Chapter one

1. Introduction

1.1 Chemistry of chalcones:

Chalcones represent an important group of natural as well as synthetic products; can be synthesized by condensation of simple or substituted aromatic aldehyde with simple or substituted acetophenone in the presence of alkali (Abegaz *et al*, 2002; Wu *et al*, 2006; Hijova, 2006; Swamy *et al*, 2008). This family of the organic compunds is very interested because they have a unique structural feature of having a carbonyl functional group in conjugation with carbon-carbon double bond and the whole molecule is in conjugation. The presence of α, β- unsaturated keto group or enone function, is found to be responsible for their biological activity (Baviskar *et al*, 2008; Prasad *et al*, 2008; Vaijayanthi & Mathiyalagan, 2011).

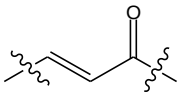


Figure 1.1: Enone functional group

Generally, chalcones possess a wide range of pharmacological activities such as antibacterial, antitumour, anticancer, antitubercular, anti-inflammatory, antioxidant, antimalarial, antileishmanial (Cheng *et al*, 2000; Ngameni *et al*; 2007; Baviskar *et al*, 2008; Maria *et al*, 2008; Vazquez-Rodriguez *et al* 2010), sunscreen agents and sweeteners (Jayapal *et al*, 2010). Chalcones are also well known intermediates for synthesizing various heterocyclic compounds (Prasad *et al*, 2008).

1.1.1 Spectral properties of chalcones:

The conjugation of π electrons in the enone function gives the chalcone some of the extra stabilization which is normally the conjugation with the two benzene rings in their structures. The expected characterization of this enone function by the methods

of spectroscopy is one of the most important guides to make sure that the chalcone has been formed (Navale *et al*, 2010). Different spectral properties has been reviewed (Wu *et al*, 2006; Ngameni *et al*, 2007).

1.1.1.1. **IR spectral features of enones:**

Both the C=O and C=C group stretching in the enone function will affected by conjugation. The nonconjugated C=O group stretch at 1730 cm^{-1} while the conjugated stretch lowered by about 40 cm^{-1}**.** The carbonyl group in chalcone is located in high conjugated system, as the enone group of chalcone located between two aromatic rings, it is stretched lowered even more. but this effect is not significantly in the case of C=C group. The nonconjugated C=C group stretch weekly at 1640 cm^{-1} while the conjugated group stretch strongly and slightly lowered by approximately 20 cm^{-1} than the noncongugated C=C and conjugated C=O **(**Clayden *et al*, 2009**;** Glushkov *et al*, 2012**).**

1.1.1.2. **^{1}H-NMR spectral features of enones:**

There are two protons in the enone function, located between three bond, can be coupled. The farther proton to the oxygen atom is the more deshielded by conjugation than the other. The other proton normally less shielded and gives beak at about 7.8 ppm with the same coupling constant (Kumar *et al*, 2010).

1.1.1.3. **^{13}C-NMR spectral features of enones:**

The C1 in the enone function is affected by both conjugation and attached oxygen atom, the chemical shift lowered to the smaller chemical shift in about 190 ppm, less by 20 ppm than nonconjugated carbonyl group. The C2 and C3 affected by conjugation and give a beak at about 124 and 142 ppm which at about 10 ppm less than the nonconjugated alkene (Lahtchev *et al*, 2008).

1.1.1.4. **Mass spectral features of enones:**

The entire or attached single bonds of a chalcone enone function are susceptible to underwent fragmentation, and those present attached to the C1 of enone function are more likely to breakdown due to electrophilicity of carbon of carbonyl group. Generally, the fragmentation of chalcone is also effected by the constituents attached to the aromatic rings (Navale *et al*, 2010).

1.1.2 Synthesis of chalcones:

1.1.2.1. Claisen–Schmidt condensation:

Claisen–Schmidt condensation is the validated method and the more popular to synthesized chalcones by condensation of aromatic aldehyde with methyl ketones in the presence of an alkali and ethanol as a solvent. Ethanol is the most common solvent, in other studies methanol has been used (Wang *et al*, 2007; Jamal *et al*, 2009; Navale *et al*, 2010). Usually sodium hydroxide is used as catalyst and sometimes potassium hydroxide. However literature showed that some chalcones can be prepared under reflux in the presence of piperidine whereas some other reactions attempt this condition has been failed (Jain *et al*, 2004; Wang *et al*, 2007; Baviskar *et al*, 2008; Jamal *et al*, 2009).

1.1.2.2. Synthesis of chalcones using acidic conditions:

Chalcones preparation can be performed under acidic catalyst, using HCl, BF_3, B_2O_3, *p*-toluene sulfonic acid, etc. The most common method applies ethanol saturated with HCl. The yields are low and vary between 10% - 40% (Patil *et al*, 2009). $SOCl_2$/EtOH can be used as alternative option for acidic catalysis to the gaseous HCl (Jayapal & Sreedhar, 2010) in aldol condensation. This method give yield ranged between 64-81%.

1.1.2.3. Synthesis of chalcones using PEG as solvent:

Chalcone can also be prepare using poly ethylene glycol (PEG) giving yield percent between 80-83%, which has been found as an environmentally benign reaction solvent, is non-toxic, inexpensive, potentially recyclable and water soluble, which facilitates its removal from the reaction product (Sreedhar *et al* 2010).

1.1.2.4. Synthesis of chalcones using Solid Phase:

Cheng *et al*, (2000) proposed a solid phase method of economic porous for preparation of anti-malarial chalcones, using a resin-attached aldehydes for Claisen–Schmidt condensation.

1.1.2.5. Synthesis of chalcones using microwave irradiation:

One of the best methods for saving time, high yield and clean reaction is by applying successful microwave irradiation for the preparation of target molecules (Suryawanshi *et al* 2008; Patil *et al*, 2009; Guoxi *et al*, 2011).

A fast synthesis of chalcone in three minutes under microwave irradiation has been reported (Liu & Go 2007), but the fastest condensation of acetophenone and benzaldehyde under microwave using solid catalyst has also reported by Krishnakumar *et al*, (2011), here in the reaction was achieved in 1 minute. Kumar *et al*, (2010) describe the microwave irradiation as a cost effective route to chalcone.

1.1.3 Reactions of chalcones:

The reactivity of chalcones is depending on electrophilic C1 and C3 at enone group, normally both of these sites of reaction will involve in chalcone transformation particularly in heterocycles synthesis, the most important reaction of this kind of compounds. The major problem in enone reaction is that some reagent with different types of nucleophile reacts with both of C1 and C3 leading to regioselectivity problem (Katritzky *et al*, 2001).

1.1.3.1. Synthesis of isoxazolidin-3-yl-3-phosphonate:

A solution of the nitrone and a substituted chalcone in toluene when stirred at 70 ^{0}C furnished isoxazole derivatives (Piotrowska *et al*, 2011).

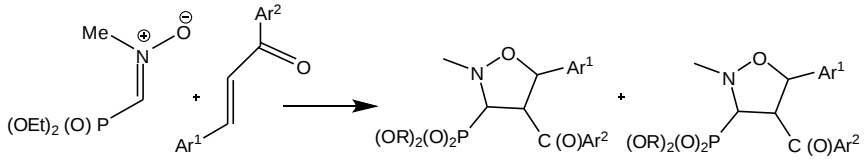


Figure 1.2: Synthesis of isoxazolidin-3-yl-3-phosphonates

1.1.3.2. Reduction of chalcones to dihydrochalcones by Zn/HOAc:

Chalcone under Zn dust and acetic acid in the presence of an ultrasonic irradiation gave dihydrochalcone (Zhang *et al*, 2008).

