CHAPTER – II

REVIEW OF LITERATURE

CONTENTS

2.1 CHEMISTRY OF CHALCONES

Sahu et al.[1] showed that Chalcones (1,3-diaryl-2-propen-1-ones) and their heterocyclic analogues, belong to the flavonoid family, which possess a number of interesting biological properties such as antioxidant, cytotoxic, anticancer, antimicrobial, antiprotozoal, antiulcer, antihistaminic and anti-inflammatory activities.

Both functional groups properties are shared by molecules having a carbon-oxygen double bond and a carbon-carbon double bond. In unsaturated carbonyl compounds, the oxygen-carbon double bond and the carbon-carbon double bond are separated only by one carbon-carbon single bond, and both double bonds are conjugated. Chalcones are unsaturated ketones comprised of two aromatic rings with different substituents, [A] and [B]**.** These two rings are joined by a remarkably electrophilic three-carbon unsaturated carbonyl system, creating a nearly planar or linear structure. (Fig.2.1) . Zhu et al.[2] reported the design and synthesis and evaluation of performance towards anti-lung cancer by inducing reactive oxygen species.

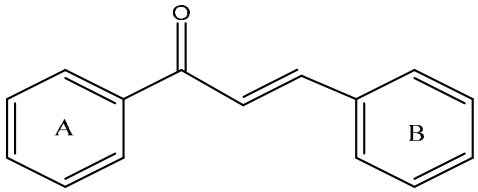


Fig. 2.1: Chalcone Structure

Unsaturated carbonyl systems are a particular class of biologically active chemicals that are mostly used as a building block for the creation of heterocyclic and biodynamic systems. Additionally, it's critical to synthetic and medical organic chemistry. Lin et al.[3] Studied the anti-tuberculosis activity of chalcones.The chalcone is a bichromophoric molecules, which are separated by a keto-vinyl chain and at is a significant group of naturally occurring flavonoids with a wide range of biological roles. Their reactivity is due to presence of a unsaturated keto functional group, which gives them their activity. Chalcones are abundant in nature, particularly in vibrant flowers. Ebenezer at al.[4] reported the Benzimidazole and its derivatives as potent-bioactive substances.

Pyrimidines have intriguing potential as bioactive molecules, heterocyclic compounds containing nitrogen, oxygen, and sulphur have recently received a lot of

attention. Examples of substances with these qualities include pyrazole, benzimidazole, and triazole, which have been shown to have antiproliferative, anti-inflammatory, kinase inhibitory, antibacterial, and anticancer effects. Meanwhile, because of their potential for use as antitubercular, antibacterial, antioxidant, cytotoxic, and anticancer medications, heterocycles containing oxygen as well as sulphur, such benzofuran, benzopyran, and benzothiophene derivatives, have attracted the attention of medicinal chemists. Numerous researchers have concentrated their research on the synthesis of chalcone derivatives using heterocyclic scaffolds due to the broad benefits of organic molecules containing these moieties. With the presence of a heterocyclic ring in the structure, several bioactive chalcones are produced. Due to their remarkable biological activities, these compounds have recently undergone significant development.

In the field of naturally occurring compounds, vibrant compounds are known as Chalcones, Kotahecki and Tambor[5] presented groundbreaking findings. The Greek word "chalcos," which means "bronze," from where this term "Chalcone" originated. Syahri et al.[6] reported a group of naturally occurring compounds known as chalcones has a wide range of characteristics and biological activity.

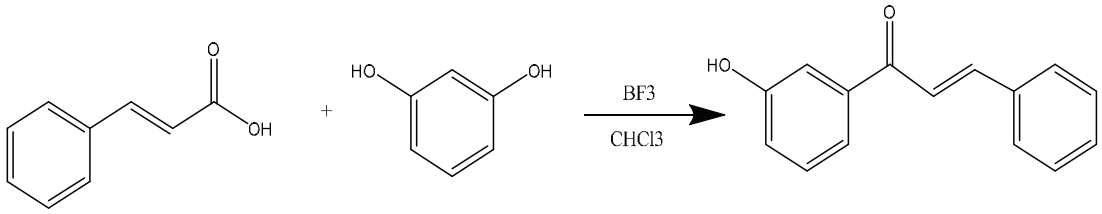
Chalcones are one of the most important classes of natural products existing in many plant species. In nature, they serve as precursors for flavonoids and isoflavonoids biosynthesis. They are 1,3-diphenyl-2-propen- 1-ones (two aromatic rings connected with a carbonyl moiety). According to Shalaby et al.[7], chalcones are crucial flavonoid and isoflavonoid precursors. Many chalcones are prepared by Claisen-Schmidt condensation of methyl ketones with aldehydes in a basic environment[8]. These substances exhibit antimalarial action against variants of plasmodium that are both; chloroquine-sensitive and chloroquine-resistant falsciparum[6]. The synthesis of chalcones was recently reported utilising acetic acid and perchloric acid under acidic conditions[9,10]. Numerous chalcones have been identified as potent tyrosinases as new depigmenting agents since they act as antioxidants and inhibitors[8,11].

All of the chalcones turn pink, when exposed to concentrated H_2SO_4 (a positive Wilson test), and turn violet, when exposed to an alcoholic ferric chloride solution. Chalcones with traces of iodine are heated for two hours in

dimethylsulphoxide (DMSO) produced matching flavones. Chalcones are oxidized with hydrogen peroxide in a methanolic sodium hydroxide solution. These were converted to flavonols, and these flavonols fluoresced conspicuously in ethanolic solution. and concentrated sulfuric acid. Hsueh et al.[12] reported the formation of sulfonyl dihydrobenzo[c] xanthen -7- ones core using double cyclocondensation.

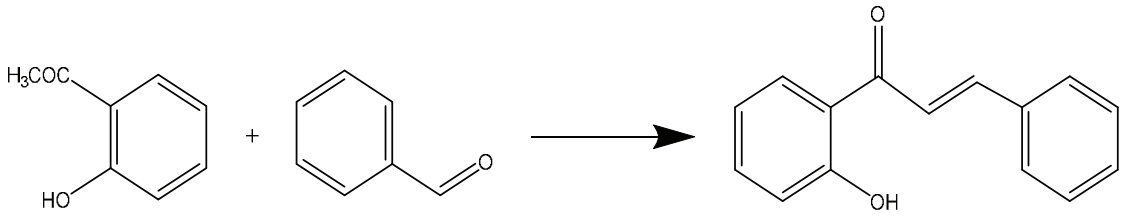
2.2 SYNTHESIS OF CHALCONES

When cinnamic acid and resorcinol are condensed in chloroform in the presence of boron trifluoride (Scheme-2.1)[13,14], chalcone is obtained.



