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The chemistry of pyrido[2,3-*d*]pyrimidines and their applications

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ABSTRACT

This review discusses the importance of pyridopyrimidines and focused on the chemistry and applications of the most abundance isomer: pyrido[2,3-d]pyrimidine derivatives.

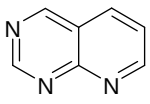
Keywords: Pyridine, Pyrimidine, pyrido[2,3-*d*]pyrimidine.

INTRODUCTION

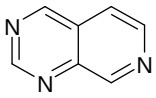
The heterocyclic fusion of pyrimidine and pyridine rings resulted in formation of pyridopyrimidines, the structural analogs of biogenic quinazolines and pteridines. Pyridopyrimidines and related fused heterocycles are of interest as potential bioactive molecules. Also, due to the presence of pyridopyrimidine moiety in some important drugs, interest in the construction of such molecules has been aroused. In the last few years, an enormous number of papers and reviews have been reported dealing with the chemistry and applications of this class of compounds. [1-7]

Structure of pyridopyrimidines

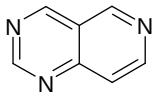
There are four possible isomeric structures for pyrido[*d*]pyrimidines, depending on the position of the nitrogen atom in the pyridine moiety.



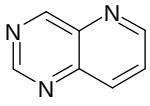
Pyrido[2,3-*d*]pyrimidine



Pyrido[3,4-*d*]pyrimidine

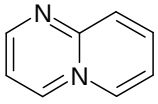


Pyrido[4,3-*d*]pyrimidine

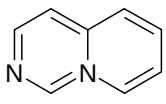


Pyrido[3,2-*d*]pyrimidine

Besides two possible isomeric structures for pyrido[1,2-*a*]pyrimidines and pyrido[1,2-*c*]pyrimidines.



Pyrido[1,2-*a*]pyrimidine

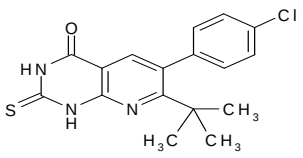


Pyrido[1,2-*c*]pyrimidine

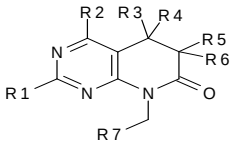
Importance of pyridopyrimidines

Undoubtly, pyridopyrimidines have high significance in the field of pharmaceutical and biotechnological sciences with wide spectrum of biological activities and several applications were reported for these six types as:

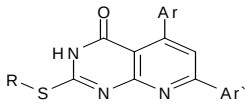
Pyrido[2,3-*d*]pyrimidines are the most abundance isomer in the literature and hence, this scaffold is associated with a wide range of biological activities, such as molluscicidal agents against *Biomphalaria alexandrina* snails,[8] anticancer,[9-11] antimicrobial,[12-14] anti-inflammatory and analgesic,[15,16] antiviral,[17-19] antihypertensive, [20] potent inhibitor of dihydrofolate reductase (DHFR) [21,22] which is an important target site in most of the parasitic diseases, Tyrosine kinase inhibitor, [23, 24] Cyclin-Dependent Kinase 4 (CDK4) inhibitor,[4] antihistaminic,[25] calcium channel antagonist,[26] antileishmanial,[27] diarrhea, [28] and diuretic activities [29].



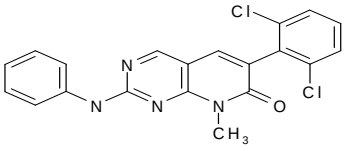
analgesic



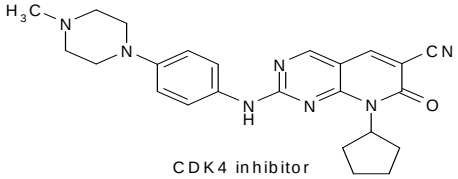
antihypertensives



anti-inflammatory

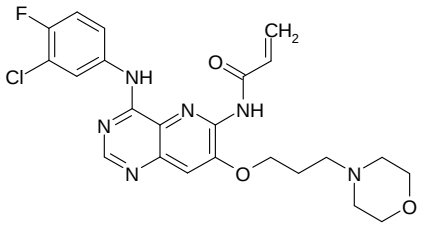


TKI-28



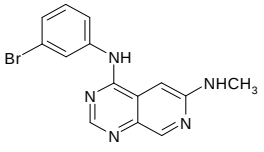
CDK4 inhibitor

However, the pyrido[3,2-*d*]pyrimidine isomer is the least described in the literature because of its difficult and expensive syntheses. Pyrido[3,2-*d*]pyrimidines have been reported as antimalarial,[30] as tyrosine kinase inhibitors,[3,31] as dihydrofolate reductase inhibitors,[32] as anti-HCV agents [33, 34] and as immunosuppressive drugs[35].

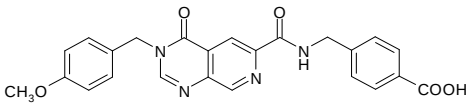


Tyrosine kinase inhibitors

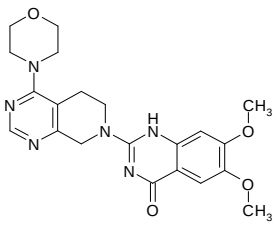
On the other hand, pyrido[3,4-*d*]pyrimidines are well known as potential anticancer agents,[36] tyrosine kinase inhibitors [37-39] and matrix metalloproteinase-13 (MMP-13) inhibitors.[40] Also, individual members of this class of compounds are α1-adrenoceptor antagonists and are used in medicine for nervous dysfunction.[41] They also efficiently inhibit the action of dehydrofolate reductase causing the death of many pathogenic microorganisms [42] .



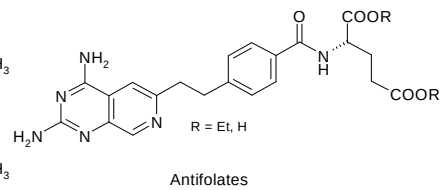
Anticancer



MMP inhibitor



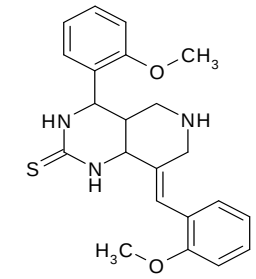
a-adrenoceptor antagonists



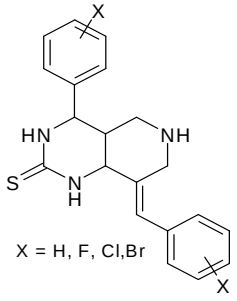
Antifolates
methotrexate (MTX) analogue

While, pyrido[4,3-*d*]pyrimidines have been identified as acetylcholinesteras (AChE) and butyrylcholinesterase (BChE) enzyme inhibitors,[43] as anticancer, [44] as selective bacterial protein synthesis inhibitors,[45] as antitubercular,[46] and as tyrosinekinases of the epidermal growth factor receptor family.[47] One of the recent

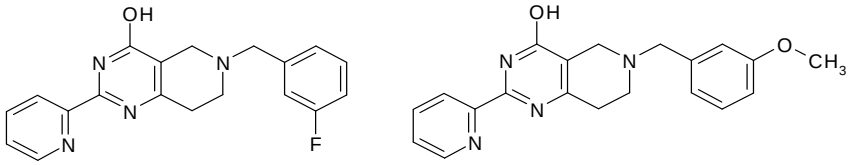
applications of *N*-substituted pyrido[4,3-*d*]pyrimidines is the production of self-assembled rosettes and nanotubes[48].



AChE and BChE enzyme inhibitor

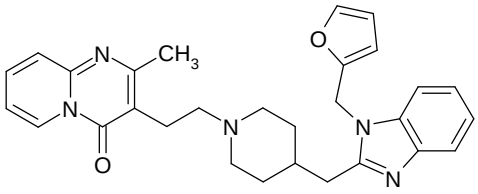


Anticancer

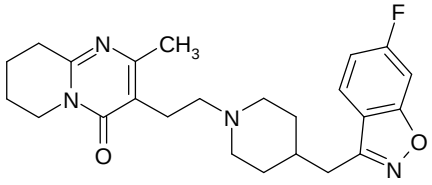


Bacterial protein synthesis inhibitors

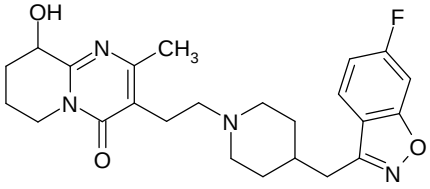
Pyrido[1,2-*a*]pyrimidine isomers are found to be biologically active in a wide range; such as antimalarial agents,[49] psychotropic agents (Risperidone and Paliperidone) for treatment of *Schizophrenia* , [50,51] antiallergic agent (Ramastine),[52] the human leukocyte elastase inhibitor (SSR-69071),[53] anti-ulcer agent,[54] central nervous system stimulants (CNS),[55] urease inhibitor,[56] aggregation of human platelets inhibitor [57].



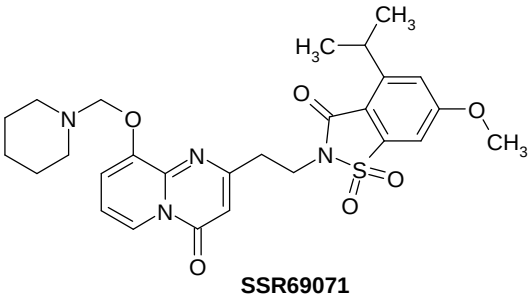
Ramastine



Risperidone



Paliperidon



SSR69071

However, the pyrido[1,2-*c*]pyrimidines are reported for their effects on leukocyte functions in vitro and anti-inflammatory activity,[58] as antimicrobial,[59] and as possessing a dual SSRI and 5-HT(1A) activity [60].

It is not feasible to discuss the chemistry and applications of all these types in this report, since each type needs and deserves a separate treatment and presentation. So, the scope of the present work will be focused on the first type: pyrido[2,3-*d*]pyrimidine derivatives.

Synthesis of some pyrido[2,3-d]pyrimidine ring system

Synthesis of pyrido[2,3-*d*]pyrimidine derivatives was performed according to the following general strategies:

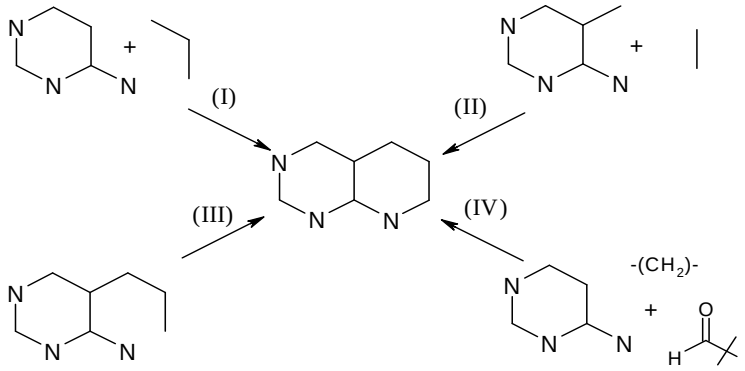
(i) Fusion of the pyridine ring onto the pyrimidine ring system

(ii) Fusion of the pyrimidine ring onto the pyridine ring system

(iii) From Acyclic Intermediates

(i) Fusion of the pyridine ring onto the pyrimidine ring system

There are four general approaches for the synthesis of pyrido[2,3-*d*]pyrimidines starting from pyrimidine ring system, all of which utilize an appropriately substituted 4-aminopyrimidine. The pyridine ring may be formed *via* the addition of three carbon atoms (route I**),** or two carbon atoms (route II), or by the intramolecular cyclization of propionyl derivative (route III) or recently by one-pot reaction of three-component including 4-aminopyrimidine (route IV).

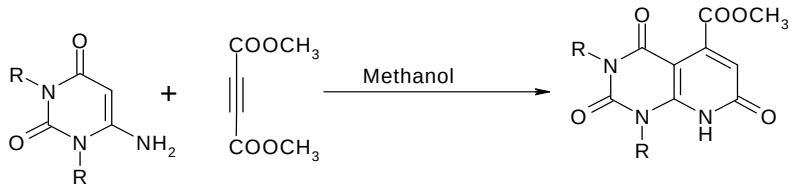


Route I synthesis:

The reaction consists of an electrophilic attack on the 5-position of the pyrimidine ring and thus only those pyrimidines that are activated toward electrophilic substitution by the presence of electron donating substituents at the 2 and 4 positions undergo cyclization. 6-aminouracil, 6-amino-1,3-dimethyluracil, 2,4-diamino- pyrimidin-6(1*H*)-one, 6-amino-1-ethyl-1*H*-pyrimidine-2,4-dione and 6-amino-2-thiouracil have all been converted into pyrido[2,3-*d*]pyrimidines. A wide variety of reagents have been used in this reaction; for example:

a. ***Dimethyl acetylenedicarboxylate (DMAD):***

Recently unsabstituted 6-aminouracil (**1a**) [10,61] and its *N*-alkyl derivative **1b** [62,63] have been found to react with dimethyl acetylenedicarboxylate (DMAD) (**2**) in protic media to give 5-carboxamido-7-oxopyrido[2,3-*d*]pyrimidines (**3**) and the probable mechanism has been described[10].

