Synthesis and Antimicrobial Activity of Novel 3-[5-(4-substituted) phenyl-1,3,4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)-ones

DISSERTATION-II

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OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE
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PHARMACEUTICAL CHEMISTRY

By

Sunusi Hudu Hantsu
(11509241**)**

Under the guidance of

Dr. Vivek Gupta
Associate Professor

School of Pharmaceutical Sciences
Lovely Professional University
Punjab - 144411

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TOPIC APPROVAL PERFORMA

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SR.NO.	NAME OF STUDENT	REGISTRATION NO	BATCH	SECTION	CONTACT NUMBER
1	Sunusi Hudu Hantsu	11509241	2015	Y1503	08037487399

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PROPOSED TOPIC : SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NOVEL 3-[5-(4-SUBSTITUTED) PHENYL-1,3,4-OXADIAZOLE- 2-YL]-2-STYRYL QUINAZOLIN-4(3H)-ONE

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Sr.No.	**Parameter**	**Rating (out of 10)**
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2	Project Feasibility: Project can be timely carried out in-house with low-cost and available resources in the University by the students.	7.50
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DAA Nominee Name: Dr. Sazal Patyar	UID: 17050	Recommended (Y/N): Yes

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Overall Remarks: Approved

PAC CHAIRPERSON Name: 11045::Dr. Monica Gulati **Approval Date:** 30 Nov 2016

Abstract

Previous studies by Rajitha *et al.* and Gupta *et al*. have demonstrated the effectiveness of synthesized series of 3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)-one derivatives as antimicrobial agents and the improved potency of addition of non-substituted styryl group at position 2 of the quinazolinone ring. In this work the effect of substitution of electron withdrawing groups at the phenyl-1, 3, 4-oxadiazole moiety was investigated. Nitro group (NO_2) and fluorine group (F) were substituted each at the 4- position of phenyl-1, 3, 4-oxadiazole moiety to produce 3-(5-(4-nitrophenyl)-1, 3, 4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one and 3-(5-(4-fluorophenyl)-1, 3, 4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one derivatives respectively. Synthesized compound were confirmed by infra red and nuclear magnetic resonance spectra. Their antimicrobial activity was tested against Gram-positive *Bacillus subtilis* and Gram-negative *Escherichia coli* using cup plate method. Both derivatives were found to have more antibacterial activity than the unsubstituted phenyl-1,3,4-oxadiazole derivatives synthesized by Gupta *et al.* and Rajitha *et al.*. This confirmed the effectiveness of this substitution in improving the potency of the antimicrobial activity of the 3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)-one series. Further, the fluorinated derivative was found to have more antimicrobial activity compared to nitro derivative.

Keywords: 4-nitrophenyl)-1, 3, 4-oxadiazol-2-yl, 4-flourophenyl)-1, 3, 4-oxadiazol-2-yl, quinazolin-4(3H)-one, antibacterial activity.

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Sunusi Hudu Hantsu

Declaration by the Candidate

This is to declare that the written submission and the work described in this dissertation-II entitled "**Synthesis and antimicrobial activity of novel 3-[5-(4-substituted)phenyl-1,3,4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)-ones**" represents original 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 stuck 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 a cause for disciplinary action by the School, and can also evoke penal action from the sources which have not been properly cited, or from whom proper permission has not been taken when required.

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This dissertation-II encompasses the information generated by me based on literature survey and experimental work carried out in the university. I assure and hold full responsibility for its genuineness.

Sunusi Hudu Hantsu

Forwarded Through

Dr. Vivek Gupta
Associate Professor
Department of Pharmaceutical Chemistry,
School of Pharmaceutical Sciences,
Lovely Professional University,
Phagwara-144411, Punjab (India).

Certificate by Supervisor

The work described in this dissertation-II entitled "**Synthesis and antimicrobial activity of novel 3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)-ones**" has been carried out by Sunusi Hudu Hantsu under my supervision. I certify that this is his bonafide work. The work described is original, and has not been submitted for any degree to this or any other university.

Date:

Place:

Dr. Vivek Gupta
Associate Professor
Department of Pharmaceutical Chemistry,
School of Pharmaceutical Sciences,
Lovely Professional University,
Phagwara-144411, Punjab, (India).

Certificate by School

This is certified that the work described in this dissertation-II entitled "**Synthesis and antimicrobial activity of novel 3-[5-(4-substituted) phenyl-1,3,4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)-ones**" has been carried out by Sunusi Hudu Hantsu at the School of Pharmaceutical Sciences, Lovely Professional University, Punjab, India.

HOD/COD

Dr. Amit Mittal

Associate Professor

Dr. Monica Gulati

Professor and Senior Dean

Head of School

School of Pharmaceutical Sciences,

Lovely Professional University,

Phagwara-144411, Punjab, (India).

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CHAPTER 1

INTRODUCTION

1.1 Introduction to Antimicrobials and Antimicrobial Resistance

Resistance to antimicrobials has become one of the major challenges in the pharmaceutical and public health sector. It costs the world billions of Dollars, and endangers the lives and health of millions of people. Its continuous proliferation has been likened to ineffective use of existing antibiotics, a decline in the number of companies and groups involved in the development of new antimicrobial agents, and lack of novel strategies [1, 2, 3]. These, therefore, increases the need to discover and develop new antimicrobial agents.

Antimicrobials are drugs that are capable of stopping or slowing the growth, and spread of pathogenic bacteria and other microorganisms such as fungi, protozoa, virus, etc. These agents are classified based on the microorganisms they can inhibit. So, they are broadly classified as antifungal, antiprotozoal, antiviral agents, etc. They have for decades been a subject of considerable importance and interests in medicinal chemistry and therapeutics. Antibiotics, although sometimes used interchangeably with antimicrobials, and is a more specific term for antibacterial agents. [1,4]

Since the discovery of the first commercialized antibiotic, penicillin, by Sir Alexander Fleming in 1928, antimicrobials have played revolutionary roles in medicinal chemistry and healthcare. Besides the treatment of microbial infections, antibiotics are used in multiple ways in organ transplantation, surgery, cancer chemotherapy, etc.[1,4,5]

1.2 Antimicrobial Resistance

The ability of a microorganism such as bacteria, fungi, virus to stop the inhibitory action of an antimicrobial agent against it is known as antimicrobial resistance. When resistance occurs, the microorganism changes itself on exposure to the antimicrobial and the agent becomes no longer effective against it. [5]

WHO recently stressed the need for research and development to focus more on development and discovery of new antibiotics with specific emphasis on antibiotics against drug resistant Gram-negative bacteria, and those for pediatrics; and against highly morbid community diseases such as gonorrhea, typhoid and ESBL-producing *Enterobacteriaeceae*. In a February 2017 released report tagged, ‘global priority list of antibiotic resistant bacteria to guide, research, discovery and development of new antibiotics’, world Health Organization (WHO) identified carbapenem-resistant *Acinobacter baumannii and Enterobacteriaeceae* as being of critical priority. High priority pathogens are vancomycin-resistant *Enterococcus faecium, Stayphyllococcus aureus,* vancomycin intermediate, methicillin resistant, and as

well as *Campylobacter*; fluoroquinolone resistant, *Salmonella spp; Helicobacter pylori*; clarithromycin resistant, and fluoroquinolone resistant; 3rd generation fluoroquinolone resistant; cephalosporin resistant. *Streptococcus pneumonia;* penicillin non susceptible, *Haemophilus influenza;* ampicillin resistant and *Shigella spp;* fluoroquinolone resistant were identified as medium priority pathogens by the report. [6]

1.3 Causes of Antimicrobial Resistance

Antimicrobial resistance is caused by many factors. Cheap and most common among them are:[4,3,7]

i. Inappropriate and wrong prescription of antimicrobial drugs, sometimes for infections where they are ineffective like viral diseases.

ii. Poor quality of antimicrobial drugs.

iii. Non-adherence to prescription by patients who often miss or change the dosage, interval and duration of use;

iv. Poor infection control measures.

1.4 Combating Antimicrobial Resistance

The United States (CDC) Center for Disease Control and Prevention, European Centre for Disease Control and Prevention (ECDC), the World Health Organization (WHO) and other international agencies have proposed four responsive strategies to fight and control antimicrobial resistance:

1) Preventing Microbial Infections and Spread of Drug Resistant Microbes: This can be achieved by immunization, safe and hygienic food preparation, hand washing, using antibiotics only when necessary.

2) Tracking drug resistant infections and any underlying cause or risk factors in order to develop new and targeted strategies to prevent and control it.

3) Efficient Use of Available Antimicrobials: This is done by using the right antibiotics and only when necessary, correct prescribing, administration (dosage, intervals and duration), and stopping inappropriate usage of antibiotics in humans and animals in a process called antibiotic stewardship.

4) Research and Development of New Antimicrobial Drugs and Diagnostics

Using various medicinal chemistry and drug discovery and development strategies to design, improve and develop newer drugs and therapies. Novel drugs with different mechanisms of action, broad spectrum of activity and less susceptibility to be resisted by bacteria and other microorganisms can be developed by adopting new synthetic and medicinal chemistry strategies. This is where the discipline of pharmaceutical and medicinal chemistry becomes

significant and comes to play a role. Various strategies such as derivatization and conjugation have demonstrated their effectiveness in the improvement of existing antimicrobial drugs, and in the design and development of new ones with synergistic actions, drawing from the knowledge of existing drugs and antimicrobial resistance.[8]

1.5 Quinazolinones and Styryl quinazolinones

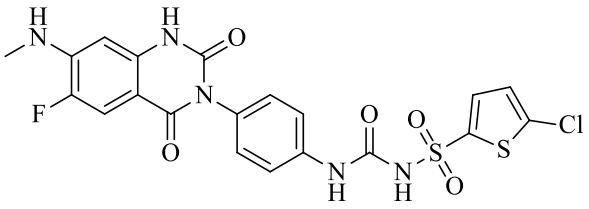
Quinazolinones are heterocyclic compounds that consist primarily of quinazoline (a bicyclic moiety formed by the fusion of benzene and pyrimidine rings) with a ketone (=O) group at position -4 or -2. Several other substitutions are then carried out by different groups at different positions to form several derivatives. Quinazolinones have applications not only in pharmaceutical and medicinal chemistry, but also in veterinary, agrochemical and other areas of chemistry. They can be naturally occurring, semi-synthetic or synthetic.[9-12]

Quinazolinones are very important in synthetic and medicinal chemistry. They are known to have strong and broad spectrum activities. They have antimicrobial, antihypertensive, anticancer, antiviral, anti-inflammatory, antipsychotic, antioxidant, anticonvulsant, antidepressant, antiarrhythmic, antitubercular, antifungal, analgesic, antidiabetic activities. Two main types of quinazolinone derivatives exist. They are quinazolinone-4-ones and quinazolinone-2-ones. The first types are more common, more researched and more used as medicinal agents. Various substituents; both simple atoms or groups, and complex moieties are attached at various positions on the quinazolinone scaffold to derive potent and broad spectrum agents. [9-12,]

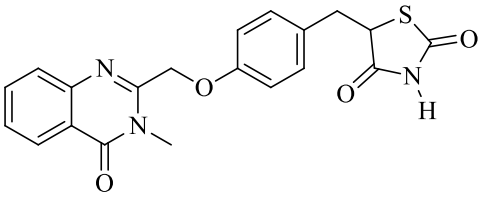
Styryl group especially 2-styryl is an important group used as substituent to improve the activity and potency of compounds. [10] It has been proven to enhance the antibacterial of several quinazolinone derivatives. [10] So, 2-styrylquinazolin-4(3H)-ones represent another scaffold of important antimicrobial agents. [13-15,].

1.6 Commercially Available Drugs Based on Quinazolinone Nucleus

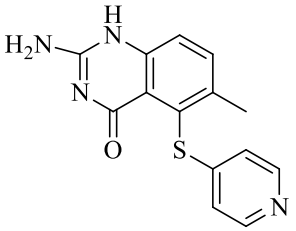
Already there are commercially available drugs containing the quinazolinone scaffold. Examples of such drugs are: Elinogrel, Balaglitazone and Nolatrexed.



Elinogrel



Balaglitazone



Nolatrexed

Fig. 1. Commercially Available Drugs Based on Quinazolinone Nucleus

1.7 Oxadiazole and its Derivatives

One of the important moieties that can be fused or substituted at quinazolinones to obtain medicinally potent agents is oxadiazole and its derivatives. Oxadiazole is a penta-atomic heterocyclic compound consisting of two carbon atoms, two nitrogen atoms and an oxygen atom that can be arranged into four different isomers based on the position of the two nitrogen atoms from the oxygen atom in the ring. 1, 3, 4-oxadiazole which has one nitrogen at position 3 and the other at position 5 is the most potent biologically and chemically. It is also the most studied together with the 1, 2, 4-isomer to some extent. Most of the biological activities of oxadiazole have been attributed to the presence of N=C-O. [16]. Antimicrobial [16-18], anticonvulsant, anti-inflammatory, antitubercular [17], antioxidant [16] and anticancer [16], are some of the medicinally important activities possessed by oxadiazoles.[16-17]. They have also been shown to have antimalarial, muscle relaxant, antitumor, analgesic, anti-convulsant, diuretic, hypnotic and sedative properties. Oxadiazoles have also find application as bioisosteres for esters, carboxylic acids and carboxamide.