Scheme 2.1

Chalcones play a crucial role as intermediates in the synthesis of pyrazoles, isoxazoles, and pyrimidines. They are created through the catalytic aldol condensation of 2-hydroxyacetophenones with benzaldehydes[15-17]. The 2-hydroxyacetophenone and benzaldehyde can react to afford chalcone in the presence of 0.1 M NaOH (Scheme-2.2)[18,19].



Scheme 2.2

2.3 MEDICINAL IMPORTANCE OF CHALCONES

The 3,4-methylenedioxychalcones have anticonvulsant activity[20], while halosubstituted methylenedioxychalcones have uterotropic, estrogenic, and anti-fertility properties[21]. The 3,4-dimethoxychaleones and its derivatives exhibited antibacterial action[22]. Chalcones with halo, nitro, or amino groups exhibited antibacterial[23], antiviral[24], antifungal[25,26], and anti-allergic activities. Their activity is

increased by the number of hydroxyl substitutions on both rings[27], specifically at positions 2 and 2' or 4 and 4' in chalcones.

The main component of a Chinese medication (the root of *Sophara subprotstrata)*, isoprenyl chalcone sophradin, and its synthesised analogues were found to be efficient anti-ulcer agents[28]. The 2',4'-dihydroxy-3'-methoxychalcone promoted *Pitysaranima calomelaons* spore germination at lower doses and reduced it at higher concentrations[29]. A benzofuranylehalcone called mecinarone has vascular and cardiac effects[30]. While 2',4'-dihydroxy-3',6'-dimethoxy chalcone, isolated from *Polygonum senegalense*, exhibited molluscicidal activity[31].

Certain 2',4'-dihydroxychalcones have been found to have anthelmintic activity also[32]**.** The 3, 4, 2', 6'-tetrahydroxychalcones and their methoxy derivatives have lower capillary fragility[33]. Dihydrochalcones have antimicrobial properties and these can be used to treat coronary insufficiency and cardiac arrhythmia[34,35]. It was revealed that naphthylchalcones have a germicidal effect[36]. Dihydrochalcones have been found to hinder plant growth[37]. The chalcones (flavokawains) isolated from pepper (*P. methysticum*) have been found to exhibit amoebic activity[38]**.** It has been proved that 7, 8-dihydrochalcones have antithyroid effects. The 2,4,4'-trihydroxy and 2,4,4',6-tetrahydroxychalcones have demonstrated effective antitumor activity[39].

A number of novel iodochalcones, flavones, and other chemicals were synthesised by Mokle et al.[33]. Research on flavonols' *in vivo* antibacterial activity is little encouraging. It was shown that a number of substances were more effective than tetracycline. A variety of hydroxychalcones were synthesized and evaluated by Sabzevari et al.[34] for a capacity to combat cancer. Every hydroxychalcone breaks down the mitochondrial membrane by reducing hepatocyte GSH and oxidizing it to GSSG with improved potential and absorption of oxygen. A variety of aryloxypropanolamines were synthesized by Pratap et al.[35]. Chalcones were investigated for antihyperglycemic effectiveness in mice that were either sucrose-laden (SLM) or not (NSL). Streptozotocin was used to create diabetes in the animal (STZ).

The antibacterial activity of various 4-hydroxychalcones and 4-carboxychaIcones was investigated by Kromann et al.[36] who discovered that the carboxychalcones have more antibacterial activity than the parent phenol molecule

(due to their greater aqueous solubility). Lin et al.[37] synthesized a number of chalcones using the Claisen-Schmidt condensation method and tested them for anticancer and anti-inflammatory properties. Strong cytotoxic and anti-inflammatory activities were reported to be present in 2-hydroxychalcones and 2',5'-dihydroxychalcones.

Numerous tetrahydroxychalcones were prepared by Khatib et al.[38] and tested for their capacity to inhibit tyrosinase. It was discovered that two chalcones, 2,3,3',4'-tetrahydroxychalcone and 2,4,2',4'-tetrahydroxychalcone, significantly inhibited tyrosinase. Churkin et al.[39] showed biologically active thiophene derivatives. IV. Synthesis and antiviral activity of unsaturated ketones of the thiophene series. Choudhury et al.[40] identified eight chalcones, dihydrochalcones, and flavones from *Flemingia chappar*. The maximum antifungal activity of 2',4'-dihydroxy-dihydrochalcone was seen *in vitro* against *Curvularia lunata, Atlemaria solani*, and *Helminthosporiim oryzae*.

Several chalcone compounds, with anti-inflammatory and capillary strengthening activities were synthesized by Oganesyan et al.[41]. A class of anti-seborrheic chalcones was prepared by Hinrich et al.[42]. Chalcones stop neutrophils from releasing lysosomal p-glucuronidase[43].

The antibacterial and antifungal activity of several chalcones and flavones was examined by Vibhute and Wadje[44], who discovered that every chalcone and flavone tested was both antibacterial (against *Xanthomonas oryzae* and *Xanthomonas citri*) and antifungal (against *Altemaria tenuis* and *Curvularia lunata*). It was discovered that hydroxy derivatives effectively inhibited bacteria and fungi both. Herbicide chalcone compounds containing triazolyl or imidazolyl substituents were prepared by Lewis et al.[45]. Five of the thirteen phenanthryl and naphthylchalcones were produced by Misra et al.[46] were germicidal. Chalcones inhibited the development of *Diplodia maydis* in liquid cultures has been reported by Ray et al.[47]. Two chalcones counteract ascorbic acid's effects on suppressing hypocotyl growth in *Amaranthus caudatus* seedlings[48]**.** The cytosolic epoxide hydrolase enzyme was successfully inhibited by chalcone oxide derivatives that had a single p-substituent on either phenyl ring[49].

Iwata et al.[50] reported that 3-hydroxy chalcones with a methyl group in the 3',4',2'-positions and isoliquiritigenin homologs had strong inhibitory activities in

phosphorylation which implied antitumorigenic characteristics. Almeida et al.[51] showed identification of a chalcone molecule with best binding energy after molecular docking calculations.

