DESIGN, SYNTHESIS AND CHARACTERIZATION OF N-PHENYLPYRAZOLINE AND 3, 4-DIHYDROPYRIMIDINE FROM CHALCONE DERIVATIVES AND STUDY THEIR BIOLOGICAL ACTIVITIES

Dissertation submitted to

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In partial fulfilment of the requirement

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COLLEGE OF PHARMACY

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CERTIFICATE

This is to certify that the dissertation entitled – **DESIGN, SYNTHESIS AND CHARACTERIZATION OF N-PHENYLPYRAZOLINE AND 3,4-DIHYDROPYRIMIDINE FROM CHALCONE DERIVATIVES AND STUDY THEIR BIOLOGICAL ACTIVITIES** was done by **Ms.S.KARPAGAM (Reg.no.261215753)** in the Department of Pharmaceutical Chemistry, College of Pharmacy, Madurai Medical College, Madurai- 625020, in partial fulfillment of the requirement for the Degree of Master of pharmacy in Pharmaceutical chemistry under guidance and supervision of **Prof. (Mrs.) R. THARABAI, M.Pharm.**,HOD, Department of Pharmaceutical Chemistry during the academic year 2013-2014.

The dissertation is forwarded to the Controller of Examination, The Tamil Nadu Dr.M.G.R. Medical University, Chennai.

Station: Madurai.

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Evaluation certificate

Internal Examiner

External Examiner

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CONTENTS

DETAILS OF ABBREVIATION

°C	: Degree Centigrade
%	: Percentage
gm	: Gram
mg	: Milligram
µg	: Microgram
mol	: Mole
Ar	: Aromatic
Rf	: Retention factor
Str	: Stretching
DMSO	: Dimethyl sulfoxide
mm	: Millimeter
M.wt	: Molecular weight
M.F	: Molecular formula
α	: Alpha
β	: Beta
δ	: Delta
ppm	: Parts Per Million
m/z	: Mass Charge
pH	: Hydrogen ion concentration.

INTRODUCTION

1. GENERAL INTRODUCTION

Medicinal Chemistry is a Science Which includes all branches of Chemistry and biology. The discipline of Medicinal chemistry is devoted to the discovery and development of new agents for treating diseases.

Most of this activity is directed to new natural or synthetic organic compounds. Inorganic compounds continue to be important in therapy,

Eg: Trace elements in nutritional therapy, antacids and radiopharmaceuticals but organic compounds with increasingly specific pharmacological activities are clearly dominant.

The structures of biologically molecules usually contains more than one type of functional group. This means that the properties of these molecule are a mixture of those of each of the functional group present plus properties characteristic of the compound.

Pharmaceutical chemistry is a branch of science that makes use of the general law of chemistry to study drugs in respect to their synthesis, composition, physical and chemical properties, their use of treating disease.

Once a new pharmaceutical lead compound has been found out , extensive efforts are put in to make series of analogue with better activity.

Nowadays Medicinal chemistry involved in molecular design and molecular docking for better biological activity with less toxic effects.

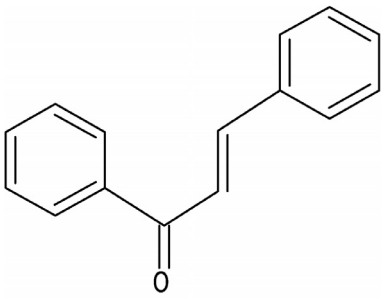
Medicinal chemistry remains a challenging field which involves invention of new drugs to treat emerging diseases.

1.1 CHALCONES[57]

Flavonoids comprise a large family of plant derived poly phenolic compounds classified as anthocyanidins, flavonols, chalcones, flavones, isoflavones. Chalcones an important intermediate of flavonoid synthetic pathway, has been shown to exhibit diverse biological and pharmacological activities.

Chalcones are unsaturated ketone containing the reactive keto ethylenic group -CO CH=CH. These are coloured compounds because of the presence of chromophore.

Chalcones are also called as benzalacetophenone or benzylidine acetophenone or phenyl styryl ketone.



1,3 - Diphenyl - 2 - Propane- 1- one.

Different methods are available for the preparation of chalcones. The most convenient method is the claisen-schmidt condensation of equimolar quantities of aryl methylketone and aryl aldehyde.

This reaction is catalyzed by acids and bases under homogenous or heterogenous conditions.

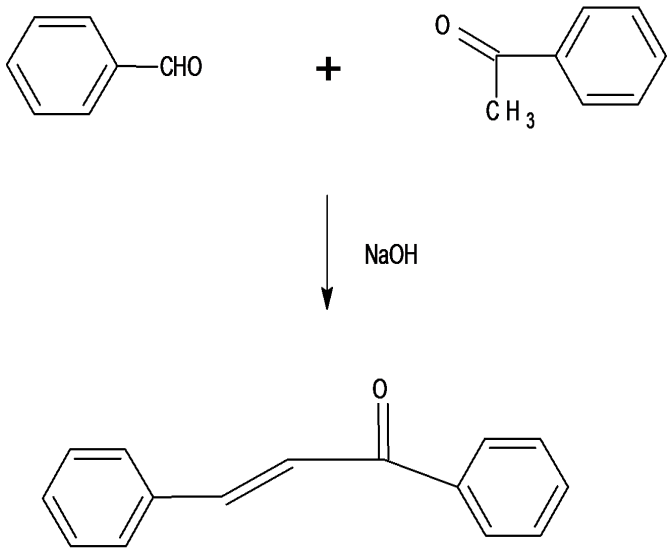
Chalcone derivative have wide variety of biological activities reported for these compounds include anti-inflammatory, anti-fungal, antibacterial, antimalarial and antitumor activity.

Chalcones with antioxidant activity (and compounds with such activity in general) have been demonstrated to have anticancer, anti cardiovascular, anti inflammatory and many other activities.

Claisen-schmidt Reaction:

This is the most convenient method for synthesis of chalcones. in this reaction equimolar quantities of substituted accetophenone condensed with substituted aldehydes in the presence of aqueous alcoholic alkali.

The condensation of aromatic aldehydes having no -hydrogen, with aliphatic aldehydes, ketones or esters, having active hydrogen, in the presence of 10% alkali solution to give - unsaturated aldehydes or ketones is known as claisen schmidt reaction.



Various condensing agents used in synthesis of chalcones:

Alkali:

It is most used condensing agents for synthesis of chalcones. It is used as an Aqueous solution of suitable concentraton 30%, 40%, 50%, 70%.

Hydrochloric acid:

dry hydrochloric acid gas in a suitable solvent like ethylacetate at 0°C was used as a condensing agent in a few synthesis of chalcone from aromatic ketones.

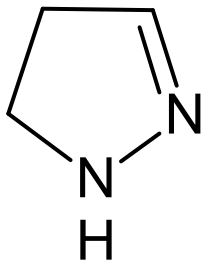
Other condensing agents:

1. Amino acid

2. Perchloric acid

1.2 PYRAZOLINE[58]

Among nitrogen containing five membered heterocycles, pyrazolines have proved to be the most useful framework for biological activities. The pharmaceutical importance of these compounds lies in the fact that they can be effectively utilized as antibacterial, antifungal, antiviral, antiparasitic, antitubercular and insecticidal agents. In 1967 Jarboe, reviewed the chemistry of pyrazolines,which have been studied extensively for their biodynamic behavior and industrial applications.



Synthetic aspects:

Different methods for the preparation of 2-pyrazoline derivatives documented in literature are as follows.

1. The most common procedure for the synthesis of 2-pyrazolines is the reaction of an aliphatic or aromatic hydrazine with α,β-unsaturated carbonyl compounds.

2. 2-Pyrazolines synthesized by the cycloaddition of diazomethane with substituted chalcones.

3. 2-Pyrazolines can also be prepared by the condensation of chalcone dibromidewith hydrazine.

4. Epoxidation of chalcones i.e. epoxy ketones which reacted with hydrazine and phenyl hydrazine to give pyrazolines.

5. A number of diarylidene cycloalkanones on reaction with hydrazine hydrate produce pyrazolines.

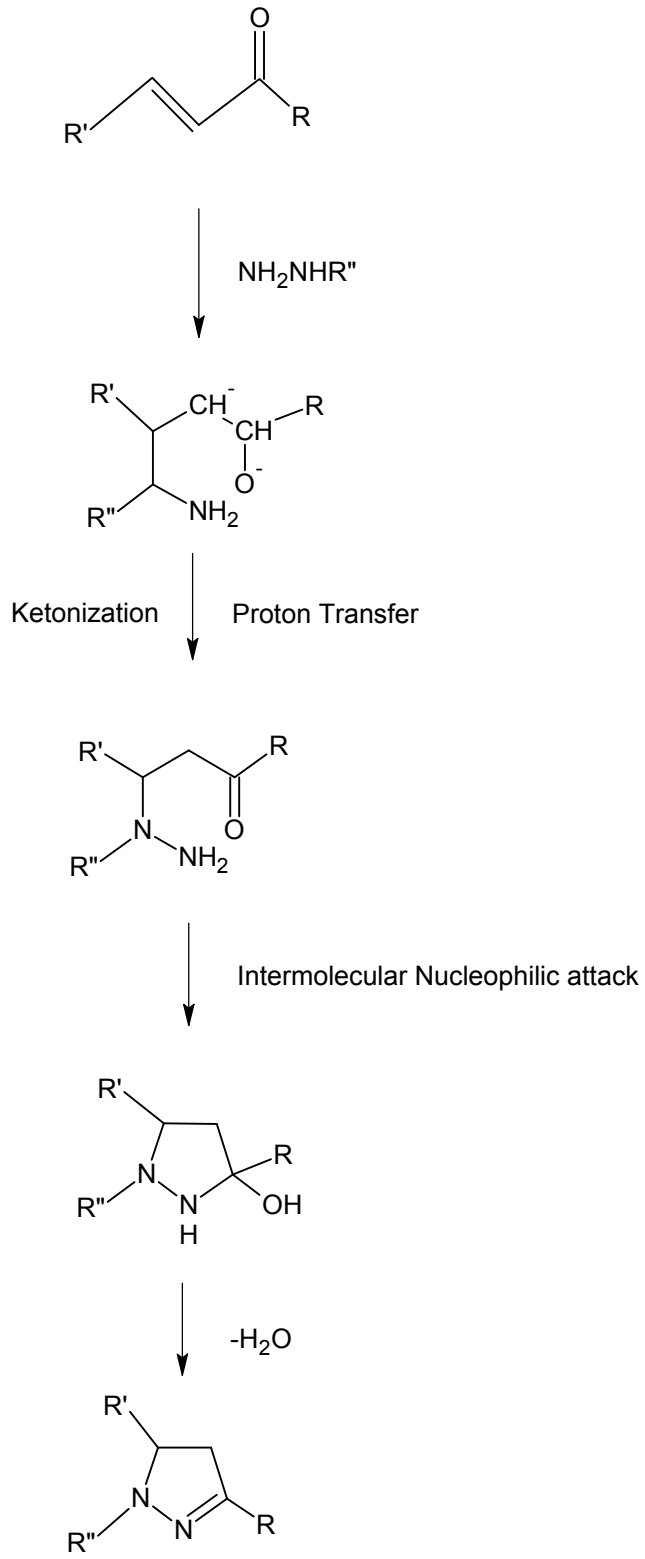
6. Dipolar cyclo addition of nitrilimines to dimethyl fumarate, fumaro nitrile and the N-aryl maleimides yields the corresponding pyrazolines.

7. Reaction of Et 2-(phenylazo)-3-oxobutanoates with nicotinic acid hydrazide using glacial acetic acid gives following type of pyrazoline derivatives.

Therapeutic importance:

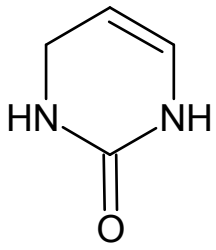
Pyrazole belongs to the family of azoles i.e. five-membered ring containing nitrogen and carbon atom. Considerable attention has been focused on pyrazolines and substituted pyrazolines due to their interesting biological activities. The dihydro pyrazoles are called pyrazolines. Some substituted pyrazolines and their derivatives have been reported to possess some interesting biological activities such as anticancer, insecticidal, antibacterial etc. They have found to possess antifungal, antidepressant, anticonvulsant, anti-inflammatory, antibacterial and anti- tumor properties.

Mechanism:


O
R'
R
NH2NHR"
R'
CH-
CH
R
O-
R"
NH2
Ketonization
Proton Transfer
R'
R
N
O
R"
NH2
Intermolecular Nucleophilic attack
R'
R
N
R"
N
OH
H
-H2O
R'
N
R"
N
R

1.3- 3,4 DIHYDROPYRIMIDINE[59]

Pyrimidine is a six membered hetero cyclic ring having two nitrogen atoms in their ring. Dihydropyrimidine are the compounds which are obtained by cyclocondensation reaction which having different products. The dihydropyrimidine synthetic products has different medicinal uses such as Antihypertesive, Antibacterial, Antifungal, ad Anti-oxidant property.



3,4-dihydropyrimidin-2(1*H*)-one

Biolgical imporatance:

In medicinal chemistry Pyrimidine derivatives have been very well known for their therapeutic applications. The presence of pyrimidine base in thymine, cytosine and uracil, which are the essential building blocks of nucleic acids, DNA and RNA is one of the possible reason for their activities. Vitamins are essential for the body. Pyrimidine ring is found in vitamins similar to riboflavin, thiamine and folic acid.

Preparation of 3,4-dihydropyrimidine from chalcone:

A mixture of equimolar quantities of chalcone and urea were dissolved in 25ml of ethanol and 5ml of potassium hydroxide and refluxed on water bath for 8hr. the solvent was evaporated and the precipitation was recrystallized from ethanol.

1.4 - ANTI-OXIDANT[61]

An anti-oxidant is a molecules that inhibits the oxidation of other molecules. Oxidation is a chemical reaction that transfer electrons or hydrogen from a substance to an oxidizing agent.

Oxidation reaction can produce free radicals. In turn, these radicals can start chain reaction. When the reaction occurs in a cell, it can cause damage or death to the cell. Anti-oxidants terminate these chain reaction by remove free radical intermediates, and inhibit other oxidation reaction. So anti-oxidants are often reducing agents such as thiols, ascorbic acid or polyphenols.

Mechanism of Anti-oxidant:

LMWAs (Low Molecularr Weight antioxidants) are small molecules that have frequently infiltrate cells, accumulate (at high concentrations) in specific compartments associated with oxidative damage, and then are regenerated by the cell.

In human tissues, cellular LMWAs are obtained from various sources. Glutathione, nicotinamide, adenine dinucleotide and carosins are synthesized by the cells. Uric acid and billirubin are waste products of cellular metabolism. Ascorbic acid, tocopherols and poyphenols are anti-oxidants obtained from the diet.

Conditions Associated with oxidative damage:

- Ageing
- Atherosclerosis
- Cancer
- Cataracts
- Diabetes
- Arthritis and inflammatory disease
- Pulmonary infaction
- Pancreatitis
- Ischemia
- Skin lesions
- Parkinson's disease
- Renal damage.

1.5 INFLAMMATION[60]

The word comes from the latin "inflammo", meaning " I set alight, I ignite" is a complex biological response of vascular tissues to harmful stimuli, including pathogens, damaged cells or irritants. The classical signs of acute inflammation are pain, heat, redness, swelling and loss of function. Inflammation is a defence mechanism of the body to remove the injurious stimuli and to initiate the healing process.

Inflammation can be classified as acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes(granulocytes) from the blood into the injured tissues. Prolonged inflammation known as chronc inflammation is a dangerous, out of control immunological reaction.

Acute inflammation:

Causative Agent - Bacterial pathogens, injured tissues.

Major cell involved - Neutrophils, basophils, eosinophils, mononuclear cells (monocyte, Macrophage)

Onset - Immediate.

Duration - Few days.

Out comes - Resolution, abcess formation, chronic inflammation.

Chronic inflammation:

Causative agent - Non-degradable pathogens, viral infection, persistant foreign Bodies or autoimmune reactions.

Major cells - Mononuclear cells, (monocytes, macrophages, lymphocytes, Plasma cells), Fibroblasts.

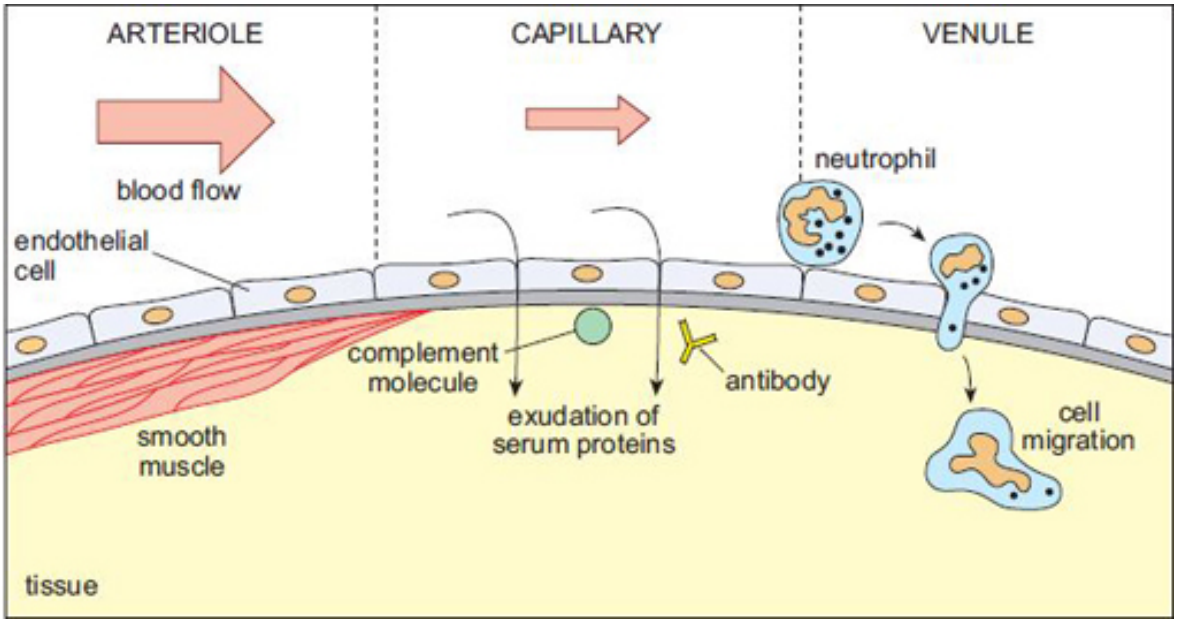
Onset - Delayed.

Duration - Upto many months or years.

Outcomes - Tissue destruction, fibrosis, necrosis.

Causes of inflammation:

The main causes of inflammation are burn, chemical irritants, toxins, ionizing radiations, stress, trauma and alcohol.



Mechanism of inflammation:

The mechanism of inflammatory pathway is classified as follows :

- Arachidonic acid (AA) dependent pathway which includes Cyclo oxygnase(COX), Lipoxygenase(LOX) and Phospholipase A_2 (PlA_2) as mediators.
- AA – indendent pathway which include nitric oxide synthase(NOS), Peroxisome, Proliferator activated receptor(PPAR) and NSAID activated gene – 1(NAG - 1).

Mediators of inflammation:

The mediators of inflammation are histamine, bradySkinins, prostoglandins, thrombaxane A_2, prostacyclin, leukotrienes, platelet activating factor and interleukin-1.

1.6 - DIABETES MELLITUS[60]

Diabetes mellitus is a disorder of carbohydrate, fat, protein metabolism. A defective or deficient insulin secretory response, which translates into impaired glucose use is a characteristic feature of Diabetes mellitus.

Classification and incidence:

Diabetes Mellitus represents a group of disorder that have hyperglycemia as a common feature. it may arise secondarily from any disease causing extensive destruction of pancreatic islets, such as pancreatitis, tumors, certain drugs, iron overload (Hemochromatosis).

The most common and important forms of diabetes mellitus arise from primary disorders of the islet cell insulin system.

Types of Diabetes Mellitus:

Primary (idiopathic)

Type-I (Insulin dependent Diabetes mellitus)

Type-II(Non-insulin dependent Diabetes Mellitus)

Secondary

Chronic Pancreatitis.

Hormonal Tumors (eg. Pheochromocytoma).

Type-I DM is also called as Juvenile Diabetes.

Type-II DM is also called as Adult-onset diabetes.

Pathogenesis of Type I DM:

This form of Diabetes results from a severe, absolute lack of insulin caused by a reduction in the beta cell mass. Type-I diabetes usually developed in childhood, becoming manifest and severe at puberty. without insulin they develope serious metabolic complications such as acetic keto acidosis and coma.

The interlocking mechanism are resposible for the islet cell destruction.

1.Genetic susceptiblity

2.Autoimmunity

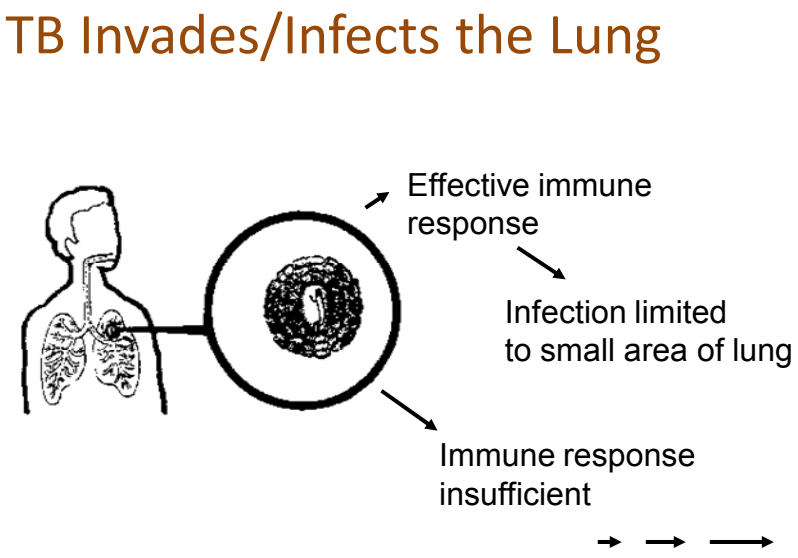
3.Environmental insult

Pathogenesis of type II DM:

This type of DM is commonly seen in more than 30 years old. The metabolic defects that characterize type-II Diabetes are a dearrangement in Beta cell secretion of insulin and an inability of peripheral tissues to respond to insulin.

1.7 - TUBERCULOSIS[40]

Tuberculosis is a chronic disease and a major health problem in developing countries. About 1/3rd of the wolrd population is infected with Mycobacterium tuberculosis. As per WHO estimate, 9 million people globally develop active TB and 1.7 million die of it annually. In india , it is estimated that nearly 2 million people develop active disease every year and about 0.5 million



Common symptoms

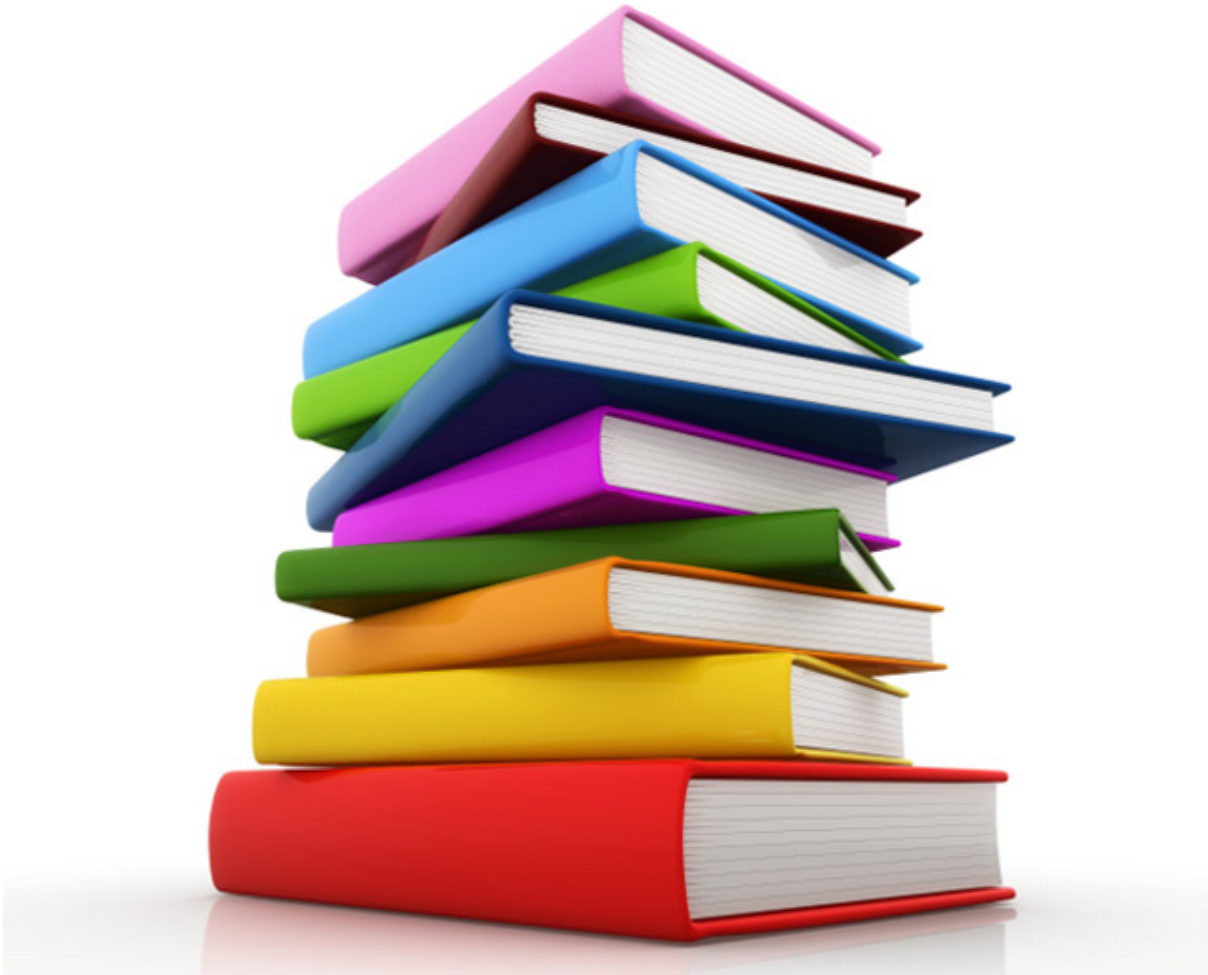
- Cough (2-3 weeks or more)
- Coughing Up blood
- Chest pain
- Fever
- Night sweat

- Feeling week and tired
- Losing weight
- No appetite

Treatment for tuberculosis:

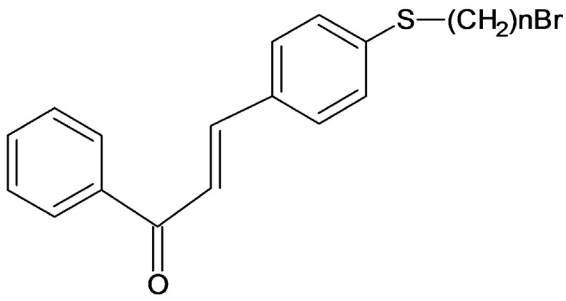
- ❖ Most TB is Curable but four or more drugs required for the simplest regimen.
- ❖ 6-9 or more months of treatment required.
- ❖ Person must be isolated until non-infectious.
- ❖ Directly observed therapy to assure adherence/completion recommended
- ❖ Side effects and toxicity common.
- ❖ Other medical and Psycho social conditions for complicate therapy when TB may be severe and drug-drug interaction common.

LITERATURE REVIEW

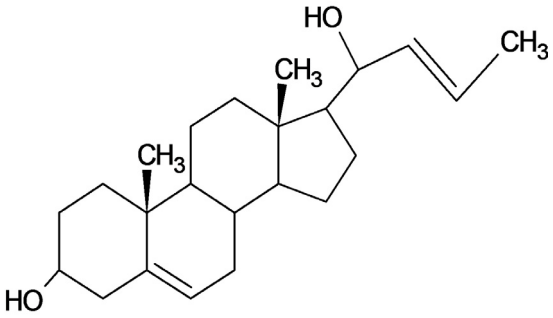


2. LITERATURE REVIEW

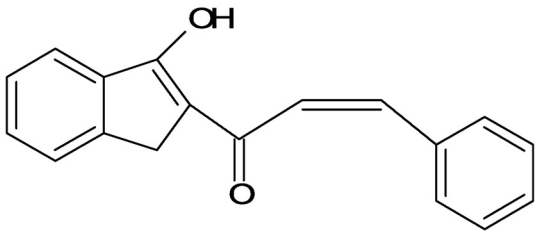
1. Nowaskowska *et al.,* Synthesized 4- amino alkyl thio chalcones with antibacterial and anti fungal activities, 2008.



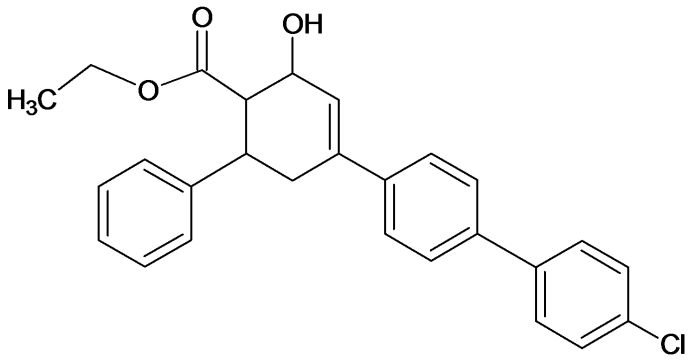
2. Abid *et al.,* screened the efficient and facile synhesis of 17- chalconyl derivatives of Pregnolone and their evaluation as anti microbial agents, 2011.



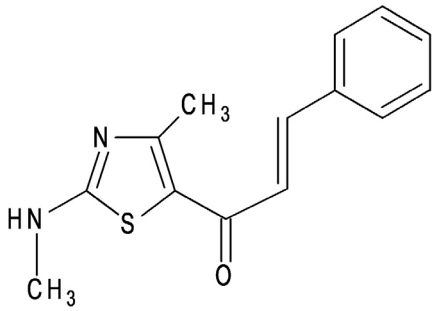
3. Swamy *et al.,* reported the 3- hydroxxy benzofuran substituted chalcones with antimicrobial activity, 2008.



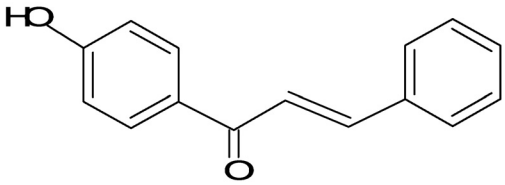
4. Mayekar *et al.,* reported that a series of chalcones and cyclohexanone derivatives were derived from 6-methoxy 2-napthalaldehyde with evaluation of their biological activity against all the bacterial and fungal strains like escherichia coli, staphylococcus aureus, 2010.



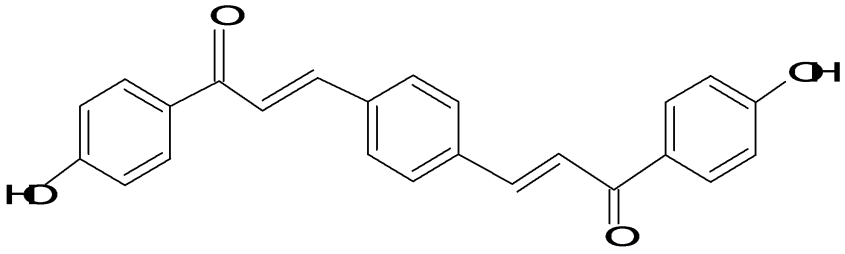
5. Liaras *et al.,* reported on synthesis of thiazole chalcone derivatives with antibacterial acivity, 2011.



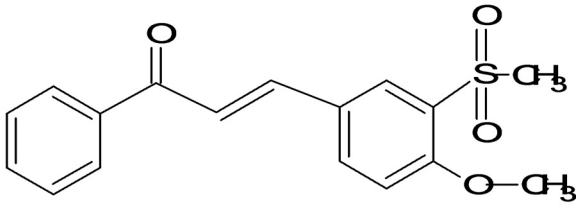
6. Nielson *et al.,* investigated the antibacterial activity of hydroxy chalcones, 2004.



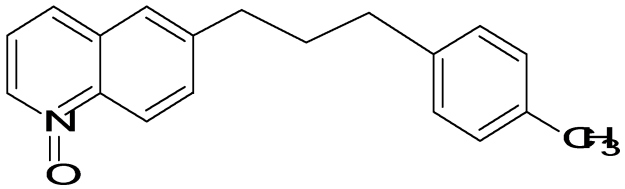
7. Chitra *et al.,* synthesized four copolysters from 3,3-(1,4 phenylene) bis (1-(4-hydroxy phenyl) prop 2-en-1-one and 3,3-(1,4phenylene) bis (1-(4-hydroxy -3-methoxy phenyl) prop-2-en-1-one) with anti bacterial activity, 2010.



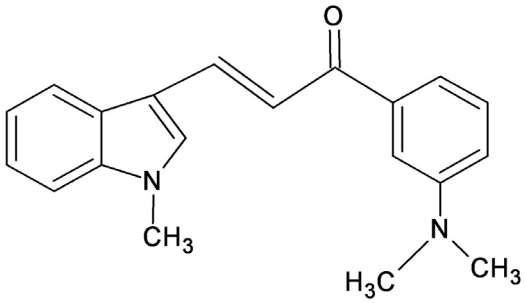
8. Carla *et al.,* reported on a synthesis of sulfonamide 4 methoxy chalcone derivatives with antileshmanial activity against leshmania braziliensis, 2009.



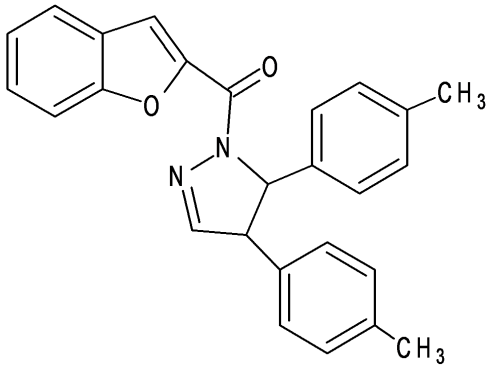
9. Taveres *et al.,* evaluated a series of new 6-quinolinyl and quinolinyl N- Oxide chalcones with anticancer activity, 2011.



