INTRODUCTION

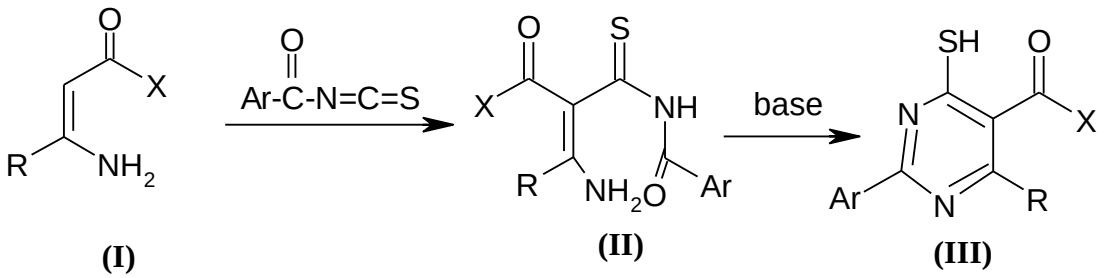
The pyrimidine and pyridazine nuclei have been employed as a basis for synthesis of a large numbers of chemotherapeutic agents, and a large number of their derivatives have been separated to posses various biological properties. Pyrimidine derivatives are used as antitumour, antimalarial, antiflammatory, antibacterial and other pharmacological properties [1-5].Also , the pyridazine derivatives exhibited different biological activities [6-11] as anticancer , anti-inflammatory , herbicides , antibacterial , antimicrobial , antitumer , pesticides and antiplatelet.

Synthesis of Pyrimidine

Pyrimidine may be synthesized according to one of the following methods:

1- From enamino ketones or enamino esters and aroyl isothiocynate:

Addition of enamino ketones or enamino esters (**I**) to benzoyl isothiocyantes or alkoxy carbonyl isothiocyanates gave the intermediate (**II**) which was cyclized in basic medium to give pryimidine thione (**III**)[1,2]



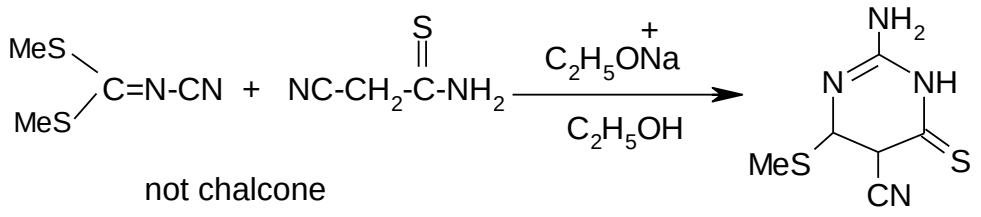
(I) **(II)** **(III)**

	x	Ar
a,	CH_3	C_6H_5
b,	OC_2H_5	p-Cl-C_6H_4

From chalcone:

(a) From chalcone and cyanamide:

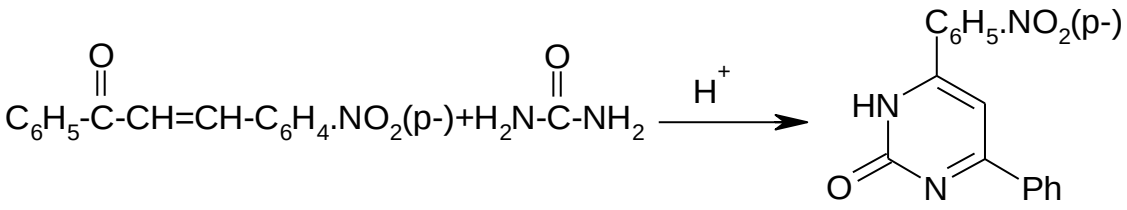
Cycloaddition of [$(MeS)_2C$: N-CN] with $NC-CH_2-CS-NH_2$ in ethanol containing sodium ethoxide yield pyrimidine thione (**IV**) after acidification [3].



(IV)

(b) From chalcone and urea:

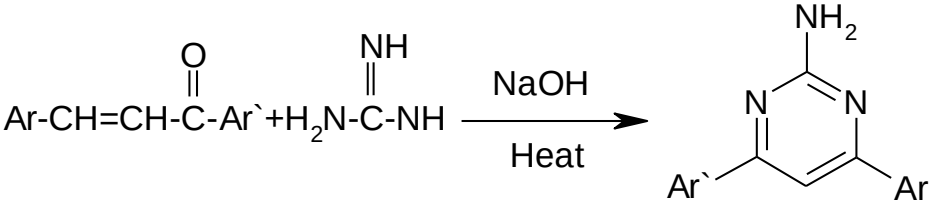
The condensation of urea with p-nitrobenzylidene acetophenone in the presence of acid gave pyrimidine (**V**)[4].



(V)

(c) From chalcone and guanidine:

Reaction of 1,3-diaryl-1,2-propen-1-one with guanidine in the presence of sodium hydroxide afforded the corresponding 2-amino-4,6-diaryl pyrimidine (**VI**)[5].

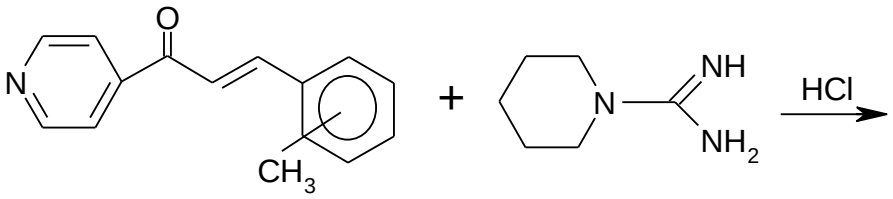


Chalcone

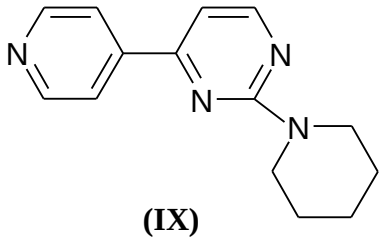
(VI)

(d) From chalcone and amidine:

Chalcone (**VII**) reacts with amidine (**VIII**) to produce pyrimidine (**IX**)



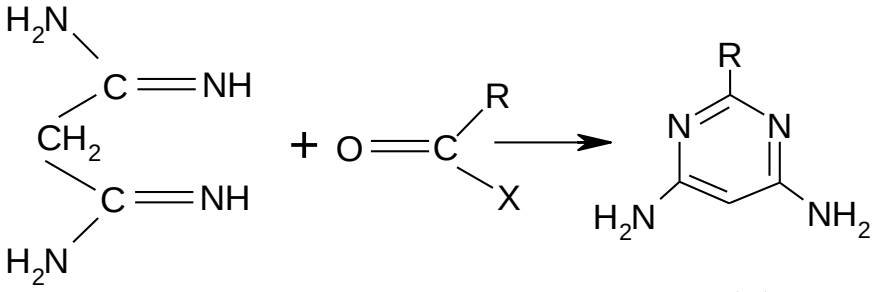
(VII) **(VIII)**



(IX)

3- From malonodiamidine and ester or amide:

Condensation of malonodiamidine and esters or amide yielded 4,6-diamino pyrimidine (**X**)[6].



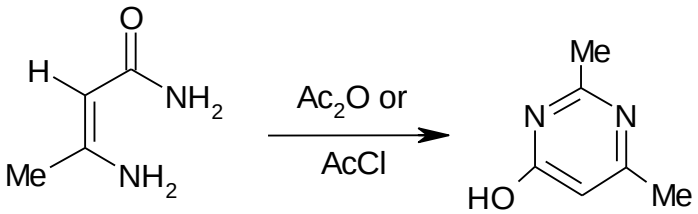
(X)

X = OC_2H_5, NH_2

4- From β-amino crotonamide:

Reaction of β-aminocrotonamide with acetylating agents (acetic anhydride or acetyl chloride) gave β-acetamide crotonamide

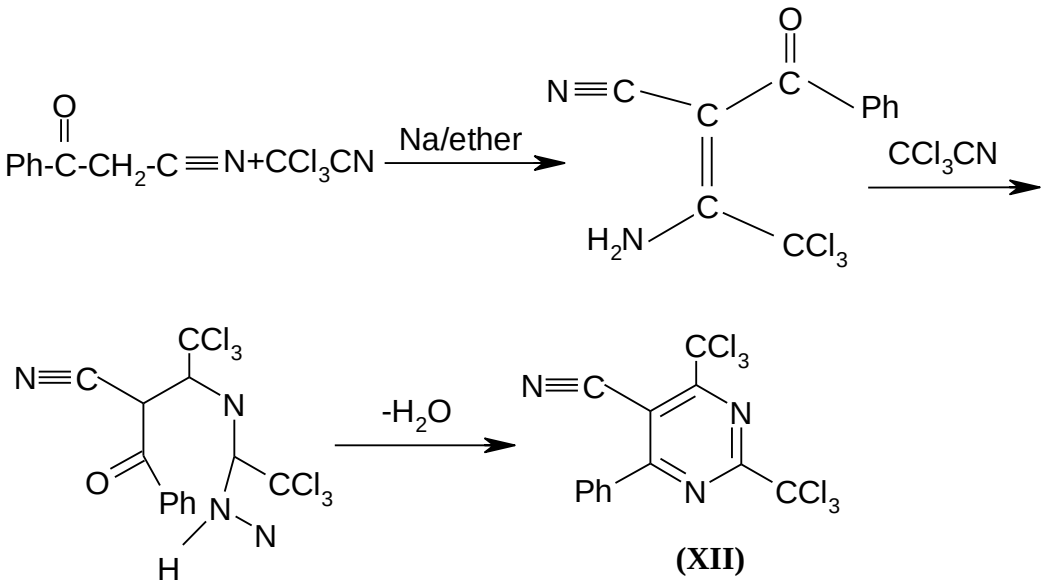
which on treatment with base, cyclized to give 2,4-dimethyl-6-hydroxy pyrimidine (**XI**)[7].



(XI)

5- From benzoyl acrylonitrile:

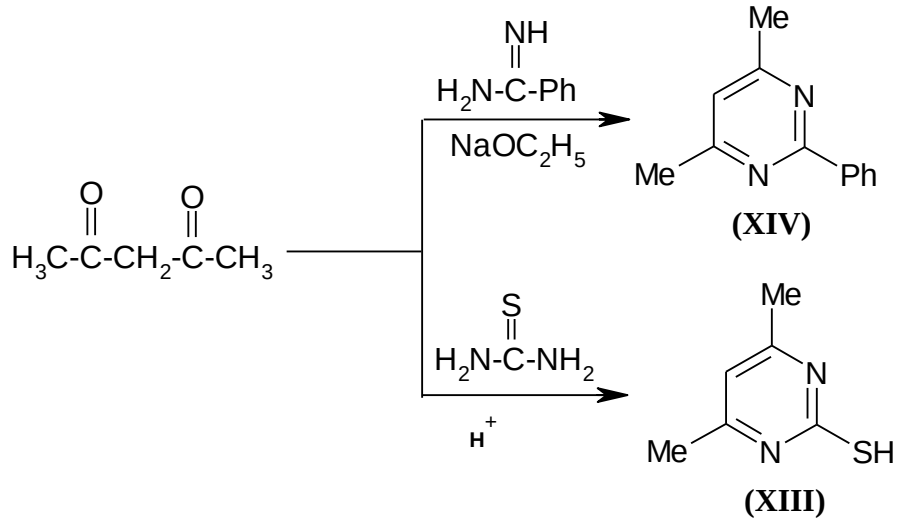
Reaction of benzoyl acetonitrile with trichloroacetonitrile in presence of sodium and ether afforded 2,4-bis-trichloromethyl-5-cyano-6-phenylpyrimidine (**XII**)[8].



(XII)

6- From β-diketone and urea, amidine and / or guanidine:

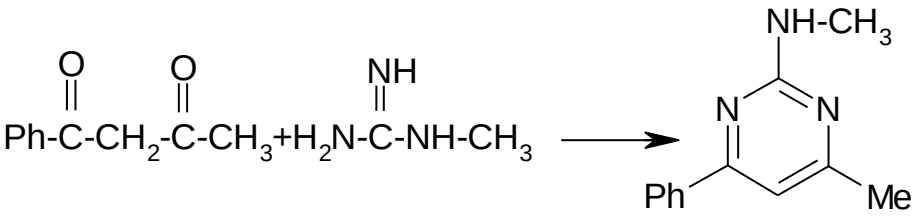
(a) Acetylacetone condense with thiourea in acid medium and gave pyrimidine or/with benzamidine in ethanol containing sodium ethoxide and gave 4,6-dimethyl pyrimidine derivatives (**XIII, XIV**)[9].



(XIV)

(XIII)

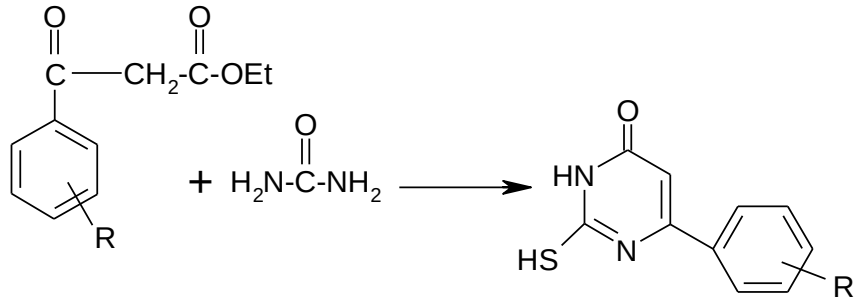
(b) 1-Phenyl-1,3-butanedione cyclocondensed with N-methyl guanidine to give pyrimidine derivatives (**XV**)[10].



(XV)

7- From β-keto ester and thiourea:

Cyclocondensation of ethyl aroylacetate with thiourea gave compound (**XVI**)[11] which showed poor anticonvulsant activity.