Iwata et al.[52] reported that some chalcones are capable of phototransforming in solution from ferrous to cis isomers. The isomerization of 3-hydroxy-3'-methyl chalcone from trans to cis was found to occur under the influence of daylight in a methanolic solution. The presence of a hydroxy group in the 2- or 4- position of the trans chalcone structure prevents phototransformation into the cis-isomer. The phototransformed cis-3-hydroxy-3'-methyl chalcone had greater antitumorigenic activity than the original trans form. Nielsen et al.[53] synthesized a large number of substituted chalcones and tested them for their ability to inhibit lymphocytes and fight leishmaniasis and found that the steric interactions between the chalcones and the target are essential for compound potency. Chalcone derivatives inhibited the synthesis of denovo inducible nitric oxide synthase and cylcooxygenase-2, suggesting that they may be used to treat inflammatory diseases[54]. It has also been demonstrated that several chalcone chemicals inhibit famesyl protein transferase.

Chalcones can obstruct the development and function of effector cytotoxic T lymphocytes[55]. A chalcone derivative having a 3,4-dihydroxycinnamoyl structure is 3,4-dihydroxychalcone. The 3,4,2'-trihydroxychalcone, 3,4,2-dihydroxychalcone, and 3,4,2',4'-tetrahydroxychalcone were ten times more effective than cyclo-oxygenase activity at suppressing epidermal 12-lipoxygenase activity. Both enzyme activities were minimal or not at all affected by the chalcone derivatives with a cinnamoyl or 4-hydroxycinnamoyl structure in the molecule. Chalcone oxides block the activities of glutathione 5-transferase and cytosolic epoxide hydrolase by binding to an active location where the chalcone's carbonyl group interacts with an acidic area known to be crucial for initiating epoxide hydrolysis[55,56].

Chalcones are useful probes for comparing secretory events because they restrict the release of histamine by human basophils, when they are triggered by various stimuli. At doses, larger than 0.5 mM, chalcone and its derivatives, in particular 4-hydroxychalcone, hindered the mitochondrial electron transport system as powerful uncouplers of oxidative phosphorylation. Analogues of chalcone thiophene had only moderate antiviral activity. Adenosine-3',5'-cylcic monophosphate

phosphodiesterase was inhibited by prenyl chalcones and Diels-Alder adducts of mulberry tree chalcones in medicinal plants[40]. The cytosolic epoxide hydrolase activity in the liver is suppressed by chalcones, p-naphthoflavones, and a-naphthoflavones. Chalcone, quercetin, and fisetin were the most effective and membrane-permeable inhibitors of histamine release from human basophils. A variety of chalcones were developed by Oganesyan et al.[41]. They also investigated the relationship between anti-inflammatory and hypoglycemic actions.

Chalcones have been demonstrated to inhibit thyroxine-5'-deiodinase, causing them to have anticancer effects[56]. The virus is rendered inactive by a chalcone that has been found to be specifically active against human rhinoviruses[57] by binding with a particular region on the viral capsid protein. The molluscicidal activity of 24 chalcones and 12 chalcone epoxides was examined by Adewunmi et al.[58]. The epoxides had little impact compared to the chalcones, which were extremely powerful against Biomphalaria glabrata.

Two active chalcones from *Glycerrhiza uralensis*, liqueritigenin and isoliquiritigenin inhibited rat liver mitochondrial monoamine oxidase[59] (MAO). The reason is that the second molecule was more effective than the first, MAO inhibition was substrate-competitive. In mouse and rat liver, 4-phenylchalcones, chalconeoxides, and related compounds were made and tested for their ability to inhibit GST and cytosolic epoxide hydrolase, which resulted in a concentration-dependent decrease in tumor-promoter-induced histamine release[60]. The cytosolic epoxide hydrolase was inhibited by a number of substances more effectively than the parent chemical, 4'-phenylchalconeoxide, although the inhibition was decreased by the presence of bulky substituents in the 4th and 2nd positions. While chaleones were found to be inhibitors of cytosolic GST acting on cw-stilbene oxide, chalcone oxides were revealed to be selective inhibitors of cytosolic epoxide hydrolase acting on mms-stilbene oxide.

A group of chalcone compounds were prepared by Mehta et al.[61], a new class of antimitotic medications that can be used to treat gout. Chaleones antiviral action was shown by their ability to bind to the hydrophobic pocket-corresponding region of the viral protein VPI P-baorel of HRV[62]. The antifeedent activity of chaleones from the genera *Lonchocarpus* and *Tephrosia* against larvae of Spodoptera littoralis and

Spodoptera exempt was examined by Simmonds et al.[63], and reported a link between the activity and the molecular structure of the compounds was.

The possible conversion of flavones to 2'-hydroxychalcones was associated with the antiallergic effect of 2'-hydroxychalcones[64]. Several chalcones inhibited the gastric H*, K+ - ATP ase and Na+, K+ - ATP ase enzymes in comparison to the inhibition brought on by sophradin and sofalcone[65]. It was reported that chalcones prevented 74% of the liver damage caused by galactosamine[66] even at higher doses (5000 mgKg-1). Nematollahi et al.[67] reported recent advancements pertaining to the antibacterial, antiviral, antiparasitic, and antifungal activities of chalcones and their derivatives are deliberated, focusing on the relevant mechanisms of action, crucial challenges, and future prospects. Collins-Burow et al.[68] suggestsed that phytochemicals affect multiple signaling pathways that converge at the level of transcriptional regulation. The ability of flavonoids to regulate MAPK-responsive pathways in a selective manner indicates a mechanism by which phytochemicals may influence human health and disease. Liu et al.[69], assessed the responses of the flavonoid pathway to UV-B radiation treatments and its correlation to the lipid peroxide and antioxidant systems in C. mongolica. In UV-B radiation experiments, plants were exposed to UV-B radiation treatments with a intensity of 30 J/s for 1, 4 and 24 h, respectively

Licochalcone, which was obtained from an ethanol extract of dried Chinese licorice roots, inhibited Leishmania major's development both in vitro and in vivo by alkylating the thiol group in N-acetyl-L-cysteine. The 2-hydroxychalcone inhibited glutathione-S-transferase isoforms, and this inhibition is reversible. Chaleones decreased the amount of reactive oxygen species that human neutrophils released by interfering with the membrane N-iMet Leu Phe (FMLP) receptor[70]. Yuan et al.[71] represented the first report of the natural phenylpropanoid-dihydrochalcone hybrid compound, and lays foundation for the study on the bioactive principles of the ethnic hypoglycemic medicinal plant. Janković et al.[72], studied to test antioxidative potency of chalcones in *in vitro* model in serum (native conditions), so as with exogenously induced oxidative stress. Tao et al.[73], studied that pyrene based chalcone derivatives possess the potential for optical data storage and optical limiting. Moreover, our study further proved the superiority of ISRE on enhancing the TPA of nonlinear materials.