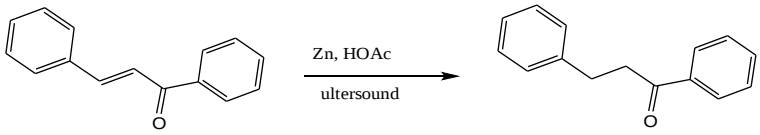


Figure 1.3: Reduction of Chalcones to Dihydrochalcones

1.1.3.3. Oxidation of chalcones by N – chloronicotinamide:

Chalcone can be oxidizing by NCN in the presence of HCl and $NaClO_4$ to give benzoic acid and phenyl acetaldehyde (Vaijayanthi & Mathiyalagan, 2011).

1.1.3.4. Synthesis of benzofuranones from chalcones:

Benzofuranones can be obtained from the reaction of chalcone containing carboxylic acid group in presence of ethanol (Padaratz *et al*, 2009).

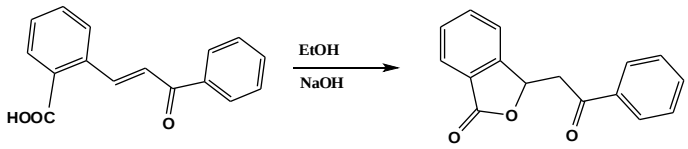


Figure 1.4: Synthesis of benzofuranone from chalcone

1.1.3.5. Synthesis of pyrazolines from chalcones:

Cycloaddition condensation reactions of chalcone with hydrazine hydrate, phenylhydrazine or 4-nitrophenylhydrazine in the presence of formic or acetic acid gave the corresponding dihydropyrazole (Patil *et al* 2009; Rostom *et al*, 2011).

1.1.3.6. Synthesis of pyrimidines from chalcones:

Pyrimidines achieved by reaction of the chalcone with urea, thiourea or substituted thiourea in absolute ethanol containing concentrated hydrochloric acid or in the presence of a basic catalyst (Rostom *et al*, 2011).

1.1.3.7. Synthesis of flavanones from chalcones:

2- hydroxychalcones cyclized in glacial acetic acid to give flavanones (Patil *et al* 2009).

1.1.4 Biological activities of chalcones:

Some chalcones possess a moderate activity against *Staphylococcus aureus* and *Escherichia coli* and very good activity against fungi of *Aspergillus flavus* (Swamy and Agasimundin, 2008).

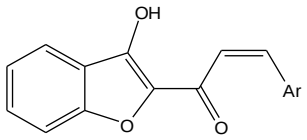


Figure 1.5: General structure of some chalcones with anti microbial activity

Thiazolyl chalcones have been developed and exhibited activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhosa*, *Aspergillus niger* and *Candida albicans* (Baviskar *et al*, 2008).

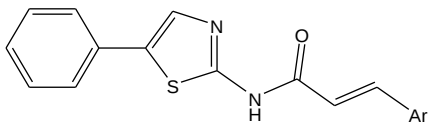


Figure 1.6: Thiazolyl chalcones with anti bacterial activity

The chalcones of 1-(substitutedphenyl)-3-(substitutedphenyl)- 2-propen-1-ones were tested for antibacterial and antifungal activity. Compounds with electron releasing groups such as methoxy and hydroxyl groups showed better antibacterial activity than the others not having such groups. Compounds having pharmacophores such as, chloro, dichloro and fluoro groups have exhibited more antifungal activity (Prasad *et*

al, 2008), whereas the ferrocenyl chalcones were found selectively active against Plasmodium (Wu *et al*, 2006)

Certain chalcones possess significant antiinflammatory activity through their antioxidant activity (Maria *et al*, 2008).

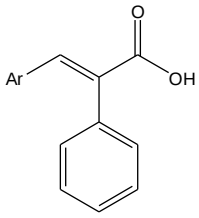


Figure 1.7: Anti-inflammatory and antioxidant chalcones

Anto *et al,* (1995) reported that chalcones has antioxidant and anti-cancer activity particularly that containing hydroxyl group.

1.2 Chemistry of pyrimidines:

Pyrimidines are six-member aromatic heterocyclic compounds similar to benzene and pyridine, containing two nitrogen atoms at positions 1 and 3.

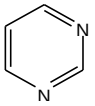
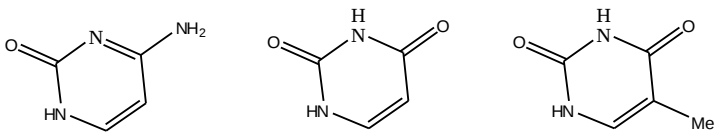


Figure 1.8: Chemical structure of pyrimidine

Pyrimidines are present throughout nature in various forms such as vitamins and are the building blocks of numerous natural products that have antibiotics, antiviral, fungicidal, insecticidal, antibacterial, antihypertensive, and anticonvulsant activity (Ho & Yao, 2009).

The most commonly recognized pyrimidines are the bases of RNA and DNA, the most abundant being cytosine, thymine and uracil.



cytosine uracil thymine

Figure 1.9: The bases of RNA pyrimidines derivatives

Pyrimidines have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy of AIDS. Barbitone, the first barbiturate hypnotic sedative and anticonvulsant is a pyrimidine derivative **(**Clayden *et al*, 2009).

1.2.1 Physical properties of pyrimidines:

The nitrogen atoms in the pyrimidine ring have a similar sort to that of the pyridine-nitrogen, in which the lone pair of electrons do not delocalized round the ring. It is locates in the sp^2 orbital in the plane of the ring making stable imine with very week base features.

The presence of the nitrogen atoms in the pyrimidine ring plays a vital role on its reactivity, by lowering the energy of the entire π orbitals on the ring. This effect makes the HOMO less reactive nucleophile and the LUMO more reactive electrophile, and hence very electron-deficient ring (Clayden *et al*, 2009).

1.2.1.1. **IR spectral features of pyrimidines:**

The C-H bending of the aromatic ring (out of plane) has strong absorption in the region of the finger print of about 750 cm^{-1}, whereas it is stretches at near of 3000 cm^{-1}. The C=N is stretch at 1600 cm^{-1}.

1.2.1.2. ^{1}H-NMR spectral features of pyrimidines:

The unsubstituted pyrimidine contains three types of protons as below. The proton in carbon 2 has a higher deshielding due to the electronegativity of nitrogen atoms.

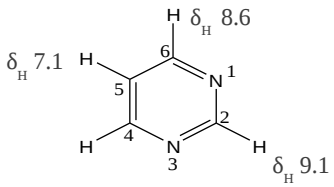


Figure 1.10: The chemical shifts of protons in pyrimidine ring

The proton on the carbon five has a chemical shift approximately the same as those of benzene ring, but the others, near to the more electronegative nitrogen atom, have higher chemical shift (Clayden *et al*, 2009).

1.2.1.3. ^{13}C-NMR spectral features of pyrimidines:

Carbon 4 and 6 have the same chemical shift for similarity, and it is not significantly different from the carbon 2. These carbons 2, 4 and 6 were affected by the electronegativity of nitrogen atoms, but the carbon 5 has a little effect and therefore it has a lower chemical shift among the entire carbons on the rings (Clayden *et al*, 2009).