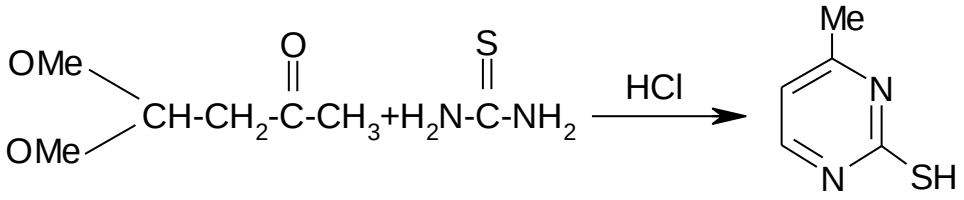


(XVI)

R = H, 4-MeO, 4-Cl, 3,4,5-$(MeO)_3$

8- From acetyl derivatives and thiourea:

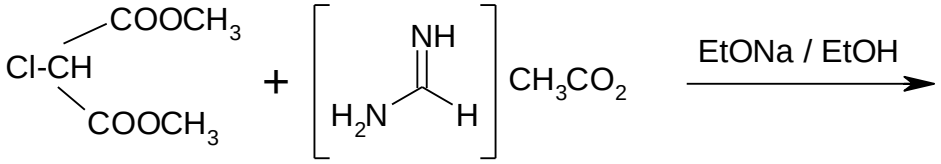
Acetyl derivatives condensed with thiourea in the presence of aqueous HCl at 60 °C and gave 2-mercapto-4-methylpyrimidine (**XVII**)[12].



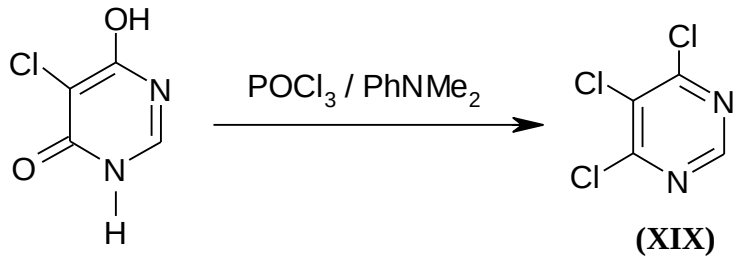
(XVII)

9- From chloromalonate and formamidine acetate:

Reaction of dimethyl chloromalonate and formamidine acetate in presence of sodium ethoxide gave 4,6-dihydroxy-5-chloro-pyrimidine (**XVIII**) also when (**XVI**) treated with phosphorus oxychloride in presence of N, N-dimethylaniline gave trichloro pyrimidine (**XIX**)[13].



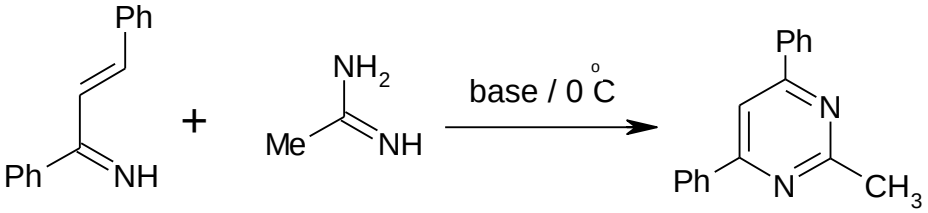
(XVIII)



(XIX)

10- From α,β-unsaturated imine and amidine or guanidine:

A series of polysubstituted pyrimidine (**XX**) were synthesized from α,β-unsaturated imines and amidine or guanidine derivatives in a convenent one-pot procedure.



(XX)

Synthesis of pyridazine:

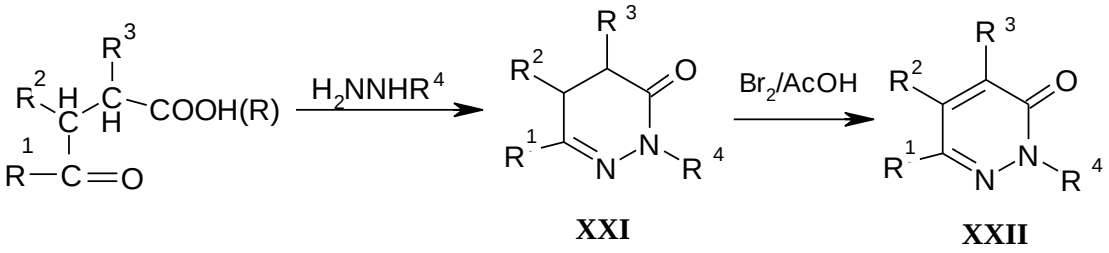
There are some characteristic features of pyridazine synthesis. Almost all important and efficient synthetic approaches for pyridazines use hydrazine or substituted hydrazines as the source of the two nitrogen rings, while the carbon part of the skeleton may originate from starting compounds of different functionality. In

general, synthesis from [4+2] fragments constitute the major part of synthesis of pyridazines.

Recently, many transformation of various heterocycles into pyridazines have been reported.

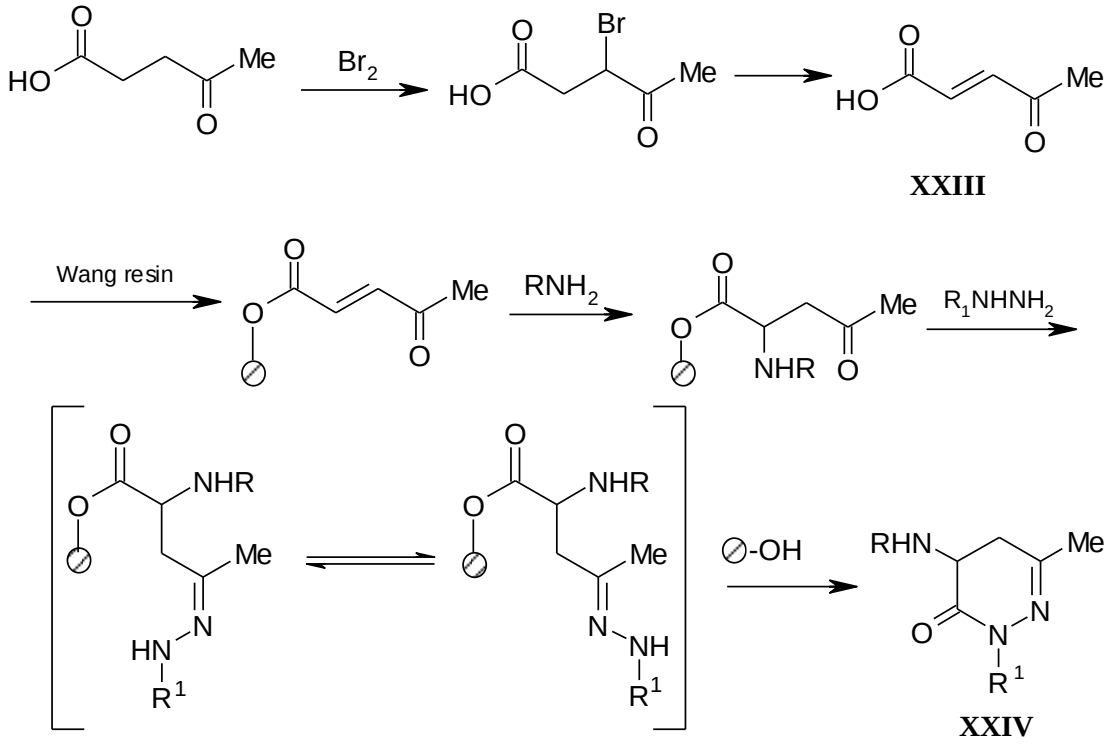
A. From carbonyl compounds:

Saturated 4-keto acids and their esters react with hydrazines to form 4,5-dihydro-3(2H)-pyridazinones **XXI**, which can be oxidized by bromine in glacial acetic acid to the corresponding 3(2H)-pyridazinones **XXII**. Unsaturated 4-keto acids yield **XXII** directly[14].



XXI **XXII**

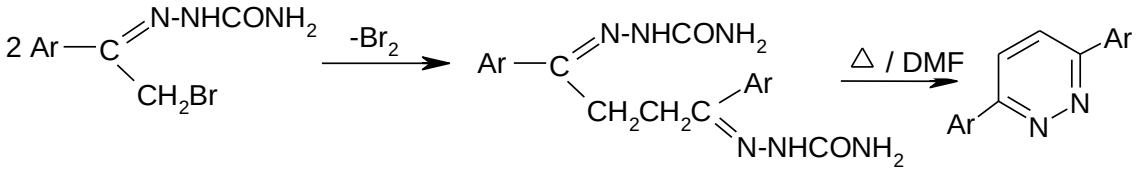
Expedient method for solid-phase synthesis of some 4-substituted-4,5-dihydropyridazin-3(2H)-ones starting from 4-oxo-pent-2-enoic acid **XXIII**. The solid-phase route began with anhoring **XXIII** on Wang resin followed by Michael addition with primary amines. The final step was an intramolecular cyclization of the hydrazone intermediate[15].



XXIII

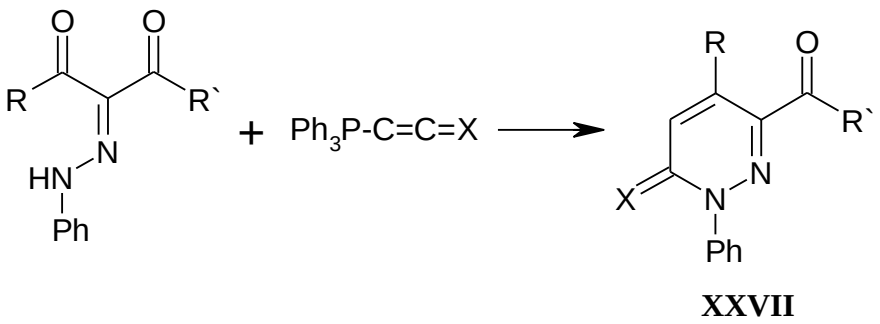
XXIV

Semicarbazones of phenacyl bromides are reduced electrochemically to **XXV** which give, upon heating in dimethylformamide, 3,6-diarylpyridazines **XXVI** [16].



XXV **XXVI**

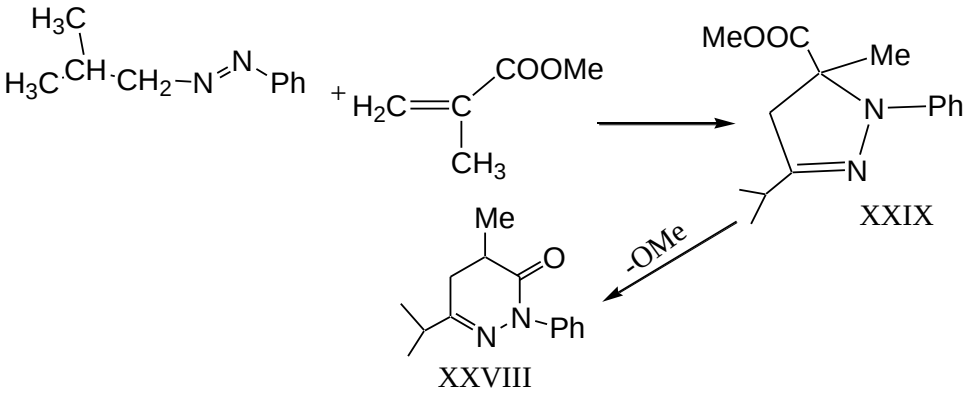
Pyridazines **XXVII** can be synthesized from 2-phenylhydrazones of 1,2,3-tricarbonyl compounds and phosphacumulenylides[17].



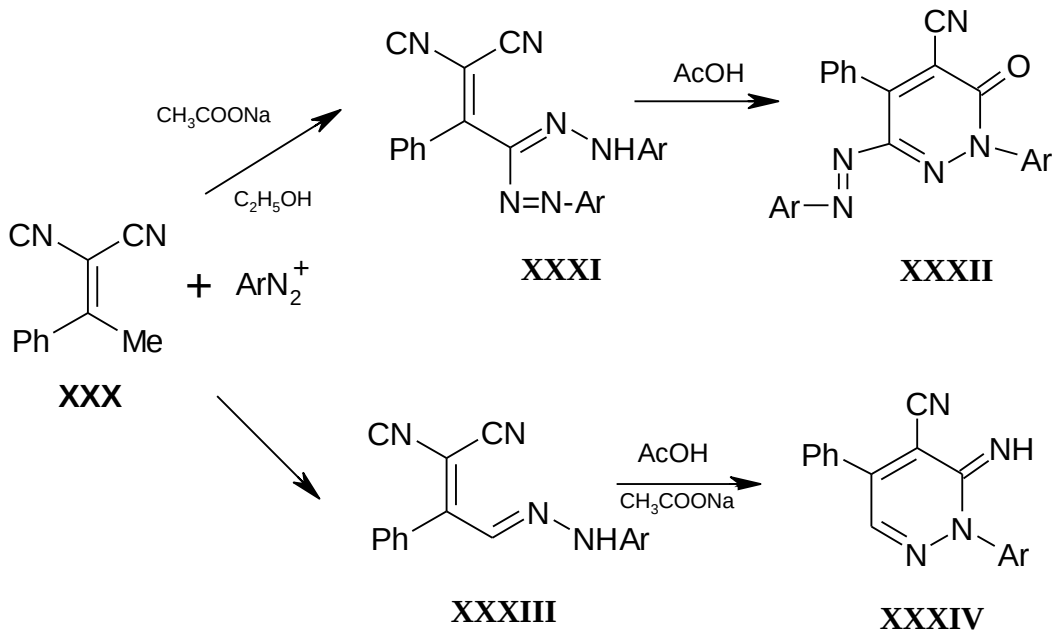
XXVII

X = O, NPh, etc.

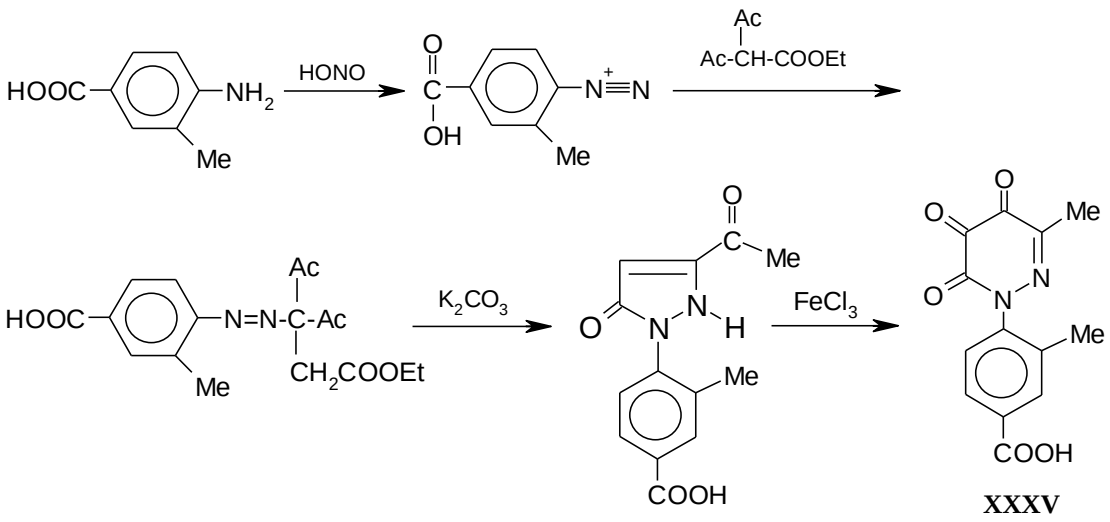
Isobutyraldehyde phenylhydrazone, when treated with an excess of methyl methacrylate at 120 °C, gave a mixture of pyridazinone **XXVIII** and pyrazoline **XXIX** in a ratio 2:1 as a result of different cyclization paths[18].



