Introduction

CHEMISTRY OF PYRIMIDINE

SYNITHESIS OF PYRIMIDINE DERIVATIVES

Pyrimidine derivatives were generally prepared by four types of ring synthesis (I, II, III and IV) according to the nature of compounds which combine together to form the pyrimidine nucleus⁽¹⁾.

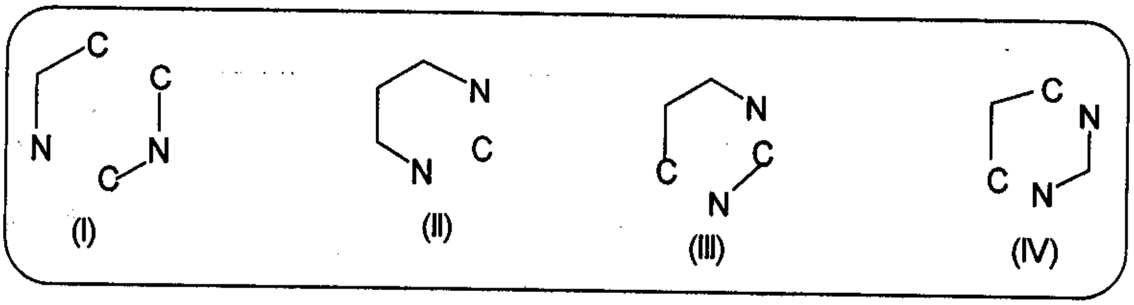
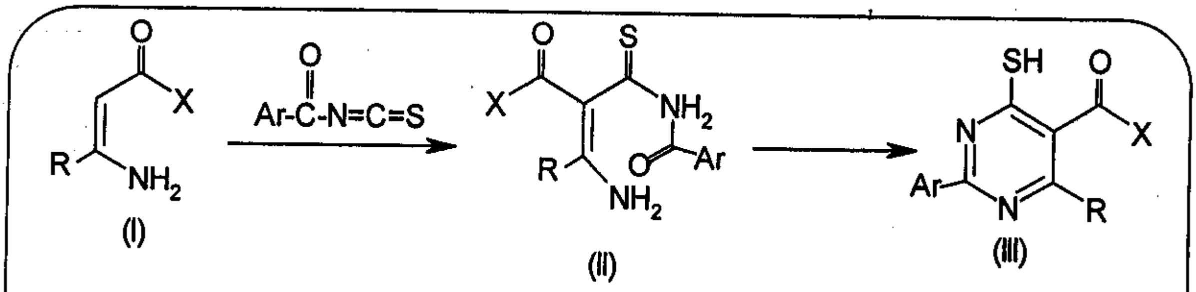


Fig (1): Some possible condensation to form the pyrimidine ring

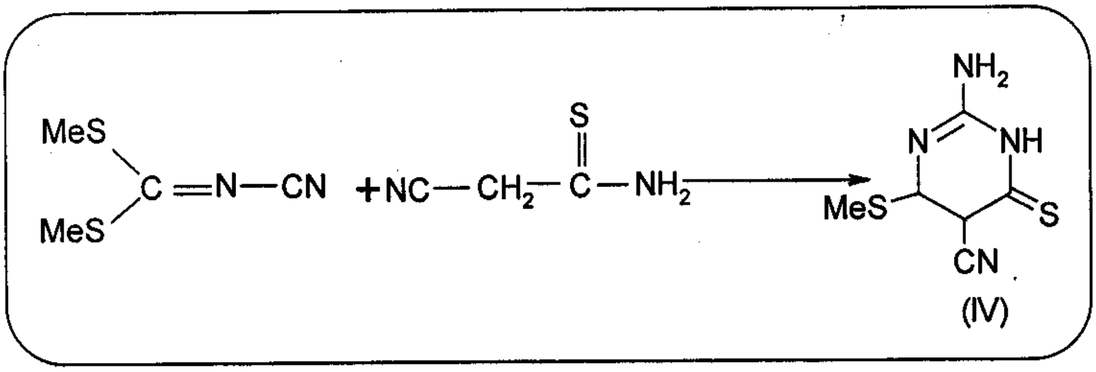
1. Type (I): synthesis of pyrimidine ring from N-C-C and C-N-C fragments:

Addition of enaminoketones or enaminoesters (I) to benzoyl isothiocyanates or alkoxycarbonyl isothiocyanates gave the intermediate (II) which cyclized in base medium to give pyrimidine thione(III) (2,3)



	X	Ar
a,	CH_3	C_6H_5
b,	OC_2H_5	p-ClC_6H_4

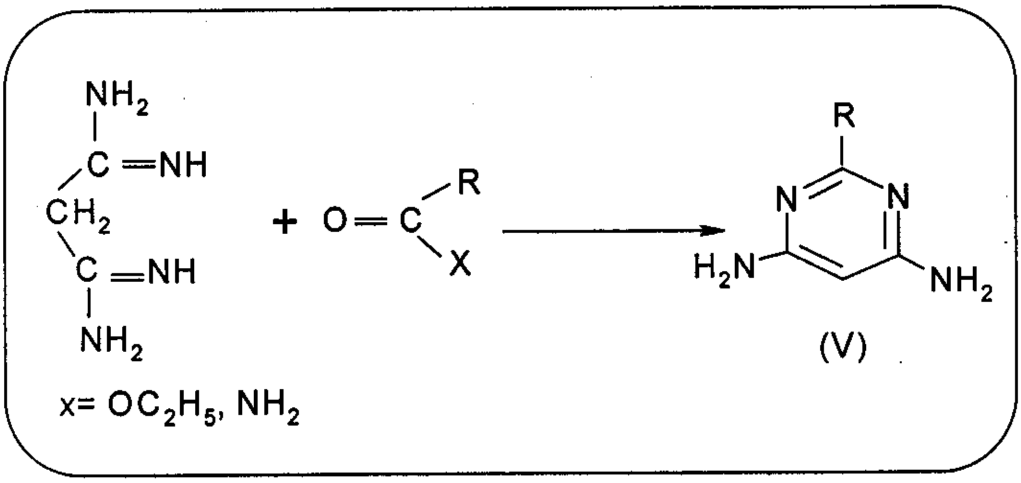
بي له سلام ⇐ Cycloaddition of chalcon [$(MeS)_2C{:}N$-CN] with NC-CH_2-CS-NH_2 in ethanol containing sodium ethoxide yielded pyrimidine thione (IV) after acidification [(4)].



(IV)

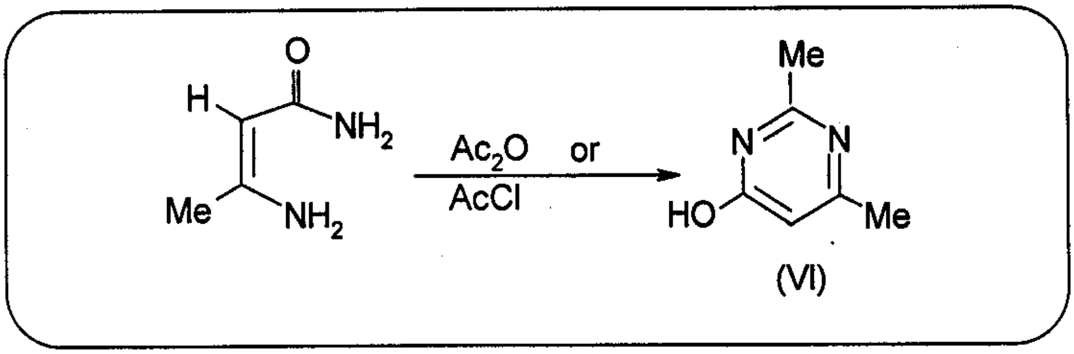
2. Type (II): Synthesis of pyrimidine ring from N-C-C-C-N and C- fragments:

Condensation of malonodiamidine and esters or amide as one carbon fragment yielded 4,6-diaminopyrimidine (V) [(5)].