Substituents such as phenyl or substituted phenyl groups are added at different positions on the oxadiazole ring to improve its potency and derive other activities as can be seen in the commercially available drugs such as furamizole and in Gupta *et al.*[11-23]

1.8 Commercially Available Drugs Based on Oxadiazole Nucleus

The anticancer drug, Zlibotentan; the antiretroviral agent, Raltegravir; antihypertensive agents, tidazosin and Nesapidil; and the antibiotic, furamizole are examples of drugs which contain oxadiazole moiety [17-18].

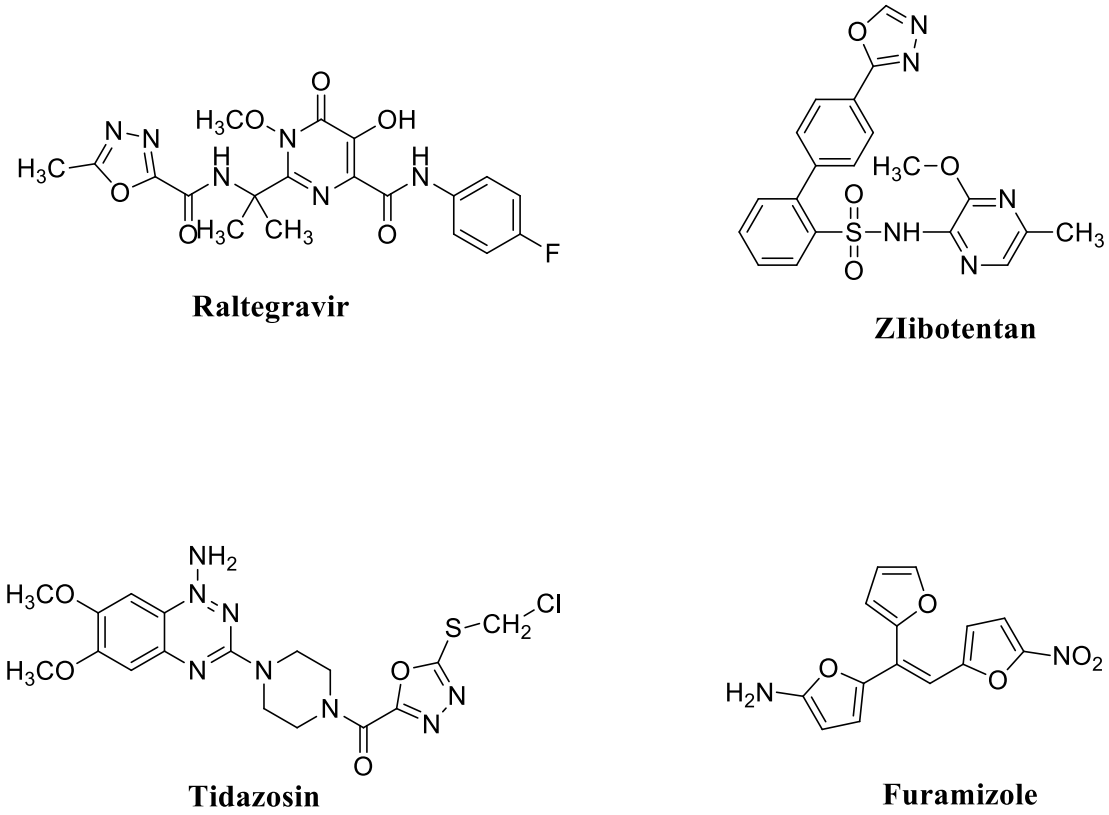


Fig. 2. Commercially Available Drugs Based on Oxadiazole Nucleus

1.9 Combination of 2-Styrylquinazolin-4(3H)-one and 1, 3, 5-Oxadiazole Moieties as an Antimicrobial Strategy Drug Design Strategy

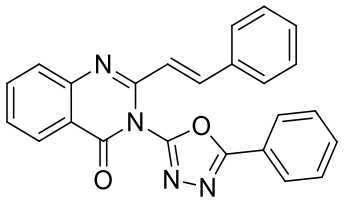
A combination of the three different moieties described above as an antimicrobial drug development strategy will give a more potent compounds with synergistic effect. This has been demonstrated by the work of Rajitha *et al.* and Gupta *et al*. Both synthesized a series of 3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)-one derivatives and tested their antimicrobial activity. Addition of non-substituted styryl group at position 2 of the quinazolinone ring has significantly improved the antimicrobial activity according to both studies. Gupta *et al* revealed further that, the 2-styrylquinazolin-4(3H)-one derivatives have better antibacterial activity than antifungal activity. [18]

CHAPTER 2

REVIEW OF LITERATURE

Several studies have been carried out regarding the antimicrobial activity of quinazolin-4(3H)- one in conjugation with oxadiazole derivatives. Below is a summary of some of them:

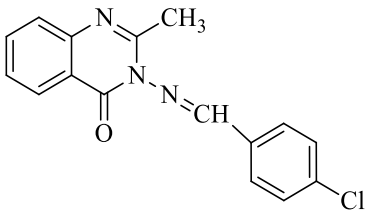
Daina *et al*., (2014) synthesized and studied the biological action of novel quinazolinone-1,3,4-oxadiazole conjugates. In the study, compound **(7)** obtained by reaction of 2-2-dimethylquinazolinone and 4-substituted benzaldehydes to produce a derivative with styryl moiety exhibited and display important role in the antimicrobial infections. [16]



(7)

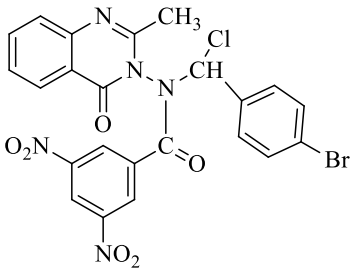
Fig. 3. 3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one

Jabar *et al* (2012) synthesized and evaluated quinazolinone derivatives incorporated with oxadiazole and triazole moieties. The synthesized derivatives were examined against *E. coli*, and *P. mirabilis*. Compounds **(10)** and **(11)** indicated great antibacterial activity.[17]



(10)

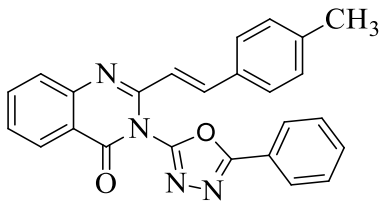
Fig.4. 3-((4-chlorobenzylidene)amino)-2-methylquinazolin-4(3H)-one



(11)

Fig.5. N-((4-bromophenyl)chloromethyl)-N-(2-methyl-4-oxoquinazolin-3(4H)-yl)-3,5-dinitrobenzamide

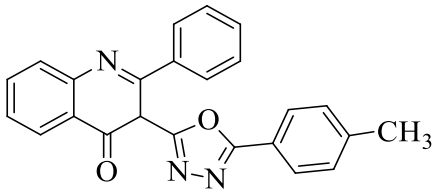
Iproliya *et al*. (2012) combined novel quinazolinone derivatives and considered their antimicrobial action. The outcome demonstrated that compound **(3)** 3-[5-Phenyl-1,3,4-oxadiazole- 2yl]-2-{substituted styryl) quinazolinone standout as; the most active compounds of the series.[18]



(3)

Fig.6. 2-(4-methylstyryl)-3-(5-phenyl-1,3,4-oxadiazol-2-yl)quinazolin-4(3H)-one

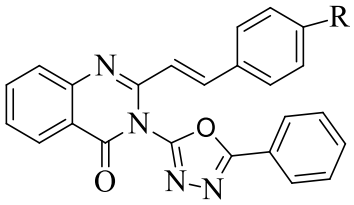
Kumar *et al*., (2012) synthesized and screened some novel quinazolinone derivatives. IC_{50} estimation of two compounds in the series as carried out. The outcomes demonstrated that substitution of electronegative molecules lead to low anticancer action. IC_{50} estimate for the two compounds was 1.0 and 1.5 µM. Of these two compounds, **(4)** 2-phenyl-3-(5-(p-tolyl)-1,3,4-oxadiazole 2yl) quinazolin-4(3H)-one was more active. The two also indicated significant level of action against K_{562} cell lines.[19]



(4)

Fig.7. 2-Phenyl-3-(5-(p-tolyl)-1,3,4-oxadiazol-2-yl)quinolin-4(3H)-one

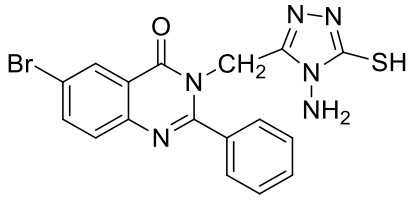
Sowjanya *et al*. (2011) synthesized and evaluated the antimicrobial activity of various quinazolinone derivatives. The activity test was done by the help of cup plate method and screened by four trials of pathogenic bacterial strains. Among the series of compound, the outcome was found that unsubstituted styryl compound **(1)** 3-(5-phenyl-4H-pyrazol-3-yl)- 2-styrylquinazolin-4(3H)- one demonstrated important action. [20]



(1)

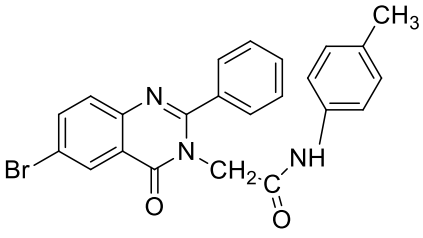
Fig.8. 3-[5-Phenyl-1,3,4-oxadiazole-2yl]-2-(substituted stryryl)quinazolin-4(3H)-one

Rajveer *et al*., (2010) synthesized various substituted 6-bromo-quinazolinones analogues. The synthesized compounds were observed for their antibacterial action by standard methods. Among the tested compounds 1-amino-2-mercaptotriazole analogue of quinazolinone **(8)** and compound **(9)** were found to demonstrate an appreciable antibacterial action. Quinazolinone derivatives were observed to be in the range of 66.16 % and 87.46% percent separately in their antibacterial when compared with standard ampicillin 100%.[21]



(8)

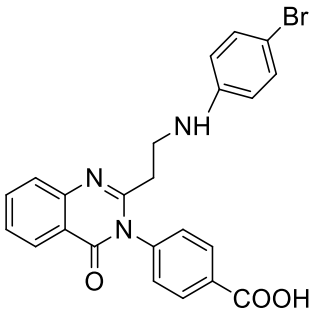
Fig. 9. 3-((4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)methyl)-6-bromo-2-phenylquinazolin-4(3H)-one



(9)

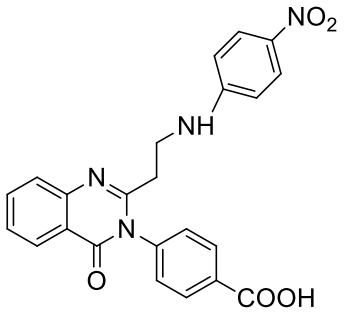
Fig. 10. 2-(6-bromo-4-oxo-2-phenylquinazolin-3(4H)-yl)-N-(p-tolyl)acetamide

Kiruthiga *el al*. (2009) synthesized various quinazolinone derivatives and evaluated their antibacterial action by turbidimetric method utilizing streptomycin sulfate as standard. The result of the compounds showed that **(5)** and **(6)** displayed direct activity against *Escherichia coli*. This work recommended that novel quinazolinone derivatives of aromatic compounds have direct antibacterial activity. [22]



(5)

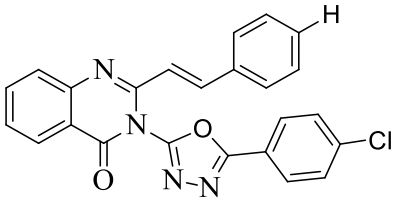
Fig.11. 4-(2-(2-((4-bromophenylamino)ethyl)-4-oxoquinazolin-4(3H)-yl)benzoic acid



(6)

Fig. 12. 4-(2-(2-((4-nitrophenyl)amino)ethyl)-4-oxoquinazolin-4(3H)-yl)benzoic acid

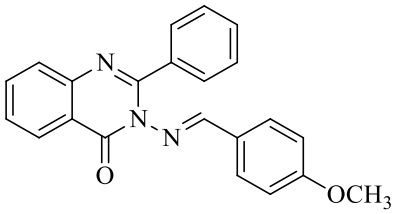
Gupta *et al*. (2007) designed a series of 3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)-one derivatives and tested their antimicrobial activity. They found that addition of non-substituted styryl group at position 2 of the quinazolinone ring has significantly improved the antimicrobial activity. They went further and reveal that the 2-styrylquinazolin-4(3H)-one derivatives have better antibacterial activity than antifungal activity. The outcome demonstrated important role in activity. Just nonsubstituted styryl compound demonstrated good lesson in this research. **(2)** 3-[5-(4-chlorophenyl) - 1,3,4-oxadiazole-2-yl)- 2-styrylquinazolin-4(3H)one was observed active among readied arrangement. Every active compound indicated better antibacterial action.[23]



(2)