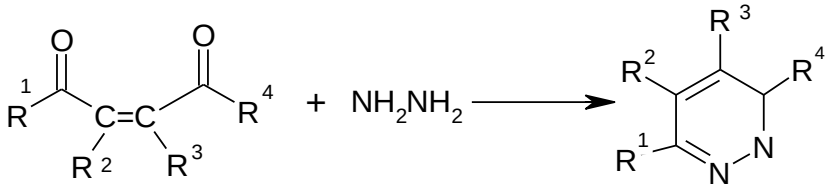
Aryl diazonium salts couple to various compounds with a reactive methylene group, and subsequent cyclization leads to pyridazine derivatives. In this manner, pyridazines were prepared from a dimmer of ω-cyanoacetophenone [19], a dimmer of ethyl cyanoacetate[20], 3-amino-2-cyano-4-ethoxycarbonylcrotononitrile[21], and other activated crotononitriles[22]. However, dicyano compound **XXX**, when treated with an aryl diazonium salt in ethanol and in the presence of sodium acetate, forms hydrazone **XXXI** which, upon heating in acetic acid, is transformed into pyridazine **XXXII**. The same reaction proceeded differently in acetic acid and in the presence of sodium acetate to give **XXXIV** via **XXXIII**[23].



Treatment of 4-amino-3-methylbenzoic acid in H_2O with conc. HCl and sodium nitrite followed by addition of ethyl 3-acetyl-4-oxopentanoate and pyridine in ethanol, the resulting 3-methyl-4-[N`-(2-ethoxycarbonyl-1-acetylethylidene)hydrazine]benzoic acid treated with K_2CO_3, to produce 3-methyl-4-(3-acetyl-5-oxo-2-pyrazolin-1-yl)benzoic acid which on further treatment with $FeCl_3$ in acetic acid afforded pyridazine **XXXV** (24)



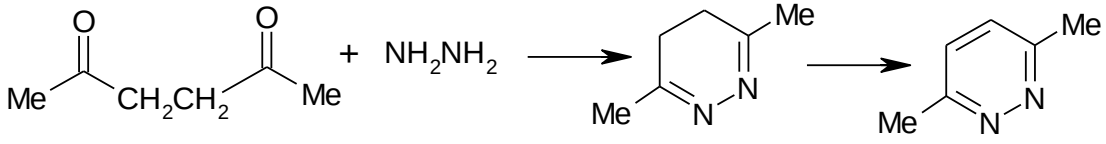
Unsaturated 1,4-diketones and hydrazine form pyridazines **XXXVI**. The reactions are usually performed in the presence of mineral acid, otherwise N-aminopyrroles **XXXVII** may be formed[25].



XXXVI

[R^1=Me, R^2 = 2-Me, 4-(COOH)C_6H_3][24].

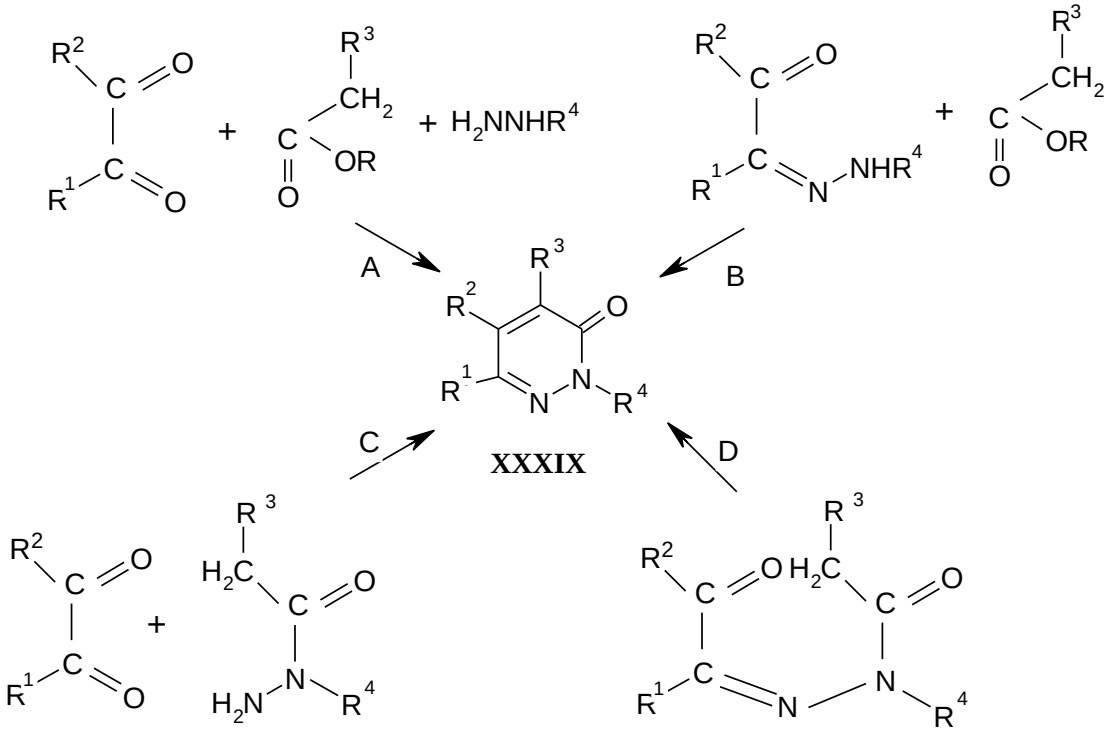
Saturated 1,4-diketones and hydrazine give dihydropyridazines. Some of the latter are not particularly stable and are hydrogenated in the presence of air or during distillation, into the more stable pyridazines thus acetonylacetone gives a good yield of 3,6-dimethylpyridazine **XXXVIII**[26].



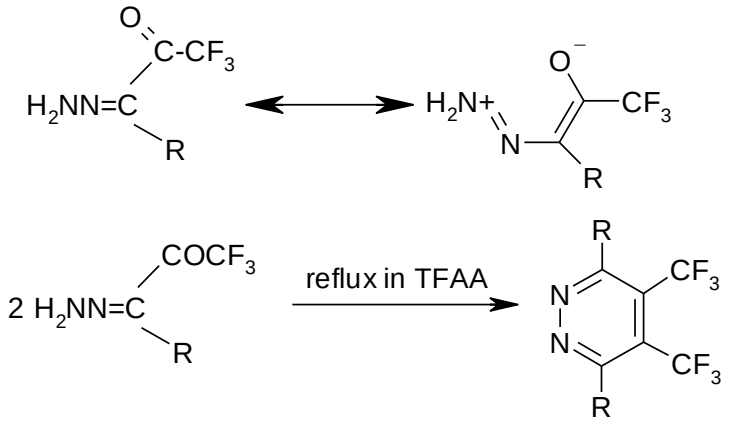
XXXVIII

1,2-Dicarbonyl compounds (1,2-diketones, α-keto acids, glyoxal) react with esters containing a reactive α-methylene group (malonic, acetoacetic, cyanoacetic, benzoylacetic, hippuric esters), and a hydrazine in the presence of sodium ethoxide to form 3(2H)-pyridazinones **XXXIX** (route A). However, the preferred synthetic method is either first to make the monohydrazone of the 1,2-

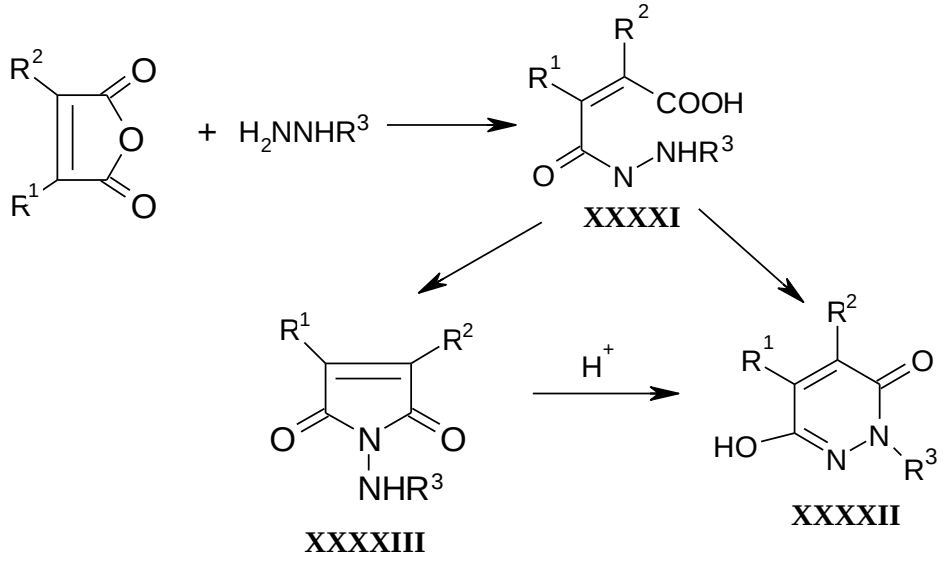
dicarbonyl compound (particularly for aromatic diketones) and then condense this with the ester containing the reactive methylene group (route B), or prepare the acid hydrazide and condense this with the 1,2-dicarbonyl compound, where in the presence of sodium ethoxide the pyridazinone is formed directly (route C), whereas in the absence of base the hydrazone is formed (route D), which can then be cyclized in a separate step. Route C and D are particularly useful for aliphatic dicarbonyl compounds[(27)].



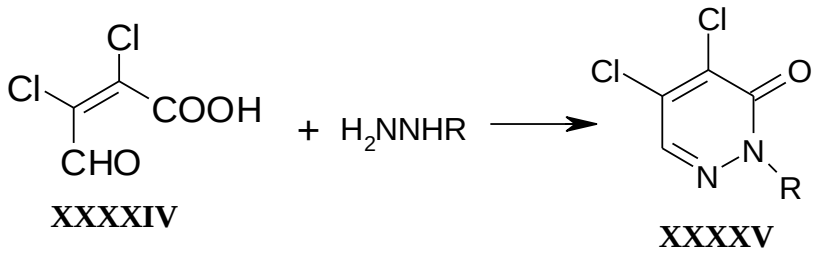
Acid catalyzed selfcondensation of 3-hydrazono-1,1,1-trifluoroalkan-2-ones prepared from 1,1,1-trifluoroalkan-2,3-diones and hydrazine hydrate afforded 4,5-bis(trifluoromethyl)pyridazines **XXXX**[(28)].



Maleic anhydride or its substituted derivatives react with hydrazines to give either the corresponding pyridazinones **XXXXII** directly or the intermediate 3-carboxyacrylohydrazine **XXXXI**, which can then be cyclized on heating. The intermediates **XXXXI**, when dehydrated in acid media, give either N-aminomaleimides **XXXXIII** or pyridazinones **XXXXII**. The former are isomerised in acid to pyridazinones, and the formation of **XXXXIII** can be prevented if the condensation is carried out in strongly acid solution[(29)].

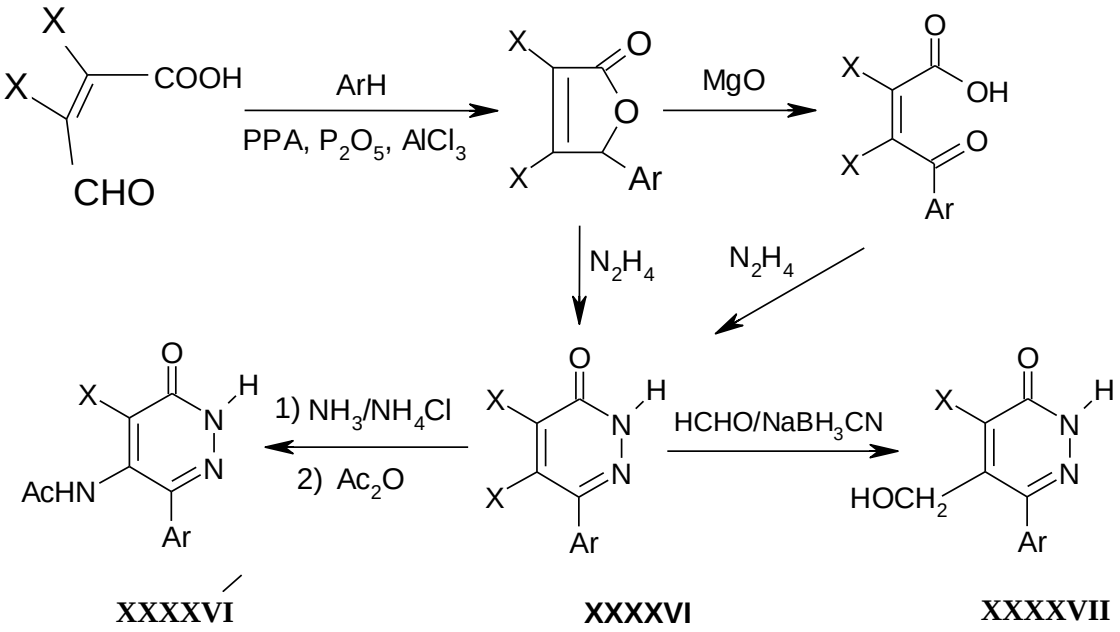


3-Formylacrylic acids or esters, such as mucochloric acid **XXXXIV** react with hydrazines to give 4,5-dichloropyridazinones **XXXXV**[30].



XXXXIV **XXXXV**

Also, 3-aryl-4,5-dihalo-3(2H)-pyridazinone XXXXVI is obtained from the reaction of mucochloric acid and hydrazine [31].



