GREEN SYNTHESIS AND CHARACTERIZATION OF BIOACTIVE QUINAZOLINONE SCHIFF BASE

Submitted in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

by

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This is to certify that the project entitled **Green Synthesis and Characterization of Bio active Quinazolinone Schiff Base** is a bonafide work of **Shaikh Heena Babu Raziya (Roll No.16PH49), Satpute Swati Kulbhushan Shakuntala (Roll No.16PH43), Bhoir Rahul Pramod Sunita (Roll No.16PH10), Pathan Shahabaz Abdul Wahab Shabana Begum (Roll No.16PH47)** submitted for the appreciation of the degree of Bachelor of Pharmacy in Department of Pharmaceutical Chemistry.

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Prof. Jayshree Patil

Declaration

I declare that this written submission represents my ideas in my own words and where others ideas or words have been included, I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that any violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

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ABSTRACT

Schiff bases have gained importance in medicinal and pharmaceutical fields due to a broad spectrum of biological activities and have been utilized as synthons in the preparation of a number of industrial and biologically active compounds. Quinazolines and quinazolinones are medicinally important nitrogen hetero cyclic compounds. The combination of unique structural features, extensive functionalization, and very high biological activity found, both building blocks are tethered together to synthesize new chemical entity (NCE) 3-(benzylideneamino)-2-methyl-quinazolin-4-one, i.e. schiff base using lemon juice as green solvent. Utilization of fruit juices as a natural and biocatalyst permits mild and highly selective transformation and synthesis in a simplistic and environmentally friendly manner. The present synthesis proceeds via synthesis of Methyl-2- acetamidobenzoate from methyl anthranilate followed by cyclization to produce 3-amino-2-methyl quinazolin-4-one which on treament with benzaldehyde produces schiff base.The synthesized product was identified by its physical properties, melting point, TLC, FTIR and characterized by NMR. It is screened for antibacterial and antioxidant properties. Compared with traditional methods, this green method was more convenient and held without generation of pollution in shorter reaction time, safer to analyst, low cost and simple to run.

Keywords: Schiff base, Quinazolinone, fruit juice, bio catalyst

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Keywords and Glossary

Keywords:

Azomethine, Schiff bases, biological activities, imines, Quinazoline, Green chemistry, antibacterial, antioxidant, Green solvent, lemon juice, biocatalyst.

Glossary

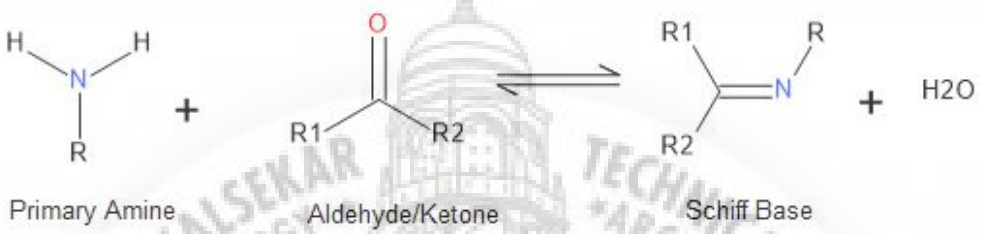
AAB :	Methyl 2-Acetamidobenzoate
QZN :	3-Amino-2-methyl-4-quinazolinone
FTIR:	Fourier Transform Infrared Spectroscopy
LR:	Laboratory Reagent
NMR :	Nuclear Magnetic Resonance
Ppm :	parts per million
Rf :	Retardation Factor
SAR:	Structure Activity Relationship
SB :	Schiff base

1. Introduction

1.1 Schiff base: A versatile Pharmacophore

Structurally diverse, biologically active scaffolds are easily tethered together by simple azomethine linkage (-C=N-), allowing rapid access to vast libraries of structurally diverse molecular hybrids with diverse biological properties. Schiff bases are a favoured class of compounds with fascinating biological properties. It is an important class of compounds that gain popularity to their ease of preparation from readily available inexpensive starting materials (aldehydes/ketones and primary amines) [1].

Schiff bases are the compounds containing imine or azomethine (–C=N–) functional group. These are the condensation products of primary amines with carbonyl compounds and were first reported by Hugo Schiff.



Schiff bases form an important class of the most widely used organic compounds and have a wide variety of applications in many fields including analytical, biological, and inorganic chemistry. Schiff bases have acquired value in medicinal and pharmaceutical fields due to a comprehensive spectrum of biological activities like anti-inflammatory, analgesic, antimicrobial, anticonvulsant, antitubercular, anticancer, antioxidant, anthelmintic, and so forth [2].

The first preparation of imines was reported in the 19th century by Schiff (1864). Since then a variety of methods for the synthesis of imines have been described. The classical synthesis reported by Schiff involves the condensation of carbonyl compounds with an amine under azeotropic distillation. Molecular sieves are then used to completely remove water formed in the system. In the 1990s an *in situ* method for water elimination was developed, using dehydrating solvents such as tetramethyl orthosilicate or trimethyl orthoformate[3].

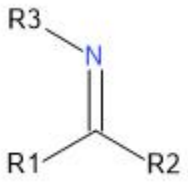
Schiff bases are able to stabilize numerous different metals in various oxidation states controlling the performance of metals in a large variety of advantageous catalytic transformations. Most commonly Schiff bases have NO or N_2O_2-donor groups but the oxygen atoms can be replaced by Sulphur, nitrogen, or selenium atoms.

Although the Schiff bases are known to be good chelating agents, and easily prepared and characterized, small interest has been given to their uses for analytical purposes because of two serious drawbacks, they are insoluble in aqueous solutions and they decompose easily in acidic solutions, limiting their use to basic conditions[4].

In this study, we have roped 2-Methyl-3-amino-4-quinazolinone with Benzaldehyde by simple azomethine linkage to produce Schiff base 3-benzylideneamino-2-methyl-quinazolin-4-one.

1.1.1. Structure and properties of Schiff base

The functional group of Schiff base contain a carbon-nitrogen double bond with nitrogen atom connected to an alkyl, aryl, cycloalkyl or heterocyclic groups which may be variously substituted, other than with hydrogen [5].



General formula of Schiff base

The general formula of azomethine group which is the most common structural feature of Schiff bases. Schiff base is having azomethine linkage (R is an organic side chain). Schiff bases are weak bases and are easily hydrolysed by dilute mineral acids, but not by aqueous alkali. They also form insoluble salts with strong acids through coordination of the electrons on nitrogen atom of azomethine group [6]. Most of the Schiff bases are stable in alkaline solutions. Aromatic aldehydes especially with an effective conjugation system, form stable Schiff bases, where as those from aliphatic aldehydes are found to be less stable. Aliphatic Schiff bases have a tendency to polymerize and are difficult to isolate [7].

1.2. Green Chemistry

Green Chemistry is defined as invention, design, development and application of chemical products and processes to reduce or to eliminate the use and generation of substances hazardous to human health and environment [9]. It is also defined as environmentally benign chemistry, which aims to design new chemical methods/products that can reduce environmental pollution. Its objective is to target pollution at the design stage, even before it begins. If chemists are taught to synthesize products and materials without using hazardous substances, then much waste, hazards and cost can be evaded [10].

Due to these beneficial properties, concern for the environmental demands and strong interest in the development of green chemistry, new sustainable catalysts and new environmentally benign processes have been investigated which are both economically and technologically feasible [11].

Green chemistry is the branch of chemistry that involves tools techniques and technologies. It is facilitative to chemists and chemical engineers in research, development and production, for development of more eco-friendly and efficient products which may also have significant commercial welfare. It is going to now become an essential tool in the synthetic chemistry. It is a latest mode of looking at organic synthesis and the design of drug molecules, offering essential environmental and economic advantages over traditional synthetic processes. The recent interest in green chemistry has produced a new challenge for organic synthesis in that novel reaction conditions need to be found which reduce the emission of volatile organic solvents and the usage of hazardous toxic chemicals. They improve selectivity, reduces reaction time, and simplifies separation and purification of products than the conventional methods [12].

Synthesis of Schiff base is often carried out with acid catalyst and in general by refluxing the mixture of aldehyde (or ketone) and amine in organic medium. Classical organic synthesis of Schiff bases usually encounters the difficulty of removing solvents from the reaction mixture. To overcome the problems in the removal of water, secondary method has been utilized in which Lewis acid is used as catalyst which speed up nucleophilic attack of amines on carbonyl carbon as well as serving as dehydrating agent for release of the water [13].

Present study also involves application of eco-friendly and inexpensive natural catalysts like lemon juice.

