A SYNOPSIS

of the thesis

Synthesis and Characterization of Some New Oxazole Containing Heterocyclic Compounds and Study of Their Biological Activities

To be Submitted
As a partial fulfilment for the award of the degree of

DOCTOR OF PHILOSOPHY

in

Chemistry

By

Katariya Kanubhai Dulabhai

Under the supervision of

Prof. Shailesh R. Shah

Department of Chemistry
Faculty of Science
Maharaja Sayajirao University of Baroda
Vadodara 390 002
India

May 2018

Synopsis of the Thesis

To be submitted to The Maharaja Sayajirao University of Baroda for the award of the degree of DOCTOR OF PHILOSOPHY in Chemistry.

Name of Student: KATARIYA KANUBHAI DULABHAI

Title of the Thesis: 'Synthesis and Characterization of Some Oxazole Containing Heterocyclic Compounds and Study of Their Biological Activities'

Name of the Supervisor: Prof. Shailesh. R. Shah
The Maharaja Sayajirao University of Baroda

Faculty: Faculty of Science, The Maharaja Sayajirao University of Baroda.

Department: Department of Chemistry

Registration No. : FOS/1932

Date of Registration: 24th March 2015

KATARIYA KANUBHAI D.
Research Student

PROF. SHAILESH R. SHAH
Research Guide

The Thesis will be presented in form of the following chapters:

Chapter I
Introduction

Chapter II
Synthesis, of 1-(4-aryl)-3-hydroxy-3-(2-aryloxazol-4-yl)propan-1-one and (E)-1-(4-aryl)-3-(2-aryloxazol-4-yl)propen-1-one and their antidiabetic and anticancer activity.

Chapter III
Synthesis, and anti-inflammatory activity of 3-aryl-5-(2-phenyloxazol-4-yl)-4,5-dihydro-isoxazoles.

Chapter IV
Synthesis and antimicrobial activities of (E)-3-(2-(4-chlorophenyl)-5-methyloxazol-4-yl)-1-aryl-prop-2-en-1-ones and (3-(2-(4-chlorophenyl)-5-methyl-oxazol-4-yl)-5-aryl-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanones.

Chapter V
Synthesis and antitubercular activity of (E)-N'-((2-(4-aryl)-5-methyloxazol-4-yl)methylene) isonicotino-/picolino-hydrazides and their docking study.

Chapter VI (A)
Synthesis, antimicrobial and antitubercular, activities of (E)-4-((2-(6-bromo-/6-chloro-2-methylquinolin-4-yl)hydrazono)methyl)-2-(4-aryl)-5-methyl-oxazoles and their docking study.

Chapter VII (B)
Synthesis and antimicrobial activities of (E)-6-bromo-/6-chloro-4-(2-(4-oxybenzylidene) hydrazinyl)-2-methylquinoline and their docking study.

Chapter: I
Introduction

Chemistry and Medicinal Chemistry

Medicinal chemistry is an important branch of chemistry; it is the science that deals with discovery and design of new therapeutic agents and their development in to useful medicines. Medicinal chemistry is an interdisciplinary science creating the inter-phase between chemistry and life sciences. Medicinal Chemistry involves synthesis of new molecules and/or isolation of compounds from nature and their investigation and application as drugs.

Heterocyclic compounds and their use as a therapeutic agents

The cyclic organic compounds containing at least one of the hetero atoms (O,N,S) are called heterocyclic compounds. The hetero atoms and the heterocyclic compounds are extremely important not only in organic chemistry but in every extent of life. Biological molecules such as DNA and RNA, chlorophyll, haemoglobin, vitamins and many more contains the heterocyclic ring in major skeleton. Heterocyclic compounds show a wide range of applications as pharmaceuticals, agrochemicals, dyes, pigments, polymers.

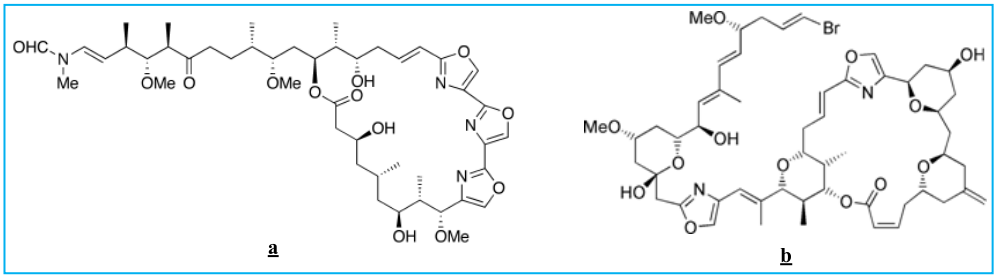
It has been established that heterocyclic compounds play an important role in designing new class of structural entities for medicinal applications. Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents. In the medicinal world, the chemistry of heterocycles has played a vital role in combating many deadly diseases. Due to the presence of hetero atom the organic compounds are able to interact with the enzymes and other bio molecules. Due to all these reasons study and understanding of heterocyclic chemistry is very useful.