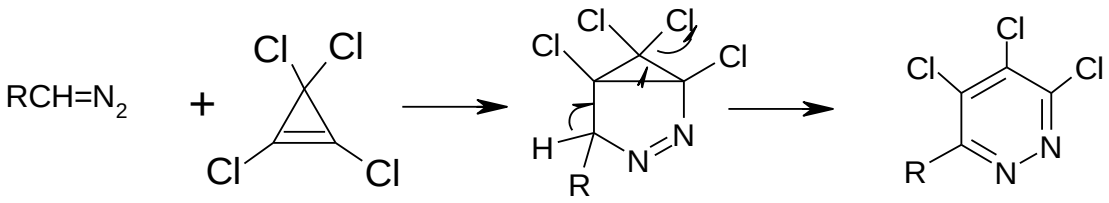
XXXXVI **XXXXVI** **XXXXVII**

B. Cycloaddition reactions:

A pyridazine ring can be formed by a cycloaddition reaction of diazo compounds or diazonium salts with aliphatic or cyclic compounds. It can also be formed by cycloaddition of various.

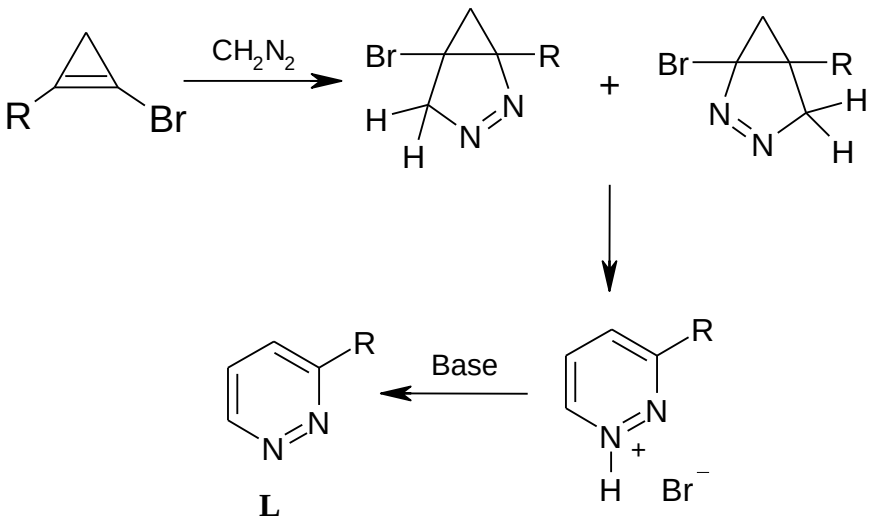
1,2,4,5-tetrazines and dienophiles in inverse electron demand Diels-Alder reactions.

Thus, tetrachlorocyclopropene and diazo compounds were reacted by [3+2] cycloaddition reactions, the cycloadducts **XXXXVIII** formed first, then rearrange in acid or alkali to pyridazine **XXXXIX**[32].



XXXXVIII **XXXXIX**

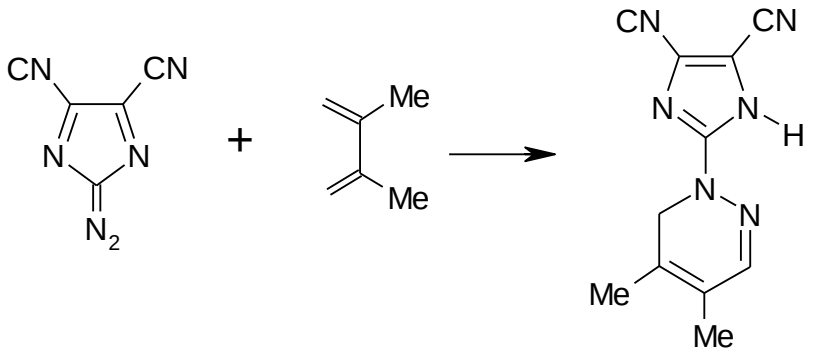
Reaction of 1-bromocyclopropenes with diazo-compounds leads to pyrazoles which opened and rearrange to pyridazines **L** [33].



L

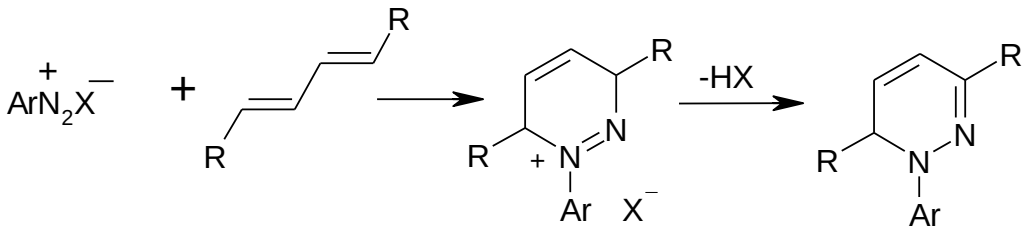
2-Diazo-4,5-dicyanoimidazole undergoes cycloaddition with 2,3-dimethylbuta-1,3-diene at room temperature to give pyridazinyl-imidazole **LI**. It has been proposed that the reaction proceeds by

initial attack of terminal nitrogen atom to give a transient aziridine, followed by ring opening and hydrogen transfer[34].



LI

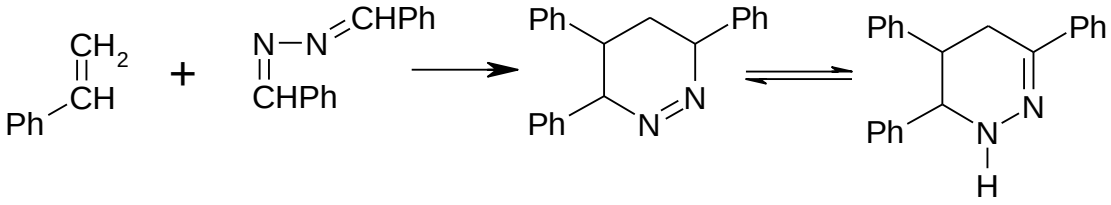
However, the reaction between dienes and aromatic diazonium salts are not coupling products, but rather, dihydropyridazines **LII**. A detailed investigation of this reaction, in particular with electron-rich dienes, revealed the cycloaddition is concerted, and 3,6-dihydropyridazines **LII** are formed first. They are transformed further into 1,6-dihydropyridazines **LIII**[35].



LII **LIII**

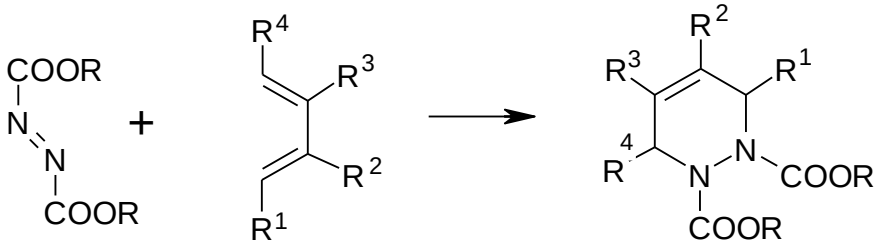
Upon heating a mixture of benzaldehyde and hydrazine salt in the presence of styrene, 3,5,6-triphenyl-1,4,5,6-tetrahydropyridazine **LIV** was obtained. The pyridazine formation is explained on the

basis of cycloaddition of benzaldehyde azine to styrene followed by tautomerization [(36)].



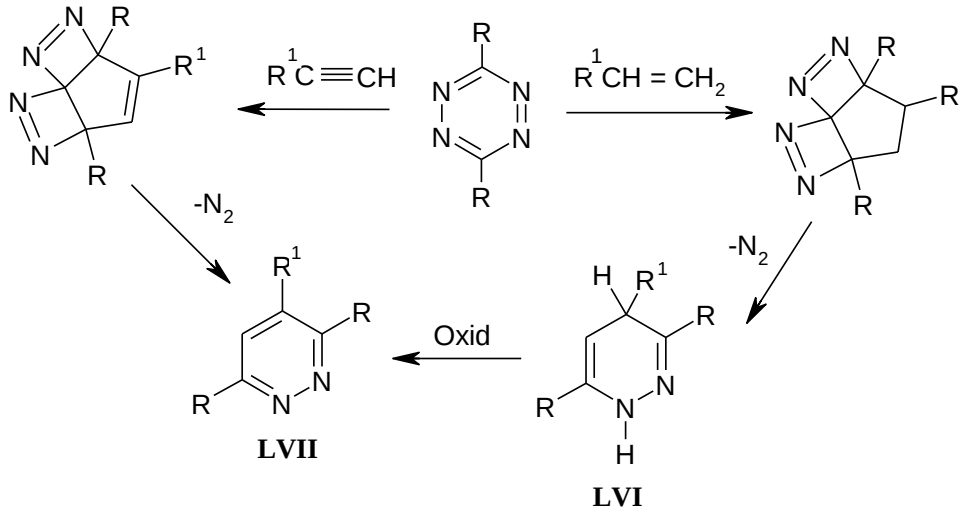
LIV

Similarly 1,2,3,6-tetrahydropyridazines **LV**, can be prepared by [4+2] cycloaddition reactions. An azo dienophile such as a dialkyl azodicarboxylate reacts with a conjugated diene to give **LV**[(37)].

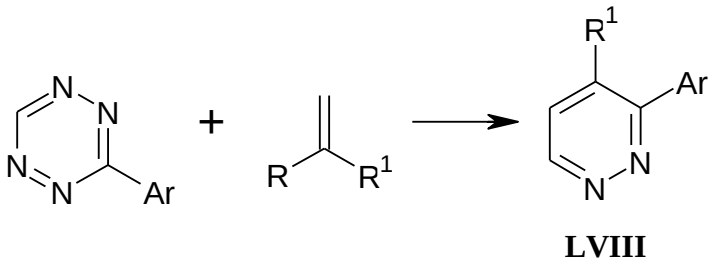


LV

The cycloaddition reaction between 1,2,4,5-tetrazines with strongly electrophilic substituents at positions 3 and 6 and alkenes produces 1,4-dihydropyridazines **LVI** which are easily oxidized o pyridazines **LVII**. The latter are obtained directly from alkynes which are, however, less reactive and give lower yields[(38)].

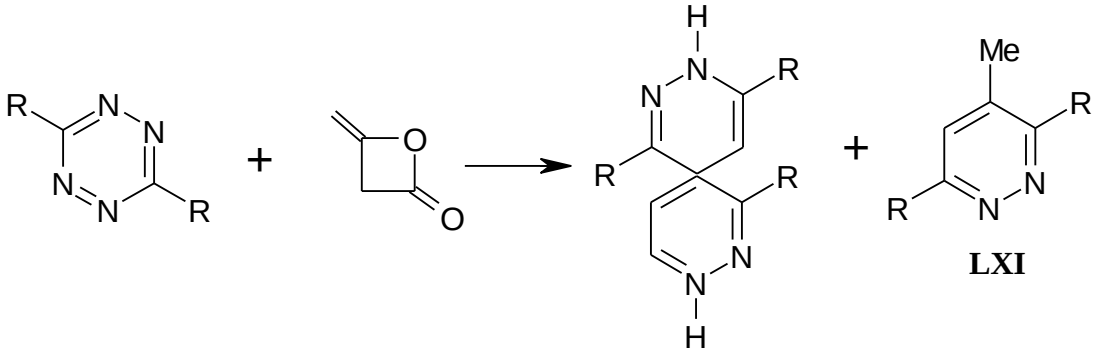


Ketene acetals react with various 3-substituted aryl-1,2,4,5-tetrazines to give almost exclusively the ortho isomers **LVIII**. An exception is 1,1-bisdimethylaminoethene, which afforded both regions isomers **LVIII** and **LIX**, the ratio being solvent dependent[(39)].



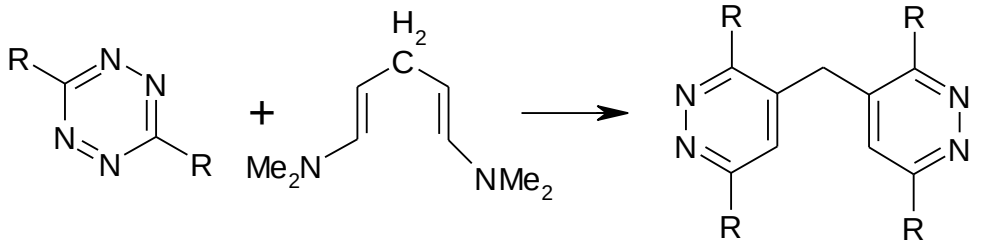
R_1 = SMe, OMe, OEt, NMe_2

Diketene reacted with 3,6-disubstituted tetrazine to give spiro-bipyridazine **LX** accompanied by a small amount of substituted pyridazine **LXI**[(40)].



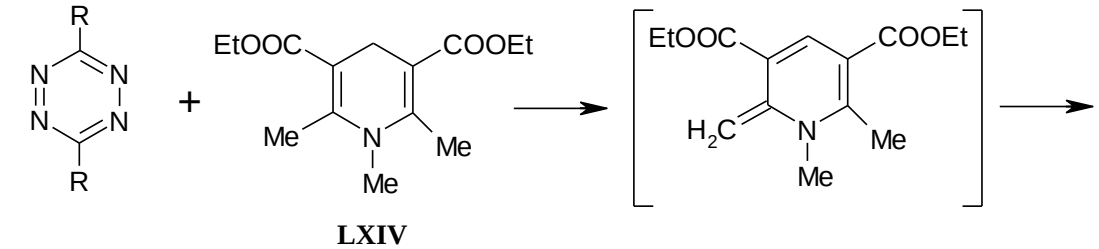
LX **LXI**

Dienamine **LXII** was reacted with tetrazine to give 4,4`-dipyridazinyl-methane **LXIII**[41].

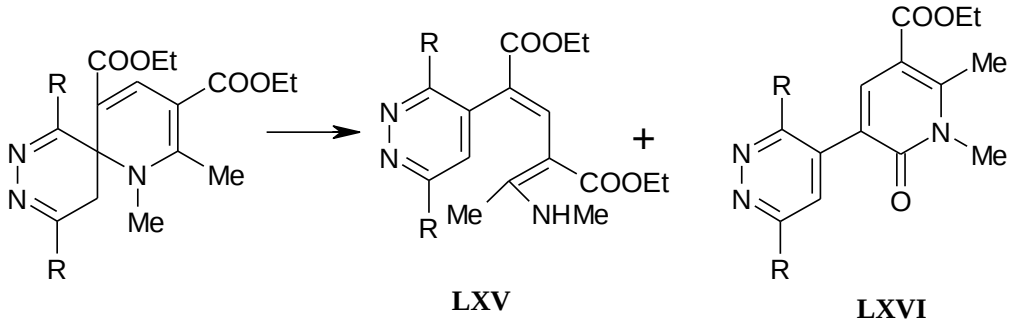


LXII **LXIII**

The reaction of N-methyldihydropyridines **LXIV** with tetrazine, leads, to pyridazines **LXV** and **LXVI** as a result of successive oxidation addition, ring opening and recyclization [42].