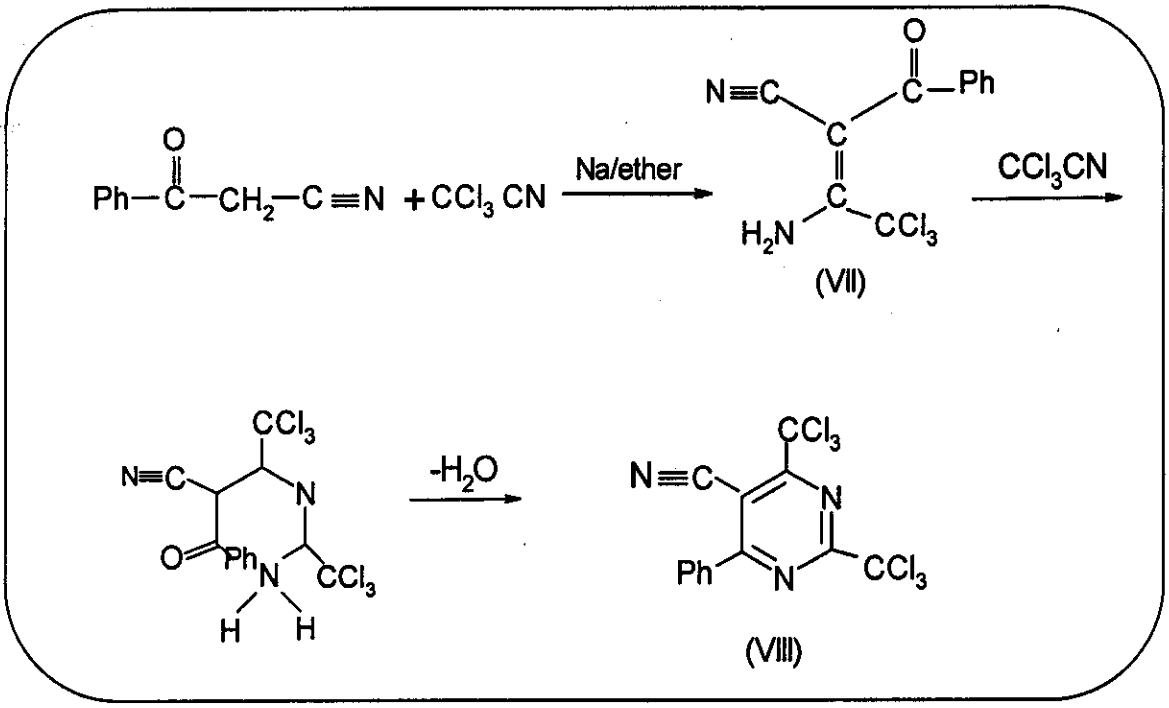
(V)

Reaction of β-aminocrotonamide with acetylating reagents (acetic anhydride or acetylchloride) gave β-acetamido-croton-amide which on treatment with base, cyclized to gave 2,6-dimethyl-4-hydroxypyrimidine(VI) [(6)].

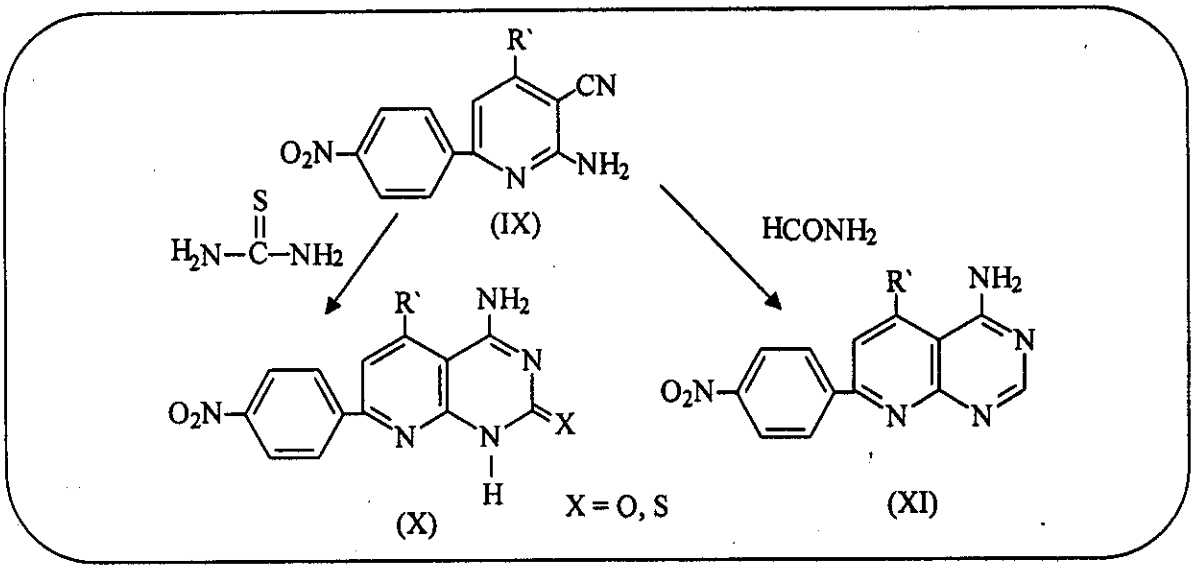


3. Type(III): Synthesis of Pyrimidine ring from C-C-C-N and C-N fragments:

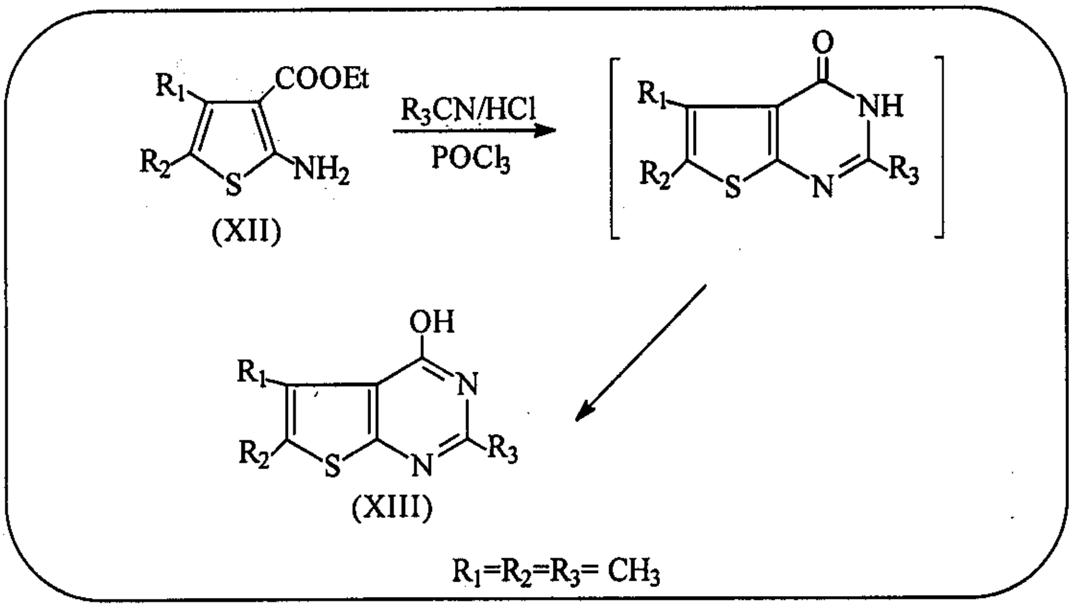
Reaction of benzoylacetonitrile with trichloroacetonitrile gave acrylonitrile derivatives (VII) which reacted with another molecule of trichloroacetonitrile to afforded 2,4-bis-trichloromethyl-5-cyano-6-phenylpyrimidine (VIII) (7).



Condensation of 2-amino-3-cyano-4,6-disubstituted pyridine (IX) (R = 4-ClC_6H_4, 4-$MeOC_6H_4$) with thiourea and formamide gave pyrido-(2,3-d) pyrimidine derivatives (8) (X), and (XI) respectively.

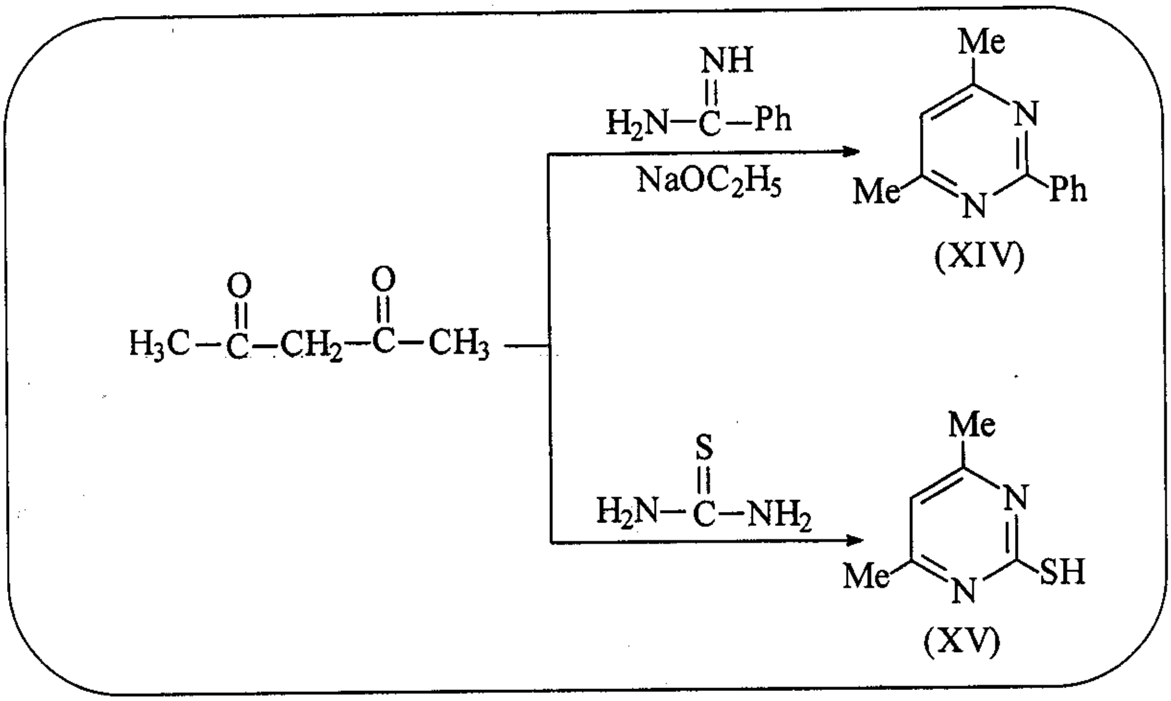


Reaction of 2-amino-3-carbethoxy-4,5-disubstituted thiophenes (XII) with nitriles gave the intermediates 2-subestetuted 4-hydroxy thieno [2,3-d] pyrimidines, subsequent heating under reflux in phosphours oxychloride gave thienopyrimidine (XIII) (9).

