.62 (s, 1H), 7.91 (d, J = 3.5 Hz, 1H), 8.66 (s, 1H), 9.18 (s, 1H), 12.12 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d^6) δ= 17.72,19.04,21.66,56.49. Mass(*m/z*)=422.3(M$^+$). Anal. Calcd. For $C_{22}H_{20}ClN_5S$: C, 62.62; H, 4.78; N, 16.60; found: C, 62.60; H, 4.74; N, 16.58.

4-(2-((2,7-dichloroquinolin-3-yl)methylene)hydrazineyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine(9e):



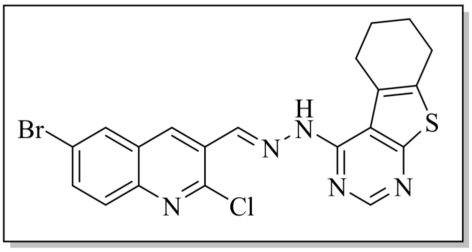
Yellow color; Yield: 88%; M.P.: 221-223 °C; IR(KBr,υ_{max},cm^{-1}): 3363.97, 3047.63, 2847.03, 1612, 1442, 702; ^{1}H NMR (400 MHz, DMSO-d^6) δ 1.77 (s, 4H), 2.72 (s, 2H), 2.91 (s, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.89 (s, 1H), 7.96 (s, 2H), 8.55 (s, 1H), 9.23 (s, 1H), 12.03 (s, 1H); Mass(*m/z*):428.5(M$^+$). Anal. Calcd. For $C_{20}H_{15}Cl_2N_5S$: C, 56.08; H, 3.53; N, 16.35; found: C, 56.03; H, 3.50; N, 16.31.

4-(2-((2-chloro-6-fluroquinolin-3-yl)methylene)hydrazineyl-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine(9g):



Yellow color; Yield: 62%; M.P.: 234-236 °C; IR(KBr,υ_{max},cm^{-1}): 3363.97, 3063.06, 2847.03, 1612, 1442, 725; Mass(*m/z*):412.2(M^{+}). Anal. Calcd. For $C_{20}H_{15}ClFN_5S$: C, 58.32; H, 3.67; N, 17.00; found: C, 58.30; H, 3.64; N, 17.00.

4-(2-((6-bromo-2-chloroquinolin-3-yl)methylene)hydrazineyl)-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine(9h):



Yellow color; Yield: 78%; M.P.:241-243 °C; Mass(*m/z*)=474.2(M^{+}). Anal. Calcd. For $C_{21}H_{18}ClN_5S$: C, 50.81; H, 3.20; N, 14.81; found: C, 50.63; H, 3.16; N, 14.72.