Oxazole

Oxazole is a five member heterocycle with two important hetero atoms Nitrogen and Oxygen included in its cyclic structure and is a member of the family of heterocyclic compounds called azoles. Oxazole is considered as a prime scaffold for the drug discovery. The unique structure nature of oxazole moiety endows its derivatives exerting diverse supra molecular interactions such as hydrogen bonds, coordination bonds, ion-dipole, cation-p, p-p stacking interactions, van der Waals force and hydrophobic effects. So oxazole-based compounds display extensively potential applications [1] such as medicinal, agricultural, chemical,

supramolecular as well as materials sciences. In medicinal chemistry, oxazole compounds could readily bind with a variety of enzymes in biological systems and show broad biological activities [2] such as antibacterial, antifungal, antiviral, antitubercular, anticancer, anti-inflammatory activities.[3,4]

A number of oxazole containing natural products have been isolated and characterized in *recent years*. [5] They are oxazole containing macrolides isolated from marine sources e.g. as shown below. Tri-oxazole macrolide **kabiramide a** and **phorboxazole b** isolated from Indian Ocean sponges. These developments have lead to few novel and highly efficient syntheses of oxazole.



Aim and Objectives

- ✓ Synthesis of oxazole containing new compounds with therapeutic interest.
- ✓ Synthesis of the new compounds with combination of two or more heterocycles with oxazole as one of them.
- ✓ Investigation of the new heterocyclic compounds having oxazole moiety for their biological activities.
- ✓ A wide population is affected by diseases such as diabetes, cancer, bacterial and fungal infections and muscular inflammation. So various biological activity studies for the new molecules may include the medicinal activities such as Anticancer, Antidiabetic, Anti-inflammatory, Antifungal, and Antibacterial activities.

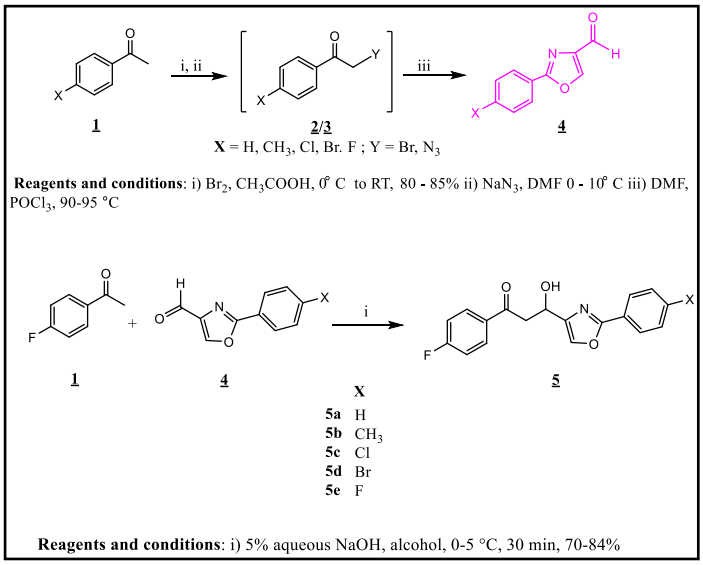
Chapter: II

Synthesis, of 1-(4-aryl)-3-hydroxy-3-(2-aryloxazol-4-yl)propan-1-one and (E)-1-(4-aryl)-3-(2-aryloxazol-4-yl)propen-1-one and their antidiabetic and anticancer activity.

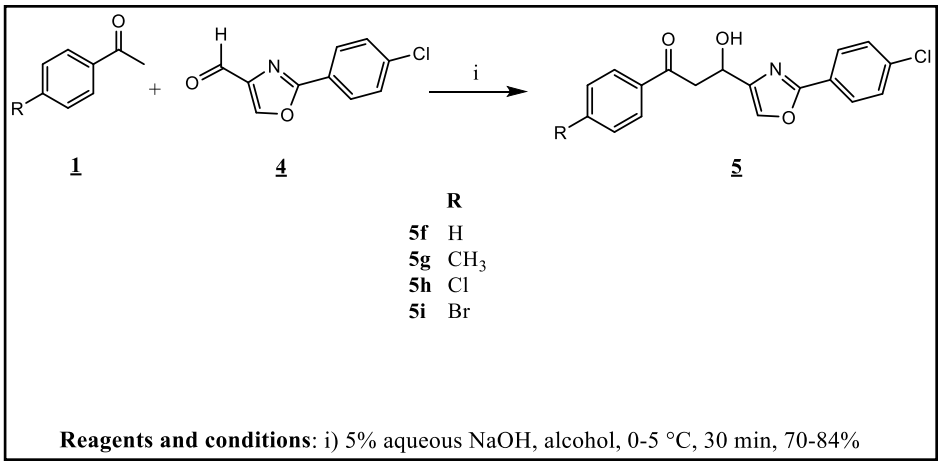
Introduction:

Chalcones or (*E*)-1,3-diphenyl-2-propene-1-ones are the open chain precursor of flavonoids and isoflavonoids. [6] The chemistry of chalcones has remained a fascination among researchers due to its simple chemistry, ease of synthesis, large number of replaceable hydrogen to yield large number of derivatives, and variety of promising biological activities [7, 8]. The presence of α-β unsaturated keto function makes chalcones very prone to undergo reactions with various nucleophiles to give biologically active heterocyclic compounds.