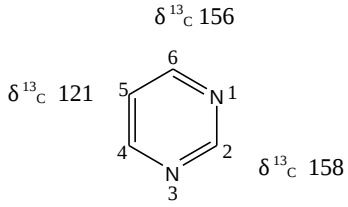


Figure 1.11: The chemical shift of ^{13}C pyrimidine ring

1.2.2 Synthesis of pyrimidines ring system:

The pyrimidine ring system is usually constructed by a base catalyst reaction between a 1,3 dicarbonyl or its related compounds and with a reagent bearing an N–C–N fragment such as urea, amidine, or guanidine in [3+3] strategy as shown in Figure 1.9 (Tyagarajan and Chakravarty, 2005; Heravi *et al*, 2009).

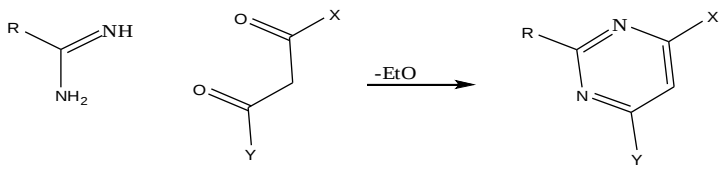


Figure 1.12: [3+3] Synthetic strategy of pyrimidines

There is a wide range of possibilities: the 2- substituent, R, can be H, NH_2, OH, or SH by use of formamidine, guanidine, urea, or thiourea respectively; and X and Y can be H, OH, or NH_2 by the use of aldehyde, ester, or nitrile substituents.

1.2.2.1. Synthesis of pyrimidines via direct oxidative one-pot reaction:

The reaction between a 1,3- diketone, benzaldehydes and ammonium acetate in the presence of catalytic amounts of heteropolyacids under refluxing conditions produces pyrimidines in good yields (Heravi *et al*, 2009).

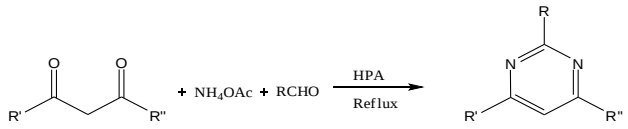


Figure 1.13: Synthesis of pyrimidine via direct oxidative reaction

1.2.2.2. Synthesis of pyrimidines via microwave assistance:

Treatment of a mixture of acetophenone and ammonium acetate in formamide under microwave irradiation for 800 seconds at 215 ^oC produced 4-phenylpyrimidine in 51% yield (Tyagarajan and Chakravarty, 2005).

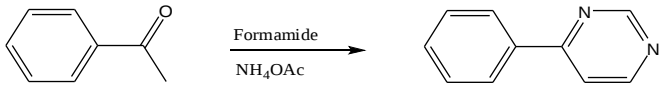


Figure 1.14: Synthesis of pyrimidine via microwave assistance

1.2.2.3. Synthesis of 2,4- diamino-6-hydroxypyrimidine:

The 2,4-diamino-6-hydroxypyrimidine can be obtained in 80% yield from guanidine and cynoacetate.

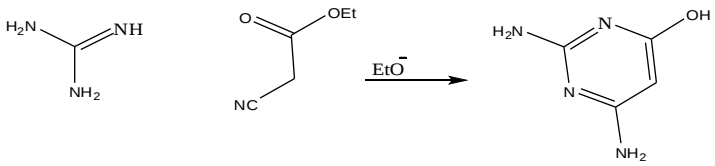


Figure 1.15: Synthesis of 2,4-diamino-6-hydroxypyrimidine

1.2.2.4. Synthesis of pyrimidine-2,4,6 (1*H*,3*H*,5*H*)-trione:

Barbituric acid can be obtained in 79% yield from the reaction of urea and malonic ester in the presence of ethoxide (Ackland, *et al*, 1993).

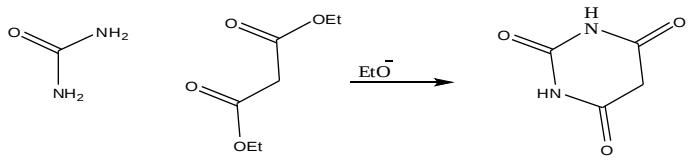


Figure 1.16: Synthesis of pyrimidine-2,4,6 (1*H*,3*H*,5*H*)-trione

A variant of this approach utilizes Micheal-type addition to α β unsaturated ester.

1.2.2.5. Synthesis of pyrido[4,3-d] pyrimidines:

Treatment of substituted pyridine with alkyl amines or ammonia at mild conditions afford the pyrido [4,3-d] pyrimidines in moderate to good yields (Mo *et al*, 2011).

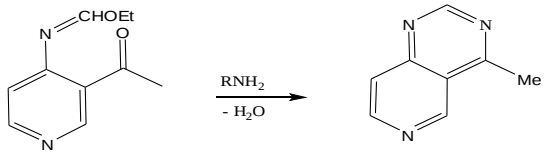


Figure 1.17: Synthesis of pyrido[4,3-d] pyrimidines

1.2.2.6. Synthesis of 2H- pyrido[4,3-d] pyrimidines:

It can be prepared in high yield from ethyl-4-amino-1-tert-butoxycarbonyl-1,2,5,6-tetrahydropyridine-3-carboxylate, allyl isocyanate, and diisopropylethylamine in toluene (Lanier *et al*, 2007).

Figure 1.18: Synthesis of 2H- pyrido[4,3-d] pyrimidines

1.2.2.7. Synthesis of cytosine:

Cytosine can be synthesized by condensation of cyanoacetaldehyde and urea (Powner *et al*, 2009).

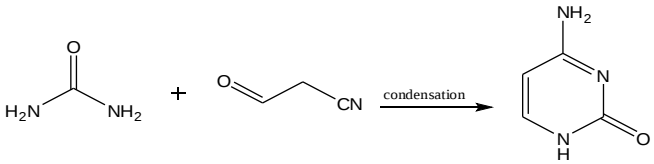


Figure 1.19: Synthesis of cytosine

1.2.2.8. Synthesis of anhydroarabinonucleoside:

It can be prepared by the reaction of pentose amino-oxazolines and cyanoacetylene in the presence of phosphate buffer (Powner *et al*, 2009).

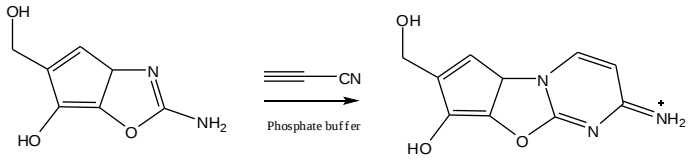


Figure 1.20: Synthesis of anhydroarabinonucleoside

1.2.2.9. Synthesis of steroidal pyrimidines:

It can synthesized from the Bis (methylthio) methylene-4-cholesten-3-one and guanidine nitrate in the presence of NaAcO in ethanol (Laitonjam *et al*, 2002; Barthakur *et al*, 2009).