4.11.4 Representative Spectra:

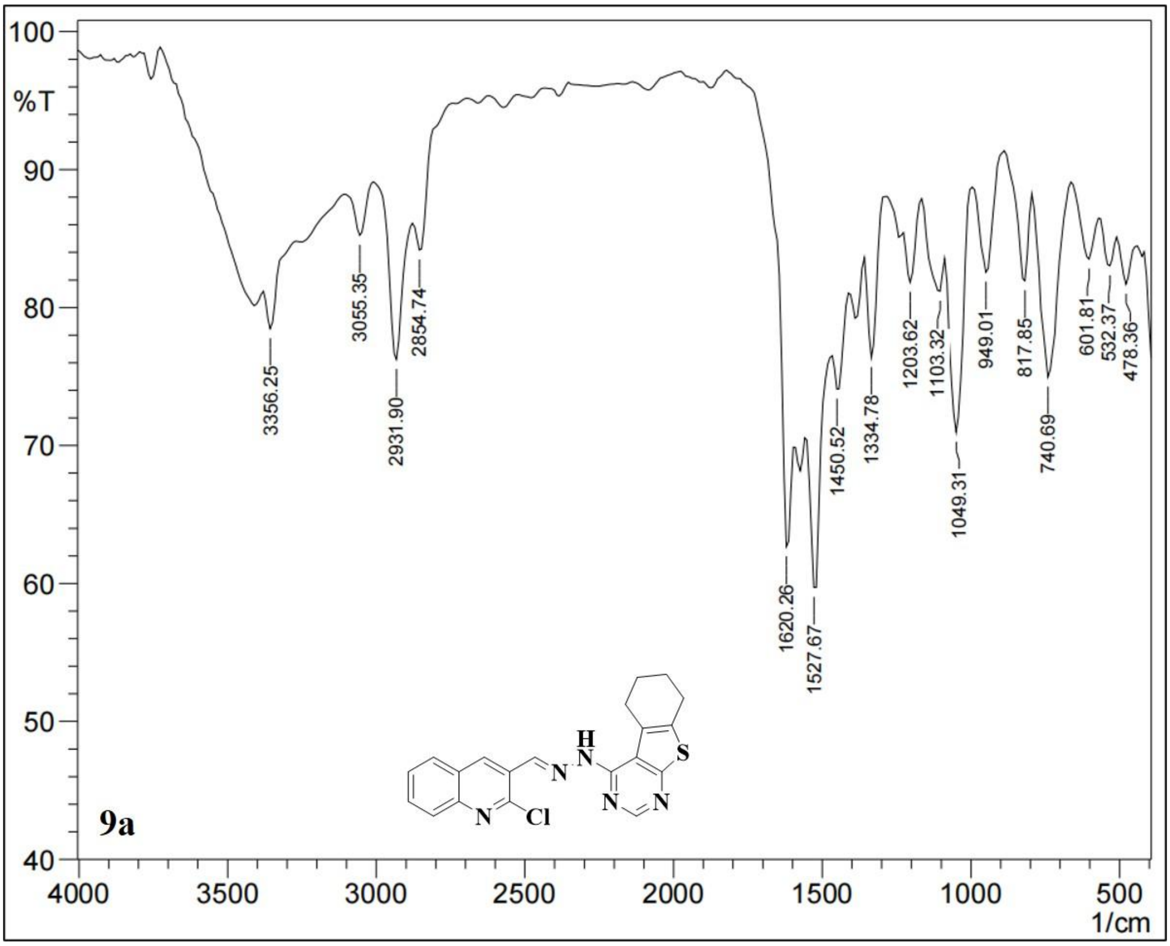


Fig.4.2: Representative IR spectrum of compound 9a

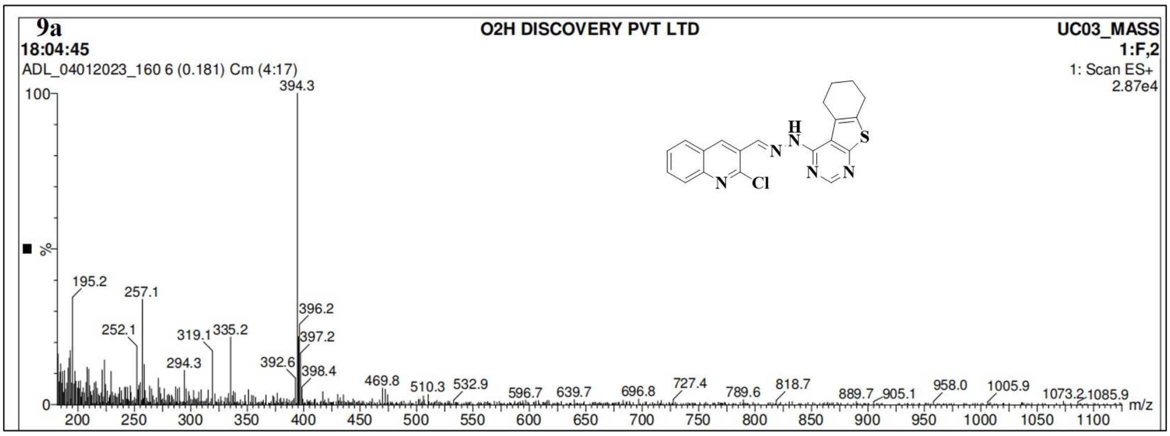


Fig.4.3: Representative mass spectrum of compound 9a

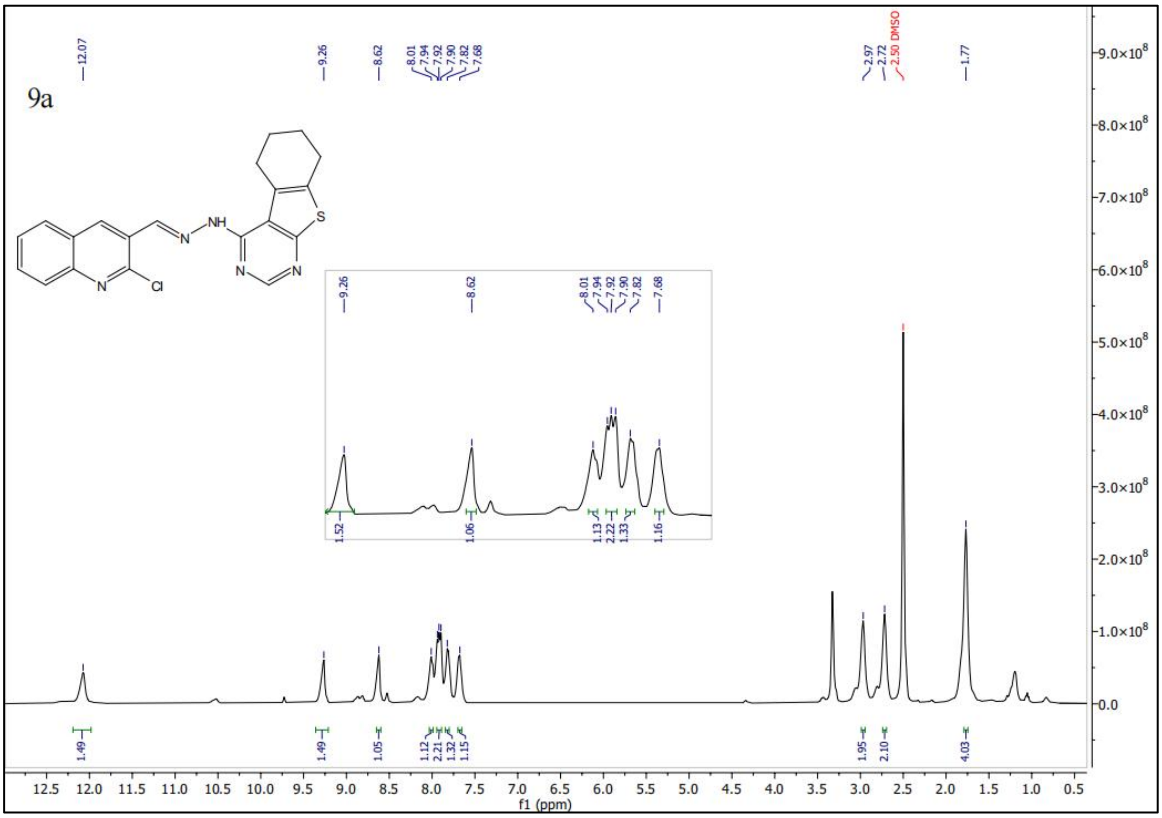