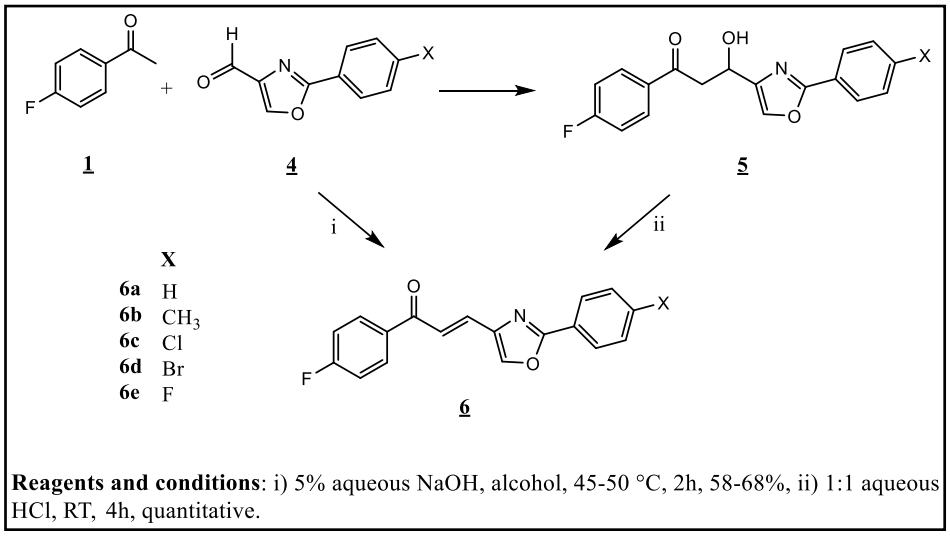
Synthesis:



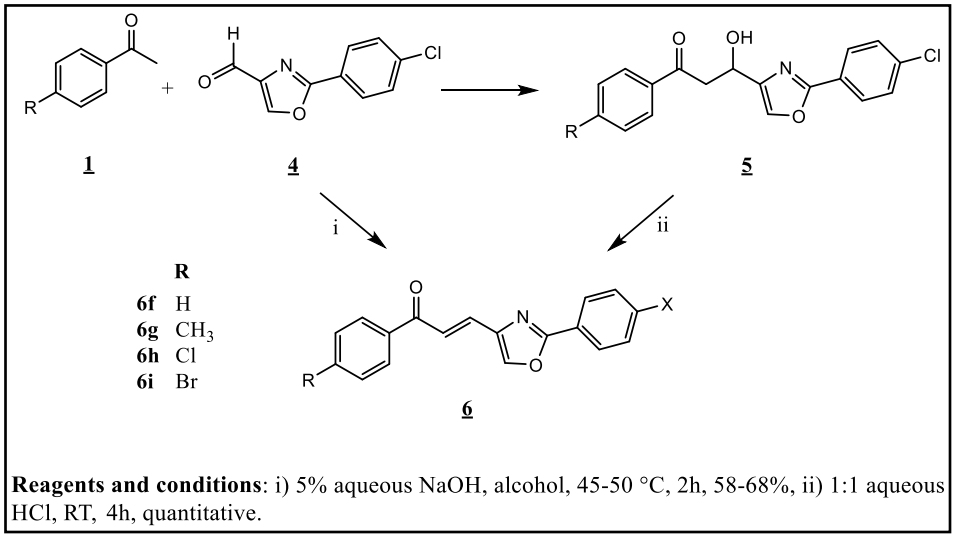
Synthesis:



Synthesis:



Reagents and conditions: i) 5% aqueous NaOH, alcohol, 45-50 °C, 2h, 58-68%, ii) 1:1 aqueous HCl, RT, 4h, quantitative.



Reagents and conditions: i) 5% aqueous NaOH, alcohol, 45-50 °C, 2h, 58-68%, ii) 1:1 aqueous HCl, RT, 4h, quantitative.

Biological Evaluation

Antidiabetic Activity:

All the newly synthesized compounds have been tested for antidiabetic activity. Oral glucose tolerance test (OGTT) was carried out and Glucose concentration in the serum was measured using glucose oxidase-peroxidase method by spectrophotometer.

Anticancer Activity:

Anticancer screening has been done using 60 different human tumour cell lines of 9 different kinds of cancers at NCI, USA.

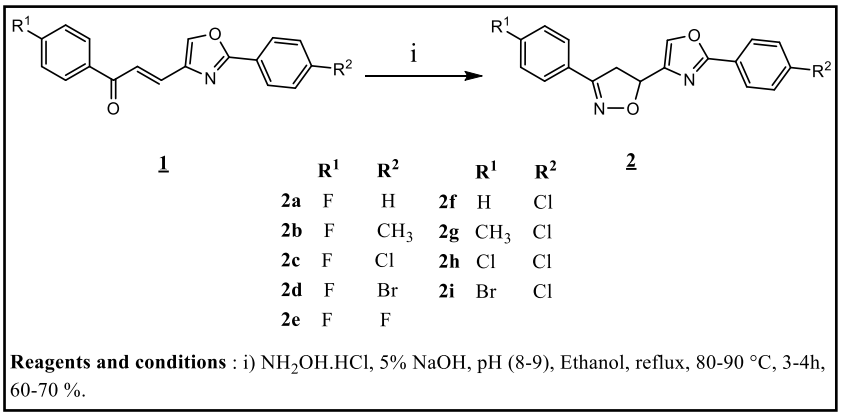
Chapter: III

Synthesis, and anti-inflammatory activity of 3-aryl-5-(2-phenyloxazol-4-yl)-4,5-dihydro-isoxazoles.

Introduction:

Chalcones which are α,β-unsaturated ketones are reactive compounds and undergo reactions at carbon number 1 and 3 with nucleophiles and may undergo cyclization to give some important heterocyclic compounds. Isoxazole is another member of the azole family. It is the oxygen analogue of pyrazole in which one of the nitrogen is replaced with oxygen. Isoxazoline is a dihydro isoxazole. Isoxazolines have marked their individual existence because of diverse biological activities such as antibacterial, antifungal, antiviral, antitubercular, anticancer, anti-inflammatory. [9, 10] Number of reports shows the importance of oxazole and isoxazole as anti-inflammatory agents.