Phrutivorapongkul et al.[74] found novel chalcone derivatives from the stem bark of *Millettia leucantha* (leguminosae), where dihydrochalcones showed only minor anti-herpes simplex virus (HSV) activity. Numerous chalcones were prepared by Climent et al.[75] and it was found that they exhibit anti-inflammatory, anti-cancer, and diuretic characteristics. Chalcones were synthesised by Lunardi et al.[76] and found to be leishmanicidal and trypanocidal *Leishmania brasiliensis* and *Trypanosoma cruzi's in vitro* growth were suppressed by all these compounds, where tested at various concentrations with no discernible harm to host macrophages.

A new enaminone synthon was employed to prepared a number of retinoid-like chalcones[77-81] as well as other licochalcone A derivatives. These new compounds have been tested *in vitro* as potential antimalarial medications. They exhibited a potent and consistent inhibitory action on the *in vitro* growth of *Plasmadium falciparum*. Several analogues trapped in the Z- or E- state were examined for anti-plasmodial action[82-85]. Kidwai et al.[86] synthesized base catalysed pyrimidine using microwave. Jagir, Mukut et al.[87], a facial microwave-induced one-pot synthesis of novel pyrimido [4,5-d] pyrimidines and pyrido [2,3- d] pyrimidines under solvent-free conditions. Nagaraj et al.[88], a series of novel bis-chalcones 3 were prepared by the reaction of 5,5′-methylene-bis-salicylaldehyde 2 with various acetophenones, subsequent treatment of 3 with thiourea or guanidine resulted to the corresponding bis-thiazines or bispyrimidines in good yields. All the new compounds have been characterized by IR, ^{1}H NMR, MS and elemental analysis. The antibacterial, antifungal and anti-inflammatory activities of the compounds have also been evaluated. Adib et al.[89], a simple and efficient synthesis of 2,4,6-triarylpyridines is described from a novel reaction between chalcones and ammonium acetate under solvent-free conditions in excellent yields. Wu et al.[90] showed the silica gel-catalyzed synthesis of 5-amino-2-aryl-3H-chromeno [4,3,2-de][1,6] naphthyridine-4-carbonitriles and 5-amino-2-aryl-3H-quinolino [4,3,2-de][1,6]naphthyridine-4-carbonitriles were simply achieved upon the one-pot cascade reaction of malononitrile with substituted 2-hydroxyacetophenone (or 2-aminoacetophenone) and aromatic aldehyde in aqueous media.). Ramesh et al.[91] showed to select substituents by using Topliss modified approach to synthesize new 1,3 oxazines with antimicrobial effect. In the series of 6-[4-substitutedphenyl]-4-phenyl-6H-1,3-oxazin-2-amines and N-[6-(4-substitutedphenyl)-4-phenyl-6H-1,3-oxazinyl] acetamides, substituents at fourth

position of the phenyl ring were selected according to the Topliss modified approach and the initial set of compounds was synthesized. The antimicrobial screening revealed that compounds with methoxy substituent having negative sigma (-0.04) and negative pi (-0.27) values are good antimicrobial agents showing low minimum inhibitory concentration (MIC). Mamoru et al.[92], various 2-alkylthio-1,3-thiazine derivatives were synthesized by the reactions of S-alkylthiocarbamates with α,β-unsaturated ketones in the presence of BF 3· Et 2 O. The thiazine was converted into two isomeric dehydrated products in the presence of a Lewis acid. Waterinckx et al.[93], new, efficient, and straightforward synthesis of 3-arylmethyl-4-chloromethyl-2-imino-1,3-thiazolidines and 2-(N-acylimino)-3-arylmethyl-4-chloromethyl-1,3-thiazolidines has been developed by ring transformation of 1-arylmethyl-2-(thiocyanomethyl) aziridines upon treatment with a catalytic amount of titanium(IV) chloride in dichloromethane. Van Allan et al.[94], prepared a certain pyrylium salts by using chalcone and boron trifluoride etherate. Mcnaught[95], the systematic name of a compound is designed so that one may deduce from it, the molecular structure of the compound, as indicated by its graphic formula. In other words, it is essentially a verbal substitute for the graphic formula and, in its most elaborate form, provides precisely the same structural information. This chapter provides a guide to the nomenclature of heterocyclic compounds. Houben-Weyl Methods of Molecular Transformations. Hetarenes and related ring systems: Six- Membered Hetarenes with two identical Heteroatoms covering research of Peptide and peptidomimetic,five membered hetarenes with one chalcogen and one heteroatom. Ullmann's Encyclopedia of Industrial Chemistry is the benchmark reference in chemistry and chemical and life science engineering, covering inorganic and organic chemicals, advanced materials, pharmaceuticals. Heterocyclic compounds play a vital role in the metabolism of living cells. Their practical applications range from extensive clinical use to fields as diverse as agriculture, photography, biocide formulation and polymer science. Modern heterocyclic chemistry covering heterocyclic compounds synthesis, structure and chemical and physical properties.[96-102]

2.4 INTRODUCTION TO PYRIMIDINE

The 6-membered heterocyclic compounds with two hetero atoms containing two or more fused rings are of our main concern because of their wide applications.

Pyrimidines are 6-membered heterocyclic compounds, containing two nitrogen atoms at positions 1 and 3 of the six membered rings.

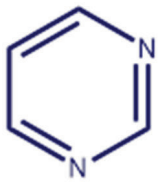


Fig. 2.2

It has a formula molecular $C_4H_4N_2$and its molecular weight is 80.088 g mol^{-1}. It is a colourless compound, having melting point 20- 22.5°C and boiling point 123-124°C. It is weak base (pKa = 1.23) that forms a number of solid derivatives such as hydrochloride, methiodide and its λ_{max} value is 240 nm.

The reactivity of pyrimidine ring is approximately equivalent to that of 3-nitropyridine. The electrophilic substitution reactions are difficult as compared to nucleophilic substitutions. Because of weak basicity of nitrogen, the electrophilic reagent attack is more difficult on pyrimidine ring but in presence of activating groups, the electrophilic attack becomes feasible and takes place at 5^{th} position of the ring. The unsubstituted pyrimidine undergoes 5-halogenation under vigorous conditions, but it becomes easier, when one or more activating substituent are present.