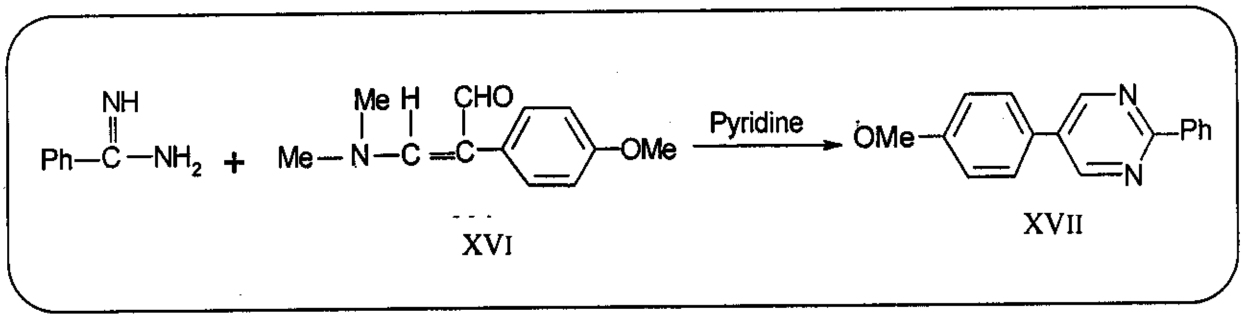


4. Type (IV): Synthesis of pyrimidine ring from C-C-C and N-C-N fragments;

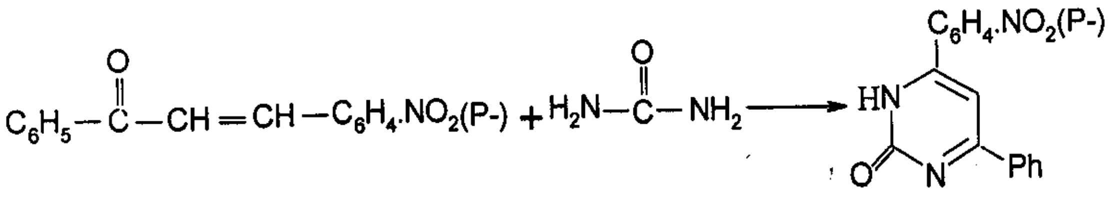
It is included the condensation of an amidines, urea, thiourea, guanidine and their derivatives with β-diketones or chalcon Acetylacetone condense with thiourea in acid medium and/or benzamidine in ethanol containing sodium ethoxide and gave 4, 6-dimethyl pyrimidine derivatives (XIV, XV)⁽¹⁰⁾.



On the other hand the cyclocondensation of benzamidine with β-(dimethylamino)-α-p-anisylacrylaldhyde (XVI) in pyridine gave compound (XVII)⁽¹¹⁾ respectively.

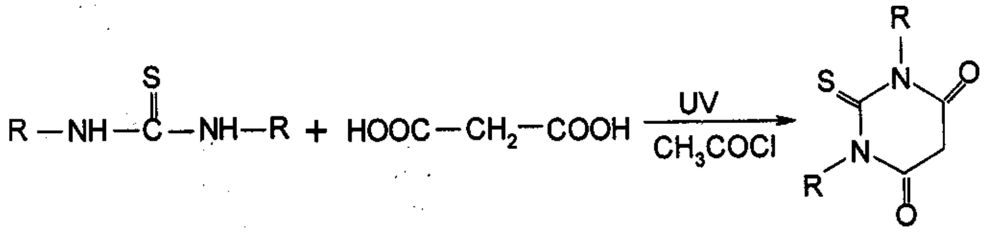


The condensation of urea with chalcon in the presence of acid gave pyrimidinone (XVIII)⁽¹²⁾.



XVIII

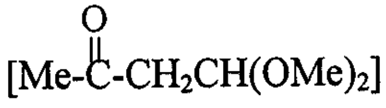
Photochemical reaction of diarylthiourea with malonic acid and acetyl chloride gave pyrimidine thion (XIX) (13).



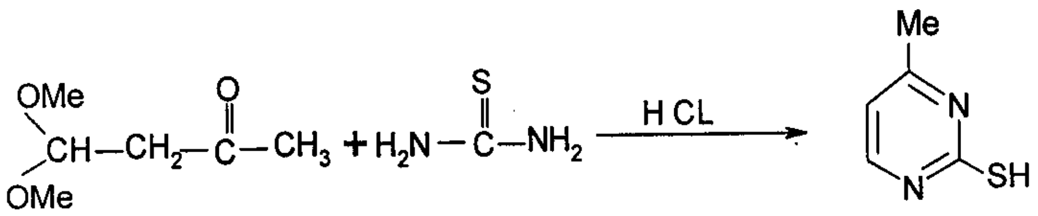
XIX

R=C_6H_5, p-Cl C_6H_4, o-OCH_3 C_6H_5, p-OCH_3 C_6H_4, o-CH_3 C_6H_4

Acetal derivatives

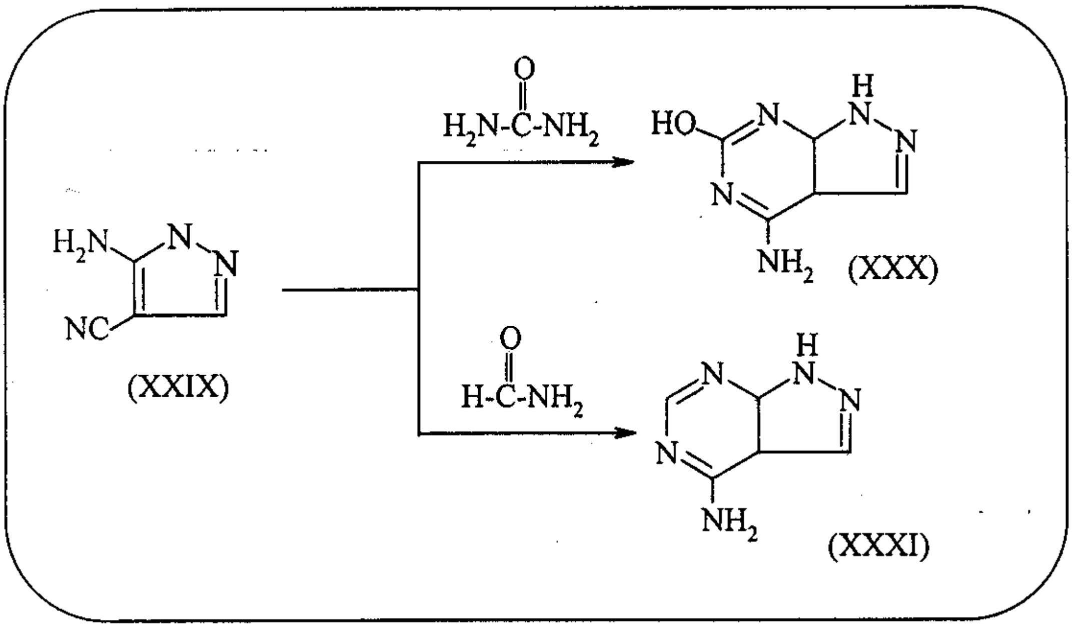


$[Me\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2CH(OMe)_2]$ condensed with thiourea in the presence of aqueous HCl at 60°C gave 2-mercapto-4-methylpyrimidine (XX) (14).