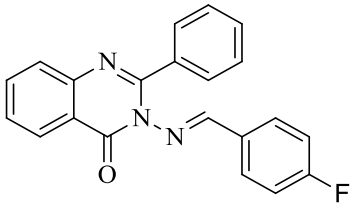
Fig.13. 3-(5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one

Nanda *et al*., (2007) evaluated and synthesized numerous quinazolinone derivatives. The antibacterial evaluation was done by turbidimetric technique. The result of the synthesized compounds proved the improved antibacterial action of the quinazolinone scaffold. The compounds indicated comparable antibacterial action towards microorganism with standard ampicillin. Compound **(12)** was more active against *B. subtilis*, **(13)** was more active on *S. aureus* while compound **(14)** was more active against *S. dysenteriae*.[24]



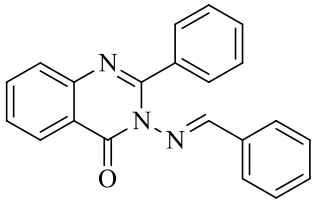
(12)

Fig.14. 3-((4-methoxybenzylidene)amino)-2-phenylquinazolin-4(3H)-one



(13)

Fig. 15 3-((4-fluorobenzylidene)amino)-2-phenylquinazolin-4(3H)-one



(14)

Fig.16 3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one

CHAPTER 3

RATIONALE AND SCOPE OF THE STUDY

This study involved the synthesis and antimicrobial evaluation of novel 3-[5(4-substituted) phenyl-1,3,4 oxadiazole-2yl]-2-styrylquinazolin-4(3H)-one derivatives. Although several series of 3-[5(4-substituted) phenyl-1,3,4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)-one derivatives have been synthesized and their antimicrobial activity tested. There is need to probe the effect of substitution of electron withdrawing groups at the phenyl-1,3,4-oxadiazole moiety to the antimicrobial activity of these scaffold. The synthesis was carried out using limited available laboratory resources. Melting point, IR and NMR spectroscopy were used to confirm the identity of the synthesized compounds. The evaluation of the antibacterial activity was carried out using cup plate method by measuring zone inhibition. [16-24]

CHAPTER 4

OBJECTIVES OF THE STUDY

Aim: synthesis and antimicrobial activity of novel 3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)-one derivatives.

Objectives: The specific objectives of the study are:

- To synthesize 3-(5-(4-nitrophenyl)-1, 3, 4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one and 3-(5-(4-fluorophenyl)-1, 3, 4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one
- To confirm the identity of the synthesized compounds using infra red and nuclear magnetic resonance spectroscopy.
- To test the antimicrobial activity of the synthesized compounds against bacteria strain *Bacillus subtilis* and *Escherichia coli* using cup plate method
- To evaluate the effect of substitution of electron withdrawing groups like nitro and flouro groups on the phenyl-1,3,4-oxadiazole moiety of the of 3-[5(4-substituted) phenyl 1,3,4-oxadiazole-2yl]-2- styrylquinazolin-4(3H)-one to the antimicrobial activity of the scaffold and with standard antibiotics likes penicillin, streptomycin etc.

CHAPTER 5

MATERIALS AND RESEARCH METHODOLOGY

5.1 Materials

5.1.1 Reagents

Table 1. List of Reagents Used

S. No.	Chemical Name	Company Name
1	Acetic acid	Loba
2	Benzaldehyde	Loba
3	Sodium acetate	Finar
4	Bromine	CDH
5	Semicarbazide hydrochloride	CDH
7	4-Fluorobenzaldehyde	S.d fine-chem Limited
8	4-Nitrobenzaldehyde	Loba
9	Anthranilic acid	Loba
10	Ethanol	CYU
11	Methanol	Loba

5.1.2 Equipments and Instruments

Table 4. List of Instruments Used

S. No.	Instruments	Manufacturer
1	FT-IR Spectrophotometer	Shimadzu
2	NMR Spectrometer	Bruker Avance
3	Rotary evaporator	IKA German
4	Hot air oven	Almicro Pvt,Ltd
5	Refrigerator	Kelvinator India
6	Magnetic stirrer	Remi Sales Ahemdabad
7	Heating mantle	Popular Traders
8	General glass ware	Perfit Ambala
9	Incubator	Remi Sales Ahemdabad
10	Water bath	Popular Trade Ambala
11	Melting point apparatus	Popular Trader Ambala

12	Digital weighing balance	Shimadzu
13	Vacuum pump	Bombay Scientific
14	Magnetic beeds	Remi Sales Ahmedabad

5.2. Methods

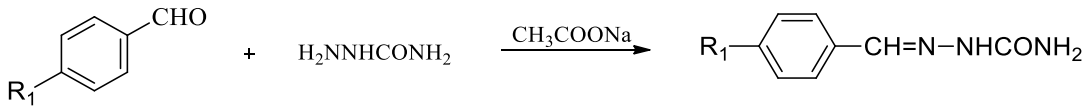
5.2.1 Determination of Melting Point and IR and ^{1}HNMR Spectra

All the reactions were monitored by determination of melting point. Open glass capillaries were used to determine the melting point on popular melting point apparatus. A spectrum, Infrared (IR) was recorded as KBr pellets on Shemadzu FT-IR Spectrometer. The unit of IR peaks is presented in cm^{-1}. (^{1}H NMR) Nuclear magnetic resonance spectra were recorded on Bruker Avance II 400 MHz using DMSO as the solvent. The abbreviations used to indicate the multiplicity are: s, singlet; d, doublet; m, multiplet. Chemical shifts were reported as δ (ppm) relative to tetra methyl silane (TMS) as internal standard.[19-21]

5.2.2 Chemical Synthesis

Step I. synthesis of 4-substitutedbenzaldehyde semicarbazone

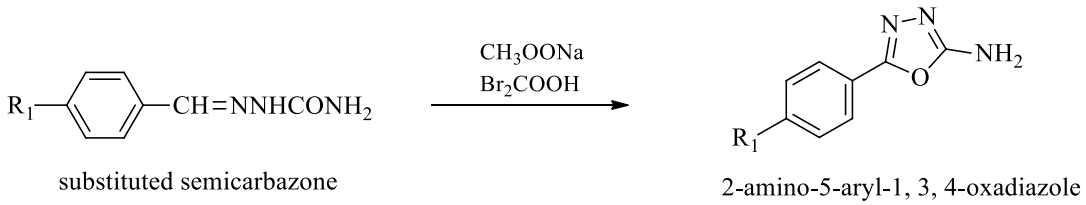
Procedure: 0.01M of aromatic aldehyde (required) was dissolving in aldehyde free alcohol. 0.01M of semicarbazide hydrochloride slowly was added with continuous stirring to an above solution and 0.02M sodium acetate dissolved in 20 ml of distilled water. The precipitated was filtered off, dried, and recrystallized from ethanol (95%).[23]



R_1= NO_2 and F

Synthesis of 2-amino-aryl- 1, 3, 4-oxadiazole

Procedure: 0.01M of semicarbazone (substituted) was measured and 0.02M of sodium acetate was also measured and dissolved in 30-40 ml of glacial acetic acid with continuous stirring. Also Bromine was measured 0.7 ml in 5 ml of glacial acetic acid then, was added and mixed slowly to it. The solution was stirred for at least a 1hr and then poured later onto crushed ice. The product was separated, dried, and recrystallized from ethanol (95%).[23]



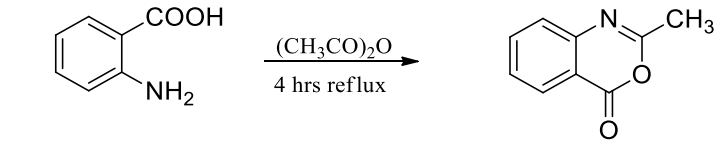
substituted semicarbazone

2-amino-5-aryl-1, 3, 4-oxadiazole

Where $R_1 = NO_2$ and F

Step II. Synthesis of 2-methyl benzoxazinone

Procedure: 0.01M of 2-amino benzoic acid was taken in acetic anhydride in a 250 ml round bottom flask fitted with a refluxed under anhydrous condition for four hrs. Excess of acetic anhydride was distilled off. The resulting mixture was used for the next step.[23]

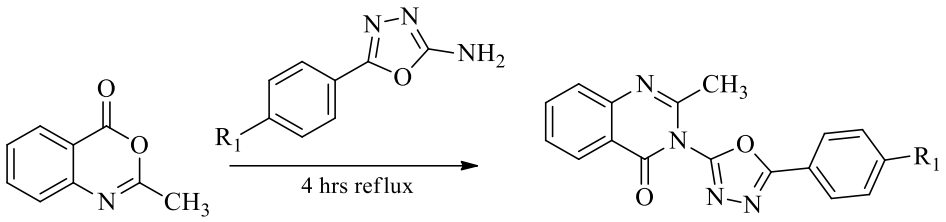


2-aminobenzoic acid

2-methyl benzoxazin-4(3H)-one

Step III. Synthesis of 2-methyl-3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2-yl]-quinazolin-4(3H)-one

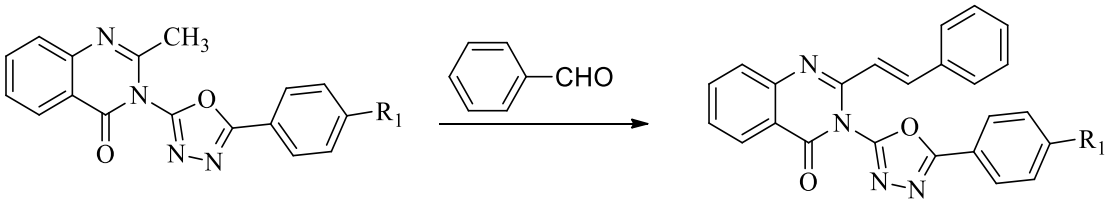
Procedure: To the benzoxazine, 0.01M of 2-amino-5-aryl-1, 3, 4-oxadiazole was measured and 10 ml of glacial acetic acid was added and refluxed under anhydrous condition for 4 hrs. Then after cooling it was poured into crushed ice. The response mixture was separated out, also it then filtered thoroughly, washed with cold distilled water, dried, and recrystallized with ethanol (95%).[23]



Where $R_1 = NO_2$ and F

Step IV Synthesis of 3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)

Procedure: benzaldehyde 0.012M was refluxed with equimolar quantity of 2-methyl-3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2-yl]-quinazolin-4(3H)-one were taken and reacted in the presence of 5.2 mL glacial acetic acid for 18 hrs. A sticky like oily matter was generated which was then purified by using acetone to remove impurities. then the final compound which was dried and recrystallized from hot ethanol.[23]



Where R_1 = NO_2 and F

5.3 Work Plan

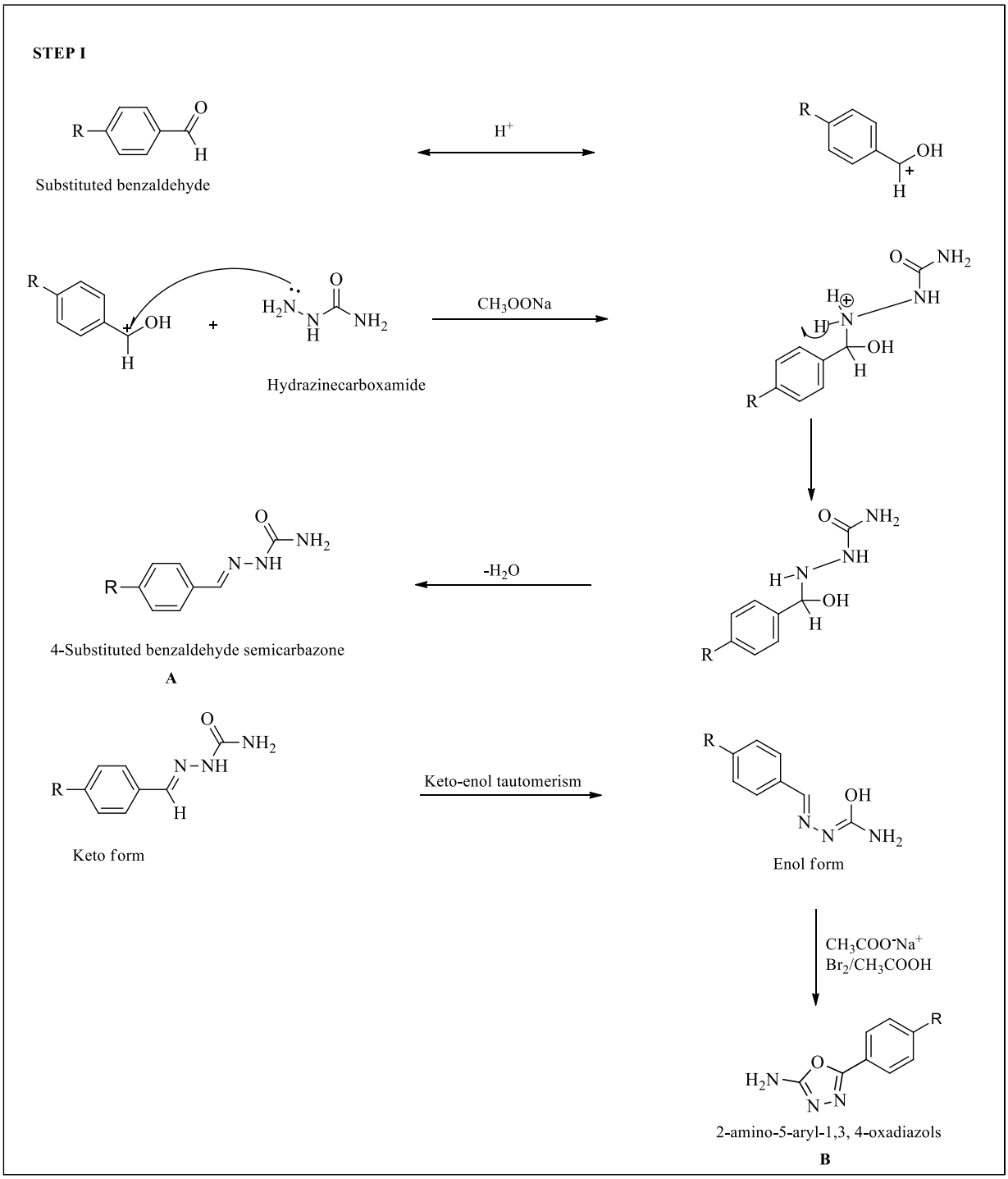


Fig. 17: Scheme I. Synthesis of 4-substituted benzaldehyde semicarbazone and 2-amino-5-aryl-1, 3, 4-oxadiazole