1.3. Quinazoline: A Fused Heterocycle

Many heterocyclic scaffolds can be considered as privilege structures. Most frequently, nitrogen heterocycles or various positional combinations of nitrogen atoms, sulphur, and oxygen in five- or six-membered rings can be found. According to statistics, more than 85% of all biologically active chemical entities contain a heterocycle. This info indicates the central role of heterocycles in modern drug design. The application of heterocycles provides a useful tool for modification of solubility, lipophilicity, polarity, and hydrogen bonding capacity of biologically active agents, which results in the optimization of the ADME/Toxic properties of drugs or drug candidates. Hence, heterocycles have critical significance for medicinal chemists, because exploiting them, it is possible to expand the available drug-like chemical space and direct more effective drug discovery programs [14].

Many of the nitrogen heterocyclic compounds are an integral part of natural products, having immense biological potential. Quinazoline and quinazolinone are nitrogen containing heterocyclic compounds that exhibits numerous biological activities. Quinazolinone ring is further conferred with a carbonyl group. The first quinazolinone was synthesized by P. Gries in 1869 as 2-cyanoquinazolin-4(3H)-one [15]. Depending on the varying position of nitrogen atoms, quinazoline ring has four isomeric forms i.e. quinazoline, quinoxaline, cinnoline, and phthalazine (Figure-1).

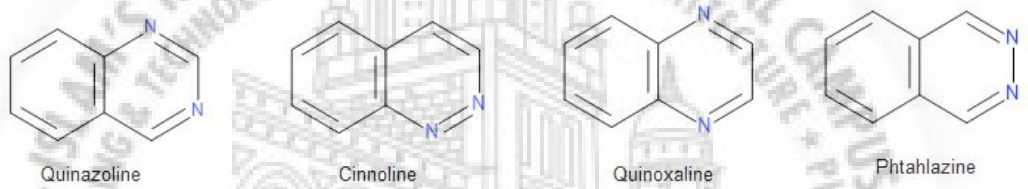


Figure 1: Isomers of Quinazoline

Various substitution form of carbonyl group on quinazolinone results in two isomeric forms i.e. 2(1H)-quinazolinones, and 4(3H)-quinazolinones. A dicarbonyl form, 2,4(1H,3H)-quinazolinedione is also known to exist (Figure-2).

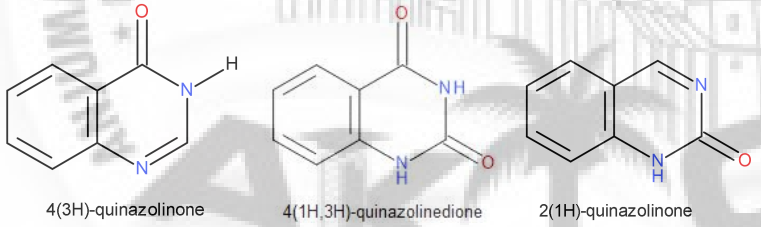


Figure 2: Isomers of Quinazolinone

In recent years, the quinazoline/quinazolinone scaffold has been extensively derivatized via several structural modifications to produce fascinating new molecular hybrids. It is exciting to observe that among the recent patents available, many of them focus on the promising anticancer activity of quinazoline and quinazolinone containing compounds. However, their biological activity is certainly not limited to anticancer only, they are also known to evoke many different biological and physiological effects in vitro and in vivo respectively. The interest in quinazolines and quinazolinones is ever growing, since they offer a diverse chemical space for exploration of medicinal potential [16]. Quinazoline heterocycles are ubiquitous in pharmaceutical compounds and drugs. They are important subunits of a broad variety of natural products as well as synthetic pharmaceuticals possessing anti-inflammatory, antiviral, antimalarial and anticancer activities [17].

Quinazolinones and quinazolines are noteworthy in medicinal chemistry, because of wide range of their antibacterial, antifungal, anti-inflammatory, antimalarial, anti-HIV, antiviral, antituberculosis properties and also their inhibitory effects on thymidylate synthase, poly-(ADP-ribose) polymerase (PARP) and tyrosine kinase. There are several approved drugs

with quinazoline structure in the market such as, prazosin hydrochloride, doxazosin mesylate and terazosin hydrochloride [18].

1.4. Anti-bacterial activity

The increase in the mortality rate associated with infectious diseases is directly related to bacteria that exhibit multiple resistance to antibiotics. The lack of effective treatments is the main cause of this problem. The development of new antibacterial agents with novel and more efficient mechanisms of action is definitely an urgent medical need [19] .

The antibacterial agents acting on bacteria are called bacteriostatic / bactericidal. Bacteriostatic are those having the property of inhibiting bacterial multiplication, multiplication resumes upon removal of the agent. While bactericidal are those having the property of killing bacteria. Bactericidal action differs from bacteriostatic only in being irreversible i.e. the destroyed organism can no longer multiply, even after being removed from contact with the agent. In some cases, the agent causes lysis (dissolving) of the cells, in other cases the cells remain intact and may even continue to be metabolically active [20]. Antibacterial agents include disinfectants and the antimicrobial drugs i.e. chemotherapeutic agents and antibiotics. Schiff bases have been pointed to as promising antibacterial agents.

The antibacterial activities of the synthesized compounds were evaluated in vitro using cup plate method.

1.5. Antioxidant activity

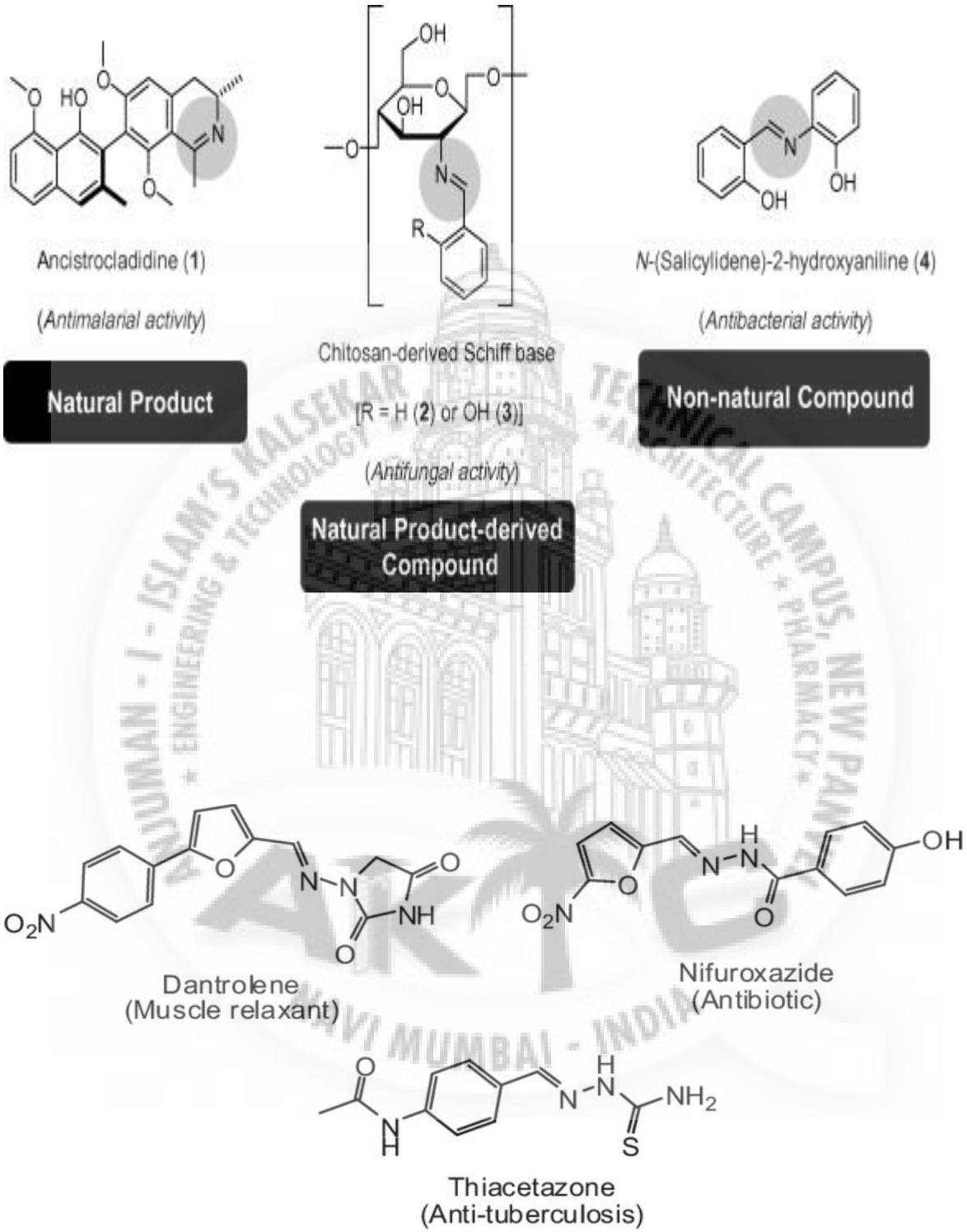
Free radicals are having single electron in their outermost shell and becomes more reactive. They are unstable and try to become stable, either by accepting or donating an electron [21]. The free radicals are generated in living systems as a part of the normal physiological process [22]. Generation of free radicals or reactive oxygen species (ROS) during metabolism and other activities beyond the antioxidant capacity of a biological system gives rise to oxidative stress [23-24].The ROS and free radicals mediated reactions are involved in various pathological conditions such as anaemia, asthma, arthritis, inflammation, neurodegeneration, cancer, mutagenesis, Alzheimer's, AIDS, ageing process and perhaps dementia, malaria [25-27] .