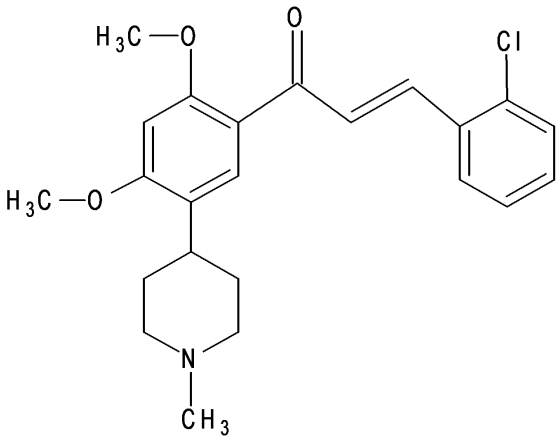
10. Kumar *et al.,* synthesized a series of indolyl chalcones and eveluated in vitro for their anticancer activity against three human cancer cell lines, 2010.



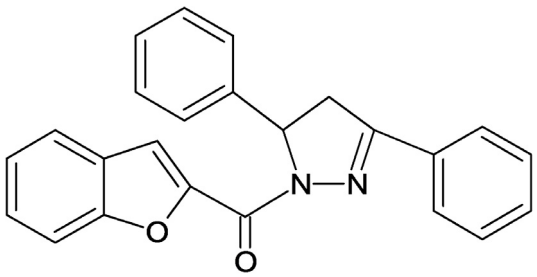
11. Parekh *et al.,* synthesized a series of benzofuran 2-yl (4,5-dihydro -3,5-substituted diphenyl pyrazol-1-yl) methanone derivatives with anticancer activity, 2011.



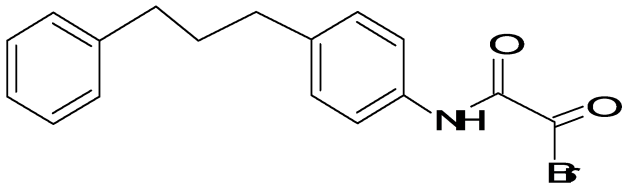
12. Liu *et al.,* reported on N-methyl piperidinyl chalcones with anticancer activity,2006.



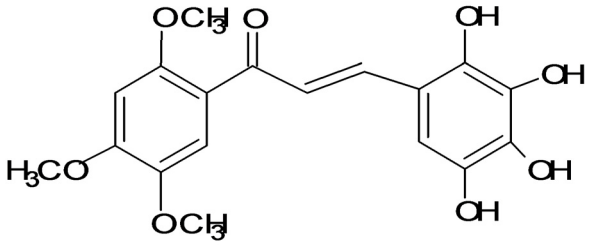
13. Parekh *et al.,* synthesized indolyl chalcones derivatives with anticancer activity. For their anti proliferative activity and reversal of multi drug resistance on human MDR1-gene transferred mouse lymphoma cells, 2011.



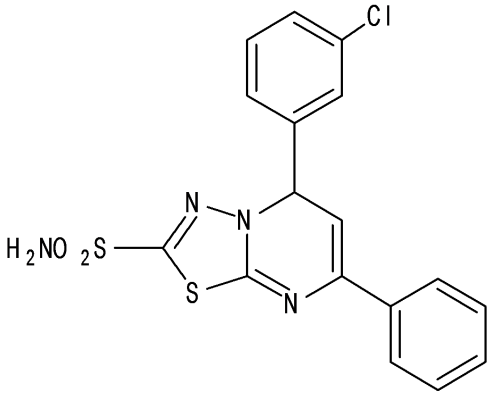
14. Romagnoli *et al.,* Synthesized novel series of α-bromo acrylolylamido chalcones which had the highest activity towards the five cell lines, 2009.



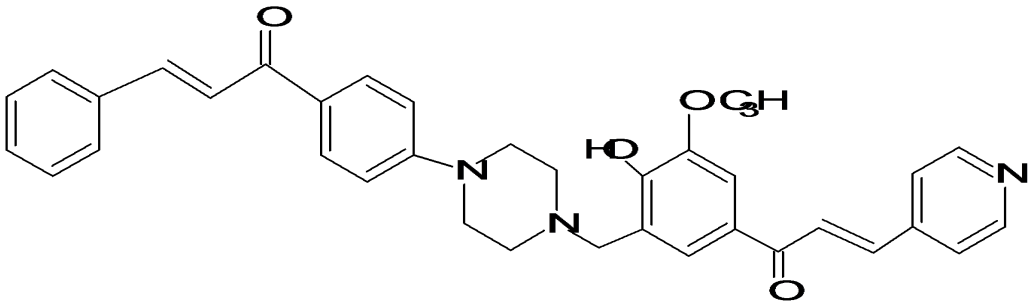
15. Rao *et al.,* reported a series of twenty three 3', 4', 5' – trimethoxy chalcones analogues as inhibitors of nitric oxide production in LPS treated macrophages and tumor cell proliferation, 2009.



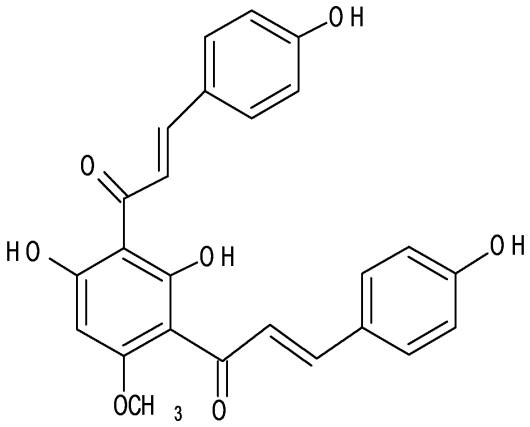
16. Sayed *et al.,* reported a series of sulfonamide derivatives of (1,3,4) thiadiazolo (3,2) pyrimidine were formed and investigated as antitumor agents. Some of the newly prepared compounds were tested for their invitro and invivo antitumor activities, 2011.



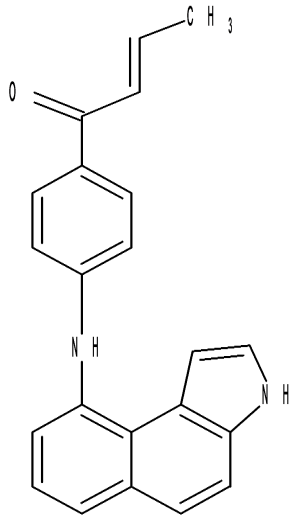
17. Reddy *et al.,* synthesized a series of novel bichalcone analogues and evaluated in lipopolysaccharide activated microglial cells as inhibitors of nitirc oxide and for invitro anticancer activity using a limited panel of four human cell lines, 2010.



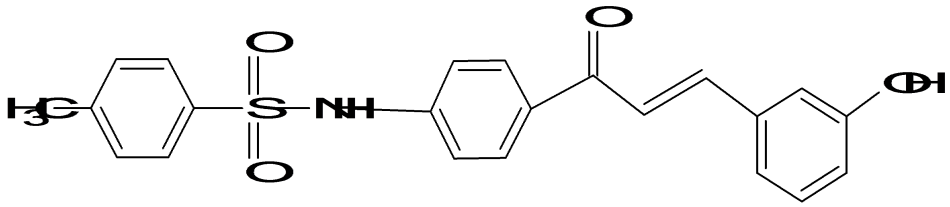
18. Susanne *et al.,* synthesized a series of 2'-hydroxy chalcones and their oxidative cyclization products for their antioxidant and lipoxygenase inhibitory activity.



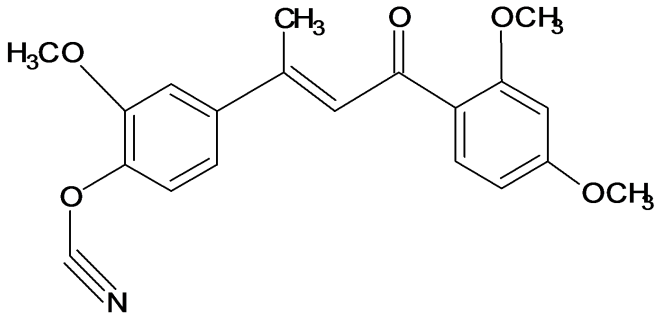
19. Via *et al.,* synthesized and evaluate the conjucates of α,β- unsaturated ketone systems phenyl butanone and diaryl propanone with the tricyclic planar pyrroloquinoline nucleus, 2008.



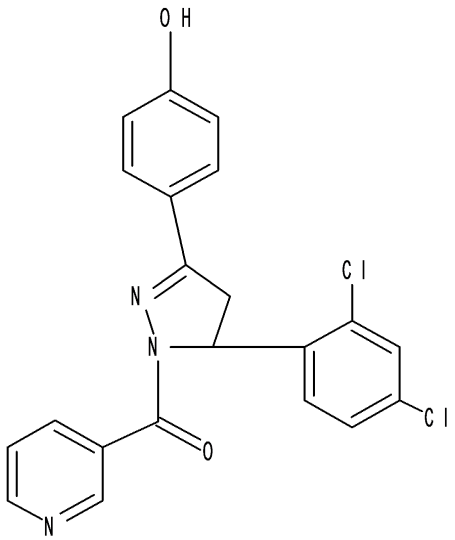
20. Seo *et al.,* synthesized the chalcones a new clss of glycoside inhibitors. Non amino chalcones had no inhibitory activity. However amino chalcones had strong glycosidase (α,glucosidase, α, amylase and β, amylase) inhibitory activities, 2005.



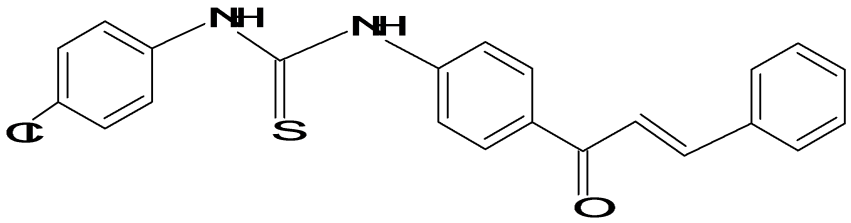
21. Eric *et al.,* studied a targeted series of chalcone and dienone hybrid compounds containing aminoquinoline and nucleoside templates was synthesized and evaluated for in vitro antimalarial activity,2010.



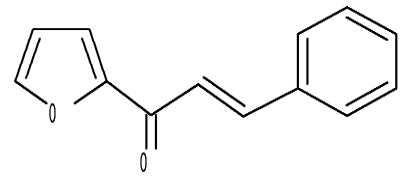
22. Acharya *et al.,* were synthesized a series of 1,3,5 tri substituted pyrazoline and evaluated in vitro antimalarial efficacy against chloroquine sensitive as well as chloroquine resistant strains of plasmodium falciparum, 2010.

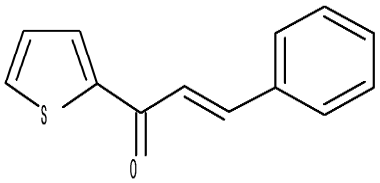


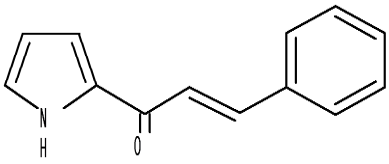
23. Said *et al.,* synthesized a series of diazepine, pyrimidine, fused triazolo pyrimidine and imide derivatives with analgesic activity, 2009.



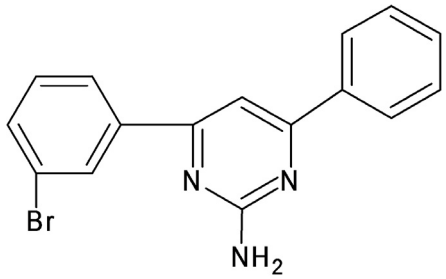
24. Thanh-Dao Tran *et al.,* discoverd some heterocyclic chalcone analogues such as Pyridine 2-yl chalcones, Furan 2-yl chalcones, and Thiophene 2-yl chalcones and screened for their antibacterial activity, 2012.



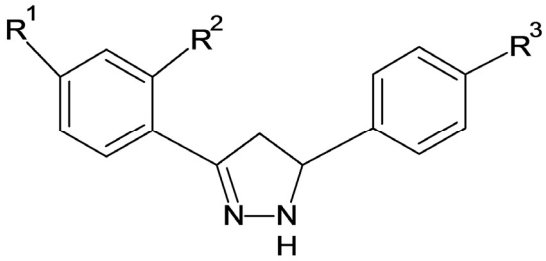




25. Nimavat and Joshi *et al.,* synthesized 2-amino-4-(3-bromo phenyl)-6-aryl-Pyrimidine from chalcone on treatment with guanidine hydrochloride and screened for their antitubercular activity,2013.



26. Setharaman venkatraman *et al.,* synthesized some novel Pyrazolines from chalcones and evaluated for antibacterial and anti inflammatory.

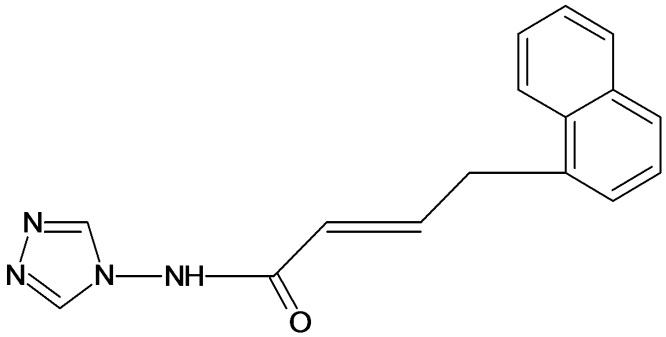


R1=H, 4-OCH3, 4-CH3, 4-OH

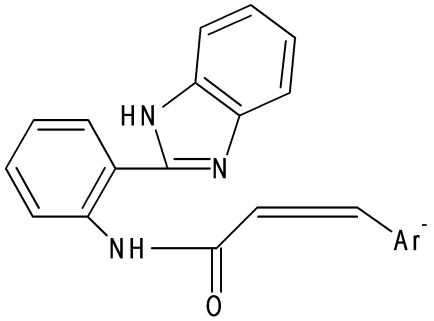
R2= 2-0H, H

R3= 4-NO2, 4-OCH3, 4-Cl, 4-NO2.

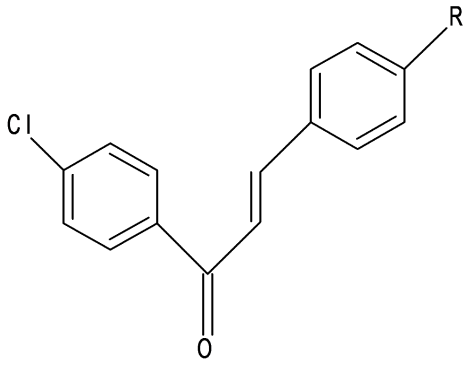
27. Ashvin D. Panchal *et al.,* synthesized triazole linked chalcone derivatives as antibacterial and antifungals.



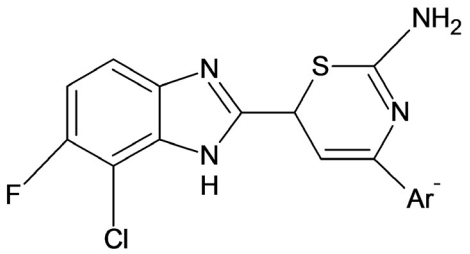
28. Sahoo Biswa Mohan *et al.,* carried out the synthesis of Benzimidazolyl chalcones derivatives, 2010.



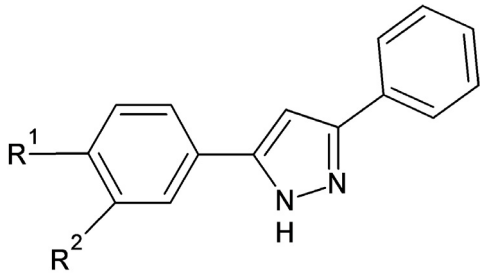
29. S.Mhan *et al.,* synthesized some chloro, methoxy substituted chalcone derivatives and tested for anti microbial activity, 2012.



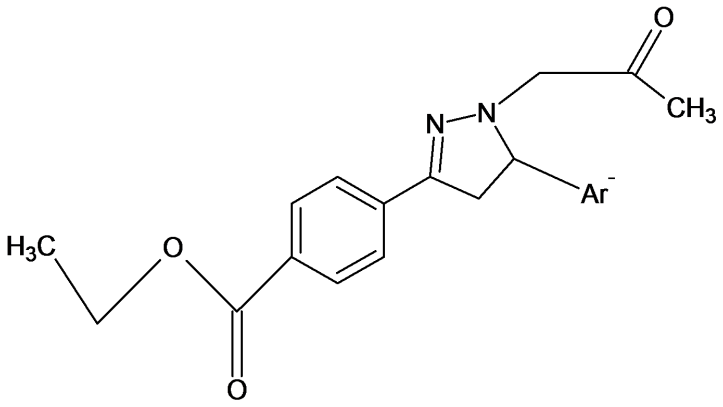
30. Gayathri Banda *et al.,* synthesized fluoro, chloro 2- substituted Benzimidazole thiazine derivatives and evaluated for Antibacterial and Analgesic activities, 2012.



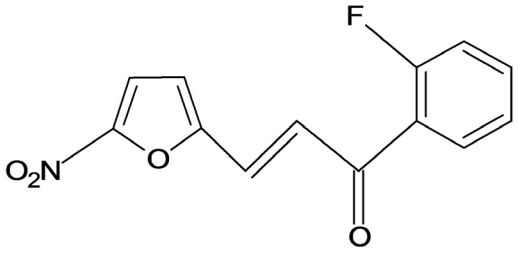
31. Kalirajan *et al.,* reported on synthesis and biological evaluation of some heterocyclic derivatives of chalcones, 2009.



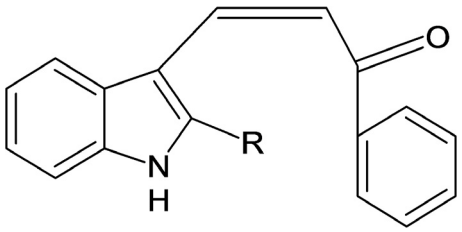
32. P.Prasanna Raja *et al.,* reported the synthesis and biological evaluation of some chalcone derivatives as esters, 2010.



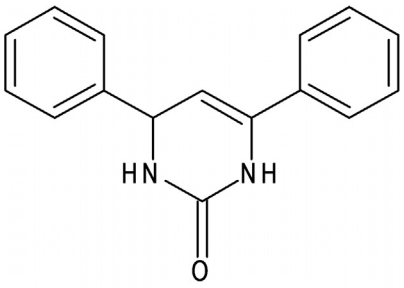
33. Devaux, Nuhrich *et al.,* discovered some nitrofuryl chalcones as Antibacterials, 1978.



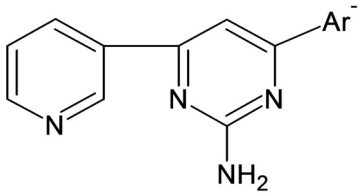
34. Dandia *et al.,* prepared chalcones having indole moiety and studied for Antibacterial and Anti fungal activities, 1993.



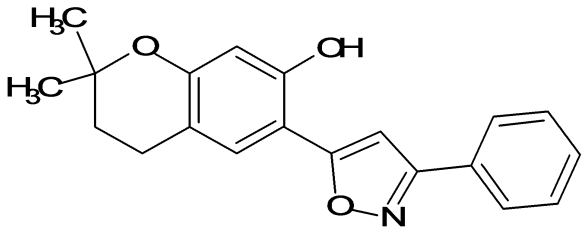
35. Javad Safaei Ghomi *et al.,* reported on synthesis of Pyrimidine 2-ones under ultrasound irradiation from chalcones, 2010.



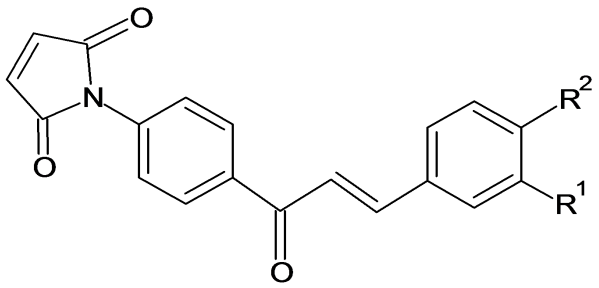
36. M.V.Jyothi *et al.,* synthesized some novel chalcones of 3-acetyl pyridine and their Pyrimidine derivatives and screened for antimicrobial activity, 2012.



37. Kapubalu *et al.,* synthesized a series of novel isoxazole derivatives via chalcone derivatives and evaluate with their bioogical activity, 2011.

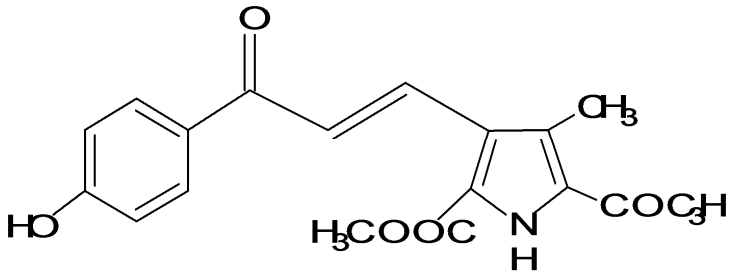


38. Mustafa *et al.,* studied a targeted series of noval chalcone derivatives containing 4,7-ethano-isoxazole-1,3-dione with antibacterial activity, 2013.

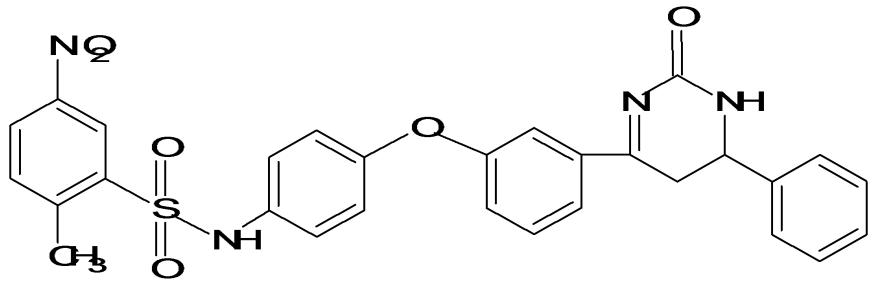


R1-OH., R2- OH

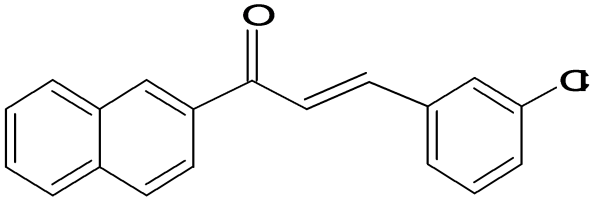
39. Tribbhuvan singh *et al.,* reported on synthesized novel Aryl and hetero Aryl chalcone analogues with Anti inflammatory and Antibacterial activity, 2012.



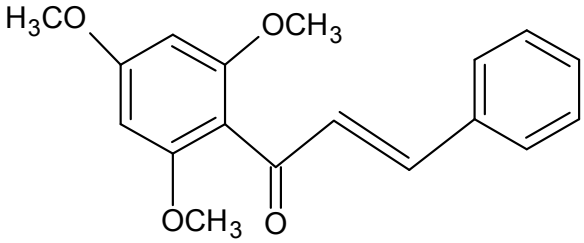
40. Rajashri *et al.,* synthesized on study of novel chalcone derivatives and Evaluate their antimicrobial activity, 2012.



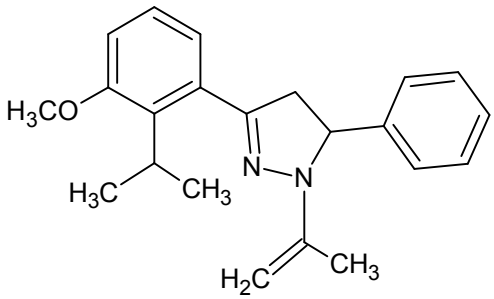
41. Varun arora *et al.,* reported on synthesis and evaluation of chalcone derivatives of 2-acetyl napthalene with antifungal and antibacterial activity, 2012.



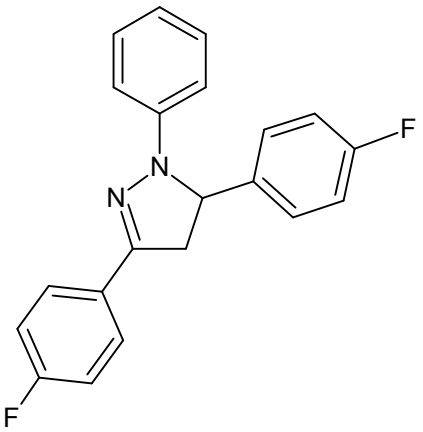
42. Yerra Koteswara Rao *et al.,* synthesized 2-oxygenated chalcone derivatives with anticancer activity, 2004.



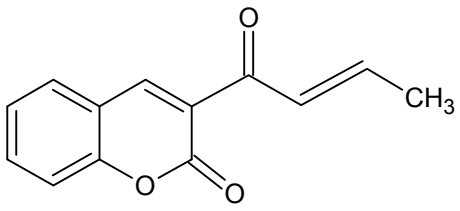
43. SD.Tala *et al.,* reported on synthesis of some new chalcone and pyrazole derivatives with antimicrobial activity, 2013.



44. Seranthimata samshudin *et al.*, synthesized functionalized derivatives of versatile synthon 4,4-dihydro chalcones derivatives with antimicrobial activity, 2012.



45. Y.Rajendra Prasad *et al*., reported QSAR studies on chalcone derivatives as Antibacterial agent against Bacillus pumilis, 2008.



AIM AND PLAN OF WORK

3. AIM OF STUDY

In the present study I have decided synthesis of two nucleus from chalcone derivatives. One is N-phenylpyrazoline and the other one is 3,4-dihydropyrimidine

The N-phenyl Pyrazoline ring with aryl substitution at third and fifth position exhibits better biological activities.

The 3,4 dihydropyrimidine with aryl substitution at fourth and sixth position exhibits better biological activities.

N-phenyl Pyrazoline with phenyl substitution at third position and different substituted phenyl attachments at fifth position.

3,4-dihydropyrimidine with phenyl substitution at fourth position and different substituted phenyl attachments at sixth position.

The resultant compounds of N-phenylpyrazoine and 3,4-dihydropyrimidine respectively from chalcone, will be evaluated for anti-oxidant, anti-diabetic, anti-inflammatory and anti-tuberculosis activities.

PLAN OF WORK:

- Designing the molecules using software tools like Molinspiration & Chemdoodle.
- Establishing the methods of synthesis for the proposed compounds.
- Carry out the preliminary test for such as solubility, melting point, Rf-value etc.

  The synthesized compound structures are confirmed by spectrum analysis using FTIR, ^{1}HNMR, and MASS spectra.
- The compounds are screened for biological activities such as anti-oxidant, anti-diabetic, anti-inflammatory and anti-tubercuosis activities.

EXPERIMENTAL WORK

4.EXPERIMENTAL WORK

4.1 MOLECULAR DESIGN

The Software tools like Chemdoodle, Molinspiration, Chemsketch were used to design the molecule for synthesis.

A) Chemdoodle:

It is used to assess the *LIPINSKI'S RULE*. It is the rule of five used by *LIPINSKI* to improve the bioavailability of the drug. Lipinski rule states that the orally active drugs have:

- Molecular weight ≤ 500
- logP ≤ 5
- hydrogen bond acceptors ≤ 10
- hydrogen bond donors ≤ 5

The molecules violating any one of the above rule will not have proper bio-availability.

B) Molinspiration:

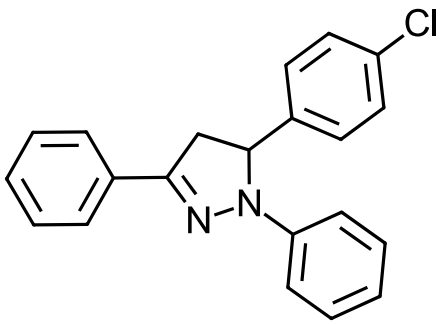
Virtual Screening is the computational chemistry technique to assess the large drug databases to identify the new drug molecules. It screens the molecules and provides the bioactivity score between -3 and 3. Molecules with highest bioactivity score will be more biologically active and produces better activity.

C) Chemsketch:

It is a software tool used for the prediction of molecular properties such as molecular mass, LogP, molar refractivity, parachor, molar volume, surface tension, polarizability and elemental composition.

LIPINSKI'S RULE PREDICTED BY CHEMDOODLE

COMPOUND K1



Molecular Formula = $C_{21}H_{17}ClN_2$

Molecular Mass = 332.8260 u

Hydrogen Bond Acceptor Count = 2

Hydrogen Bond Donor Count = 0

T_b = 837.4301 K

T_f = 386.7200 K

XlogP v2.0 = 6.1740

CMR = 102.8040 cm^3/mol

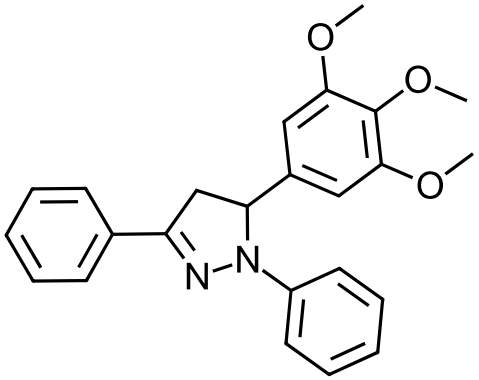
AMR = 100.8590 cm^3/mol

Bioavailability Score = 0.1700

Lipinski's Rule of 5 Violations Count = 1

www.chemdoodle.com

COMPOUND K2



Molecular Formula = $C_{24}H_{24}N_2O_3$

Molecular Mass = 388.4590 u

Hydrogen Bond Acceptor Count = 5

Hydrogen Bond Donor Count = 0

T_b = 935.6600 K

T_f = 429.3801 K

XlogP v2.0 = 5.1830

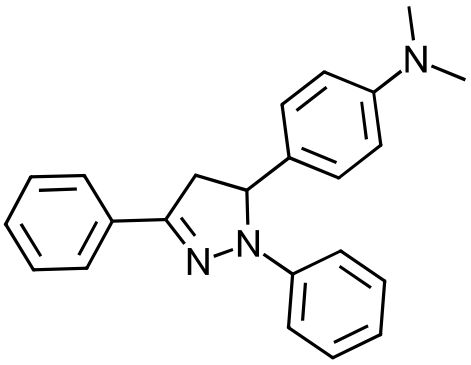
CMR = 116.3970 cm^3/mol

AMR = 115.5050 cm^3/mol

Bioavailability Score = 0.1700

Lipinski's Rule of 5 Violations Count = 1

COMOPOUND K3



Molecular Formula = $C_{23}H_{23}N_3$

Molecular Mass = 341.4488 u

Hydrogen Bond Acceptor Count = 3

Hydrogen Bond Donor Count = 0

T_b = 858.2001 K

T_f = 411.8100 K

XlogP v2.0 = 6.1830

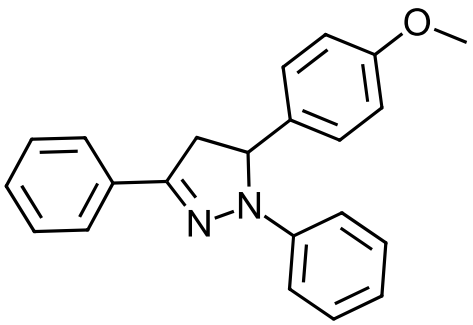
CMR = 110.8530 cm³/mol

AMR = 110.1760 cm³/mol

Bioavailability Score = 0.1700

Lipinski's Rule of 5 Violations Count = 1

COMPOUND K4



Molecular Formula = $C_{22}H_{20}N_2O$

Molecular Mass = 328.4070 u

Hydrogen Bond Acceptor Count = 3

Hydrogen Bond Donor Count = 0

T_b = 845.3000 K

T_f = 390.3000 K

XlogP v2.0 = 5.8890

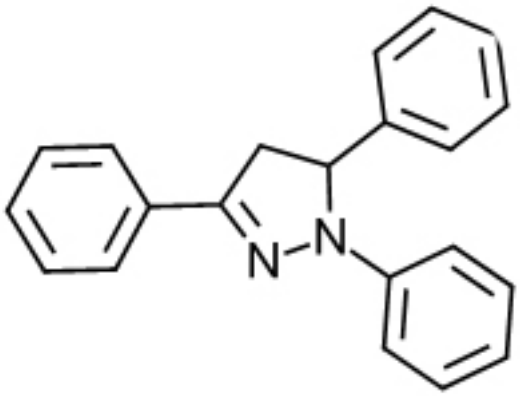
CMR = 104.0590 cm^3/mol

AMR = 102.4010 cm^3/mol

Bioavailability Score = 0.1700

Lipinski's Rule of 5 Violations Count = 1

COMPOUND K5



Molecular Formula = $C_{21}H_{18}N_2$

Molecular Mass =298.38

Hydrogen Bond Acceptor Count = 3

Hydrogen Bond Donor Count = 0

T_b = 840

T_f = 298

XlogP v2.0 = 4.20

CMR = 99

AMR = 98.5

Bioavailability Score = 0.15

Lipinski's Rule of Violations Count = 1

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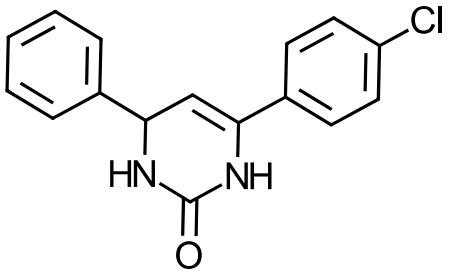
COMPOUND K6