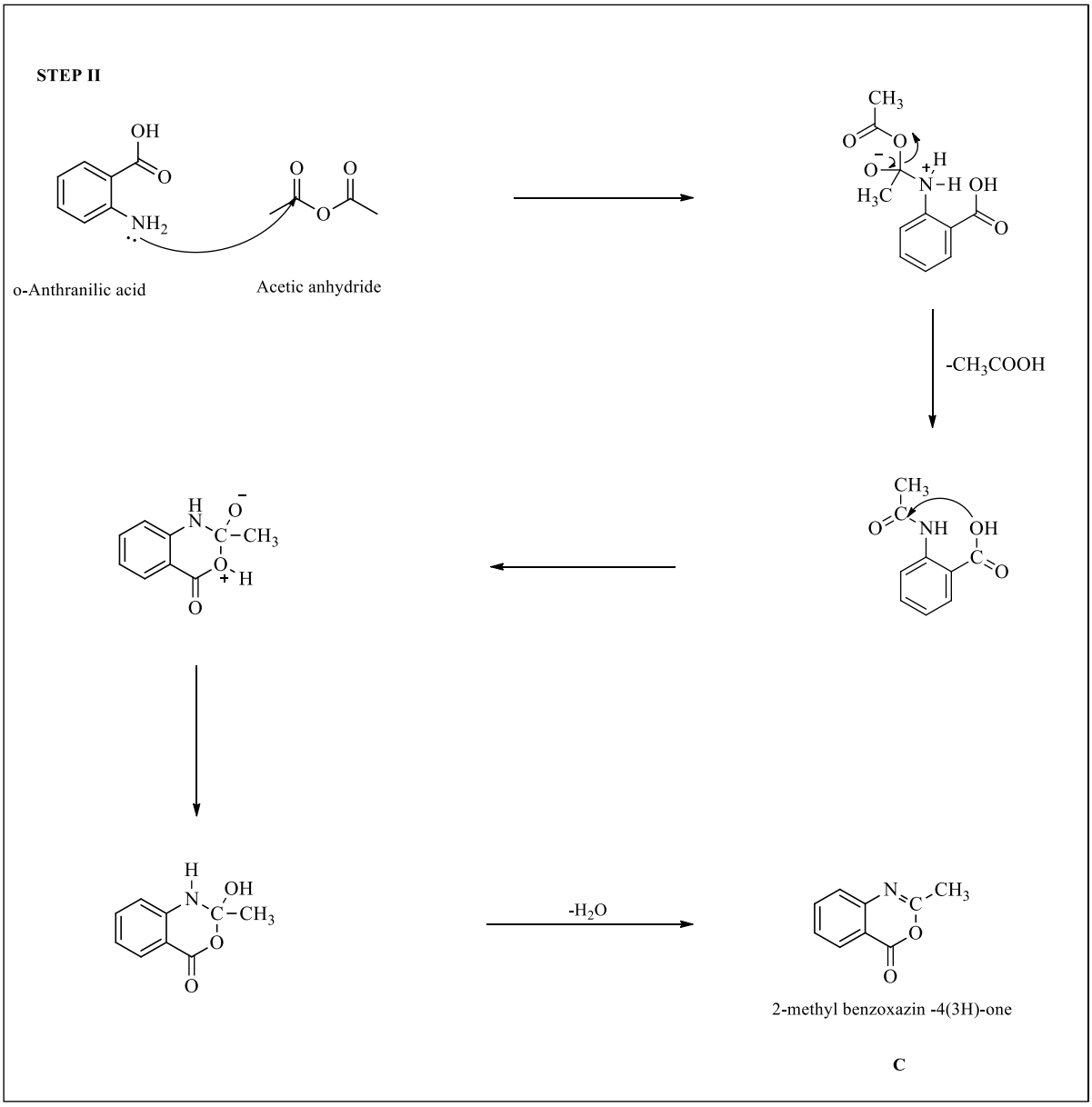


Fig. 18 Scheme II. Synthesis of 2-methyl benzoxazin-4(3H)-one

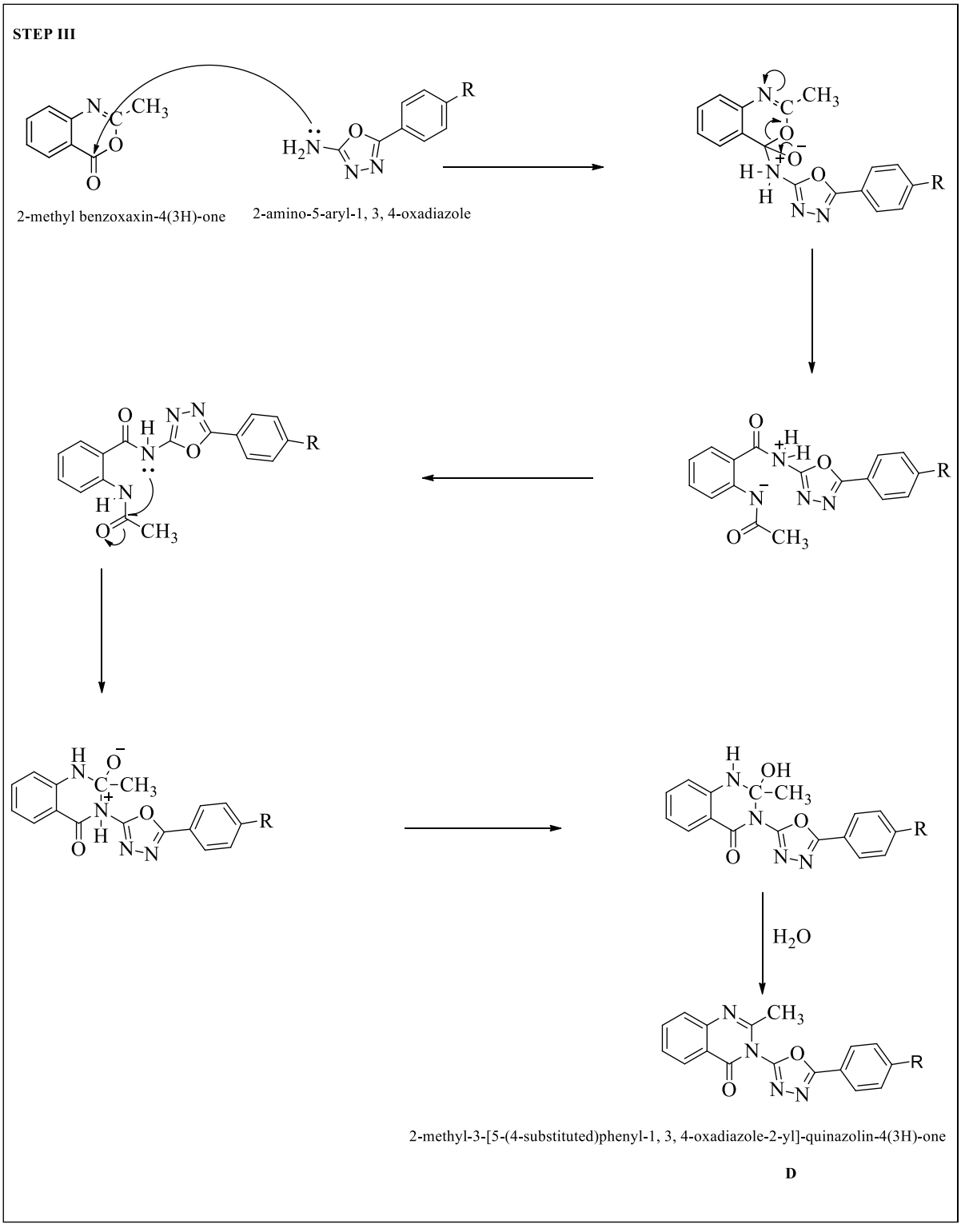


Fig. 19 Scheme III. Synthesis of 2-methyl-3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2-yl]-quinazolin-4(3H)-one

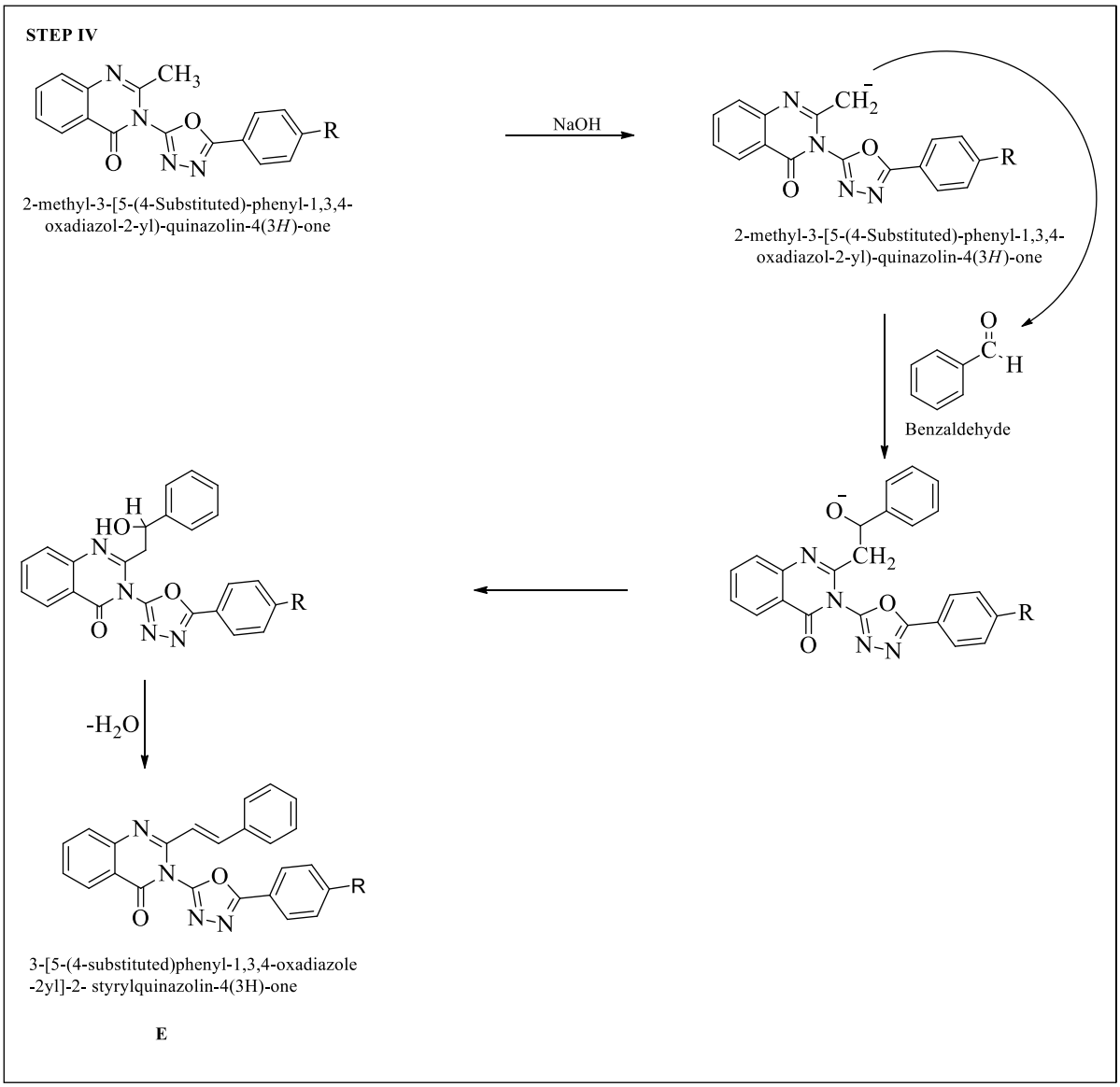


Fig. 20 Scheme IV. Synthesis of title compound that is 3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)