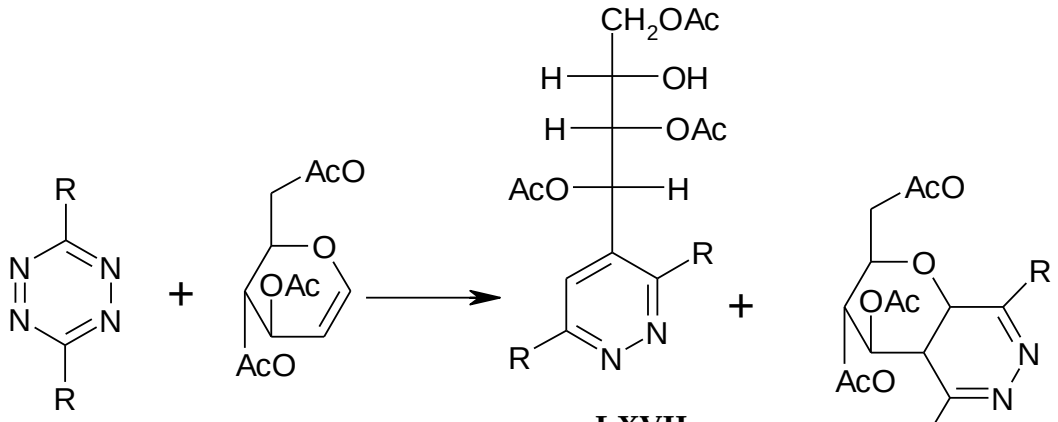


LXIV



LXV **LXVI**

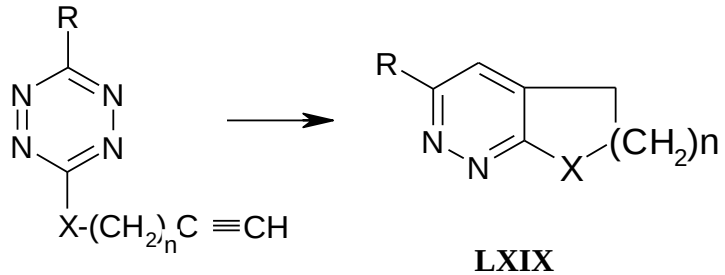
Reaction of 3,6-disubstituted tetrazine with unsaturated sugars was utilized for synthesis of pyridazine. The double bond of some unsaturated sugars has been involved in this reaction to give the corresponding pyridazines after prolonged heating. A mixture of two products **LXVII** and **LXVIII** was obtained, the bicyclic **LXVIII** compound being formed only in 2-3% yield[43].



LXVII

LXVIII

Intramolecular cycloaddition of 1,2,4,5-tetrazines with acetylenic side chain has been used to prepare various condensed heterocyclic rings **LXIX** [44].

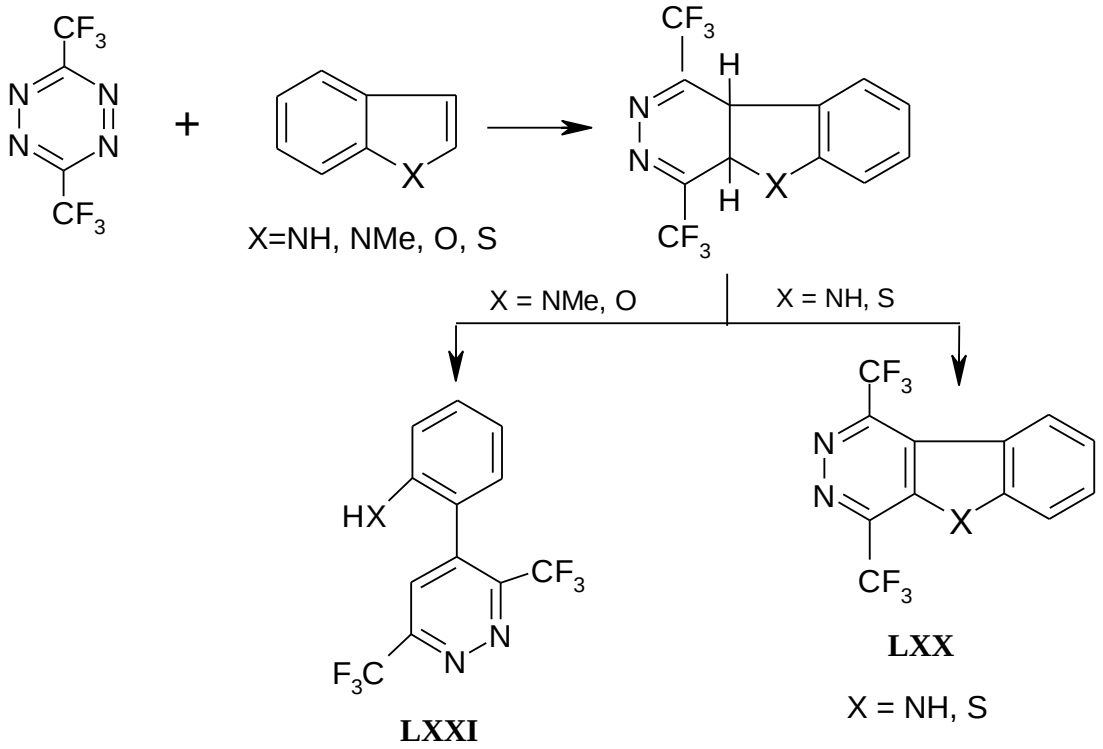


LXIX

X = O, NH
R = SMe, SOMe, SO_2Me, Ph

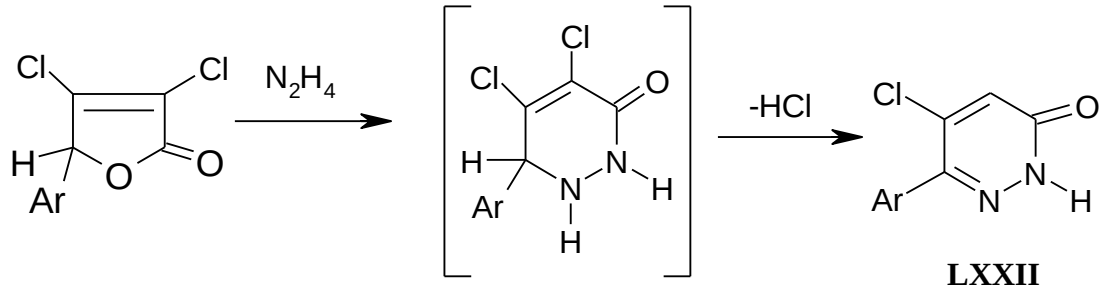
Finally, 3,6-disubstituted tetrazine was reacted with various heterocycles have been used as dienophiles in these cycloaddition. Thus, 3,5-bis(trifluoromethyl)-1,2,4,5-tetrazine reacts with some

benzoazoles, the cycloadducts formed undergo [4+2] cycloreverse or/with nitrogen elimination to give condensed pyridazines as shown in the case of indole and benzothiophene to produce compound **LXX**. However, the cycloadducts from N-methylindole and benzofuran may undergo ring opening to give substituted pyridazines **LXXI**[45].



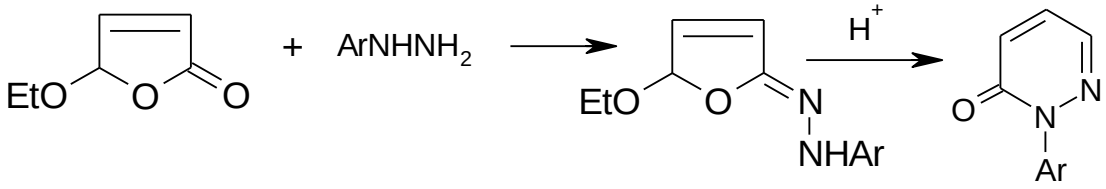
C. From other heterocycles:

A third important method for the preparation of pyridazines is the modification or rearrangement of other ring structures. A closely related synthesis involves the treatment of aromatic γ-lactones with hydrazine. Hydrazine adds across the lactone ring oxygen bridge, forming a dihydropyridazinone which loses HCl spontaneously to yield the fully aromatic ring **LXXII** system[46].



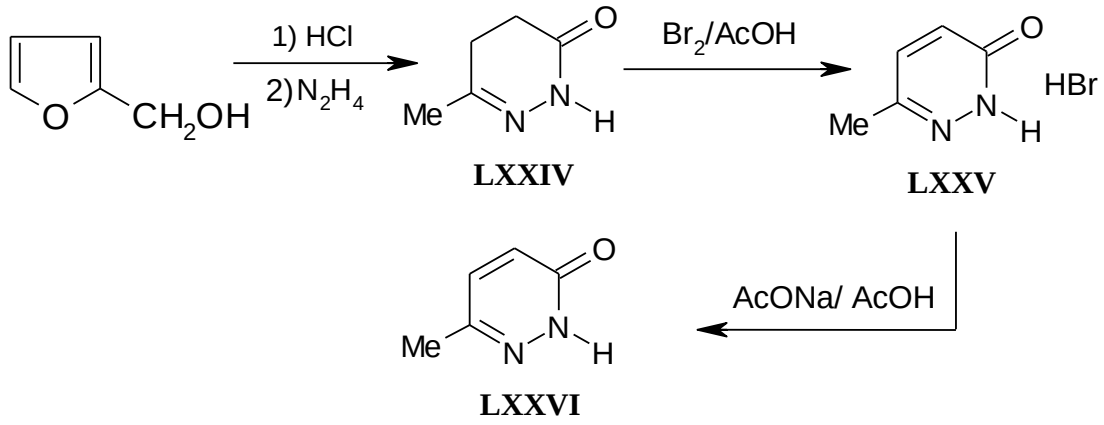
LXXII

A similar reaction in which the aromatic ring system is replaced by an ethoxy group is reported to give excellent yields[47]. In this case the hydrazine condenses to the carbonyl group first, followed by ring opening and cyclization to the pyridazinone **LXXIII**.



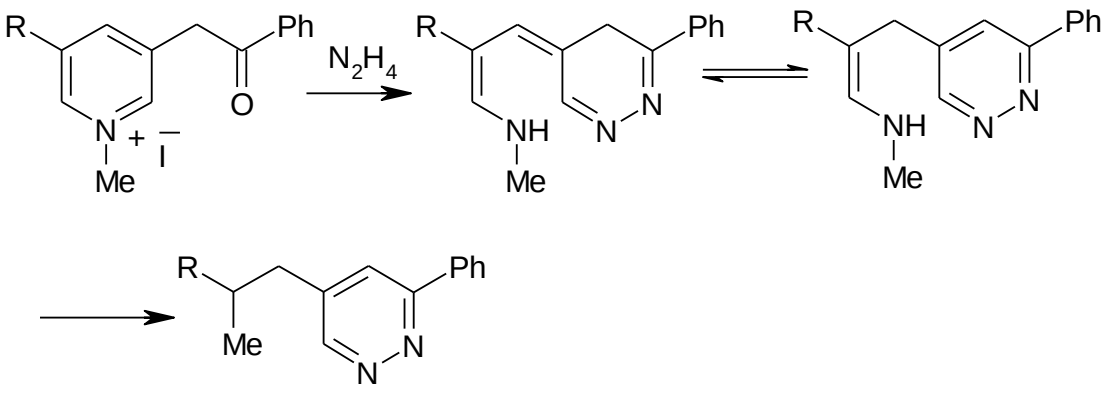
LXXIII

Furfuryl alcohol was refluxed with butanol in the presence of conc. HCl, hydrazine hydrate and sodium hydroxide were added and refluxed to give 87% dihydropyridazinone **LXXIV**. Dehydrogenation of **LXXIV** with Br_2 in acetic acid gave 92.3% pyridazinone HBr **LXXV** which was treated with sodium acetate in acetic acid to give free pyridazinone **LXXVI**[48].



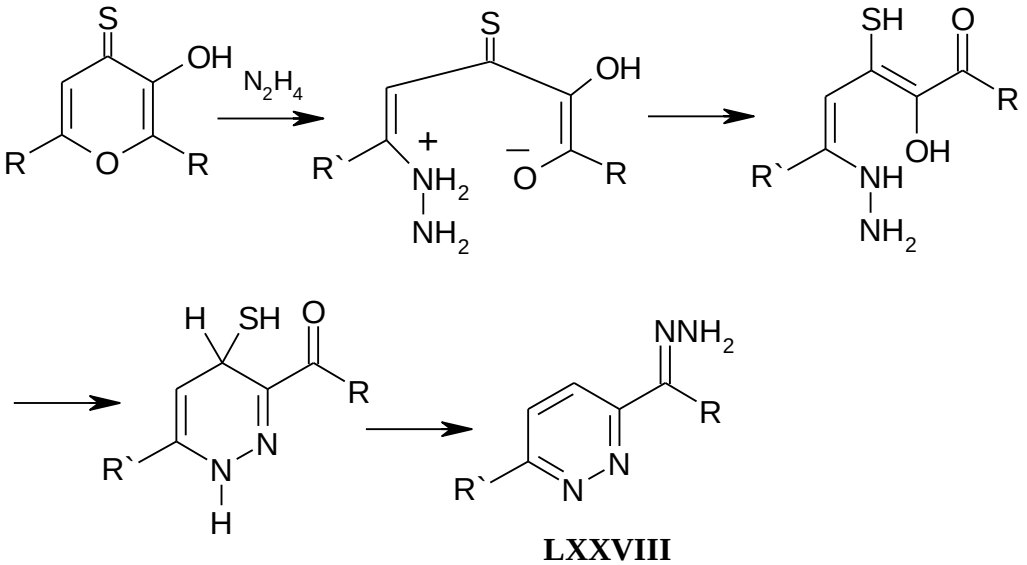
LXXIV **LXXV** **LXXVI**

There are few examples of six-membered heterocycles being transformed into pyridazines. 3-Phenacylpyridinium methiodide, when treated with hydrazine under Wolff-Kishner reduction conditions, is transformed into 6-phenyl-4-propylpyridazine **LXXVII**[(49)].