2.5 SOME IMPORTANT NATURALLY OCCURRING DERIVATIVES OF PYRIMIDINE

Pyrimidines are essential for any form of life because it is an important pharmacore. Being integral part of DNA and RNA, it interacts with the synthesis and functions of nucleic acids. Ortic acid, is thought to be the key precursor in the biosynthesis of all naturally occurring pyrimidines. It has been used in combination with 4-amino-5-imidazole carboxamide for the treatment of liver disease. Uracil, is a constituent of nucleic acid and widely distributed in nature. It is excellent starting material for the preparation of pyrimidines, pteridines and purines. Thymine, is not found in ribonucleic acid but present in deoxyribonucleic acid. Alloxan, induces permanent diabetes in many animals, but not in humans. Cytosine, is widely distributed in nature being a constituent of nucleic acid and it can be isolated by hydrolyzing thymus nucleic acids.

Thiamine, (vitamin B_1), is a water-soluble vitamin of the B-complex family. Its structure consists of aminopyrimidine and a thiazole ring linked by a methylene bridge. The thiazole is substituted with methyl and hydroxyethyl side chains. All living organisms use thiamine, but it is synthesized only in bacteria, fungi and plants. Adenine, is a nucleobase and chemical component of DNA and RNA. The shape of adenine is complementary to either thymine in DNA or uracil in RNA. Uric acid, is the product of the metabolic breakdown of purine nucleotides. Guanine is one of the four main nucleobases found in the nucleic acids and derivative of purine consisting of fused pyrimidine-imidazole ring system with conjugated double bonds.

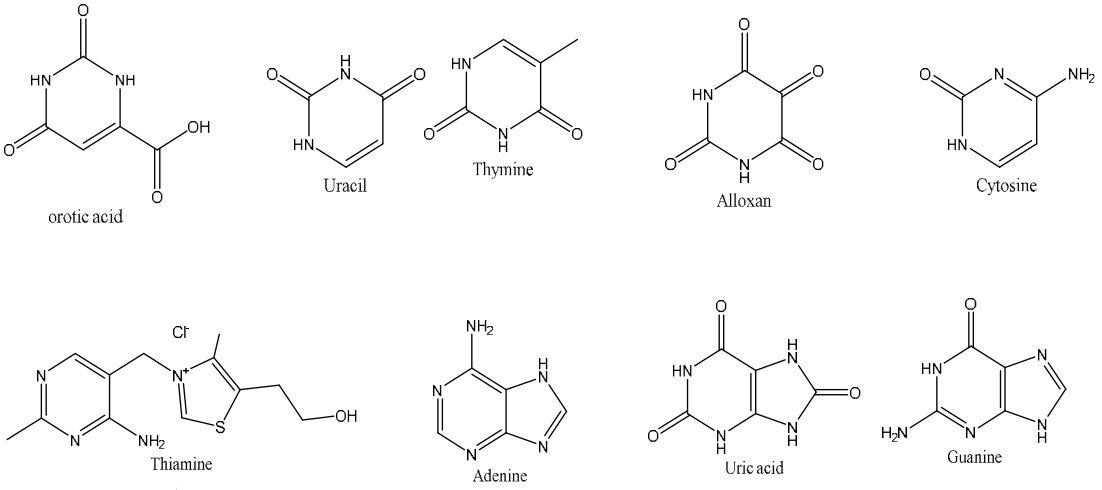


Fig. 2.3

Certain pyrimidine derivatives are also used as agrochemical and dyes industries. In agrochemical, such as bensulfuron- methyl is used as systemic herbicides that inhibit biosynthesis of the essential amino acids valine and isoleucine; Nuarimol is systemic fungicide that acts by inhibiting ergosterol biosynthesis and it is used to control a wide range of pathogenic fungi, such as powdery mildews on fruit. Pyrimidine is also used in dye industries as isoindoline pigments (Pigment yellow) for the coloration of paints and plastics.

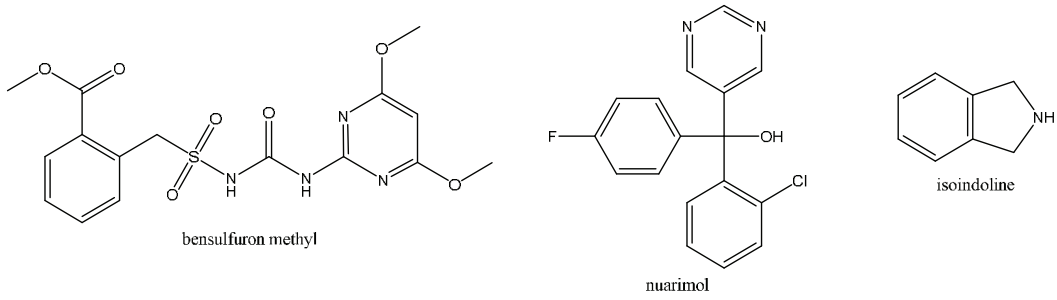


Fig. 2.4

Heterocyclic compounds, pyrimidines are one of the most important heterocycles with remarkable pharmacological activities because it is an essential constituent of all cells and thus all living matters. Pyrimidines have occupied a unique place and remarkably contributed to medicinal chemistry. There are very important class of pharmaceutical compounds. The various compounds such as alkaloids, essential amino acids, vitamins, haemoglobin, hormones, large number of synthetic drugs and dyes contain pyrimidine heterocyclic ring systems. The presence of pyrimidine nucleus in the compounds enhances their medicinal and biological activities. The several pyrimidine nucleoside analogues have been developed as antiviral agents: AZT is the most widely used anti-AIDS drug; stavudine, which is effective in the treatment of HIV infections and AIDS and lamivudine, which is used to treat both hepatitis B and AIDS.

2.6 BIOLOGICAL ACTIVITY OF PYRIMIDINE BASED COMPOUNDS

Because of their biological relevance, pyrimidines is the topic of a lot of synthetic activity. The pyrimidine nucleus can be found in a variety of natural products that are essential to biological processes and living creatures. Pyrimidine derivatives have a long history in medicinal chemistry because of their therapeutic potential. Several pyrimidine derivatives have been created as chemotherapeutic medicines over the last three decades and have found widespread clinical use. Some biologically important pyrimidine-based derivatives are;

2.6.1 ANTIMICROBIAL ACTIVITY

Abdel-Gawad et al.[103] synthesised various novel pyrazolo [3,4-d] pyrimidines and tested their antibacterial and antifungal properties *in vitro* at 100 pg mL^{-1} using

ampicillin and elaforam as reference compounds. Ismail[104] synthesised certain sulfur-containing pyrazolo [3,4-d] pyrimidines, and some of these compounds exhibited antimicrobial action, when compared to typical antibacterial and antifungal agents, chloramphenicol and terbinafine.