Molecular Formula = $C_{16}H_{13}ClN_2O$

Molecular Mass = 284.7401 u

Hydrogen Bond Acceptor Count = 3

Hydrogen Bond Donor Count = 2

T_b = 728.7100 K

T_f = 397.0100 K

XlogP v2.0 = 3.7280

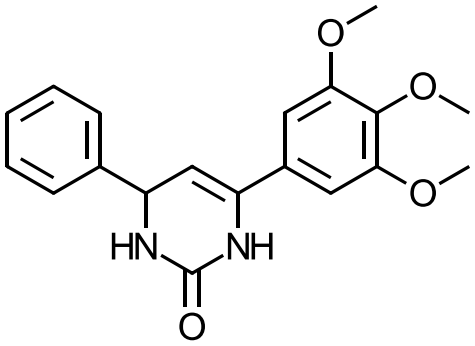
CMR = 81.1670 cm³/mol

AMR = 81.1304 cm³/mol

Bioavailability Score = 0.5500

Lipinski's Rule of 5 Violations Count = 0

COMPOUND K7



Molecular Formula = $C_{19}H_{20}N_2O_4$

Molecular Mass = 340.3731 u

Hydrogen Bond Acceptor Count = 6

Hydrogen Bond Donor Count = 2

T_b = 826.9399 K

T_f = 439.6700 K

XlogP v2.0 = 2.7370

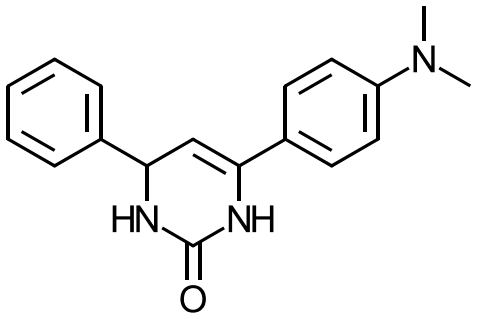
CMR = 94.7600 cm³/mol

AMR = 95.7764 cm³/mol

Bioavailability Score = 0.5500

Lipinski's Rule of 5 Violations Count = 0

COMPOUND K8



Molecular Formula = $C_{18}H_{19}N_3O$

Molecular Mass = 293.3630 u

Hydrogen Bond Acceptor Count = 4

Hydrogen Bond Donor Count = 2

T_b = 749.4800 K

T_f = 422.1000 K

XlogP v2.0 = 3.7370

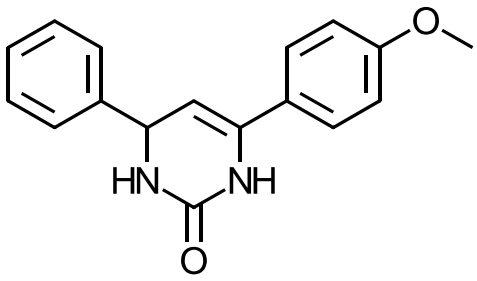
CMR = 89.2160 cm³/mol

AMR = 91.2394 cm³/mol

Bioavailability Score = 0.5500

Lipinski's Rule of 5 Violations Count = 0

COMPOUND K9



Molecular Formula = $C_{17}H_{16}N_2O_2$

Molecular Mass = 280.3211 u

Hydrogen Bond Acceptor Count = 4

Hydrogen Bond Donor Count = 2

T_b = 736.5800 K

T_f = 400.5900 K

XlogP v2.0 = 3.4430

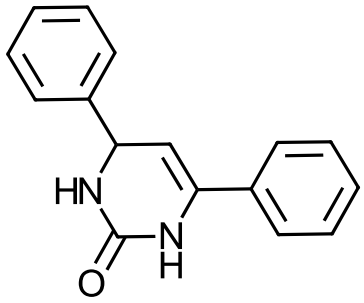
CMR = 82.4220 cm³/mol

AMR = 83.4644 cm³/mol

Bioavailability Score = 0.5500

Lipinski's Rule of 5 Violations Count = 0

COMPOUND K10



Molecular Formula = $C_{16}H_{14}N_2O$

Molecular Mass = 250.2951 u

Hydrogen Bond Acceptor Count = 3

Hydrogen Bond Donor Count = 2

XlogP v2.0 = 3.1060

AMR = 76.9124 cm^3/mol

CMR = 76.2530 cm^3/mol

T_b = 691.3999 K

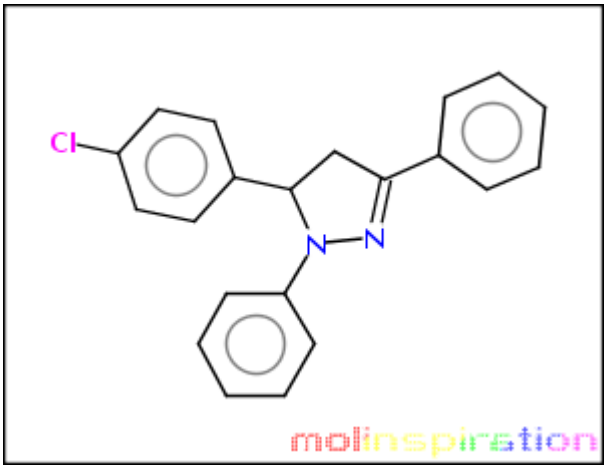
T_f = 381.0500 K

Bioavailability Score = 0.5500

Lipinski's Rule of 5 Violations Count = 0

BIOACTIVITY SCORE BY MOLINSPIRATION

COMPOUND K1



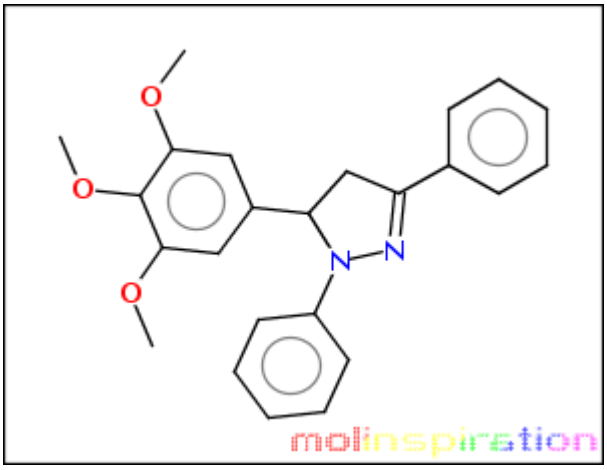
Molinspiration property engine v2013.09

miLogP	5.937
TPSA	15.602
natoms	24.0
MW	332.834
nON	2
nOHNH	0
nviolations	1
nrotb	3
volume	299.229

Molinspiration bioactivity score v2011.06

GPCR ligand	-0.30
Ion channel modulator	-0.66
Kinase inhibitor	-0.73
Nuclear receptor ligand	-0.00
Protease inhibitor	-0.64
Enzyme inhibitor	-0.27

COMPOUND K2



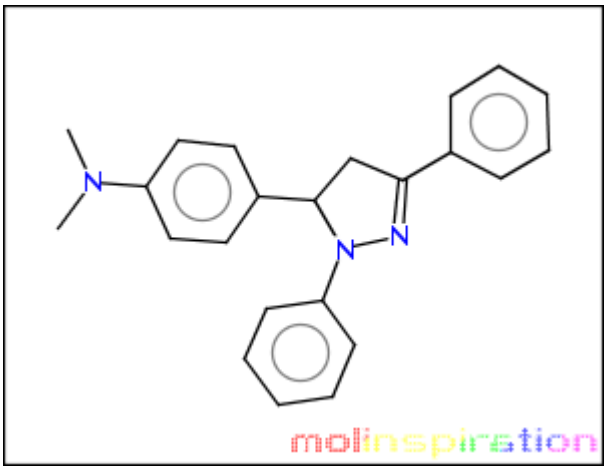
Molinspiration property engine v2013.09

miLogP	4.89
TPSA	43.304
natoms	29.0
MW	388.467
nON	5
nOHNH	0
nviolations	0
nrotb	6
volume	362.33

Molinspiration bioactivity score v2011.06

GPCR ligand	-0.31
Ion channel modulator	-0.64
Kinase inhibitor	-0.62
Nuclear receptor ligand	-0.08
Protease inhibitor	-0.59
Enzyme inhibitor	-0.25

COMPOUND K3



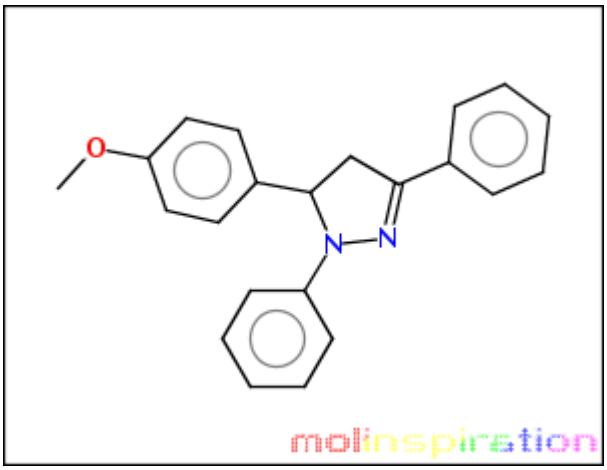
Molinspiration property engine v2013.09

miLogP	5.361
TPSA	18.84
natoms	26.0
MW	341.458
nON	3
nOHNH	0
nviolations	1
nrotb	4
volume	331.599

Molinspiration bioactivity score v2011.06

GPCR ligand	-0.27
Ion channel modulator	-0.62
Kinase inhibitor	-0.63
Nuclear receptor ligand	0.04
Protease inhibitor	-0.56
Enzyme inhibitor	-0.23

COMPOUND K4



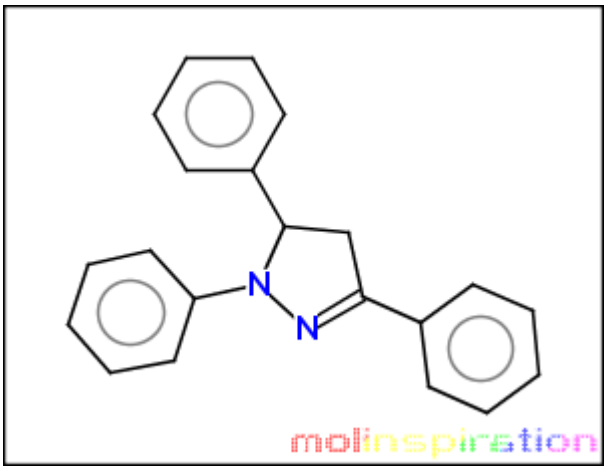
Molinspiration property engine v2013.09

miLogP	5.316
TPSA	24.836
natoms	25.0
MW	328.415
nON	3
nOHNH	0
nviolations	1
nrotb	4
volume	311.238

Molinspiration bioactivity score v2011.06

GPCR ligand	-0.34
Ion channel modulator	-0.71
Kinase inhibitor	-0.72
Nuclear receptor ligand	0.00
Protease inhibitor	-0.62
Enzyme inhibitor	-0.28

COMPOUND K5



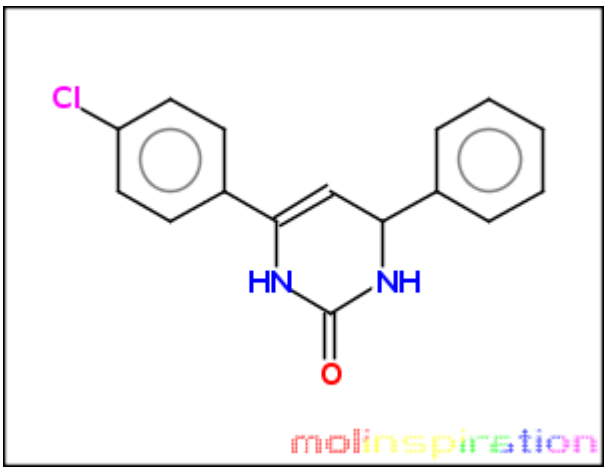
Molinspiration property engine v2013.09

miLogP	5.259
TPSA	15.602
natoms	23.0
MW	298.389
nON	2
nOHNH	0
nviolations	1
nrotb	3
volume	285.693

Molinspiration bioactivity score v2011.06

GPCR ligand	-0.32
Ion channel modulator	-0.68
Kinase inhibitor	-0.74
Nuclear receptor ligand	0.02
Protease inhibitor	-0.64
Enzyme inhibitor	-0.25

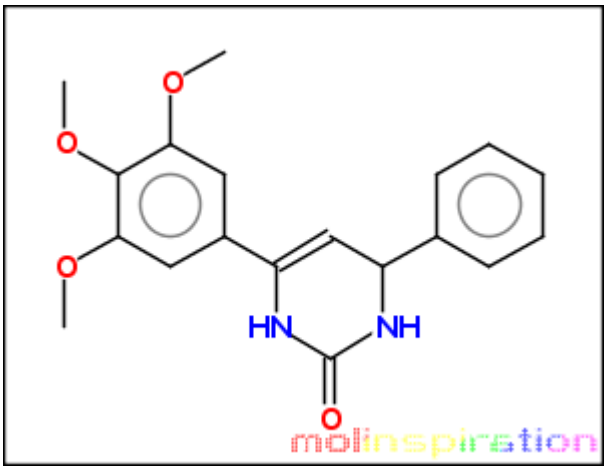
COMPOUND K6



Molinspiration property engine v2013.09
miLogP 3.712
TPSA 41.125
natoms 20.0
MW 284.746
nON 3
nOHNH 2
nviolations 0
nrotb 2
volume 246.179

Molinspiration bioactivity score v2011.06
GPCR ligand -0.26
Ion channel modulator -0.36
Kinase inhibitor -0.63
Nuclear receptor ligand -0.65
Protease inhibitor -0.62
Enzyme inhibitor -0.46

COMPOUND K7



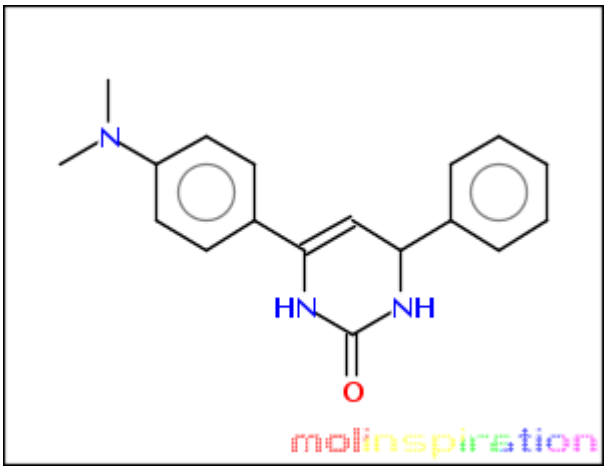
Molinspiration property engine v2013.09

miLogP	2.665
TPSA	68.827
natoms	25.0
MW	340.379
nON	6
nOHNH	2
nviolations	0
nrotb	5
volume	309.28

Molinspiration bioactivity score v2011.06

GPCR ligand	-0.18
Ion channel modulator	-0.36
Kinase inhibitor	-0.46
Nuclear receptor ligand	-0.49
Protease inhibitor	-0.48
Enzyme inhibitor	-0.41

COMPOUND K8



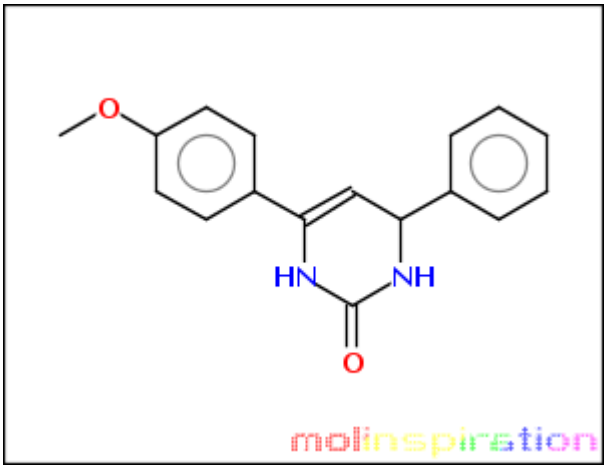
Molinspiration property engine v2013.09

miLogP	3.136
TPSA	44.363
natoms	22.0
MW	293.37
nON	4
nOHNH	2
nviolations	0
nrotb	3
volume	278.549

Molinspiration bioactivity score v2011.06

GPCR ligand	-0.18
Ion channel modulator	-0.36
Kinase inhibitor	-0.46
Nuclear receptor ligand	-0.49
Protease inhibitor	-0.48
SEnzyme inhibitor	-0.41

COMPOUND K9



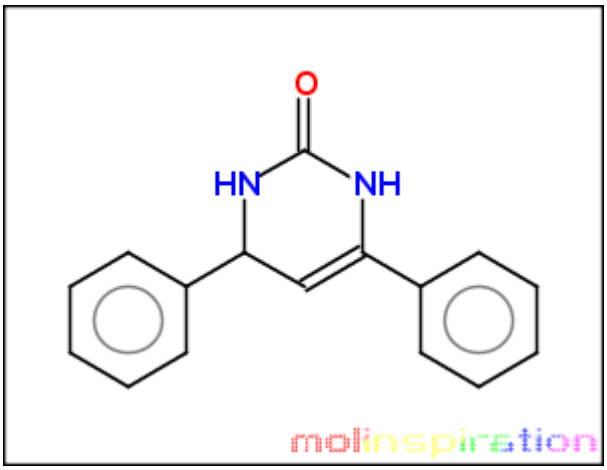
Molinspiration property engine v2013.09

miLogP	3.091
TPSA	50.359
natoms	21.0
MW	280.327
nON	4
nOHNH	2
nviolations	0
nrotb	3
volume	258.189

Molinspiration bioactivity score v2011.06

GPCR ligand	-0.27
Ion channel modulator	-0.43
Kinase inhibitor	-0.59
Nuclear receptor ligand	-0.57
Protease inhibitor	-0.57
Enzyme inhibitor	-0.45

COMPOUND K10



Molinspiration property engine v2013.09

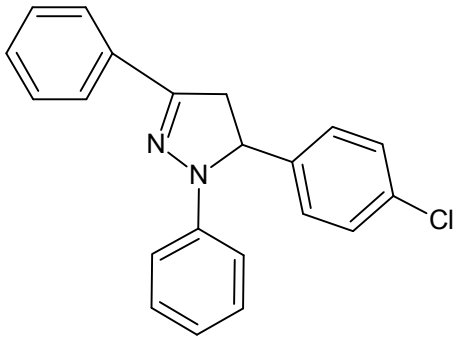
miLogP	3.034
TPSA	41.125
natoms	19.0
MW	250.301
nON	3
nOHNH	2
nviolations	0
nrotb	2
volume	232.643

Molinspiration bioactivity score v2011.06

GPCR ligand	-0.32
Ion channel modulator	-0.37
Kinase inhibitor	-0.68
Nuclear receptor ligand	-0.70
Protease inhibitor	-0.64
Enzyme inhibitor	-0.45

MOLECULAR PROPERTIES USING CHEMSKETCH

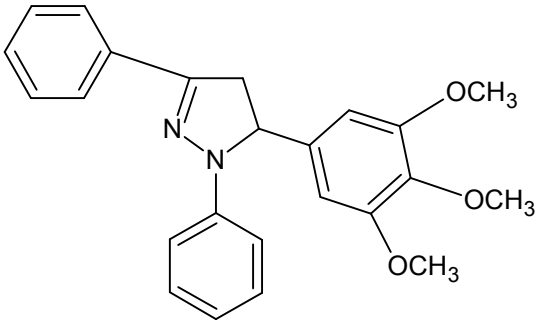
COMPOUND K1



5-(4-chlorophenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazole

Molecular Formula	= $C_{21}H_{17}ClN_2$
Formula Weight	= 332.82608
Composition	= C(75.78%) H(5.15%) Cl(10.65%) N(8.42%)
Molar Refractivity	= 100.74 ± 0.5 cm^3
Molar Volume	= 281.3 ± 7.0 cm^3
Parachor	= 728.7 ± 8.0 cm^3
Index of Refraction	= 1.635 ± 0.05
Surface Tension	= 44.9 ± 7.0 dyne/cm
Density	= 1.18 ± 0.1 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 39.93 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 332.108026 Da
Nominal Mass	= 332 Da
Average Mass	= 332.8261 Da
M+	= 332.107478 Da
M-	= 332.108575 Da
[M+H]+	= 333.115303 Da
[M+H]-	= 333.1164 Da
[M-H]+	= 331.099653 Da
[M-H]-	= 331.10075 Da

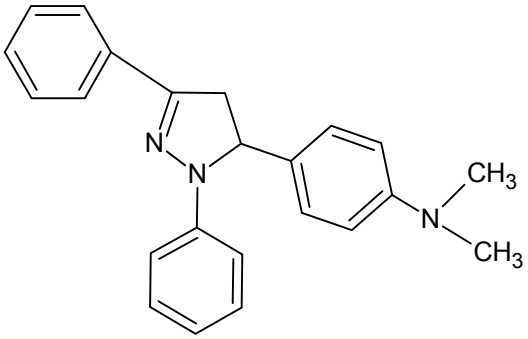
COMPOUND K2



5(3,4,5 trimethoxyphenyl)-1,3 -diphenyl -4,5 -dihydro -1Hpyrazole

Molecular Formula	= $C_{24}H_{24}N_2O_3$
Formula Weight	= 388.45896
Composition	= C(74.21%) H(6.23%) N(7.21%) O(12.36%)
Molar Refractivity	= 113.58 ± 0.5 cm^3
Molar Volume	= 337.0 ± 7.0 cm^3
Parachor	= 850.6 ± 8.0 cm^3
Index of Refraction	= 1.588 ± 0.05
Surface Tension	= 40.5 ± 7.0 dyne/cm
Density	= 1.15 ± 0.1 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 45.02 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 388.178693 Da
Nominal Mass	= 388 Da
Average Mass	= 388.459 Da
M+	= 388.178144 Da
M-	= 388.179241 Da
[M+H]+	= 389.185969 Da
[M+H]-	= 389.187066 Da
[M-H]+	= 387.170319 Da
[M-H]-	= 387.171416 Da

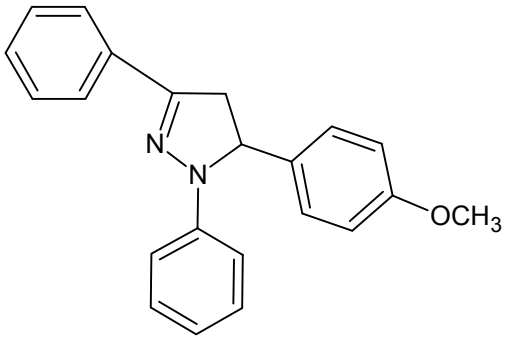
COMPOUND K3



4-(1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-*N*,*N*-dimethylaniline

Molecular Formula	= $C_{23}H_{23}N_3$
Formula Weight	= 341.44882
Composition	= C(80.90%) H(6.79%) N(12.31%)
Molar Refractivity	= 108.94 ± 0.5 cm^3
Molar Volume	= 313.2 ± 7.0 cm^3
Parachor	= 796.1 ± 8.0 cm^3
Index of Refraction	= 1.612 ± 0.05
Surface Tension	= 41.7 ± 7.0 dyne/cm
Density	= 1.09 ± 0.1 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 43.18 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 341.189198 Da
Nominal Mass	= 341 Da
Average Mass	= 341.4488 Da
M+	= 341.188649 Da
M-	= 341.189746 Da
[M+H]+	= 342.196474 Da
[M+H]-	= 342.197571 Da
[M-H]+	= 340.180824 Da
[M-H]-	= 340.181921 Da

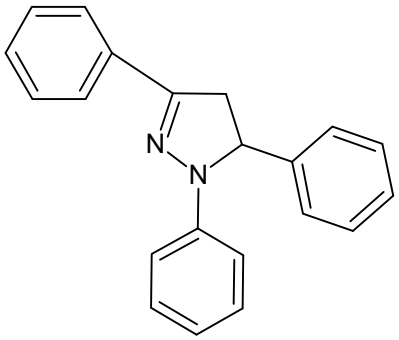
COMPOUND K4



5-(4-methoxyphenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazole

Molecular Formula	= $C_{22}H_{20}N_2O$
Formula Weight	= 328.407
Composition	= C(80.46%) H(6.14%) N(8.53%) O(4.87%)
Molar Refractivity	= 101.95 ± 0.5 cm^3
Molar Volume	= 293.7 ± 7.0 cm^3
Parachor	= 750.1 ± 8.0 cm^3
Index of Refraction	= 1.610 ± 0.05
Surface Tension	= 42.5 ± 7.0 dyne/cm
Density	= 1.11 ± 0.1 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 40.41 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 328.157563 Da
Nominal Mass	= 328 Da
Average Mass	= 328.407 Da
M+	= 328.157015 Da
M-	= 328.158112 Da
[M+H]+	= 329.16484 Da
[M+H]-	= 329.165937 Da
[M-H]+	= 327.14919 Da
[M-H]-	= 327.150287 Da

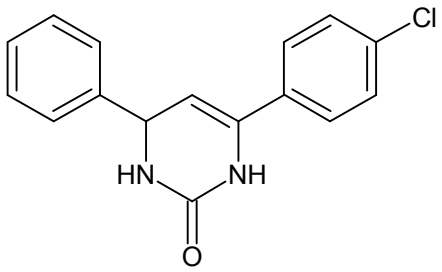
COMPOUND K5



1,3,5-triphenyl-4,5-dihydro-1*H*-pyrazole

Molecular Formula	= $C_{21}H_{18}N_2$
Formula Weight	= 298.38102
Composition	= C(84.53%) H(6.08%) N(9.39%)
Molar Refractivity	= 96.14 ± 0.5 cm^3
Molar Volume	= 272.0 ± 7.0 cm^3
Parachor	= 699.8 ± 8.0 cm^3
Index of Refraction	= 1.624 ± 0.05
Surface Tension	= 43.7 ± 7.0 dyne/cm
Density	= 1.09 ± 0.1 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 38.11 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 298.146999 Da
Nominal Mass	= 298 Da
Average Mass	= 298.381 Da
M+	= 298.14645 Da
M-	= 298.147547 Da
[M+H]+	= 299.154275 Da
[M+H]-	= 299.155372 Da
[M-H]+	= 297.138625 Da
[M-H]-	= 297.139722 Da

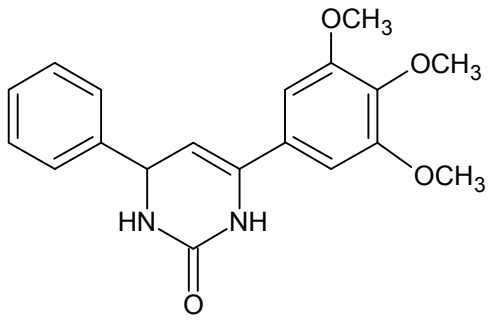
COMPOUND K6



6-(4-chlorophenyl)-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one

Molecular Formula	= $C_{16}H_{13}ClN_2O$
Formula Weight	= 284.74022
Composition	= C(67.49%) H(4.60%) Cl(12.45%) N(9.84%) O(5.62%)
Molar Refractivity	= 78.65 ± 0.3 cm^3
Molar Volume	= 226.6 ± 3.0 cm^3
Parachor	= 588.8 ± 6.0 cm^3
Index of Refraction	= 1.610 ± 0.02
Surface Tension	= 45.5 ± 3.0 dyne/cm
Density	= 1.256 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 31.18 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 284.071641 Da
Nominal Mass	= 284 Da
Average Mass	= 284.7402 Da
M+	= 284.071092 Da
M-	= 284.072189 Da
[M+H]+	= 285.078917 Da
[M+H]-	= 285.080014 Da
[M-H]+	= 283.063267 Da
[M-H]-	= 283.064364 Da

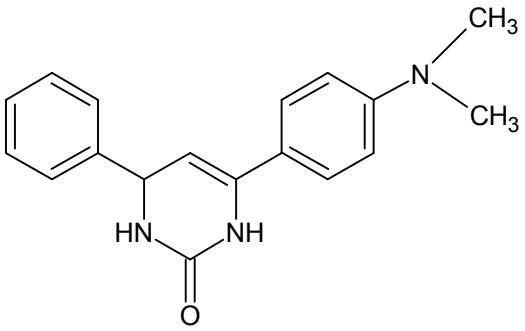
COMPOUND K7



4-phenyl-6-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one

Molecular Formula	= $C_{19}H_{20}N_2O_4$
Formula Weight	= 340.3731
Composition	= C(67.05%) H(5.92%) N(8.23%) O(18.80%)
Molar Refractivity	= 93.79 ± 0.3 cm^3
Molar Volume	= 286.6 ± 3.0 cm^3
Parachor	= 727.6 ± 6.0 cm^3
Index of Refraction	= 1.568 ± 0.02
Surface Tension	= 41.4 ± 3.0 dyne/cm
Density	= 1.187 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 37.18 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 340.142307 Da
Nominal Mass	= 340 Da
Average Mass	= 340.3731 Da
M+	= 340.141759 Da
M-	= 340.142856 Da
[M+H]+	= 341.149584 Da
[M+H]-	= 341.150681 Da
[M-H]+	= 339.133933 Da
[M-H]-	= 339.135031 Da

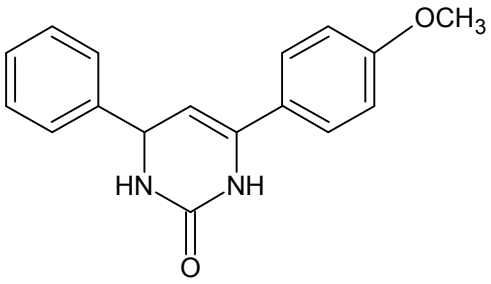
COMPOUND K8



6-[4-(dimethylamino)phenyl]-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one

Molecular Formula	= $C_{18}H_{19}N_3O$
Formula Weight	= 293.36296
Composition	= C(73.69%) H(6.53%) N(14.32%) O(5.45%)
Molar Refractivity	= 88.07 ± 0.3 cm^3
Molar Volume	= 252.6 ± 3.0 cm^3
Parachor	= 656.4 ± 6.0 cm^3
Index of Refraction	= 1.614 ± 0.02
Surface Tension	= 45.5 ± 3.0 dyne/cm
Density	= 1.161 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 34.91 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 293.152812 Da
Nominal Mass	= 293 Da
Average Mass	= 293.363 Da
M+	= 293.152264 Da
M-	= 293.153361 Da
[M+H]+	= 294.160089 Da
[M+H]-	= 294.161186 Da
[M-H]+	= 292.144439 Da
[M-H]-	= 292.145536 Da

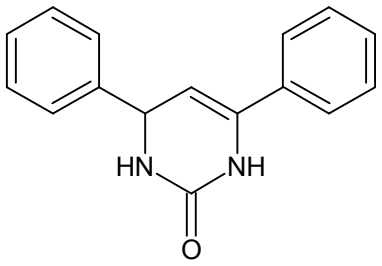
COMPOUND K9



6-(4-methoxyphenyl)-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one

Molecular Formula	= $C_{17}H_{16}N_2O_2$
Formula Weight	= 280.32114
Composition	= C(72.84%) H(5.75%) N(9.99%) O(11.42%)
Molar Refractivity	= 80.44 ± 0.3 cm^3
Molar Volume	= 238.6 ± 3.0 cm^3
Parachor	= 610.3 ± 6.0 cm^3
Index of Refraction	= 1.589 ± 0.02
Surface Tension	= 42.7 ± 3.0 dyne/cm
Density	= 1.174 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 31.88 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 280.121178 Da
Nominal Mass	= 280 Da
Average Mass	= 280.3211 Da
M+	= 280.120629 Da
M-	= 280.121726 Da
[M+H]+	= 281.128454 Da
[M+H]-	= 281.129551 Da
[M-H]+	= 279.112804 Da
[M-H]-	= 279.113901 Da

COMPOUND K10



4,6-diphenyl-3,4-dihydropyrimidin-2(1*H*)-one

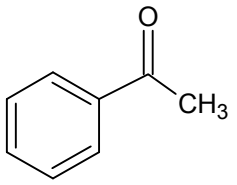
Molecular Formula	= $C_{16}H_{14}N_2O$
Formula Weight	= 250.29516
Composition	= C(76.78%) H(5.64%) N(11.19%) O(6.39%)
Molar Refractivity	= 73.76 ± 0.3 cm^3
Molar Volume	= 214.6 ± 3.0 cm^3
Parachor	= 551.7 ± 6.0 cm^3
Index of Refraction	= 1.603 ± 0.02
Surface Tension	= 43.6 ± 3.0 dyne/cm
Density	= 1.165 ± 0.06 g/cm^3
Dielectric Constant	= Not available
Polarizability	= 29.24 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	= 250.110613 Da
Nominal Mass	= 250 Da
Average Mass	= 250.2952 Da
M+	= 250.110064 Da
M-	= 250.111162 Da
[M+H]+	= 251.11789 Da
[M+H]-	= 251.118987 Da
[M-H]+	= 249.102239 Da
[M-H]-	= 249.103337 Da

TABLE-1: LIST OF CHEMICALS USED

S.N0	NAME OF CHEMICALS	MANUFATURER
1	Acetophenone	Sigma Aldrich
2	Benzophenone	Sigma Aldrich
3	Benzaldehyde	CDH Lab
4	P-dimethylamino benzaldehyde	CDH Lab
5	P-chloro benzaldehyde	CDH Lab
6	Anisaldehyde	CDH Lab
7	3,4,5-trimethoxy benzaldehyde	Sigma Aldrich
8	Ethanol	HPLC
9	Urea	HPLC
10	Sodium hydroxide	CDH Lab
11	Glacial acetic acid	CDH Lab
12	Concentrated sulfuric acid	CDH Lab
13	Dioxane	CDH Lab
14	Potassium hydroxide	HPLC

4.2- SCHEME OF SYNTHESIS

SCHEME OF REACTION-I (Synthesis of compound K1-K5)



1-phenylethanone

\+

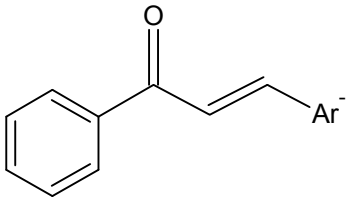
Ar - CHO

Substituted benzaldehye

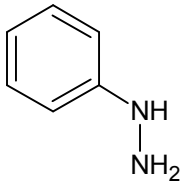
Ethanol

NaOH

STEP 1



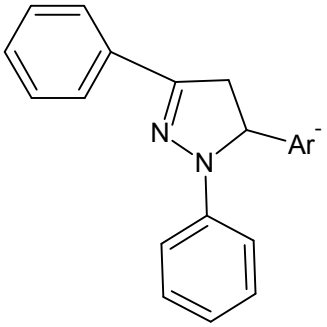
2E -1phenyl -3substituted prop -2en -1one



phenylhydrazine

glacial acetic acid

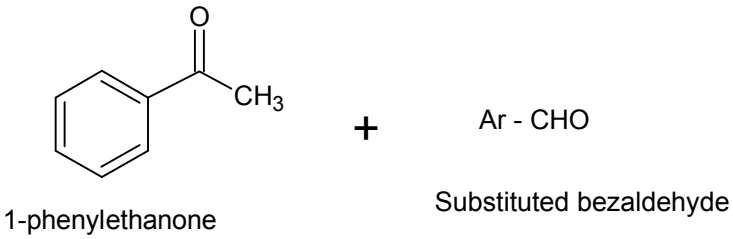
STEP 2

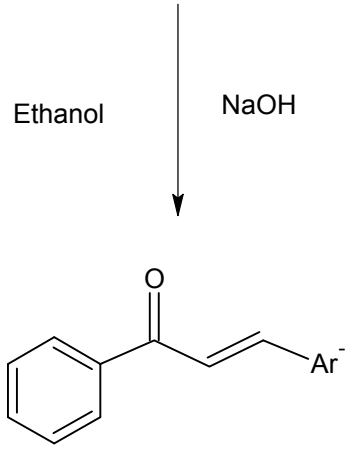


5- aryl 1,3 -diphenyl 4,5 -diyhdro -1H - Pyrazole

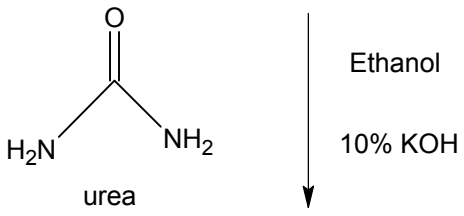
SCHEME OF REACTION-II

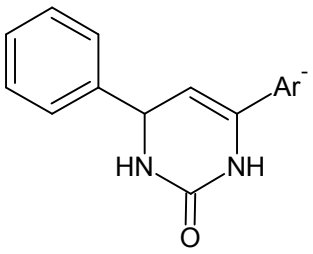
SYNTHESIS OF COMPOUND-K6-K10





2(E)-1 -phenyl -3 -substituted prop -2en -1one





2(E)-1 -phenyl -3 -substituted prop -2en -1one

4.3 MOLECULAR SYNTHESIS[37,54]

Synthesis of Compound K1

STEP- 1

Synthesis of (2E)-3-(4-chlorophenyl)-1-phenylprop-2-en-1- one (Chalcone)

Chemicals Required:

Acetophenone	- 0.01M
4-chloro benzaldehyde	- 0.01M
Ethanol	- 20ml
Sodium hydroxide	- 0.01M
Dilute Hydrochloric acid	- 0.01M

Procedure:

The solution of acetophenone (0.01M) and 4-chloro benzaldehyde (0.01M) in ethanol(20ml) at room temperature was add sodium hydroxide (0.01M) with constant stirring. The reaction mixture was stirred further until a precipitate was formed. The reaction mixture was diluted with ice water and neutralized by using (0.01M) diliuted hydrochloric acid. The product was filtered and recrystallized from ethanol.