Synthesis:

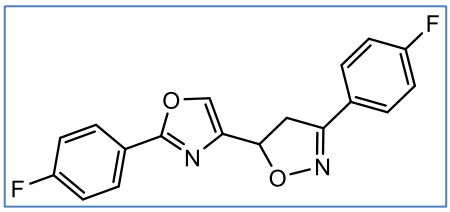


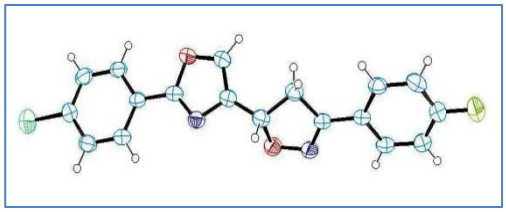
1 **2**

	R^1	R^2		R^1	R^2
2a	F	H	**2f**	H	Cl
2b	F	CH_3	**2g**	CH_3	Cl
2c	F	Cl	**2h**	Cl	Cl
2d	F	Br	**2i**	Br	Cl
2e	F	F			

Reagents and conditions : i) $NH_2OH.HCl$, 5% NaOH, pH (8-9), Ethanol, reflux, 80-90 °C, 3-4h, 60-70 %.

Single Crystal X-ray Analysis:





2e and its ORTEP diaGram

Biological Evaluation

Anti-inflammatory Activity:

in vivo anti-inflammatory activity of all the newly synthesized compounds were carried out on Male SD rats (8-10 weeks) and Rat TNF-α was measured in the plasma.

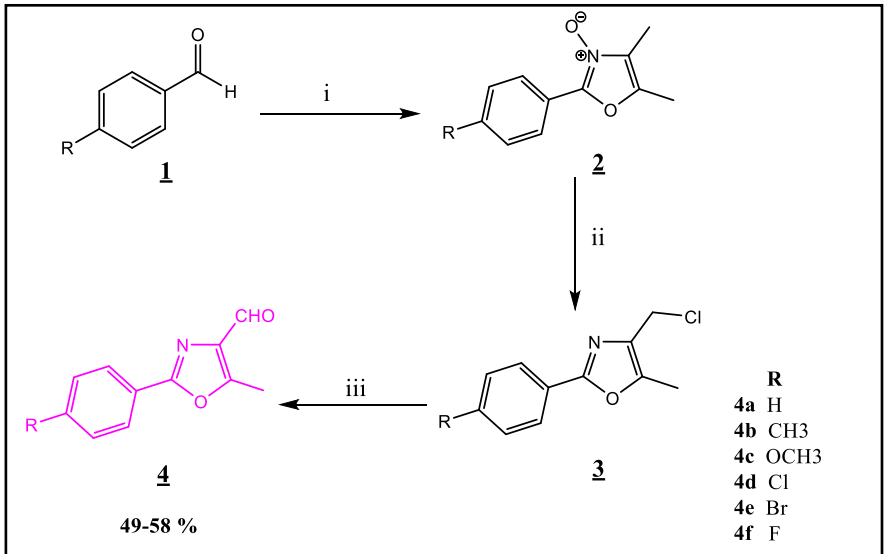
Chapter: IV

Synthesis and antimicrobial activities of (E)-3-(2-(4-chlorophenyl)-5-methyloxazol-4-yl)-1-aryl-prop-2-en-1-ones and (3-(2-(4-chlorophenyl)-5-methyl-oxazol-4-yl)-5-aryl-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanones.

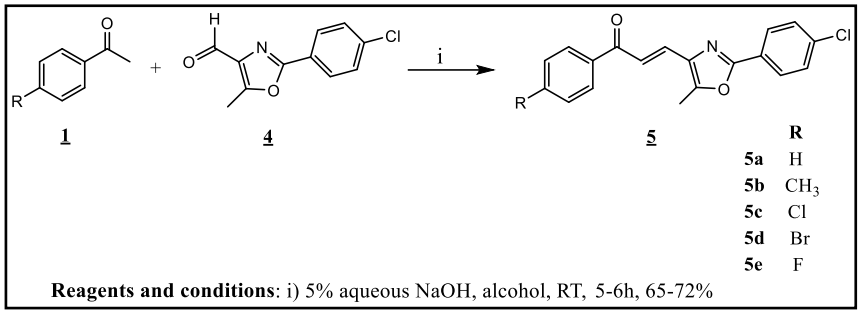
Introduction:

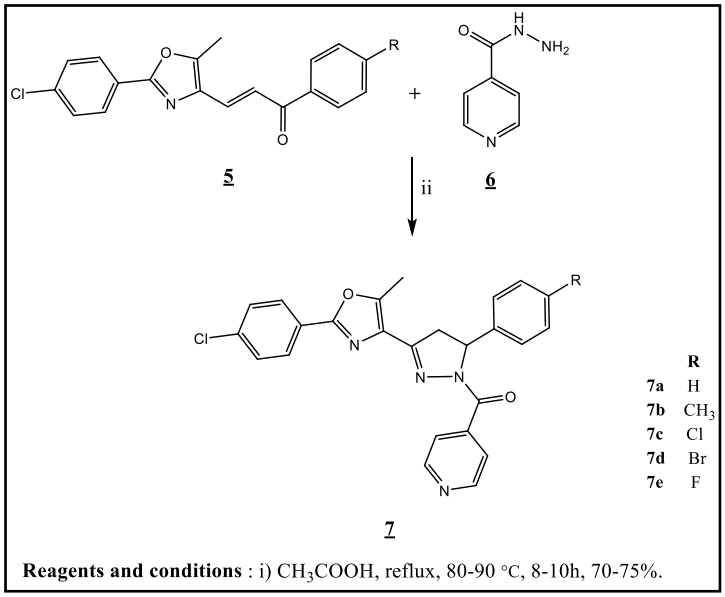
The nitrogen containing compounds have played an important role in drug discovery due to their diverse pharmacological actions. Various Nitrogen containing heterocyclic compounds such as pyrazolines, pyrazoles and pyrrolones have been studied widely for the development of pharmaceutically important antimicrobial agents. Pyrazoline derivatives were reported to possess numerous prominent pharmacological activities; antimicrobial, anti-TB, anti-HIV, anticancer, antidepressant and anticonvulsant. [11, 12] The pyrazoline ring contains N–N bond linkage which is considered to be the key factor in their biological actions.

Synthesis:



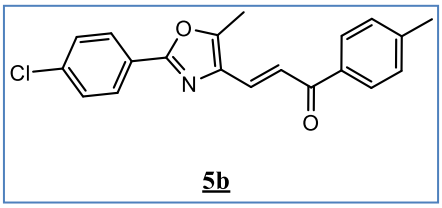
Reagents and conditions : (i) Diacetyl monoxime, AcOH, HCl (g),0-5 °C, 60-90 min; (ii) $POCl_3$, 1,2-dichloroethane, 60 °C, 3h; (iii) Bis-TBAC, $CHCl_3$, reflux,3h,

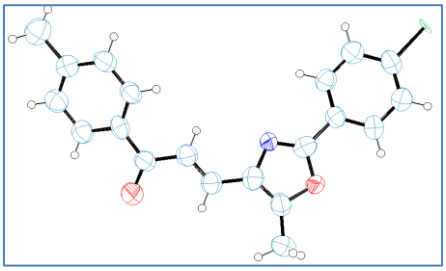




Single Crystal X-ray Structure:

Single crystal of one of the chalcone (**5b**) has been developed from Ethanol.





ORTEP DiaGram (**5b**)

Biological Evaluation

Anti-microbial Activity:

Antimicrobial activity of all the newly synthesized compounds was carried out against *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 619) as Gram positive bacteria *Escherichia coli* (MTCC 739), *Pseudomonas aeruginosa* (MTCC 741) as Gram negative bacteria and fungi *Aspergillus niger* (MTCC 282) and *Candida albicans* (MTCC 183) species using paper disc-diffusion technique [13]. And MIC of the compound was determined by agar streak dilution method [14].

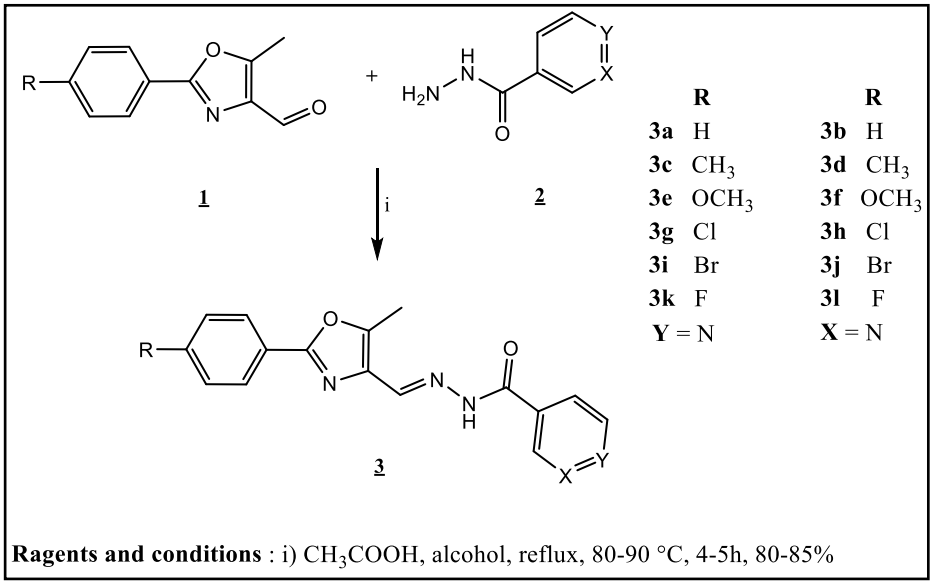
Chapter: V

Synthesis and antitubercular activity of (E)-N'-((2-(4-aryl)-5-methyloxazol-4-yl)methylene) isonicotino-/picolino-hydrazides and their docking study.

Introduction:

Pyridine is a versatile bioactive heterocycle having its wide presence in many synthetic drugs such as rosiglitazone (antidiabetic), pioglitazone (hypoglycemic), lansoprazole (proton-pump inhibitor).The compounds containing pyridine scaffold exhibit anticancer, anti-inflammatory, anti-ulcer, antimycobacterial, and antimicrobial activities [15, 16]. While isonicotinic acid hydrazide (isoniazid or INH), a first-line anti-TB drug is one of the most effective agents used for the treatment of Mycobacterium tuberculosis.[17] Recently, the concept of hybrid molecules has been the most interesting topic in medicinal chemistry, where two or more pharmacophores are linked covalently resulting into one molecule. The two units of final molecule may leads to enhanced bio activity.