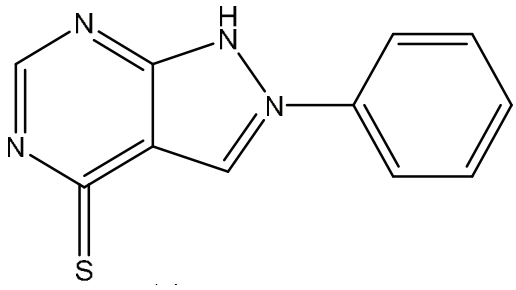


Fig. 2.5

Condensed pyrimidine derivatives were produced by Ashok et al.[105], *S. aureus*, *S. typhi*, *E. coli*, *B. subtilis*, and *S. cervisiae* were all evaluated with these chemicals.

Khatri et al.[106] produced various new amino pyrimidines and tested their antibacterial efficacy against gramme positive, gramme negative, and antifungal organisms such as *Aspergillus niger*.

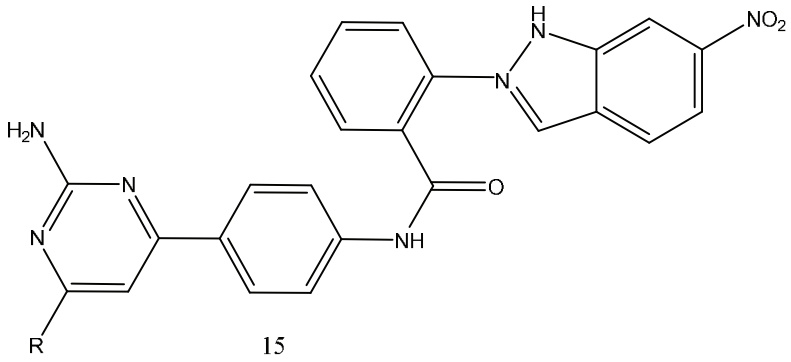


Fig. 2.6

Oyama and Ito[107,] electrophilic cyclization via the boronate complex between various homoallylic boronates and Selectfluor is reported. This reaction provided a fluoromethylated cyclopropane ring that was difficult to synthesize by previous methods. The use of phenyl lithium, which activated the homoallylic boronate, was important for the reaction.

Bodke et al.[108] prepared some novel benzofuro [3,2-d] pyrimidines, which were tested for their antibacterial and antifungal properties. Nimavat et al.[109] synthesised a series of 1,6 dihydro-2-mercapto-4-aryl-6-(3'-bromophenyl)-pyrimidines, all of which exhibited significant antibacterial action.

Some 5H-pyrazolo [3',4':4,5] thiazo[3,2-a] pyrimidines were synthesised by Sherif et al.[110] and some of these compounds demonstrated antibacterial action. antibacterial thienopyrimidine compounds were prepared by Shah et al.[111]. Thakral et al.[112] synthesised pyrido [2,3-d] pyrimidines. Their antibacterial and antifungal activity was tested which was found to be modest.

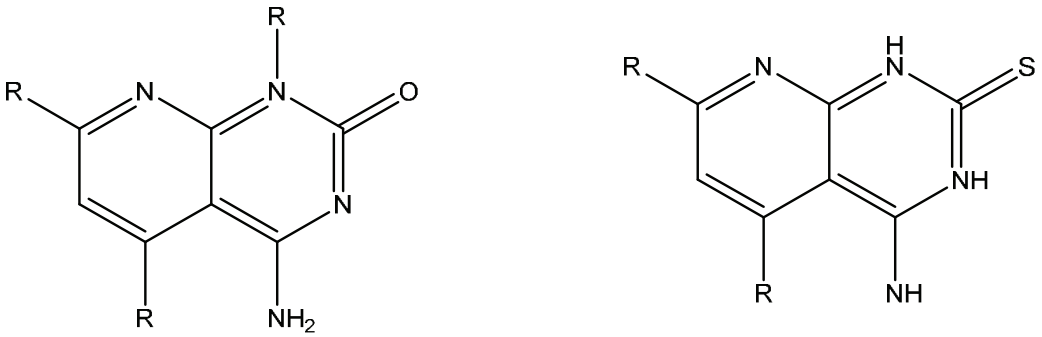


Fig. 2.7

New pyrimidine derivatives were synthesised by Dhokale et al.[113]. The antibacterial activity of the compounds created was moderate.

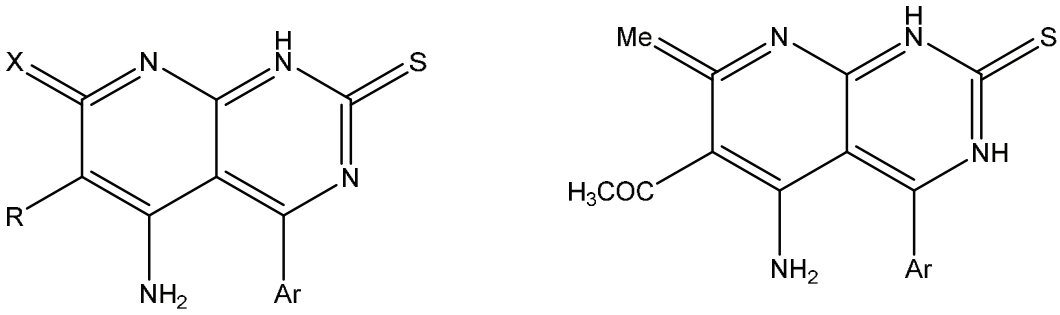


Fig. 2.8

Some pyrido [2,3-d] pyrimidines were synthesised by Bedarir et al.[114]. Some of these compounds were shown to have antibacterial properties. Novel thiazolo [4,5-d] pyrimidines were synthesised by Balkan et al.[115]. The microdilution method was used to test them against bacteria and yeasts. New pyrimidine and pyrazolo [3,4-d]

pyrimidine derivatives were synthesised by Zhang et al.[116]. The antibacterial activity of all of these produced compounds was evaluated *in vitro*.