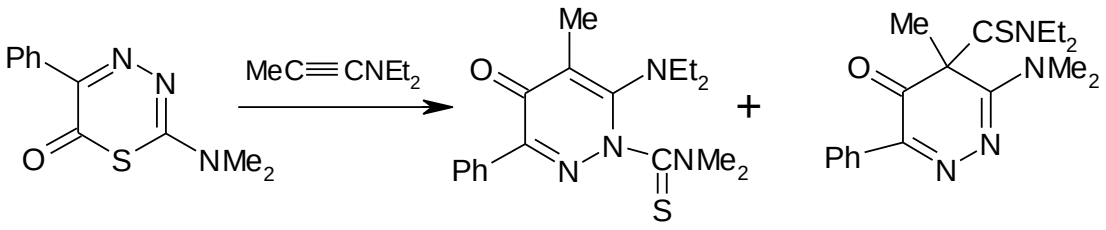
LXXVII

4H-Pyranthiones, when treated with hydrazine can give pyridazines. Perhaps hydrazine attacks position 6, followed by elimination of hydrogen sulfide to give **LXXVIII**[(50)].



LXXVIII

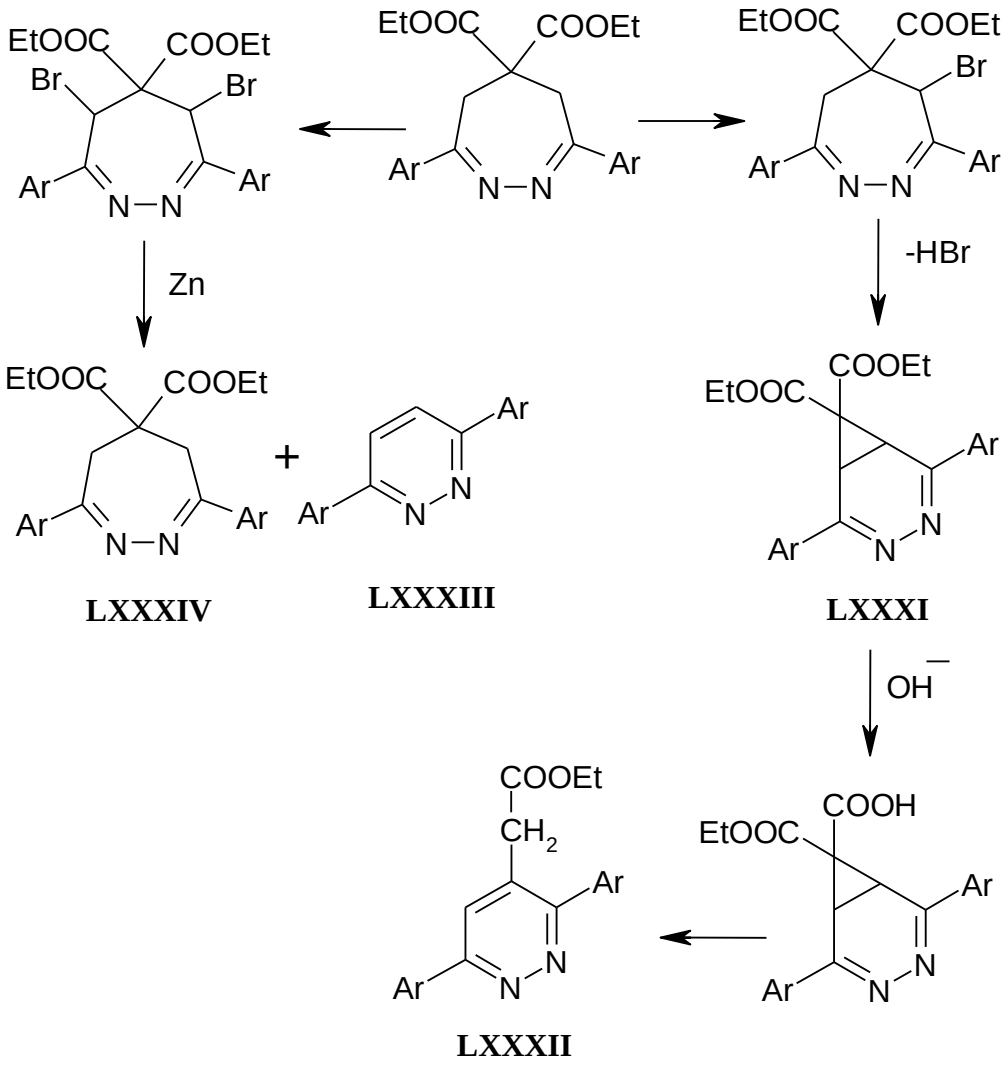
2-Dimethylamino-5-phenyl-1,3,4-thiadiazin-6-one reacts with the electron rich 1-diethylaminopropyne to give two pyridazines **LXXIX** and **LXXX**, in 72% and 2% yield, respectively. The formation of both compounds is explained by the initial addition of yanamine, ring opening, and cyclization in two ways[(51)].



LXXIX **LXXX**

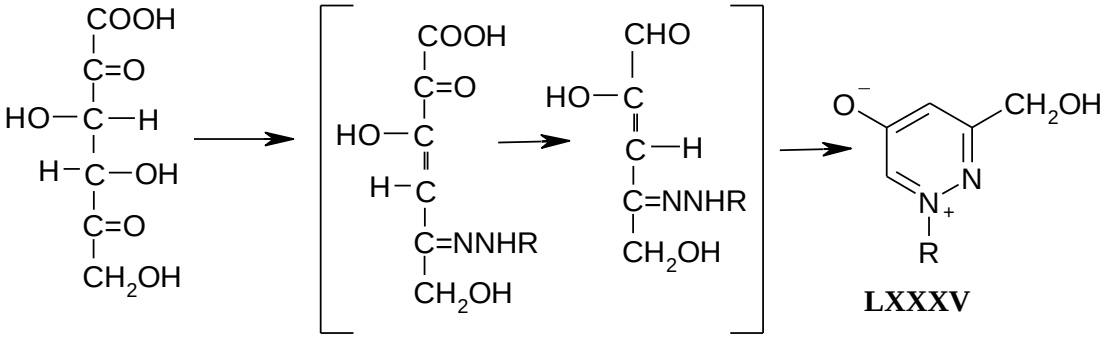
Some 1,2-diazipines are also transformed into pyridazines. Upon bromination they are transformed into diazanorcaradiene derivatives **LXXXI** which upon partial saponification and heating at 140°C give the corresponding pyridazines **LXXXII**. The dehalogenation with zinc in boiling ethanol gives diarylpyridazines

LXXXIII as the main products, together with the dihydrodiazepine **LXXXIV**[52].



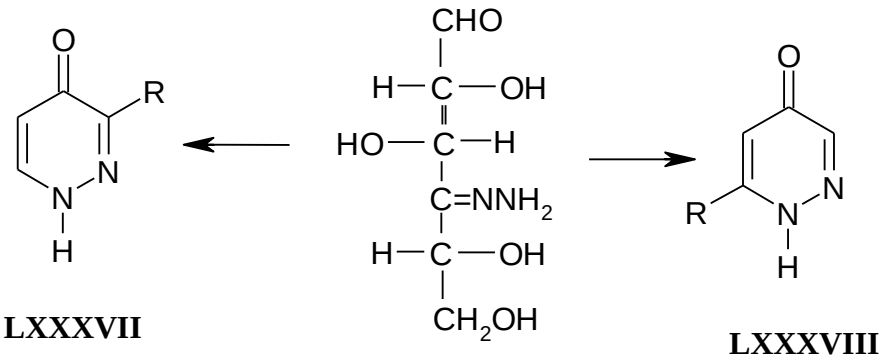
D. From carbohydrates:

Several synthesis of pyridazines from monosaccharides have been described. Calcium 2,5-diketo-D-gluconate reacts with monosubstituted hydrazines to give the corresponding pyridazinium derivatives of the Zwitterionic type **LXXXV**[53]. The reaction proceeds by hydrazone formation, dehydration, decarboxylation and cyclization.



LXXXV

In similar manner D-xylohexes-4-uloses **LXXXVI** is transformed as a mixture of 3- and 6-substituted products **LXXXVII**, **LXXXVIII** [54].

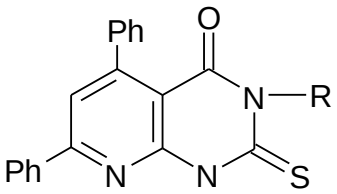


LXXXVII **LXXXVI** **LXXXVIII**

Biological activity of pyrimidine derivatives:

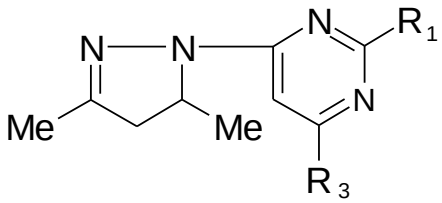
Pyrimidine nucleus has been employed as a basis for the synthesis of chemotherapeutic agents and a large number of its derivatives has been reported to posses various biological properties such as antitumor[55], material[56][57], diuretic[58], anti-inflammatory[59][60,61], antithyroid[62],[57], antibacterial[63], antifungal[64] and antifeishmorial[65].

Pyrido[2,3-d]pyrimidin-4(5H)-ones (**LXXXIX**) and all the compounds which prepared by methylation and substituted with amines had antibacterial activity[66].



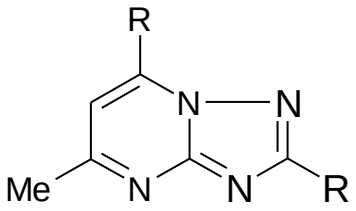
(LXXXIX)

Pyrazolyl pyrimidine derivatives (XC) showed antibacterial activity against piricularia, orgazae, hehminthosporium, orgza and shaerotheco fuliginea[67].



(XC)

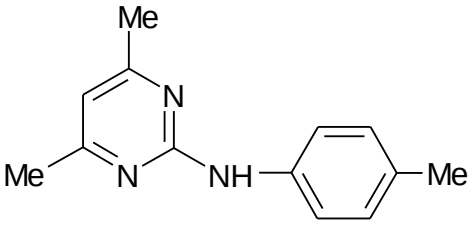
s-triazolo[4,5-a]pyrimidine (XCI) are useful as vasodilator, anticholesteremice and blood platelet aggregation inhibitors[68].



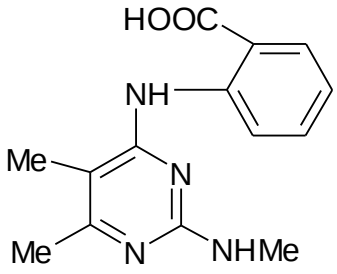
(XCI)

Arylamino pyrimidine e.g. 2-(4-toluidino)pyrimidine (**XCII**) showed antidiabetic and antimycotic activity lowered blood sugar levels by 12% [(69)].

Also, o-carboxy phenyl amino pyrimidine (**XCIII**) is useful as inflammation inhibitors[(69)].

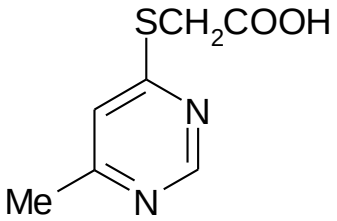


(XCII)



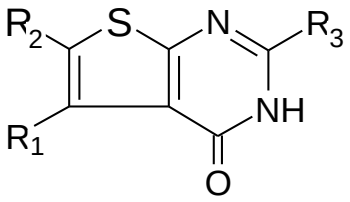
(XCIII)

Pharmacological studies of 6-methyl-4-pyrimidinylthioacetic acid (**XCIV**) showed that it possess hypotipidimic and central nervous system depressant activity in mice[(70)].



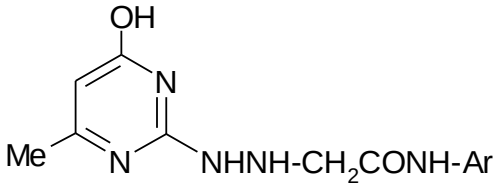
(XCIV)

Thieno-[2,3-d]pyrimidine (**XCV**) showed analgesic activity equal or superior to that of aspirine[(71)].



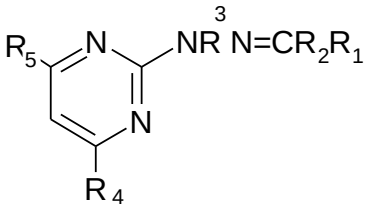
(XCV)

Hydrazine derivatives of pyrimidine are found to possess various biological activities, for example, 2-(N-arylcarbamoylmethyl)-hydrazine-4-hydroxy-6-methylpyrimidine (**XCVI**) showed antibacterial and antitubercular activities[(72)].



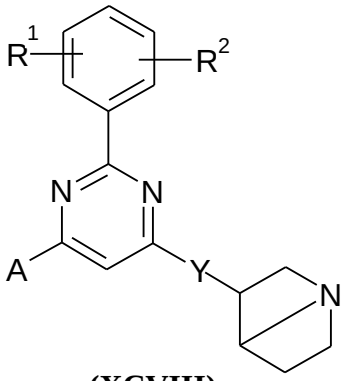
(XCVI)

2-Alkylidenehydrazinopyrimidine (**XCVII**) useful as agrochemical fungicides.



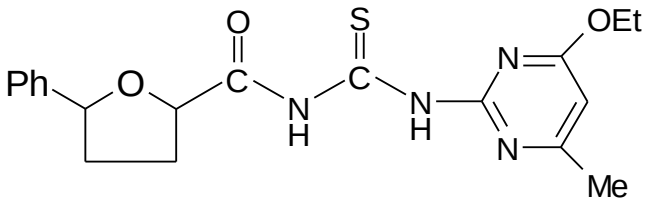
(XCVII)

Also, it was reported[(73)], that the pyrimidine derivatives (**XCVIII**); R_1, R_2 = H, OH, alkoxy, CF_3, halo, A = Me, CF_3, Me_3C; Y = O, NH] were useful as muscarinic agonistin treating central nervous disorders such as dementa.