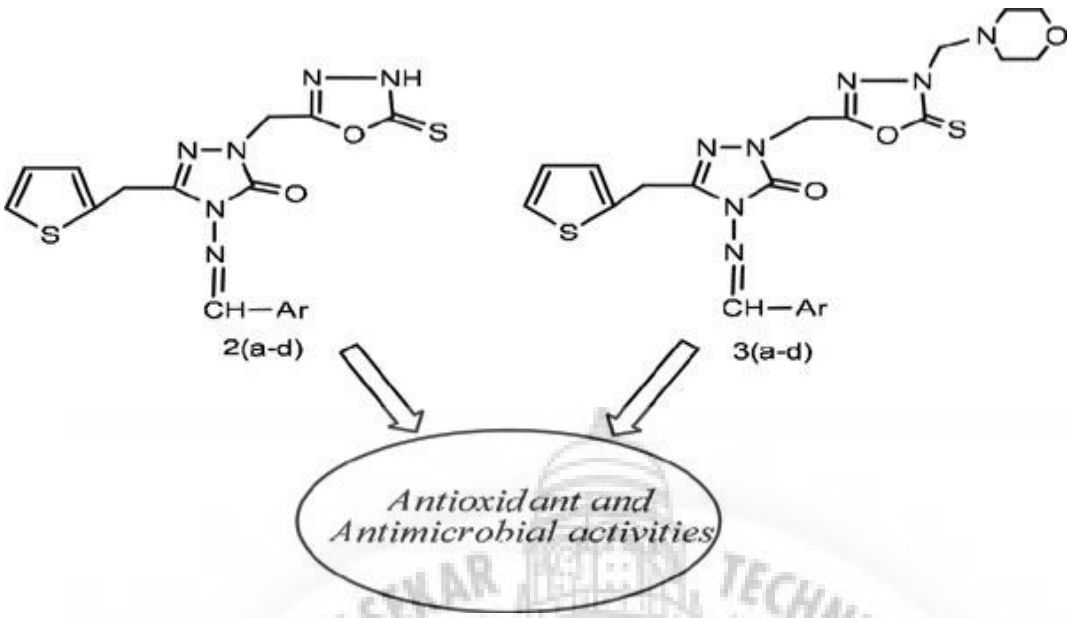
1.5.1. Hydrogen peroxide scavenging assay

Hydrogen peroxide is a weak oxidizing agent and can deactivate a few enzymes straightaway, usually by oxidation of essential thiol (-SH) groups. Hydrogen peroxide can cross cell membranes quickly, once inside the cell, H_2O_2 can likely react with Fe2+, and perhaps Cu2+ ions to form hydroxyl radical and this may be the root of many of its toxic effects. It is therefore biologically advantageous for cells to control the amount of hydrogen peroxide that is allowed to accumulate [28].

Our Synthesized Schiff base is screened for in vitro scavenging activity by Hydrogen peroxide scavenging assay and antibacterial activity.

1.6. Bioactive Schiff Base [29,30,31]




2(a-d)
3(a-d)
Antioxidant and
Antimicrobial activities

2. Review of Literature

1. **Anu Kajal *et al.* (2013)** summarized information on the diverse biological activities and also highlights the recently synthesized numerous Schiff bases as potential bioactive core.

2. **Abdul Hameed *et al.* (2018)** covers recent efforts in the synthesis and biological screening of quinazoline/quinazolinone based compounds from 2011-2016.

3. **JP Patil *et al.* (2014)** synthesized a series of acetamide derivatives of 2- Methyl-3 amino-4-quinazolinone by condensation of Methyl anthranilate, acetic anhydride and Hydrazine hydrate.

4. **S K Sahu *et al.* (2008)** synthesized various 3-{(1-aryl/alkylaminomethyl-2-oxo-1,2-Dihydroindole-3-ylidene) amino}-2-methyl-6-quinazolin-4-(3H)-ones with the objective of developing better anti-inflammatory compounds with antimicrobial activities.

5. **Pramanik Tanay *et al.* (2018)** successfully demonstrated the green synthesis of Schiff bases (SB) bearing different substituents in good yield via microwave induced reaction in fruit juice medium.

6. **Garima Yadav *et al.* (2015)** revealed green synthesis which involves the use of fruit juice of Citrus limetta, Vitis lanata and aqueous extract of Mangifera indica as natural acid catalysts

7. **Serhat Keser *et al*. (2012)** determined H_2O_2 radical scavenging and total antioxidant activity of Crataegus monogyna (hawthorn) water and ethanol extracts of leaves, flowers and fruits.

8. **Demir Mulazimoglu Aysen *et al.* (2010)** studied synthesis, characterization and investigation of antibacterial activities of Schiff base ligands.

3. *Objective and Plan of work*

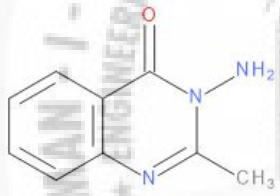
1. Schiff bases have gained importance in medicinal and pharmaceutical fields due to a broad spectrum of biological activities like anti-inflammatory, analgesic, antimicrobial, anticonvulsant, antitubercular, anticancer, antioxidant, anthelmintic, and so forth. [32] Quinazoline and quinazolinone derivatives have continued to attract a widespread interest for a long time due to their diverse pharmacological activities [33].
2. Green chemistry is going to now become an essential tool in the synthetic chemistry. It is a latest means of looking at organic synthesis and the design of drug molecules, contributing significant environmental and economic benefits over traditional synthetic processes.

   All these factors have fascinated us towards Quinazolinone chemistry. Considering the importance of quinazolinone moiety regarding synthetic and pharmacological aspects, we have selected it for our project wok.

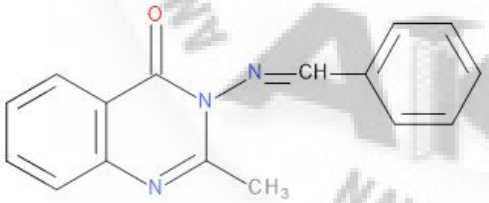
   The model skeleton of compound planned for the synthesis is as depicted below.