Eissa et al.[117] prepared a novel class of tetrahydro benzothieno pyrimidines and C albicans was used to evaluate activity of synthesised compounds, as well as against a variety of gram-positive and gram-negative bacteria. Their MIC was found. Ibrahim et al.[118] prepared thiazolo [4,5-c] pyrido [1,2-a] pyrimidines with potent antibacterial properties. Innocenti et al.[119], Fused pyrimidine cores are privileged kinase scaffolds, yet few examples of the 2-amino-pyrido[3,4-d]pyrimidine chemotype have been disclosed in the context of kinase inhibitor programs. Furthermore, no general synthetic route has been reported to access 2-amino-pyrido[3,4-d]pyrimidine derivatives and reported a versatile and efficient chemical approach to this class of molecules. Strategy involvesed the concise preparation of 8-chloro-2-(methylthio)pyrido[3,4-d]pyrimidine intermediates and their efficient derivatisation to give novel compounds with potential as kinase inhibitors.

Patel and Mehta[120] synthesized 2-amino-4-substituted-phenyl-6-(8-quinolinol-5-yl) pyrimidines with moderate to powerful antibacterial activity.

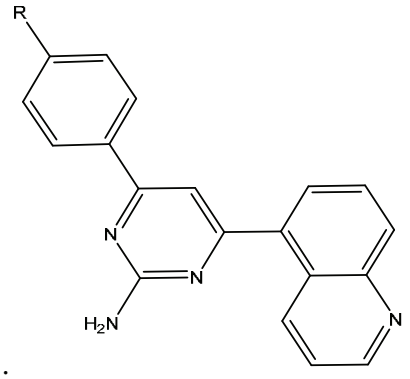


Fig. 2.9

New pyrimidine derivatives with antibacterial action were synthesised by Verma et al.[121].

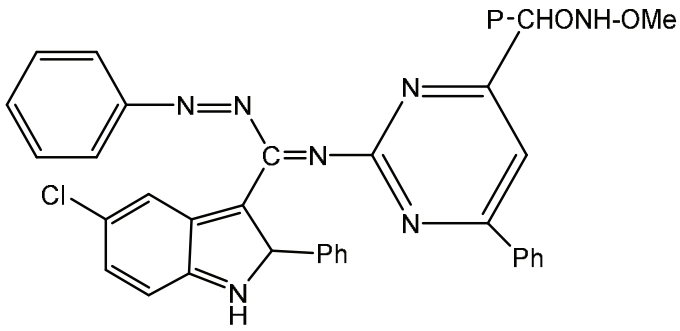


Fig. 2.10

2.6.2 ANTICANCER ACTIVITY

Some 5H-pyrimido [3',2':5,6] thipyrano [4,3-d] pyrimidines were synthesised by Primofiore et al.[122]. An *in vitro* assay on human tumour cell lines was used to investigate the antiproliferative efficacy of these drugs (HL-60 andHelA). These fluorinated thiazolo [4,5-d] pyrimidines were synthesised by Fahmy et al.[123]. The chemicals were found to be active on 60 human cell lines.

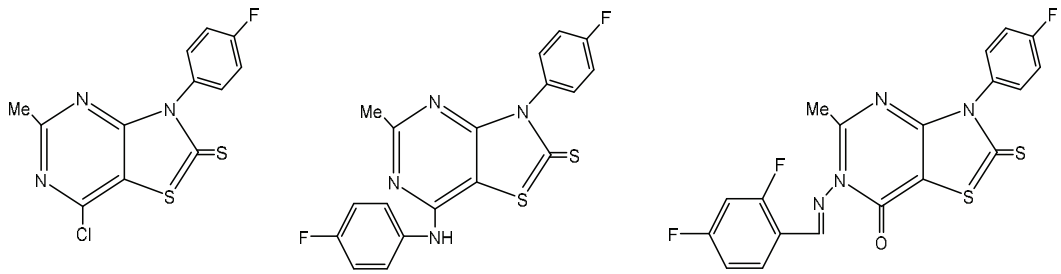


Fig. 2.11

Some 3,4-dihydro-lH-pyrimidine-2-ones were synthesised by Schroeder[124] **.** They showed dual FGFR/VEGFR tyrosine kinase inhibition capability. A series of pyrido [2,3-d] pyrimidines were synthesised by Veanch et al.[125]. These have substantially stronger anticancer properties. Donkor et al.[126] prepared a new class of 6-substituted-2,4-diaminothieno[2,3-d]pyrimidines and listed for *P. carinii*, *T. gondii*, and *M. avium*. These drugs were found to block dihydrofolate reductase.

Some pyrazolo [3,4-d] pyrimidines were synthesised by Kim et al.[127]. The anilino compounds outperformed 4-benzyl compounds in terms of inhibitory efficacy in this series. The 2,4-diamino pyrrolo[2,3-d]pyrimidine derivatives were synthesised by Rosowsky et al.[128]. They are dihydrofolate reductase inhibitors in *P. carinii*, *T. gondii*, and *M avium*. Burchat et al.[129] synthesized pyrazolo [3,4-d] pyrimidines and pyrrolo[2,3-d]pyrimidines. These chemicals are strong kinase inhibitors. Fluorinated

thiazolo [4,5-d] pyrimidines were synthesised by Fahmy et al.[130]. The NCI selected nine of these newly produced drugs for *in vitro* anticancer testing.

Babu et al.[131] prepared new substituted pyrimidines containing benzofurans, all of which had anticancer action.

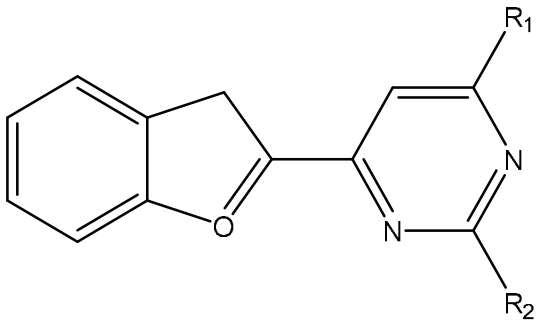


Fig. 2.12

Some 2-anilino-4-(lH-pyrrol-3-yl) pyrimidines were produced by Wang et al.[132] shown anti-cancer action.

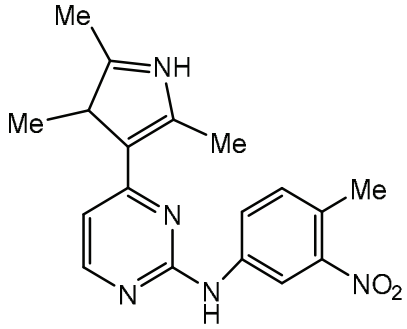


Fig. 2.13

Deasi et al.[133] reported a series of pyrimidino [2,l-c][l,2,4] triazin-8-ones and l,2,4-triazolo[4,3-a]pyrimidine-7-ones. These two compounds were found to have potent anticancer properties.