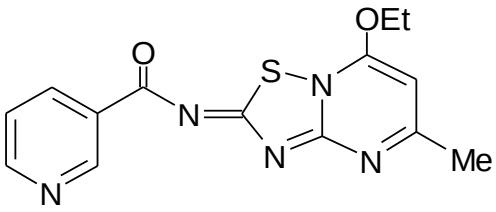


(XCVIII)

Substituted acyl (thio) urea and/or thiadiazolo[2,3-a]pyrimidine derivatives (**XCIX**) and (**C**) are used as potent inhibitors of influenza virus neuraminidase[(74)].



(XCIX)



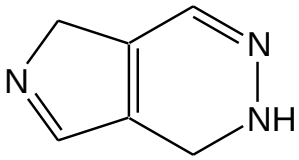
(C)

Biological activity of pyridazine derivatives

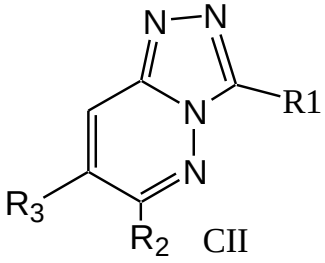
A large number of pyridazine derivatives display biological and pharmaceutical activities. Thus, in this part we will demonstrate some examples.

Treatment of cancer: (Anticancer activity)

Pyrrolo[3,4-d]pyridazine (CI)[75,76] and triazolo[4,3-b]pyridazines (CII) [77,78]were evaluated in vitro through anticancer screening.



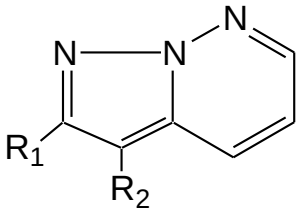
CI



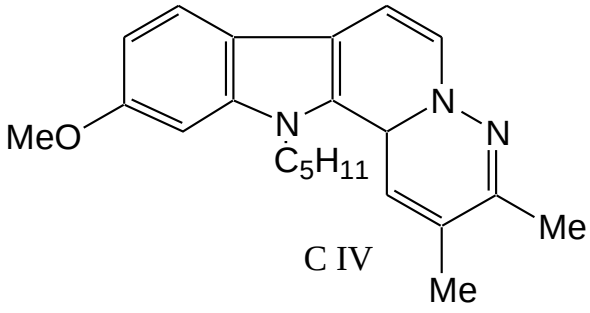
CII

R_1= (un) sub. phenyl, furyl, thienyl and pyridyl
R_2= substituted NH2 and OH
R_3= (un) substituted cycloalkyl and aryl

Also, both of pyrazolo[1,5-b]pyridazines (CIII) and compound (CIV) are used as anticancer agents [79,80].



CIII



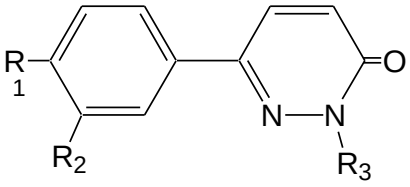
C IV

R_1= H,alkyl, alkoxy and halo
R_2= 1,3-oxazine

Anti-inflammatory activity:

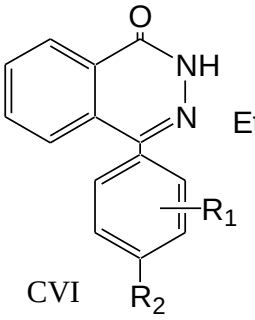
A novel series of 2,3-diaryl-pyrazolo[1,5-b]pyridazines underwent clinical evaluation for treatment of the inflammatory

pain[81,82] . While other, substituted pyridazinone [83,84] (CV), hydrophthalazines [85] (CVI) and pyrrolopyridazine [86] (CVII) are useful for treatment of inflammatory diseases.



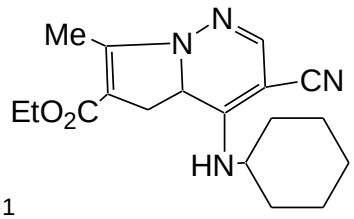
CV

R_1= alkayl, alkoxy and halo
R_2= H, alkoxy and alkaylthio
R_3=OH, CN, alkyl and cycloalkyl



CVI

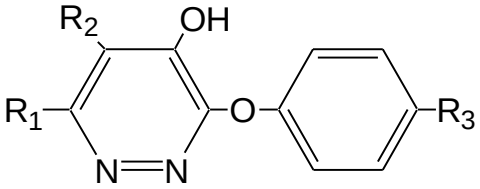
R_1= aminosub. alkyl
R_2= H and halo



CVII

Herbicides:

3-aryloxy-6-substituted pyridazines (CVIII) have high herbicidal activity [87,88].

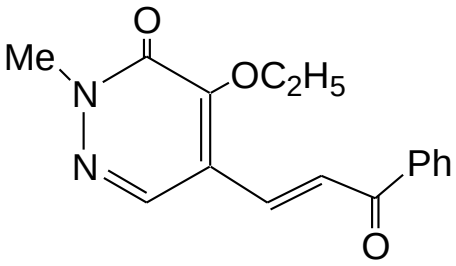


CVIII

R_1= H, halo,CN, cycloalkyl and alkoxy
R_2= H,halo, alkoxy, ROCO and PhO
R_3=CHO, CN, COOH,NO_2 and OH

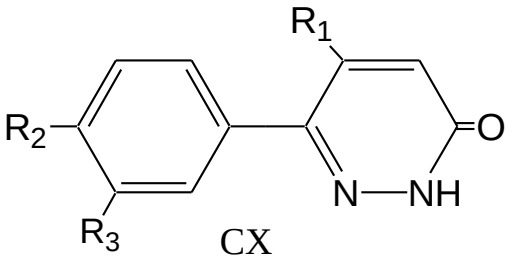
Antiplatelet agents:

In the search for novel antiplatelet agents, a convenient and efficient methods for the preparation of pyridazine derivatives like 4-ethoxy-2-methyl-5-(3-oxo-3-phenylpropenyl)pyridazin-3-(2H)-one (CIX) were reported [89,90].



CIX

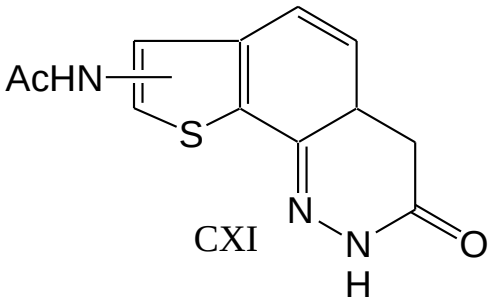
on the other hand, 6-aryl-5-amino(alkylamino)-3-(2H)-pyridazinons (CX) are useful as potential platelet aggregation inhibitors [91,92] .



CX

R_1=NH_2 and $N(CH_3)_2$
R_2,R_3= H and OCH_3

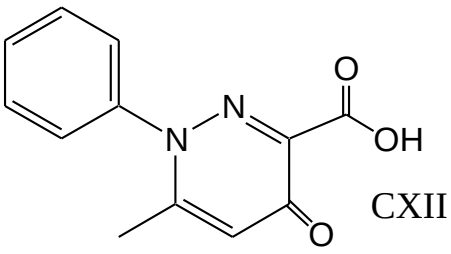
Also, a number of thienocinnolin-3(2H)-ones (CXI) were tested for their inhibiting collagen induced platelet aggregation and antihypertensive [93].



CXI

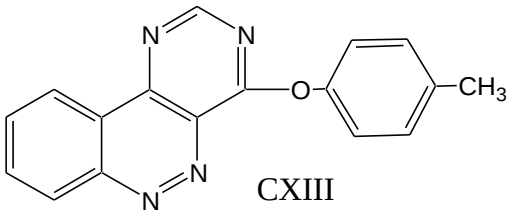
Antibacterial agents:

Pyridazines like 1-aryl-1,4-dihydro-4-oxo-6-methylpyridazin-3-carboxylic acid (CXII) have shown interesting antibacterial activity against both gram-positive and gram-negative organisms [94,95] .



CXII

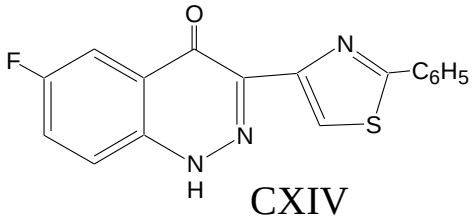
Also, substituted 4-aryloxypyrimido[5,4-c]cinnolines (CXIII) displayed antibacterial activity against Escherichia Coli, Pseudomonas Aeruginosa and Bacillus Cirroflagellus [96] .



CXIII

Antimicrobial activity:

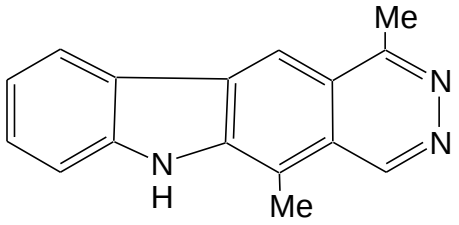
A number of pyridazines like 6-fluoro-3-(2-phenylthiazol-4-yl)-1H-cinnolin-4-one (CXIV) were screened for their antimicrobial activity [97,98] .



CXIV

Antitumor agent

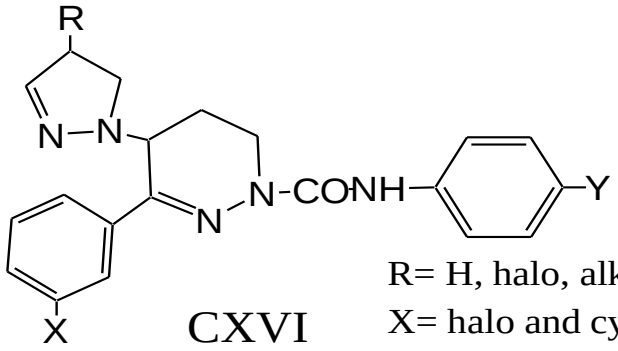
In addition to the above biological activities of pyridazines, 1,5-dimethyl-6H-pyridazino[4,5-b]carbazole (CXV) has been tested for its antitumor nature [99] .



CXV

Pesticides:

Furthermore, 4-(pyrazol-1-yl)tetrahydropyridazines (CXVI) are used as pesticides [100] .

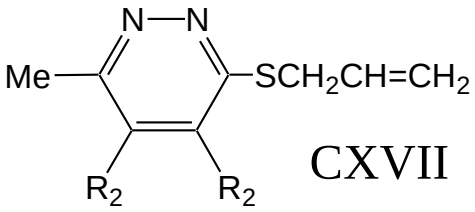


CXVI

R= H, halo, alkl, alkoxy, alkylthio, OH and NO_2
X= halo and cyano
Y= halo and haloalkayl

Other biological effects:

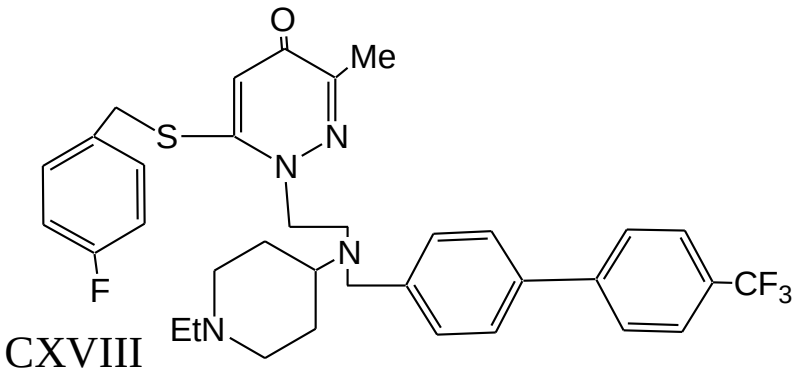
4,5-substituted-3-alkoxy-6-allythiopyridazine derivatives (CXVII) exhibit a superior effect for prevention and treatment of hepatic induced by carbon tetrachloride and for prevention of human tissues from radiation [101] .



CXVII

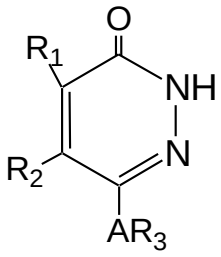
R_1,R_2=$(CH_2)_4$

Pyridazinone of type (CXVIII) is used for treating atherosclerosis [102] .



CXVIII

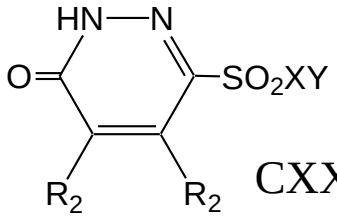
Also, sulfeny,sulfinyl and sulfonylpyridazinones (CXIX) are inhibitors for treating / preventing diabetic composition in mammals [102] .



CXIX

R_1,R_2 = H and methyl
R_3= heteroaryl
A= S,SO and SO_2

On the other hand, sulfonylpyridazinones (CXX) are used as therapeutic agents for ischemic tissue damage [103] .



CXX

R_1,R_2=Hand methyl
XY= $CH_2CHOHAr$ and CH_2COAr

1,3,4-oxadiazole-substituted pyridazines exhibit high antifungal activity against wheat seeding rust fungi [104] .

TYPES OF SYNTHETIC SURFACE ACTIVE AGENTS

Introduction:

Surfactant is an abbreviation for surface active agent, which means active a the surface, or defined as those which affect the interfacial tension between two surface such as solid-liquid, liquid-liquid or liquid-gas. They include compounds with emulsifying, wetting softening and detersive properties, but not all the surfactants must fulfill all the above requirements, the chemical composition of the surfactants is an important factor in its behaviour.

Surfactants have an amphiphilic nature, they contain in their molecular structure two parts with different polarity, one which soluble in solvent is called the hydrophilic part and one which insoluble is called the hydrophobic part, the schematic representation of surfactant molecule is in Fig. 1.

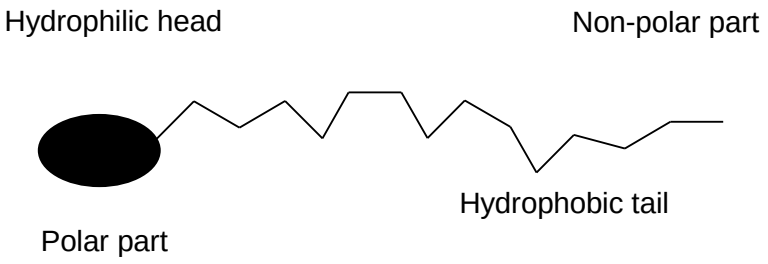


Fig. 1. Schematic representation of surfactant molecule.