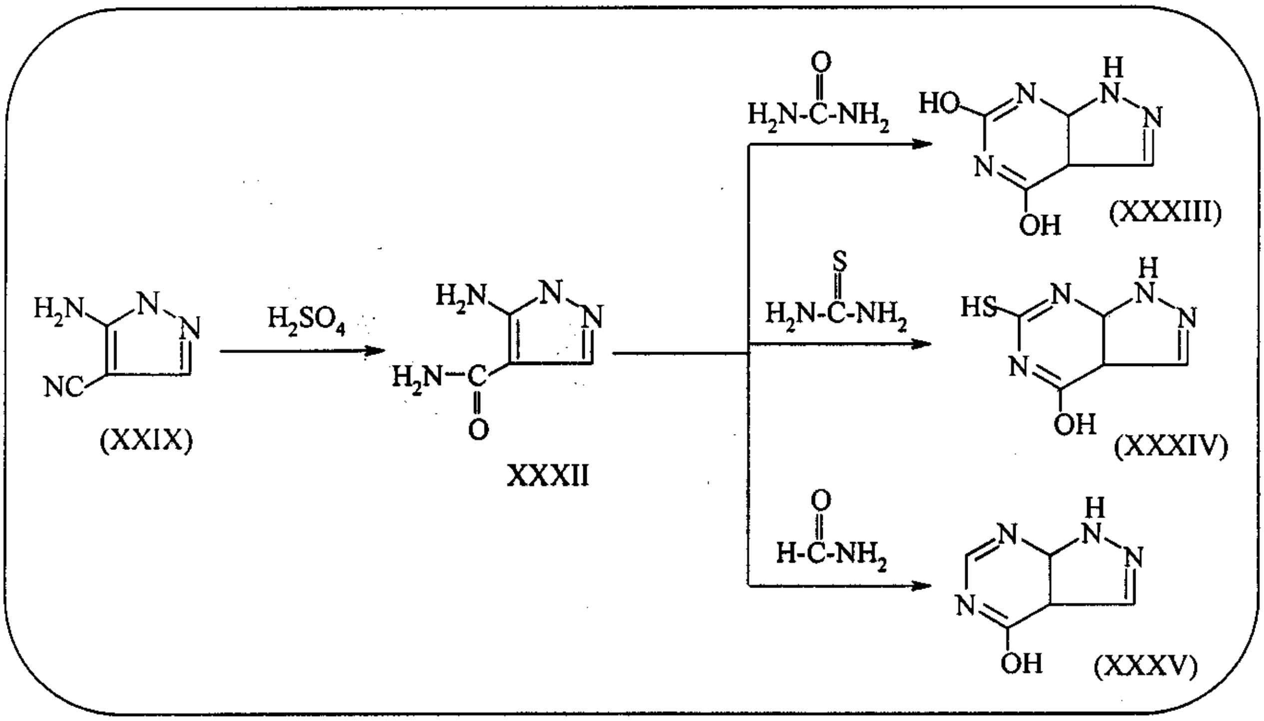


(XX)

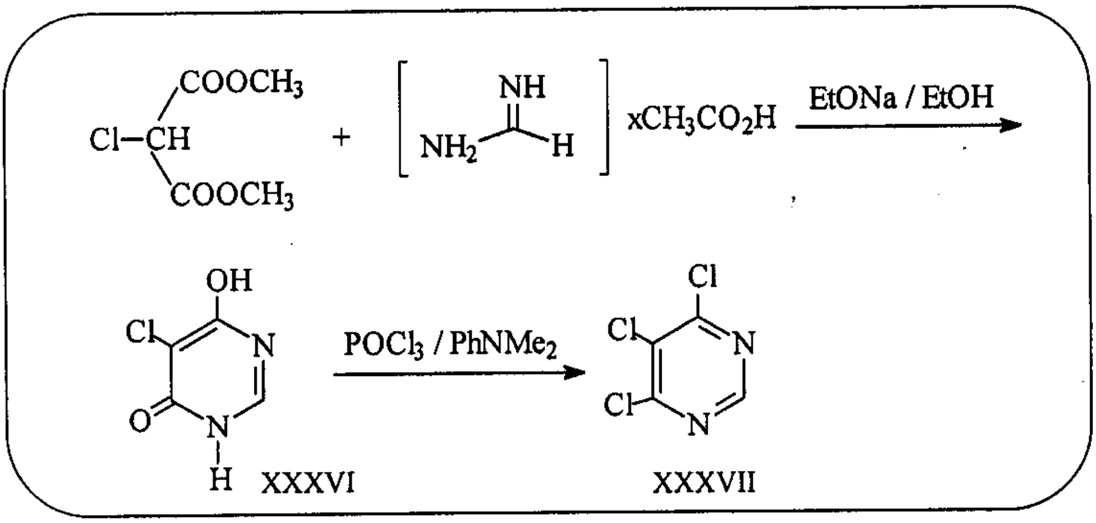
Cyclocondensation of ethyl aroylacetate with thiourea gave compound (XXI) (15) which showed poor anticonvulsant activity.



The hydrolysis of nitrile group (XXIX) with conc. sulphuric acid gave 3-amino-4-pyrazole carboxamide (XXXII) which isolated as sulphate. This sulphate when heated with urea, thiourea and formamide gave pyrimidine derivatives (XXXIII), (XXXIV) and (XXXV) respectively.



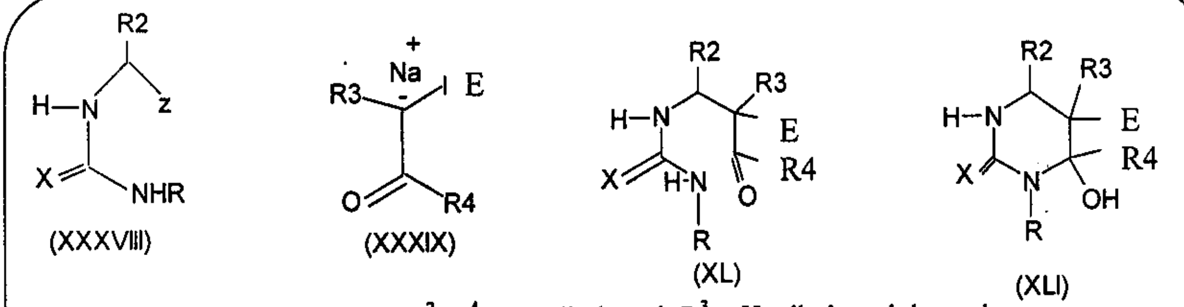
Reaction of dimethyl chloromalonate and formmidine acetate in presence of sodium ethoxide gave 4,6-dihydroxy-5-chloropyrimidine (XXXVI) also when (XXXVI) treated with phosphorus oxychloride in presence of N, N-dimethyl aniline gave trichloropyrimidine (XXXVII) (20).



XXXVI

XXXVII

Reaction of tosyl or azido group of thiourea and urea (XXXVIII) with sodium enolate (XXXIX) containing an electron withdrawing group such as esters, thioester or acyl group gave (XL) which spontaneously undergo heterocyclization and gave (XLI)(21).

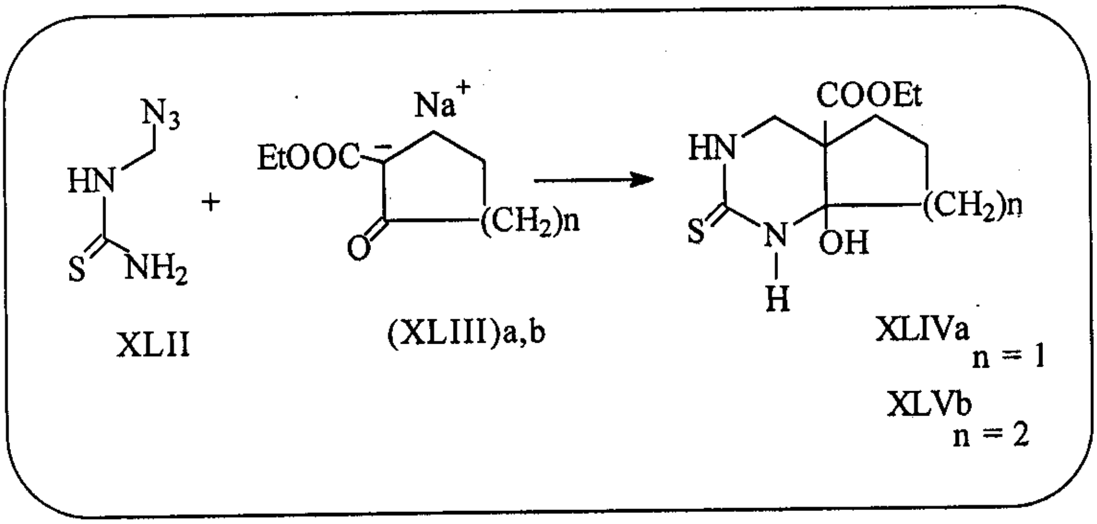


(XXXVIII) (XXXIX) (XL) (XLI)

Z = Ts or N_3; X = S, O; R^2, R^4 = H, alkyl, aryl; R^3 = H, alkyl, aryl, benzyl.

E = COOR, COR, SO_2R

Reaction of azidomethyl thiourea (XLII) with ethyl 2-oxocyclopentane carboxylate or ethyl 2-oxocylohexane carboxylate (XLIII)a,b gave (XLIV)$_a$ and (XLIV)$_b$ (22).



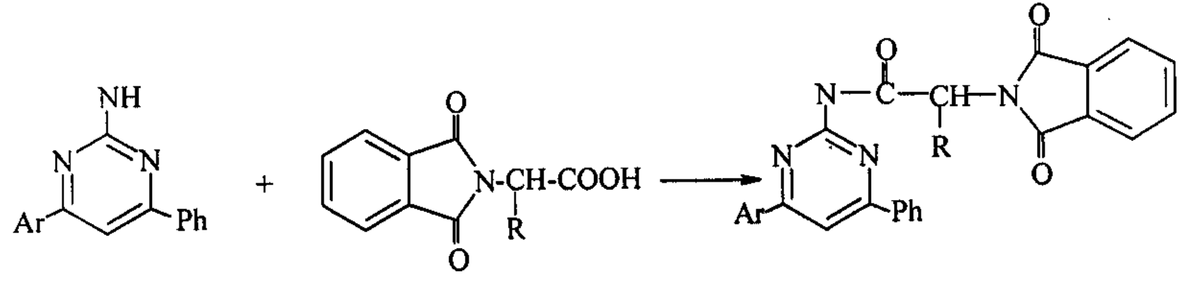
CHEMICAL REACTIONS OF PYRIMIDINE DERIVATIVES

Pyrimdine is analogue to pyridine ring by replacing -CH=CH- by N=CH in 3-position, the presence of another electronegative heteroatom caused more π-deficiency at carbon atom which obviously be deactivated towards electrophilic reagents. Such reactions are therefore very slow and many reagents react at nitrogen rather than at carbon, but pyrimidine is active towards nucleophilic reagent at 2,4 and 6-positions.