Fig.4.4: Representative ^{1}H NMR spectrum of compound 9a

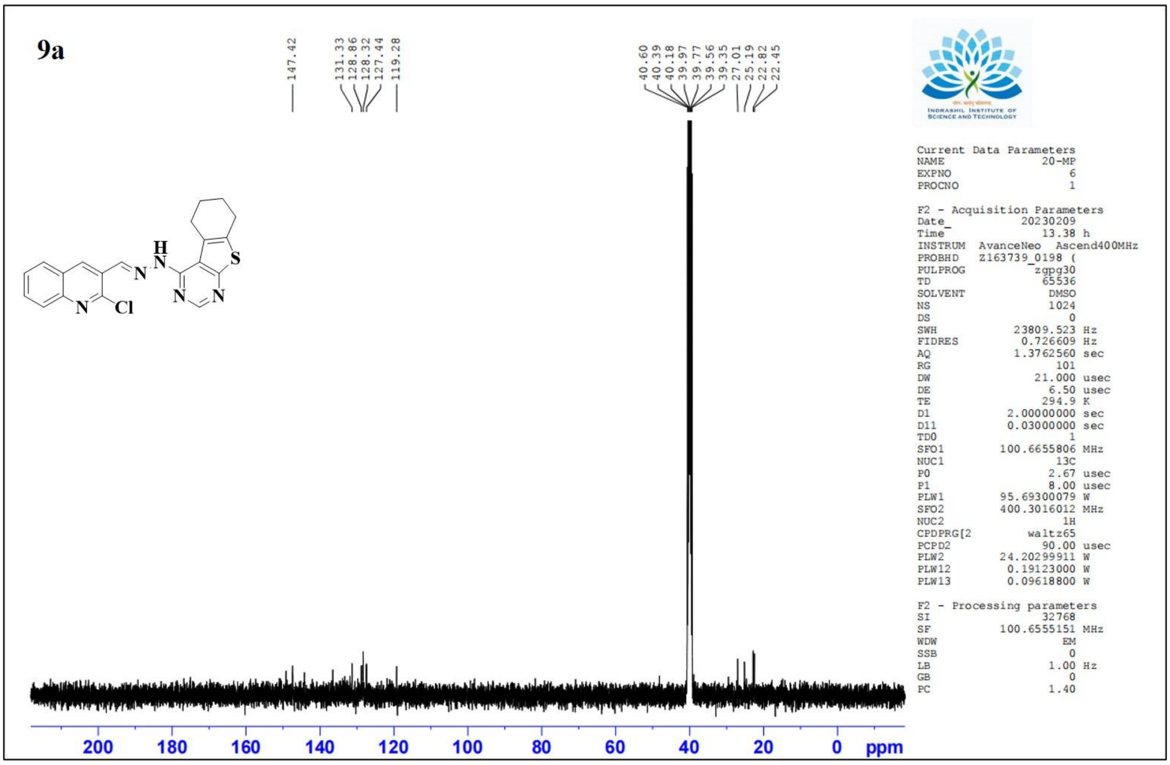


Fig4.5: Representative ^{13}C NMR spectrum of compound 9a

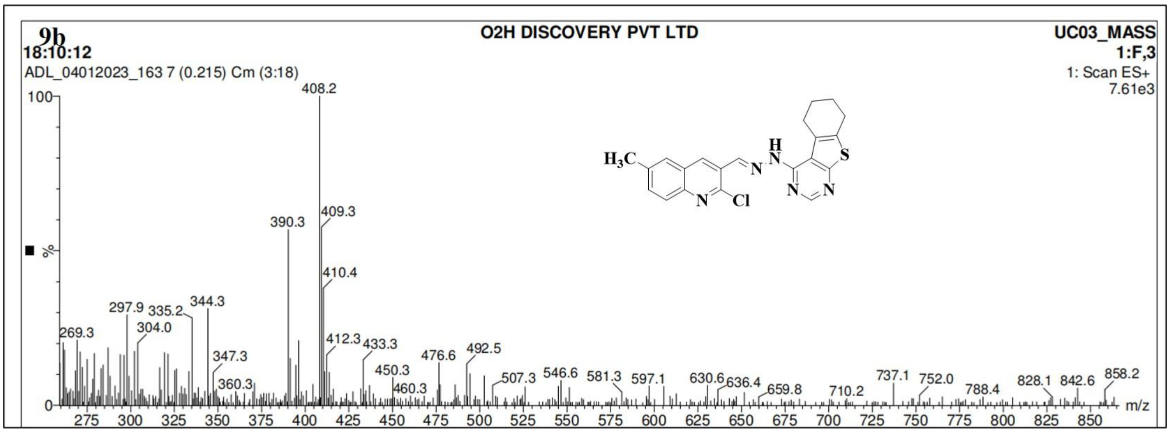


Fig.4.6: Representative mass spectrum of compound 9b