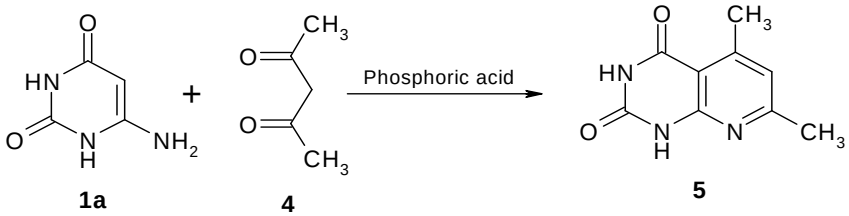


1 **2** **3**

a: R = H
b: R = CH_3

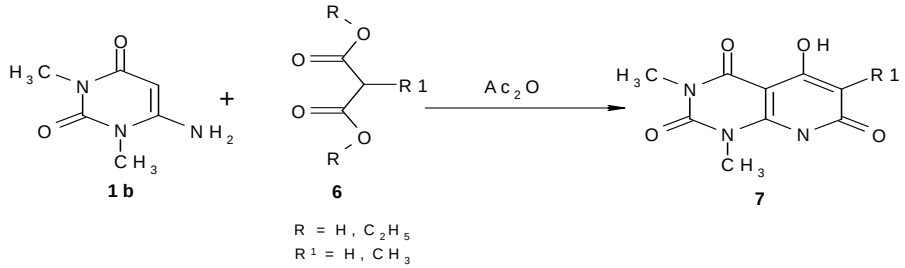
b. ***1, 3-Dicarbonyl compounds:***

6-Aminopyrimidlnes also react readily with 1,3-diketones to yield various 5, 6 and 7 substituted pyrido[2,3-*d*]pyrimidines. Acetyl acetone (**4**) and 6-aminouracil (**1a**), for example yielded 5,7-dimethylpyrido[2,3-*d*]pyrimidine-2,4-dione (**5**) when heated together in phosphoric acid[64].

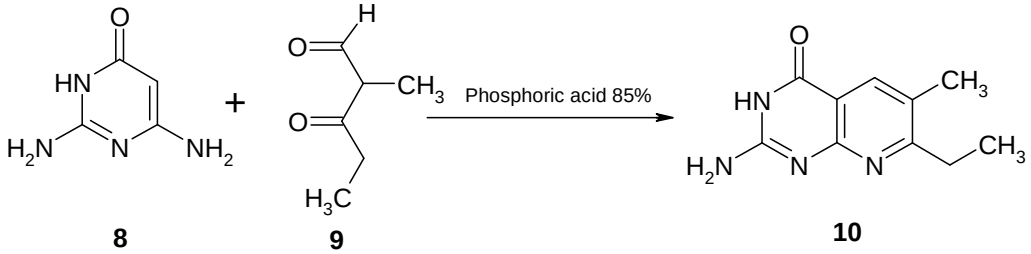


1a **4** **5**

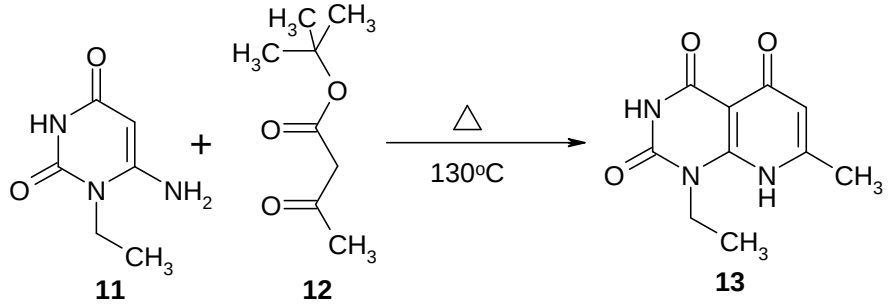
Another example for symmetrical diketones, the reaction of malonic acid or ethyl malonate derivatives **6** with 6-amino-1,3-dimethyluracil (**1b**), for the synthesis of 6-substituted-5-hydroxypyrido[2,3-*d*]pyrimidin-7-ones **7** [65, 66] .



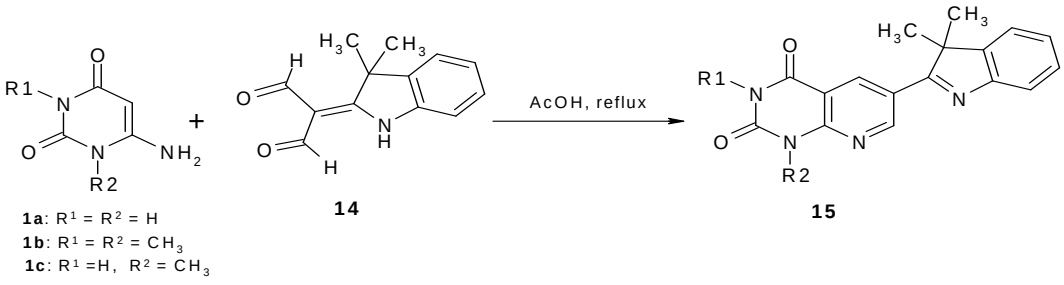
Also, treatment of 2,4-diaminopyrimidine-6(l*H*)-one (**8**) with 2-methyl-3-oxopentanal (**9**) in phosphoric acid 85% afforded 2-amino-7-ethyl-6-methylpyrido[2,3-*d*]pyrimidin-4-(3*H*)-one (**10**)[64] as the only isolated product which resulted from reaction of the aldehyde function with the 5-position of the pyrimidine ring. Whereas, with unsymmetrical diketones the orientation of the reaction is controlled by the reaction of the most reactive carbonyl group with the 5- position of the pyrimidine ring.



Moreover, Kumaran *et al.*,[67] synthesized 1-ethyl-7-methyl-1*H*,8*H*-pyrido[2,3-*d*]pyrimidine-2,4,5-trione (**13**) *via* heating 6-Amino-1-ethyl-1*H*-pyrimidine-2,4-dione (**11**) in *t*-butyl acetoacetate (**12**) (solvent free condition).

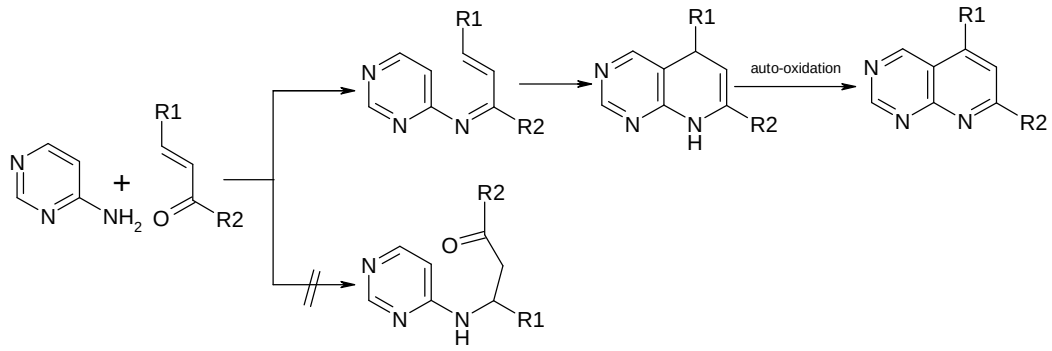


Recently, Rashidi *et al*,[68] has prepared 6-(3,3-dimethyl-3*H*-indol-2-yl)-pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **15** by treatment of 6-aminouracils **1a-c** with substituted aminomethylene malondialdehyde **14.**

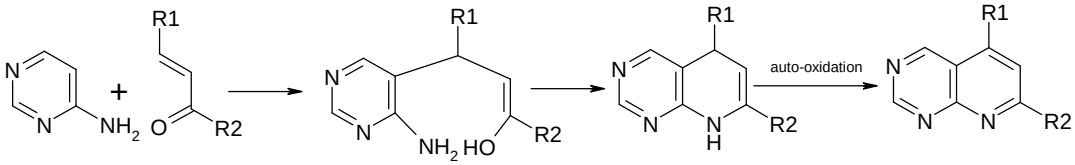


c. ***α,β -Unsaturated ketones:***

The reaction of 6-aminopyrimidines with the appropriate α,β-unsaturated ketones gave the corresponding pyrido[2,3-*d*]pyrimidine derivatives.[69] The reaction is proposed to involve nucleophilic attack by the amino group of the 6-aminopyrimidines on the carbonyl carbon of the α,β -unsaturated ketones, a reversal of the standard regiochemistry of the Skraup-Doebner-Miller pyridine synthesis,[70] to form Schiff's base adducts, followed by cyclization and oxidation to give pyrido[2,3-*d*]pyrimidines (Scheme 1) [71, 72] or the reaction proceeded *via* a sequence of Michael addition followed by cyclization to afford dihydropyridine adduct. The latter adduct from a Hantzsch synthesis afforded the fully oxidized (aromatic) pyridine derivative *via* auto-oxidation (Scheme 2) [73, 74].

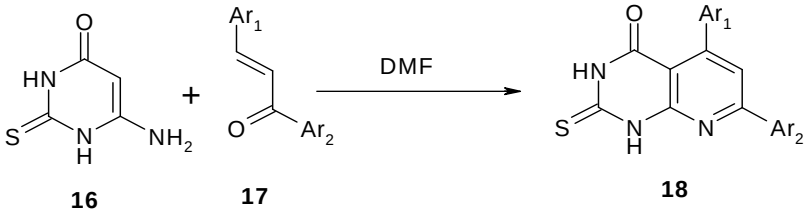


Scheme 1

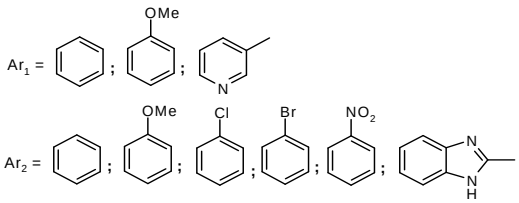


Scheme 2

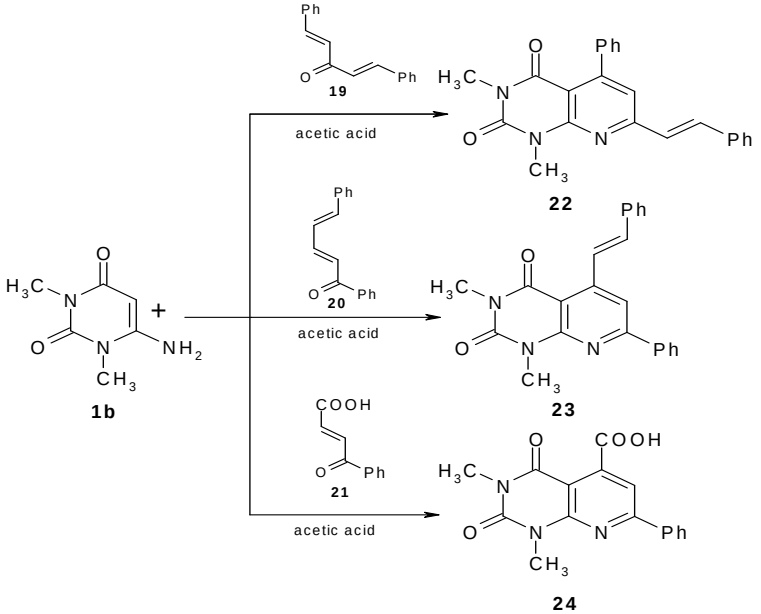
Thus, the reaction of 6-amino-2,3-dihydro-2-thioxo-4(*1H*)-pyrimidinone (**16**) with α,β-unsaturated ketones **17** in boiling DMF furnished the pyrido[2,3-*d*]pyrimidines **18** [71, 72, 75] .



16 **17** **18**

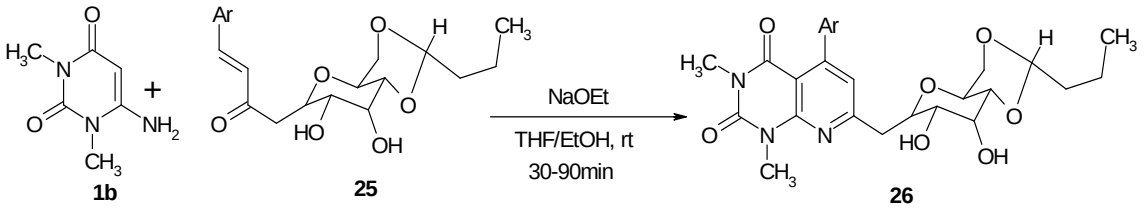


Also, treatment of 6-amino-1,3-dimethyluracil (**1b**) with 1,5-diphenyl-1,4-pentadien-3-one (**19**), 1,5-diphenyl-1,3-pentadien-5-one (**20**) or 1-benzoyl-1-butenoic acid (**21**) gave pyrido[2,3-*d*]pyrimidin-2,4-diones **22**, **23** and **24**, respectively [69,73] .