1. Reaction of pyrimidine with amino acids:

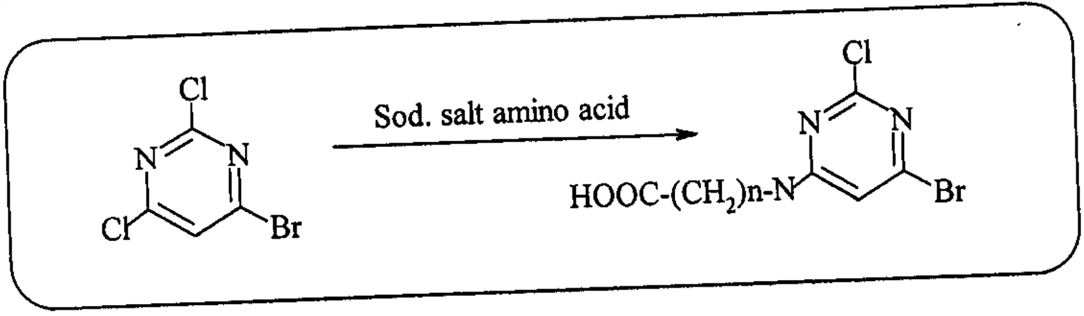
The considerable biological, pharmacological and therapeutical possibilities inherent in amino acids and peptides leads to synthesis of such compounds to react with different heterocyclic nucleus.

It was reported(23), that N-pyrimidine amino acids were prepared to have different biological activity via the reaction of amino pyrimidine derivatives with amino acids as glycine, DL-alanine, DL-phenyl alanine, DL-valine and DL-serine.

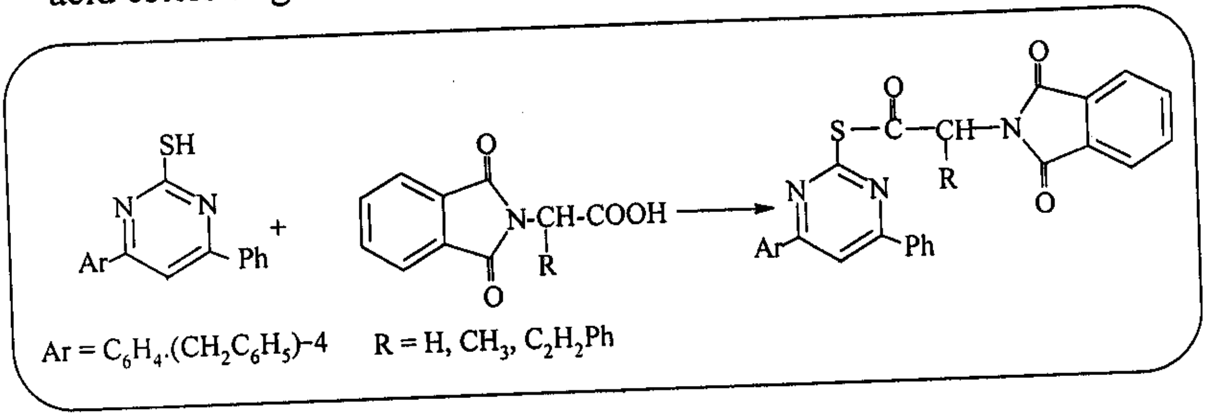


$Ar = C_{10}H_6.(OCH_3)\text{-}2$ $R = H, CH_3, C_2H_2Ph$

Several N-(2-chloro-5-bromo-4-pyrimidinyl)-amino acid derivatives were prepared starting from 2,4-dichloro-5-bromopyrimidine and sodium salt of amino acids(24).



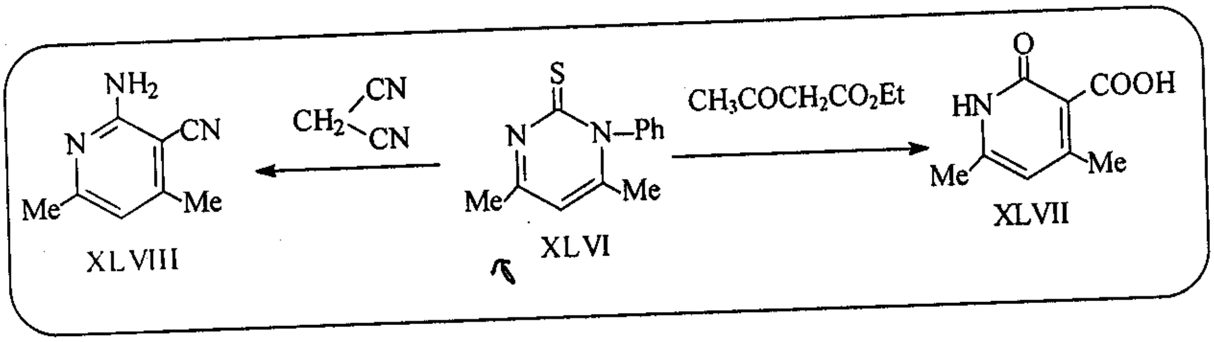
Also 2-mercaptopyrimidine reacted with amino acids or amino acid esters to give the corresponding pyrimidinyl amino acid(25).



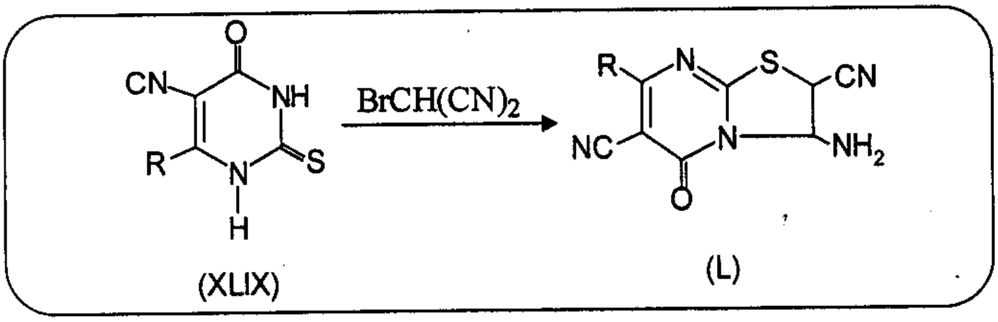
$Ar = C_6H_4.(CH_2C_6H_5)$-4   R = H, CH_3, C_2H_2Ph

2. Reaction of Pyrimidine with compounds containing active methylene group:

Reaction of 2-thiopyrimidine derivative (XLVI) with ethyl acetoacetate gave pyridine derivative (XLVII)(26). Also treating (XLVI) with malononitrile gave (XLVIII)(26).



6-Aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles (XLIX); R = Ph, $\text{4-CLC}_6\text{H}_4$, $\text{4-MeOC}_6\text{H}_4$) reacted with bromomalonitrile to give 3-amino-7-aryl-5-oxo-5H-thiazolo-[3,2-a]-pyrimidine-2,6-dicarbonitriles (L) (27).

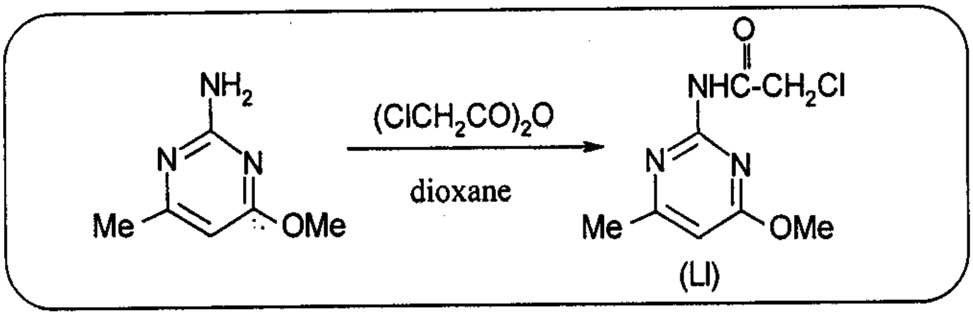


(XLIX) (L)

3. Acylation:

a) N-Acylation

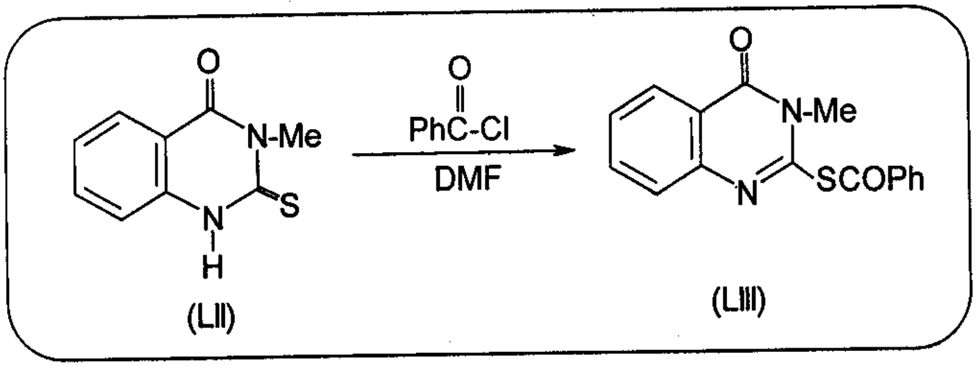
The reaction of 2-amino-4-methoxy-6-methylpyrimidine with dichloroacetic anhydride [$(\text{CLCH}_2\text{CO})_2\text{O}$] in dioxane gave 2-chloroacetamindio-4-methoxy-6-methyl-pyrimidine (LI)(28).