Plan of Work

1. Synthesis of 3-amino-2-methyl-4-quinazolinone [34]



2. Synthesis of 3-(benzylideneamino)-2-methyl-quinazolin-4-one, SCHIFF BASE (SB)



3. Structural analysis of synthesized compounds.

a) Melting point
b) Thin layer chromatography
c) Infrared spectra
d) NMR spectra

4. Bioactivity Studies
   a) Antibacterial Activity
   b) Hydrogen Peroxide Scavenging activity

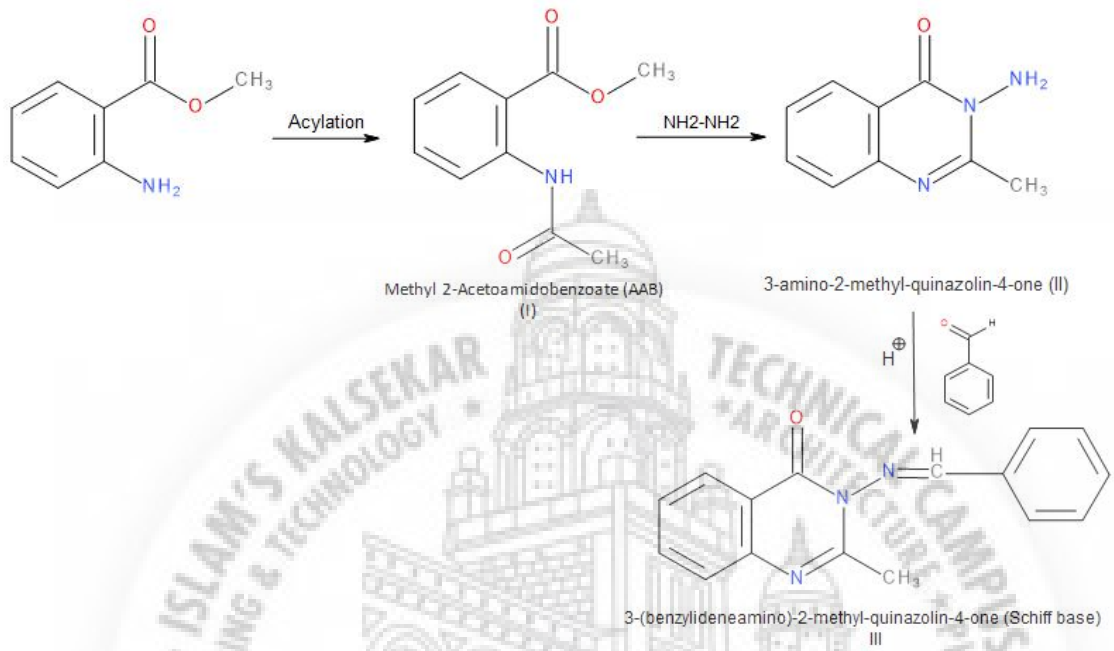
4.Experimental Work

GENERAL REMARK

- All chemicals used were of Laboratory Reagent (LR) Grade and were procured from commercial sources.
- The synthesized derivatives were characterized by melting point, TLC, FT-IR, and NMR.
- Thin Layer Chromatography was performed using Silica Gel G (Merck Index) coated on glass plates and the spots were visualized under UV light.
- Melting points were taken in open glass capillary tubes in liquid paraffin bath and were uncorrected.
- IR spectra were recorded on SHIMADZU spectrophotometer.
- Proton NMR spectra were recorded on ECZR Series 600 MHz NMR SPECTROMETER with TMS as an internal standard. Chemical shifts (δ) were expressed in parts per million (δ ppm).

4.1. Synthetic Exertion

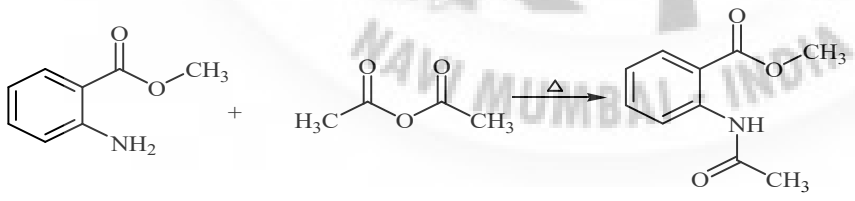
Synthetic Scheme:



4.1.1 Synthesis of Methyl 2-Acetamidobenzoate I (AAB)

Treatment of methyl Anthranilate with acetic anhydride produces Methyl-2-acetamidobenzoate.

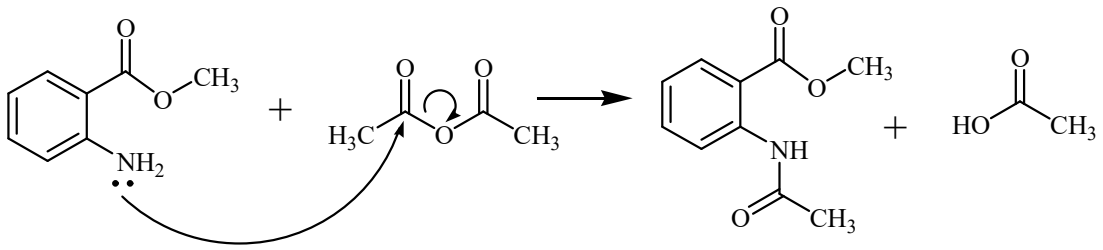
Chemical Reaction



Methyl anthranilate | Acetic anhydride | Methyl 2-acetamidobenzoate

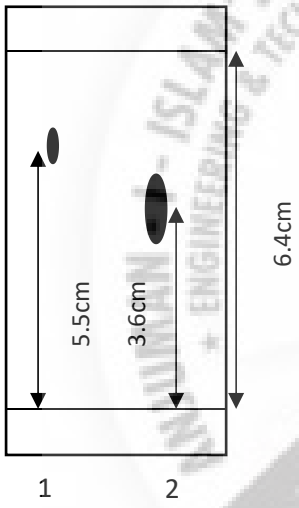
(I)

Mechanism



Procedure

In 100 ml RBF, a solution of Methyl Anthranilate (0.016 mol) in acetic anhydride (0.127 mol) was refluxed for 15 minutes. The reaction mixture was cooled, poured into cold water (50 ml) containing a drop of pyridine and stirred until the oil solidifies. Crude product was filtered, washed with cold water (4x50) and dried it at 100^0C. The product was recrystallised from ethanol.



Melting point 100^0 - 102^0C

Yield 66.52%

Rf 0.56 (Chloroform)

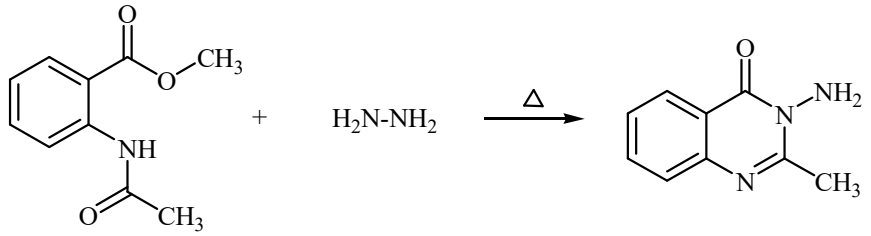
1. Methyl Anthranilate

2. Methyl 2-Acetamidobenzoate

4.1.2 Synthesis of 3-Amino-2-methyl-4-quinazolinone II (A-QZN)

Condensation of Methyl 2-acetamidobenzoate with hydrazine hydrate yields 2-Methyl-3-amino-4-quinazolinone.

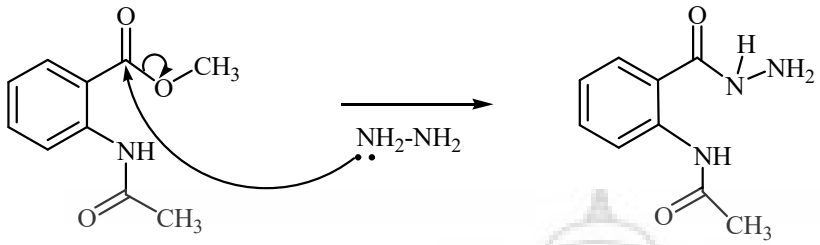
Chemical Reaction



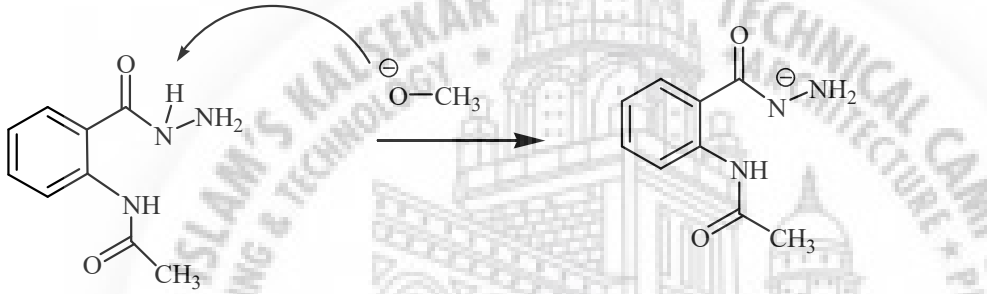
Methyl 2-acetamidobenzoate | Hydrazine hydrate | 3-amino-2-Methyl-4-quinazolinone (II)