1b

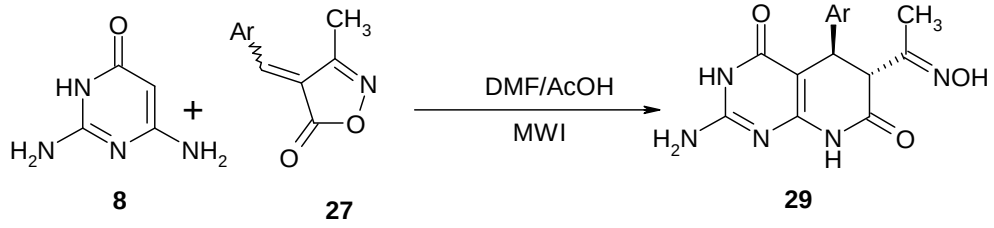
Recently, a novel class of pyrido[2,3-*d*]pyrimidine-C-*β*-D-glycosides (**26**) was synthesized by the condensation of α,β-unsaturated C-*β*-glycosidic ketones (**25**) with 6-amino-1,3-dimethyluracil (**1b**)[76].



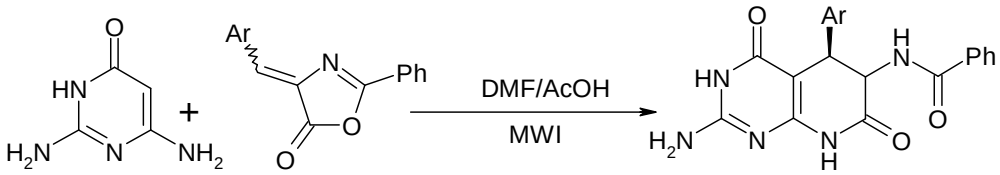
1b **25** **26**

Ar = C_6H_5, $C_6H_4.OCH_3$(p), $C_6H_4.CH_3$(p), $C_6H_4.Cl$(p), $C_6H_4.F$(p), $C_6H_4.Br$(p), pyrrole

Moreover, reaction of 2,6-diaminopyrimidin-4(3*H*)-one (**8**) with 4-arylidene-3-methylisoxazol-5(4*H*)-one (**27**) or 4-arylidene-2-phenyloxazol-5(4*H*)-one (**28**) under microwave irradiation (MWI) is described and pyrido[2,3-*d*]pyrimidine-4,7-dione derivatives **29** and **30** are synthesized presumably *via* a sequence of Michael addition, cyclization and ring opening. In this reaction, glacial acetic acid acts as both solvent and catalyst [74].



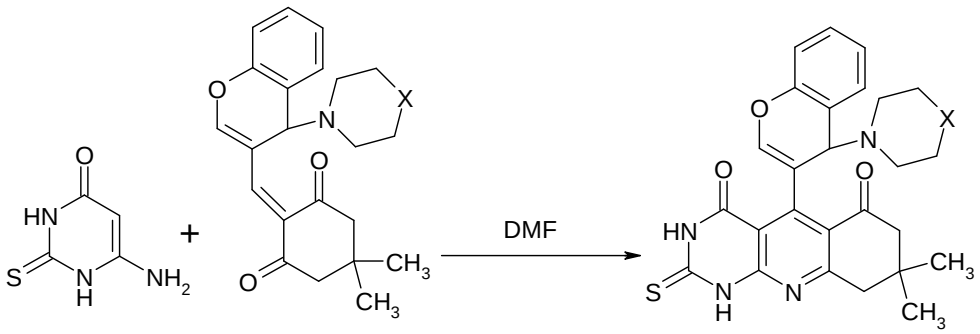
8 **27** **29**



8 **28** **30**

Ar = C_6H_5, $C_6H_4.Cl$(p), $C_6H_4.F$(p), $C_6H_4.Br$(p)

Similarly, 6-aminothiouracil **16** reacted with α,β-unsaturated ketones **31** to give 5-chromeno-pyrido[2,3-*d*]pyrimidine derivatives **32** [16] .

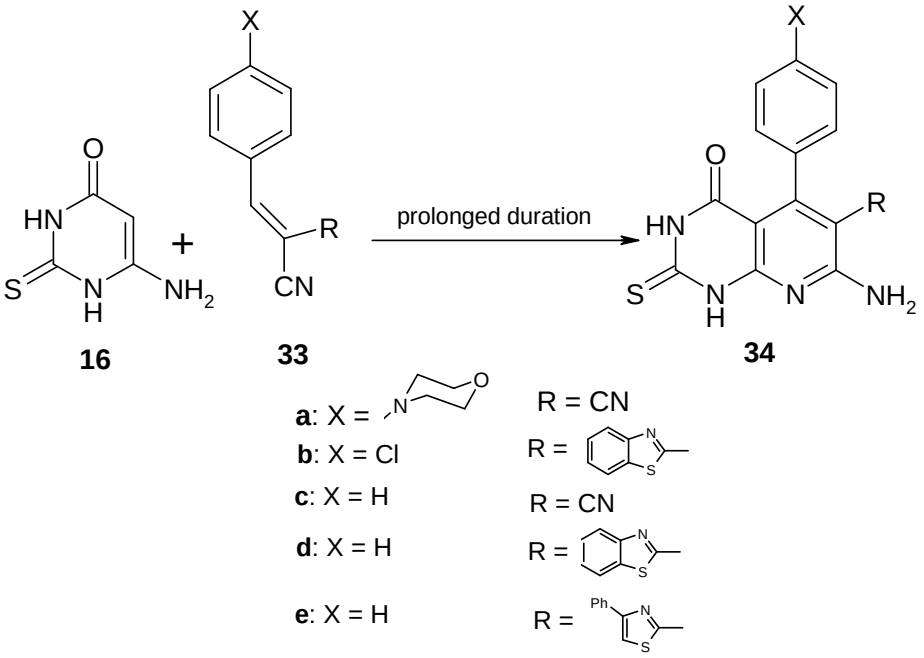


16 **31** **32**

X = O, NH, N-CH_3

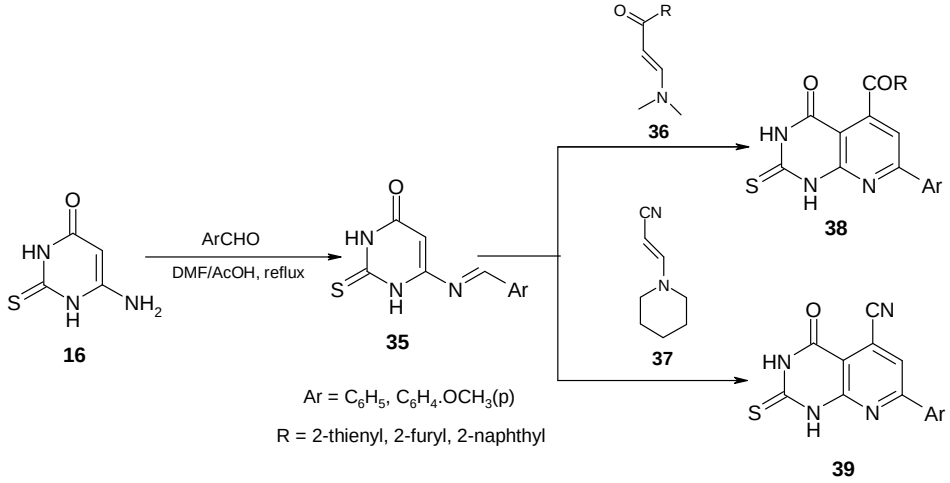
d. ***With arylidene:***

7-Amino-5,6-disbstituted-2-thioxopyrido[2,3-*d*]pyrimidin-4-(1*H*)-ones **34a-e** **[**77-80] prepared by treatment of arylidene derivatives **33** with 6-aminothiouracil **16**. The prolonged duration reaction and dry conditions is required to furnish the oxidized form **34a-e**.



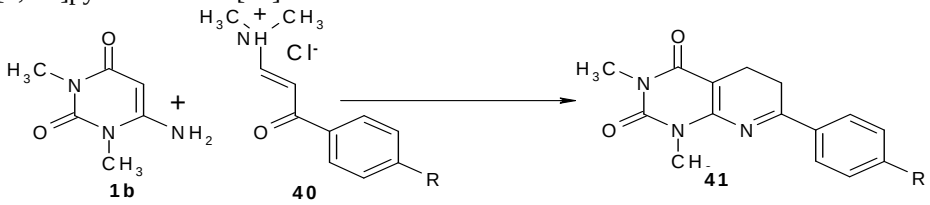
e. ***With enaminones and enaminonitrile***:

The condensation of 6-amino-2-thiouracil **16** with aromatic aldehydes afforded azomethine derivatives **35**. The formed azomethines underwent [4+2] cycloaddition with enaminones **36** and enaminonitrile **37** to form the corresponding condensed pyrido[2,3-*d*]pyrimidines **38** and **39**, respectively *via* amines elimination [81] .

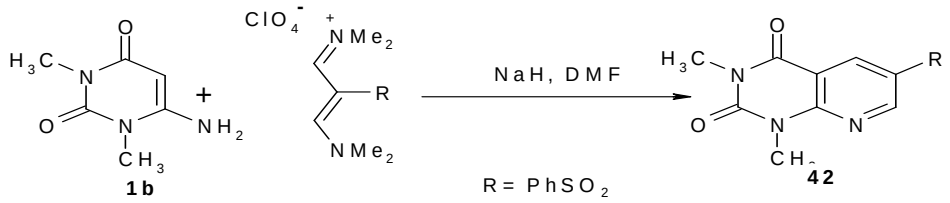


f. ***With Mannich bases:***

Condensation of 6-amino-1,3-dimethyluracil (**1b**) with aryl-alkanone Mannich bases **40**, gave 7-aryl-5,6-dihydropyrido[2,3-*d*]pyrimidines **41** [82] .



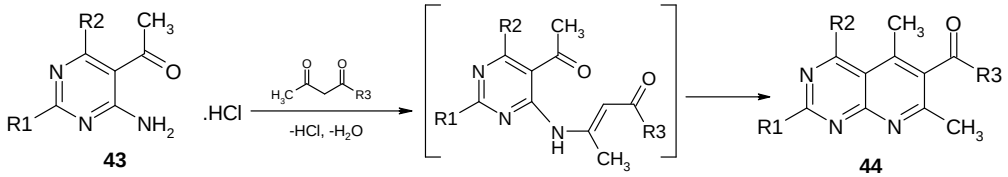
Also, an efficient one-pot preparation of 6-substituted pyrido[2,3-*d*]pyrimidines **42** by cyclocondensation of 6-amino-1,3-dimethyluracil (**1b**) with symmetrical vinamidinium salts under basic conditions has been developed.[83]



Route II synthesis:

This type of synthesis normally involves the reaction of an active methylene compound containing an adjacent functional group capable of cyclization with 5-acyl, 5-formyl, or 5-cyano-4-aminopyrimidines.

Reaction of 2,6-disubstituted-5-acetyl-4-aminopyrimidine hydrochlorides **43** with acetylacetone or benzoylacetone afforded new substituted 6-acylpyrido[2,3-*d*]pyrimidines **44** [84] .

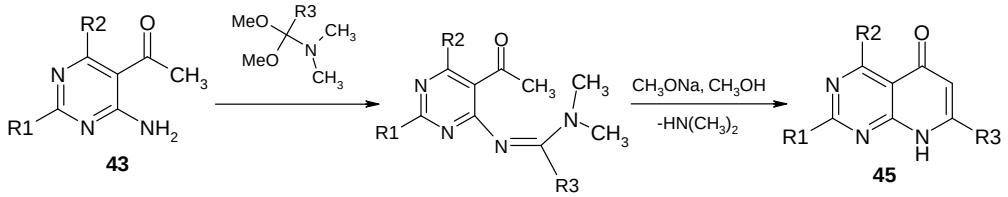


R_1 = C_6H_5, C_6H_4.Cl(p)

R_2 = CH_3

R_3 = CH_3, C_6H_5

Also, 7-substituted-pyrido[2,3-*d*]pyrimidin-5-ones **45 [**85] were synthesized by the interaction of 2,6-disubstituted-4-amino-5-acetylpyrimidines **43** with *N*,*N*-dimethylformamide dimethyl acetal or *N*,*N*-dimethylacetamide dimethyl acetal followed by cyclization under the action of sodium methoxide in methanol.