(LI)

b) S-Acylation:

The acylation of 2-thioxo-4-quinazolone (LII) by benzoyl chloride in DMF and triethyl amine gave 60% S-benzoyl derivatives (LIII) (29).

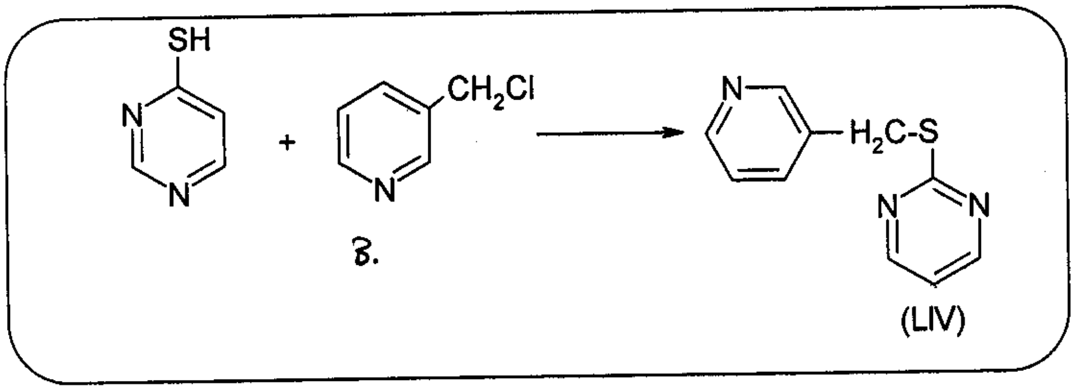


(LII) (LIII)

4. Alkylation:

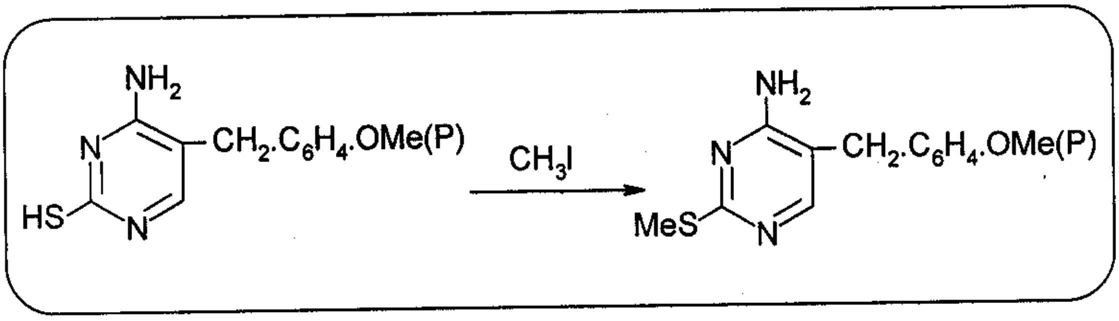
a) S-alkylation:

Reaction of pyrimidine-2-thione with picolyl chloride gave S-alkyl derivatives (LIV) (30), which used as branchoscretolytic agent.



(LIV)

Also reaction of pyrimidinethione derivatives (LV) with methyl iodide gave 50% of S-methyl derivatives (LVI) (31).

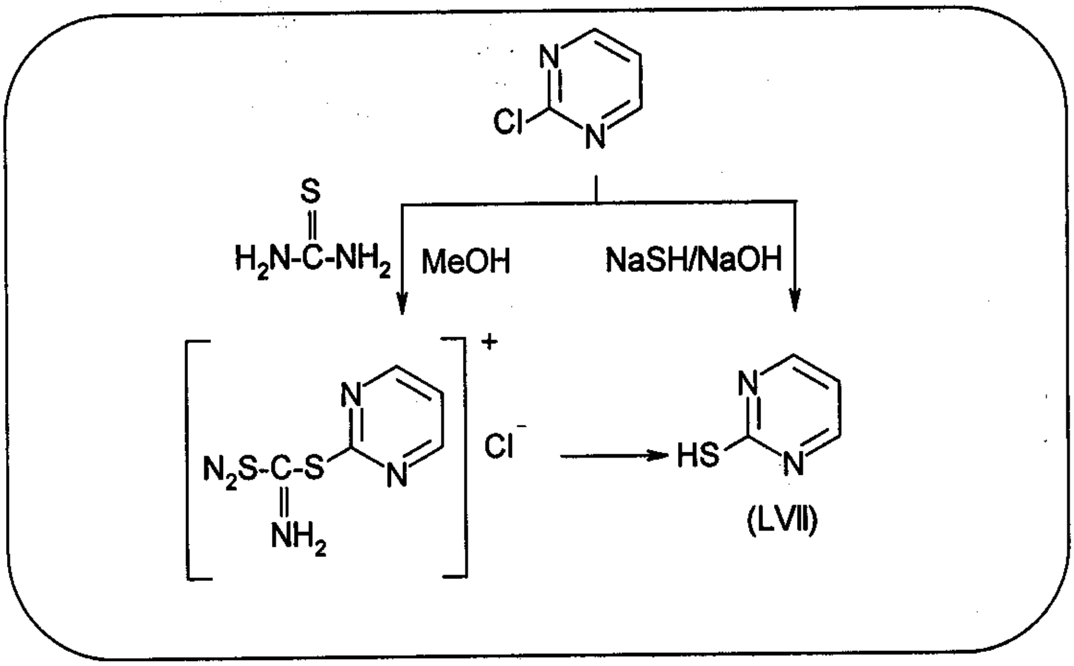


5. Nucleophilic substitution:

2,4- and 6-positions of pyrimidine ring "activated" for nucelophilic attack by the presence of adjacent electron attracting nitrogen atoms, there are very few cases known of direct nucleophilic displacement of halogens or other labile group are known.

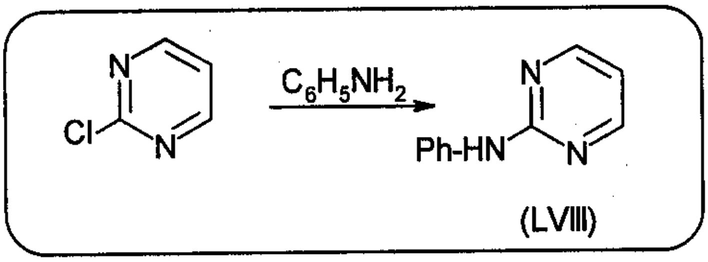
a. Thiation:

2-Chloropyrimidine was converted into 2-mercaptopyrimidine (LVII) by sodium hydrogen sulphide and/or thiourea in methanol (32).

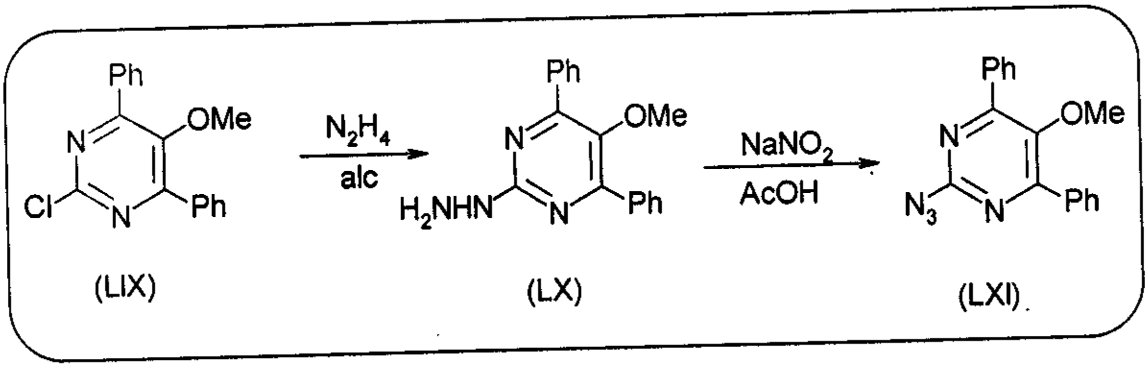


b. Reaction with amines, hydrazines and hydroxyl amine:

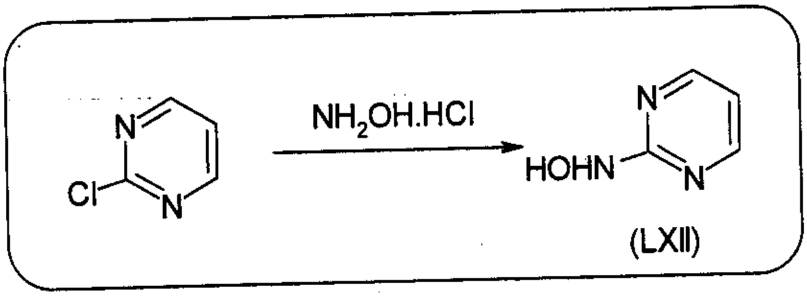
2-Chloropyrimidine reacted with aniline to give 2-anilino-pyrimidine (LVIII)(33).