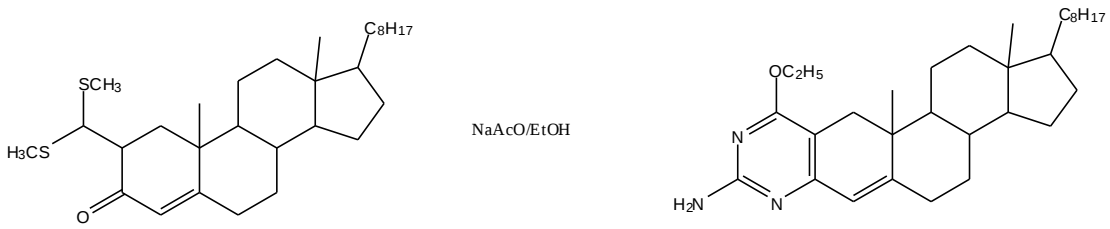


Figure 1.21: Synthesis of steroidal pyrimidines

1.2.2.10. Synthesis of 5-Amino-2-mercaptopyrimidine-4,6-diol:

It is the product of reaction of thiourea with diethyl aminomalonate hydrochloride (Holschbach *et al*, 2006; Venu *et al*, 2008).

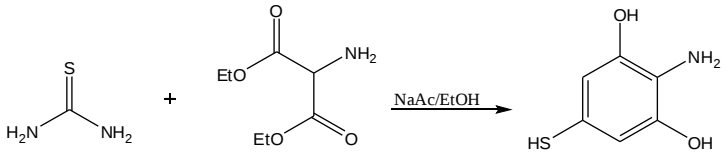


Figure 1.22: Synthesis of 5-Amino-2-mercaptopyrimidine-4,6-diol

1.2.2.11. Synthesis of pyrazolo[1,5-a]pyrimidine:

Reactiion of 2-cyano-3-(5-amino-3-methyl-pyrazol-4-yl)azo-4,6-disubstituted-thieno[2,3-b]pyridine with 1,3-diketone in glacial acetic acid furnish pyrazole [1,5-a] primidine (Ho, 2005).

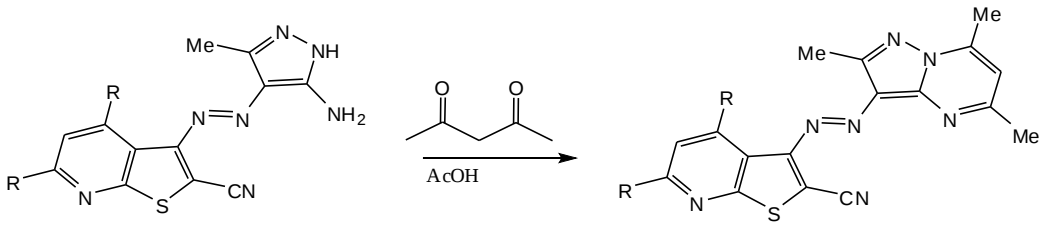


Figure 1.23: Synthesis of pyrazolo[1,5-a]pyrimidine:

1.2.3 Reactions of Pyrimidines:

The pyrimidine ring is highly electron-deficient and therefore it reacts as electrophile. The nucleophilic substitution of chloride or iodide by amine groups is the most common reaction (Achelle *et al*, 2008).

1.2.3.1. Synthesis of 2,4-bis anilino pyrimidines:

Primary aromatic amine reacts with 2,4-dichloropyrimidine in the presence of butanol and acid catalyst (Breault *et al*, 2003)

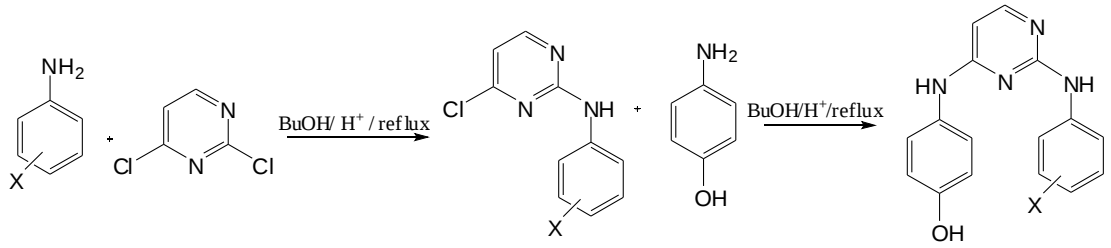


Figure 1.24: Synthesis of 2,4-bis anilino pyrimidines

1.2.3.2. Sonogashira cross-coupling reaction

The Sonogashira cross-coupling is one of the most common methods to introduce an ethynyl moiety on aryl compounds. Normally the iodoaryl was used for substitution

with alkyne in THF and basic conditions using NEt_3, CuI and Pd $(PPh_3)_2Cl_2$ (Achelle *et al*, 2008).

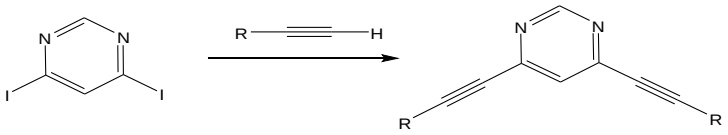


Figure 1.25: Sonogashira cross-coupling reaction

1.2.3.3. Synthesis of iodopyrimidinols:

It can be prepared with reflux of iodine and pyrimidine in basic condition (Liu *et al*, 2007).

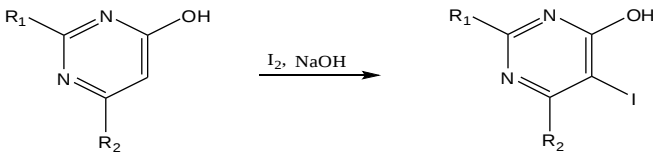


Figure 1.26: Synthesis of iodopyrimidinols

1.2.3.4. Protonation of pyrimidine

As a week base the pyrimidine could be protonated on one nitrogen, the di-protonation is very difficult as the mono-cation destabilized with the second nitrogen atom (Joule and Mills, 2010).

1.2.3.5. Transformation of pyrimidine to pyrazole

In hot hydrazine with aqueous alkali pyrimidine will transform to pyrazole (Joule and Mills, 2010).

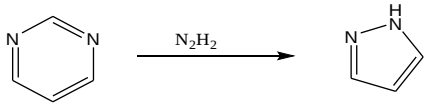


Figure 1.27: Synthesis of iodopyrimidinols

1.2.3.6. Reaction of uracil with dimethyldioxirane

Uracil could be oxidised to diol at room temprature through epoxide intermediate to diol by dimethyldioxirane using dichoromethan as solvent (Joule and Mills, 2010).

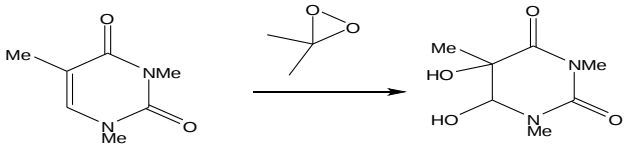


Figure 1.28: Reaction of uracil with dimethyldioxirane

1.2.4. Biological activities of pyrimidines:

The 2,4- bis anilino pyrimidines were identified as potent inhibitors of CDK4, 2,7-Diphenyl-6-(phenylsulfonyl) pyrazolo [1,5-a] pyrimidine and its *p*-methoxy analogue were found to be equipotent to doxorubicin as a reference drug against HST116 colon tumor cell line, whereas pyrido[2,3-d]pyrimidine derivatives showed activity against U_{937}, THP-1 and Colo205 for cancer treatment (Breault *et al*, 2003; Kurumurthy *et al*, 2011). Some of 5,6-disubstituted (Kraljevic *et al*, 2010) and 2,5,6 trisubstituted pyrimidine derivatives also exhibited activity against carcinoma.