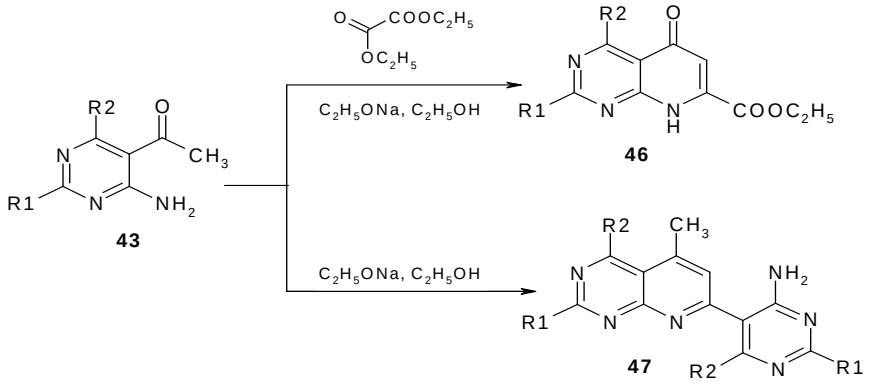


R_1 = CH_3, C_6H_5

R_2 = CH_3, C_6H_5

R_3 = H, CH_3

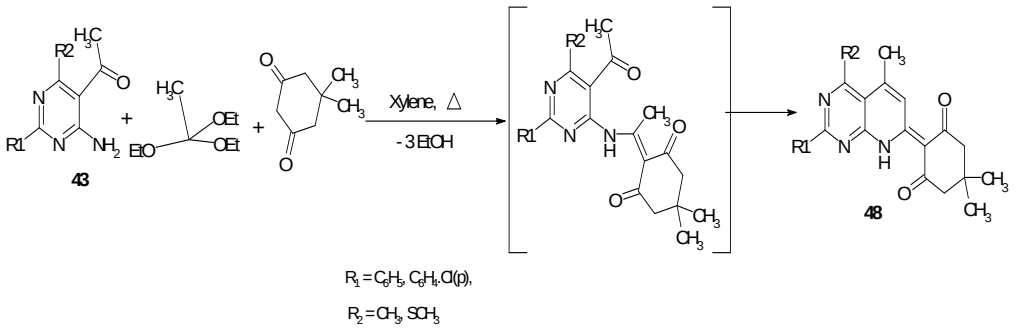
Similarly, ethyl 5-oxo-pyrido[2,3-*d*]pyrimidine-7-carboxylate **46** could be obtained *via* condensation of 5-acetyl-4-aminopyrimidines **43** with ethyl oxalate in the presence of sodium ethoxide. The products **47** of the Friedländer self condensation of the starting pyrimidines **43** have been reported [86] .



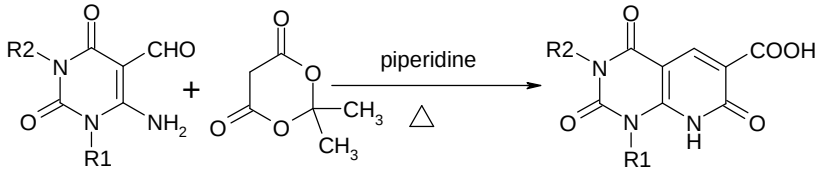
R_1 = CH_3, C_6H_5, CCL_3, C_6H_4.Cl(p), C_6H_4.NO_2(p)

R_2 = CH_3, C_6H_5, SCH_3

A three component condensation of 5-acetyl-4-aminopyrimidine derivatives **43** with dimedone and triethyl orthoacetate gave 7-(1,3-dioxocyclohex-2-ylidene)-7,8-dihydropyrido[2,3-*d*]pyrimidine derivatives **48** [87] .

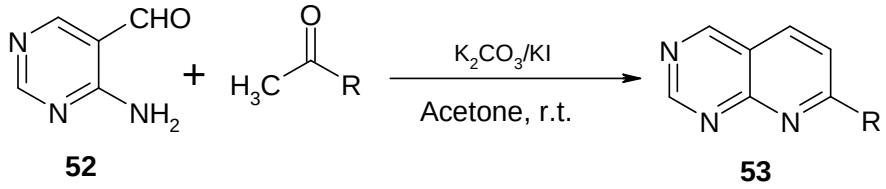


On the other hand, 6-amino-5-formyluracils **49a-c** reacted with Meldrum's acid **50** in the presence of piperidine as catalyst under thermolytic conditions to afford 6-carboxy-2,4,7-trioxopyrido[2,3-*d*]pyrimidines **51a-c** [88] .



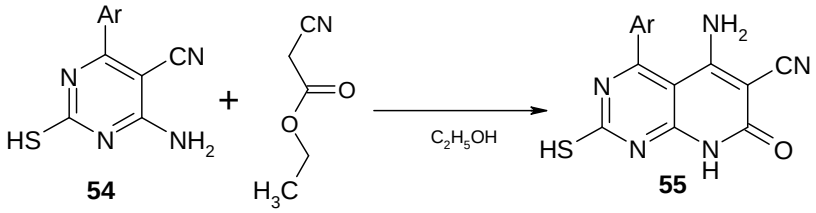
a: $R_1 = R_2 = H$
b: $R_1 = R_2 = CH_3$
c: $R_1 = C_2H_5$, $R_2 = H$

Also, 4-amino-5-formylpyrimidine **52** condensed with various aromatic ketone derivatives, in the presence of K_2CO_3 and KI in acetone, to afford the corresponding 7-substituted pyrido[2,3-*d*]pyrimidine derivatives **53** [89] .



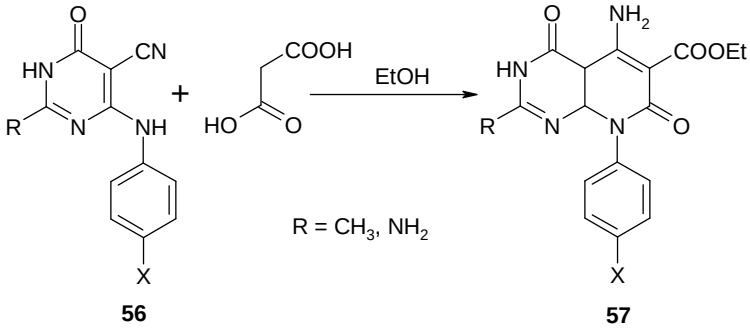
R = C_6H_5,C_6H_4.4-Cl, C_6H_4.4-CH_3-, C_6H_4.4-OCH_3, pyridinyl, thienyl, furanyl

Moreover, 5-amino-4-aryl-7-oxo-2-mercapto-pyrido[2,3-*d*]pyrimidines-6-carbonitrile **55** have been synthesized by the condensation of 4-amino-5-cyano-6-aryl-2-mercapto-5,6-dihydro pyrimidines **54** with ethylcyanoacetate [90] .



Ar = C_6H_5, C_6H_4.2-Cl, C_6H_4.4-Cl, C_6H_4.3-NO_2, C_6H_4.3-OCH_3, C_6H_4.4-OH, C_6H_4.4-SCH_3

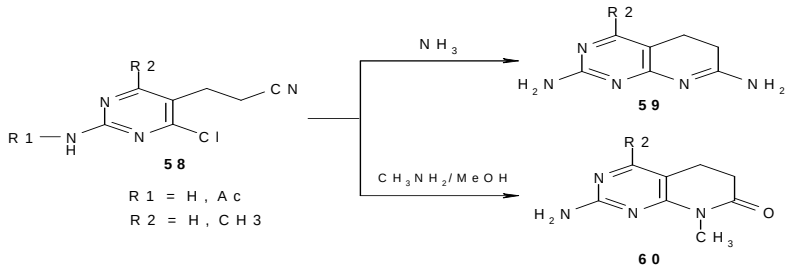
Similarly, 4-(halophenylamino)-pyrimidine-5-carbonitrile derivatives **56** treated with malonic acid in ethanol to give the corresponding ethyl 5-amino-6-oxo-pyrido[2,3-*d*]pyrimidine carboxylates **57** [91] .



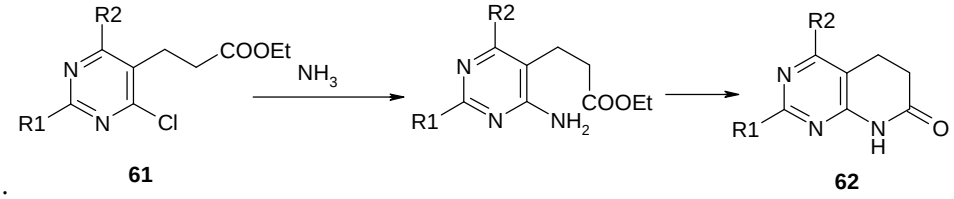
Route III synthesis:

In contrast to the previous synthesis, pyrido[2,3-*d*]pyrimidines prepared by this route are not completely "aromatic" compounds. Instead they are reduced pyridopyrimidines, and are obtained by cyclization of an aliphatic propionyl derivative.

So, the propionitrile derivative **58** yielded the pyrido[2,3-*d*]pyrimidines **59** and **60** when treated with ammonia or methylamine respectively [92,93] .



Also, when compounds **61** treated with ammonia yielded the pyrido[2,3-*d*]pyrimidines **62**[94].



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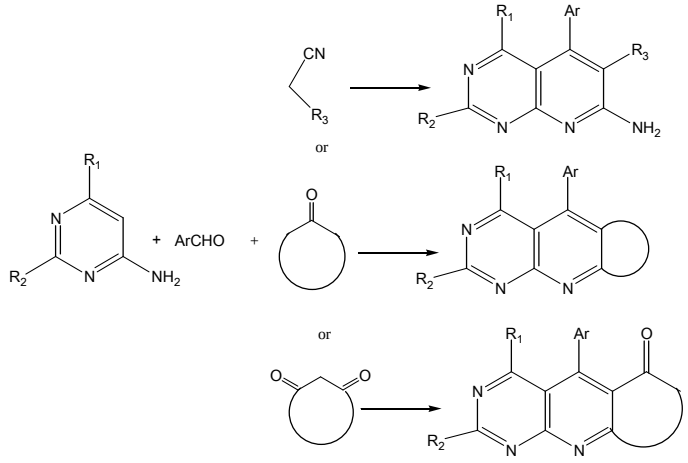
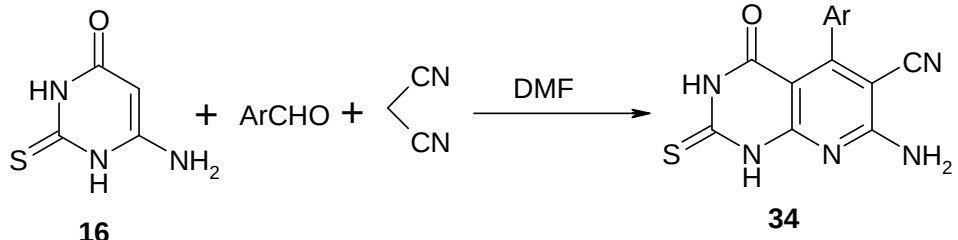
Route IV synthesis:

A series of pyrido[2,3-*d*]pyrimidines and their polycyclic derivatives have been prepared by one-pot three-component reaction of 4-aminopyrimidines, aromatic aldehydes and active methylene compounds (alkyl nitriles, cyclic ketones, cyclic diketones). This efficient synthesis was done thermally with or without using catalysis, under microwave irradiation conditions or under ultrasonic irradiation (US) as a recent trend. The reaction occurs *via* an initial formation of the arylidene, from the condensation of benzaldehyde and active methylene compounds, which suffer nucleophilic attack to give the Michael adduct. Then cyclization and auto-oxidation took place to afford the fully aromatized compound.



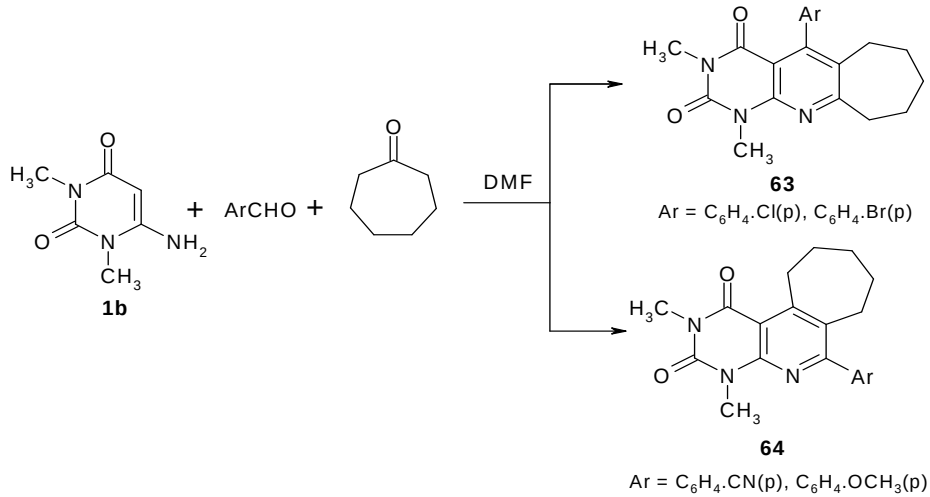
1- ***Thermal synthesis without using catalysis.***

El-Gazzar *et al*,[95] has prepared a series of pyrido[2,3-*d*]pyrimidine-2-thione derivatives **34** by the one-pot reaction of the appropriate aldehyde, malononitrile and 6-aminothiouracil **16** in dimethylformamide.

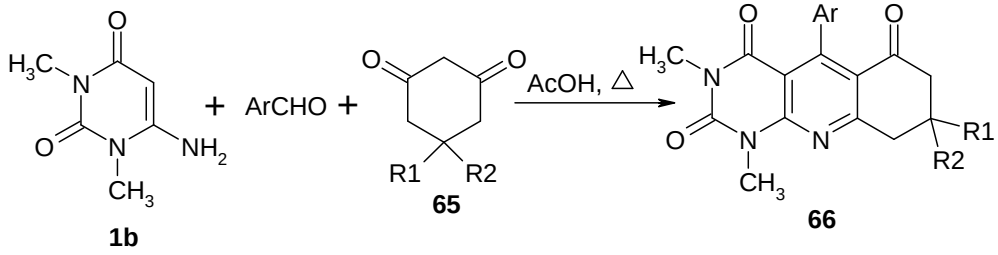


Ar = C_6H_4.Cl(p), C_6H_4.CH_3, C_6H_4.$N(CH_3)_2$

Hegab *et al*,[96] has obtained hexahydrocyclohepta[5,6]pyrido[2,3-*d*]pyrimidine-2,4-dione **63** and hexahydrocyclohepta[4,5]pyrido[2,3-*d*]pyrimidine-2,4-dione **64** during the reaction of 6-amino-1,3-dimethyluracil **1b** with equimolar amounts of cycloheptanone and appropriate benzaldehydes. The structures of products were verified by single crystal X-ray diffraction.