STEP – 2

Synthesis of 5-(4-chlorophenyl)-1,3-diphenyl-4,5-dihydro-1H-Pyrazole

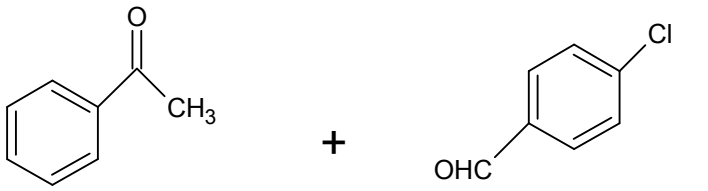
Chemicals Required:

(2E)-3-(4-chlorophenyl)-1-phenyl prop-2-en-1- one	- 0.008mol.
1,4-Dioxane	- 20ml.
Phenyl hydrazine	- 0.024mol.
Cocentrated Sulphuric acid	- 2-3 drops.
Glacial Acetic acid	- 5ml.

Procedure:

To (2E)-3-(4-chlorophenyl)-1-phenyl prop-2-en-1- one (0.0084) 20ml of 1,4-Dioxane and Phenyl hydrazine (0.024Mol) was added. To these mixture 2-3 drops of Sulphuric acid was added and the contents was allowed to get reflux for 4hrs. 5ml of glacial acetic acid was added; again reflux was done for next 2hrs. On cooling to room temperature the contents was poured on crushed ice. As a result the solid product was obtained which was recrystallized by using ethanol.

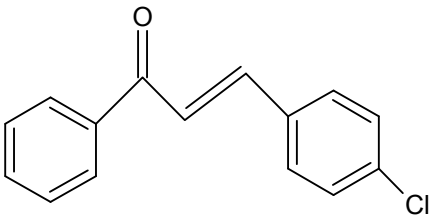
COMPOUND K1



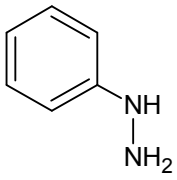
1-phenylethanone 4-chlorobenzaldehyde

Ethanol NaOH

STEP 1



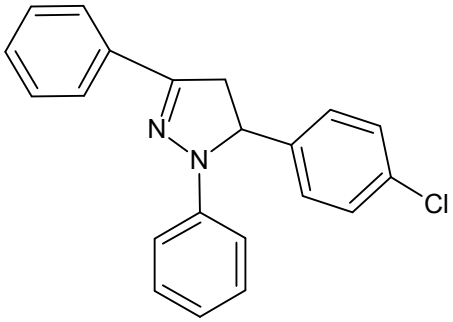
(2*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one



phenylhydrazine

glacial acetic acid

STEP 2



5-(4-chlorophenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazole

Synthesis of Compound K2

STEP- 1

Synthesis of (2E)-3-(3,4,5-methoxyphenyl)-1-phenyl prop-2-en-1- one (Chalcone)

Chemicals Required:

Acetophenone	- 0.01M
3,4,5- Trimethoxy benzaldehyde	- 0.01M
Ethanol	- 20ml
Sodium hydroxide	- 0.01M
Dilute Hydrochloric acid	- 0.01M

Procedure:

The solution of acetophenone (0.01M) and 3,4,5- Trimethoxy benzaldehyde (0.01M) in ethanol(20ml) at room temperature was add sodium hydroxide (0.01M) with constant stirring. The reaction mixture was stirred further until a precipitate was formed. The reaction mixture was diluted with ice water and neutralized by using (0.01M) diliuted hydrochloric acid. The product was filtered and recrystallized from ethanol.

STEP – 2

Synthesis of 5-(3,4,5-metoxyphenyl)-1,3-diphenyl-4,5-dihydro-1H-Pyrazole.

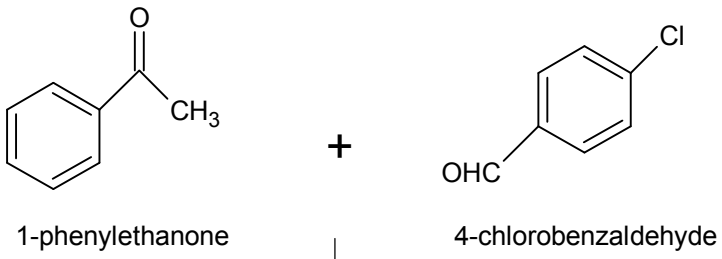
Chemicals Required:

(2E)-3-(3,4,5-methoxyphenyl)-1-phenyl prop-2-en-1- one	- 0.008mol.
1,4-Dioxane	- 20ml.
Phenyl hydrazine	- 0.024mol.
Cocentrated Sulphuric acid	- 2-3 drops.
Glacial Acetic acid	- 5ml.

Procedure:

To (2E)-3-(3,4,5-methoxyphenyl)-1-phenyl prop-2-en-1- one (0.0084) 20ml of 1,4-Dioxane and Phenyl hydrazine (0.024Mol) was added. To these mixture 2-3 drops of Sulphuric acid was added and the contents was allowed to get reflux for 4hrs. 5ml of glacial acetic acid was added; again reflux was done for next 2hrs. On cooling to room temperature the contents was poured on crushed ice. As a result the solid product was obtained which was recrystallized by using ethanol.

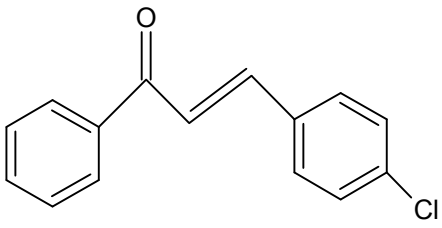
COMPOUND K2



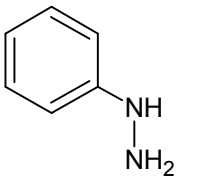
1-phenylethanone 4-chlorobenzaldehyde

Ethanol NaOH

STEP 1



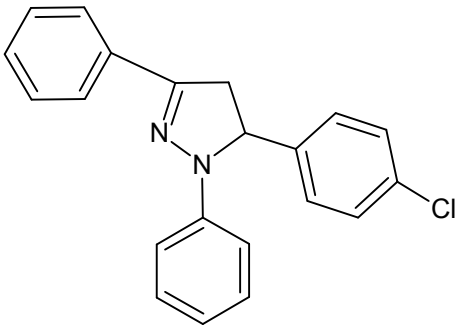
(2*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one



phenylhydrazine

glacial acetic acid

STEP 2



5-(4-chlorophenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazole

Synthesis of Compound K3

STEP- 1

Synthesis of (2E)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1- one (Chalcone)

Chemicals Required:

Acetophenone	- 0.01M
4-dimethyl benzaldehyde	- 0.01M
Ethanol	- 20ml
Sodium hydroxide	- 0.01M
Dilute Hydrochloric acid	- 0.01M

Procedure:

The solution of acetophenone (0.01M) and 4-dimethylamino benzaldehyde (0.01M) in ethanol(20ml) at room temperature was add sodium hydroxide (0.01M) with constant stirring. The reaction mixture was stirred further until a precipitate was formed. The reaction mixture was diluted with ice water and neutralized by using (0.01M) diliuted hydrochloric acid. The product was filtered and recrystallized from ethanol.

STEP – 2

Synthesis of 5-(4-(dimethyl amino)phenyl)-1,3-diphenyl-4,5-dihydro-1H-Pyrazole.

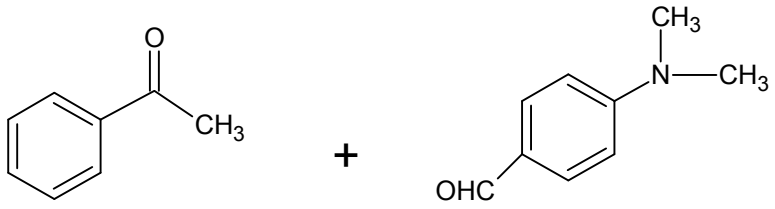
Chemicals Required:

(2E)-3-(4-(dimethyl amino)phenyl)-1-phenyl prop-2-en-1- one	- 0.008mol.
1,4-Dioxane	- 20ml.
Phenyl hydrazine	- 0.024mol.
Cocentrated Sulphuric acid	- 2-3 drops.
Glacial Acetic acid	- 5ml.

Procedure:

To (2E)-3-(4-(dimethyl amino)phenyl)-1-phenyl prop-2-en-1- one (0.0084) 20ml of 1,4-Dioxane and Phenyl hydrazine (0.024Mol) was added. To these mixture 2-3 drops of Sulphuric acid was added and the contents was allowed to get reflux for 4hrs. 5ml of glacial acetic acid was added; again reflux was done for next 2hrs. On cooling to room temperature the contents was poured on crushed ice. As a result the solid product was obtained which was recrystallized by using ethanol.

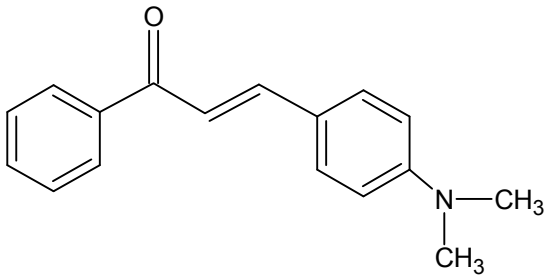
COMPOUND K3



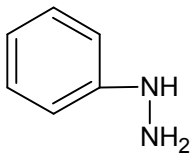
1-phenylethanone + 4-(dimethylamino)benzaldehyde

Ethanol NaOH

STEP 1



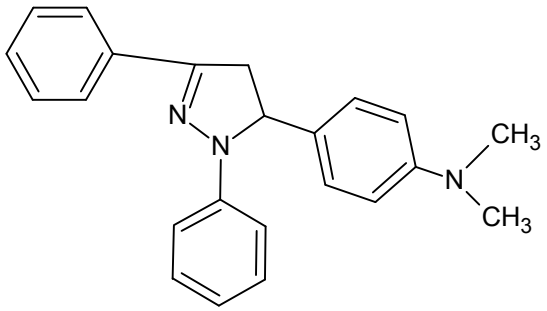
(2*E*)-3-[4-(dimethylamino)phenyl]-1-phenylprop-2-en-1-one



phenylhydrazine

glacial acetic acid

STEP 2



4-(1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-*N*,*N*-dimethylaniline

Synthesis of Compound K4

STEP- 1

Synthesis of (2E)-3-(4-metoxyphenyl)-1-phenylprop-2-en-1- one (Chalcone)

Chemicals Required:

Acetophenone	- 0.01M
4-methoxy benzaldehyde	- 0.01M
Ethanol	- 20ml
Sodium hydroxide	- 0.01M
Dilute Hydrochloric acid	- 0.01M

Procedure:

The solution of acetophenone (0.01M) and 4-methoxy benzaldehyde (0.01M) in ethanol(20ml) at room temperature was add sodium hydroxide (0.01M) with constant stirring. The reaction mixture was stirred further until a precipitate was formed. The reaction mixture was diluted with ice water and neutralized by using (0.01M) diliuted hydrochloric acid. The product was filtered and recrystallized from ethanol.

STEP – 2

Synthesis of 5-(4-methoxyphenyl)-1,3-diphenyl-4,5-dihydro-1H-Pyrazole.

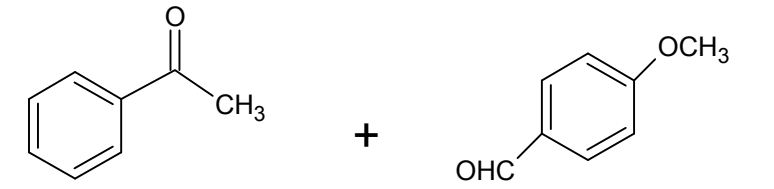
Chemicals Required:

(2E)-3-(4- methoxyphenyl)-1-phenyl prop-2-en-1- one	- 0.008mol.
1,4-Dioxane	- 20ml.
Phenyl hydrazine	- 0.024mol.
Cocentrated Sulphuric acid	- 2-3 drops.
Glacial Acetic acid	- 5ml.

Procedure:

To (2E)-3-(4-methoxyphenyl)-1-phenyl prop-2-en-1- one (0.0084) 20ml of 1,4-Dioxane and Phenyl hydrazine (0.024Mol) was added. To these mixture 2-3 drops of Sulphuric acid was added and the contents was allowed to get reflux for 4hrs. 5ml of glacial acetic acid was added; again reflux was done for next 2hrs. On cooling to room temperature the contents was poured on crushed ice. As a result the solid product was obtained which was recrystallized by using ethanol.

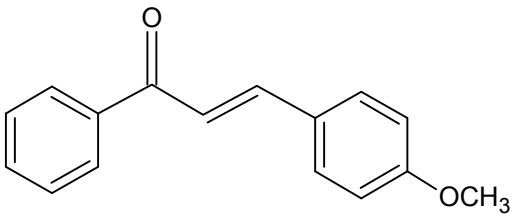
COMPOUND K4



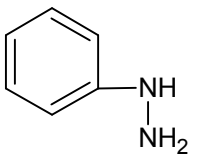
1-phenylethanone 4-methoxybenzaldehyde

Ethanol NaOH

STEP 1



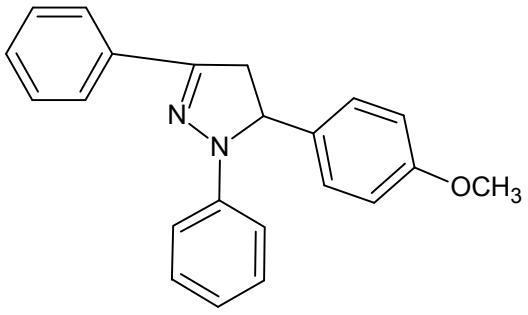
(2*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one



phenylhydrazine

glacial acetic acid

STEP 2



5-(4-methoxyphenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazole

Synthesis of Compound K5

STEP- 1

Synthesis of (2E)-1,3-diphenylprop-2-en-1- one (Chalcone)

Chemicals Required:

Acetophenone	- 0.01M
benzaldehyde	- 0.01M
Ethanol	- 20ml
Sodium hydroxide	- 0.01M
Dilute Hydrochloric acid	- 0.01M

Procedure:

The solution of acetophenone (0.01M) and benzaldehyde (0.01M) in ethanol(20ml) at room temperature was add sodium hydroxide (0.01M) with constant stirring. The reaction mixture was stirred further until a precipitate was formed. The reaction mixture was diluted with ice water and neutralized by using (0.01M) diliuted hydrochloric acid. The product was filtered and recrystallized from ethanol.

STEP – 2

Synthesis of 1,3,5-triphenyl-4,5-dihydro-1H-Pyrazole.

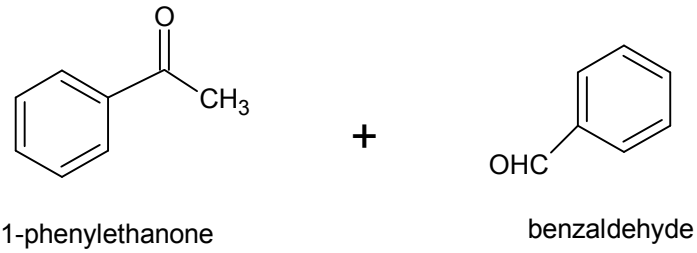
Chemicals Required:

(2E)-1,3-diphenyl prop-2-en-1- one	- 0.008mol.
1,4-Dioxane	- 20ml.
Phenyl hydrazine	- 0.024mol.
Cocentrated Sulphuric acid	- 2-3 drops.
Glacial Acetic acid	- 5ml.

Procedure:

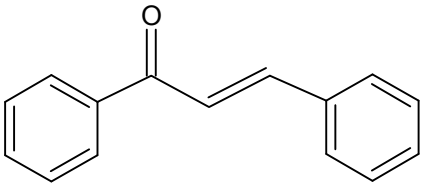
To (2E)-1,3-diphenyl prop-2-en-1- one (0.0084) 20ml of 1,4-Dioxane and Phenyl hydrazine (0.024Mol) was added. To these mixture 2-3 drops of Sulphuric acid was added and the contents was allowed to get reflux for 4hrs. 5ml of glacial acetic acid was added; again reflux was done for next 2hrs. On cooling to room temperature the contents was poured on crushed ice. As a result the solid product was obtained which was recrystallized by using ethanol.

COMPOUND K5

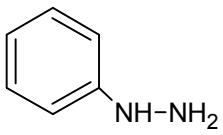


1-phenylethanone benzaldehyde

Ethanol NaOH

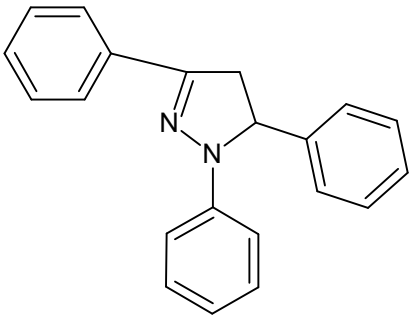


(2*E*)-1,3-diphenylprop-2-en-1-one



phenylhydrazine

glacial acetic acid



1,3,5-triphenyl-4,5-dihydro-1*H*-pyrazole

Synthesis of Compound K6

STEP- 1

Synthesis of (2E)-3-(4-chlorophenyl)-1-phenylprop-2-en-1- one (Chalcone)

Chemicals Required:

Acetophenone	- 0.01M
4-chloro benzaldehyde	- 0.01M
Ethanol	- 20ml
Sodium hydroxide	- 0.01M
Dilute Hydrochloric acid	- 0.01M

Procedure:

The solution of acetophenone (0.01M) and 4-chloro benzaldehyde (0.01M) in ethanol(20ml) at room temperature was add sodium hydroxide (0.01M) with constant stirring. The reaction mixture was stirred further until a precipitate was formed. The reaction mixture was diluted with ice water and neutralized by using (0.01M) diliuted hydrochloric acid. The product was filtered and recrystallized from ethanol.

STEP -2

Syntheisis of 6-(4-chlorophenyl)-4-phenyl-3,4-dihydro pyrimidine-2(1H)-one.

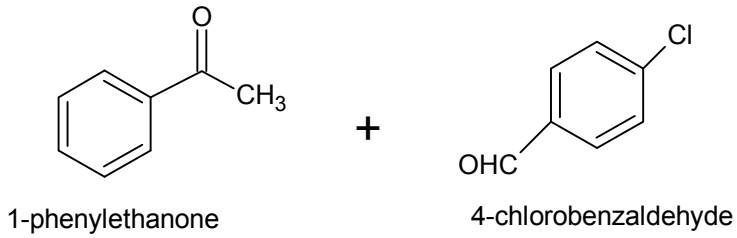
Chemicals Required:

(2E)-3-(4-chlorophenyl)-1-phenylprop-2-en-1- one	- 0.01mol.
Urea	- 0.01mol.
Ethanol	- 25ml.
10% Potassium hydroxide	- 5ml.

Procedure:

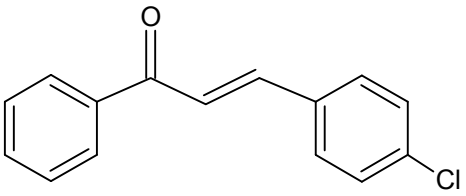
A mixture of (2E)-3-(4-chlorophenyl)-1-phenylprop-2-en-1- one (0.01mol), Urea(0.01mol) in absolute ethanol(25ml) and 10% potassium hydroxide(5ml) refluxed on a waterbath for 8hours. The reaction was monitered by TLC and the precipitation was recrystalised from absolute ethanol give pure compound.

COMPOUND K6

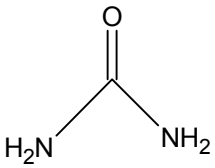


1-phenylethanone 4-chlorobenzaldehyde

Ethanol NaOH



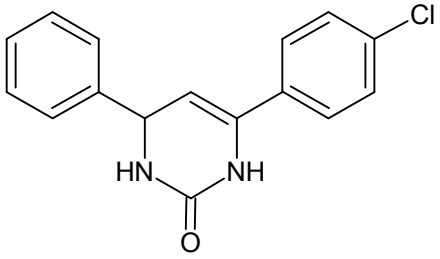
(2*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one



urea

Ethanol

10% KOH



6-(4-chlorophenyl)-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one

Synthesis of Compound K7

STEP- 1

Synthesis of (2E)-3-(3,4,5-methoxyphenyl)-1-phenyl prop-2-en-1- one (Chalcone)

Chemicals Required:

Acetophenone	- 0.01M
3,4,5- Trimethoxy benzaldehyde	- 0.01M
Ethanol	- 20ml
Sodium hydroxide	- 0.01M
Dilute Hydrochloric acid	- 0.01M

Procedure:

The solution of acetophenone (0.01M) and 3,4,5- Trimethoxy benzaldehyde (0.01M) in ethanol(20ml) at room temperature was add sodium hydroxide (0.01M) with constant stirring. The reaction mixture was stirred further until a precipitate was formed. The reaction mixture was diluted with ice water and neutralized by using (0.01M) diliuted hydrochloric acid. The product was filtered and recrystallized from ethanol.

STEP – 2

Synthesis of 4-(phenyl-6-(3,4,5-trimethoxy phenyl)-3,4-dihydropyrimidin-2(1H)-one.

Chemicals Required:

(2E)-3-(3,4,5-methoxyphenyl)-1-phenyl prop-2-en-1- one - 0.01mol.

Urea - 0.01mol .

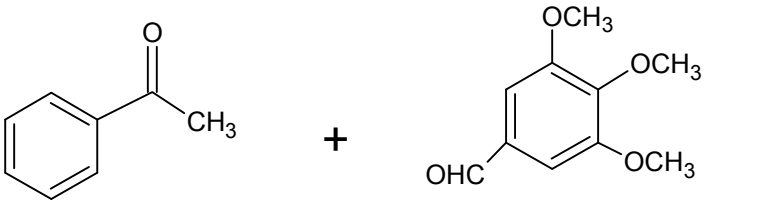
Ethanol - 25ml.

10% Potassium hydroxide - 5ml.

Procedure:

A mixture of (2E)-3-(3,4,5-methoxyphenyl)-1-phenyl prop-2-en-1- one (0.01mol), Urea(0.01mol) in absolute ethanol(25ml) and 10% potassium hydroxide(5ml) refluxed on a waterbath for 8hours. The reaction was monitered by TLC and the precipitation was recrystalised from absolute ethanol give pure compound.

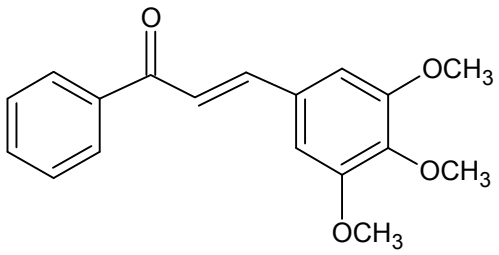
COMPOUND K7



1-phenylethanone 3,4,5-trimethoxybenzaldehyde

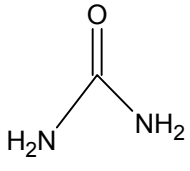
Ethanol NaOH

STEP 1



(2*E*)-1-phenyl-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one

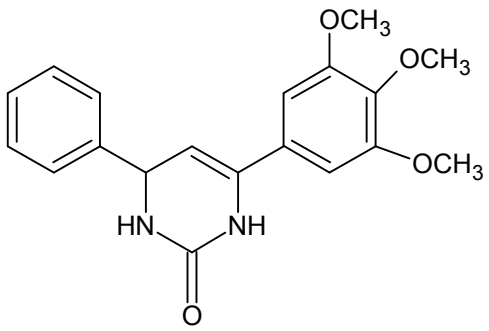
STEP 2



urea

Ethanol

10% KOH



4-phenyl-6-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one

Synthesis of Compound K8

STEP- 1

Synthesis of (2E)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1- one (Chalcone)

Chemicals Required:

Acetophenone	- 0.01M
4-dimethyl benzaldehyde	- 0.01M
Ethanol	- 20ml
Sodium hydroxide	- 0.01M
Dilute Hydrochloric acid	- 0.01M

Procedure:

The solution of acetophenone (0.01M) and 4-dimethylamino benzaldehyde (0.01M) in ethanol(20ml) at room temperature was add sodium hydroxide (0.01M) with constant stirring. The reaction mixture was stirred further until a precipitate was formed. The reaction mixture was diluted with ice water and neutralized by using (0.01M) diliuted hydrochloric acid. The product was filtered and recrystallized from ethanol.

STEP – 2

Synthesis of 6-[4-(dimethylamino)phenyl]-4-phenyl-3,4-dihydropyrimidin-2(1H)-one.

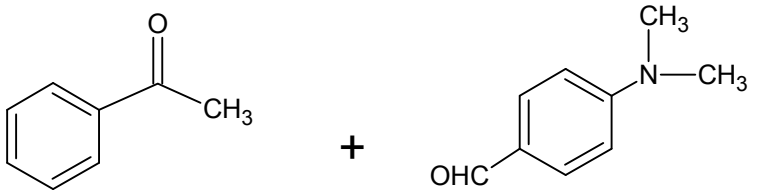
Chemicals Required:

(2E)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1- one	- 0.01mol.
Urea	- 0.01mol .
Ethanol	- 25ml.
10% Potassium hydroxide	- 5ml.

Procedure:

A mixture of (2E)-3-(4-(dimethylamino)phenyl)-1-phenylprop-2-en-1- one (0.01mol), Urea(0.01mol) in absolute ethanol(25ml) and 10% potassium hydroxide(5ml) refluxed on a waterbath for 8hours. The reaction was monitered by TLC and the precipitation was recrystalised from absolute ethanol give pure compound.

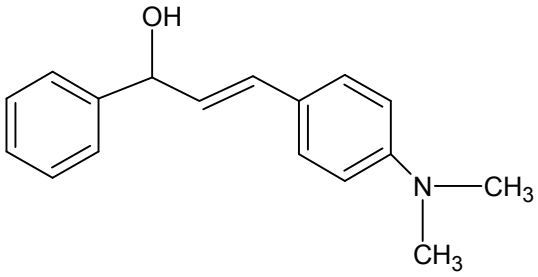
COMPOUND K8



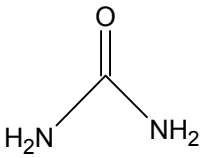
1-phenylethanone + 4-(dimethylamino)benzaldehyde

Ethanol NaOH

STEP 1



(2*E*)-3-[4-(dimethylamino)phenyl]-1-phenylprop-2-en-1-ol

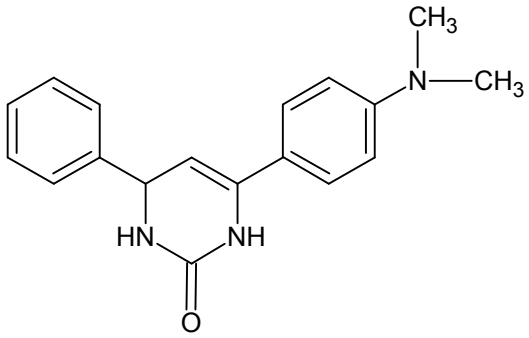


urea

Ethanol

10% KOH

STEP 2



6-[4-(dimethylamino)phenyl]-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one

Synthesis of Compound K9

STEP- 1

Synthesis of (2E)-3-(4-metoxyphenyl)-1-phenylprop-2-en-1- one (Chalcone)

Chemicals Required:

Acetophenone	- 0.01M
4-methoxy benzaldehyde	- 0.01M
Ethanol	- 20ml
Sodium hydroxide	- 0.01M
Dilute Hydrochloric acid	- 0.01M

Procedure:

The solution of acetophenone (0.01M) and 4-methoxy benzaldehyde (0.01M) in ethanol(20ml) at room temperature was add sodium hydroxide (0.01M) with constant stirring. The reaction mixture was stirred further until a precipitate was formed. The reaction mixture was diluted with ice water and neutralized by using (0.01M) diliuted hydrochloric acid. The product was filtered and recrystallized from ethanol.

STEP – 2

Synthesis of 6-(4-methoxyphenyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one.

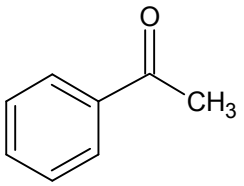
Chemicals Required:

(2E)-3-(4-metoxyphenyl)-1-phenylprop-2-en-1- one	- 0.01mol.
Urea	- 0.01mol .
Ethanol	- 25ml.
10% Potassium hydroxide	- 5ml.

Procedure:

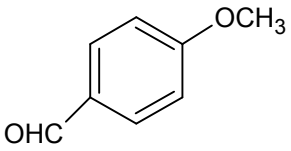
A mixture of (2E)-3-(4-metoxyphenyl)-1-phenylprop-2-en-1- one (0.01mol), Urea(0.01mol) in absolute ethanol(25ml) and 10% potassium hydroxide(5ml) refluxed on a waterbath for 8hours. The reaction was monitered by TLC and the precipitation was recrystalised from absolute ethanol give pure compound.

COMPOUND K9



1-phenylethanone

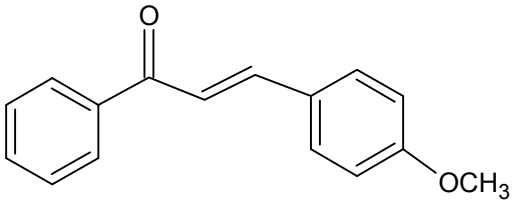
+



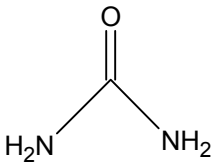
4-methoxybenzaldehyde

Ethanol NaOH

STEP 1



(2*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one

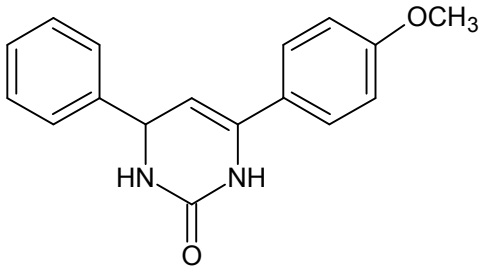


urea

Ethanol

10% KOH

STEP 2



6-(4-methoxyphenyl)-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one

Synthesis of Compound K10

STEP- 1

Synthesis of (2E)-1,3-diphenylprop-2-en-1- one (Chalcone)

Chemicals Required:

Acetophenone	- 0.01M
benzaldehyde	- 0.01M
Ethanol	- 20ml
Sodium hydroxide	- 0.01M
Dilute Hydrochloric acid	- 0.01M

Procedure:

The solution of acetophenone (0.01M) and benzaldehyde (0.01M) in ethanol(20ml) at room temperature was add sodium hydroxide (0.01M) with constant stirring. The reaction mixture was stirred further until a precipitate was formed. The reaction mixture was diluted with ice water and neutralized by using (0.01M) diliuted hydrochloric acid. The product was filtered and recrystallized from ethanol.

STEP – 2

Synthesis of 4,6-diphenyl-3,4-dihydropyrimidin-2(1H)-one.

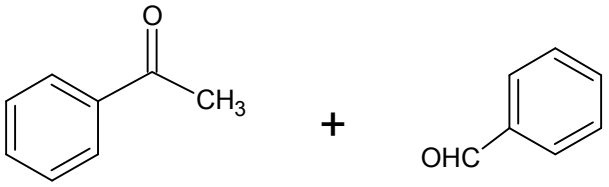
Chemicas Required:

(2E)-1,3-diphenylprop-2-en-1- one	- 0.01mol.
Urea	- 0.01mol .
Ethanol	- 25ml.
10% Potassium hydroxide	- 5ml.

Procedure:

A mixture of (2E)-1,3-diphenylprop-2-en-1- one (0.01mol), Urea(0.01mol) in absolute ethanol(25ml) and 10% potassium hydroxide(5ml) refluxed on a waterbath for 8hours. The reaction was monitered by TLC and the precipitation was recrystalised from absolute ethanol give pure compound.

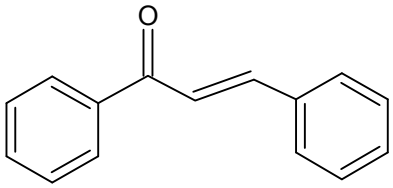
COMPOUND K10



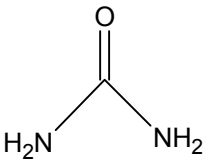
1-phenylethanone benzaldehyde

Ethanol NaOH

STEP 1



(2*E*)-1,3-diphenylprop-2-en-1-one

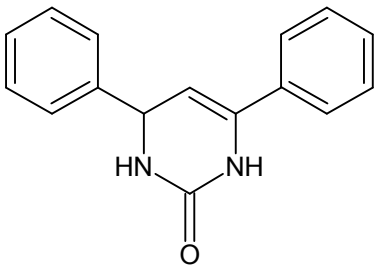


urea

Ethanol

10% KOH

STEP 2



4,6-diphenyl-3,4-dihydropyrimidin-2(1*H*)-one

4.4 ANALYTICAL TECHNIQUES[39,46]

Physical data

The physical data such as solubility and melting point was determined. The compound was soluble in DMSO, Chloroform and insoluble in water.