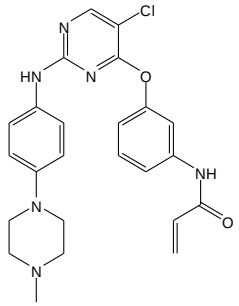


Figure 1.29: Anti-cancer pyrimidine derivative.

Several compounds of certain novel fluorine-containing pyrido[4,3-d]pyrimidines showed significant herbicidal and fungicidal activity (Mo *et al*, 2008). Thieno[2,3-d]pyrimidine-2,4-dithiones derivative showed highly inhibition activity as antibacterial reagents (Hafez *et al*, 2010). Also chlorinated pyrimidines derivatives exhibited excellent *in vitro* antifungal and antibacterial profiles (Gholap *et al*, 2008). The 2-amino-5-cyano-6-hydroxy-4-aryl pyrimidines have showed good zone of inhibition against Gram-positive and Gram-negative bacteria (Deshmukh *et al*, 2009).

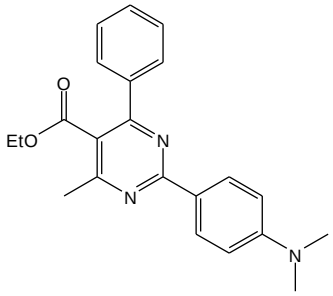


Figure 1.30: Anti-fungal and anti-bacterial pyrimidine.

The pyrimidine base-modified nucleosides have exhibited no positive antiviral activity (Kifli *et al*, 2004), but the 2,4-diamino-5-cyano-6- [2-(phosphonomethoxy) ethoxy pyrimidines and related compounds showed pronounced antiretroviral activity, comparable to that of the reference drugs (Hockova *et al*, 2004).

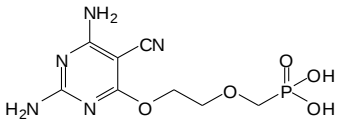


Figure 1.31: Anti-HIV pyrimidine.

Various derivatives of 2,3-dihydroimidazo[1,2-c] pyrimidines were found active for their antimycobacterial activity against H37Rv strain of M. tuberculosis (Chhabria and Jani, 2009).

Some agents of 2,4,6-trisubstituted pyrimidines types were showed *in vitro* antimalarial activity against *Plasmodium falciparum* (Agarwal *et al*, 2005).

Various monocyclic, bicyclic and tricyclic pyrimidine derivatives were experimentally exhibited a good antiinflammatory and analgesic activities (Sondhi *et al*, 2005), Phthalimide pyrimidine derivatives also presented anti-inflammatory activity (Falcao *et al*, 2006).

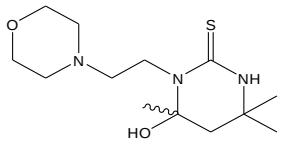


Figure 1.32: Anti-inflammatory active pyrimidine.

1.3 Chemistry of isoxazoles:

Isoxazoles are a class of five-membered heterocyclic molecules related to furan by replacing the CH group in the furan ring with N atom at position 2.

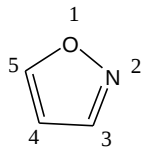


Figure 1.33: Isoxazole ring

Isoxazoles compounds having a wide a range of pharmacological activities such as hypothermic, analgesic, anti-inflammatory, antitussive, antibacterial and antiviral (Kamal *et al*, 2010).

1.3.1 Physical properties of isoxazoles:

The effect of introducing the N atom into the furan ring results in a shortening of the distance between the nitrogen and carbon atoms in the double bond and an increase in the C3 bond angle. These changes in the geometrical parameters affect the energies of the molecular orbitals, lower the unoccupied orbitals and increase the ionization energies (occupied orbitals) in isoxazole as compared to furan (Dampc *et al*, 2010).

1.3.1.1. IR spectral features of isoxzazoles:

The C-H bending of the aromatic ring of isoxazole (out of plane) in the region of the finger print at about 700 cm^{-1}, and it is stretches near to 3000 cm^{-1} (Clayden *et al*, 2009).

1.3.1.2.^{1}H-NMR spectral features of isoxazoles:

The protons in the isoxazole ring were extremely affected by the presence of the oxygen and nitrogen atoms. The proton near to oxygen has a higher chemical shift followed by the proton on carbon 3 and least on carbon 4.

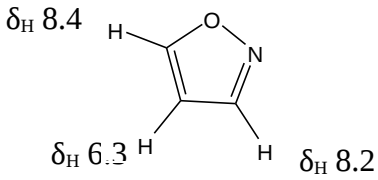


Figure 1.34: The chemical shift of protons in isoxazole ring

1.3.1.3. **^{13}C-NMR spectral features of isoxazoles:**

The ^{13}C-NMR chemical shifts of carbons on the isoxazole ring were affected by the presence of electronegative oxygen and nitrogen atoms. Carbon 5 has a higher chemical shift and carbon 4 has a lower one.

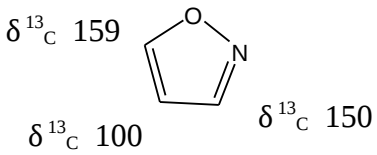


Figure 1.35: The chemical shift of ^{13}C in isoxazole ring

1.3.2 Synthesis of Isoxazoles ring system:

Isoxazoles were generally prepared from 1,3 dicarbonyl compounds and hydroxylamine (Clayden *et al*, 2009).

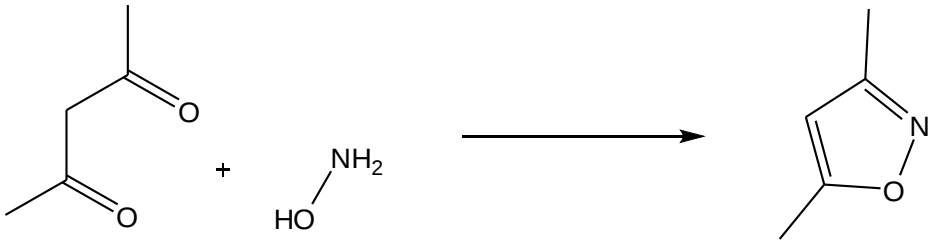


Figure 1.36: General method for cyclization to isoxazole

1.3.2.2. Synthesis of polysubstituted isoxazole:

Trisubstituted isoxazoles were regioselectively prepared in 55-81% yields by treatment of Z)-2-(Benzotriazol-1-yl)-3-(substituted)-1-phenyl-2-propen-1-one with hydroxylamine in THF (Katritzky *et al*, 2001).

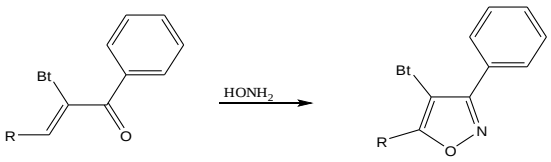


Figure 1.37: Synthesis of polysubstituted isoxazole

1.3.2.3. Synthesis of 3 -(4 -(tert-Butyldimethylsilyloxy) -3, 5-dimethoxyphenyl)-5-(3,4,5-trimethoxy-phenyl) isoxazole:

3 -(4 -(tert-Butyldimethylsilyloxy) -3, 5-dimethoxyphenyl)-5- (3,4,5-trimethoxy-phenyl) isoxazole can be prepared by the reaction of dipolarophile and oxime in the presence of Et_3N in CH_2Cl_2 under argon atmosphere (Kamal *et al*, 2010).