Mechanism

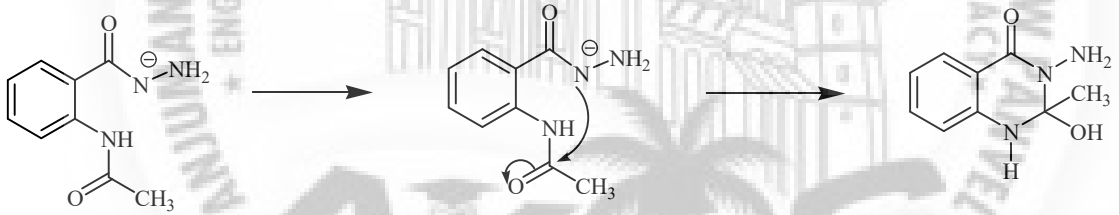
Step 1: Nucleophilic attack on carbonyl carbon



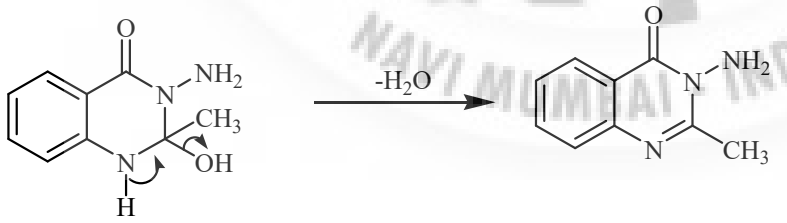
Step 2: Abstraction of proton



Step 3: Intermolecular arrangements to form cycle (Cyclization)

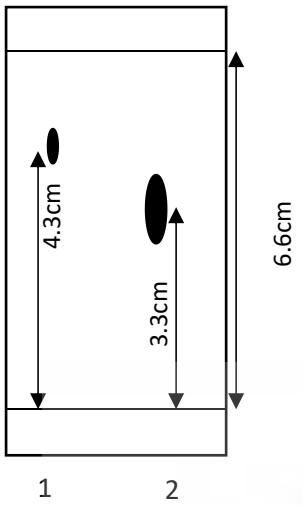


Step 4: Removal of H_2O molecule (Dehydration)



Procedure

In 100 ml RBF, a solution of hydrazine hydrate (10 ml) and Methyl 2-Acetamidobenzoate (2 gm) in ethanol was refluxed for 2 hours. The reaction mixture was cooled and stirred into cold water (50 ml). Crude product was filtered, washed with cold water and dried it at 100^0C. Crude product was recrystallised from ethanol.



Melting point 150-152^{0}C

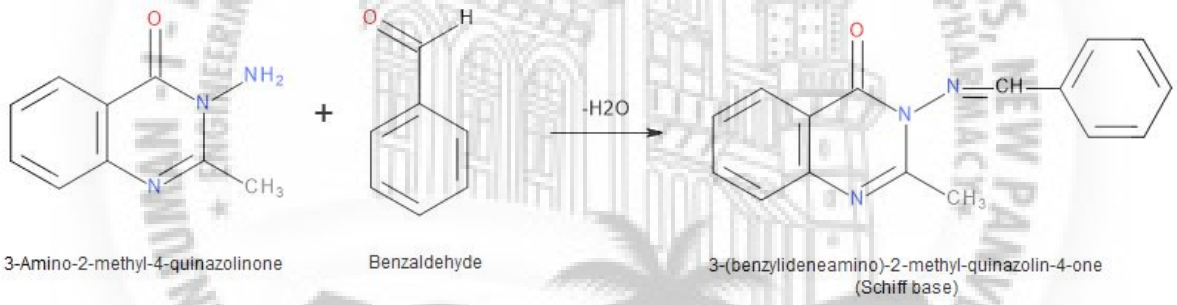
Yield 44.6%

Rf 0.5 (Chloroform)

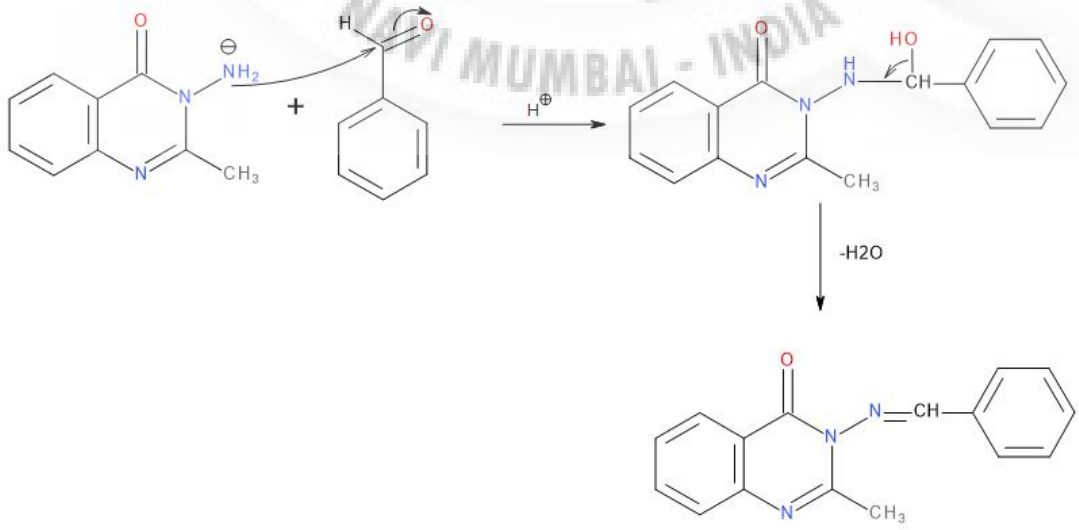
1. Methyl 2-Acetamidobenzoate
2. 2-Methyl-3-Amino-4-quinazolinone

4.1.3. Synthesis of 3-(benzylideneamino)-2-methyl-quinazolin-4-one, SCHIFF BASE (SB):

Reaction



Mechanism



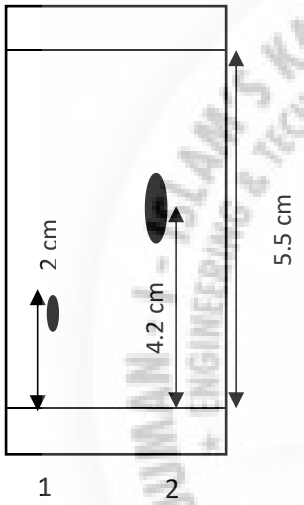
Procedure:

A. Preparation of Catalyst

Lemons were procured locally, then cut into pieces with knife. After extracting the fruit juice directly from the corresponding fresh fruits, it was filtered through normal filter paper. After filtering, the fruit juice was directly used as such for the reaction without adding any foreign chemicals into it.

B. Synthesis of SB

The equimolar amount of benzaldehyde with 3-amino-2-methyl-4-quinazolinone (QZN) was taken in beaker. In reaction mixture natural acid catalyst i.e., lemon juice was added in variable amount(8-12ml) and then kept for 10-15 min. Further reaction mixture was stirred at room temperature and monitored by TLC. After completion of reaction purified by recrystallization with minimum amount of ethanol.



Melting point 210-212^{0}C

Yield 48.12 **%**

Rf 0.76 (SB)

Chloroform:Acetone (8:2)

1. 2-Methyl-3-Amino-4-quinazolinone
2. Schiff base (SB)

4.2. Biological Study

4.2.1. Antibacterial Activity[35]

Synthesized Schiff base was screened for antibacterial activity against gram positive bacteria (S.aureus) and gram negative(E.coli) bacteria by disc diffusion method against standard antibiotic ciprofloxacin.

A. Preparation of Nutrient agar medium

Media was prepared using distilled water and sterilized by Autoclaving at 121^{0}C for 15 min.

B. Preparation of sample solution

Antibacterial activity is usually tested by making aqueous solution of samples. However, Schiff base used in the present study was insoluble in water and common organic solvents but suspension was made in Dimethyl formamide. Therefore, to study antibacterial activity of Schiff base, their suspension was prepared by using dimethyl formamide.

C. Disc diffusion method (cup plate method)

Each time fresh sterile nutrient agar medium was prepared. The proceedings were carried out aseptically. All the apparatus in need were sterilized. In each sterile petri dish 15-20 ml of molten media was added simultaneously 0.05-0.1 ml (approx. 2-3 drops) of 24 hours fresh diluted culture of organism under study was added to each petri plate. The nutrient broth culture and nutrient agar media were mixed thoroughly by rotatory motion of agar plate on a

plane surface. It was allowed to solidify at room temperature. With the help of cork borer, the cups were punched and scooped out of the set agar. The cups of the inoculated plates were then filled with test solution and ciprofloxacin solution. The plates were allowed to stay for 24 h at 37^0C and zone of inhibition was then measured.

4.2.2. Hydrogen Peroxide scavenging activity [36]**:**

The ability of the synthesized Schiff base to scavenge hydrogen peroxide was determined as follows.