The melting point of synthesized compounds were determined by the capillary tube method.

Thin Layer chromatography(TLC)

TLC analysis was carried out on commercially available silica gel plates of 0.5mm of thickness, as stationary phase. Benzene:chloroform (9:1) mobile phase was used for n-phenylpyrazoline derivatives. N-Hexane:Ethyl acetate (1:1) mobile phase was used for 3,4-dihydropyrimidine derivatives.

Instrumentation

The analytical instruments such as IR spectra, ^{1}HNMR, MASS spectra were used for the characterization of synthesized compounds.

Infrared Spectra

The IR spectra of synthesized compounds K1-K10 were recorded by FTIR (Shimadzu IR affinity I) in the range of 4000-450cm^{-1}.

Nuclear Magnetic Resonance

The bruker Avance II 400 NMR spectrometer is used to measure the chemical shift and reported in parts per million (δ ppm).

Mass spectroscopy

The molecular ion peaks are recorded by Mass spectroscopy and reported in m/z ratio.

4.5-BIOLOGICAL EVALUATION

A. INVTIRO ANTI-OXIDANT ACTIVITY

Evaluation of antioxidant capacity by phosphomolybdenum method:

Materials and method

Equipment:

UV spectrophotometer and thermostatically controlled water bath.

Reagents:

Sodium Phosphate 28mM

Ammonium molybdate 4mM

0.06M Sulphuric acid

Ethanol

Drugs:

Standard drugs: Different concentration of Ascorbic acid

Test drug : Different concentration of compounds K1-K10.

Procedure:

Anti-oxidant activity was performed by the following procedure of Hance EI Hajaji et al (46). The antioxidant activity of the compounds was evaluated by the Phosphomolybdenum method. The assay is based on the reduction of Mo (VI) – Mo (V) by the compounds and subsequent formation of a green phosphate /Mo (V) complex at acid pH. A 0.3ml of compounds (100µg/ml, 200µg/ml and 300µg/ml) was combined with 3ml of reagent solution (0.6M sulfuric acid, 28mM sodium phosphate and 4mM ammonium molybdate). In case of blank 0.3ml of ethanol was used in place of compounds. The tuves containing the reaction solution were capped and incubated in a boiling water bath at 95° C for 90 min. After cooling to room temperature, the absorbance of the solution was measured at 695nm using a UV spectrophotometer. The antioxidant capacity of each sample was compared with the absorbance of standard.

B. IN-VITRO ANTI-INFLAMMATORY ACTIVITY

Evaluation of Anti-inflammatory activity by Membrane Stabilization Assay

Instrument:

Shimadzu UV Visible spectrophotometer, Model 1800

Reagents:

0.2M sodium phosphate buffer (pH 7.4)

0.36% w/v hyposaline

10%v/v HRBC suspension in isosaline

Preparation of HRBC suspension in isosaline:

The human erythrocytes suspension was used for the in vitro membrane stabilization assay. Blood was collected from healthy volunteers who had not consumed any NSAIDs for two weeks prior to the experiment. The blood was mixed with equal volume of Alsever solution (2% dextrose, 8.0% sodium citrate, 0.5% citric acid and 0.42% sodium chloride) and centrifuged at 3000rpm. The packed cells were washed with isosaline and a 10% v/v erythrocyte suspension in isosaline was prepared.

Procedure:

The assay mixture consist of 2mL of hyposaline and 1mL of phosphate buffer and varying concentration of compounds (200µg/ml, 400µg/ml, 600µg/ml) 0.5 mL and 0.5mL of HRBC suspension in isosaline, then the final volume were made up with isosaline up to 4.5mL. The control was prepared as mentioned above except the drug was omitted, while drug control was also prepared similarly but without HRBC suspension. The reaction mixture was incubated at 56ºC for 30min in a water bath, then the tube was cooled under running water. Then the absorbance of the released haemoglobin was measured at 560nm. Diclofenac

50µg/mL was used as a reference standard. The percentage of membrane stabilization activity of the compounds were determined by the formula

$$\% \text{ membrane stabilization} = [A_{control} - (A_{test} - A_{product\ control})] / A_{control} \times 100$$

$A_{control}$ - Absorbance in control

A_{test} - Absorbance in test

$A_{product\ control}$ - Absorbance in product control.

C. IN-VITRO ANTIDIABETIC ACTIVITY[55,56]

(i) Evaluation of anti-diabetic activity by Non enzymatic glycosylation of haemoglobin assay:

Materials and Method

Equipment:

UV Spectrophotometer.

Reagents:

2% Glucose

0.06% Haemoglobin

0.02% Gentomycin

0.01M Phosphate buffer(pH 7.4)

Drugs:

Standard drugs : Different concentration of Alpha-tocopherol.

Test drug : Different concentration of Compounds K1-K10.

Procedure:

Anti-diabetic activity was performed by the following procedure of KINNARI N.MISTRY et al. The anti-diabetic activity of the compounds was evaluated by the non-enzymatic glycosylation of haemoglobin method. The assay is based on the inhibition of haemoglobin glycosylation by the compounds and subsequent formation of glucose haemoglobin complex.1Ml of compounds (100µg/ml, 200µg/ml, 300µg/ml) was combined with 1ml of 2% glucose solution then add 1ml of 0.06% haemoglobin and 0.02% Gentamycin(The solutions were prepared in 0.01M phosphate buffer(pH7.4) In case blank 1ml of phosphate buffer used in place of compounds. Mixture was incubated in dark place at

room temperature for 72 hrs. the degree of glycosylation of haemoglobin was measured at 520nm. Alpha-Tocopherol was used as a standard drug for assay.

The percentage glycosylation of Haemoglobin was calculated by using following formula = **Test – Control / Test x 100**

(ii) **Evaluation of Anti-diabetic activity by Alpha amylase enzyme inhibition Assay.**

Materials and Methods:

Equipment:

UV-Visible spectroscopy.

Incubator.

Reagents:

α-amylase enzyme.

0.1mM Acetate Buffer (7.2PH)

Potato Starch(1%w/v)

Iodine-Iodide indicator.

Drugs:

Standard drug - Different concentration of Acarbose

Test Drug - Different concentration of compounds K1-K10

Procedure:

Anti-diabetic activity was performed by the procedure of KINNARI N.MISTRY. The Anti-Diabetic activity of the compounds was evaluated by the α-amylase inhibition assay. The assay is based on the inhibition of α-amylase enzyme (α-amylase hydrolyses alpha-bonds of large alpha linked polysaccharide such as glycogen and starch to yield glucose and maltose. 1ml of compounds (100µg/ml, 200µg/ml, 300µg/ml) was combined with 1ml of potato starch(1%w/v) soution, 1ml of α-amylase enzyme(1%w/v) and 2ml of acetate buffer 0.1mM (Note:Potato starch solution, α-amylase enzyme solution and drug solution was prepared in acetate buffer). In case blank 1ml of Acetate buffer was used in the place of compounds. The above mixture was incubate for 1hr. Then 0.1ml iodine-iodide

indicator was added in the mixture (635mg iodine and 1gm potassium iodide in 250ml distilled water). Absorbance was measured at 565nm in UV-Visible spectrosocopy. The anti-diabetic activity of each synthesized compounds was compared with the % inhibition of standard.

The % Inhibition was calculated by using following formula

% Inhibition = Test - Control / Test x 100

(iii) Evaluation of Anti-diabetic activity by α-Glucosidase enzyme inhibition assay

Materials and Methods:

Equipment:

UV-Visible spectrophotometer.

Reagents:

2% w/v Sucrose

α-Glucosidase

0.2M Tris Buffer(PH8)

Drug:

Standard drug - Different concentration of Acarbose.

Test Drug - Different concentration of compound K1-K10.

Procedure:

Anti-diabetic activity was performed by the following procedure of R.MANIKANDAN et al. The anti-diabetic activity of the compound was evaluated by the α-glucosidase inhibition assay. The assay is based on the inhibition of α-Glucosidase enzyme and inhibit the formation of glucose level in blood. 1ml of compounds (100µg/ml, 200µg/ml, 300µg/ml) was combined with 1ml of 2%w/v of sucrose solution then add 1ml of 0.2M Tris Buffer PH8. The reaction was initiated by adding 1ml of α-Glucosidase enzyme (1U/ml) to it followed by incubation for 40 minutes at 35°C.Then the reaction was terminated by the addition of 2ml of 6N Hcl. Then the intensity of the colour was measured at 540nm. The % inhibition was calculated by using following formula

% inhibition = Control - Test / Control x100

D. IN-VITRO ANTI-TUBERCULOSIS ACTIVITY[53,52]

Evaluation of Anti-tuberculosis activity by Mycobacterium tuberculosis susceptibility testing.

Materials:

Versa trek Myco bottle

Mycogrowth Supplement

Sterile distilled water

Tubes with sterile saline

Tuberculin Syringes

Sterile Filter packs.

Drugs:

Standard drugs : Different concentration of Isoniazid

Test drug : Different concentration of compound K1, K2, K3, K8.

Procedure:

A. Preparation of drug solution (INH and Synthesized compounds)

1. Add 25ml of sterile distilled water to each of three drug containing (75µg) bottles. Swirl to dissolve the contents. Dilute 1:1 with sterile distilled water.
2. Remove 5ml of the rehydrated drug solution and add to a sterile tube containing 15ml of sterile distilled water. Label as above(0.1µg/ml).

B. Preparartion of Inoculum:

1. Prepare a suspension of the test organism in tubes containing sterile saline and glass beads.

2. Vortex well and allow the larger particles to settle for at least 30 minutes. Remove the upper half of suspension to a sterile tube and adjust with sterile saline , to a turbidity matching that of a 1.0 MCFarland Standard.
3. Dilute 1:10 with sterile saline. This suspension serves as the inoculum.

C. Inoculation of bottles:

1. Add 0.5 ml of inoculum to each of the drug containing and control bottles.
2. Inoculate a 7H11 agar plate with a few drops of the inoculum to serve as a purity check.
3. Invert the bottle several times to mix the contents.
4. Each bottle place onto a connector.

D. Bottle Accessioning and Reading:

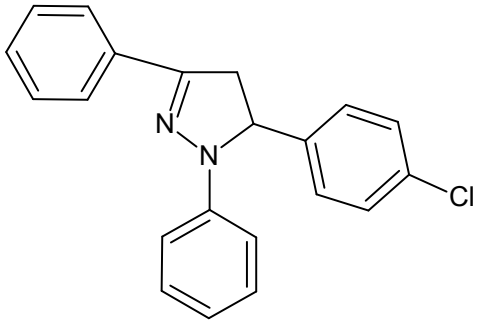
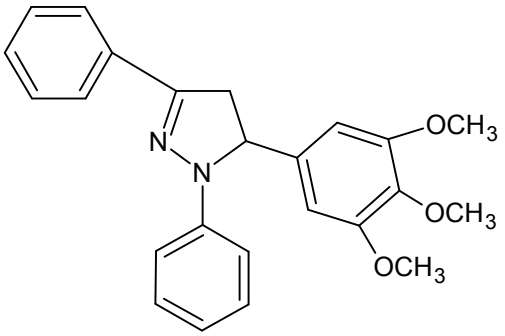
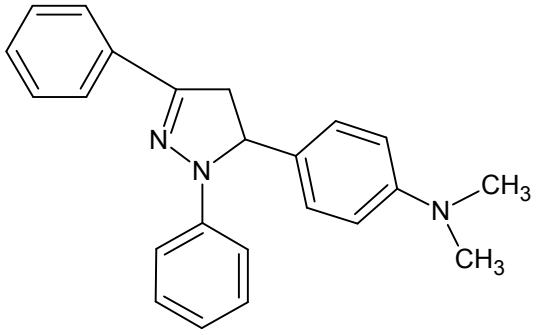
1. Accession each bottle into the ESP Myco system .
2. Record the time to the nearest 9 days.
3. Within 9 days drug and control bottle signals positive, remove from the system and confirm the presence of Mycbacterium tuberculosis by performing a kinyoun stain.

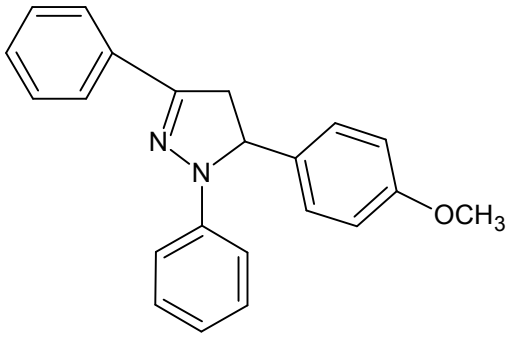
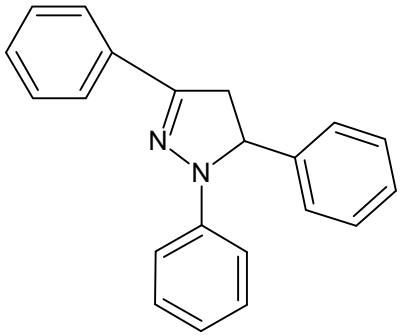
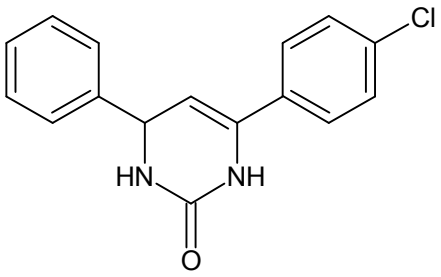
RESULT AND DISCUSSION

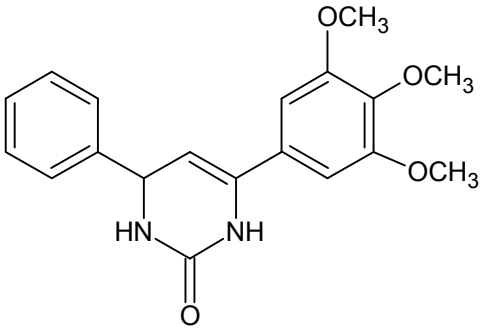
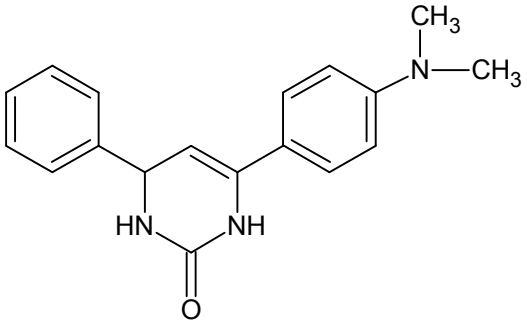
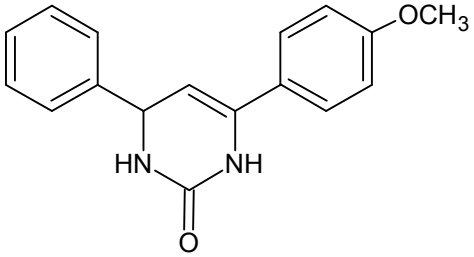
5.RESULTS AND DISCUSSION

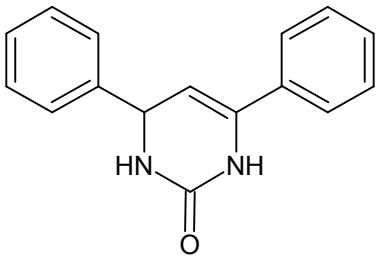
5.1 Characterization of synthesized compounds

Table-2: List of synthesied compounds with IUPAC Name

Compound	Structure with IUPAC Name
K1	 5-(4-chlorophenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazole
K2	 5(3,4,5,trimethoxyphenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole
K3	 4-(1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-*N*,*N*-dimethylaniline

Compound	Structure with IUPAC Name
K4	 5-(4-methoxyphenyl)-1,3-diphenyl-4,5-dihydro-1*H*-pyrazole
K5	 1,3,5-triphenyl-4,5-dihydro-1*H*-pyrazole
K6	 6-(4-chlorophenyl)-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one

Compound	Structure with IUPAC Name
K7	 4-phenyl-6-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one
K8	 6-[4-(dimethylamino)phenyl]-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one
K9	 6-(4-methoxyphenyl)-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one

Compound	Structure with IUPAC Name
K10	 4,6-diphenyl-3,4-dihydropyrimidin-2(1*H*)-one

Physical Data of Synthesized compounds

Table -3

Compound	Molecuar formula	Nature	Soluble in	% Yield
K1	C21H17ClN2	Brown solid	DMSO	74
K2	C24H24N2O3	Brown solid	DMSO	76
K3	C23H23N3	Brown solid	DMSO	72
K4	C22H20N2O	Brown solid	DMSO	69
K5	C21H18N2	Brown solid	DMSO	65
K6	C16H13ClN2O	Yellow solid	DMSO	73
K7	C19H20N2O4	Yellow solid	DMSO	74
K8	C18H19N30	Orange solid	DMSO	68
K9	C17H16N202	Yellow solid	DMSO	65
K10	C16H14N20	Yellow solid	DMSO	62

Physical data of synthesized compounds

Table-4

Compound	Melting point (◦C)	Rf Value
K1	173	0.45
K2	175	0.47
K3	172	0.48
K4	179	0.43
K5	171	0.39
K6	123	0.62
K7	127	0.65
K8	129	0.68
K9	126	0.7
K10	120	0.61

Elemental composition of compounds

Table-5

Compound	Elemental Composition in Percentage (%)				
	C	H	Cl	N	O
K1	84.53	6.08	10.65	8.42	-
K2	74.78	6.23	-	7.21	12.36
K3	80.90	6.79	-	12.31	-
K4	80.46	6.14	-	8.53	4.87
K5	84.53	6.08	-	9.39	-
K6	67.49	4.60	12.45	9.84	5.62
K7	67.05	5.92	-	8.23	18.80
K8	73.69	6.53	-	14.32	5.45
K9	72.84	5.75	-	9.99	11.42
K10	76.78	5.64	-	11.19	6.39

5.2 LIPINSKI PROPERTIES OF SYNTHESIZED COMPOUNDS

Table-6

Compound	Molecular Weight	LogP	H-bond donor	H-bond acceptor	Molar refractivity	Number criteria met
K1	332.82	6.174	0	2	100.85	4
K2	388.45	5.183	0	5	115.50	4
K3	341.44	6.183	0	3	110.17	4
K4	328.40	5.88	0	3	102.40	4
K5	298.38	4.83	0	4	98.52	ALL
K6	284.74	3.728	2	3	81.13	ALL
K7	340.37	2.737	2	6	95.7	ALL
K8	293.36	3.737	2	4	91.23	ALL
K9	280.32	3.44	2	4	83.46	ALL
K10	250.29	3.106	2	3	76.91	ALL

5.3 SPECTRAL ANALYSIS

IR Data of Synthesized compounds

Table-7

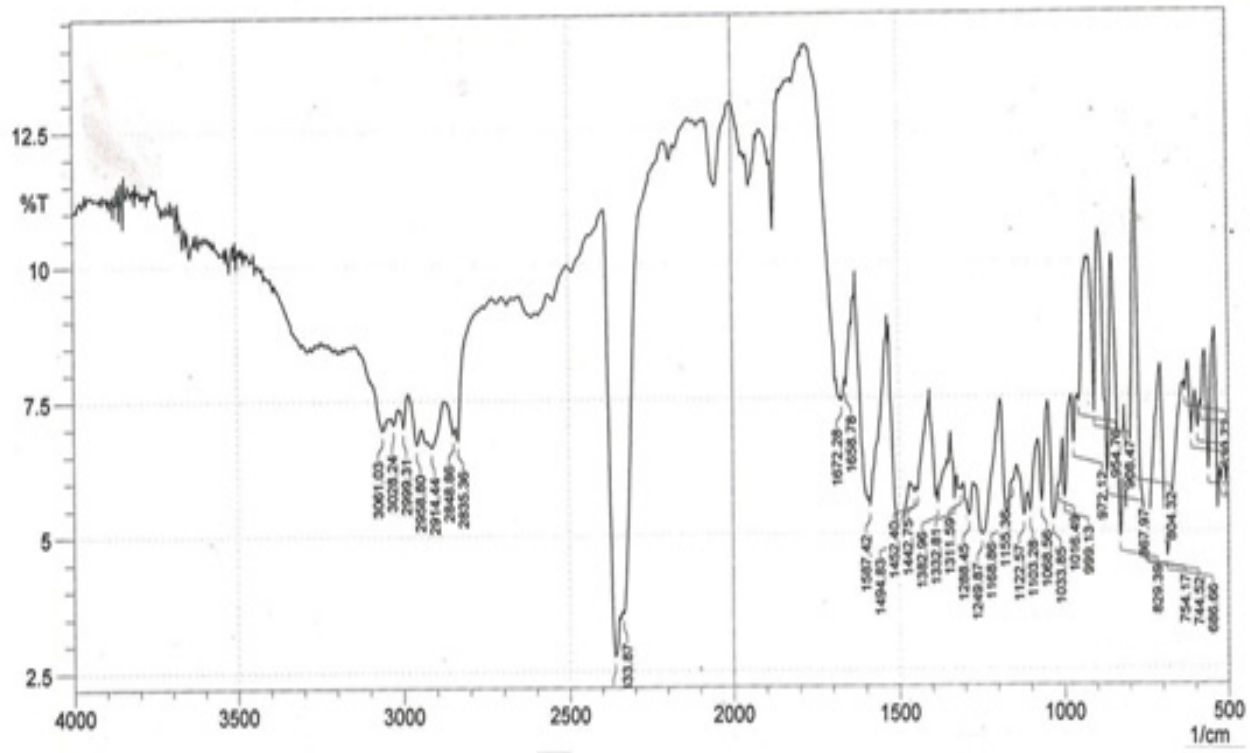
Compound K1-K5

COMPOUNDS	VIBRATION MODE	OBSERVED FREQUENCY
K1	C=C Streching	1494.83
	C=N Streching	1587.42
	C-N Streching	1033.85
	Ar - Cl Streching	754.17
	Ar-C-H Streching	3061.03
K2	C=C Streching	1579
	C=N Streching	1548
	C-N Streching	1182
	C-O-C Streching	1070
	Ar-C-H Streching	3049
K3	C=C Streching	1548
	C=N Streching	1579
	C-N Streching	1112
	Ar-N-CH3 Streching	1357
	Ar-C-H Streching	3049
K4	C=C Streching	1492
	C=N Streching	1500
	C-N Streching	1172
	Ar-OH Streching	1388
	Ar-C-H Streching	3059
K5	C=C Streching	1492
	C=N Streching	1589
	C-N Streching	1168
	Ar-C-H Streching	3059

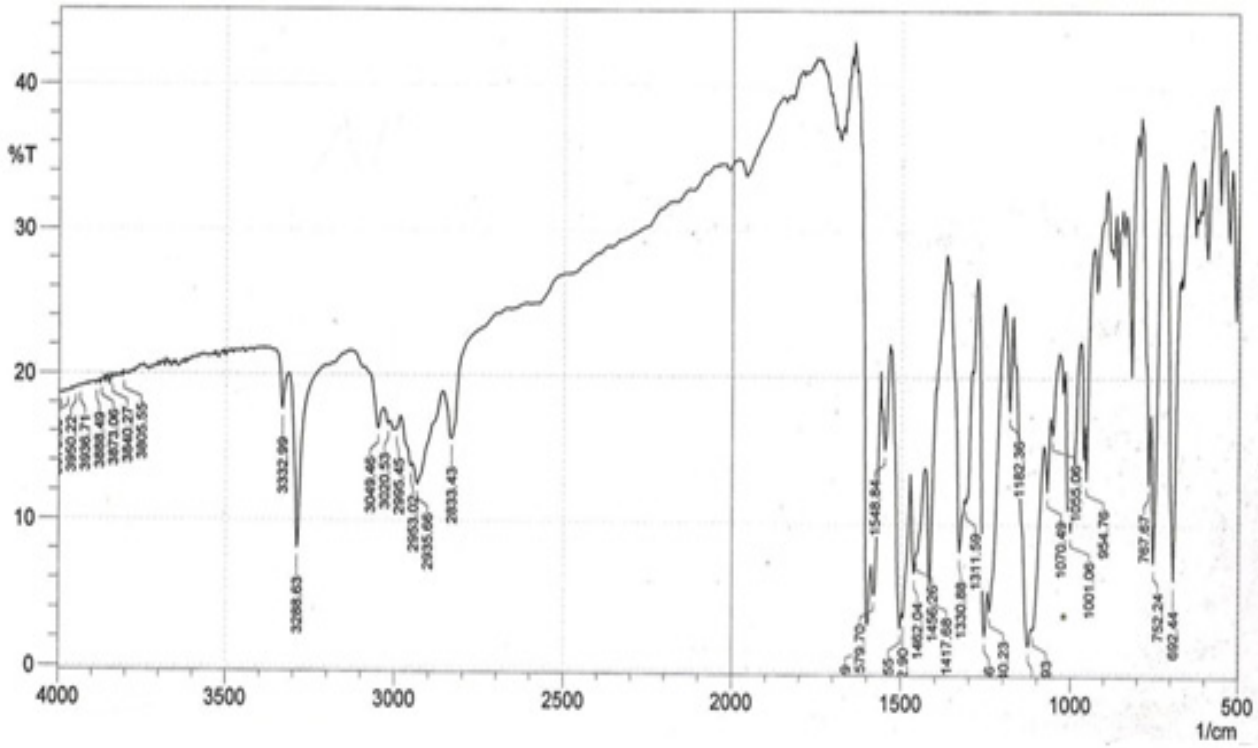
Compound K6-K10

COMPOUNDS	VIBRATION MODE	FREQUENCY Cm^{-1}
K6	C=C Streching	1480
	C-N Streching	1219.01
	Ar-C-H Streching	3059
	Ar-Cl Streching	688.59
	C=O Streching	1591
K7	C=C Streching	1581.63
	C-N Streching	1178.51
	Ar-C-H Streching	2995.45
	C-O-C Streching	1033.85
	C=O Streching	1591.63
K8	C=C Streching	1581.63
	C-N Streching	1020.34
	Ar-C-H Streching	3091
	N-CH3 Streching	1346.31
	C=O Streching	1581.63
K9	C=C Strecching	1573.91
	C-N Sterching	1213.23
	Ar-C-H Streching	3039.85
	Ar-OH Streching	1301.95
	C=O Streching	1600.92
K10	C=C Streching	1579.7
	C-N Streching	1219.01
	Ar-C-H Streching	3061.03
	C=O Streching	1598.99