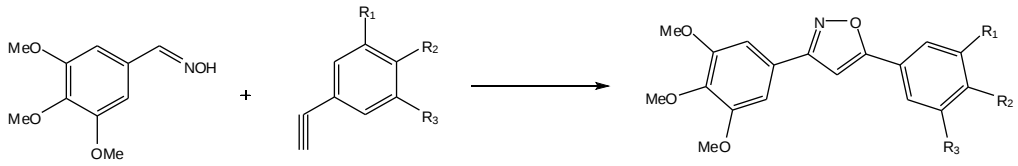


Figure 1.38: Synthesis of isoxazole from alkyne and oxime

1.3.2.4. Synthesis of 5- (3- (2- hydroxyphenyl) isoxazole -5 -yl)– N-phenyl pentanamide:

It can be prepared using the general procedure for the cycloaddition reaction, using alkyne and chloroxime (Conti *et al*, 2010; Vieira *et al*, 2009).

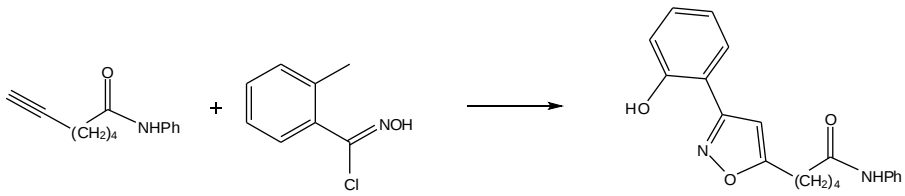


Figure 1.39: Synthesis of Isoxazole from alkyne and chloroxime

1.3.2.5. Synthesis of isoxazoles from 1,3 dicarbonyl:

Treatment of ketoester with hydroxylamine gave isoxazole in moderate yield (Yamamoto *et al*, 2007)

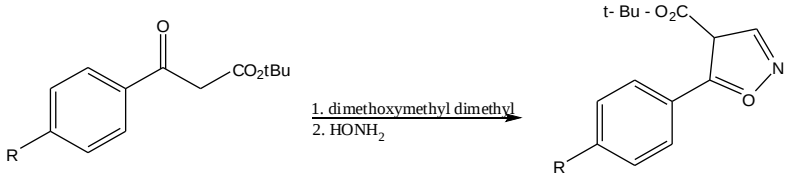


Figure 1.40: Synthesis of LPA antagonistic Isoxazole

In the same way, condensation with hydroxylamine hydrochloride in the presence of KOH yielded isoxazole in 71% (Barcelo *et al*, 2007).

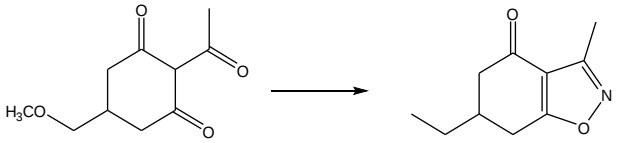


Figure 1.41: Synthesis Isoxazole using $OHNH_2.HCl$

1.3.3 Reactions of Isoxazoles:

1.3.3.1. Direct nitration of Isoxazoles:

A mixture of trifluoroacetic anhydride and fuming nitric acid can be used at low temperature to get a good yield of nitro isoxazole (Katritzky *et al*, 2005).

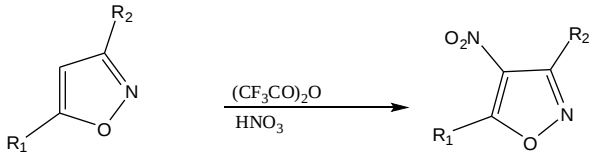


Figure 1.42: Direct nitration of Isoxazoles

1.3.3.2. Synthesis of isoxazole Schiff bases:

It can be produced by the reaction 3-amino- 5-methyl isoxazole with substituted salicylaldehyde (Prashanthi *et al*, 2008).

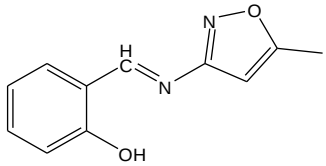


Figure 1.43: isoxazole Schiff base

1.3.3.3. Halogenation of isoxazole

Halogenation of isoxazole give 4-mono-isoxazole by N-bromosuccinimide and microwave irradiation (Joule and Mills, 2010).

1.3.3.4. Isoxazole ring opening reaction

The attempted reaction of KO*t*-Bu with isoxazole at low temperature and in the presence of THF as solvent leads to ring opening (Joule and Mills, 2010).

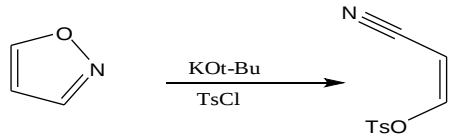


Figure 1.44: isoxazole ring opening reaction

1.3.4. Biological activities of Isoxazoles:

Compounds containing isoxazole ring exhibiting interested and important biological activities. 3,5-diaryl-isoxazole-pyrrolobenzodiazepine showed potent activity against cancer (Kamal *et al*, 2010).

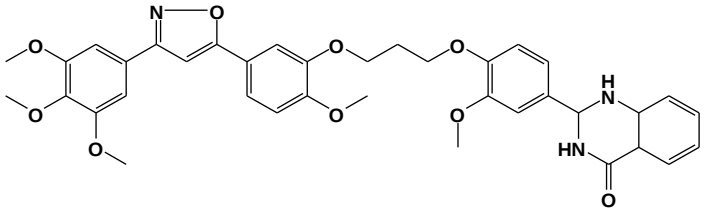


Figure 1.45: anti-cancer isoxazole derivative.

Certain compounds of 2,3,5-substituted perhydropyrrolo[3,4-d]isoxazole-4,6-diones were screened for their antibacterial activities and most of them exhibited activity against *Enterococcus faecalis* and *Staphylococcus aureus* (Agirbas *et al*, 2007).

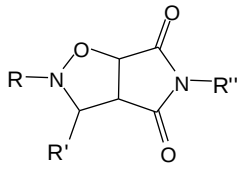


Figure 1.46: Anti-bacterial Substituted perhydropyrrolo[3,4-d]isoxazole-4,6-diones

5- (2,8- Bis (trifluoromethyl) quinolin- 4- yloxymethyl) isoxazole -3 carboxylic acid ethyl ester was reported to have excellent and very specific antituberculosis activity against *Mycobacterium tuberculosis* (Mao *et al*, 2010). Isoxazole analogs of

curcuminoids also showed high activity against multi-drug resistance *Mycobacterium tuberculosis* (Changtam *et al*, 2010).

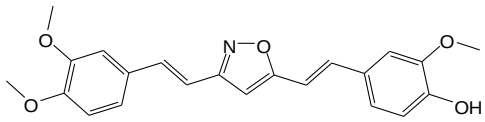


Figure 1.47: Active isoxazole against the multidrug-resistant M. tuberculosis

6-aminomethyl-6,7-dihydro-1 H-indazol-4(5H)-ones and 6-aminomethyl-6,7-dihydro-3-methyl-benzo[d]isoxazol-4(5H)-ones showed good *in vitro* features as typical antipsychotic profile (Barcelo *et al*, 2007)

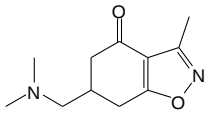


Figure 1.48: Anti-psychotic isoxazole.

[(biphenyloxy)propyl]isoxazole derivatives were exhibited anti-viral activity (Schmidtke *et al*, 2009).