Table No.3 List of Substituents

No	**R**
I	NO_2
II	F

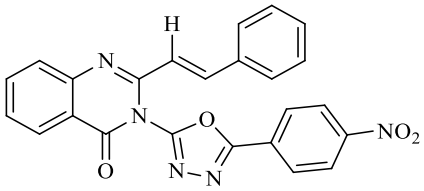


Fig. 21. Target Compound I. 3-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one

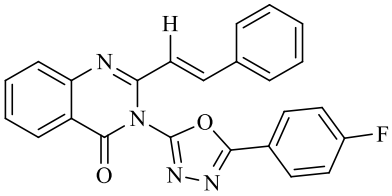


Fig.22. Target Compound II. 3-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one

5.4. Evaluation of the Antibacterial Activity

The evaluation of synthesized compound was done using cup plate method by measuring zone of inhibition. The synthesized compounds were tested for antibacterial action against bacterial strains *Bacillus subtilis,* (gram positive) and *Escherichia coli,* (gram-negative) at a concentration of 100 μg/ml, Streptomycin and penicillin were used as standard drugs in the same concentration. [20]

5.4.1 Preparation of Agar medium

Nutrient agar was used as culture medium. It was organized by dissolving 15g of the fresh open Muller Hinton Agar Medium in 500 ml of refined water. The disintegrated medium was autoclaved at 15 lbs weight at 121 ˚C for 15 minutes. [20]

5.4.2 Cup Plate Method

First of all, the bench laminar airflow was swapped with 70% alcohol, then lamp UV was switched on and then switched off after 30 minutes. Agar was filled in sterile petriplates after drying. the well were punched over the agar plates using sterile gel puncher to make diameter 6 mm. the standard drug were added and the concentration of the test compounds were taken by dissolving the synthesized compounds in dimethylsulfoxide (DMSO), and then added to these cups with a micropipette and the plate were then incubated at 37˚C for 24 hours. The zone of inhibition was measured using mm scale and recorded. Also controls were maintained employing 0.1 ml of dimethylsulfoxide (DMSO).[20]

Table No. 5 Determination of antimicrobial activities

Compound	**Zone of Inhibition (mm)**	
	Bacillus subtilis	*Escherichia coli,*
R-F	30	32
R-NO_2	18	15
Streptomycin	16	13
Penicillin	NA	NA

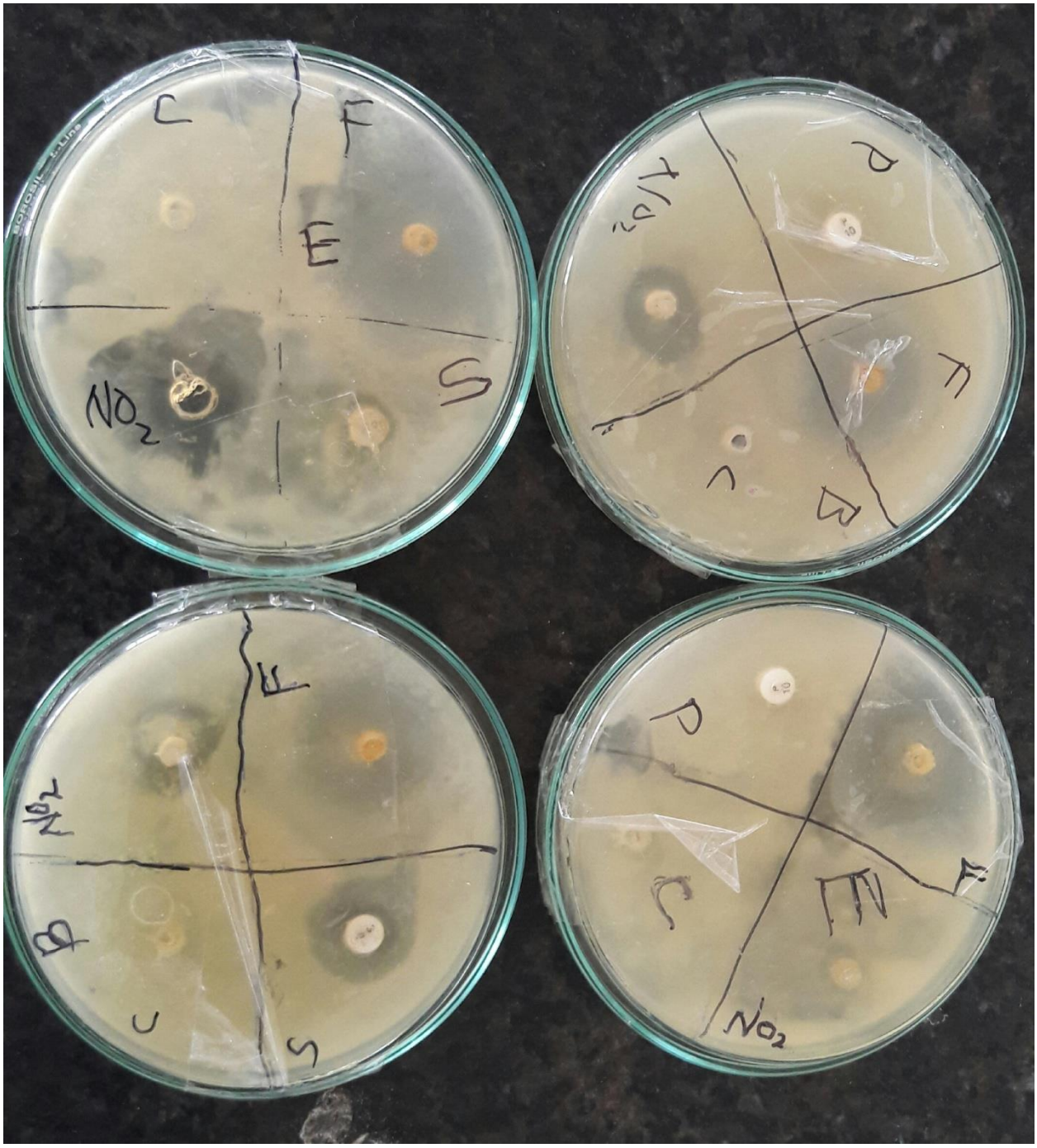


Fig. 23. Result of Antimicrobial Test for Product I and II against *Bacillus subtilis*, and *Escherichia coli*

CHAPTER 6

RESULTS AND DISCUSSION

6.1 Experimental Work

The synthesis of the intermediate and products was carried out according to reactions outlined in the scheme above. The structures of the products was identified and confirmed on the basis of their Melting point, IR and ^{1}NMR spectra.

6.1.2 Analytical Data

4-Nitrobenzaldehyde semicarbazone

Mp (˚C) 189, Mol. Wt: 208.17, formula; $C_8H_8N_4O_3$, yield-85.71%, IR (KBr pellets) cm^{-1} 1543.10 (asymmetry NO_2 str), 1345.39 (symmetry NO_2 str) 1674.27 (C=O str), 3471.02 (N-H str.), 1439.91 (C=C str), 3288.73 (C-H str), 1709.95 (C=N str), 1153.47 (C-N str), 3113.21 (C-H str)

4-Fluorobenzaldehyde semicarbazone

Mp (˚C) 169, Mol. Wt: 181.17, formula; $C_8H_8FN_3O$, yield-86.67%, IR (KBr pellets) cm^{-1} 1274.99 (Ar-C-F str.), 1674.27 (C=O str), 1709.95 (C=N str), 1154.43 (C-N str.), 3368.79 (C-H str.), 1603.86 (C=C str), 3462.34 (N-H str),

5-(4-nitrophenyl)-1, 3, 4-oxadiazol-2-amine

Mp (˚C) 211, Mol. Wt: 206.16, formula; $C_8H_6N_4O_3$, yield-72.12%, IR (KBr pellets) cm^{-1} 1542.14 (asymmetry NO_2 str), 1346.36 (Symmetry NO_2 str), 1153.47 (C-O-C in oxadiazole), 1708.02 (C=N str), 3367.82 (N-H str.), 1599.04 (C=C str), 3120.93 (C-H)

5-(4-Fluorophenyl)-1, 3, 4-oxadiazol-2-amine

Mp (˚C) 188, Mol. Wt: 179.15, formula; $C_8H_6N_3O$, yield-72.12%, IR (KBr pellets) cm^{-1} 1287.53 (Ar-C-F str), 1154.43 (C-O-C in oxadiazole), 1634.73 (C=N str), 3368.79 (N-H str.), 1611.58 (C=C str), 3449.80 (C-H str).

2-methyl-3-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)quinazolin-4(3H)-one

Mp (˚C) 238, Mol. Wt: 349.30, formula; $C_{17}H_{11}N_5O_4$, yield-80.72%, IR (KBr pellets) cm^{-1} 1674.27 (C=O str. in quinazolinone ring), 1653.05 (C=N str), 1283.57 (C-N str.), 1155.40 (C-O-C str in oxadiazole ring), 1601.93 (C=C str), 1549.23 (asymmetry NO_2 str), 1345.39 (symmetry NO_2 str) 1345.39 (C-H methyl str) 829.42 (Ar-C-H str).

2-methyl -3-(5-(4-fluorophenyl)-1, 3, 4-oxadiazol-2-yl) quinazolin-4(3H)-one

Mp (˚C) 198, Mol.Wt: 322.29, formula; $C_{17}H_{11}FN_4O_2$, yield-89.80%, IR (KBr pellets) cm^{-1} 1674.27 (C=O str. in quinazolinone ring), 1634.73 (C=N str), 1283.57 (C-N str.), 1153.47 (C-O-C str in oxadiazole ring), 1258.59 (Ar-F str.), 1471.74 (C=C str), 1346.36 (C-H methyl str), 839.06 (Ar-C-H).

3-(5-(4-nitrophenyl)-1, 3, 4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one

Mp (˚C) 231, Mol. Wt: 437.41, formula; $C_{24}H_{15}N_5O_4$, yield-75.00%, IR (KBr pellets) cm^{-1} 1674.27 (C=O str. in quinazolinone ring), 1602.90(C=C str), 1456.30 (C=N str), 1283.57 (C-N str.), 1155.40 (C-O-C str in oxadiazole ring), 1539.25 (asymmetry NO_2 str.), 1346.36 (symmetry NO_2), 1456.30 (C=C str), 1227.73(C-N str), 877.64 (Ar-C-H). ^{1}HNMR (400 MHz, DMSO); 7.23-8.05(m, Ar-H);

3-(5-(4-fluorophenyl)-1, 3, 4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one

Mp (˚C) 189, Mol. Wt: 410.40, formula; $C_{24}H_{15}FN_4O_2$, yield-84.90%, IR (KBr pellets) cm^{-1} 1676.20 (C=O str. in quinazolinone ring), 1634.73 (C=N str), 1602.90 (C=C), 1289.46 (C-N str.), 1156.40 (C-O-C str in oxadiazole ring), 1036.77 (Ar- C-F str.), 1453.41 (C=C str),1227.73(C-N str), 845.81 (Ar-C-H). ^{1}HNMR [(400 MHz, DMSO)] 7.17-8.01(m, Ar-H)

6.2 Result of the Antibacterial Activity

By using cup plate method, the synthesized compounds were tested against bacterial strains *Bacillus subtilis,* (gram positive) and *Escherichia coli,* (gram-negative). The two synthesized compounds were found to possess substantial antibacterial activity. They exhibited higher activity than the standard drugs streptomycin and penicillin. Compound II (Fig. **)**, the fluoro derivative showed higher antibacterial activity against both *Bacillus subtilis* and *Escherichia coli* compared to the nitro derivative.

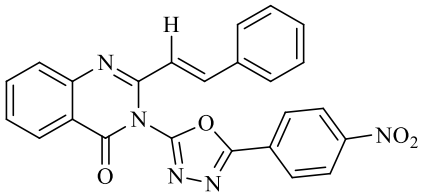


Fig. 24 Compound I

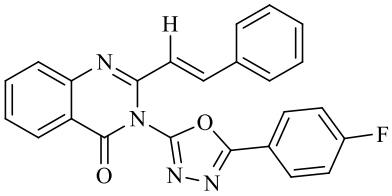


Fig. 25 Compound II

CHAPTER 7

CONCLUSION AND FUTURE SCOPE

Quinazolinones, oxadiazole and styryl groups all have antimicrobial activities. Series of 3-[5-(4-substituted)phenyl-1, 3, 4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)-one derivatives are antimicrobial agents with significant activity and potency especially those with non-substituted styryl group at position 2 of the quinazolinone. Monosubstitution of electron withdrawing groups at the oxadiazole moiety of this scaffold is an effective strategy in improving the potency of the 3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)-one series. This has been confirmed by the improved potency and yield of the synthesized products, 3-(5-(4-nitrophenyl)-1, 3, 4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one and 3-(5-(4-flourophenyl)-1, 3, 4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one derivatives. These two compounds have the potential of becoming novel antimicrobial agents on further studies and optimization.

More studies need to be carried out on the effect of more than one substitution of electron withdrawing groups on the oxadiazole moiety of of the 3-[5-(4-substituted) phenyl-1, 3, 4-oxadiazole-2yl]-2-styrylquinazolin-4(3H)-one scaffold. Study of the effect of other electron withdrawing groups on the antimicrobial activity of this scaffold as well as on its effectiveness in the inhibition of other microorganisms like fungi is a subject of further investigation.