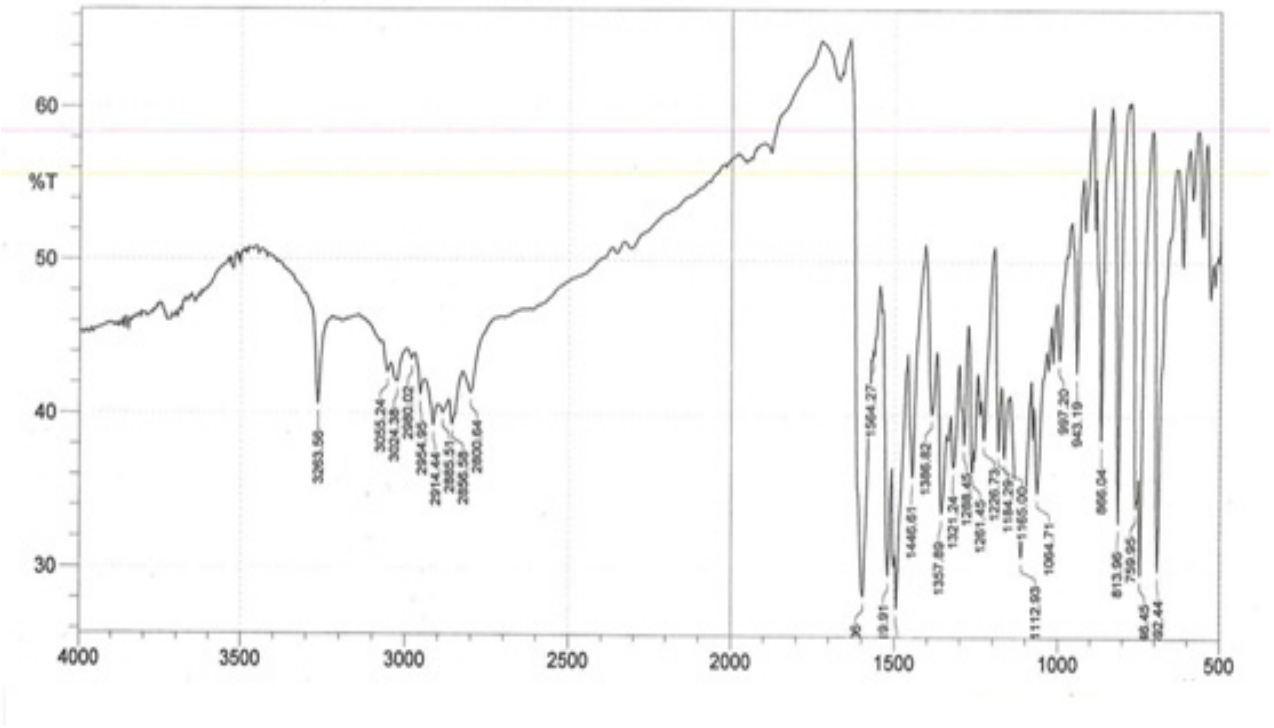
COMPOUND K1



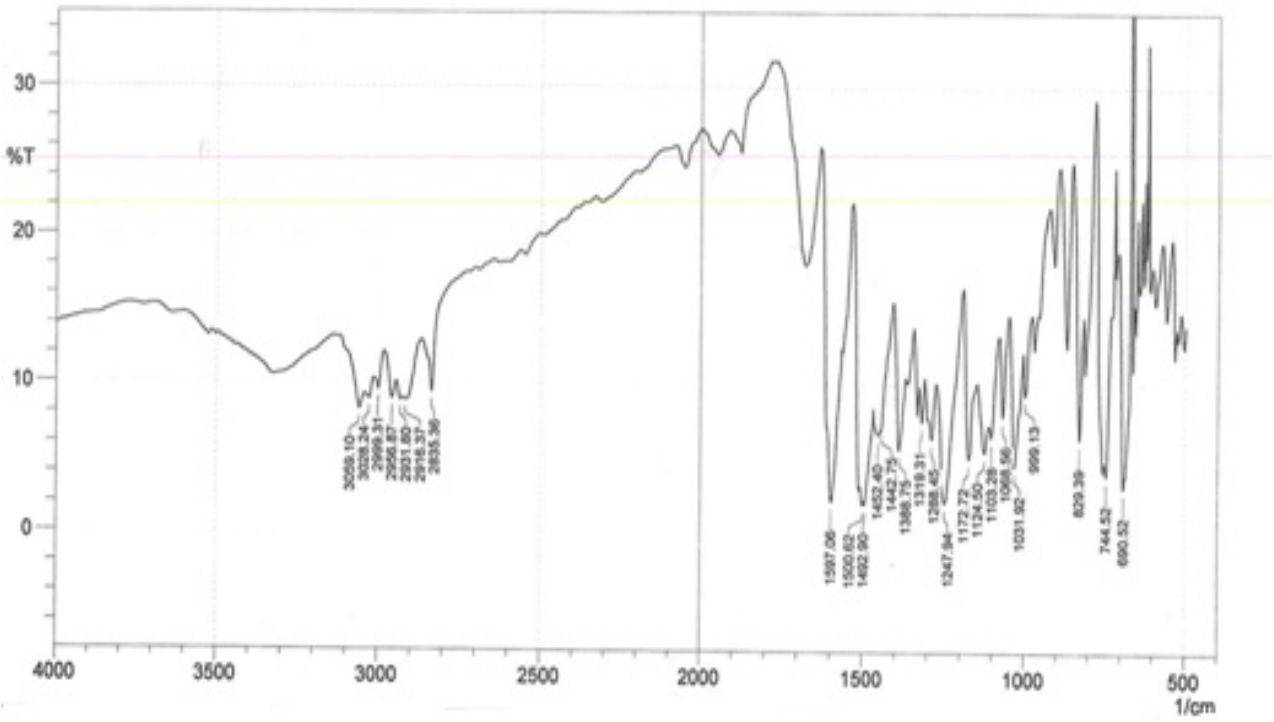
COMPOUND K2



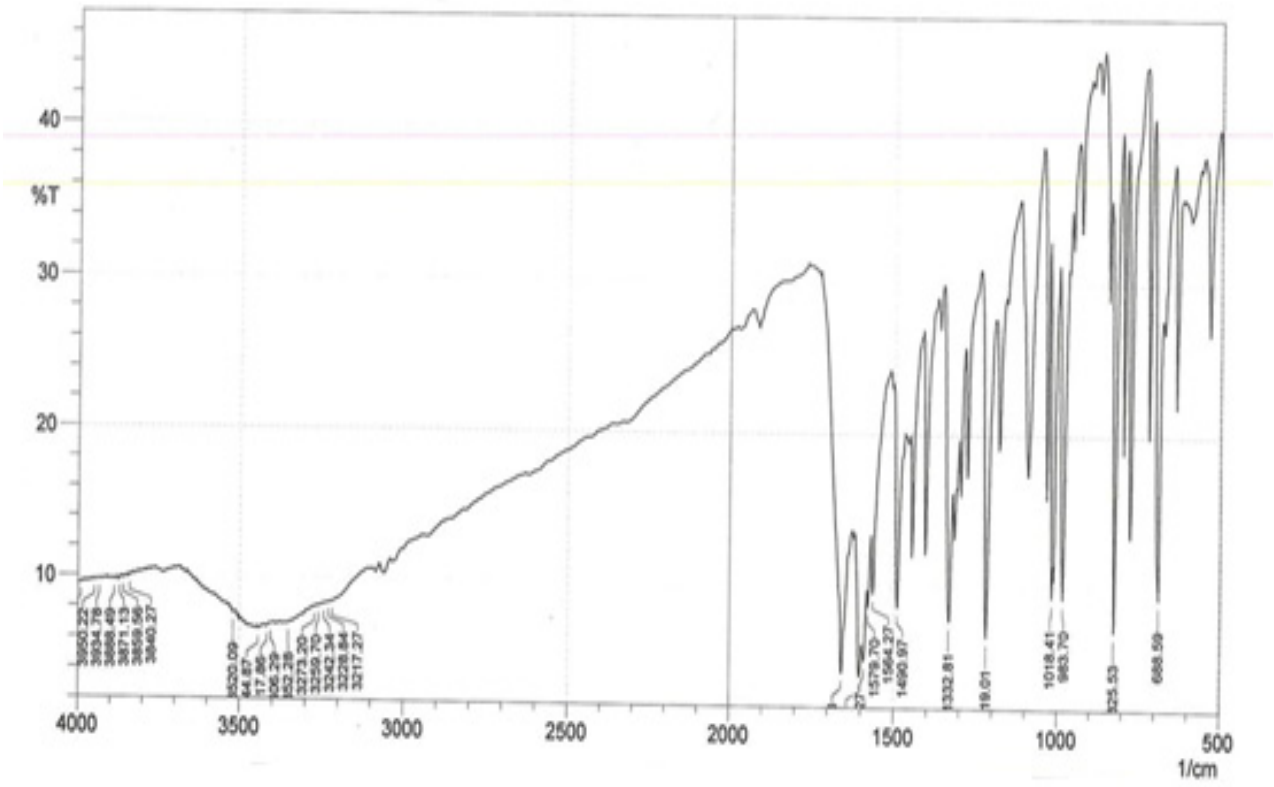
COMPOUND K3



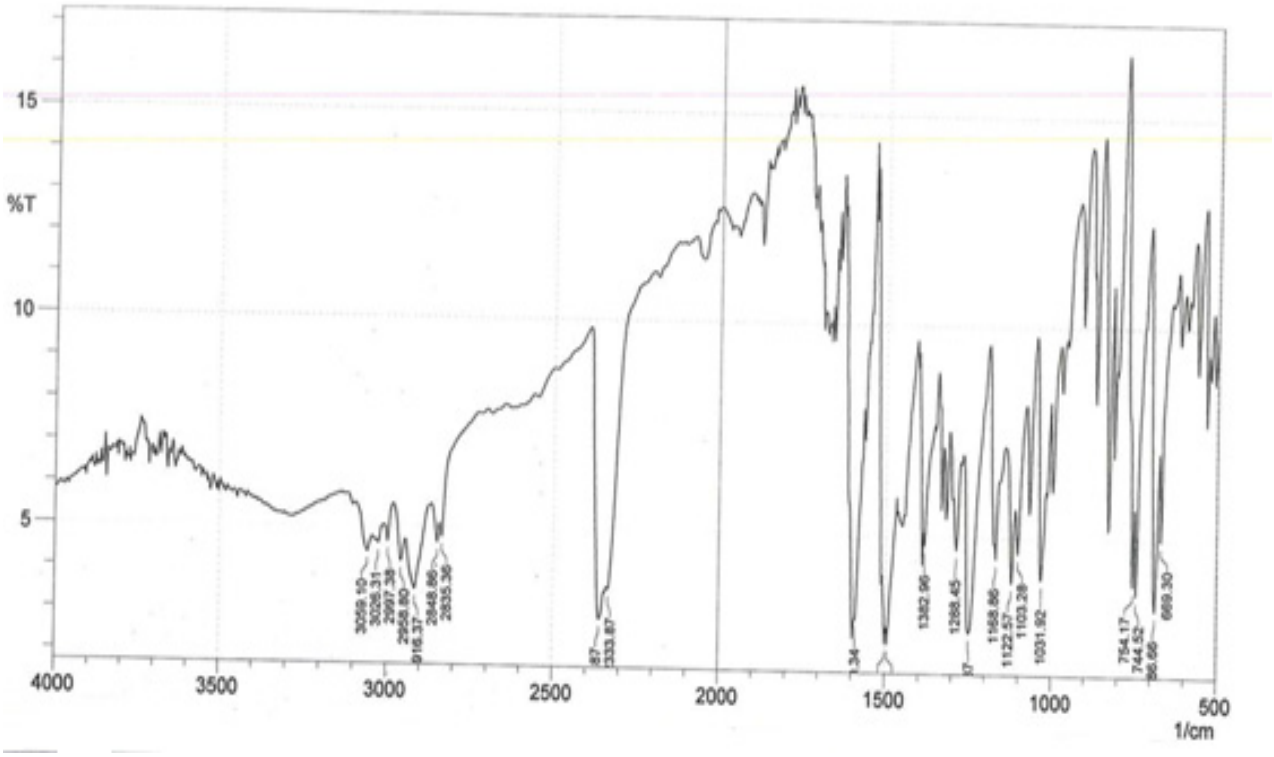
COMPOUND K4



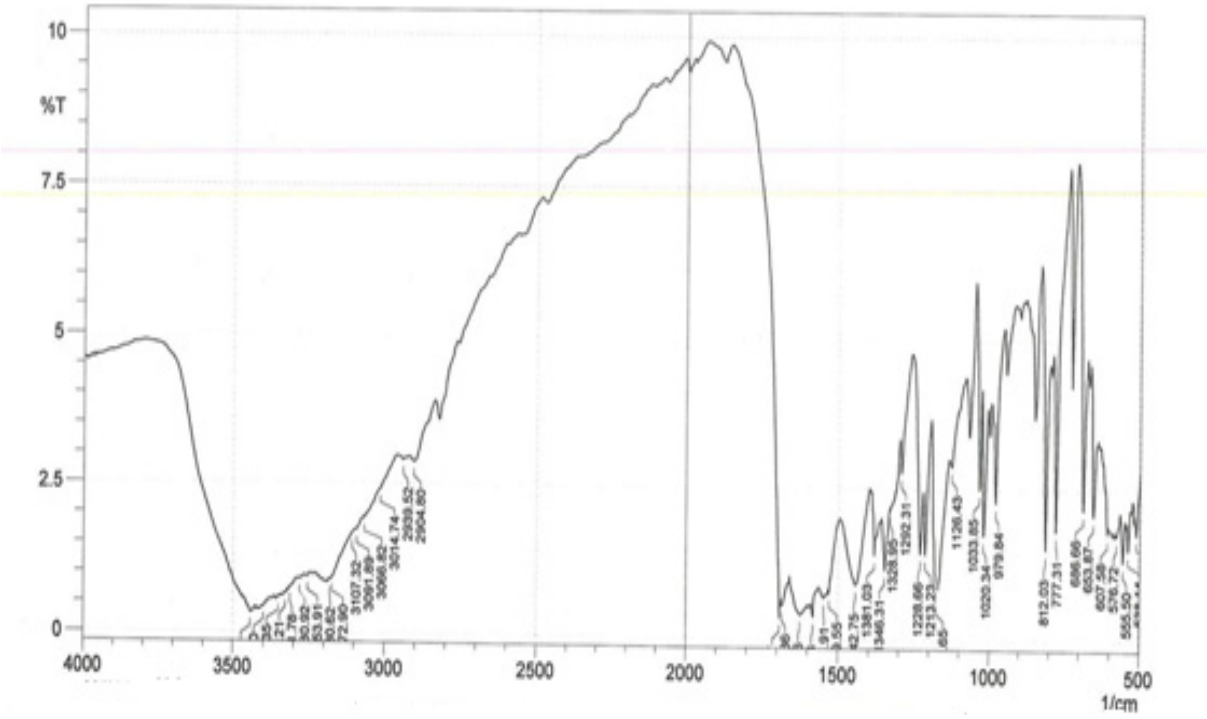
COMPOUND K5



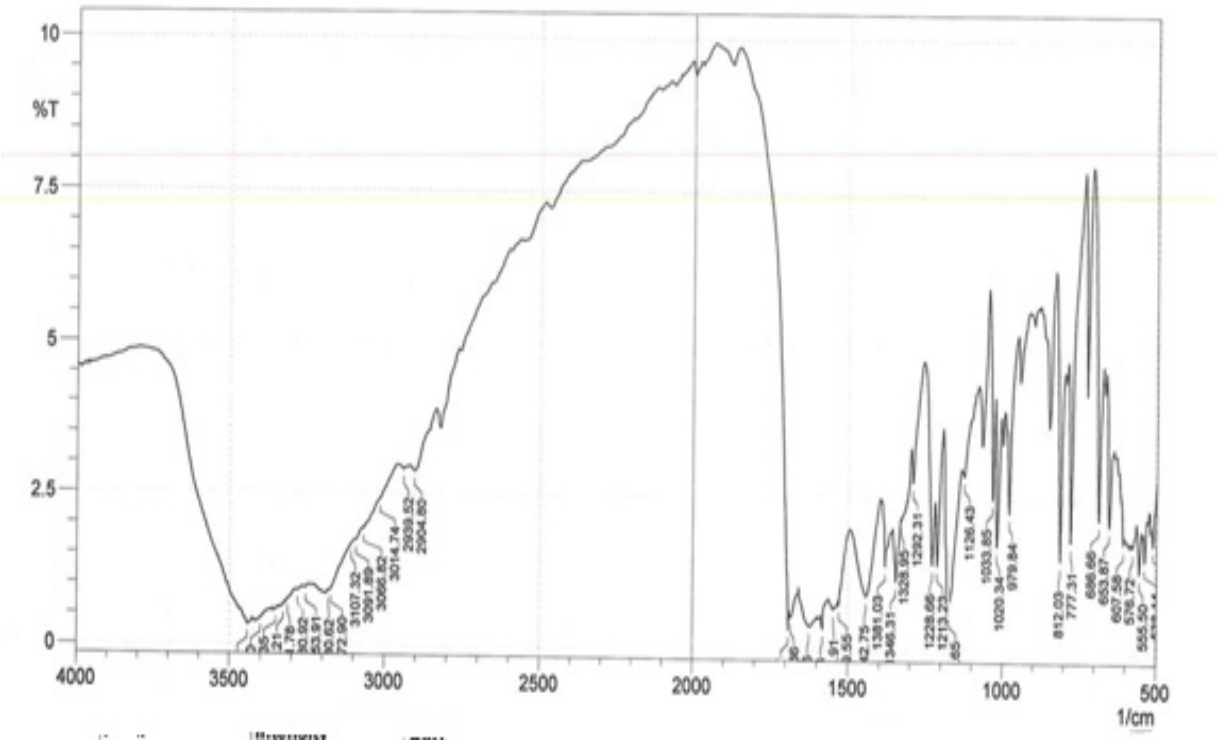
COMPOUND K6



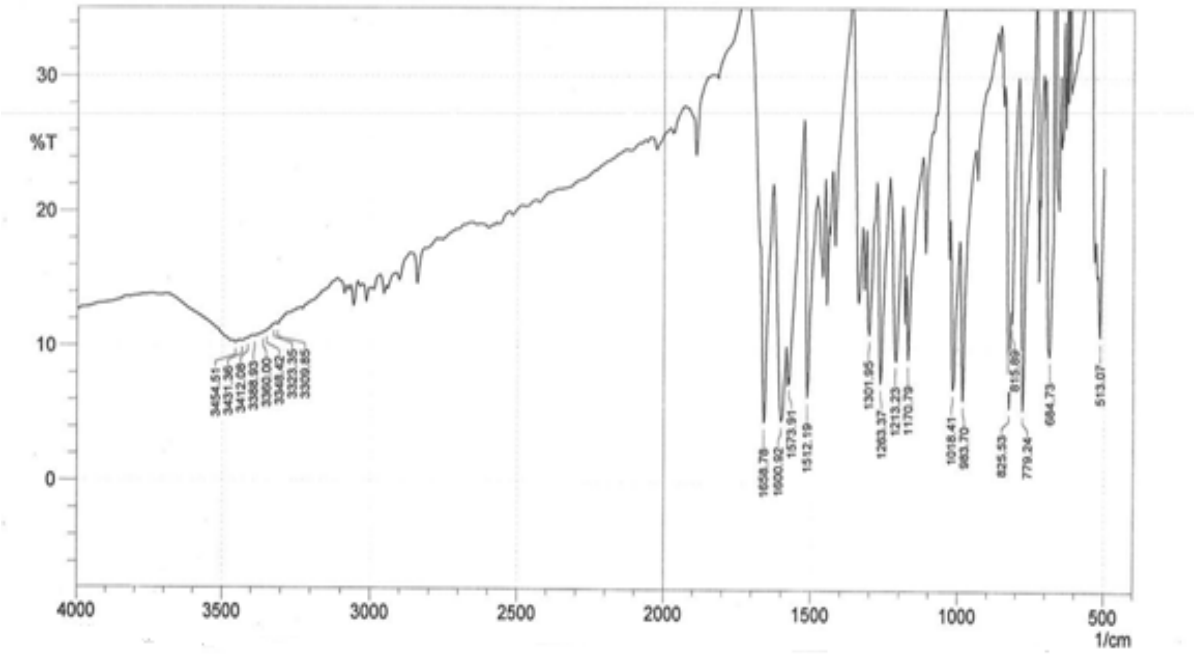
COMPOUND K7



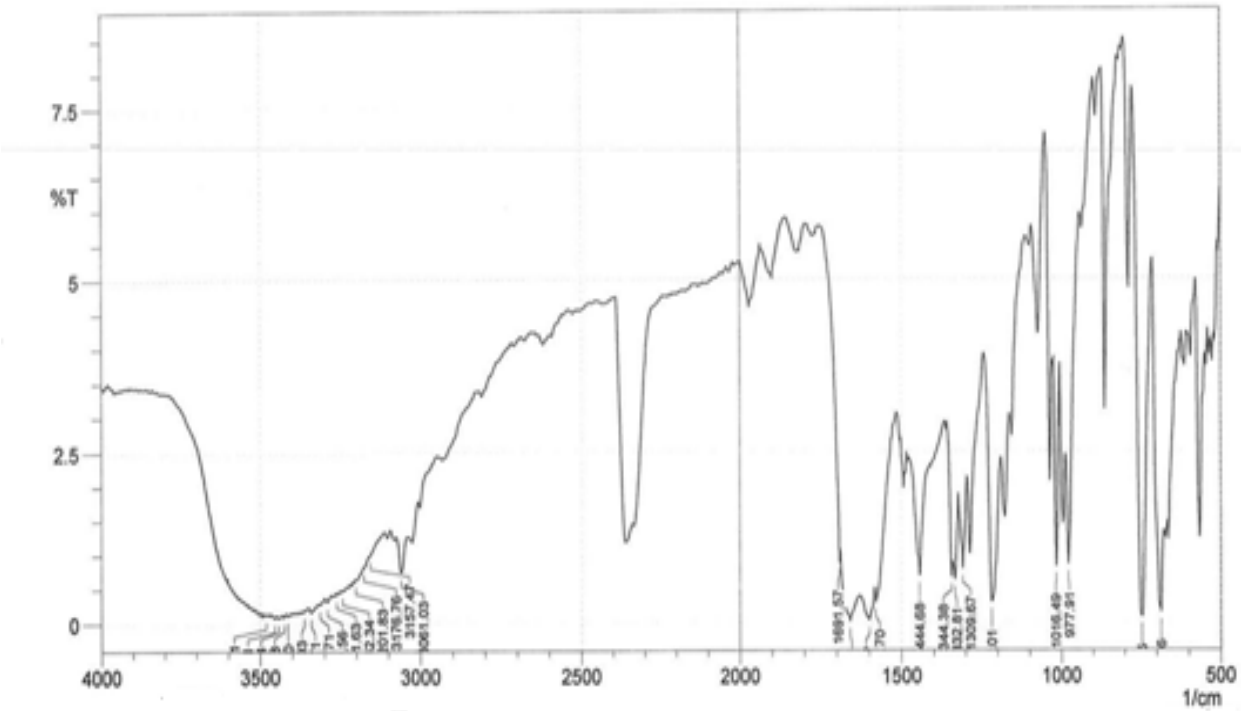
COMPOUND K8



COMPOUND K9



COMPOUND K10



1HNMR Spectral data

Table-8

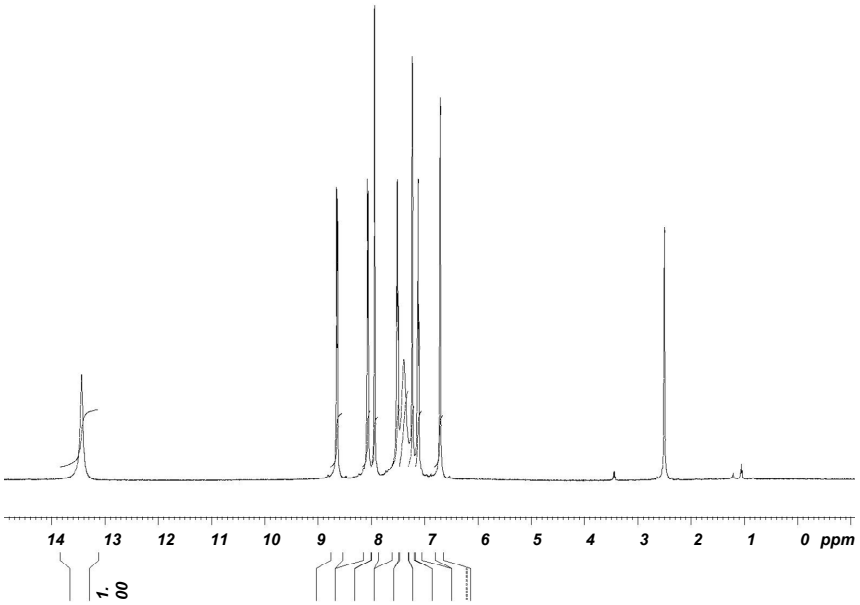
Compounds A1-A5

Compound	Chemical Shift Value	Proton nature
K1	7.2 6.8 2.6	m, 10H, Ar-H, s, 4H, Ar-H s, 1H, CH
K2	7.8 6.9 2.6 3.5	S,10H, Ar-H S, 4H, Ar-H S, 1H, CH d, 9H, OCH3
K3	7.8 6.9 6.7 2.3	10H, Ar-H 4H, Ar-H 3H, N-CH3 s, 1H, CH
K4	7.8 6.2 3.5 2.4	s, 10H, Ar-H s, 4H, Ar-H s, 3H, OCH3 d, 1H, CH
K5	7.8 7.5 2.3	s, 10H, Ar-H s, 4H, Ar-H s, 1H, CH

Compounds K6-K7

Compounds	Chemical Shift value	Proton nature
K6	7.3 6.9 2.7	s, 5H, Ar-H s, 4H, Ar-H s, 2H, 2NH
K7	7.3 6.8 2.5 3.5	s, 5H, Ar-H s, 4H, Ar-H s, 2H, 2NH s, 9H, OCH3
K8	7.8 7.3 2.5 3.5	d, 5H, Ar-H s, 4H, Ar-H s, 2H, 2NH s, 3H, N-CH3
K9	7.5 7.2 2.5 3.5	s, 5H, Ar-H s, 4H, Ar-H s, 2H, 2NH s, 3H, OCH3
K10	7.8 7.3 2.7	s, 5H, Ar-H s, 4H, Ar-H s, 2H, 2NH

COMPOUND K1



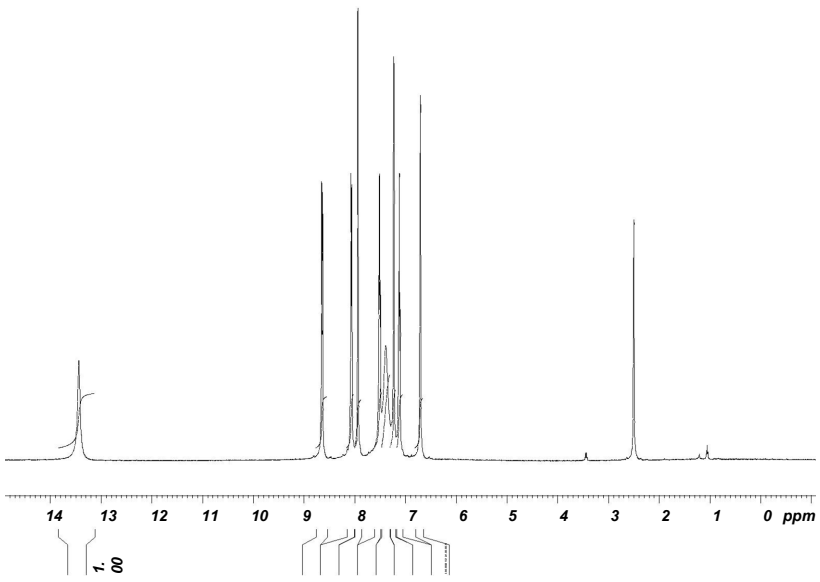
Current Data Parameters
NAME Feb08−2014
EXPNO 11
PROCNO 1

F2 − Acquisition Parameters
Date_ 20140208
Time 22.10
INSTRUM spect
PROBHD 5 mm PABBO BB−
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 32
DS 2
SWH 10330.578 Hz
FIDRES 0.315264 Hz
AQ 1.5860212 sec
RG 203
DW 48.400 usec
DE 6.50 usec
TE 300.1 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 10.65 usec
PL1 0.00 dB
PL1W 23.53637505 W
SFO1 500.1330885 MHz

F2 − Processing parameters
SI 32768
SF 500.1300035 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

COMPOUND K2



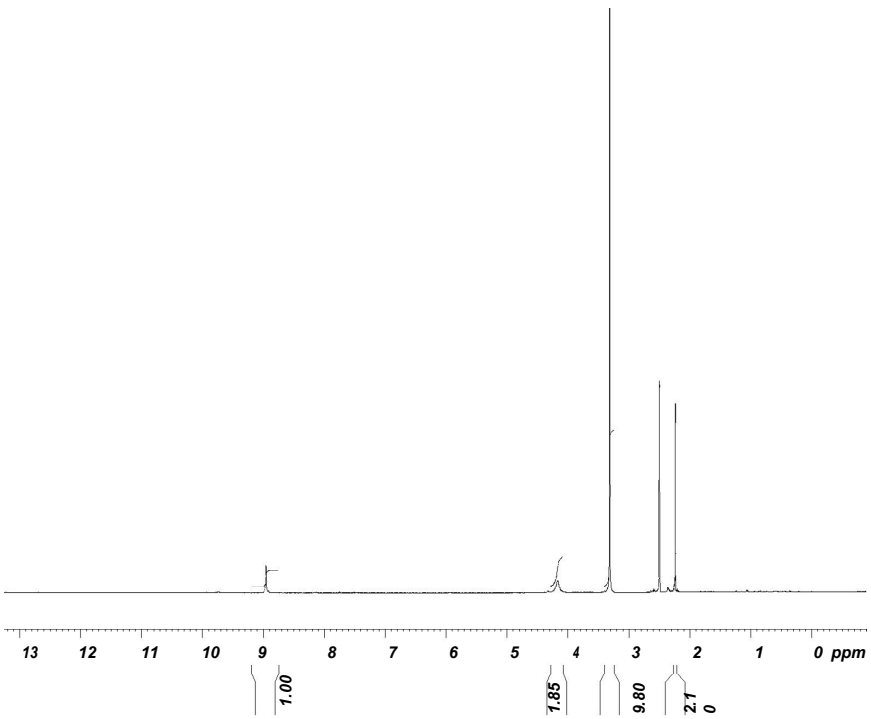
Current Data Parameters
NAME Feb08−2014
EXPNO 11
PROCNO 1

F2 − Acquisition Parameters
Date_ 20140208
Time 22.10
INSTRUM spect
PROBHD 5 mm PABBO BB−
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 32
DS 2
SWH 10330.578 Hz
FIDRES 0.315264 Hz
AQ 1.5860212 sec
RG 203
DW 48.400 usec
DE 6.50 usec
TE 300.1 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 10.65 usec
PL1 0.00 dB
PL1W 23.53637505 W
SFO1 500.1330885 MHz

F2 − Processing parameters
SI 32768
SF 500.1300035 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

COMPOUND K3



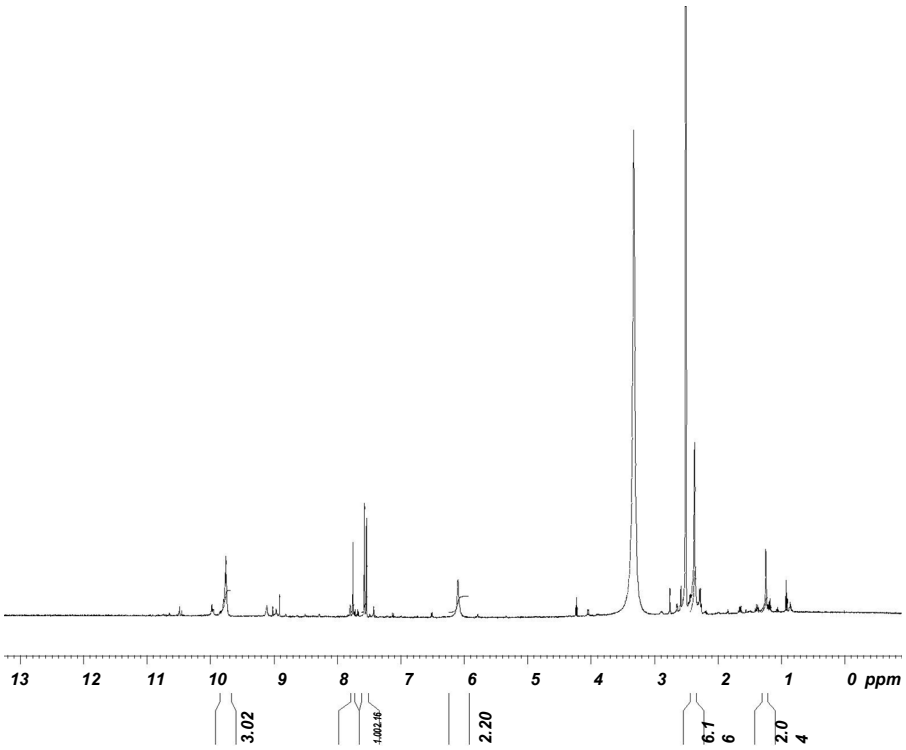
Current Data Parameters
NAME Feb08−2014
EXPNO 24
PROCNO 1

F2 − Acquisition Parameters
Date_ 20140208
Time 4.40
INSTRUM spect
PROBHD 5 mm PABBO BB−
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 32
DS 2
SWH 10330.578 Hz
FIDRES 0.315264 Hz
AQ 1.5860212 sec
RG 203
DW 48.400 usec
DE 6.50 usec
TE 299.3 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 10.65 usec
PL1 0.00 dB
PL1W 23.53637505 W
SFO1 500.1330885 MHz

F2 − Processing parameters
SI 32768
SF 500.1300043 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

COMPOUND K4



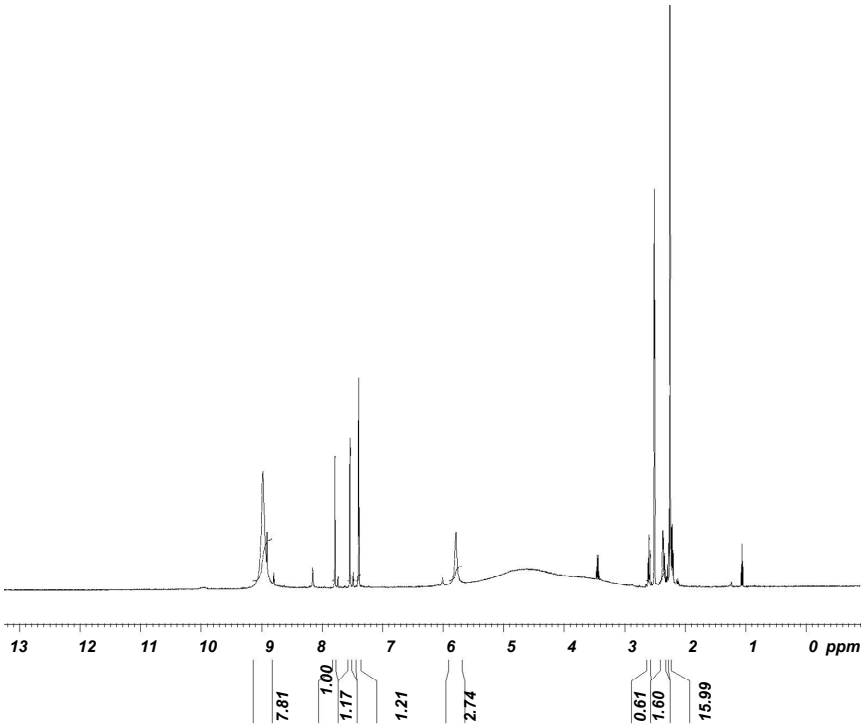
Current Data Parameters
NAME Feb08−2014
EXPNO 15
PROCNO 1

F2 − Acquisition Parameters
Date_ 20140208
Time 22.23
INSTRUM spect
PROBHD 5 mm PABBO BB−
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 32
DS 2
SWH 10330.578 Hz
FIDRES 0.315264 Hz
AQ 1.5860212 sec
RG 203
DW 48.400 usec
DE 6.50 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 10.65 usec
PL1 0.00 dB
PL1W 23.53637505 W
SFO1 500.1330885 MHz

F2 − Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

COMPOUND K5



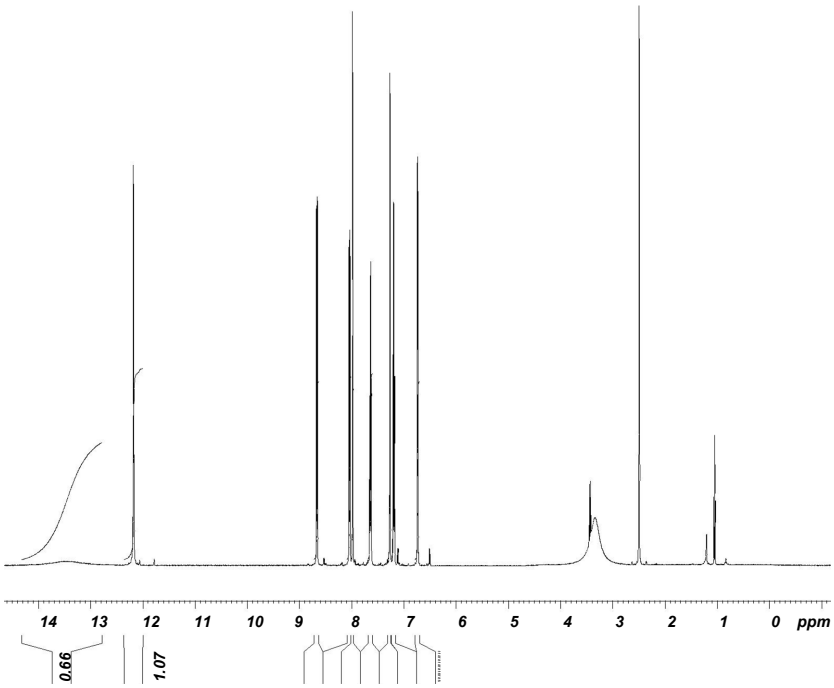
Current Data Parameters
NAME Feb08−2014
EXPNO 22
PROCNO 1

F2 − Acquisition Parameters
Date_ 20140208
Time 4.33
INSTRUM spect
PROBHD 5 mm PABBO BB−
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 32
DS 2
SWH 10330.578 Hz
FIDRES 0.315264 Hz
AQ 1.5860212 sec
RG 203
DW 48.400 usec
DE 6.50 usec
TE 299.3 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 10.65 usec
PL1 0.00 dB
PL1W 23.53637505 W
SFO1 500.1330885 MHz

F2 − Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

COMPOUND K6



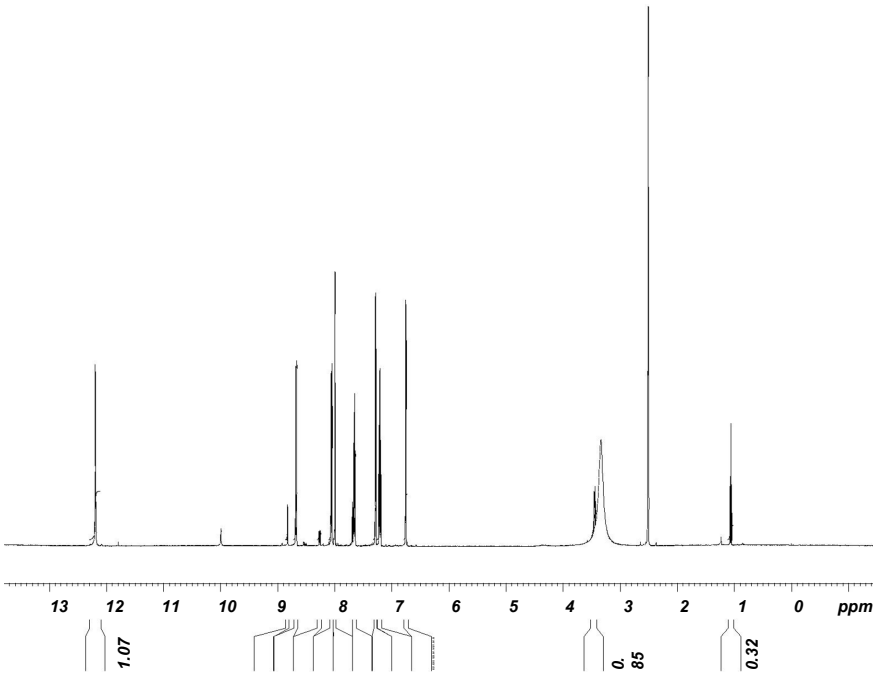
Current Data Parameters
NAME Feb09−2014
EXPNO 8
PROCNO 1

F2 − Acquisition Parameters
Date_ 20140209
Time 22.00
INSTRUM spect
PROBHD 5 mm PABBO BB−
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 32
DS 2
SWH 10330.578 Hz
FIDRES 0.315264 Hz
AQ 1.5860212 sec
RG 203
DW 48.400 usec
DE 6.50 usec
TE 300.1 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 10.65 usec
PL1 0.00 dB
PL1W 23.53637505 W
SFO1 500.1330885 MHz

F2 − Processing parameters
SI 32768
SF 500.1300041 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

COMPOUND K7



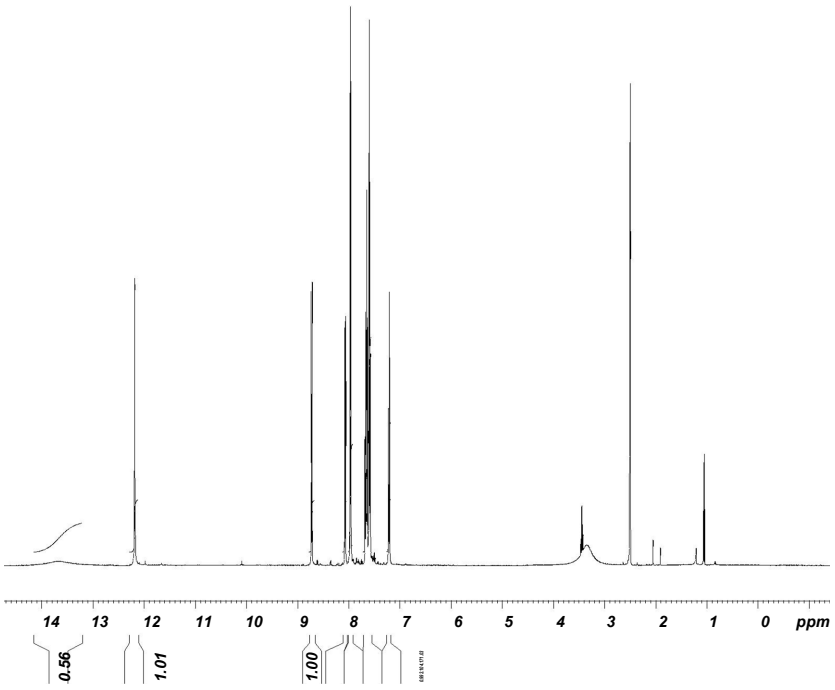
Current Data Parameters
NAME Feb09−2014
EXPNO 6
PROCNO 1