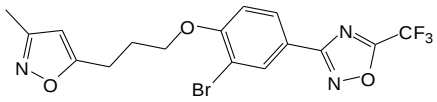


Figure 1.49: Anti-viral isoxazole.

1.4 Chemistry of pyrazoles:

Pyrazoles are five-membered ring system containing two double bonds and two nitrogen atoms adjacent to each other in tautomers form**.**

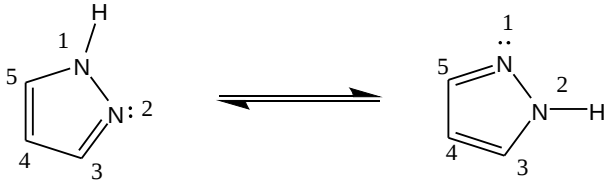


Figure 1.50: Pyrazoles ring and its tautomers

Among heterocyclic compounds pyrazoles forms the core structure of numerous biologically active compounds. It could be anti-cancer or anti-microbial agents for example. It has also high importance in the field of agrochemical (Rostom *et al*, 2011).

1.4.1 Physical properties of pyrazoles

The pyrazole ring is planar, with the maximum deviation of the C (4) and C (5) atoms out of the plane. The pyrazole ring has two nitrogen atoms, one of them participated with its lone pair in the aromatic system of the ring, and it is pyrrole- like. While the other one is a pyridine-like. The hydrogen attached to the nitrogen pyrrole-like is transferred rapidly to the other nitrogen making two tautomers (Katritzky, *et al*, 2001)

1.4.1.1. IR spectral features of pyrazoles:

At the fundamental region the stretching of N-H at 3424–3274 was expected with a broad beak due to hydrogen bonding. Another important assignment is the stretching at about 1500 due C=N at the pyrazole ring.

1.4.1.2. ^{1}H-NMR spectral features of pyrazoles:

The pyrazoles ring has a three types of protons one attached to hetero atoms of nitrogen which has a higher chemical shift, the protons at the carbon 3 and 5 are the same due to tautomerism. The proton at carbon 4 has a lower chemical shift.

δ ^{1}H 13.7

δ ^{1}H 6.25

δ ^{1}H 7.55

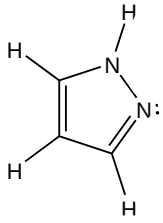


Figure 1.51: The chemical shift of protons of pyrazole ring

1.4.1.3. ^{13}C-NMR spectral features of pyrazoles:

C 3 and 5 have the same chemical shift for the reason illustrated above. The far away carbon 5 from the electronegative atoms has a higher chemical shift, Figure 2.

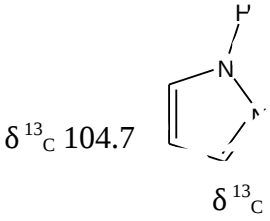


Figure 1.52: The chemical shift of ^{13}C of pyrazole ring

1.4.2 Synthesis of pyrazoles ring system:

1.4.2.1. Synthesis of pyrazoles from chalcones:

Pyrazoles can be synthesized by cyclization of chalcones using hydrazine hydrate or its derivatives (Rostom *et al*, 2011).

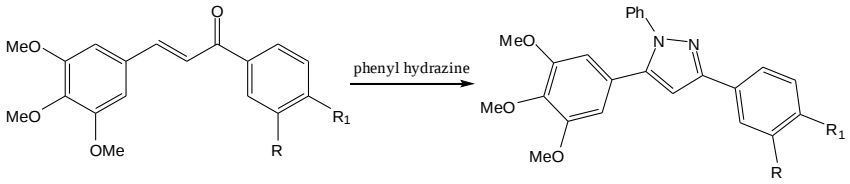


Figure 1.53: Synthesis of pyrazole from chalcone

1.4.2.2. Synthesis of pyrazoles from diketone

It can be prepared from 1,3 diketone and hydrazine hydrate or *p*-substituted phenyl hydrazine (Musad *et al*, 2011).

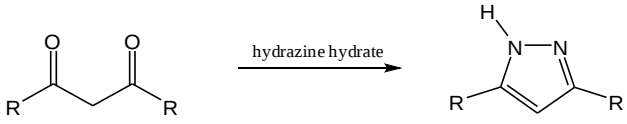


Figure 1.54: Synthesis of pyrazole from 1,3 diketone

Also a greener protocol was described to synthesized the pyrazole in a short period of time using polystyrene supported sulfonic acid (PSSA) as catalyst (Polshettiwar *et al*, 2008).

Figure 1.55: Synthesis of pyrazole using PSSA catalyst

1.4.2.3. Synthesis of pyrazole using microwave irradiation

Pyrazoles can be prepared by the reaction of phenyl hydrazine, aldehydes and ethyl acetoacetate under microwave irradiation (Kumari *et al*, 2012)

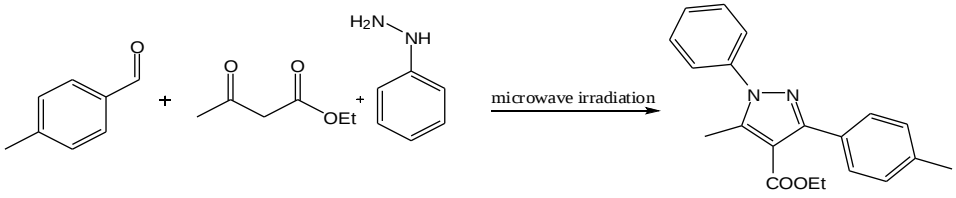


Figure 1.56: Synthesis of pyrazole from ethyl acetoacetate

This reaction can also take place using silica chloride as catalyst (Jawale *et al*, 2011).

1.4.2.4. Synthesis of pyrazole from isoxazole:

The direct transformation of isoxazole into pyrazole can take place by hydrazine in the presence of Ni as catalyst (Sviridov *et al*, 2007).

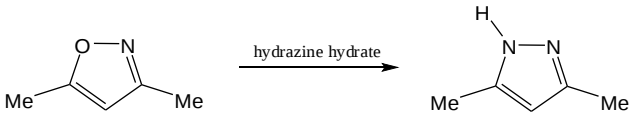


Figure 1.57: Synthesis of pyrazole from isoxazole

1.4.2.5. Synthesis of pyrazole from vinamidinium salt:

Pyrazoles can be prepared from vinamidinium salt and arylhydrazine (Kase *et al* 1998).

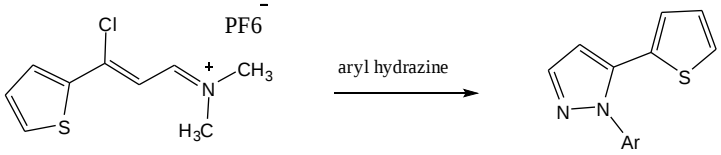


Figure 1.58: Synthesis of pyrazole from vinamidinium salt

1.4.2.7. Synthesis of 5-trifluoromethyl-3-substituted pyrazoles

It can be synthesized from pyridines and hydrazine hydrate under reflux (Krishnaiah and Narsaiah, 2002).