A solution of hydrogen peroxide (40 mM) was made up in phosphate buffer (pH 7.4). Various concentrations (250, 500 and 1000 µg/mL) of Schiff base (or ascorbic acid) were added to a hydrogen peroxide solution (0.6 mL, 40 mM). Absorbance of hydrogen peroxide at 230 nm was observed after 10 min against a blank solution containing phosphate buffer without hydrogen peroxide.

5. Results

5.1. Chemistry

5.1.1 Figure 3: FTIR spectrum of AAB

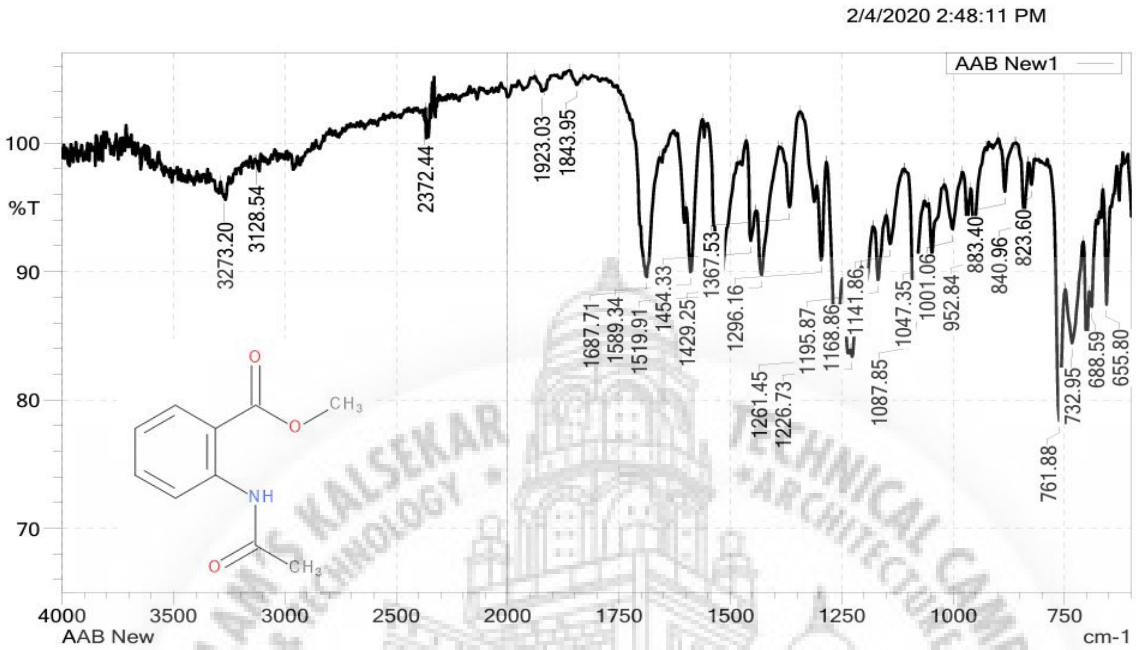


Table 1: FTIR Interpretation of AAB

Sr. No.	Peak (cm^{-1})	Corresponding Functional group
1	3273.20	NH stretch
2	1687.71	C=O amide
3	1589.34	C-N stretch
4	1843.95	C=O ester
5	1296.16	C-O bond
6	3128.54	C-H Str (Aromatic)

5.1.2 Figure 4: FTIR spectrum of QZN

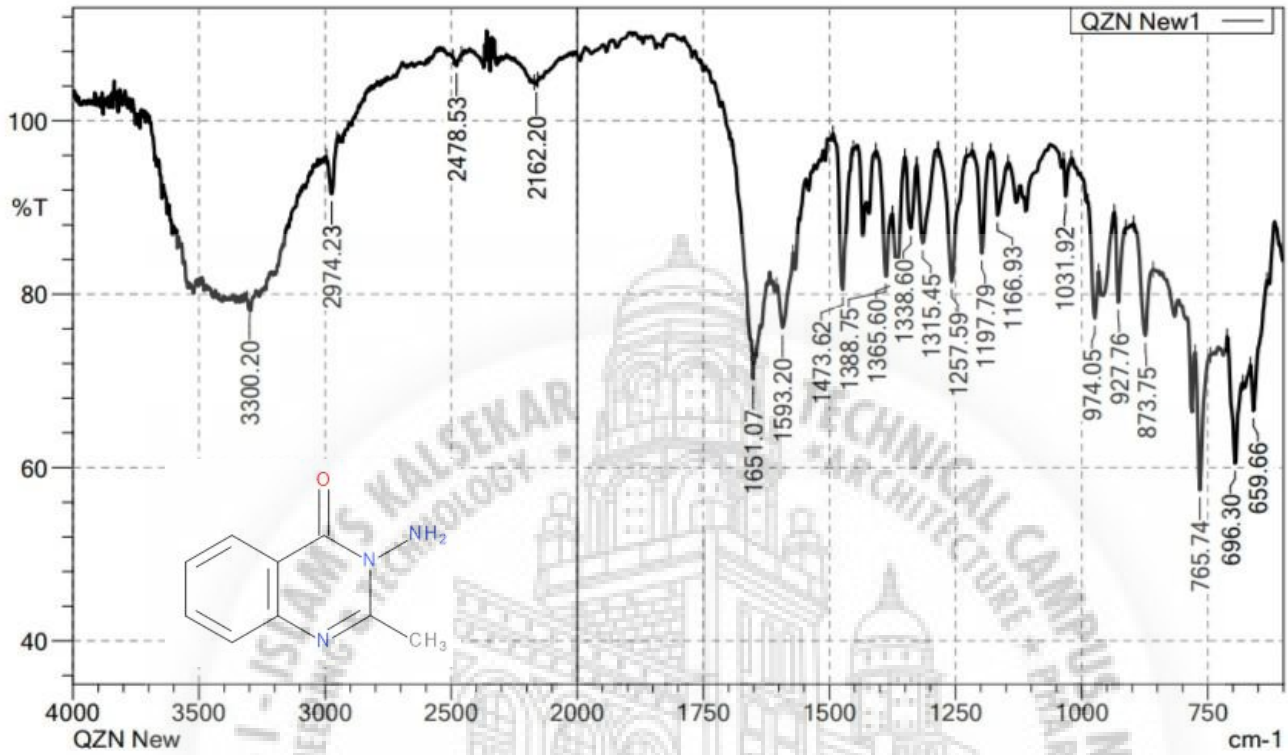


Table 2: FTIR Interpretation of QZN

Sr. No.	Peak (cm^{-1})	Corresponding Functional group
1	3300.20	NH stretch
2	2974.23	C-H stretch
3	1651.07	C=O cyclic amide
4	1593.20	N-H bend
5	1166.93	N-N bond
6	2162.20	C=N cyclic 1580-1627