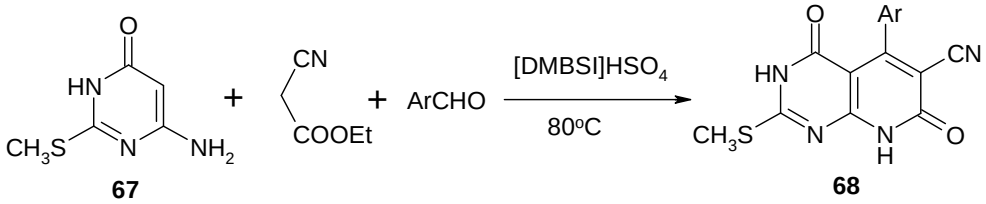


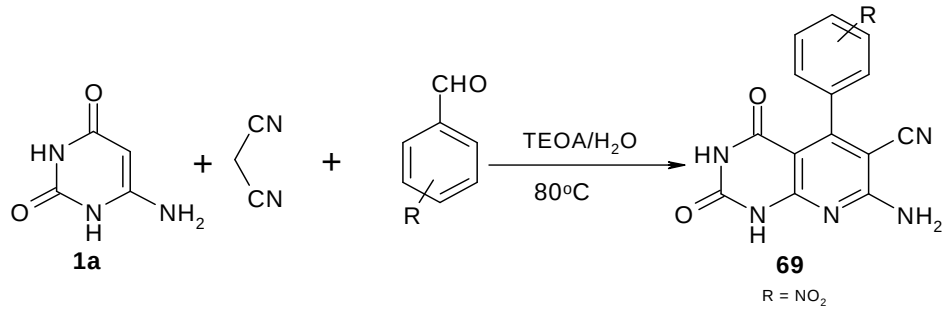
Moreover, Hassan *et al*,[97] and Tanifum *et al*,[98] reported that when 6-amino-1,3-dimethyluracil **1b** treated with an aldehydes and a cyclic 1,3-dicarbonyl compound **65**, it gave the corresponding polycyclic pyrido[2,3-*d*]pyrimidines **66**.

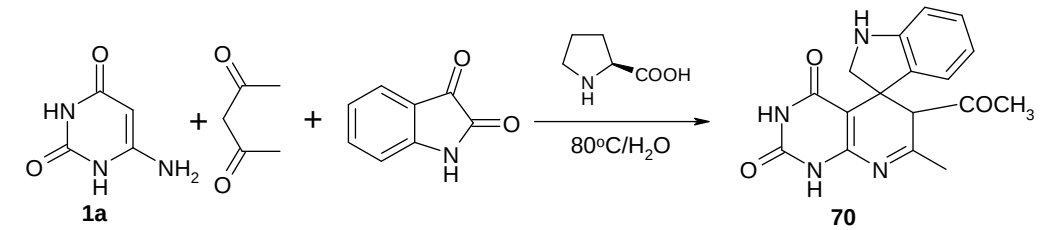


2- ***Thermal synthesis with using catalysis.***

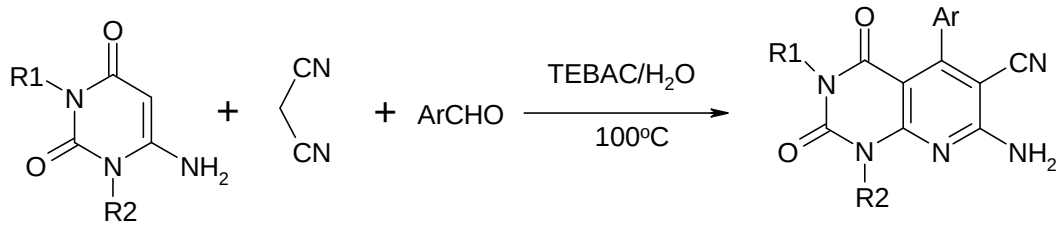
A simple one-pot method for the preparation of pyrido[2,3-*d*]pyrimidines **34**, **68-71** from 4-aminopyrimidines **67, 1a-c** and **16,** aromatic aldehydes and active methylene compounds in the presence of 1,2–dimethyl-*N*-butanesulfonic acid imidazolium hydrogen sulfate ([DMBSI]HSO_4),[99] triethanolamine (TEOA),[100] α-amino acid (L-proline),[101] ZrO_2 nanoparticles (ZrO_2-NPs),[102] Fe_3O_4 nanoparticles (Fe_3O_4-NPs,),[103] triethylbenzylammonium chloride (TEBAC) [104,105] or sodium lauryl sulfate (SDS)[106] as an efficient catalyst is described.







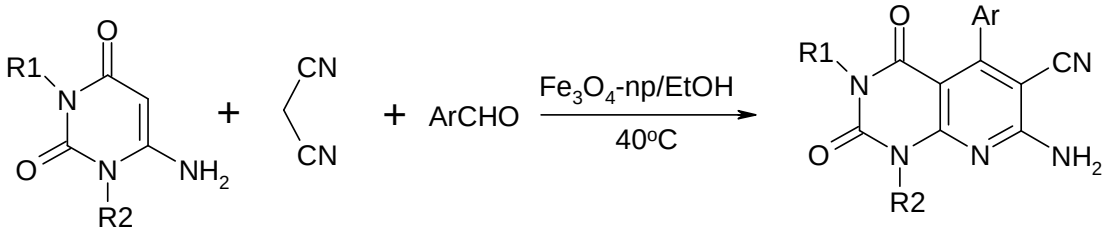
1a **70**



1c **71**

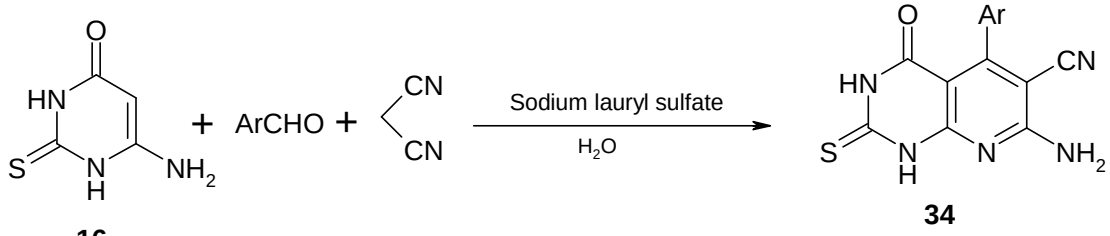
R_1 = H, R_2 = CH_3

Ar = C_6H_5, C_6H_4.4-CH_3, C_6H_4.4-Br, C_6H_4.4-Cl, C_6H_4.4-OCH_3



1a,b **71**

Ar = C_6H_5, C_6H_4.4-Cl, theinyl

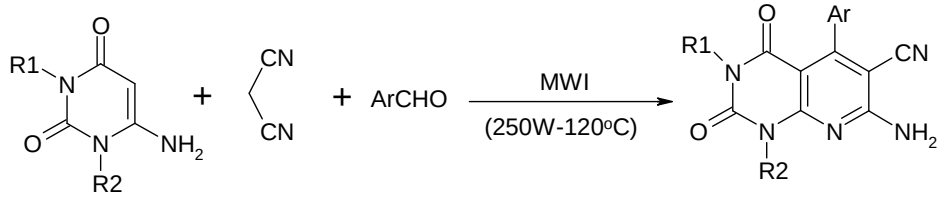


16 **34**

Ar =C_6H_5, C_6H_4.NO_2, C_6H_4.Cl(p), C_6H_4.CH_3, C_6H_4.OCH_3

3- ***Synthesis under microwave irradiation conditions***

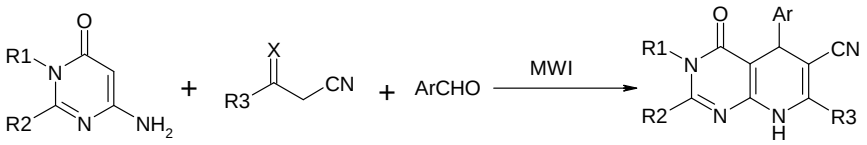
The utility of microwave energy in synthetic organic chemistry has been increasingly recognized in recent years.[107,108] MWI-irradiated multi-component reactions have some advantages such as environmentally friendly, improving the bond forming efficiency (BFE), time saving, and experimental simplicity. Thus, when 6-aminouracil derivatives **1a-c** were treated with benzaldehydes and malononitrile under microwave irradiation at 60% power and 120°C in a reactor for 5 min, it gave pyrido[2,3-*d*]pyrimidines **72** with 90-93% yields [109-111] .



1a-c **72**

Ar = C_6H_5, C_6H_4.CH_3, C_6H_4.NO_2, C_6H_4.Cl, C_6H_4.OCH_3, C_6H_4.OH

Under identical conditions, Quiroga *et al*,[112] synthesized the 6-cyano-5,8-dihydropyrido[2,3-*d*]pyrimidine-4(3*H*)-ones **74** *via* three component condensation of 6-amino pyrimidne-4-ones **73**, benzaldehyde and β-amino crotonitrile or benzoylacetonitrile.

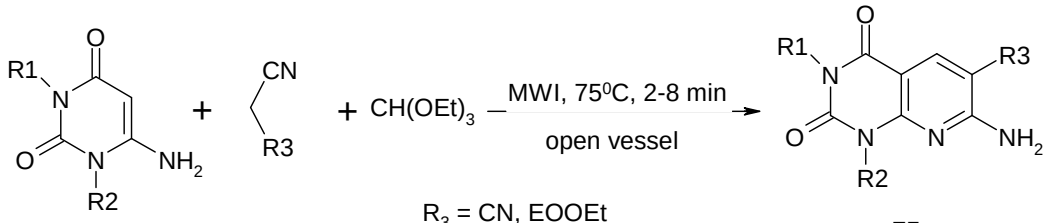


73 **74**

R_1 = H, CH_3 X = NH, O Ar = C_6H_5, C_6H_4.Cl, C_6H_4.OCH_3, C_6H_4.F, $C_6H_4NO_2$

R_2 = OCH_3, SCH_3, NH_2 R_3 = CH_3, Ph

On the other hand, pyrido[2,3-d]pyrimidines **75** has been prepared *via* one-pot three-component reaction of 4-aminouracils, alkyl nitriles and triethylorthoformate (instead of aldehydes) under microwave irradiation [113,114] .

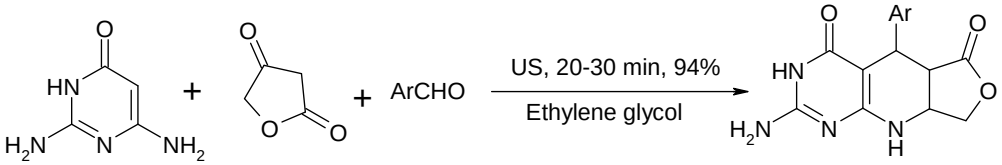


R_3 = CN, EOOEt

1a,b **75**

4- ***Synthesis under ultrasonic irradiation conditions***

Under ultrasonic irradiation conditions, a series of pyrido[2,3-*d*]pyrimidine derivatives have been reported.[115,116] Thus, Tu *et al*. synthesized a series of pyrido[2,3-*d*]pyrimidine derivatives **76** *via* one-pot condensation reaction of an aldehyde, tetrahydrofuran-2,4-dione, and 2,6-diaminopyrimidin-4(3*H*)-one in ethylene glycol under ultra sonic irradiation without catalyst [116] .



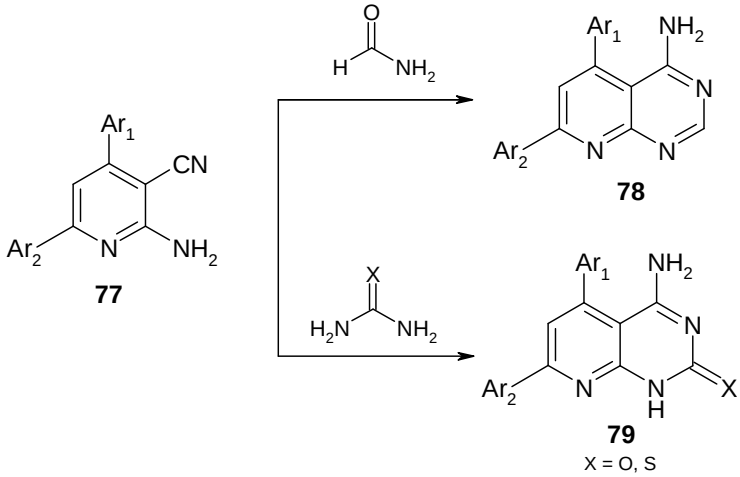
76

(ii) Fusion of the pyrimidine ring onto the pyridine ring system

Another major approach for the synthesis of pyrido[2,3-*d*]pyrimidines involves the use of the appropriately substituted pyridine derivatives as starting material. A wide variety of pyrido[2,3-*d*]pyrimidine derivatives were prepared starting from: 2- aminonicotinonitril, ethyl 2-aminonicotinates, 2-aminonicotinic acids, 2-aminonicotinamides and another pyridine derivatives.