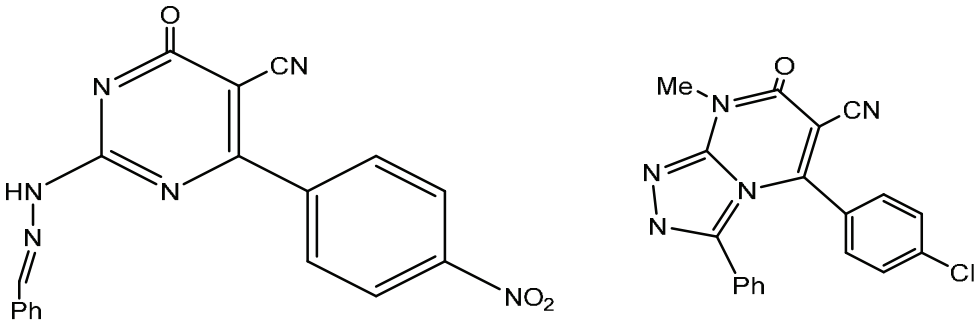


Fig. 2.14

2.6.3 ANTI-TUBERCULAR ACTIVITY:

Moukha-chafiq et al.[134] prepared 4-substituted l-[l-(2,3-dihydroxy-lpropoxy) methyl-1,2,3- triazol- (4 and 5)-yl-methyl] l-[l-(2,3-dihydroxy-lpropoxy) methyl-1,2,3- triazol- (4 and 5)-yl-methyl]. The anti-tubercular action of -lH-pyrazolo [3,4-d] pyrimidines was found to be modest.

Nimavat et al.[135] synthesized and tested 2-amino-4(31-bromophenyl)-6-arylpyximidines for anti-tubercular action. Pathak et al.[136] prepared and tested 2-thiosubstituted pyrimidines against different Mycobacteria TB strains. Some 2-amino-4,6-substituted pyrimidines and 2-mercapto-4,6-disubstituted pyrimidines were synthesised by Abd EI-Fatah et al[137]. These have a negligible anti-tubercular effect. The N-,S-, and o-mononitro- and dinitro benzyl derivatives of nitrogen heterocycles were produced and tested against *Mycobacterium tuberculosis* by Koci et al.[138].

Pasha et al.[139] prepared antitubercular 2,6-disubstituted pyrimidine-2-thiones and 2- amino-4,6-disubstituted pyrimidines.

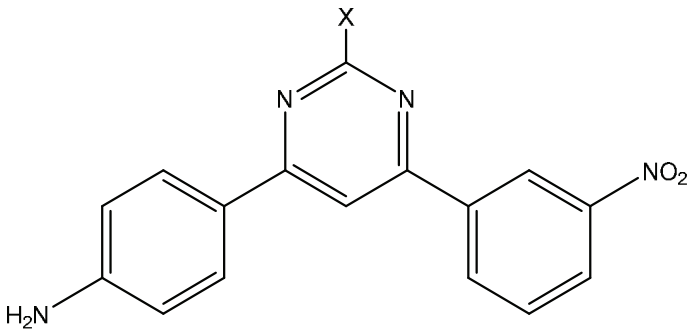


Fig. 2.15

Sixteen, out of thirty 6-aryl-2-substituted pyrimidine-4-yl phenols synthesized by Agarwal et al.[140] demonstrated anti-mycobacterial action.

2.6.4 ANTIVIRAL ACTIVITY:

Rostom et al.[141] prepared 2-(benzoxazol-2-ylamino)-3H-4-oxo pyrimidines and tested them for anti-HIV efficacy *in vitro*.

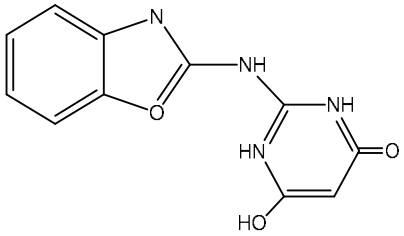


Fig. 2.16

Phaditare et al.[142] observed that 1-[(hydroxy methyl) phenyl methyl] thiophenyl pyrimidines are effective HIV-RT inhibitors. Jeong et al.[143] prepared 2'-azido-2',3'-deoxy arabinofuranosyl pyrimidines and tested them against HIV-1, HSV-1, HSV-2, and HBY viruses.

Zhou et al.[144] synthesized (Z)- and (E)-[2-fluoro-2-(hydroxyl methyl) cyclopropylidiene] methyl pyrimidines that are methylene cyclopropane nucleoside analogues.

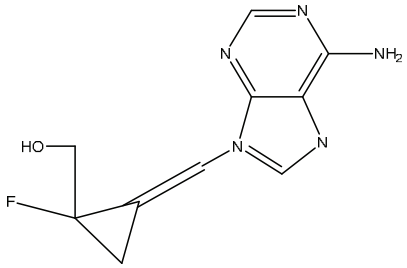


Fig. 2.17

The 2,4-diamino-5(2',5'-substituted benzyl)pyrimidines were synthesised by Rosowsky et al.[145], and these are prospective medications against opportunistic infections of AIDS and other immunological diseases. Chern et al.[146] prepared pyrazolo [3,4-d] pyrimidines, which are highly specific for human enteroviruses, especially coxsackie viruses.

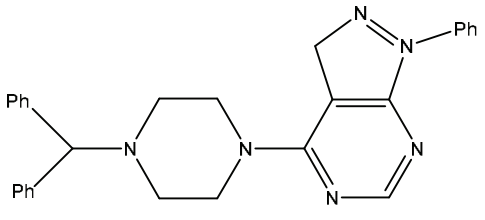


Fig. 2.18

El Otmani et al.[147] synthesised some pyrazolyl (isoxazolyl) pyrido [l,2-a] pyrimidines having anti-HIV activity. Warmstaedt et al.[148] synthesised some acyclic nucleoside phosphonates and tested against HSV-1, HSV-2 and HIV-1. They showed weak antiviral activity.

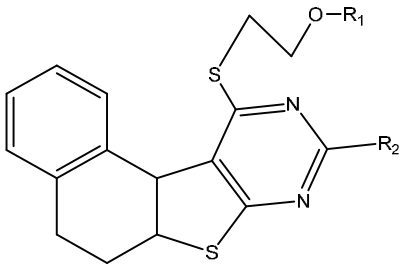


Fig. 2.19

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