Similarly, 2-chloropyrimidine derivative (LIX) was treated with hydrazine in ethanol to give (LX) and treatment with sodium nitrite in acetic acid gave 2-azidopyrimidine derivative (LXI) (34).



On the other hand, 2-chloropyrimidine was reacted with hydroxylamine hydrochloride in ethanol to give 2-hydroxy-amino pyrimidine (LXII) (35).



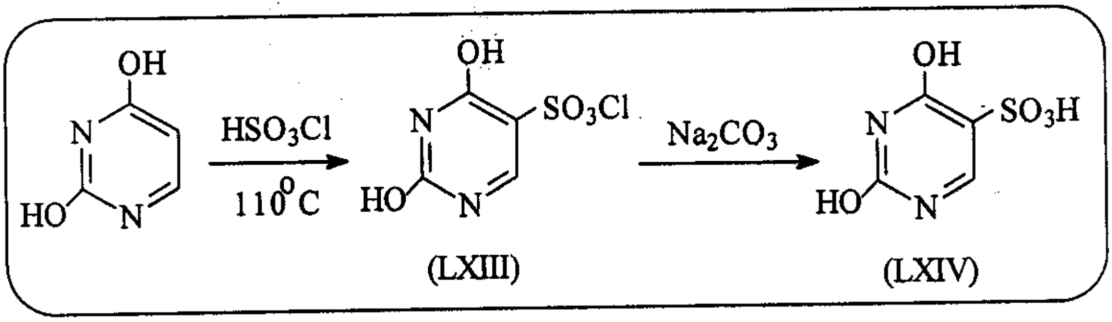
6. Electrophilic substitution:

Electrophilic reagents almost attack the pyrimidine ring at position-5, which the carbon atom least depleted in electron charge :

a. Sulphonation:

Contrary to nitration of pyrimidine which needs more than one electron releasing group, sulphonation needs only one and takes place at 5-position. Sulphontion of 2-aminopyrimidine using fuming sulfuric acid at 180 °C gave 2-amino-5-sulphopyrimidine while the use of chlorosulphonic acid gave 2-amino-5-chloro-sulphonyl pyrimidine (36).

Chlorosulphonation of 2,4-dihydroxypyrimidine at 110 °C gave 5-chloro-sulphonyl-2,4-dihydroxypyrimidine (LXIII)(37), which reacted with Na_2CO_3 or AcONa to give 2,4-dihydroxy-5-sulpho-pyrimidine (LXIV)(38).

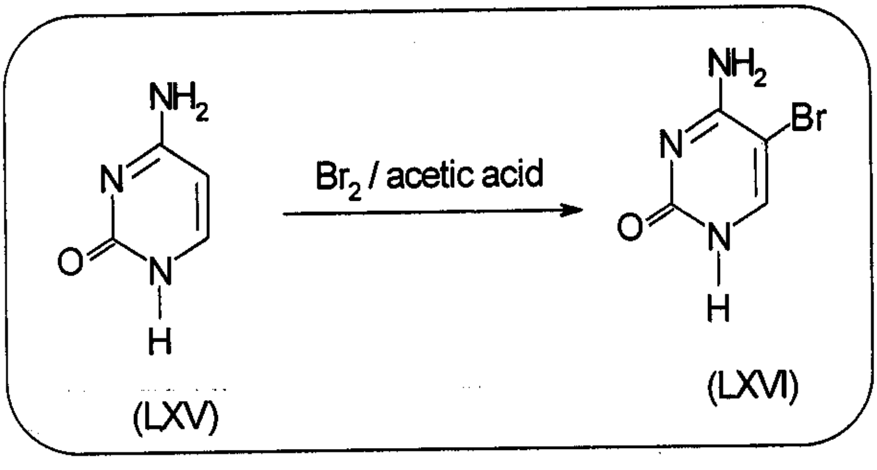


(LXIII) (LXIV)

b. Halogenation:

Typically pyrimidine having at least one electron releasing subtituent may be halogenated in position-5 by chlorine or bromine in warm aqueous solution or by bromine in acetic acid, N-chloro, N-bromosuccinimide, phosphoryl chloride or bromide and phosphorous pentachloride also used for 5-halogenation of some pyrimidine.

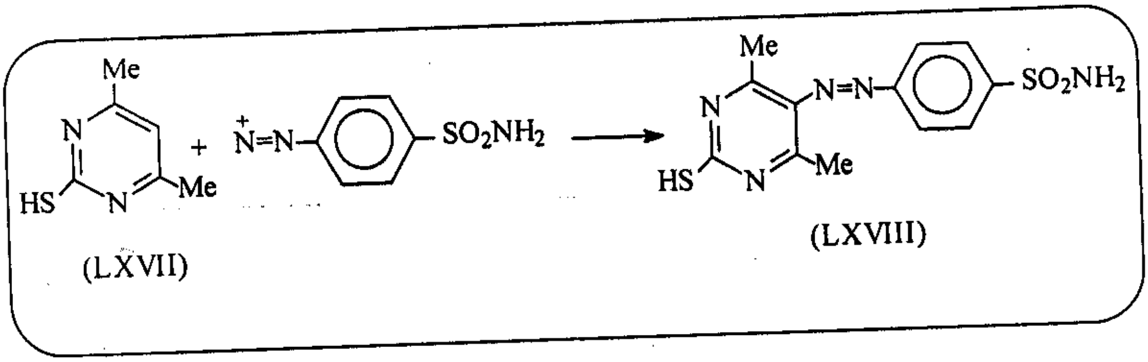
The reaction of cytosine (LXV) with bromine in acetic acid gave 5-bromocytosine (LXVI) as a major product (39).



(LXV) (LXVI)

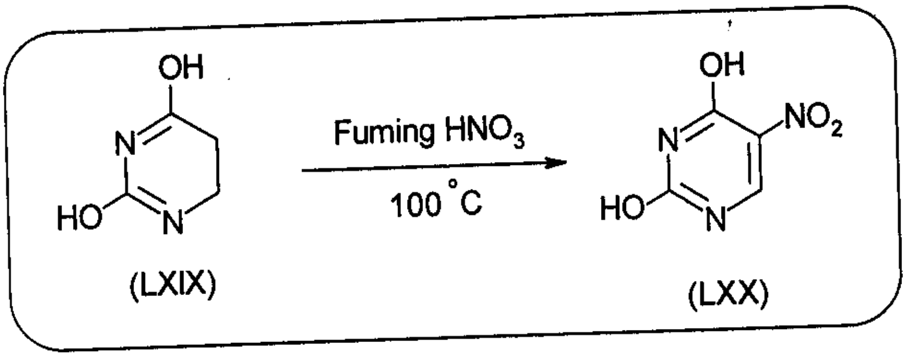
c. Diazo-coupling:

Pyrimidine may be coupled with diazotized amines to give 5-arylazo derivatives but the reaction seems to be general only when at least two electron releasing groups are present. Treatment of 4,6-dimethyl-2-mercaptopyrimidine (LXVII) with diazotized-p-amino-benzene sulphonamide leads to form of 4,6-dimethyl-5-(p-sulphonylbenzenediazo)mercaptopyrimidine (LXVIII)(40).

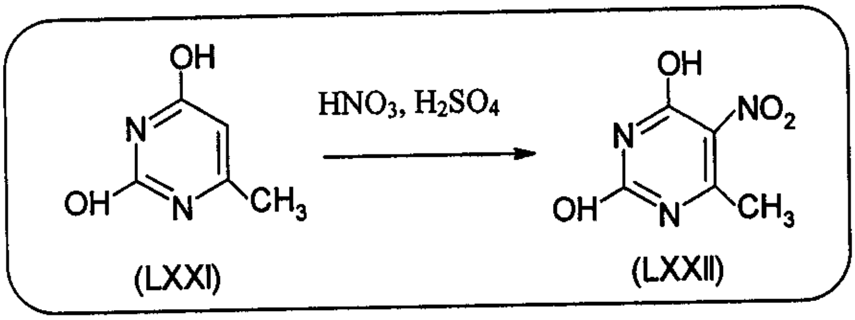


d. Nitration:

Pyrimidine and its simple alkylated derivatives don't undergo nitration but the nitration of pyrimidine having two or more electron-releasing groups may be readily carried out, the nitration of monohydroxy and monoaminopyrimidine may also be effected so dihydroxypyrimidine (uracil) (LXIX) may be nitrated using fuming nitric acid at 100 °C to give the 5-nitrouracil (LXX)(41,42).