SUPPLEMENTARY DATA

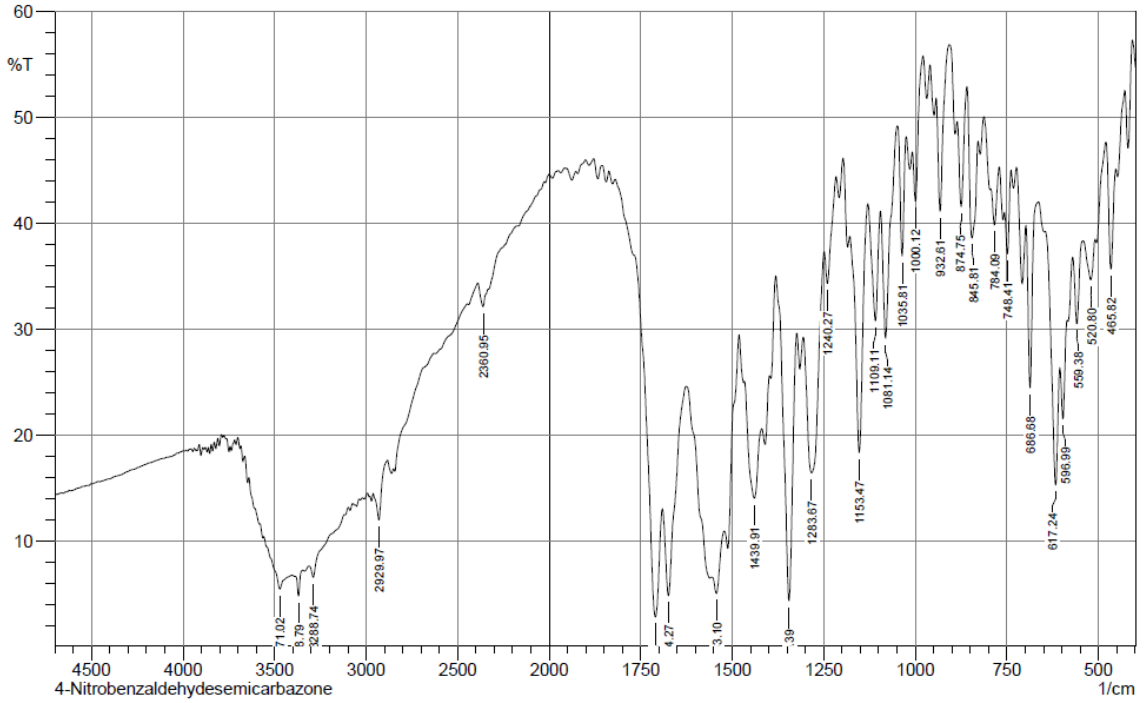


Fig. 26 IR spectra of 4-Nitrobenzaldehyde semicarbazone

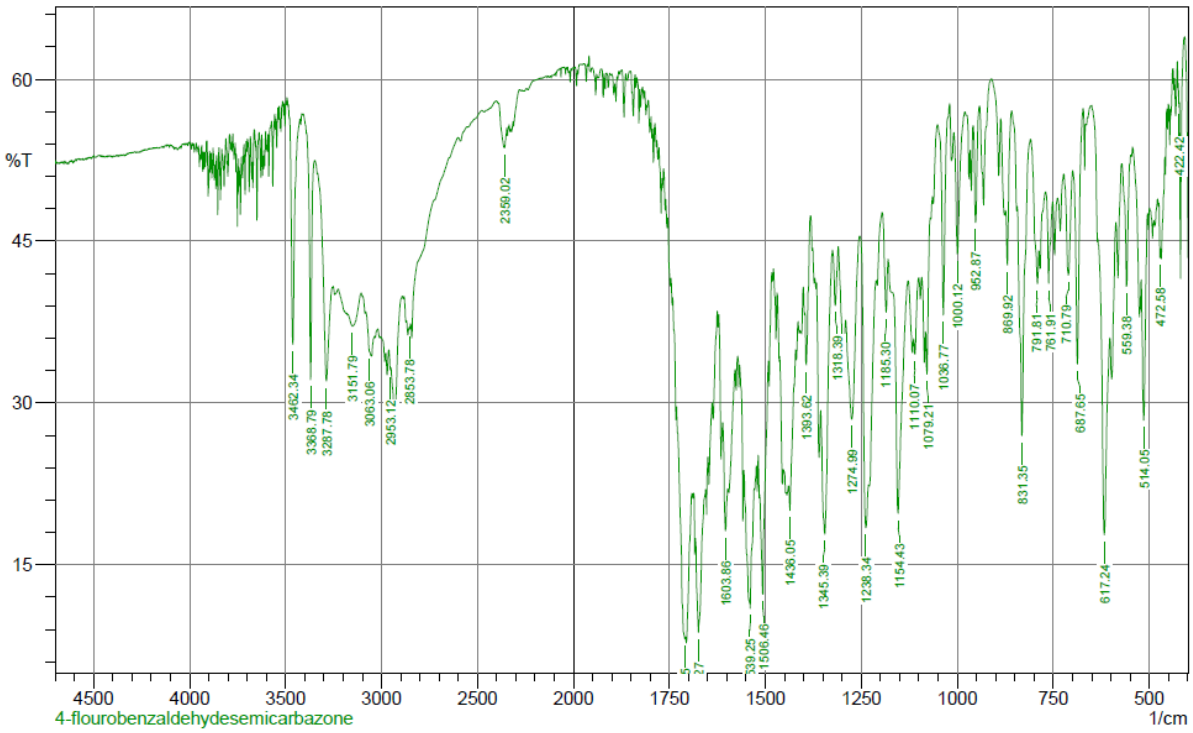


Fig. 27. IR spectra of 4-Fluorobenzaldehyde semicarbazone

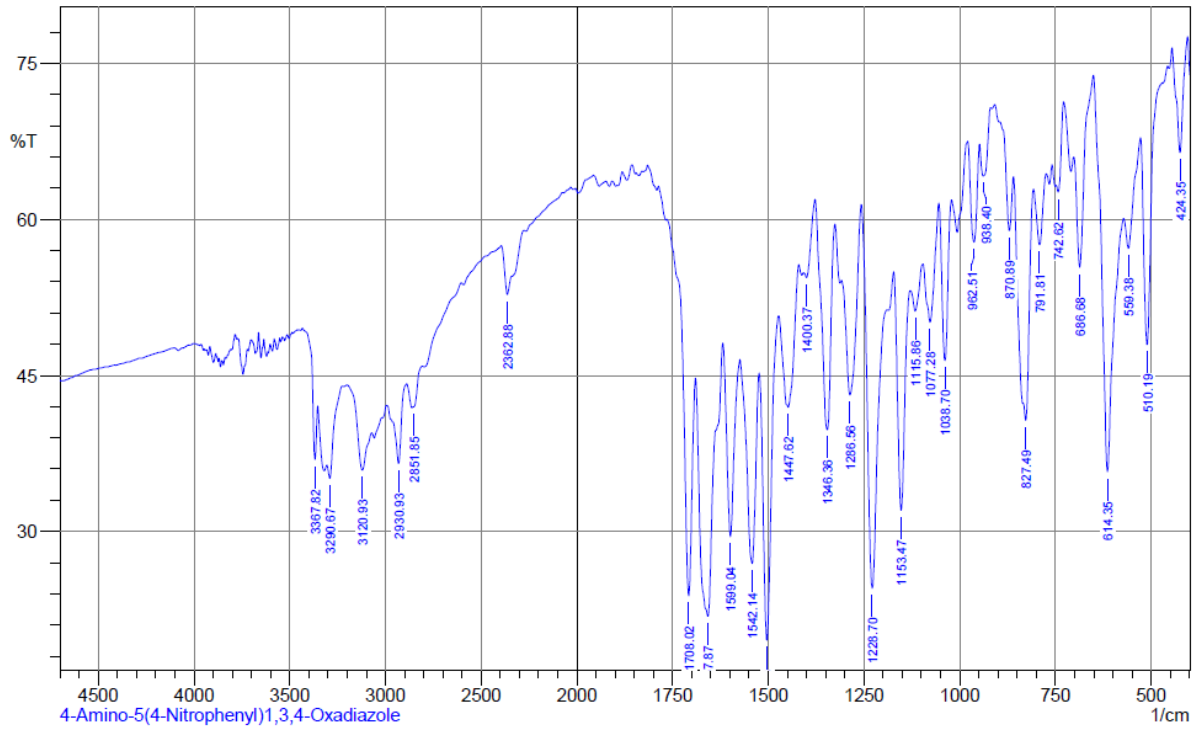


Fig. 28 IR spectra of 5-(4-nitrophenyl)-1, 3, 4-oxadiazol-2-amine

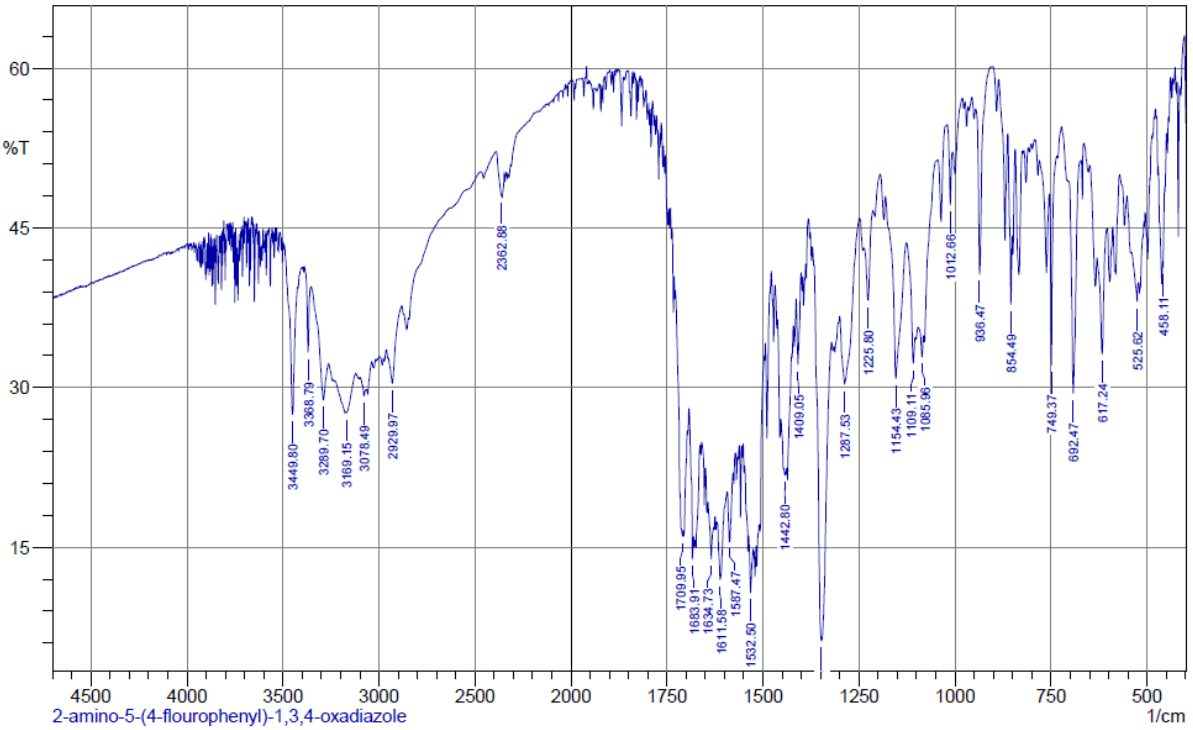


Fig. 29. IR spectra of 5-(4-Fluorophenyl)-1, 3, 4-oxadiazol-2-amine

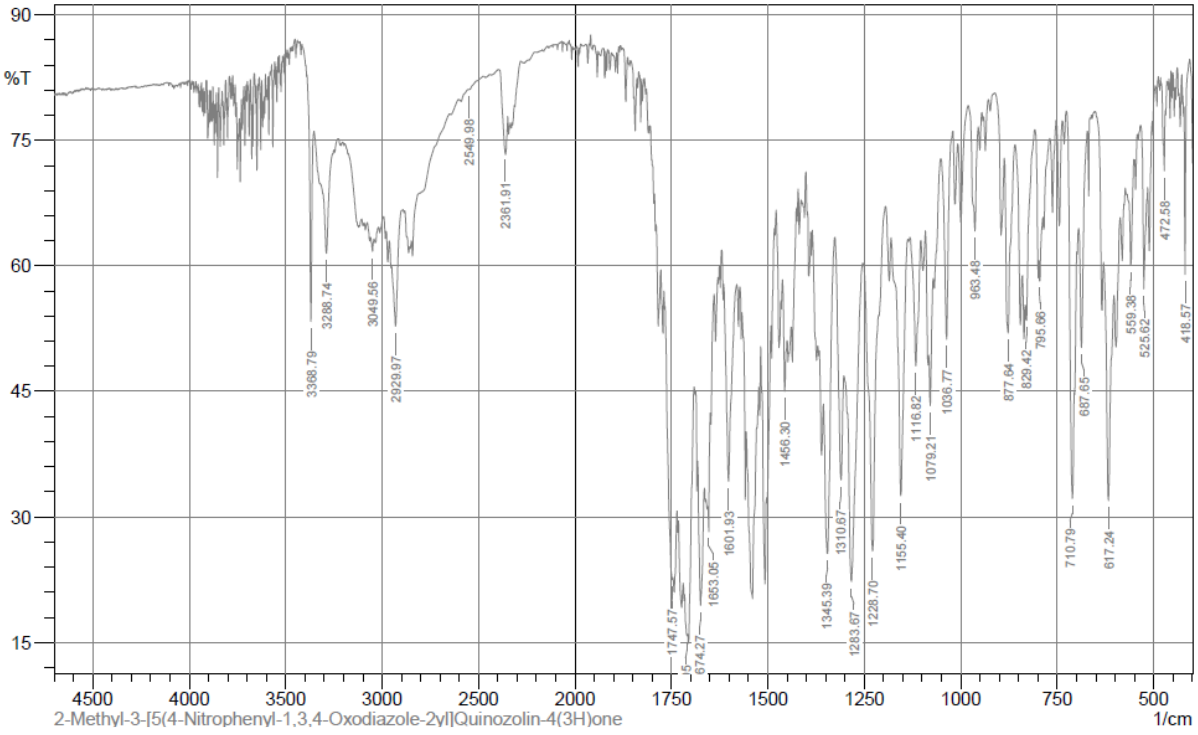


Fig. 30 IR spectra of 2-methyl-3-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)quinazolin-4(3H)-one