The hydrophobic part (tail) is commonly a hydrocarbon (branched or linear); which may contain aromatic structure. In

contrast, the hydrophilic part (head is an ionic or strongly polar group, e.g. ethylene oxide, EO) which have a great affinity to water. The hydrophilic group (head) is not necessarily placed at the end of the hydrocarbon chain, also more than one hydrophilic or hydrophobic group can be present in a surfactant molecule. Recently, novel type form of surfactants consisting of two conventional surfactant molecules linked together with a short spacer; these called Gemini (or dimeric) surfactant (Fig.2).

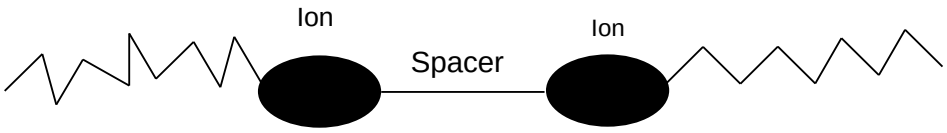


Fig. 2. Schematic representation of Gemini surfactants.

A surfactant molecule is not fully compatible with either a non-polar or polar medium. There is always a conflict between the affinity of the head and tail groups; this is giving the surfactants their unique properties (i.e., it acts as foaming, wetting, dispersing or emulsifying agents), the relative sizes and shapes of hydrophobic and hydrophilic parts play an important role for physical properties of surfactants.

Classification of surfactants:

The primary classification of surfactants is made on he basis of the charge of the polar head group. It was divided into four different main types, anionics, cationics, nonionics and amphoteric surfactants. Anionic and cationic surfactants carry negative and positive charges on their head groups, respectively, the nonionics are

uncharged head group, and amphoteric surfactants which may be anionic or cationic depending on the pH of the solution (Fig. 3).

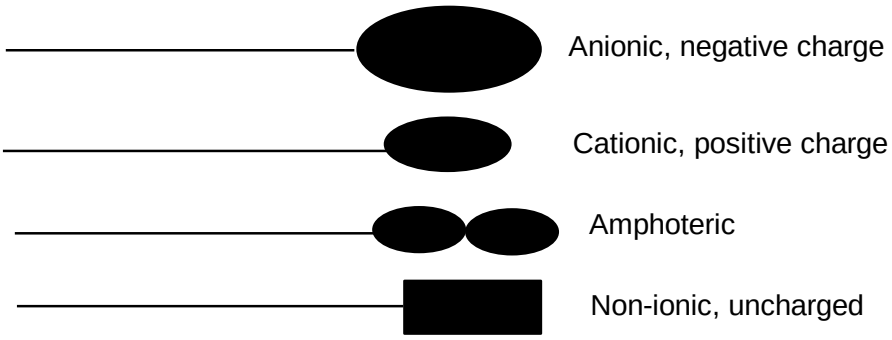
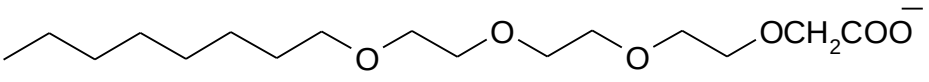


Fig. 3. The four different main types of surfactants.

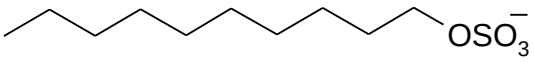
1. Anionic surfactants:

These are consisting of a linear or branched chain with polar negative group (carboxylate, sulfate, sulfonate or phosphate) which is response for surface character.

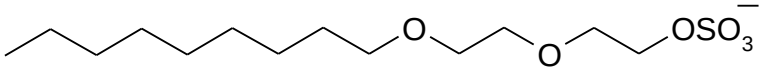
They are capable of undergoing ionization in solution to oil soluble anion and metallic cation. The most common cation used are sodium and potassium. Examples of anionic surfactants (Fig. 4).



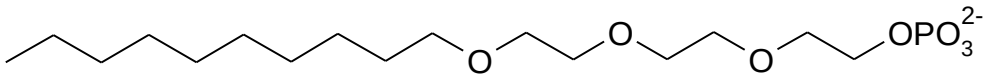
Alkyl ether carboxylate



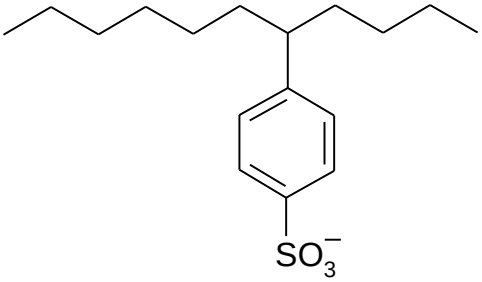
Alkyl sulfate



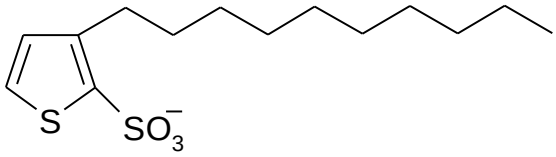
Alkyl ether sulfate



Alkyl ether phosphate



Alkyl benzene sulfonate

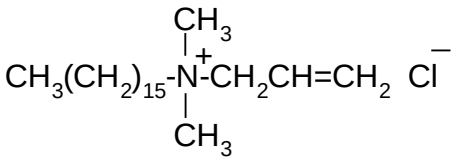


Alkyl thienyl sulfonate

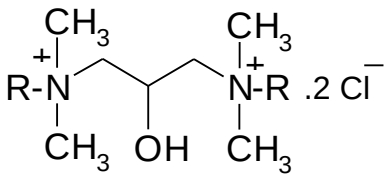
Fig. 4

2. Cationic surfactants:

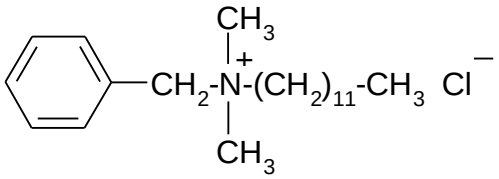
They are consist of a hydrophobic hydrocarbon group and one or more hydrophilic groups which dissociate in aqueous medium. Most of their hydrophilic groups have a nitrogen atom carrying the positive charge which is the carrier of the surface active properties of this type. Examples of cationic surfactants (Fig. 5).



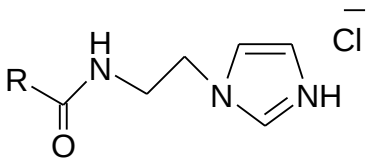
Alkyl amine salt



Alkyl diamine salt



Benyzl alkyl amine salt



Alkanol amino ethyl
imidazolinium chloride

Fig. 5

3. Amphoteric surfactants:

They are surfactants which in aqueous solutions contain a positive and a negative charge in the same molecule depending on composition and conditions of the medium, i.e. pH of the medium affects on the behaviour of the substrate. Most amphoteric surfactants are able to behave as cationic surfactant in acidic media and as anionic surfactants in alkaline media. Examples of amphoteric surfactants (Fig. 6).

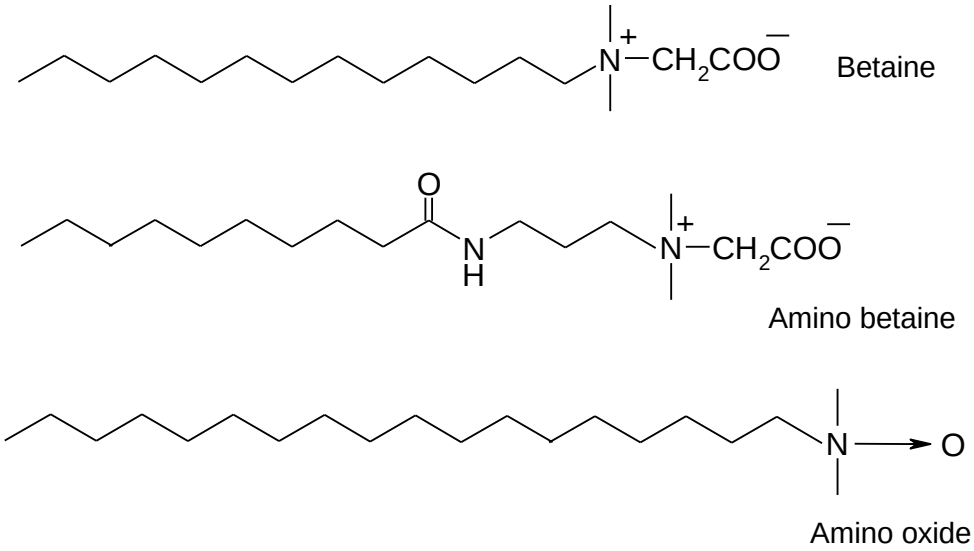
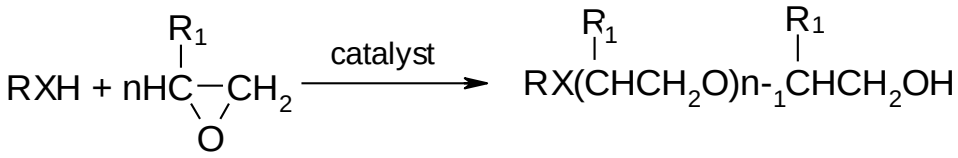


Fig. 6

4. Nonionic surfactants:

Alkylene oxide (ethylene oxide and propylene oxide) is one of the principal process employed to introduce hydrophilic functional into the molecular structure of hydrophobic compounds. He ultimate objective of the process is the production of the surface active agents having the desired hydrophile-hydrophobe balance for such commercial applications as detergency, emulsification, and wetting textile processing.

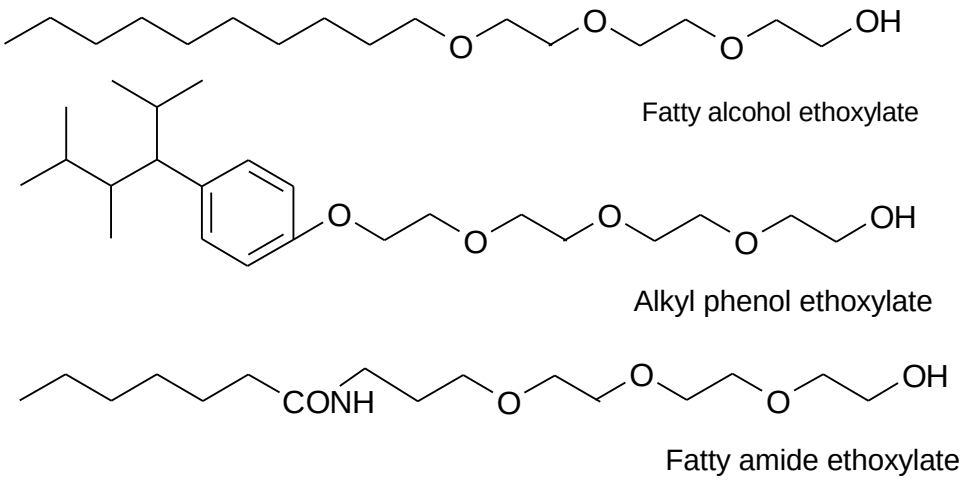
Alkylene oxide is characterized by great reactivity, this is due to their structure contains there membered ring undergo great strain and can readily be opened, result to fast added to the compounds having active hydrogen atom in their functional group to form hydroxyethyl or hydroxypropyl derivatives[105,106].



Where R = alkyl fatty chain, X = O, N or S, R_1 = H or CH_3, n = moles of EO or PO.

The active hydrogen of hydroxyalkyl derivatives are available for reaction with an additional alkylene oxide and by repetition of this process, a polyoxyethylene or polyoxypropylene compounds can be formed, most of the important nonionic surfactants are synthesized in an anhydrous environment in presence of an alkaline catalyst.

Ethylene oxide forms a large number of condensed products with fatty acid, alcohol, mercaptans, amines and amide that have good detergent. Examples of nonionic surfactants types in Fig. 7.



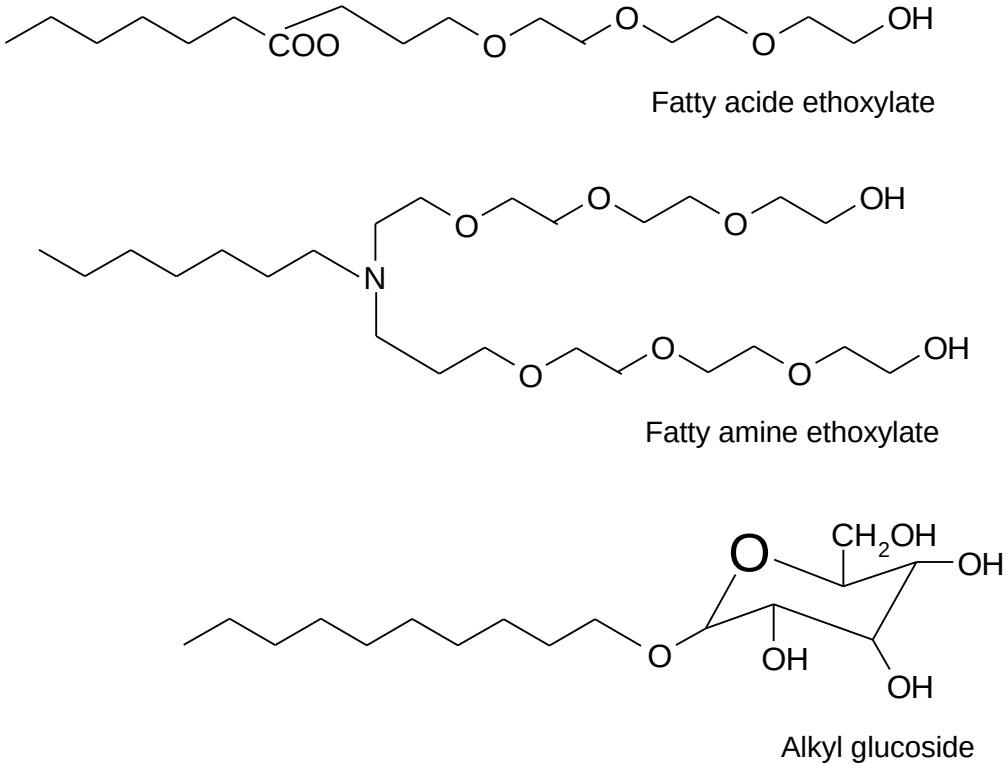

COO
O
O
O
OH
Fatty acide ethoxylate
N
O
O
O
OH
O
O
O
OH
Fatty amine ethoxylate
O
CH2OH
OH
O
OH
OH
Alkyl glucoside

Fig. 7