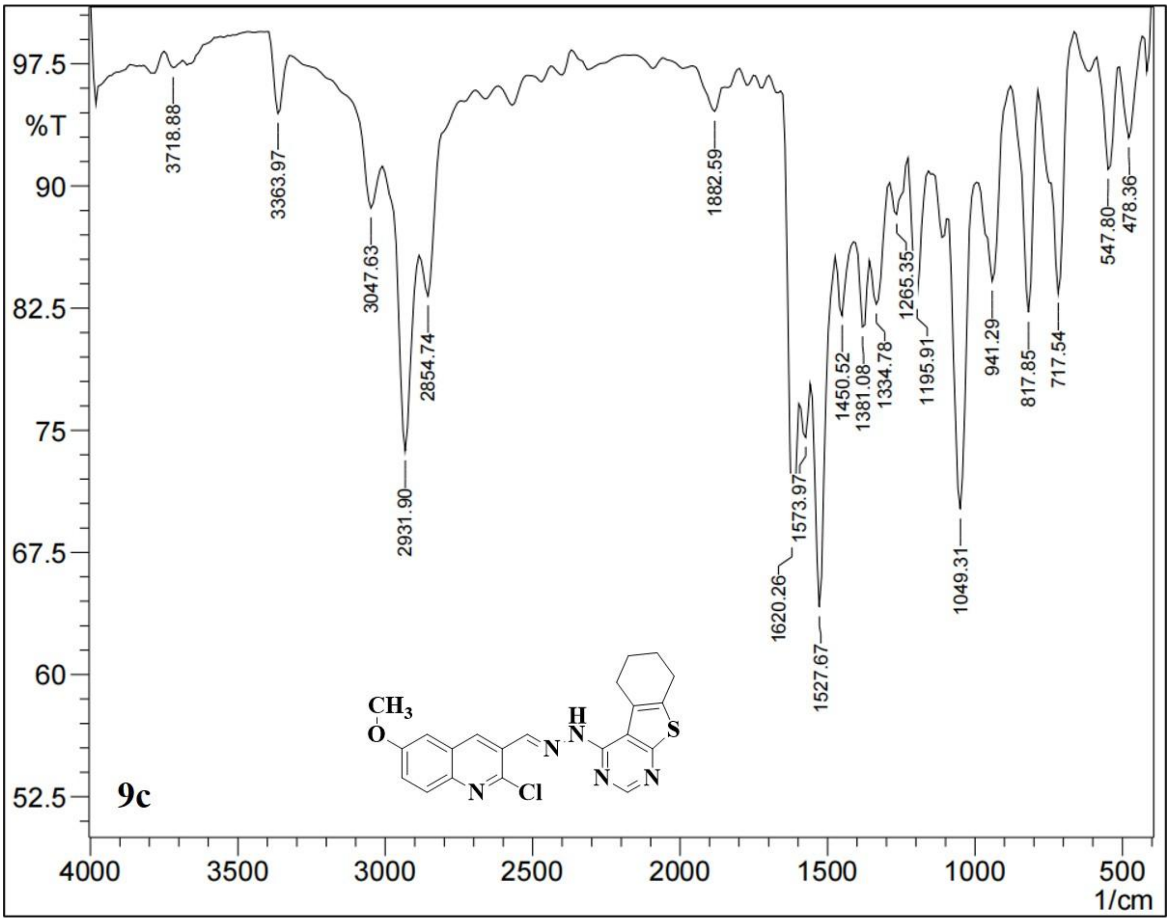


Fig.4.7: Representative IR spectrum of compound 9c

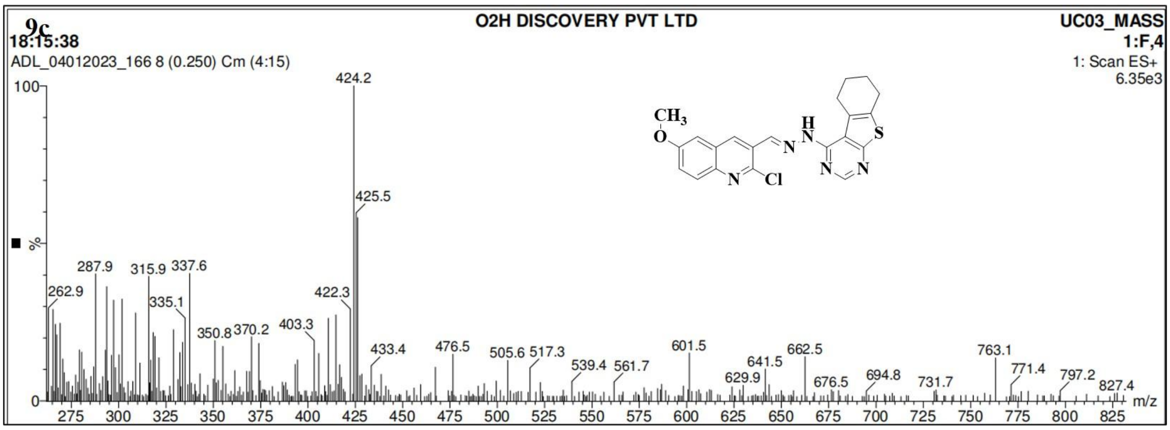


Fig.4.8: Representative mass spectrum of compound 9c

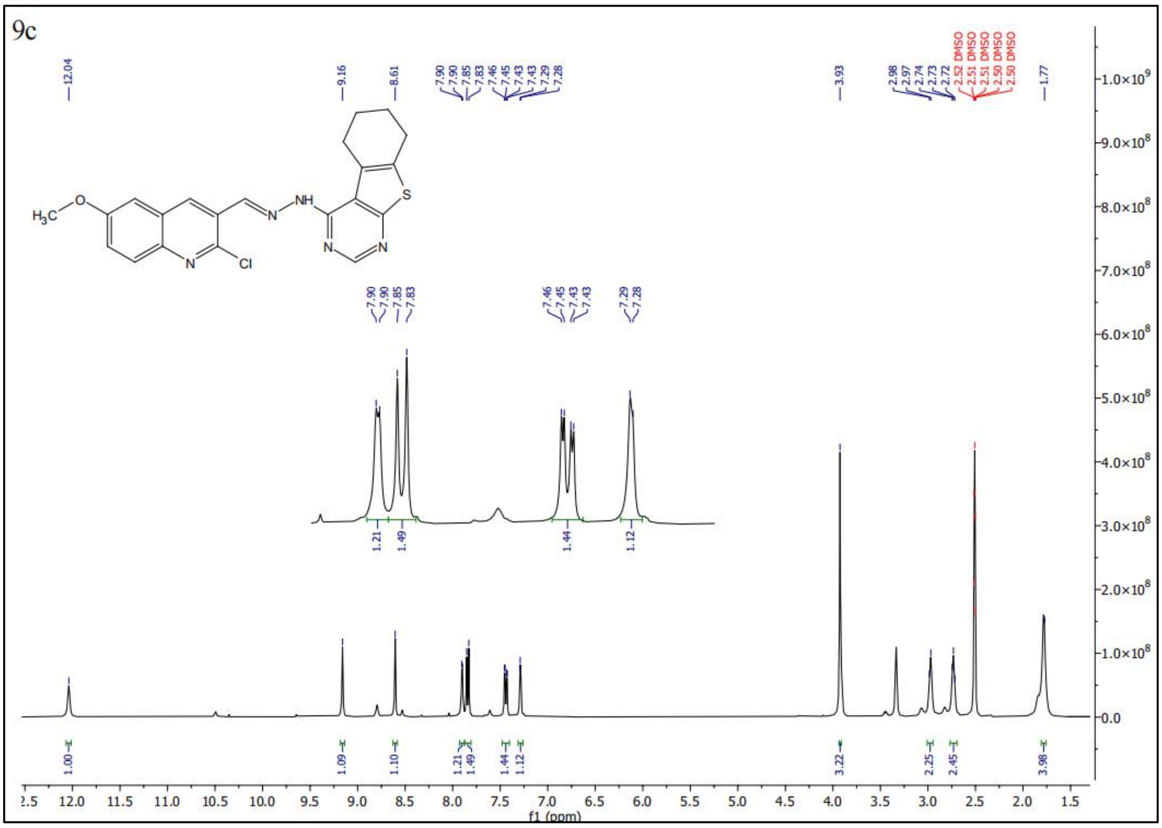


Fig.4.9: Representative ^{1}H NMR spectrum of compound 9c