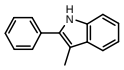
a) 2- Aminonicotinonitril:-

A series of pyrido[2,3-*d*]pyrimidine derivatives *viz* 4-amino-pyrido[2,3-*d*]pyrimidines **78**,[117-121] 4-amino-pyrido[2,3-d]pyrimidins **79**, [117,119,120] have been synthesized by the condensation reaction of 2-amino-4,6-disubstituted pyridine carbonitriles **77** with formamide, urea and thiourea, respectively.



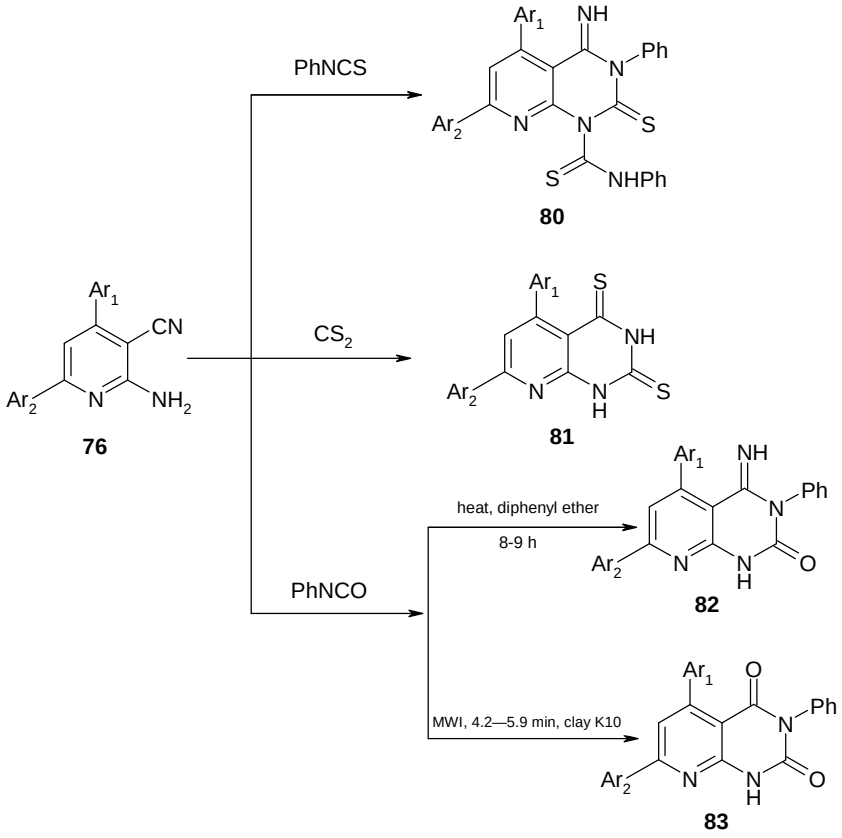
77 **78** **79**

X = O, S

Ar_1 = 2,4-dichlorophenyl, 4-methoxyphenyl, 

Ar_2 = phenyl, 4-bromophenyl, 2-hydroxyphenyl

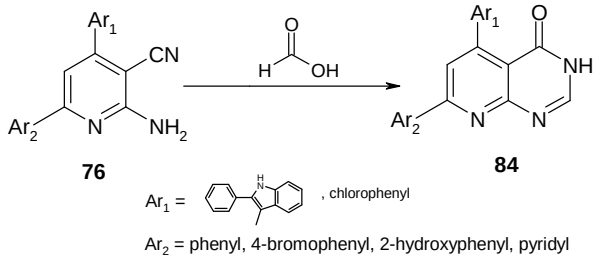
Also, 4-imino-pyrido[2,3-*d*] pyrimidin-2-thiones **80**,[122] pyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*) dithiones **81**,[122-124] and 4-imino-pyrido[2,3-*d*] pyrimidin-2-ones **82[120]** were prepared using the 2-amino-pyridine-3-carbonitrile **76** *via* the reaction with phenylisothiocyanate, carbon disulphide and phenylisocyanate, respectively. While, pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)diones **83[**125] were obtained eoc-friendly *via* condensation of compound **76** with phenylisocyanate, adsorbed over K-10 montmorillonite clay or alumina, and irradiated under microwaves.

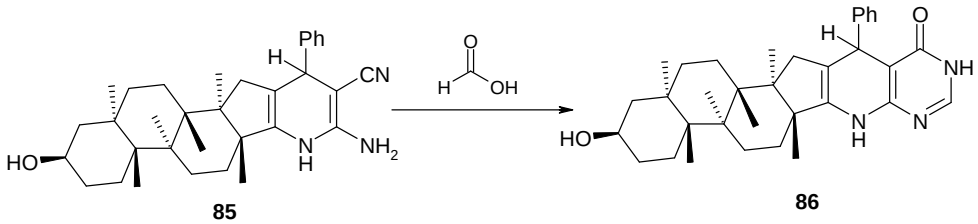


Ar_1 = 2,4-dichlorophenyl, 4-methoxyphenyl, 4-chlorophenyl, trimethoxyphenyl, methyl, cyclohexyl, furyl, indolyl

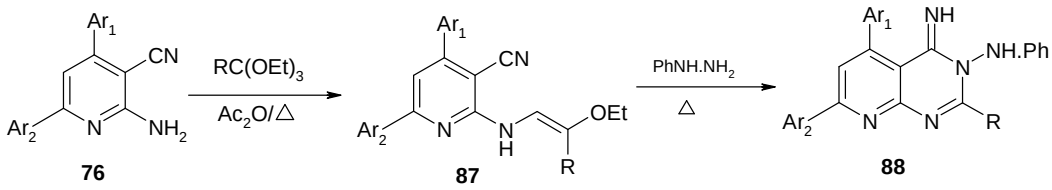
Ar_2 = phenyl, 4-bromophenyl, 2-hydroxyphenyl, naphthyl, pyridyl

Moreover, pyrido[2,3-*d*]pyrimidin-4-(3*H*)-ones **84[**118,124] and dihydro-pyrido[2,3-*d*]pyrimidin-4-(3*H*)-one **86** [15] were obtained *via* cyclization of compound **76** and **85** with formic acid, respectivily. It is believed that the nitrile group was converted into amide *via* hydrolysis followed by cyclization and Dimroth rearrangement took place to furnish the final fused pyridopyrimidinone adduct [126] .



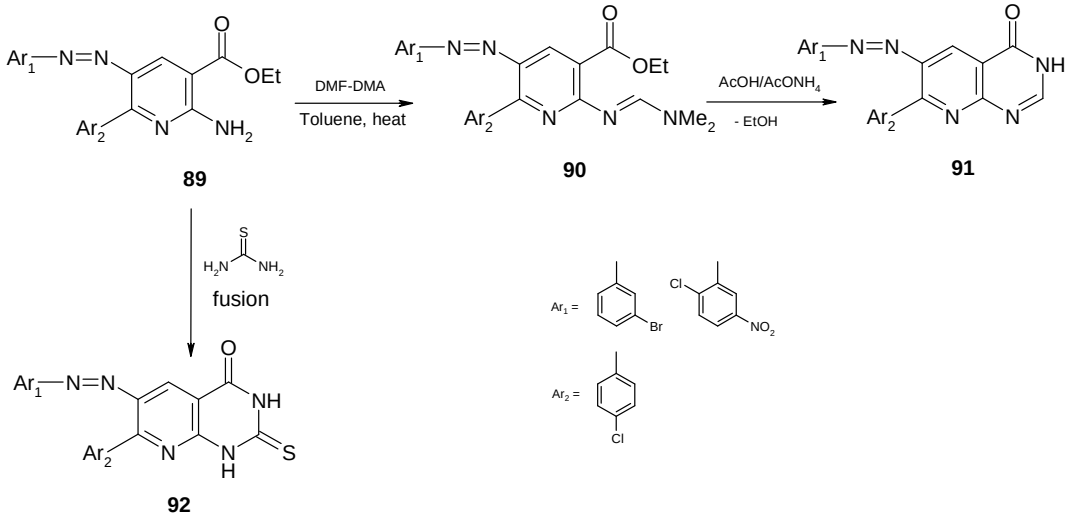


Also, treatment of compound **76** with triethyl orthoformate or triethyl orthoacetate in acetic anhydride afforded the methanimidates **87** which gave the 3-phenylamino-4-imino-pyrido[2,3-*d*]pyrimidines **88** upon treatment with phenyl hydrazine[122].

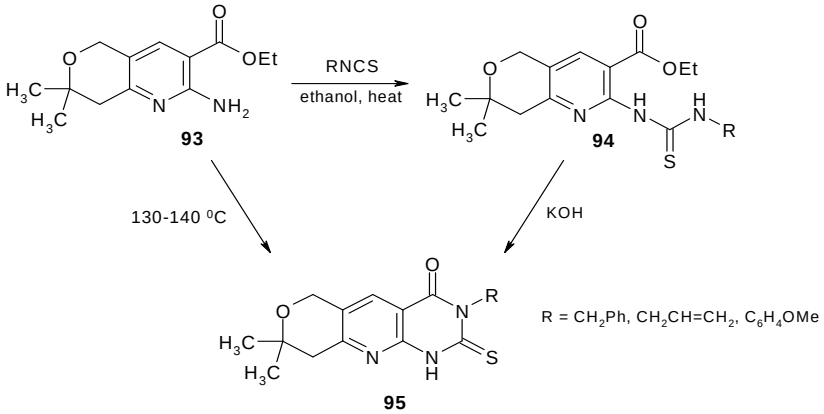


b) Ethyl 2-aminonicotinates:-

The 2-amino-5-arylazonicotinates **89** reacted with dimethylformamide dimethylacetal (DMF-DMA) to yield the corresponding amidines **90** which treated with ammonia in refluxing acetic acid to yield the corresponding pyrido[2,3-*d*]pyrimidine derivatives **91**.[127] Furthermore, fusion of the azonicotinates **89** with thiourea afforded the corresponding pyrido[2,3-*d*]pyrimidine derivatives **92 [**127].

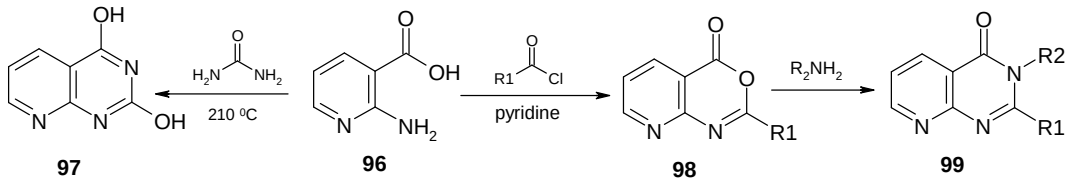


Moreover, substituted 4-oxo-2-thiopyranopyridopyrimidines **95** [128] were synthesized either by boiling ethanolic solutions of 2-amino-3-ethoxycarbonylpyrano[4,3-*b*]pyridine **93** with the isothiocyanates with subsequent heterocyclization of the 2-(N'-R-thioureido) derivatives **94** under the influence of KOH; or by condensation of pyranopyridine **93** with the isothiocyanates at 130-140°C.



c) 2-aminonicotinic acid:-

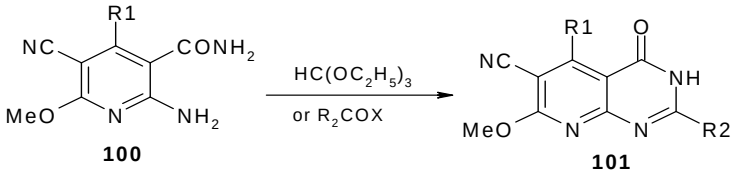
The thermal cyclization of commercially available 2-aminonicotinic acid (**96**) and urea produced pyrido[2,3-*d*]pyrimidine-2,4-diol (**97**) [129]. Furthermore, interaction of alkyl[11] or aryl chloride[130] with 2-aminonicotinic acid (**96**) in pyridine, gave pyrido[2,3-*d*][1,3]oxazin-4-ones (**98**) which in turn reacted with amines to give a series of pyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **99** with different substituents at position 2 and 3 [11,130] .



R_1 = phenyl, propyl, 4-florobenzyl, 4-chlorobenzyl
R_2 = phenyl, tolyl, H, $-NH_2$, -OH

d) 2-Aminonicotinamides:-

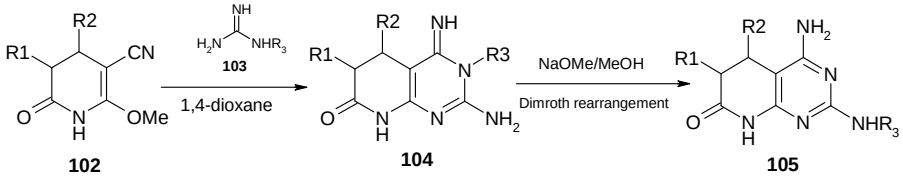
Also, pyrido[2,3-*d*]pyrimidin-4(3*H*)-one derivatives **101** were synthesized *via* fusion of 2-aminopyridine-3-carboxamide derivative **100** with triethyl orthoformate, acetic anhydride or benzoyl chloride [131] .