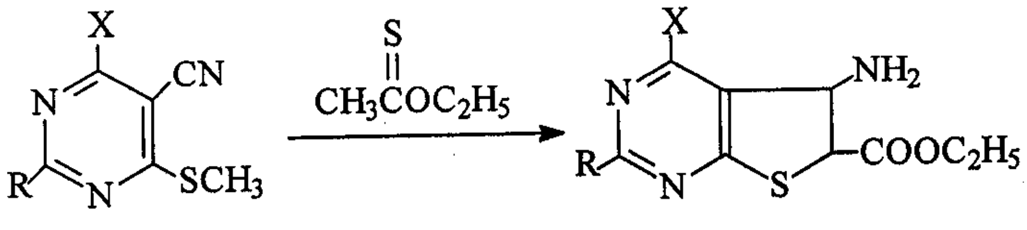


Alkyl pyrimidines undergo nitration under less vigorous conditions. For example 2,4-dihydroxy-6-methylpyrimidine (LXXI) is nitrated using one molar equivalent of nitric acid in sulfuric acid at 40-50 °C to yield 5-nitropyrimidine(LXXII) (43,44).



(LXXI) (LXXII)

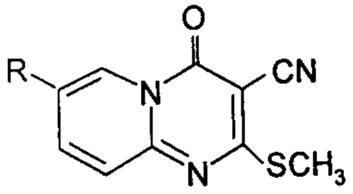
Reaction of 5-cyano-6-methylsulfanylpyrimidines (LXXIII) with ethyl thioacetate as a reagent gave pyrimidine derivatives (LXXIV) (45).



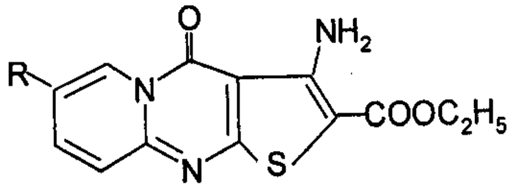
(LXXIII) (LXXIV)

1,2	R	X
a	H	OH
b	CH_3	OH
c	CF_3	OH
d	C_6H_5	NH_2
e	2- Pyridyl	NH_2
f	4-Pyridyl	NH_2

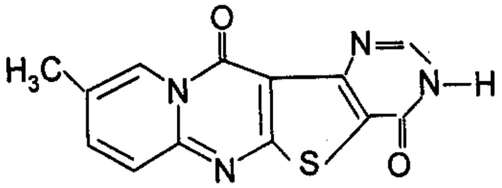
Also, 2-Methylsulfanyl-4-oxo-4-pyrimido[1,2-a]pyrimidine-3-carbonitriles(LXXV) on base catalyzed condensation-cyclization reaction with ethyl mercaptoacetate gave pyrimidine derivative (LXXVI) which further cyclized to (LXXVII)(46).



(LXXXI)

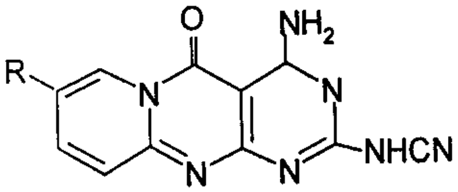


(LXXXII)



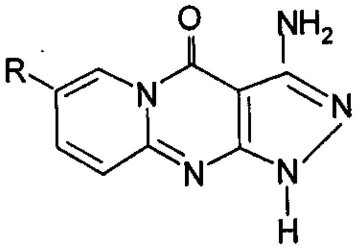
(LXXXIII)

Reaction of (LXXV) with dicyandiaminde, a (1,3-ambiphilic nucleophile) under basic condition yielded 4-amino-5-oxo-5H-pyrido[1,2-a]pyrimido[4,5-d]pyrimidine-2-yl-cyandiamide (LXXVIII) which reacted with hydrazine hydrate provided 3-amino-7-methylpyrazolo[3,4-d]pyrimido-[1,2-a]pyrimidin-4(H)-one (LXXIX)(47).



(LXXVIII)

a) R= H
b) R= CH_3

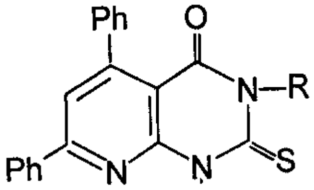


(LXXIX)

BIOLOGICAL ACTIVITY OF PYRIMIDINE DERIVATIVES

Pyrimidine nucleus has been employed as a basis for the synthesis of chemotherapeutic agents and a large number of its derivatives have been reported to posses various biological properties such as antitumor(48) antimalarial(49), duretic(50), anti-inflammatory(51), antithyroid(52), antibacterial(53), and antifungal (54).

Pyrido[2,3-d]pyrimidin-4(5H)-ones (LXXX) and all the compounds which prepared by methylation and substituted with amines had antibacterial activity (55).

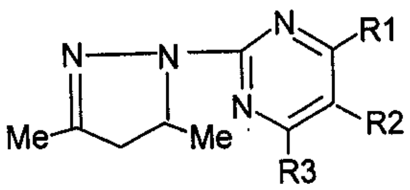


(LXXX)

(LXXXVI)

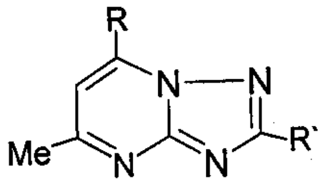
R = Me
= Amine

Pyrazoylpyrimidine derivatives (LXXXI) showed anti-bacterial activity against piricularia, orgzae, helminthosporium, orgza and sphaerotheca fuliginea(56).



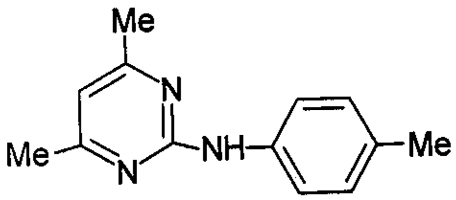
(LXXXI)

S-triazolo[4,5-a]pyrimidine (LXXXII) are useful as vasodilator, anticholesteremice and blood platelet aggregation inhibitors (57).

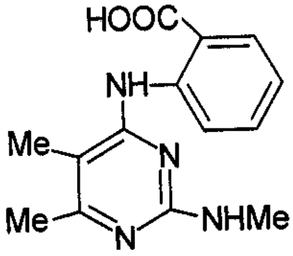


(LXXXII)

Arylaminopyrimidine e.g. 2-(4-toluidino)pyrimidine (LXXXIII) showed antidiabetic and antimycotic activities lowered blood sugar levels(58). Also, O-carboxyphenylaminopyrimidine (LXXXIV) is useful as inflammation inhibitors(58).

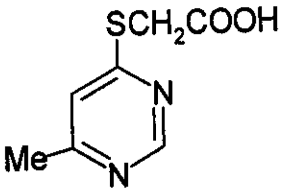


(LXXXIII)



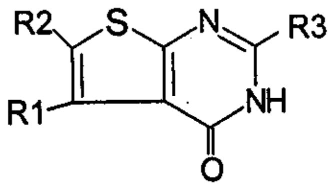
(LXXXIV)

Pharmacogical studies of 6-methyl-4-pyrimidinylthio-acetic acid (LXXXV) showed that it possess hypotipidimic and central nervous system depressant activity in mice(59).



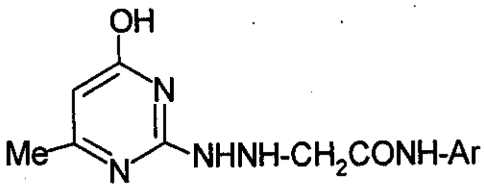
(LXXXV)

Thieno-(2,3-d)pyrimidine (LXXXVI) showed analgesic activity equal or superior to that of aspirin (60).



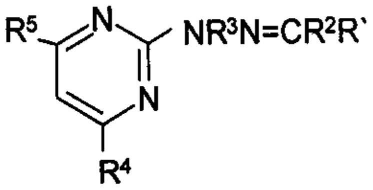
(LXXXVI)

Hydrazine derivatives of pyrimidine are found to possess various biological activities for example. 2-(N-arylcarbamoyl methyl) hydrazino-4-hydroxy-6-methyl pyrimidine (LXXXVII) showed antibacterial and antitubercular activities (61,62).



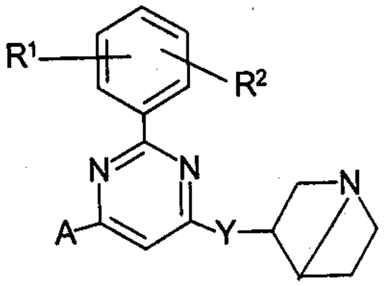
(LXXXVII)

2-Alkylidenehydrazinopyrimidine (LXXXVIII) useful as agro-chemical fungicides(63).



(LXXXVIII)

Also, it was reported (64,65), that the pyrimidine derivatives (LXXXIX); R`, R^2 = H, OH, alkoxy, CF$_3$, halo; A = [Me, CF$_3$, Me$_3$C; Y = O, NH] were useful as muscarinic agonist in treating central nervous disorders such as dementia.



(LXXXIX)