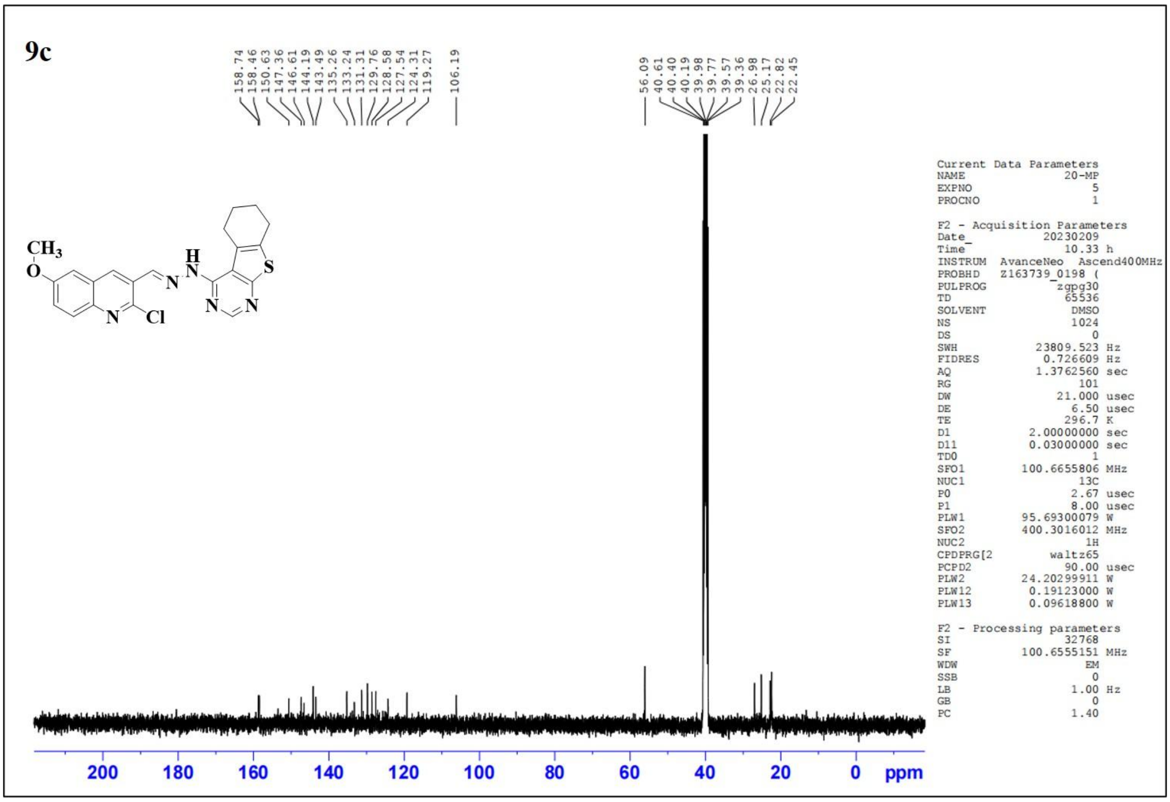


Fig.4.10: Representative ^{13}C NMR spectrum of compound 9c

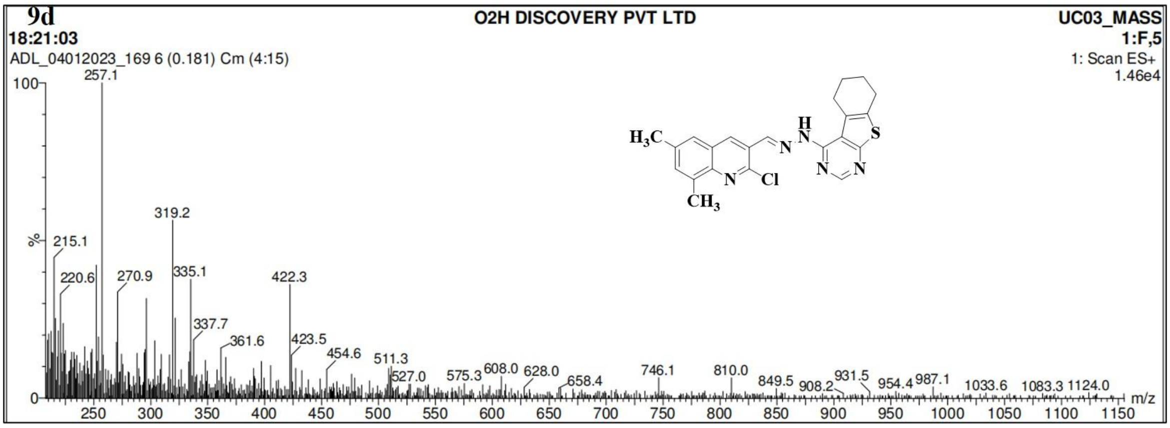


Fig.4.11: Representative mass spectrum of compound 9d

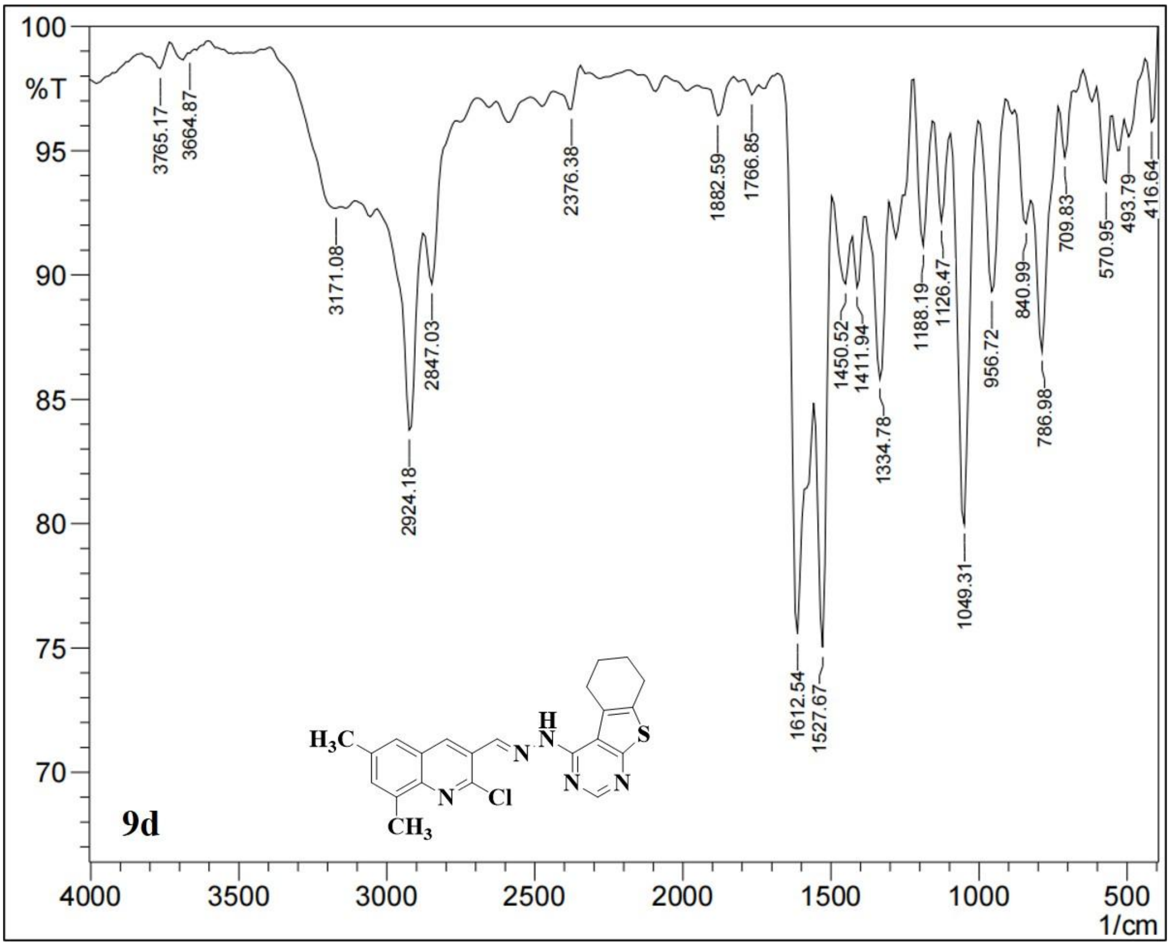


Fig.4.12: Representative IR spectrum of compound 9d