Synthesis:



	R		R
3a	H	**3b**	H
3c	CH_3	**3d**	CH_3
3e	OCH_3	**3f**	OCH_3
3g	Cl	**3h**	Cl
3i	Br	**3j**	Br
3k	F	**3l**	F
Y = N		**X** = N	

Ragents and conditions : i) CH_3COOH, alcohol, reflux, 80-90 °C, 4-5h, 80-85%

Biological Evaluation

Antitubercular Activity:

The preliminary antimycobacterial screening for the final synthesized compounds were carried out using BACTEC MGIT Method. [18] And the secondary antimycobacterial screening (MIC) for test compounds were obtained for *M. tuberculosis H37Rv,* by means of L. J. (Lowenstein and Jensen) MIC method. [19]

Chapter: VI

(A)

Synthesis, antimicrobial and antitubercular, activities of (E)-4-((2-(6-bromo-/6-chloro-2-methylquinolin-4-yl)hydrazono)methyl)-2-(4-aryl)-5-methyl-oxazoles and their docking study.

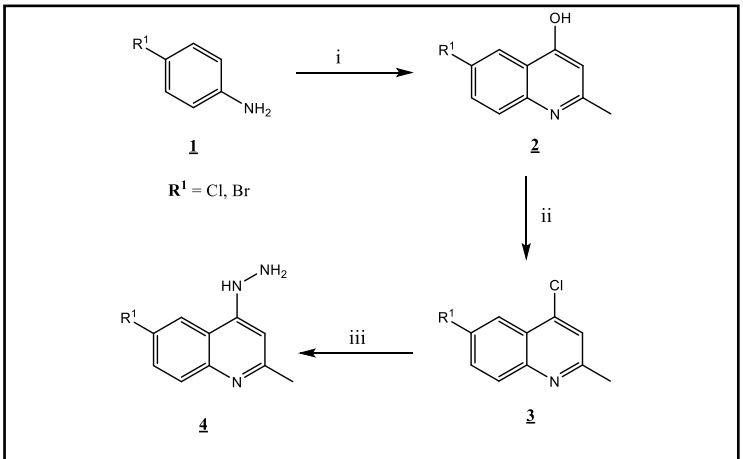
Introduction:

Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), is one of the primary health threats to mankind. Quinoline has gathered an immense attention of chemists as well as biologists as it is one of the key building block elements for many drug derivatives. It is being reported of displaying many interesting biological properties such as antitubercular, antimalarial, antimicrobial, cytotoxic, antiviral, antifungal, anti-inflammatory, anti-alzheimer and antiprotozoal activities [20, 21].

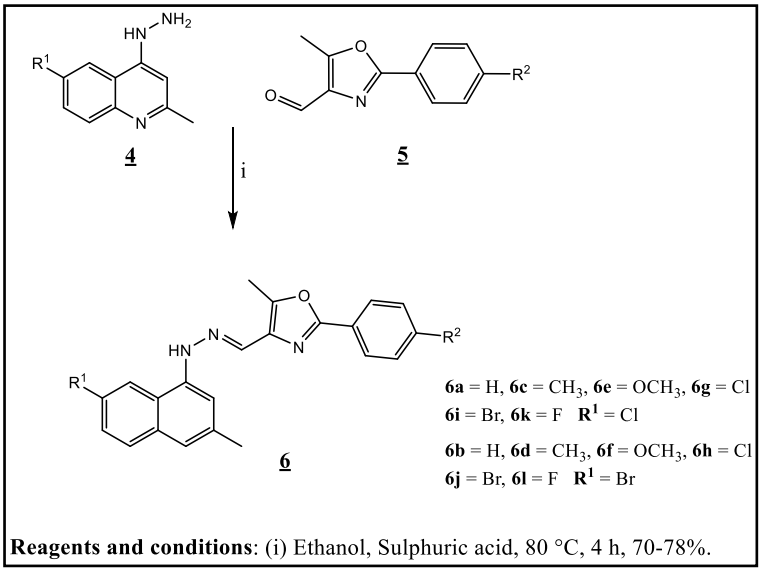
Quinoline has been considered a pharmacophore for the design of anti-TB agents. Ciprofloxacin and moxifloxacin are promising agents for the treatment of TB having quinoline moiety. [22] Quinoline based mefloquine is known for anti-tubercular activity. Hydrazones constitute a class of organic compounds which attracts the attention of medicinal chemists due to the fact that they contain azomethine group (–NH–N=C–). Hydrazone derivatives are found to possess anti-microbial, anti-convulsant, analgesic, anti-inflammatory, anti-platelet, anti-tubercular and anti-tumoral activities [23, 24].

Looking at the medicinal importance of quinoline and hydrazone compounds, some new quinoline derivatives bearing hydrazone linkage were designed and synthesised to study antimicrobial and antitubercular activities.

Synthesis:



Reagents and conditions: (i) Ethyl acetoacetate, PPA, 150 °C, 2 h; (ii) $POCl_3$,80 °C, 4 h; (iii) NH_2NH_2. H_2O, Ethanol, 90 °C, 4h, 69-72%.



Reagents and conditions: (i) Ethanol, Sulphuric acid, 80 °C, 4 h, 70-78%.