R_1 = $C_6H_4.OCH_3$(p)
R_2 = H, C_6H_5, CH_3

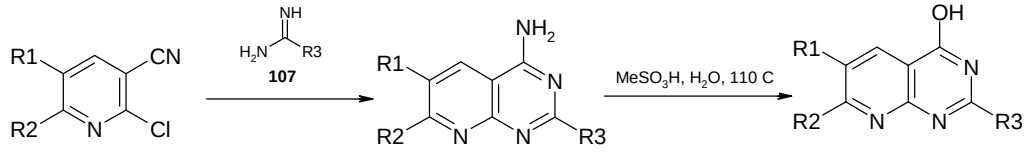
e) Another pyridine derivatives:-

Galve *et al*,[132] synthesized 3-*N*-aryl substituted 2-amino-4-imino-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones **104**, from treatment of 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles **102** with an aryl substituted guanidine **103** in 1,4-dioxane, which undergoes the Dimroth rearrangement to the 2-arylamino- pyridopyrimidine **105** by heating in NaOMe/MeOH.



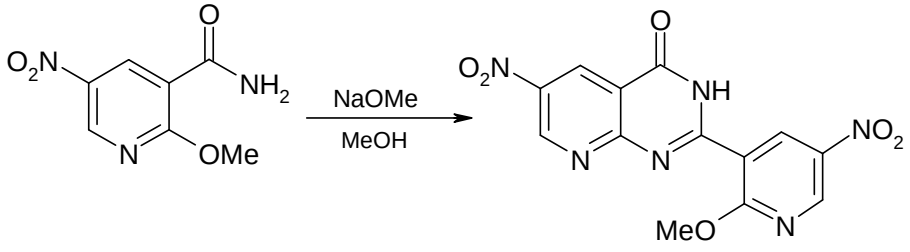
R_1 = C_6H_3-2,6-Cl_2
R_2 = H
R_3 = C_6H_4-4-Cl, C_6H_5

Similarly, addition of amidine **107** to the 2-chloronicotinonitrile **106** affords the 4-aminopyridopyrimidine derivatives **108** which could be hydrolyzed to the pyridopyrimidinone **109** with methanesulfonic acid in high yield [133] .



R_1 = C_6H_4-2-Cl
R_2 = C_6H_4-4-Cl
R_3 = *t*-Bu, *i*-Pr

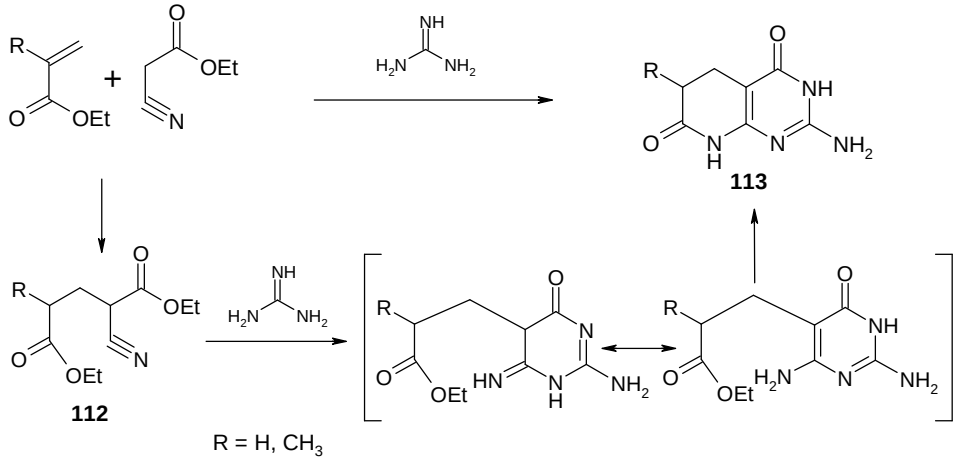
On the other hand, It was found that refluxing of 2-Methoxy-5-nitronicotinamide (**110**) in methanol in the presence of sodium methoxide afforded 2-(2-methoxy-5-nitropyridin-3-yl)-6-nitropyrido[2,3-*d*]pyrimidin-4-one (**111**) [134] .



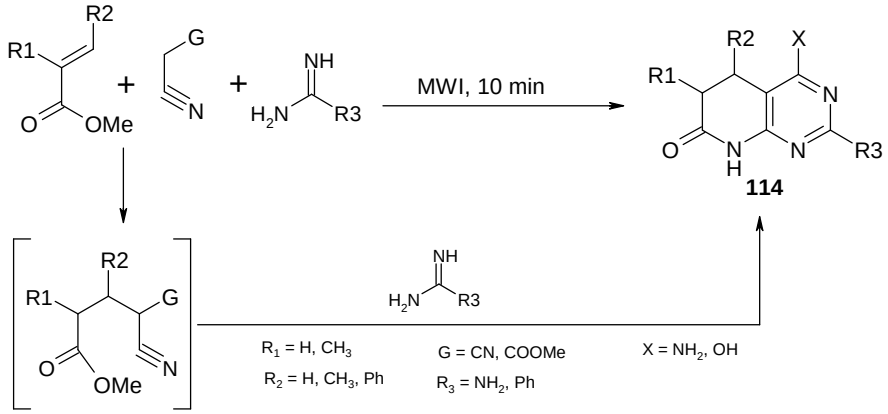
(iii) Acyclic Intermediates

Synthesis of 5,6-dihydropyrido[2,3-*d*]pyrimidine derivatives directly from acyclic precursors, in which the pyrimidine and pyridine rings were constructed simultaneously, has been reported.[**135-138**] Ethyl cyanoacetate was

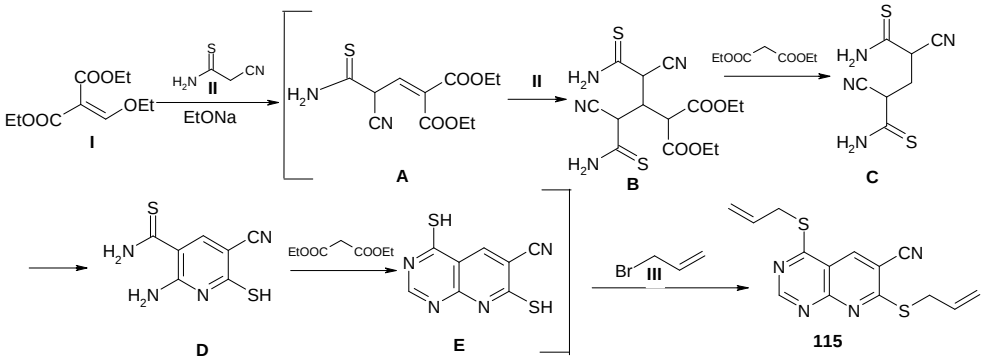
reacted with ethyl acrylates forming diethyl-2-cyanoglutarates **112** which treated with guanidine in ethanol to afford 2-amino-5,6-dihydropyrido[2,3-*d*]pyrimidin- 4,7-dione **113** [135] .



In the same manner, Mont *et al*,[**132,136**] described an efficient 3-component reaction providing 4-amino or 4-oxopyrido[2,3-*d*]pyrimidines **114** in a one-pot microwave- assisted cyclocondensation of α,β-unsaturated esters, amidine systems and malononitrile or methyl cyanoacetate [136, 137] .



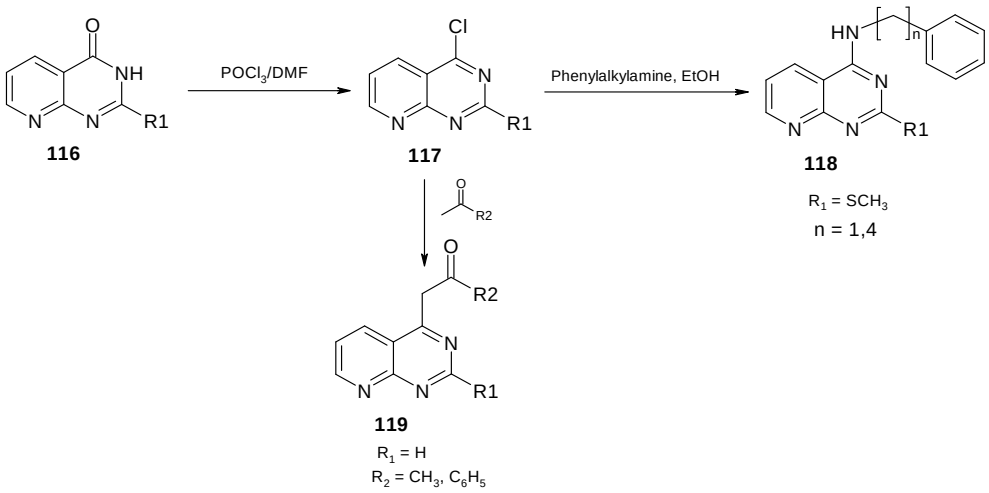
Similarly, a pyrido[2,3-*d*]pyrimidine derivatives **115** was obtained in a one-pot synthesis from diethyl ethoxymethylidenemalonic acid, cyanothioacetamide, and allyl bromide [138] . The probable reaction scheme is show as follows.



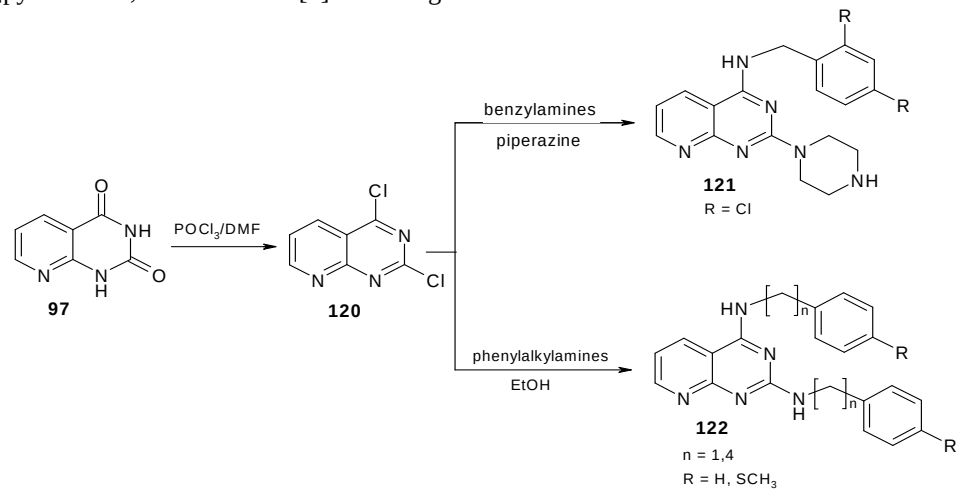
4- Reactions of pyrido[2,3-d]pyrimidines

(i) Reactions carried out on the pyrimidine ring

Treatment of pyrido[2,3-*d*]pyrimidinones or -pyrimidindiones with phosphorous oxychloride ($POCl_3$) is a simple procedure used widely in preparing chlorinated pyrimidine final products or intermediates for further transformations. Starting from 2-substituted 4-oxo-3,4-dihydropyrido[2,3-*d*]pyrimidine **116**, upon refluxing with phosphoryl chloride ($POCl_3$) in presence of dimethylformamide (DMF), yielded the corresponding key 4-chloro intermediates **117**, which were reacted either with phenylalkylamines to give the 4-(4-phenylalkylamino)-pyrido[2,3-*d*]pyrimidines **118 [**9] or with ketone carbanions such as, acetone and acetophenone to give compounds **119** [139] .