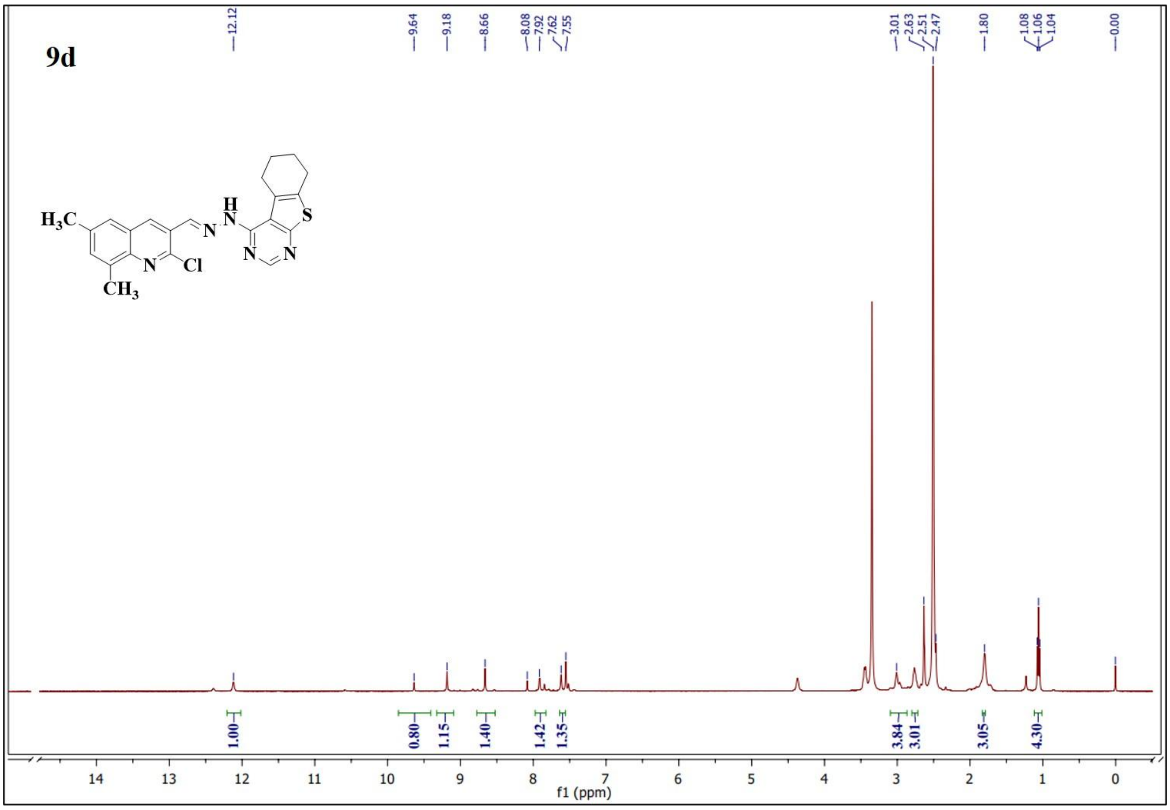


Fig.4.13: Representative [1]H NMR spectrum of compound 9d

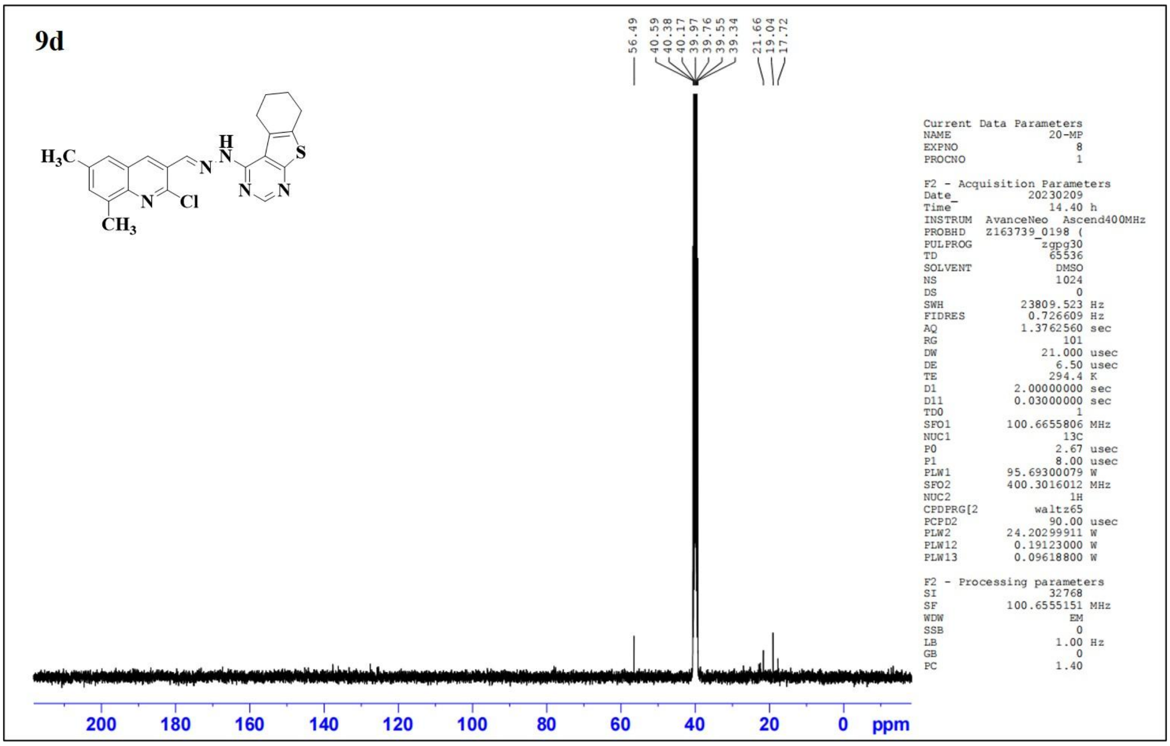


Fig.4.14: Representative [13]C NMR spectrum of compound 9d

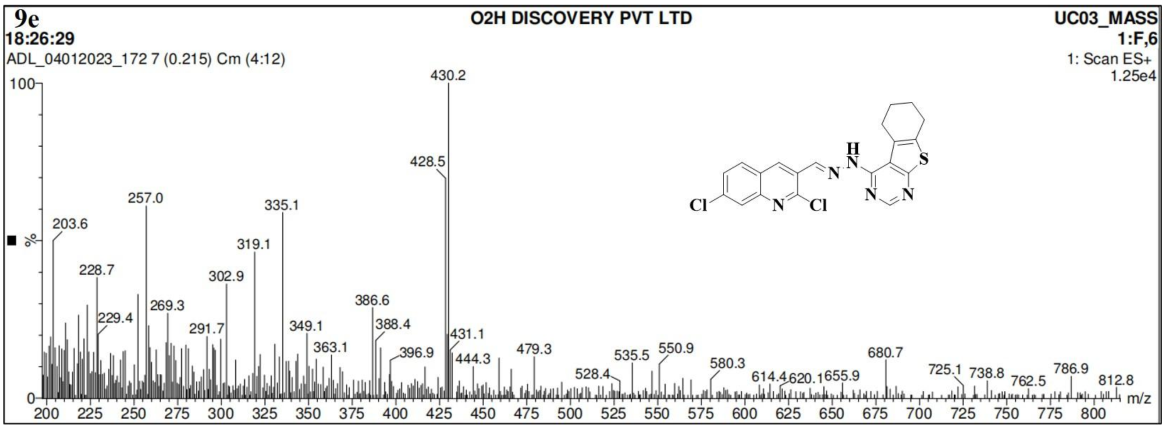