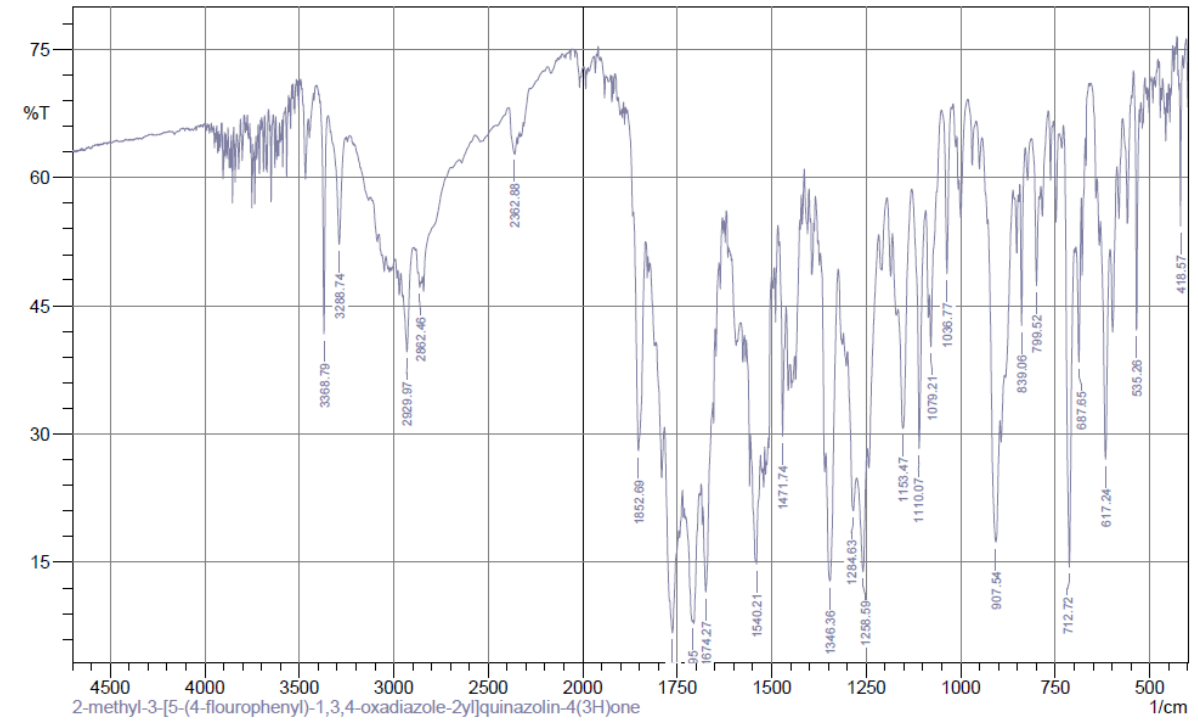


Fig. 31 IR spectra of 2-methyl -3-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)quinazolin-4(3H)-one

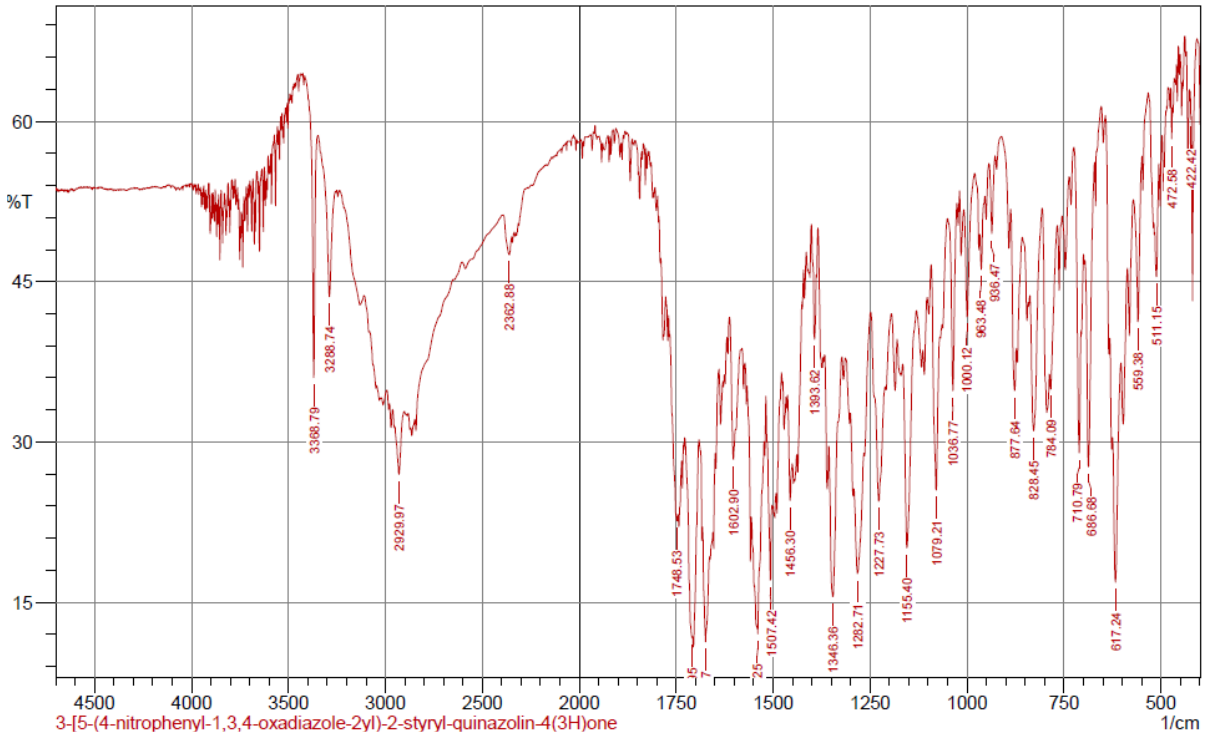


Fig. 32 IR spectra of 3-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one

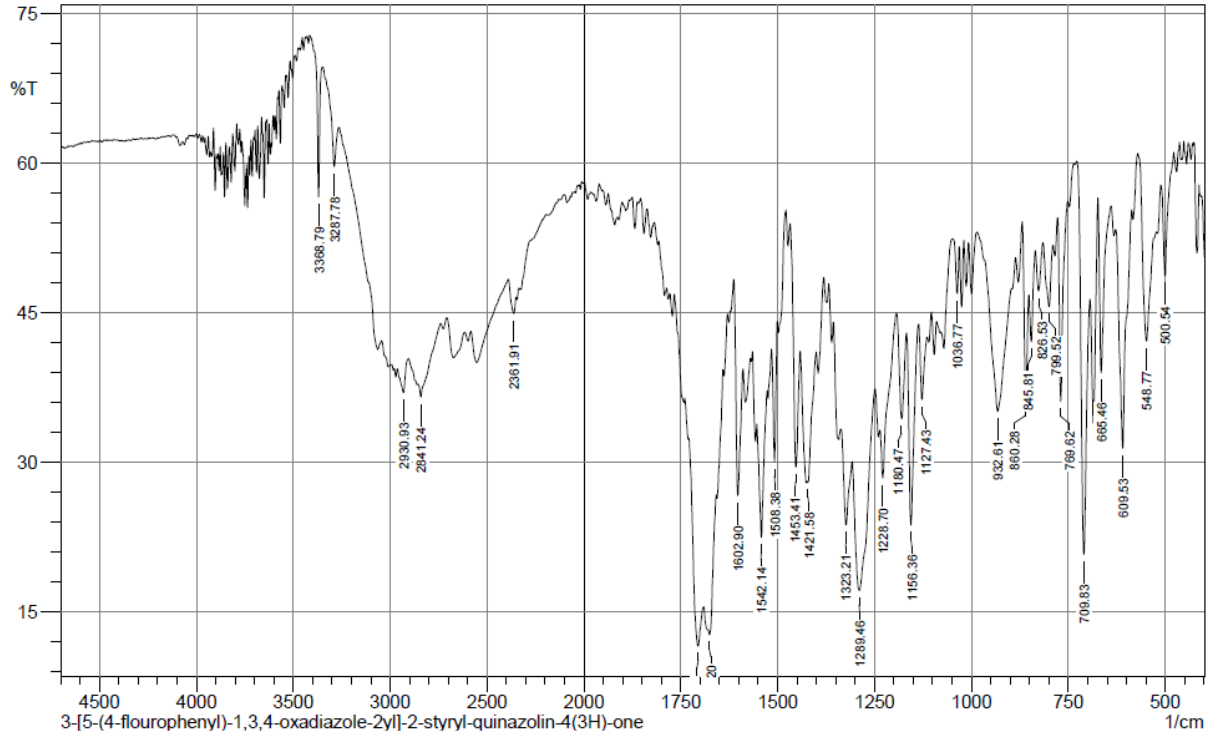


Fig. 33 IR spectra of 3-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one

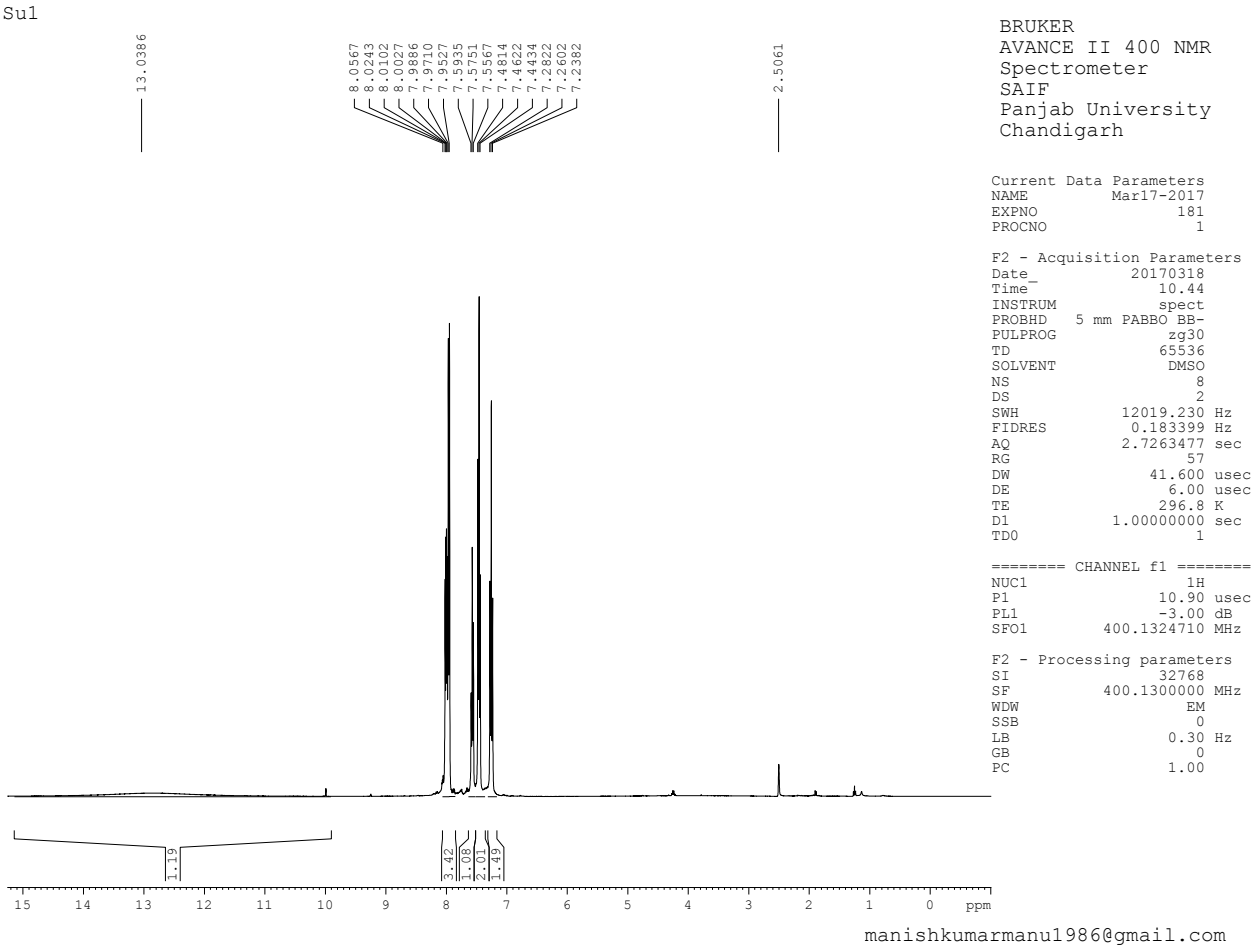


Fig. 34 [1]HNMR spectra of 3-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one