Biological Evaluation

Antitubercular Activity:

The preliminary antimycobacterial screening for the final synthesized compounds was carried out using BACTEC MGIT method. And the secondary antimycobacterial screening (MIC) for test compounds was obtained for *M. tuberculosis H37Rv*, by means of L. J. (Lowenstein and Jensen) MIC method.

Antimicrobial Activity:

Antimicrobial activity of all the newly synthesized compounds were carried out against *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 619) as Gram positive bacteria *Escherichia coli* (MTCC 739), *Pseudomonas aeruginosa* (MTCC 741) as Gram negative bacteria. And fungi *Aspergillus niger* (MTCC 282) and *Candida albicans* (MTCC 183) species using paper disc-diffusion technique. And MIC of the compound was determined by agar streak dilution method.

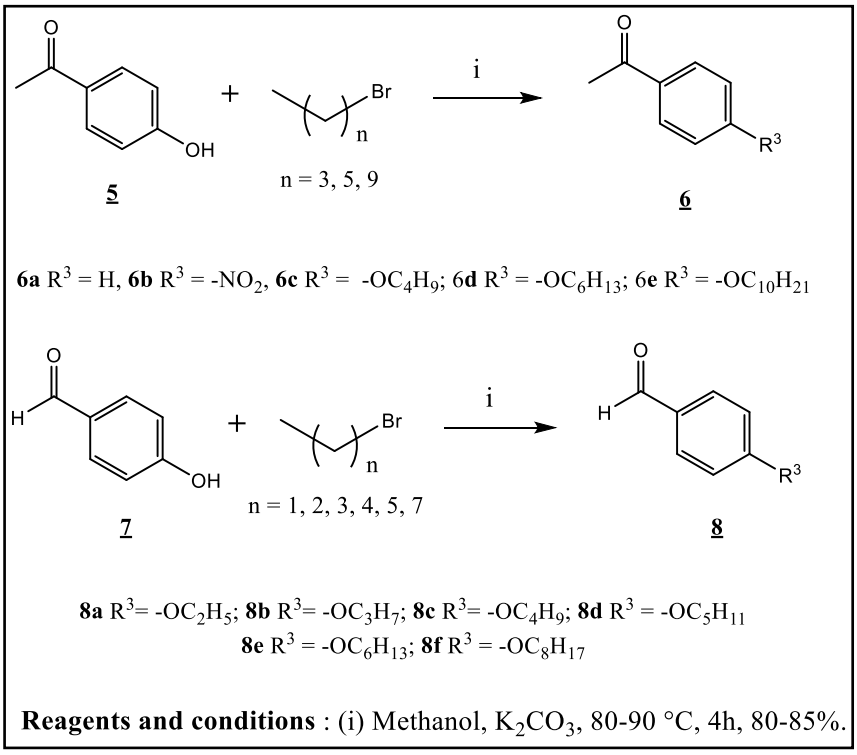
Considering enoyl-ACP reductase as the target enzyme (antibacterial taget), docking studies with newly synthesized candidates were performed.

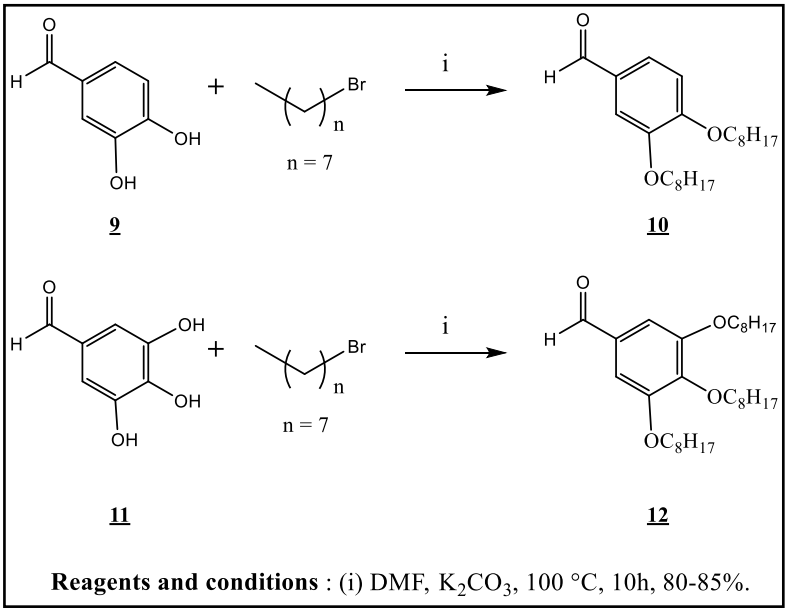
Chapter: VI

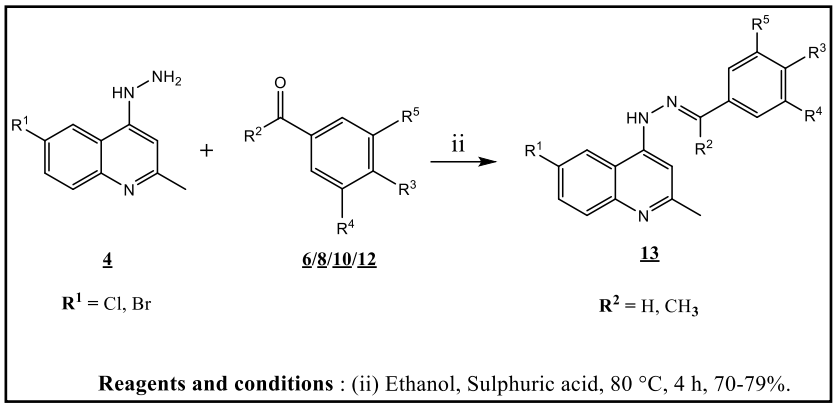
(B)

Synthesis and antimicrobial activities of (E)-6-bromo-/6-chloro-4-(2-(4-oxybenzylidene) hydrazinyl)-2-methylquinoline and their docking study.