Fig.4.15: Representative mass spectrum of compound 9e

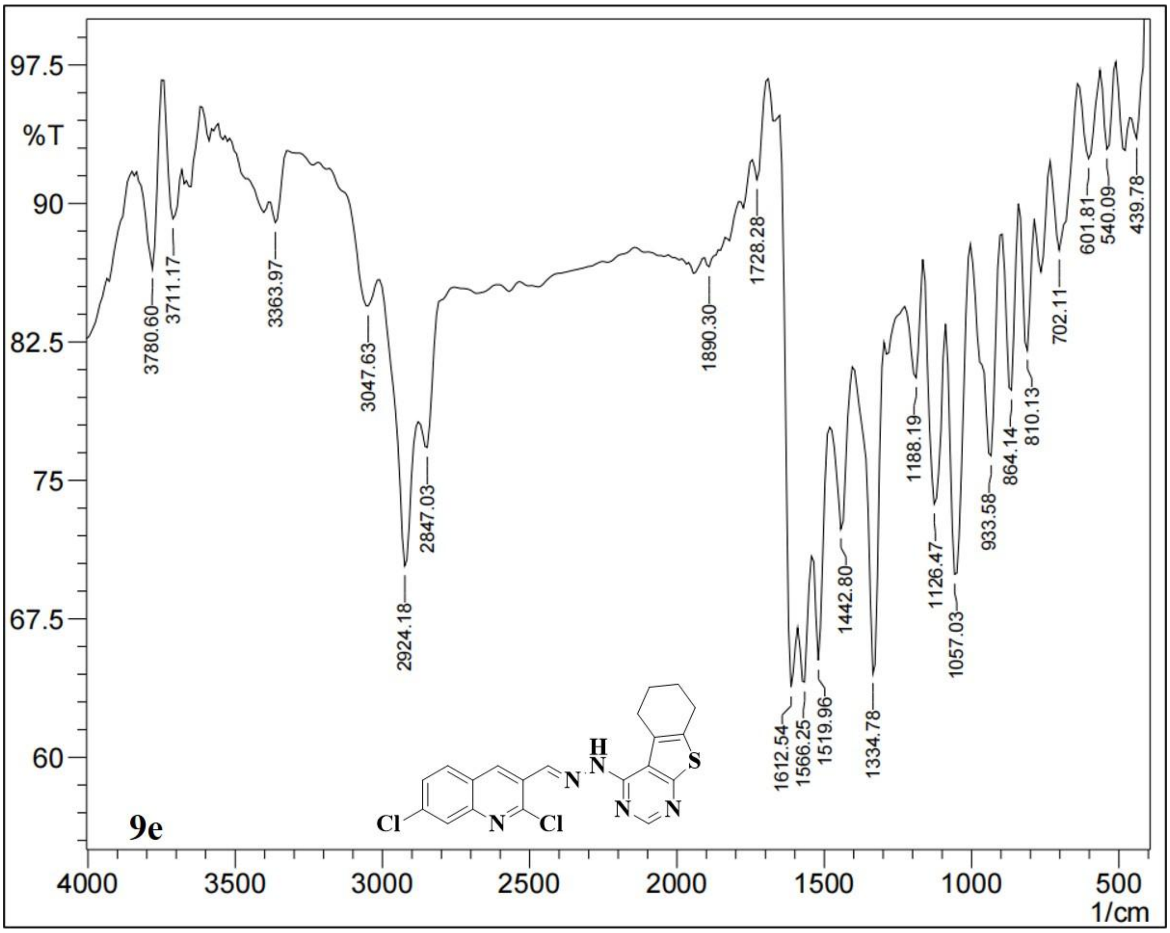


Fig.4.16: Representative IR spectrum of compound 9e

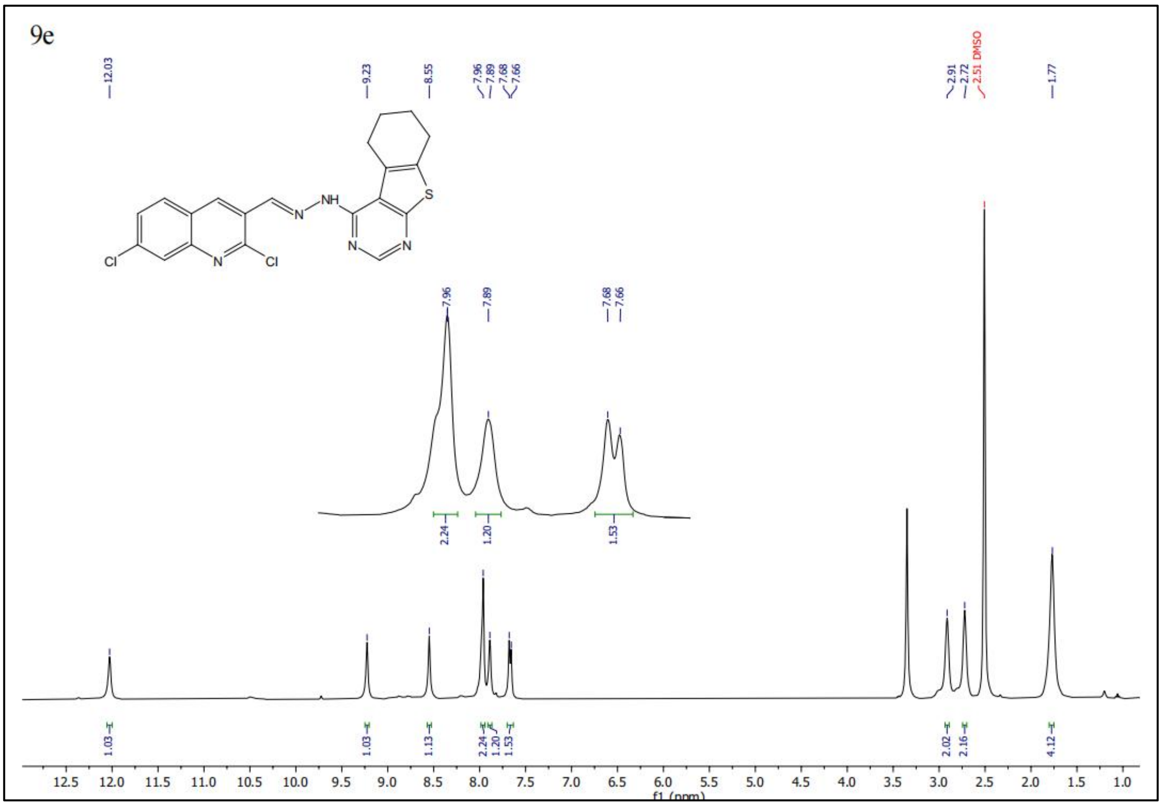


Fig.4.17: Representative ^{1}H NMR spectrum of compound 9e