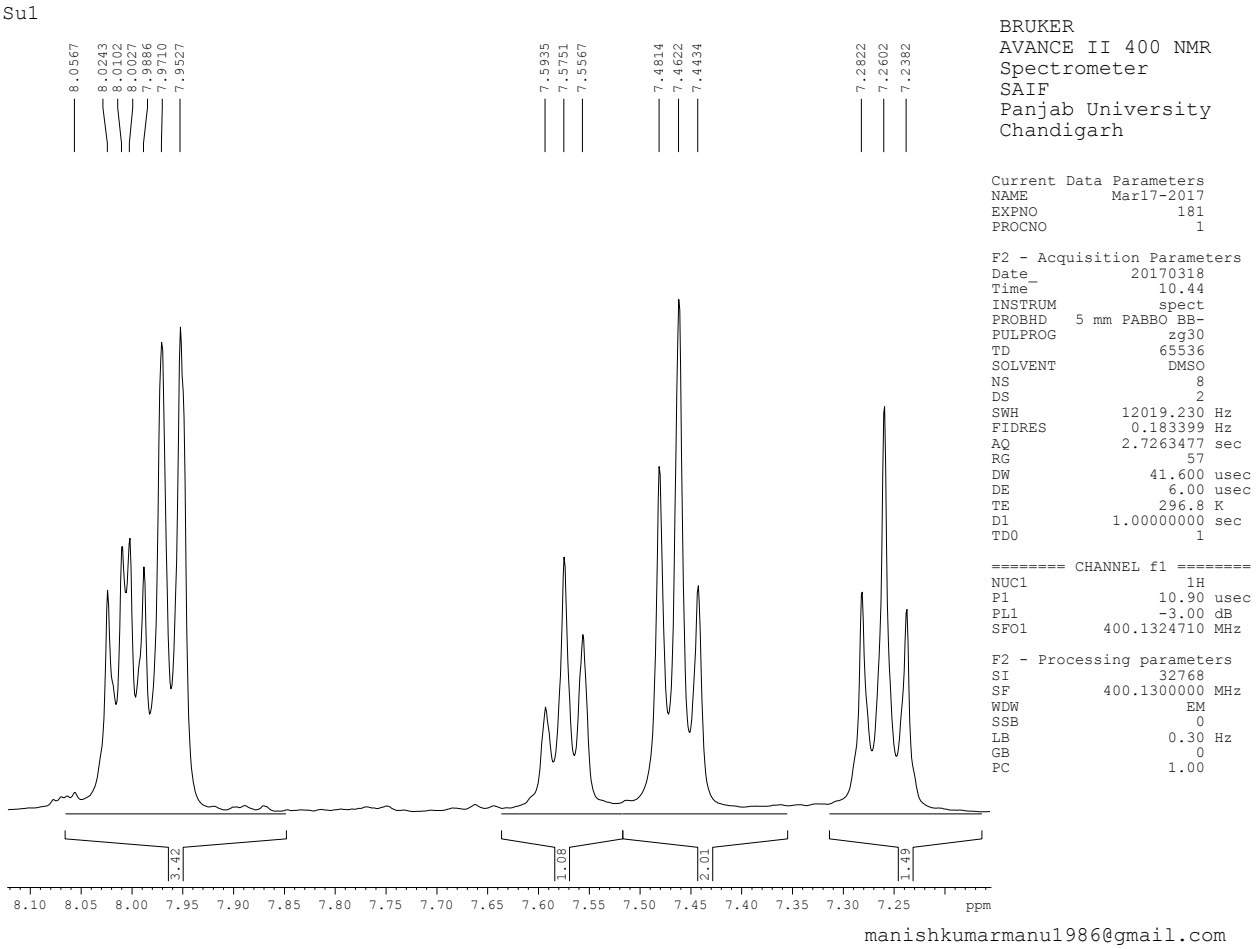


Fig. 35 Expended ^{1}HNMR spectra of 3-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one

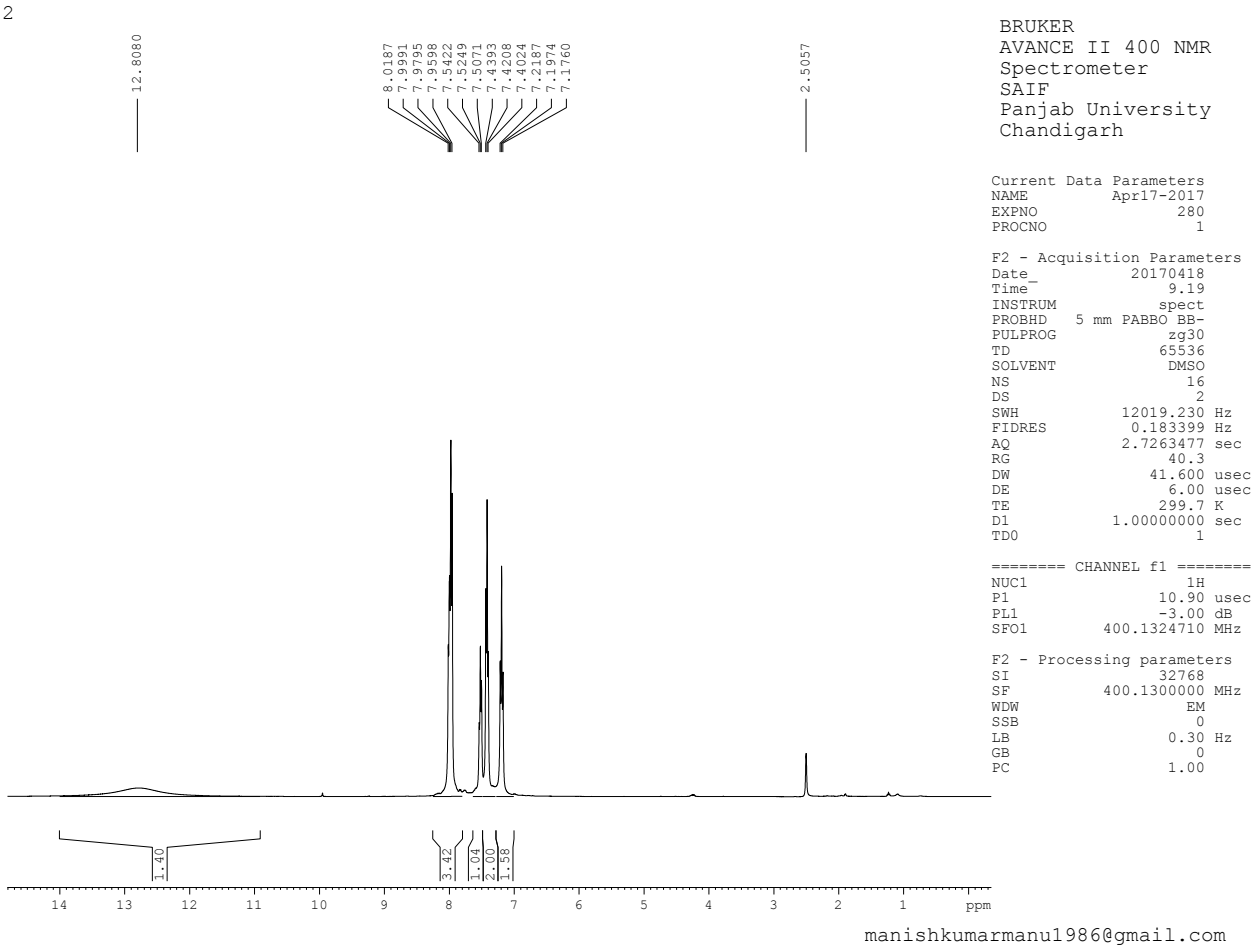


Fig. 36 [1]HNMR spectra of 3-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one

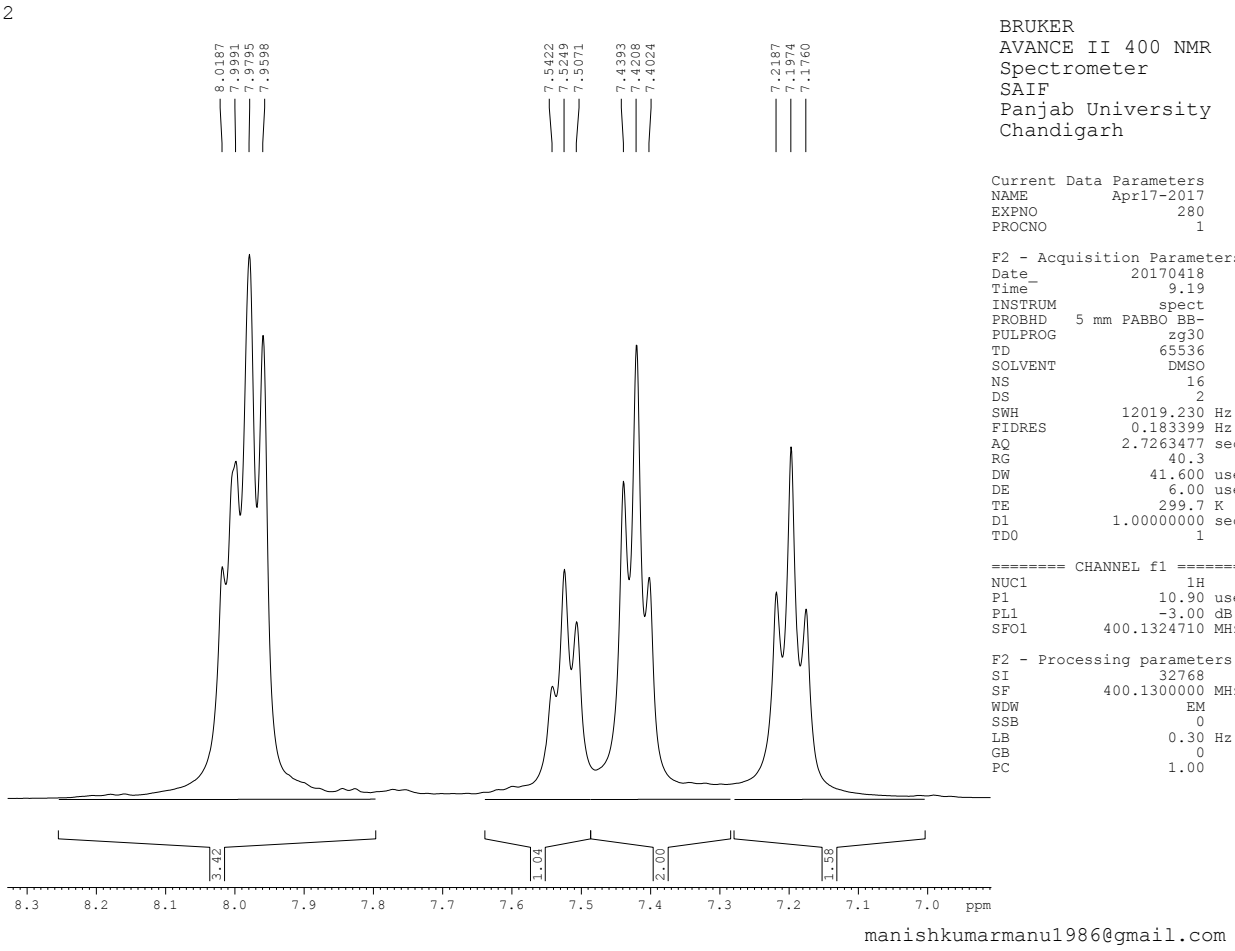


Fig. 37 Expended [1]HNMR spectra of 3-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-2-styrylquinazolin-4(3H)-one

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APPENDIX

Publications/Presentations:

1. Sunusi Hudu Hantsu, Vivek Gupta. Review of Selected Natural Antimicrobial Agents. Presented in LPU NASYA CONFERENCE "**Amalgamation of Recent Pharmaceutical Advances in Ayurveda**" held at Lovely Professional University, Punjab (India) on 22-23/04/2016.
2. Sunusi Hudu Hantsu, Vivek Gupta. Review on quinazolin-4(3H)-one scaffold in antimicrobial drug discovery. Presented in the in the "**International Conference of Pharmacy (ICP-2017)**" held at Lovely Professional University, Punjab (India) on 7-8/04/2017.
3. Sunusi Hudu Hantsu attended as delegate National Symposium on "**Next-Gen Challenges in Pharmaceutical Sciences**" held at University institute of Pharmaceutical Sciences Punjab University, Chandigarh. On March 17, 2017