5.1.3 Figure 5: FTIR spectrum of SB

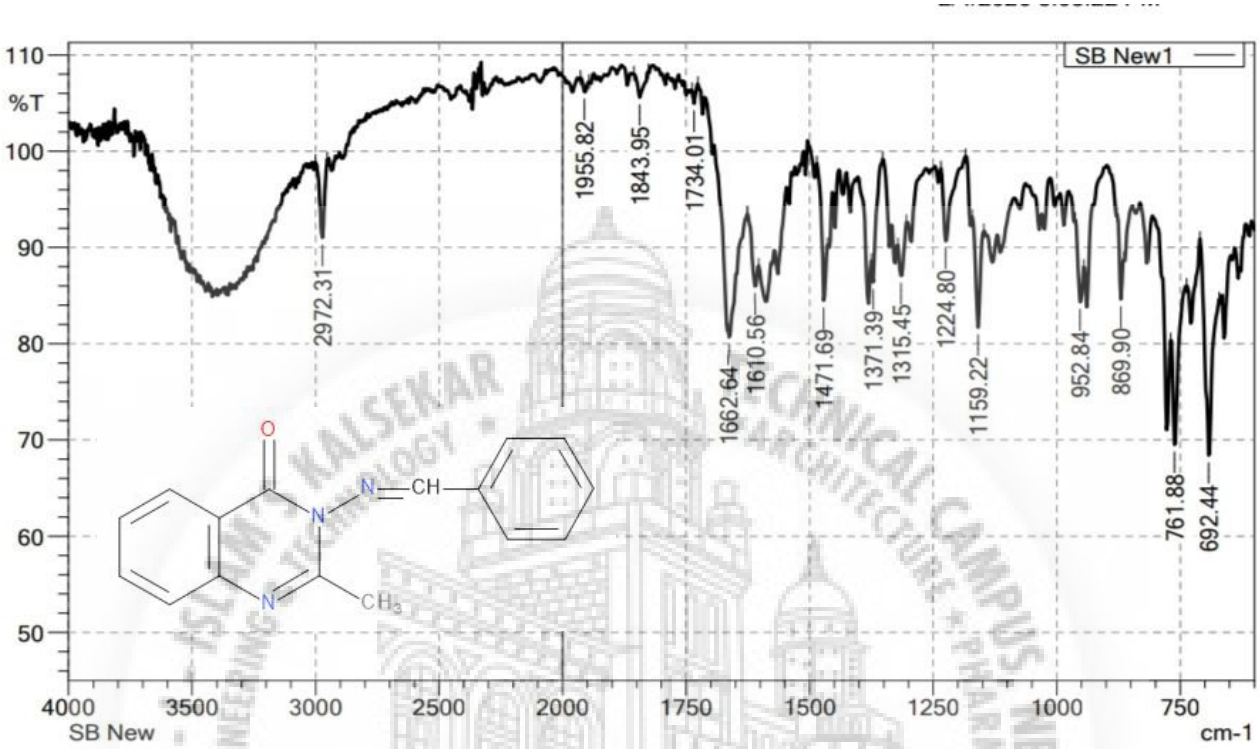


Table 3: FTIR Interpretation of SB

Sr. No.	Peak (cm^{-1})	Corresponding Functional group
1	2972.31	C-H stretch
2	1662.64	C=N imine bond
3	1159.22	N-N stretch
4	1610.56	C=O

5.1.4 PMR of 3-(benzylideneamino)-2-methyl-quinazolin-4-one (Schiff Base)

Figure 6: NMR spectrum of SB

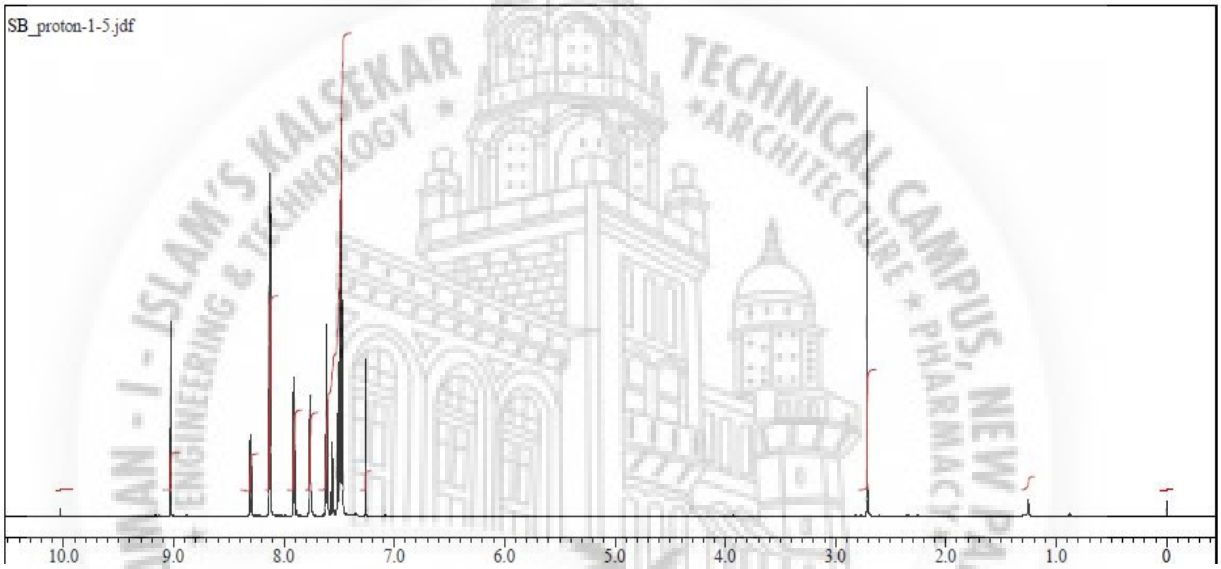


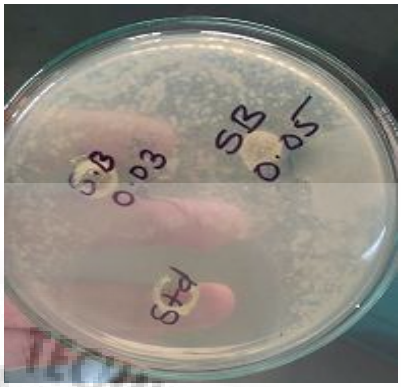
Table 4: NMR Interpretation of SB

Sr. No.	Protons	Splitting pattern	Chemical shift position
1	Ar-H	Multiplet	7.2-8.2
2	Ar-CH (1H)	Singlet	2.7
3	C-H	Singlet	1.2