F2 − Acquisition Parameters
Date_ 20140209
Time 21.53
INSTRUM spect
PROBHD 5 mm PABBO BB−
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 32
DS 2
SWH 10330.578 Hz
FIDRES 0.315264 Hz
AQ 1.5860212 sec
RG 203
DW 48.400 usec
DE 6.50 usec
TE 300.1 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 10.65 usec
PL1 0.00 dB
PL1W 23.53637505 W
SFO1 500.1330885 MHz

F2 − Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

COMPOUND K8



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NAME Feb09−2014
EXPNO 10
PROCNO 1

F2 − Acquisition Parameters
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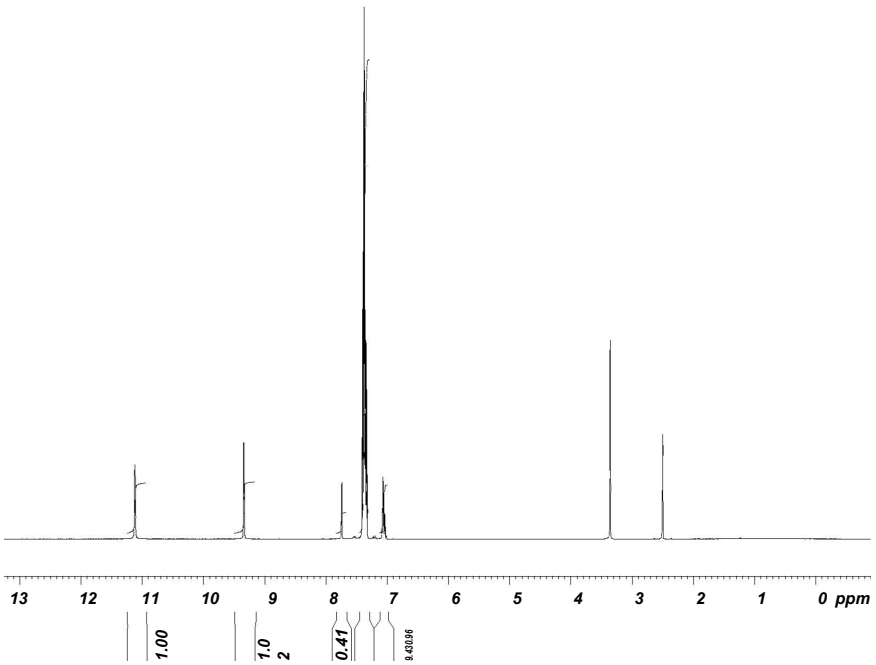
Time 22.06
INSTRUM spect
PROBHD 5 mm PABBO BB−
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 32
DS 2
SWH 10330.578 Hz
FIDRES 0.315264 Hz
AQ 1.5860212 sec
RG 203
DW 48.400 usec
DE 6.50 usec
TE 300.1 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 10.65 usec
PL1 0.00 dB
PL1W 23.53637505 W
SFO1 500.1330885 MHz

F2 − Processing parameters
SI 32768
SF 500.1300042 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

COMPOUND K9



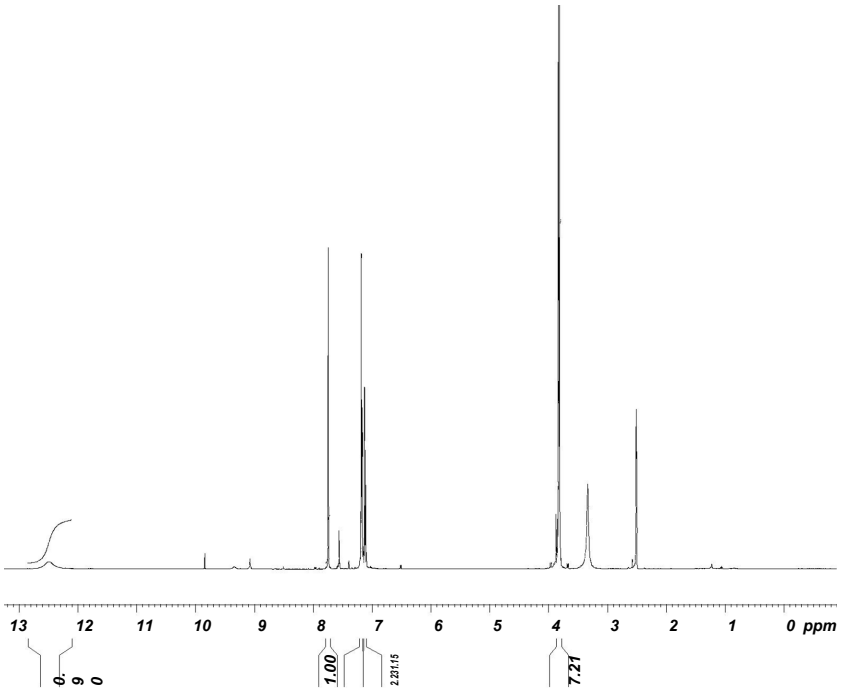
Current Data Parameters
NAME Feb09−2014
EXPNO 14
PROCNO 1

F2 − Acquisition Parameters
Date_ 20140209
Time 22.20
INSTRUM spect
PROBHD 5 mm PABBO BB−
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 32
DS 2
SWH 10330.578 Hz
FIDRES 0.315264 Hz
AQ 1.5860212 sec
RG 203
DW 48.400 usec
DE 6.50 usec
TE 300.1 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 10.65 usec
PL1 0.00 dB
PL1W 23.53637505 W
SFO1 500.1330885 MHz

F2 − Processing parameters
SI 32768
SF 500.1300043 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

COMPOUND K10



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NAME Feb09−2013
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PROCNO 1

F2 − Acquisition Parameters
Date_ 20140209
Time 4.30
INSTRUM spect
PROBHD 5 mm PABBO BB−
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 32
DS 2
SWH 10330.578 Hz
FIDRES 0.315264 Hz
AQ 1.5860212 sec
RG 203
DW 48.400 usec
DE 6.50 usec
TE 299.5 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 10.65 usec
PL1 0.00 dB
PL1W 23.53637505 W
SFO1 500.1330885 MHz

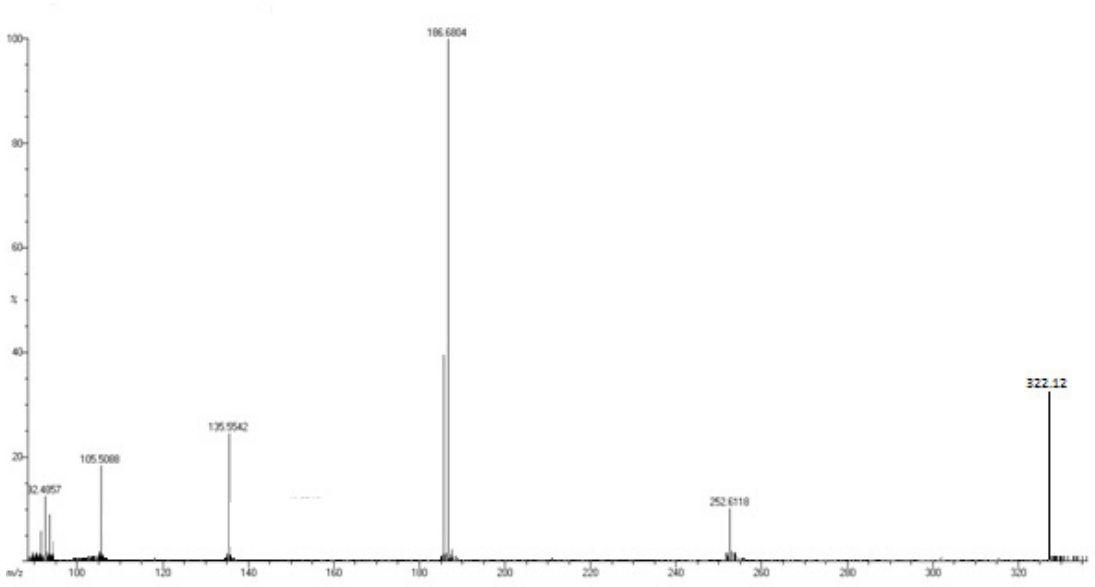
F2 − Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

MASS Spectra of synthesized compounds

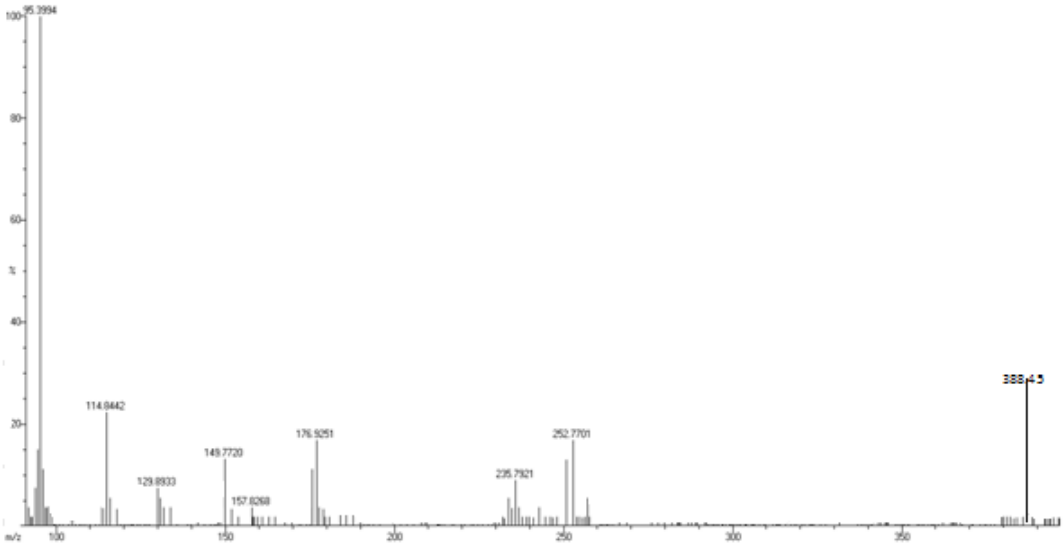
Table-9:

COMPOUND	MOLECULAR ION PEAK
K1	332.82
K2	388.45
K3	341.44
K4	328.40
K5	298.38
K6	284.74
K7	340.37
K8	293.36
K9	280.32
K10	250.29

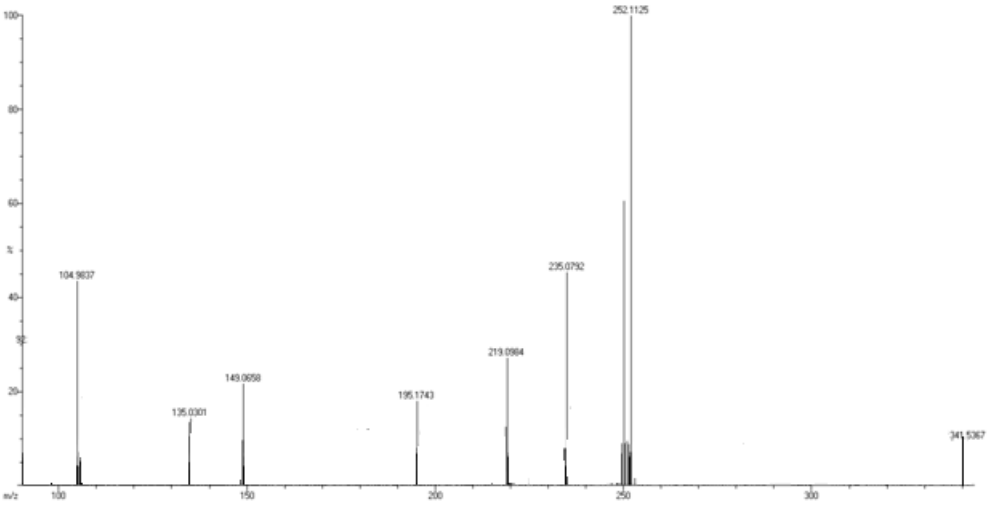
COMPOUND K1



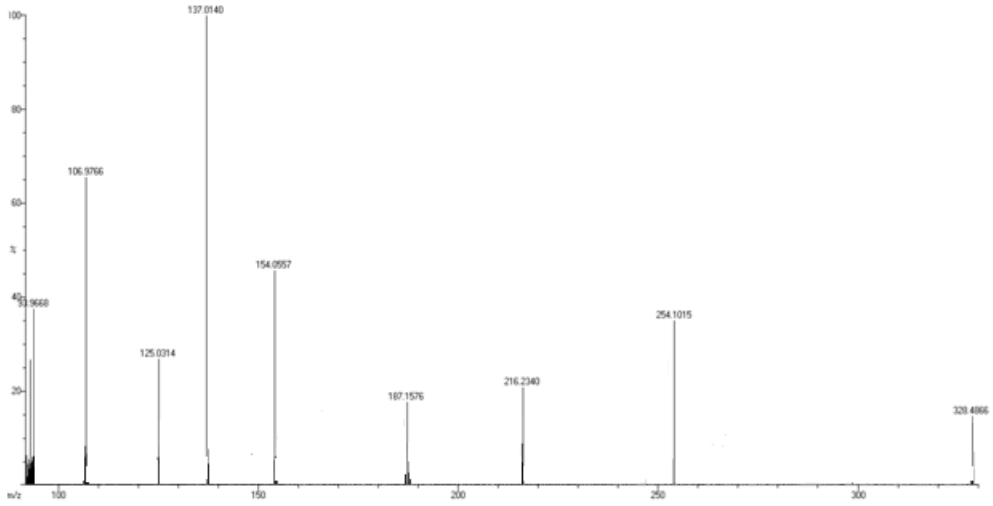
COMPOUND K2



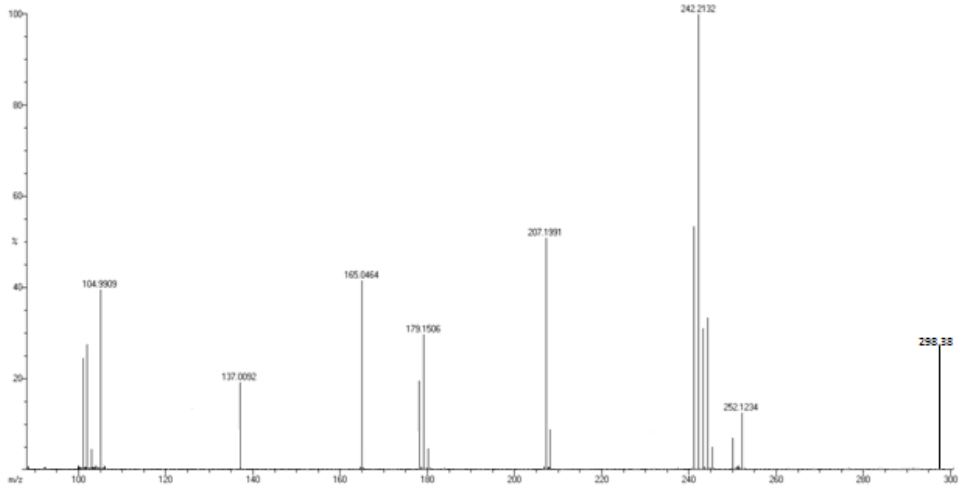
COMPOUND K3



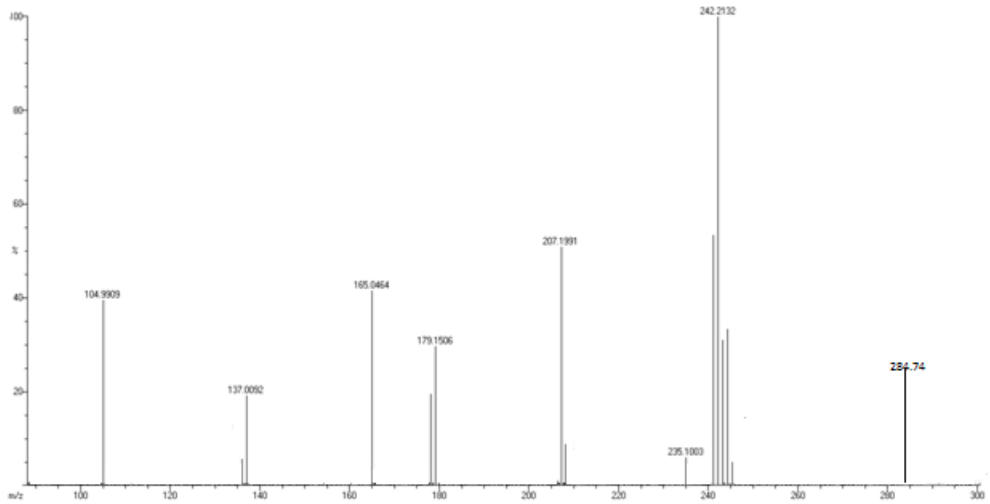
COMPOUND K4



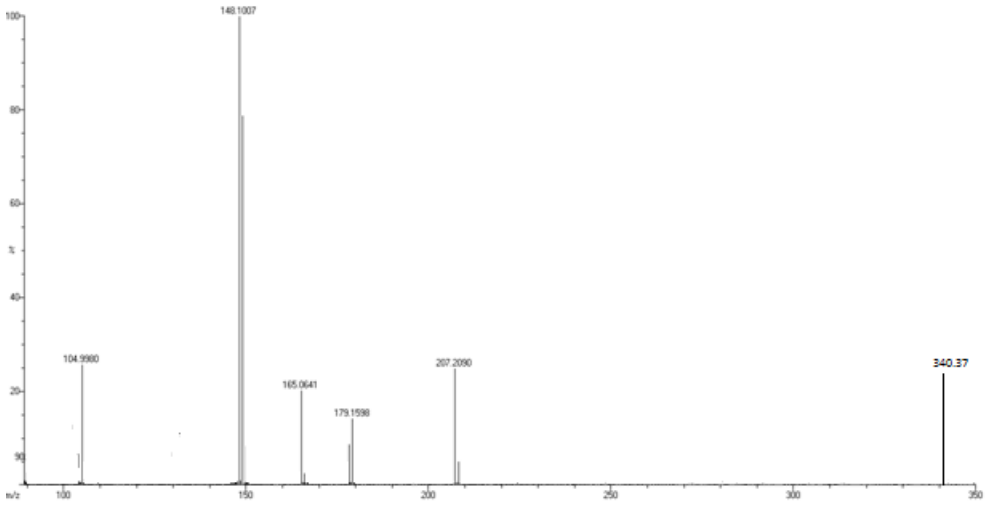
COMPOUND K5



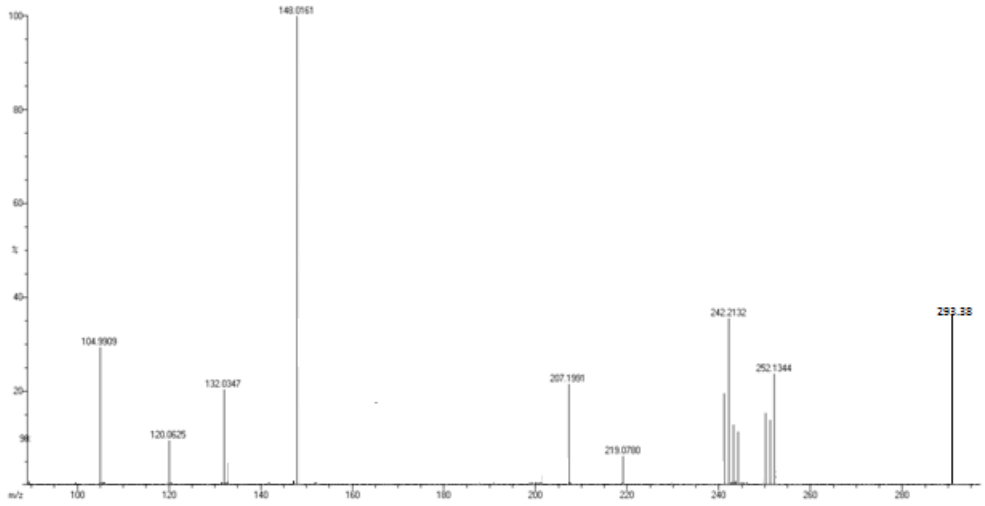
COMPOUND K6



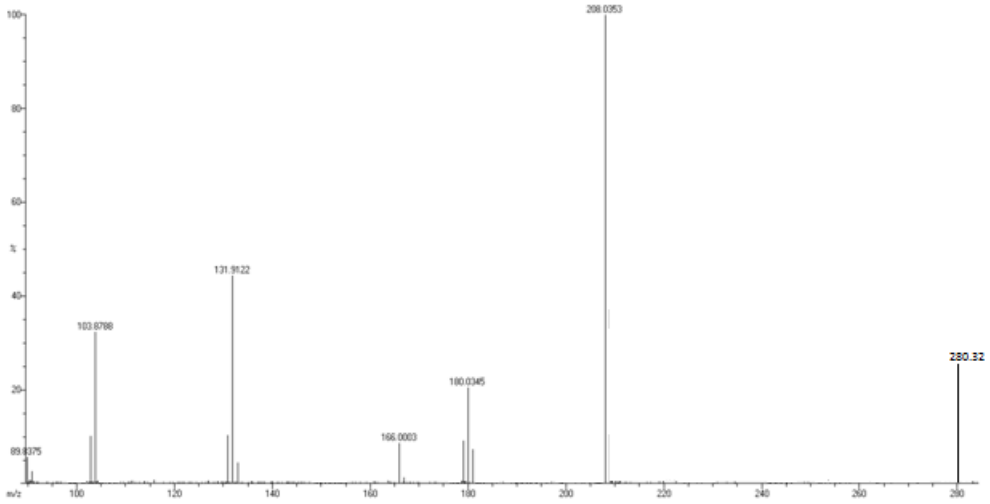
COMPOUND K7



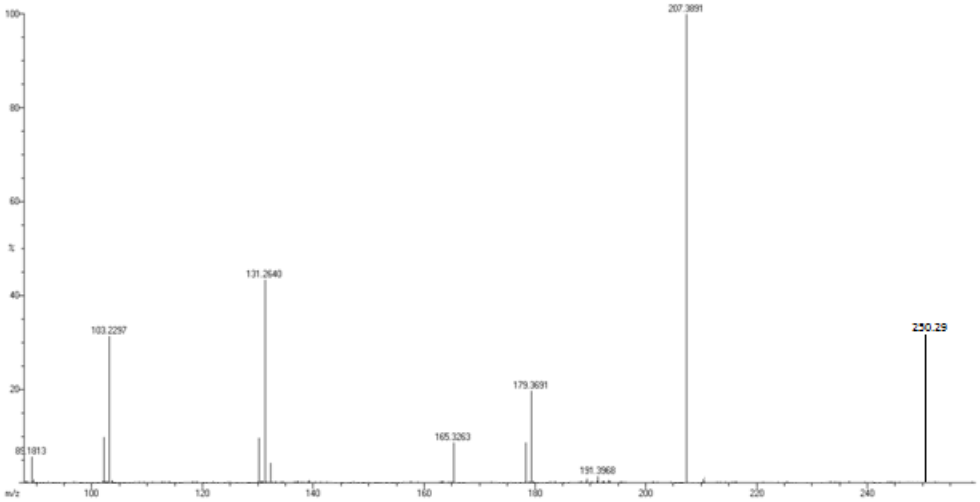
COMPOUND K8



COMPOUND K9



COMPOUND K10

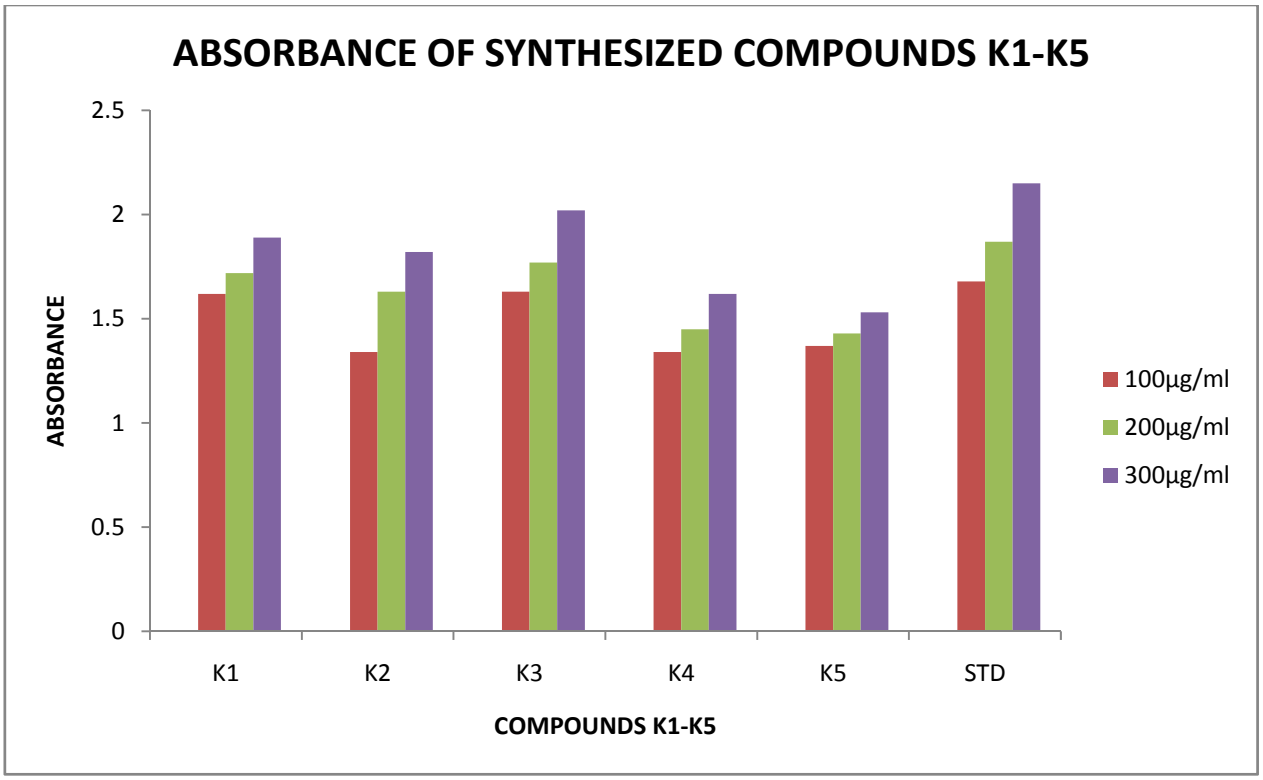


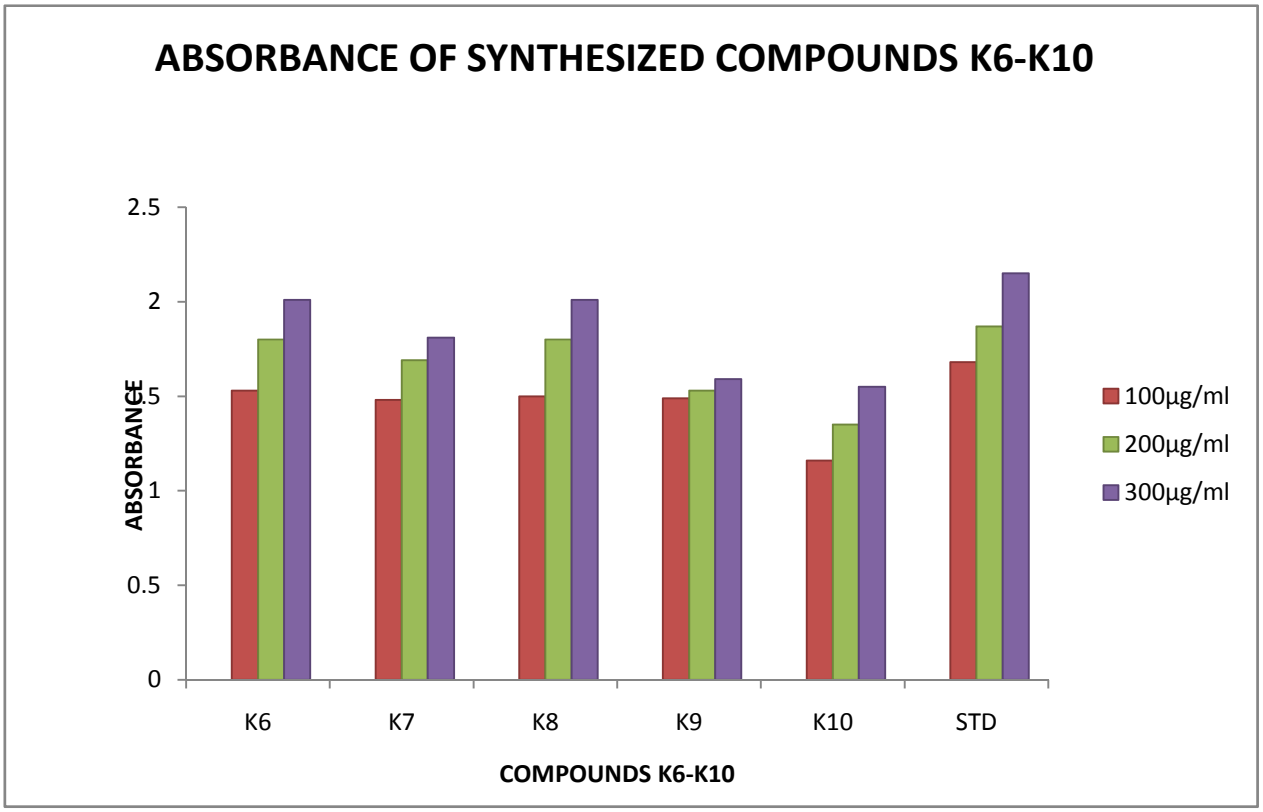
5.4 Results of Biological activity

A) In-vitro Anti-oxidant activity

Table-10: Absorbance of synthesized compounds compared with standard anti-oxidant activity.