***Synthesis*:**







Biological Evaluation

Antimicrobial Activity:

Antimicrobial activity of all the newly synthesized compounds was carried out against *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 619) as Gram positive bacteria *Escherichia coli* (MTCC 739), *Pseudomonas aeruginosa* (MTCC 741) as a Gram negative bacteria. And fungi *Aspergillus niger* (MTCC 282) and *Candida albicans* (MTCC 183) species using paper disc-diffusion technique. And MIC of the compound was determined by agar streak dilution method.

From the antimicrobial activity data it is evident that compounds reported herein exhibited good activity against the fungal strains. Molecular docking study were performed with fungal enzyme namely sterol 14 alpha demethylase (CYP51).

Conclusion:

A number of new Oxazole containing compounds have been prepared. The oxazoles have been linked with one or more other heterocycles which include oxazoline, pyrazoline, pyridine and quinoline heterocyclic moieties. Some new quinoline compounds have been synthesized and studied. The newly synthesized compounds are studied for their biological activities. The biological study includes anticancer, antidiabetic, anti-inflammatory, antibacterial, antifungal, anti-tubercular activities. Molecular docking study of some of the compounds has been carried out to understand the interactions of compounds with the respective enzymes. Structures of some of the compounds were analysed using single crystal XRD.

References:

1) Smith, A. L.; Nicolaou, K. C., *J. Med. Chem.*, 1996, **39**, 2103.
2) Gringauz, A. *Introduction to medicinal chemistry*, Wiley-VHC, 1997
3) Matsuda, H.; Morikawa, T.; Ando, S.; Iwao, T.; Masyuki, Y., *Bioorg. Med. Chem.*, 2003, **11**, 1995.
4) Zhen Z,; Zhi-Long Z,; Cheng-He Z,; *Eur. J. Med. Chem*., 2018, **144**, 444.
5) Chunlin Z,; Wen Z,; Chunquan S,; Wannian Z,; Chengguo X,; Zhenyuan M,; *Chem. Rev*., 2017, **117**, 7762.
6) Singh P.; Anand A.; Kumar V.; *Eur. J. Med. Chem*., 2014, **85**, 758.
7) Waites, C. R.; Dominick, M. A.; Sanderson, T. P.; Schilling, B. E., *Eur. J. Med. Chem.*, 2007, **100**, 248.
8) Yadav, P,; Kashmiri, L,; Ashwani, K,; Santosh, G,; Sundeep, J,; Shashi, B,; *Eur. J. Med. Chem.*, 2017, **126**, 944.
9) Lal, J,; Gupta, S,; Thavaselvam, D,; Agarwal, D,; *Eur. J. Med. Chem.*, 2013, **64**, 579.
10) Ningaiah, S,; Bhadraiah, U,; Keshavamurthy, S,; Javarasetty, C,; *Bioorg. Med. Chem. Lett*., 2013, **23**, 4532.
11) Aftab, A,; Asif, H,; Shah Alam, K,; Mohd. M,; Anil, B,; *J. Sau. Chem. Soc*., 2016, **20**, 577.
12) Mohamad, Y,; Jain, P,; *Ara. J. Chem*., 2014, **7**, 533.
13) Gillespie, S. H., (1994) Medical microbiology-illustrated. Butterworth Heinemann Ltd., United Kingdom.
14) Hawkey, P. M.; Lewis, D. A., (1994) Medical bacteriology—a practical approach. Oxford University Press, United Kingdom.
15) Saundane, A,; Yarlakatti, M,; Kalpana, R,; *Med. Chem. Res.*, 2012, **21**, 3809.
16) Desai, N,; Pandya, D,; Kotadiya, G,; Desai, P,; *Med. Chem. Res.*, 2014, **23**, 1725.
17) Amgad, V.; Habeeb, P. N.; Rao, P.; Edward, E. K., *J. Med. Chem*., 2001, **44**, 2921.
18) Isenberg, H. D., (1992) Clinical microbiology procedures handbook, vol 1. American Society for Microbiology, Washington, DC

19) Anargyros, P., Astill, D. S., Lim, I. S., Comparison of improved BACTEC and Lowenstein-Jensen media for culture of mycobacteria from clinical specimens. *J. Clin. Microbiol*., 1990, **28**, 1288.

20) Afzal, O,; Kumar, S,; Haider, R,; Ali, R,; Kumar, R,; Jaggi, M,; Bawa, S,; *Eur. J. Med. Chem*., 2015, **97**, 871.

21) Akranth, A.; Rahmt, A.; Tauquir, A.; Saha, R.; Tanwar, O.; Akhter, M.; Alam, M. M.; *Med. Chem*., 2013, **13**, 921.

22) Bhardwaj, V.; Malleshappa N.; Jalhan, S.; Patel, H. M., *J. Sau. Chem. Soc*., 2016, **20**, 406.

23) Huang, Q.; Wang, L.; W. Lu,; *Eur. J. Med. Chem*., 2013, **63**, 746.

24) Nayak, N,; Ramprasad, J,; Dalimba, U,; *J. Flu. Chem*., 2016, **183**, 59.