5.2. Bioactivity Study

5.2.1. Anti- bacterial activity of Schiff base

Gram negative E.coli

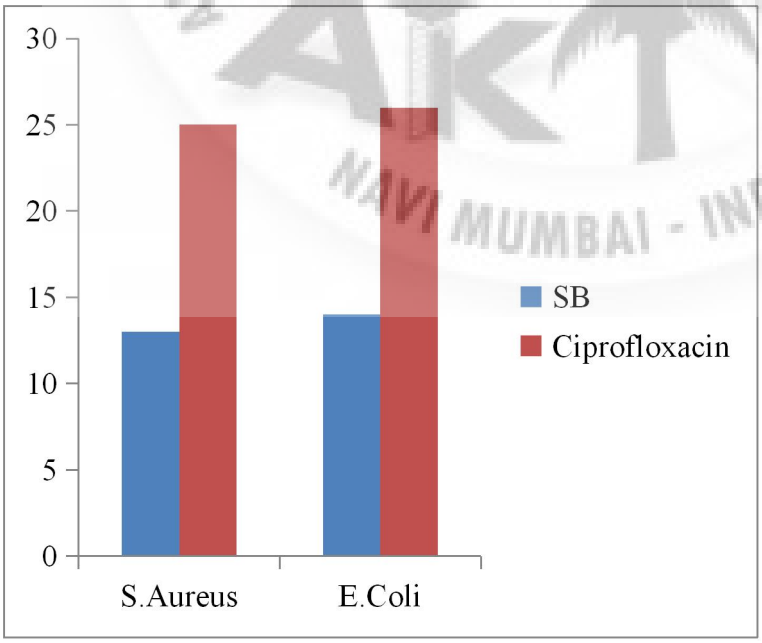


Gram positive S.aureus

Table no 5: Zone of Inhibition

Compound	S.aureus	E.coli
Schiff base	13mm	14mm
Ciprofloxacin	25mm	26mm

Figure 7: Comparative antibacterial activity of std and SB

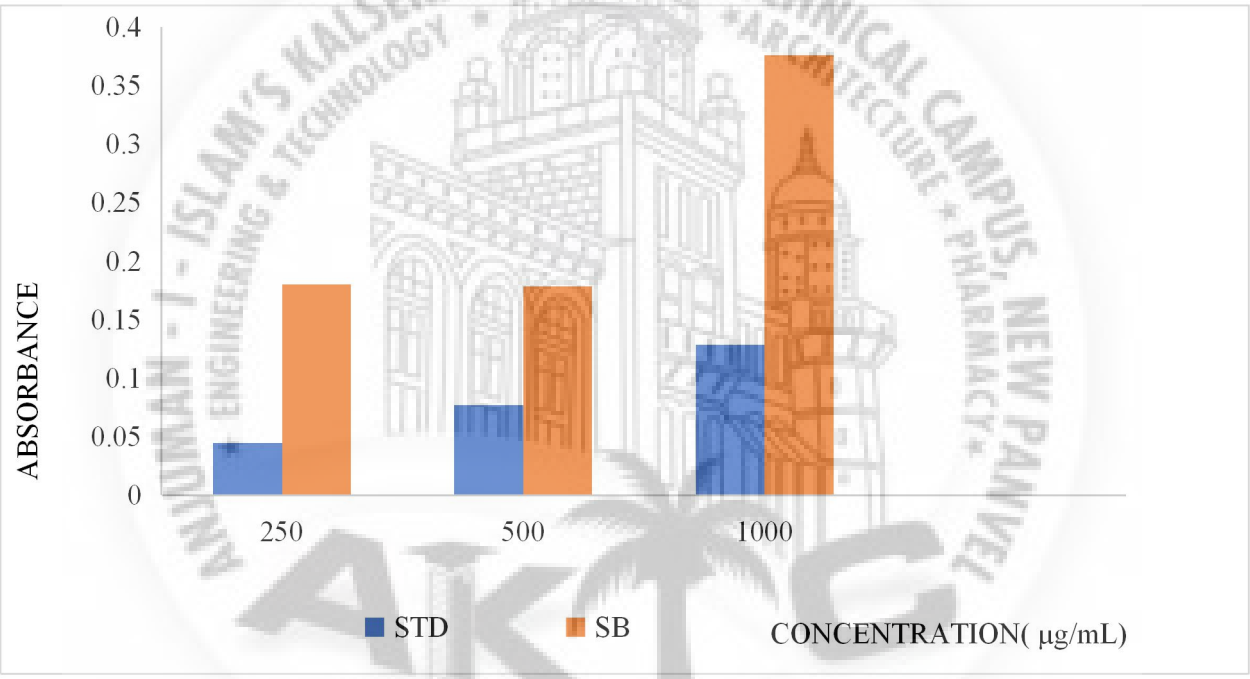


5.2.2. Hydrogen Peroxide Scavenging Activity

Table No.6: Spectrophotometric determination (Absorbance) at 230nm

Concentration (µg/ml)	Absorbance Std (Ascorbic Acid)	Absorbance SB
250	0.04437	0.18
500	0.0769	0.1782
1000	0.1286	0.3762

Figure 8: Comparative H_2O_2 scavenging activity



6.Results Discussion

6.1. Chemistry

- ✓ Green chemistry is growing at a very fast pace and provides a pre-emptive avenue for the sustainable development for future science and technology which can be useful to the design of highly effectual, environmentally friendly synthetic practices/procedures to provide life-saving medicines and to quicken lead optimisation processes in drug discovery while minimising environmental degradation. Thus there is a need to change or modify the conventional procedures as newer strategies to produce organic materials in a variety of media for their safer use which may be adopted by the chemical/pharmaceutical industry to reduce or eliminate volatile organic solvents, thus averting pollution at source, to diminish the reaction time and elimination/ minimization of side product formation.
- ✓ The present work focuses the synthesis of quinazolinone Schiff base using fruit juice i.e. lemon juice which is acting as natural biocatalyst in organic transformations such as formation of C-N bond. This synthesis has shown remarkable reduction in time i.e. from 17-20 hours as in conventional to only 15-20 min.
- ✓ Our work is initiated with the reaction between Methyl Anthranilate and acetic anhydride. With respect to mechanism, the reaction proceeds via a methyl 2-acetamidobenzoate (I) intermediate. Appearance of band of NH str (3273 cm^{-1}) and amide (1687 cm^{-1} C=O, 1589cm^{-1} C-N) in IR spectrum indicates the expected structure (I) i.e. conversion amine to amide.
- ✓ (I) undergoes nucleophilic attack of the nitrogen nucleophile i.e. Hydrazine hydrate at the carboxylic carbonyl group, which is followed by cyclisation, deprotonation and dehydration to produce the product 3-amino-2-methyl-quinazolin-4(3*H*)-one (II). Appearance of band of NH str (3300 cm^{-1}), CH str (2974 cm^{-1}), C=O cyclic amide (1651 cm^{-1}), and N-N band (1166 cm^{-1}),) in IR spectrum indicates the expected cyclized structure (II).
- ✓ Further (II) on treatment with benzaldehyde in presence of natural biocatalyst, lemon juice, occurs protonation followed by dehydration produces Schiff base i.e. 3-(benzylideneamino)-2-methyl-quinazolin-4-one. Disappearance of NH stretch band and appearance of imine, C=N str (1662 cm^{-1}) predict the conversion of primary amine from structure (II) into Schiff base (III). NMR data shows the appearance of singlet N= C<u>H</u>-C6H5 at δ 2.7 (benzylic carbon) and absence of (NH) amino proton shift from 3-7ppm confirms the formation of Schiff base.

6.2. Bioactivity

As per literature survey Schiff base is versatile bioactive molecule. So, the synthesized compound (Schiff base) was tested for their antioxidant and antibacterial activity.

- ✓ **<u>Antibacterial activity.</u>**

  The antibacterial activity was performed against gram positive bacteria (S.aureus) and gram negative (E.coli) bacteria by cup plate method using ciprofloxacin as standard (30mg/ml). It is found that Schiff base is approximately 50% active as antibacterial agent.
- ✓ **<u>Antioxidant activity</u>**

  Spectrophotometric determination of hydrogen peroxide at 230 nm is performed in the different concentrations of Schiff base 250, 500 and 1000 µg/mL using ascorbic acid as standard. The antioxidant activity of Schiff base has been shown in all the concentrations. It is observed that as the concentration increases, antioxidant activity increases. It is concentration dependant.

7.Conclusion

- Schiff bases are one of the most crucial chemical classes of compounds having a ordinary integral property of a variety of medicinal agents. This bioactive core has maintained the interest of researchers in gaining the most suggestive and conclusive access in the field of various Schiff bases of medicinal importance from last decades.
- Heterocycles are among the most frequently encountered scaffolds in drug and pharmaceutically relevant substances. A heterocyclic core is propitious for variations of substitution pattern during Structure Activity Relationship (SAR).
- Quinazolinone are excellent reservoir of bioactive substances. The stability of the Quinazoline nucleus has encouraged and influenced medicinal chemists to launch many bioactive moieties to this nucleus to synthesize new potential medicinal agents.
- Herein a cost-effective, efficient, eco-friendly and easy method of quinazolinone Schiff base has been performed by our group. The flourishing interest of fruit juice in organic synthesis is mainly due to their acidic properties, enzymatic activity, ecofriendly character, cheap and commercial availability. The catalytic activity considering the utilization of fruit juices in various organic transformations such as formation of C-C, C-N bonds in different synthetically important organic compounds have been studied.
- Our present study has successfully demonstrated the green synthesis of pharmaceutically important quinazolinone Schiff base in lemon juice medium.
- Synthesized compound was screened for hydrogen peroxide scavenging activity using standard Ascorbic acid and antimicrobial activity using standard ciprofloxacin. The results of this study showed that synthesized Quinazolinone Schiff base can be used as antioxidants having antibacterial activity.

8.Future Scope

8. Future scope

- Schiff bases and functionalized quinazolines and quinazolinones scaffolds are important pharmacophore and show a wide spectrum of interesting biological activities such as anticonvulsant, antimicrobial, anti-HIV, anti inflammatory, anti tuberculosis, antiviral, antimalarial, enzyme inhibitory, analgesic and anti-cancer. So designing of novel bio active heterocyclic/ aryl schiff bases derivatives can be synthesized by using environmental-friendly technology.
- Novel heterocyclic/aryl Schiff bases can be synthesized using different natural acid catalysts such as fruit juice of pineapple, tamarind, *Citrus limetta, Vitis lanata* and aqueous extract of *Mangifera indica.*
- The role of a cancer prevention agent is to remove free radicals. It has been demonstrated that free radicals assume an important role in the pathogenesis of specific diseases and aging. Various chemotherapeutic agents for cancer have shown toxic and/or mutagenic effects; thus, naturally occurring antioxidants have been considered. As synthesized Quinazolinone schiff base has shown antibacterial and antioxidant activity. Further it can be screened for anticancer activity and can be a novel new chemical entity as anticancer agent having antibacterial properties.
- Antiviral activity of new series of 3-(benzylideneamino)-2-phenylquinazoline-4(3H)-ones were prepared through Schiff base formation of 3-amino-2-phenyl quinazoline-4(3)H-one with various substituted carbonyl compounds were evaluated against herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), vaccinia virus, vesicular stomatitis virus, herpes simplex virus-1 TK- KOS ACVr, para influenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, Punta Toro virus, feline corona virus (FIPV), feline herpes virus, respiratory syncytial virus, influenza A H1N1 subtype, influenza A H3N2 subtype, and influenza B virus. So the extended study of our molecule may involve evaluation against COVID-19 [37].
- The eco-friendly advantages of the synthetic alternatives based on unconventional methods like microwave or ultrasound irradiation or the usage of eco-friendly solvents like water etc. are becoming progressively popular and may be adopted by the chemical/pharmaceutical industry to reduce or eliminate volatile organic solvents, thus averting pollution at source, to diminish the reaction time and elimination/minimization of side product formation.
- Thus there is a need to change or modify the conventional procedures as newer strategies to produce organic materials in a variety of media for their safer use may be advantageous by the use of green chemistry principles.

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