Compounds	Absorbance of different concentration		
	100µg/ml	**200µg/ml**	**300µg/ml**
K1	1.62±0.02	1.72±0.03	1.89±0.02
K2	1.34±0.06	1.63±0.06	1.82±0.09
K3	1.63±0.07	1.77±0.04	2.02±0.07
K4	1.34±0.03	1.45±0.04	1.62±0.04
K5	1.37±0.04	1.43±0.04	1.53±0.03
K6	1.53±0.03	1.62±0.03	1.88±0.02
K7	1.48±0.04	1.69±0.02	1.81±0.01
K8	1.5±0.03	1.8±0.03	2.01±0.05
K9	1.49±0.06	1.53±0.06	1.59±0.09
K10	1.16±0.05	1.35±0.06	1.55±0.06
Standard (Ascorbic acid)	1.68±0.04	1.87±0.06	2.15±0.05

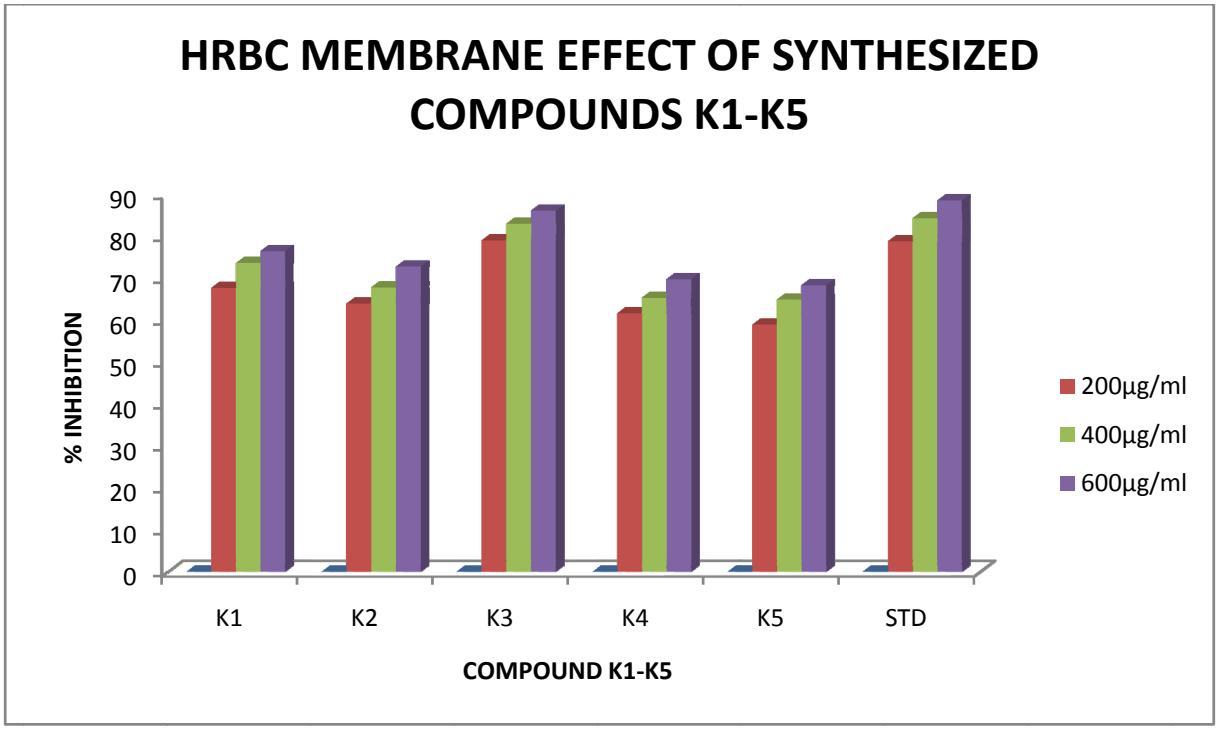

ABSORBANCE OF SYNTHESIZED COMPOUNDS K1-K5
2.5
2
1.5
1
0.5
0
ABSORBANCE
K1
K2
K3
K4
K5
STD
COMPOUNDS K1-K5
100µg/ml
200µg/ml
300µg/ml

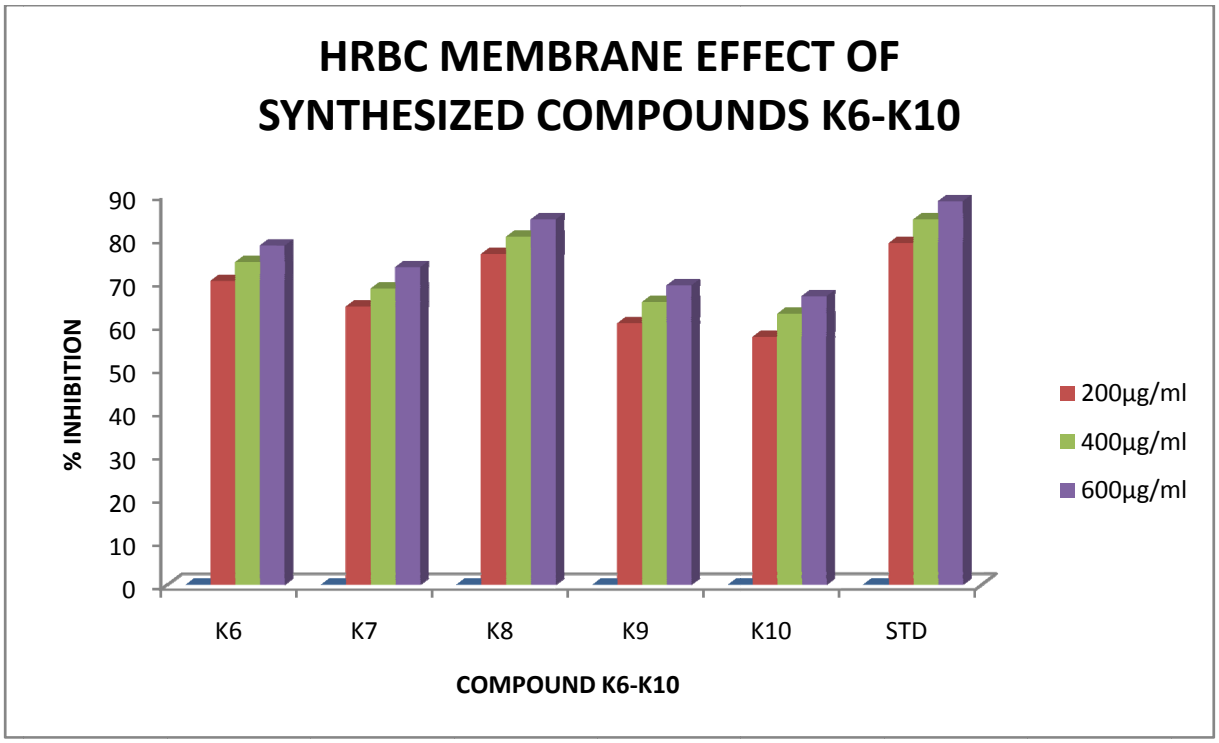

ABSORBANCE OF SYNTHESIZED COMPOUNDS K6-K10
2.5
2
1.5
1
0.5
0
ABSORBANCE
K6
K7
K8
K9
K10
STD
COMPOUNDS K6-K10
100µg/ml
200µg/ml
300µg/ml

A) MEMBRANE STABILIZATION ASSAY

Table 11: Anti-inflammatory acitivity of synthesized compounds K1-K10

COMPOUNDS	PERCENTAGE OF ACTIVITY		
	200µg/ml	400µg/ml	600µg/ml
K1	67.41±0.14	73.29±0.12	76.16±0.05
K2	63.69±0.08	67.71±0.09	72.66±0.08
K3	78.97±0.08	82.97±0.08	86.10±0.09
K4	61.44±0.05	65.13±0.07	69.54±0.06
K5	58.77±0.06	64.72±0.04	68.17±0.08
K6	70.09±0.08	74.41±0.09	78.20±0.09
K7	64.10±0.09	68.22±0.06	73.19±0.07
K8	76.25±0.02	80.19±0.06	84.22±0.08
K9	60.34±0.09	65.23±0.05	69.11±0.1
K10	56.96±0.08	62.27±0.09	66.37±0.08
STD (Diclofenac)	78.74±0.06	84.21±0.05	88.43±0.07

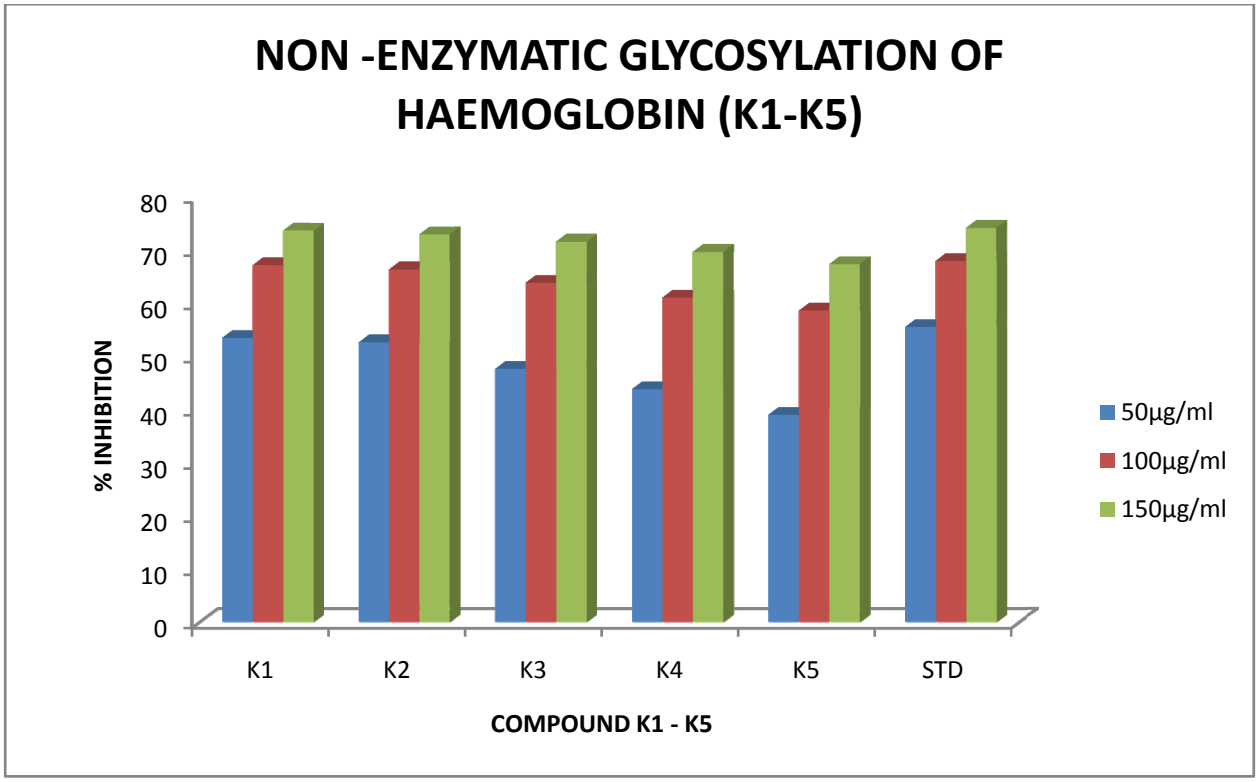

HRBC MEMBRANE EFFECT OF SYNTHESIZED COMPOUNDS K1-K5
% INHIBITION
90
80
70
60
50
40
30
20
10
0
K1
K2
K3
K4
K5
STD
COMPOUND K1-K5
200µg/ml
400µg/ml
600µg/ml


HRBC MEMBRANE EFFECT OF SYNTHESIZED COMPOUNDS K6-K10
% INHIBITION
90
80
70
60
50
40
30
20
10
0
K6
K7
K8
K9
K10
STD
COMPOUND K6-K10
200µg/ml
400µg/ml
600µg/ml

C.IN-VITRO ANTI-DIABETIC ACTIVITY

Table-12: Non-Enzymatic Glycosylation of Haemoglobin Method

COMPOUNDS	% INHIBITION OF HAEMOGLOBIN GLYCOSYLATION		
	50µg/ml	100µg/ml	150µg/ml
K1	53.42	67.07	73.58
K2	52.61	66.32	72.92
K3	47.58	63.11	71.50
K4	43.79	61.00	69.58
K5	38.95	58.52	67.26
K6	51.05	65.68	73.28
K7	49.84	64.87	71.94
K8	45.11	62.61	70.41
K9	40.29	60.04	68.53
K10	34.27	58.62	67.00
STD (Tocopherol)	55.46	67.85	74.04


NON -ENZYMATIC GLYCOSYLATION OF HAEMOGLOBIN (K1-K5)
% INHIBITION
80
70
60
50
40
30
20
10
0
K1
K2
K3
K4
K5
STD
COMPOUND K1 - K5
50µg/ml
100µg/ml
150µg/ml

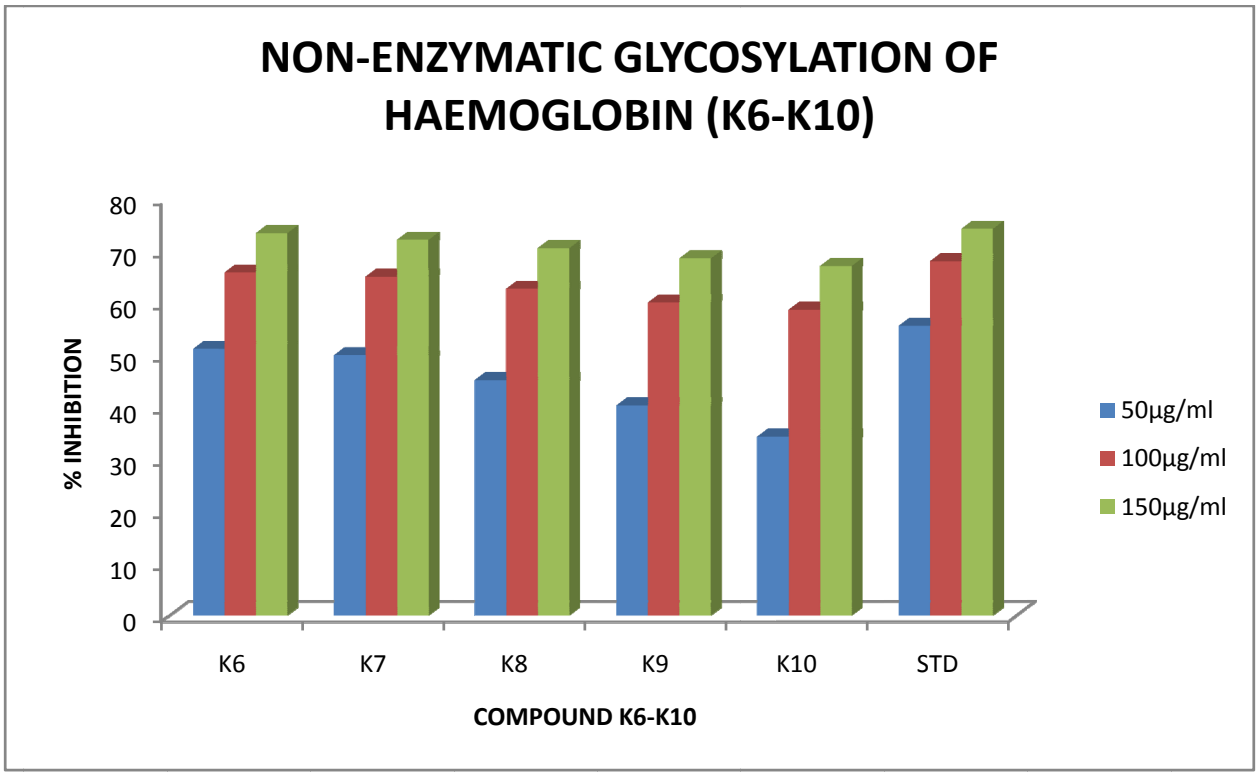
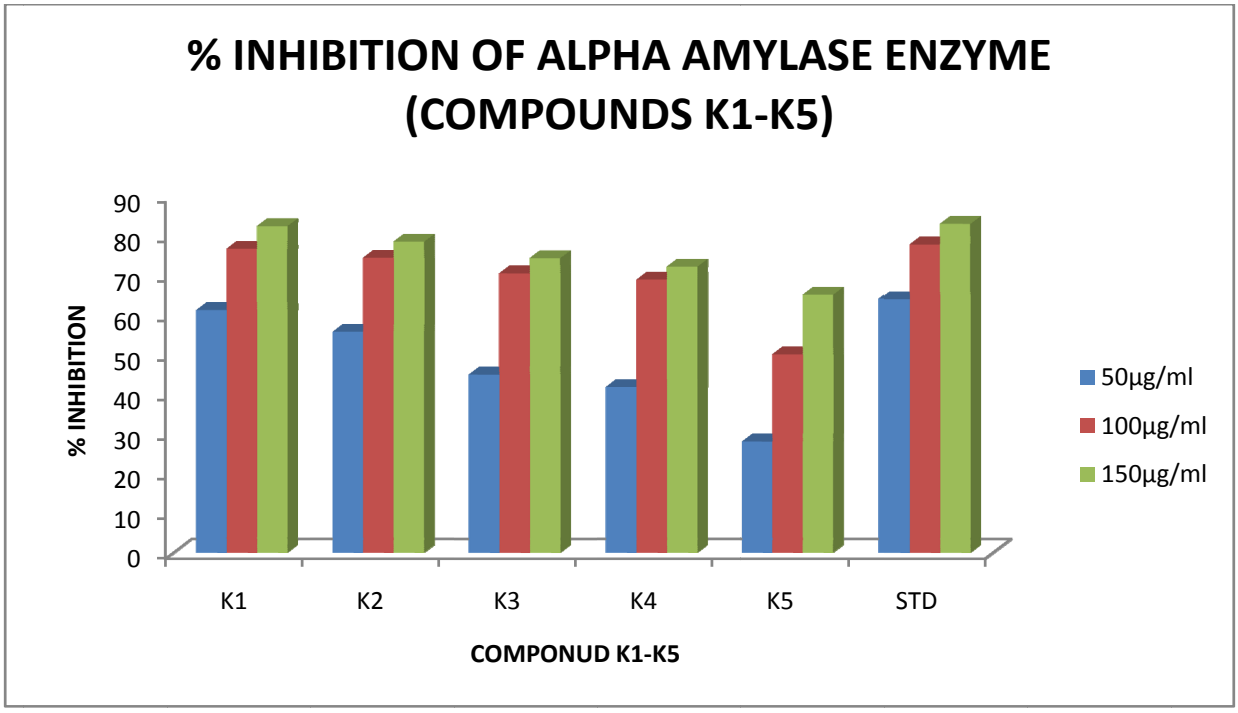

NON-ENZYMATIC GLYCOSYLATION OF HAEMOGLOBIN (K6-K10)
% INHIBITION
80
70
60
50
40
30
20
10
0
K6
K7
K8
K9
K10
STD
COMPOUND K6-K10
50µg/ml
100µg/ml
150µg/ml

Table-13: Alpha amylase enzyme inhibition assay.

COMPOUNDS	% INHIBITION OF ALPHA AMYLASE ENZYME		
	50µg/ml	**100µg/ml**	**150µg/ml**
K1	61.22	76.71	82.4
K2	55.60	74.25	78.31
K3	45.00	70.01	74.46
K4	41.71	68.7	72
K5	44.20	69.52	73.00
K6	50.03	73.13	76.42
K7	46.01	71.03	75.45
K8	44.05	69.52	73.04
K9	34.01	65.06	69.00
K10	18.12	45.13	61.18
STD (Acarbose)	64.17	77.90	82.97


% INHIBITION OF ALPHA AMYLASE ENZYME (COMPOUNDS K1-K5)
% INHIBITION
90
80
70
60
50
40
30
20
10
0
K1
K2
K3
K4
K5
STD
COMPONUD K1-K5
50µg/ml
100µg/ml
150µg/ml

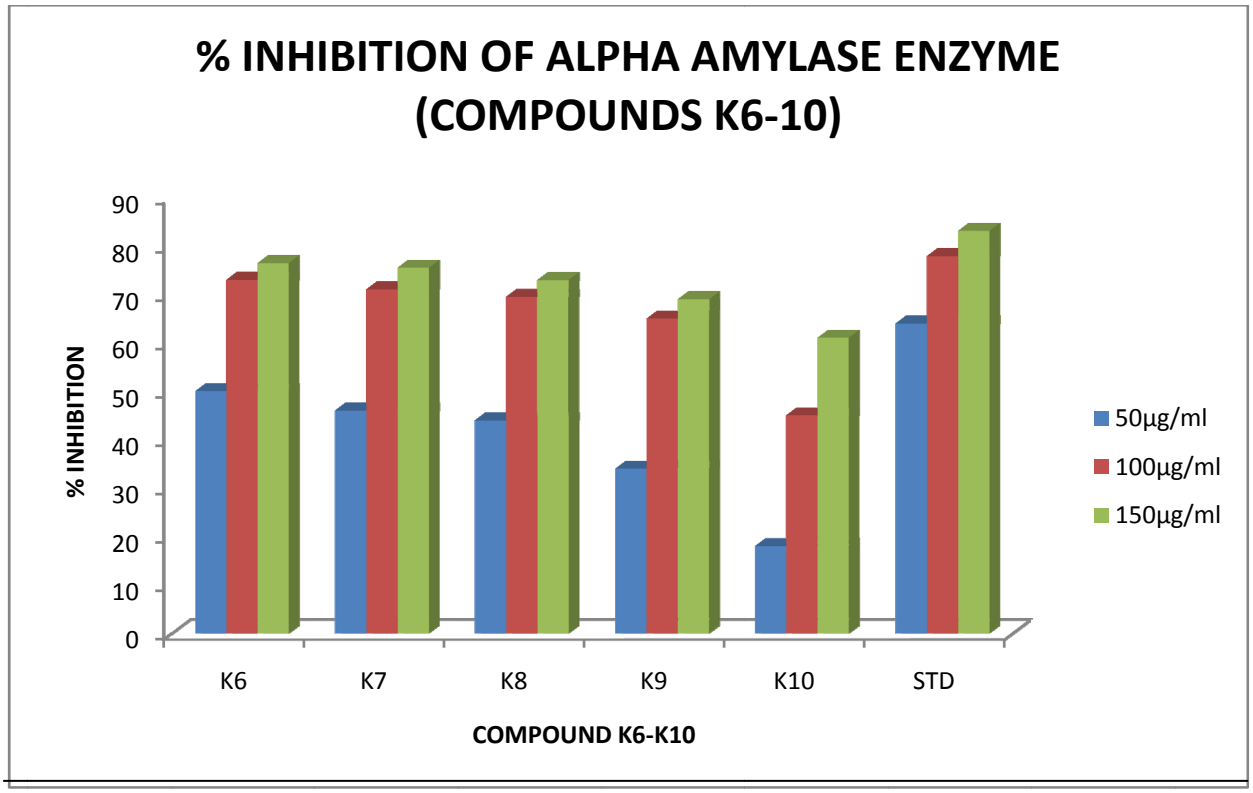
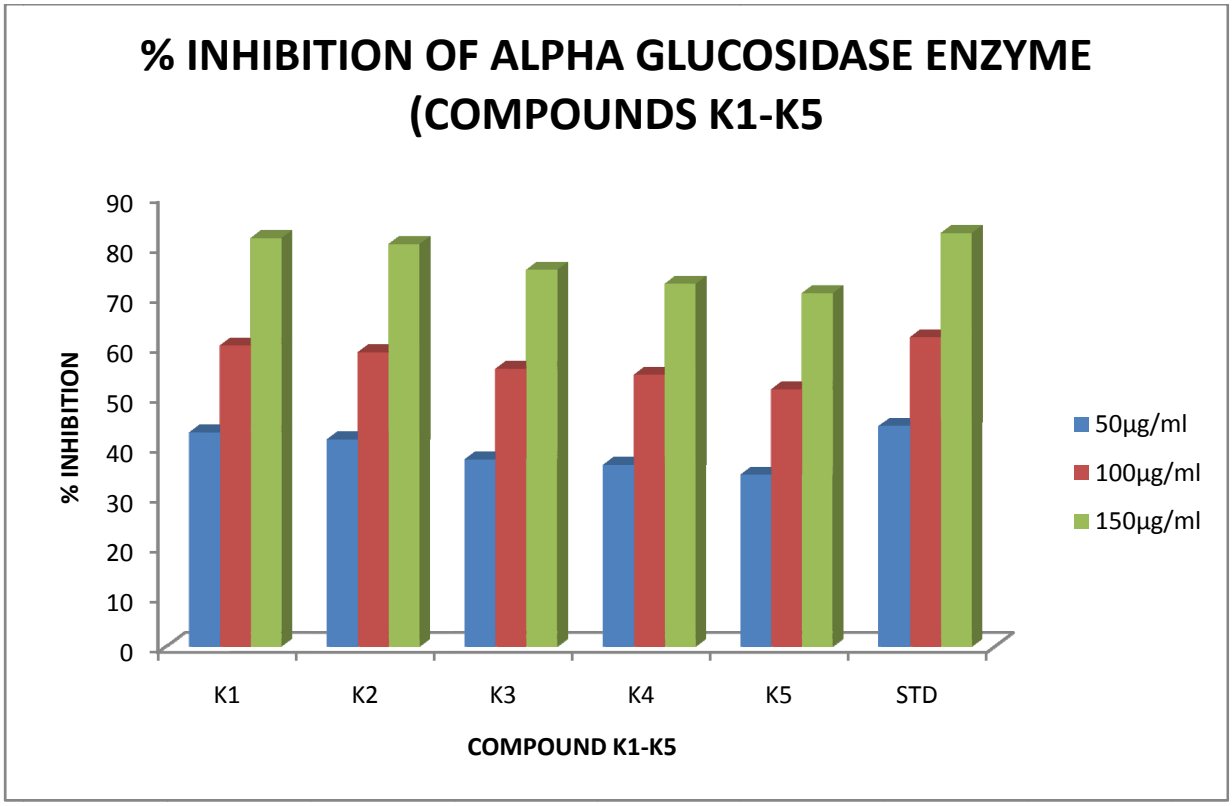
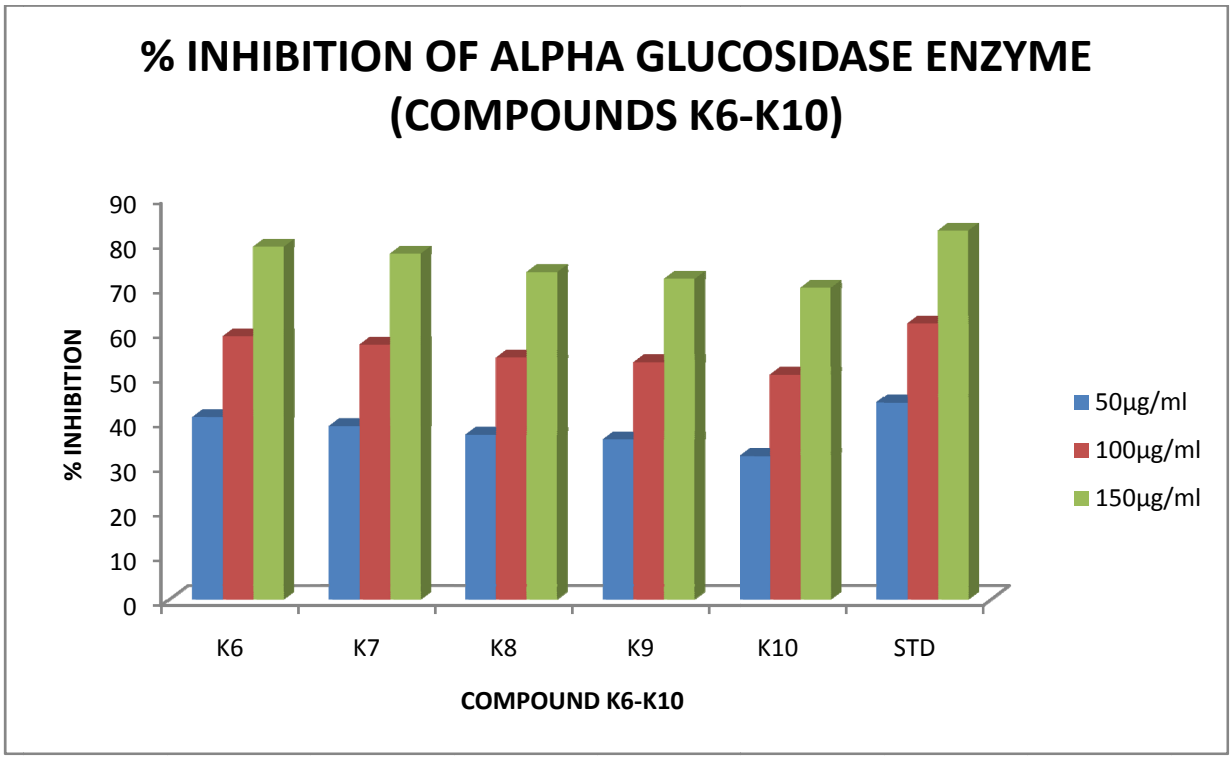

% INHIBITION OF ALPHA AMYLASE ENZYME (COMPOUNDS K6-10)
% INHIBITION
90
80
70
60
50
40
30
20
10
0
K6
K7
K8
K9
K10
STD
COMPOUND K6-K10
50µg/ml
100µg/ml
150µg/ml

Table-14: Alpha Glucosidase enzyme Inhibition Assay

COMPOUNDS	% INHIBITION OF ALPHA GLUCOSIDSE ENZYME		
	50µg/ml	100µg/ml	150µg/ml
K1	42.76	60.13	81.60
K2	41.36	58.91	80.57
K3	37.34	55.46	75.25
K4	36.32	54.34	72.54
K5	34.36	51.44	70.68
K6	78.99	40.80	58.91
K7	38.74	56.95	77.31
K8	36.88	54.15	73.33
K9	35.85	53.12	71.80
K10	32.02	50.23	69.65
STD (Acarbose)	44.07	61.81	82.63

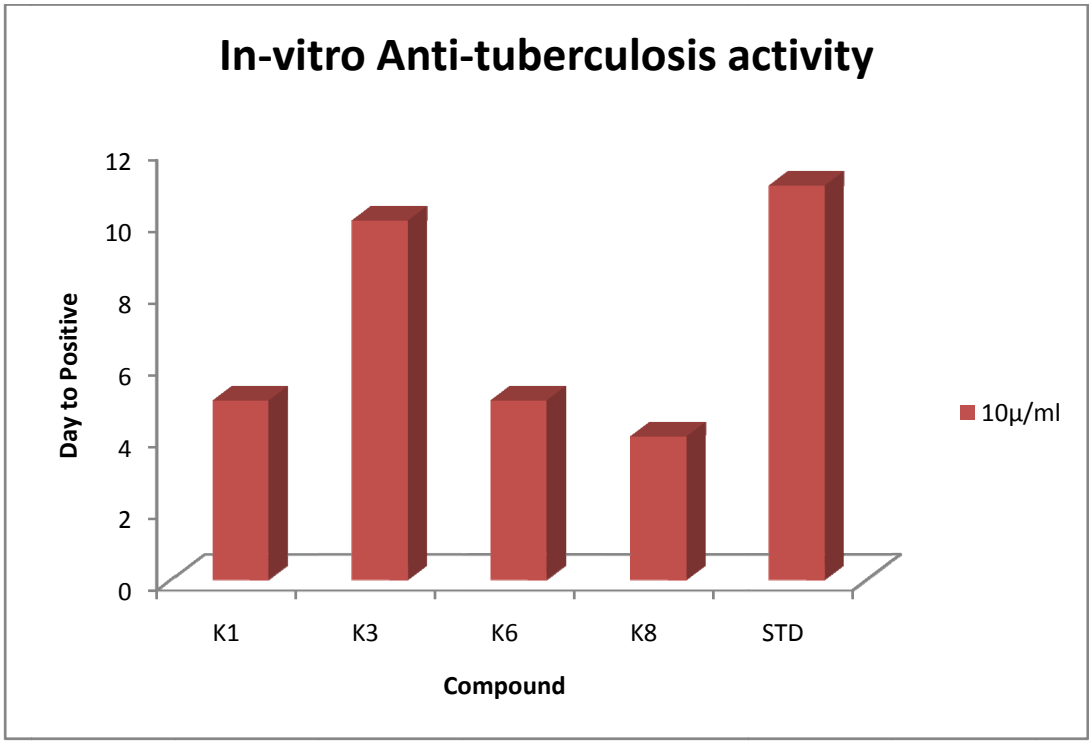

% INHIBITION OF ALPHA GLUCOSIDASE ENZYME (COMPOUNDS K1-K5
90
80
70
60
50
40
30
20
10
0
% INHIBITION
K1
K2
K3
K4
K5
STD
COMPOUND K1-K5
50µg/ml
100µg/ml
150µg/ml


% INHIBITION OF ALPHA GLUCOSIDASE ENZYME (COMPOUNDS K6-K10)
90
80
70
60
50
40
30
20
10
0
% INHIBITION
K6
K7
K8
K9
K10
STD
COMPOUND K6-K10
50µg/ml
100µg/ml
150µg/ml

D. In-vitro Anti-tuberculosis Activity

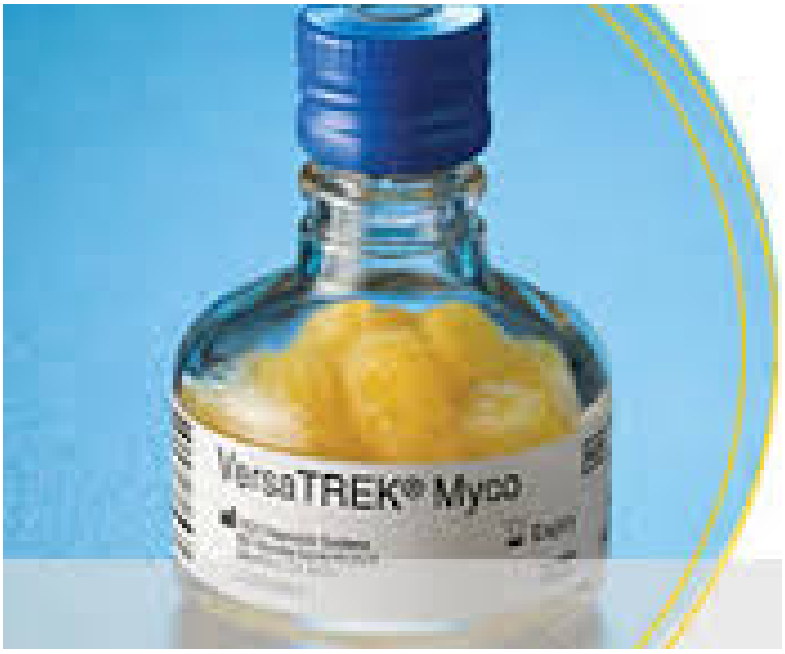
Table-15: Anti-tuberculosis activity of compounds K1, K3, K6, K8

Compounds	Concentration	Day to positive	Result
K1	10µg/ml	5 days	Resistant
K3	10µg/ml	10 days	Sensitive
K6	10µg/ml	5 days	Resistant
K8	10µg/ml	4days	Resistant
Isoniazid	10µg/ml	11 days	Sensitive
Control	10µg/ml	4 days	NIL



VERSA TREK

MYCO BOTTLE



5.5 DISCUSSION

- The molecular design of all synthesized compounds were done by using different software such as Chemdoole, Chemsketch and Molinspiration.
- The lipinski rule was predicted for all synthesized compound using CHEMDOODLE.

It shows no violation in basic properties .The results were shown in **Table.No: 6**

- The I.U.P.A.C name were predicted by using chemsketch. The results were shown in **Table.No:2**
- The pecentage yield, Mocular Formula, solubility and appearance of the compounds were pridicted and shown in **Table.No;3**
- The purity of the compounds were found out by TLC and Rf value was calculated. The results are shown in **Table.No:4**
- Melting points of compounds were predicted and shown in **Table.No:4**
- Elemental compostion were found and calculated in percentage and results obtained were shown in **Table. No:5**
- The Characterisation of synthesized compounds were confirmed by IR spectra,NMR spectra and Mass spectra.
- IRspectra interpret value shown in **Table**.**No:7**
- NMR specctra interpret value shown in **Table**.**No:8**
- Mass spectra results are shown in **Table.No.9**
- All synthesized compounds were evaluated for ant-oxidant, anti-diabatic acitivity, anti-inflammatory and anti-tuberculosis activity.
- Anti-Oxidant activity of all synthesized compounds were evaluated and results were shown in **Table.No:10**

- In Anti-diabetic evaluation Non-enzymatic Haemoglobin glycosylation assay results were shown in **Table.No:12**
- In Anti-diabetic evluation alpha amylase enzyme inhibition assay results were shown in **Table.No:13**
- In Anti-diabetic evaluation alpha glucosidase enzyme inhiition assay results were shown in **Table.No:14**
- Anti-inflammatory activty of all synthesized compounds results were shown in **Table.No:11**
- Anti-tuberculosis activity of synthesized compounds results were shown in **Table.No:15**

SUMMARY AND

CONCLUSION

6. CONCLUSION

The molecules were designed by the software tools and the lead molecules of chalcone were synthesized by " CLAISEN-SCHMIDT REACTION" followed by phenyl hydrazine and urea treatment forms N-phenylpyrazoline and 3,4-dihydropyrimidine respectively. The formation of molecules was confirmed by TLC.

The structure of synthesized compounds were confirmed by FT-IR, ^{1}HNMR, MASS Spectroscopy.

The IR data's showed relavant peaks for C=C, C=N, C=O groups. The ^{1}HNMR also showed relavant proton peaks for all synthesized compounds. The MASS spectrum confirm the molecular ion peak of all synthesized compounds.

The In-vitro anti-oxidant property for all the compounds showed positive results. The compounds K1, K3 & K6, K8 showed more potent activity. These four compounds shows N-phenylpyrazoline and 3,4-dihydropyrimidine with P-dimethyl amino benzaldehyde, P-chlorobenzaldehyde substitution at fifth and sixth position respectively. Hence the compounds may be evaluated for Anti-tuberculosis activity.

The In-vitro anti-diabetic activity of all the compounds was evaluated and compared with standard. The compounds such as K1, K2 & K6, K7 showed more potent activity. Hence N-phenylpyrazoline and 3,4-dihydropyrimidine with P-Chloro baenzaldehyde, Trimethoxy benzaldehyde substitution at fifth and sixth position respectively showed better activity.

The In-vitro anti-inflammatory activity of all the compounds was evaluated and compared with standard. All the compounds showed significant activity. The compounds such as K1, K3 & K6, K8 exhibited more potent activity.

Based on In-vitro antioxidant activity the compounds K1, K3, K6, K8 were selected and evaluated for Anti-tuberculosis activity. The compounds K3 exhibit potent activity against Mycobacterium tuberculosis. Hence N-phenylpyrazoline with phenyl substitution at third position and P-dimehtyl amino benzaldehyde substitution at fifth position showed better activity.

In Future, the compounds K1, K2, K6, K7 can be studied for In-vivo anti-diabetic activity as it exhibited significant In-vivo anti-diabetic activity.

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7. BIBLIOGRAPHY

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