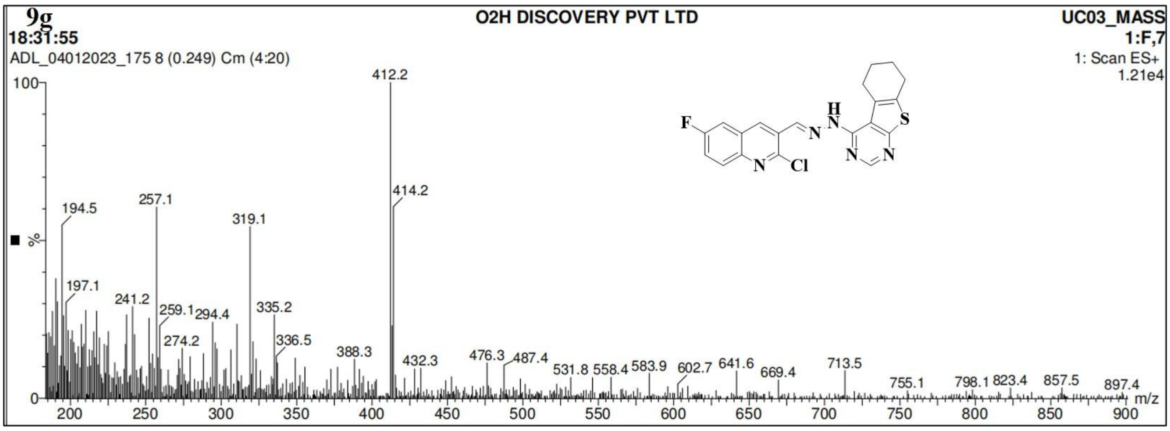


Fig.4.18: Representative mass spectrum of compound 9g

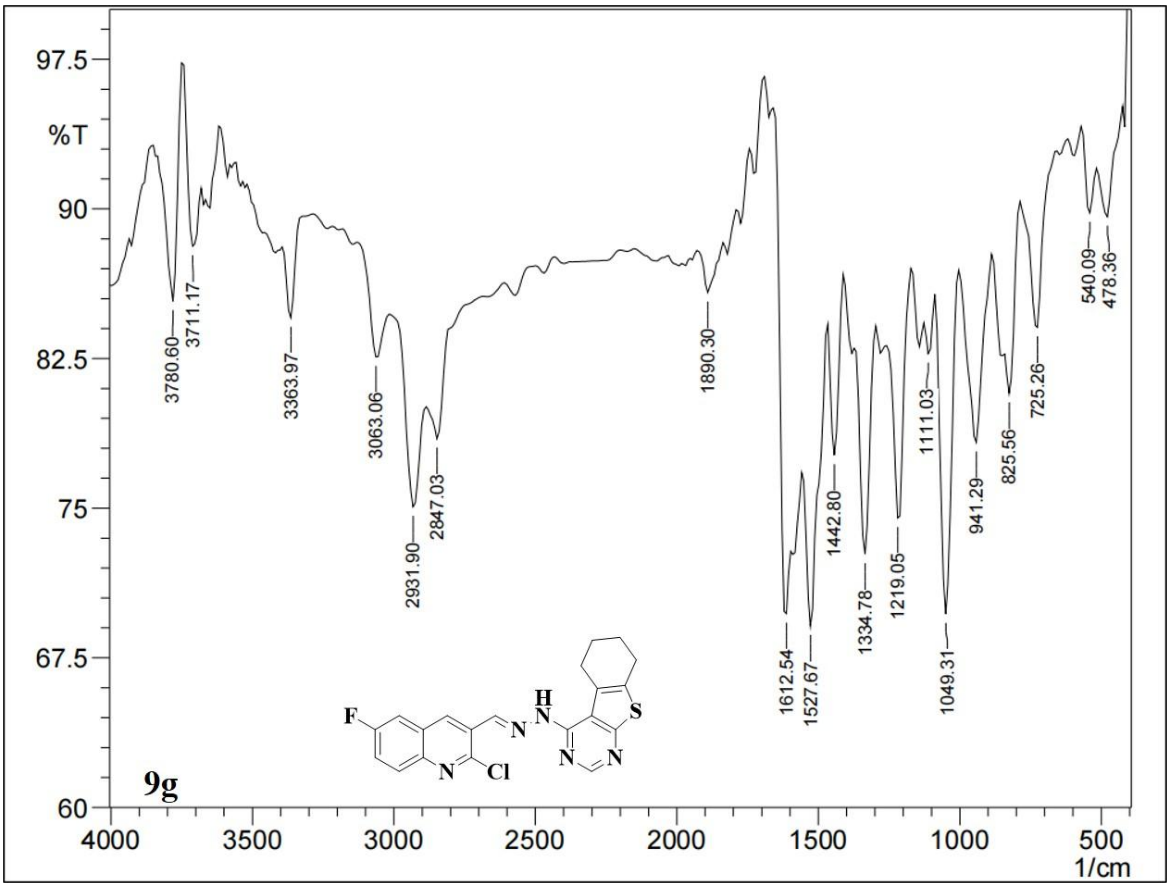


Fig.4.19: Representative IR spectrum of compound 9g

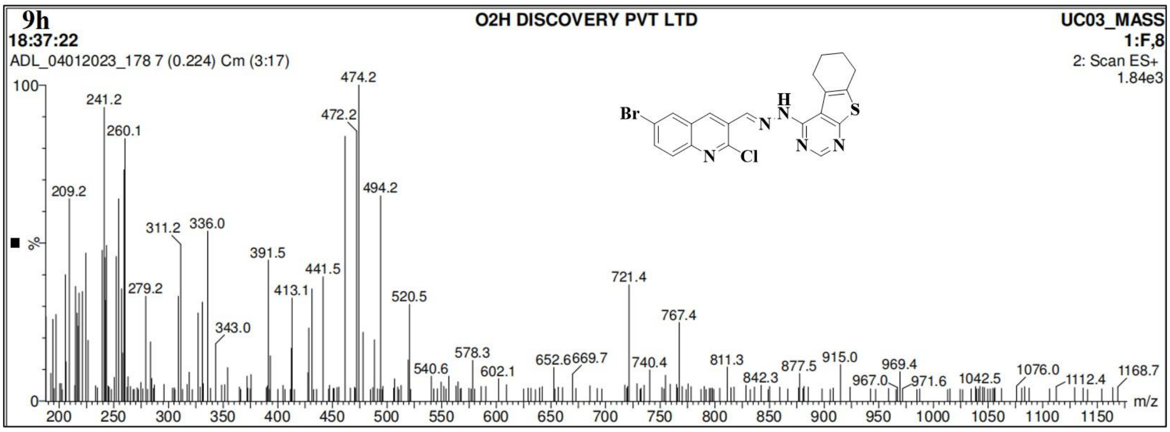


Fig.4.20: Representative mass spectrum of compound 9h