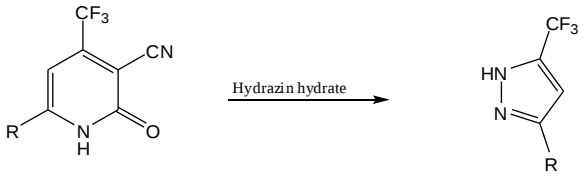


Figure 1.59: Synthesis of pyrazoles from pyridine

1.4.3 Reactions of pyrazoles:

Pyrazole ring has unique chemistry, it could acts as either nucleophile or electrophile, also it could reacts as base or acid making stabilized aromatic cation or anion respectively. The presence of pyrrole-like nitrogen feeds the ring with its lone pair of electrons make it electron-rich, whereas on the other hand the pyridine-like nitrogen lowers the energy of π orbitals, that make the pyrazole have a middle chemistry between pyrrole and pyridine (Shavnya *et al*, 2005)

1.4.3.1. Reaction of pyrazoles with alkyl halide:

Pyrazole reacts with alkyl bromides using acetonitrile or dimethylformamide as solvents with cesium as catalysts to form N- alkyl pyrazole (Velasco *et al*, 2011).

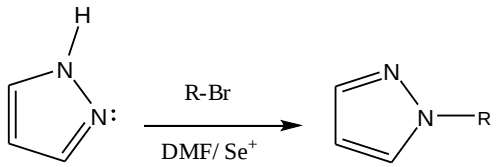


Figure 1.60: Reaction of pyrazole with alkyl halide

1.4.3.2. Reaction of pyrazole with aldehyde:

The treatment of pyrazole below with $POCl_3$ and DMF gave 4- formyl-5-chloro pyrazole in a good yield (Shavnya *et al*, 2005) and in absence of $POCl_3$ ketoform will produced.

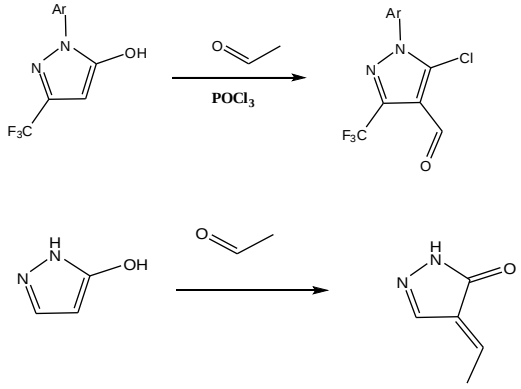
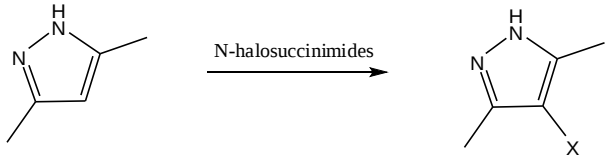


Figure 1.61: Reaction of pyrazole with aldehyde

1.4.3.3. Halogenation of pyrazole:

The 4-halo-3,5-dimethyl pyrazoles can be synthesized in good yields in the absence of a catalyst by the reaction of 3,5-dimethyl pyrazoles with N-halosuccinimides (Stefani *et al*, 2005).



X= Cl, Br or I

Figure 1.62.: Reaction of pyrazole with N-halosuccinimides

1.4.4. Biological activities of Pyrazoles:

The pyrazolo[3,4-d] pyridazinones showed good activity as PDE4 inhibitors which have a wide therapeutic application such as inflammatory and asthma (Biagini *et al*, 2010)

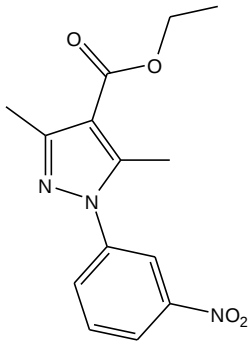


Figure 1.63: PDE4 inhibitors Pyrazole

3- and 4-substituted 5- trifluoromethyl-5-hydroxy-4,5-dihydro-1H-1-carboxyamidepyrazoles were also reported as have anti-inflammatory properties (Sauzem *et al*, 2008)

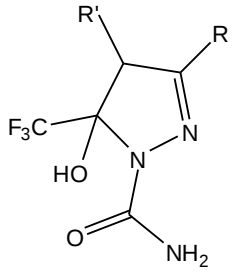


Figure 1.64: Carboxyamidepyrazoles

The steroidal pyrazoles are substrates for bile acid transporters and were showed a potential as drug carriers (Bhat *et al*, 2005).

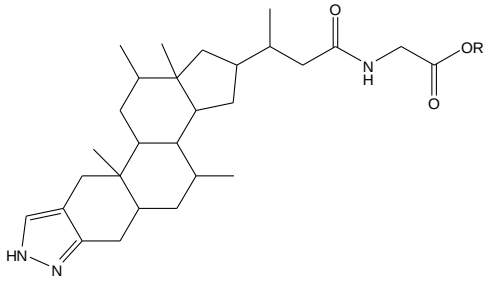
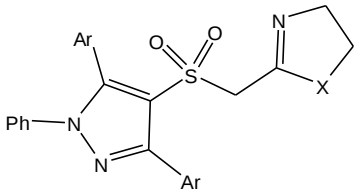


Figure 1.65: Steroidal pyrazole

A series of oxazolyl/thiazolylsulfonylmethyl pyrazoles were showed antioxidant activity (Padmaja *et al*, 2005)



X= O or S

Figure 1.66: oxazolyl thiazolyl sulfonyl methyl pyrazoles

A series of novel 5-[(E)-2-arylvinyl]pyrazoles as antibacterial agents were prepared and showed a good activity (Tanitame *et al*, 2005)

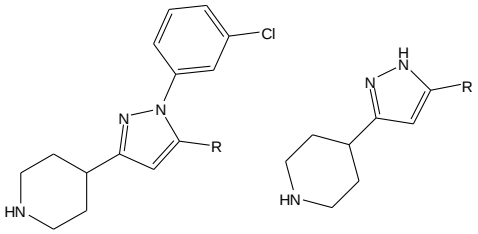


Figure 1.67: Anti-bacterial pyrazoles

5-substituted 1,4-dihydroindeno[1,2-c]pyrazoles were reported as multitargeted receptor tyrosine kinase inhibitors (Akritopoulou-Zanze *et al*, 2007).

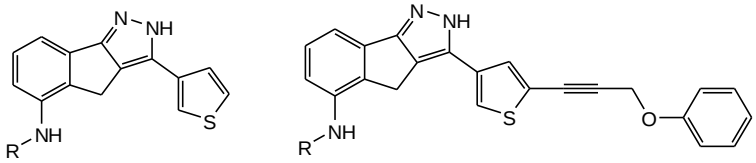


Figure 1.68: Kinase inhibitors pyrazoles

1.5 Aim and Objectives:

Literature review has revealed that five and six membered heterocycles of pyrimidine, isoxazole and pyrazole have shown very wide range of biological activity when they are incorporated in drug molecules.

The most important strategy to make such compounds is built on nucloephiclic addition of reagent to diketone or enone in 2+3 for five membered ring and 3+3 for six membered ring, the reaction need vigorous condition of high temperature and long reaction time. So the acceleration of synthesis of such compounds is highly needed.

The overall aims of this work is to synthesize some pyrimidines, isoxazoles and pyrazoles derived from substituted enone in a microwave and ultrasonic assisted reaction, then to characterize the synthetic compounds using different spectroscopic methods which included infrared, mass, proton nuclear magnetic resonance and ultraviolet-visible spectroscopy.

The achievement of these aims could be achieved by adopting the following specific objectives:

I. To synthesize and characterize a series 1,3-diaryl-1,one-3-en, chalcones.

II. To synthesize and characterize a series of 2-amino 4,6-diaryl pyrimidine, 3,5-diaryl pyrazole, 3,5-diaryl isoxazole.