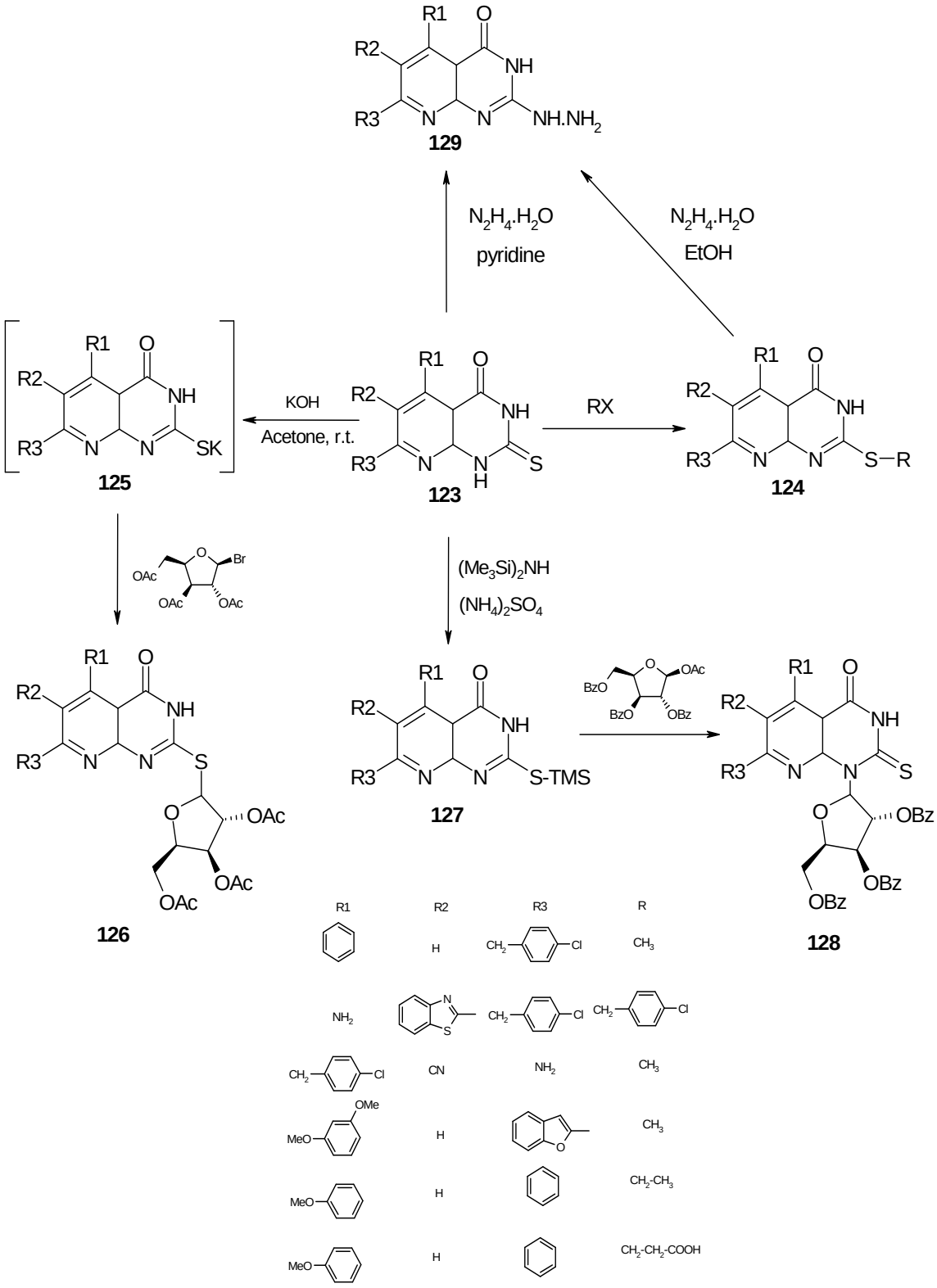
Moreover, the commercially available pyrido[2,3-*d*]pyrimidine-2,4-dione (**97**) reacted with phosphoryl chloride, under the same condition, to give the corresponding dihalides **120** which were further reacted with the appropriated amines to afford *N*substituted 2-(piperazin-1-yl)pyrido[2,3-*d*]pyrimidin-4-amine **121[**129] or *N,N'*-disubstituted pyrido[2,3-*d*]pyrimidin-2,4-diamine **122** [9] according to the condition of the reaction.



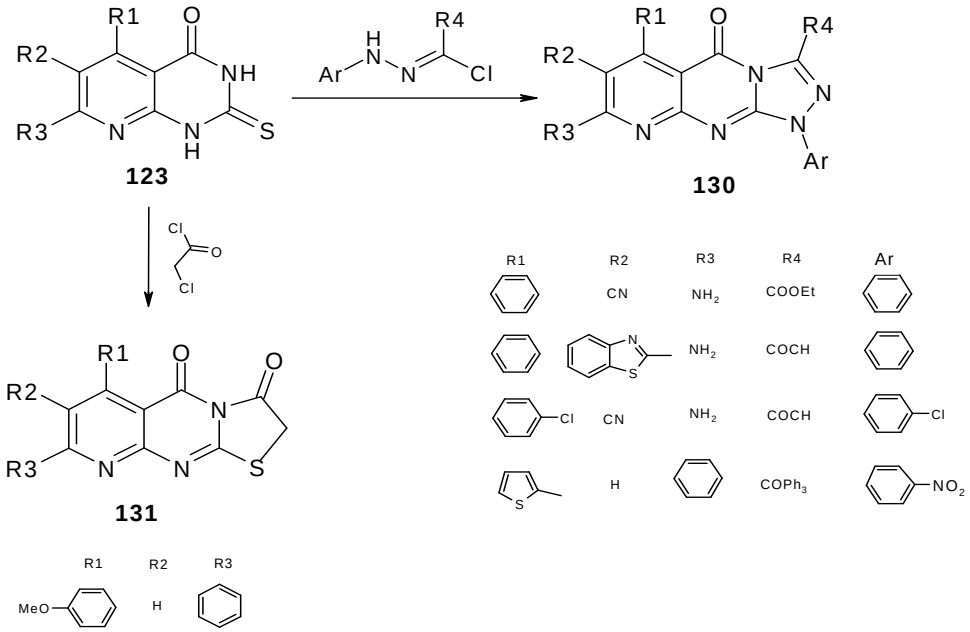
Alkylation of 2-thioxo-pyrido[2,3-*d*]pyrimidin-4(1*H*)-ones **123** took place at position 2 with alkyl halide in ethanolic sodium hydroxide (4N), [16, 79] anhydrous sodium acetate/ethanol [140] or K_2CO_3/DMF [78,141] to yield 2-alkylthiopyrido[2,3-*d*]-pyrimidine-4-one derivatives **124**.

The thioxo-derivatives **123** were converted into their potassium salts **125,** by using KOH in acetone, which were stirred at room temperature for long time with 1-bromo-2,3,5-tri-O-acetyl-α-D-arabinofuranose to yield the *S*-glycosylated nucleosides **126**.[16] While, Interaction of compounds **123** with hexamethyldisilazane ($(Me_3Si)_2NH$) formed silyloxypyrimidine derivative **127,** which in turn treated with 1-O-acetyl-2,3,5-tri-O-benzoyl-*β*-D-ribofuranose to furnish *N*-glycosylated nucleosides **128** [120] .

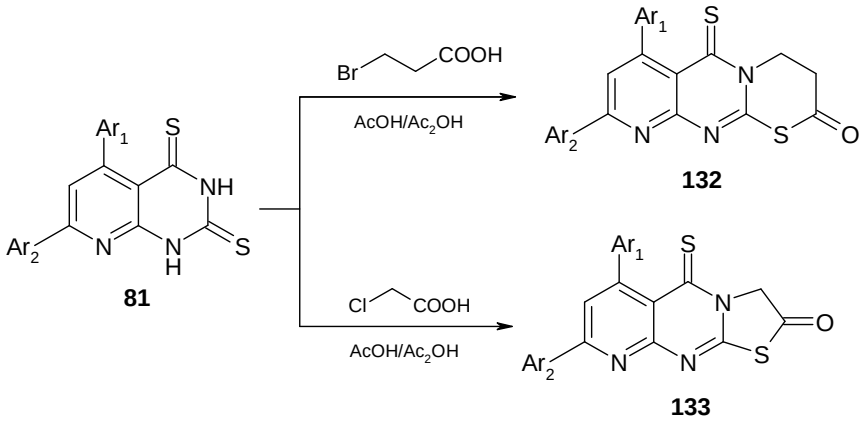
Hydrazinolysis of pyridopyrimidin-2-thiones **123** with hydrazine hydrate (80%) in pyridine afforded the sulfur free compound identified as 2-hydrazino-pyrido[2,3-*d*]pyrimidin-3-one **129**. Compound **129** could be obtained *via* nucleophilic displacement of thioalkyl group of compound **124** with hydrazine in boiling ethanol. [79]



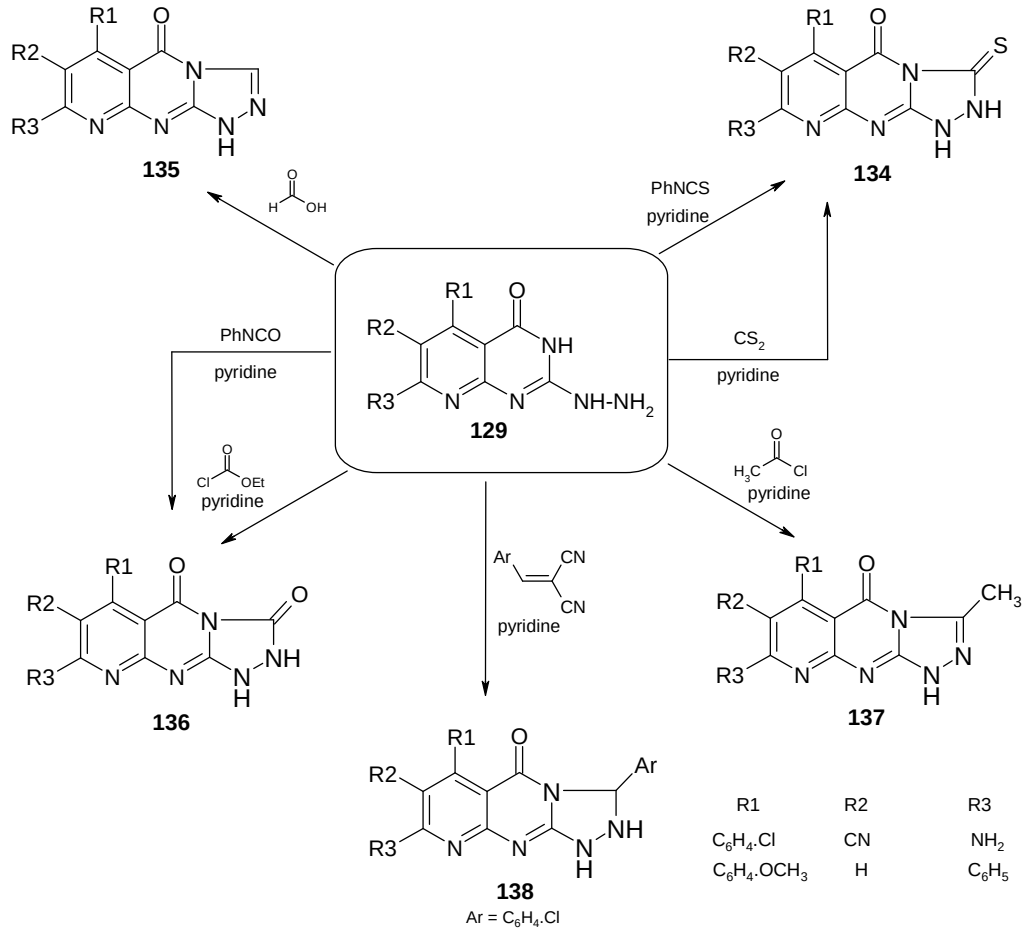
Besides aforementioned reactions, 2-thioxo-pyrido[2,3-*d*]pyrimidines **123** could be considered as a starting material for the synthesis of new polynuclear heterocycles such as pyridotriazolopyrimidins, pyridothiazolopyrimidine and pyridopyrimidothiazine derivatives. Thus, heating compound **123** with hydarzonoyl halides in boiling chloroform in the presence of triethylamine yielded the corresponding pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidin-5-one **130**.[**80,95,142]** While, refluxing of compound **123** with chloroacetyl chloride afforded pyrido[2,3-*d*]thiazolo[3,2-*a*]pyrimidine derivative **131** [75,140] .



Also, pyrido[2,3-*d*]pyrimidine-2,4-dithiones **81** reacted with *β*-bromopropionic acid or chloroacetic acid in glacial acetic acid/acetic anhydride to afford pyridopyrimidothiazine **132** and pyridopyrimidothiazole **133**, respectively [124] .

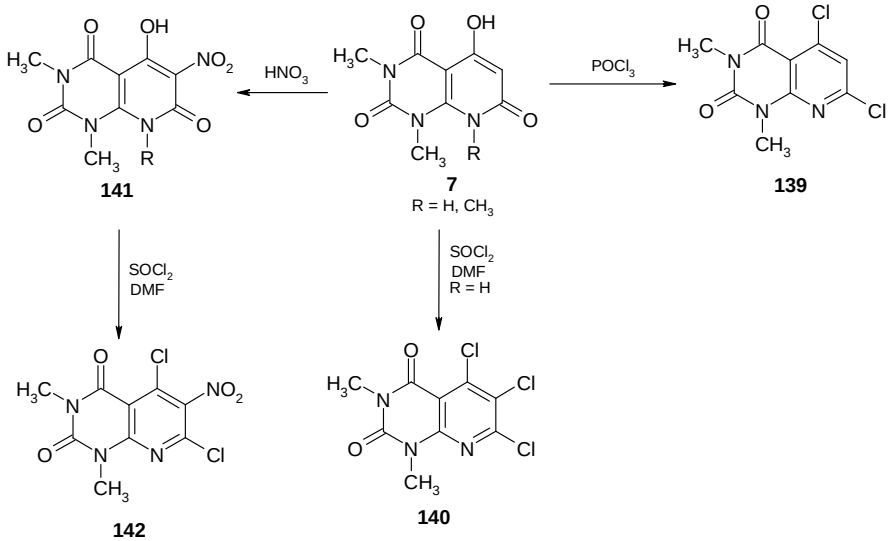


A similar cyclization to tricyclic products occurred when 2-hydrazino-pyrido[2,3-*d*]pyrimidines **129** treated with one carbon donors such as phenyl isothiocyanate or carbon disulfide, formic acid, ethyl chloroformate or phenyl isocyanate, acetyl chloride and 2-cyano-4-chloro-cinnamonitrile to give pyridotriazolopyrimidine derivatives **134-138**, respectively [79, 140, 143, 144] .



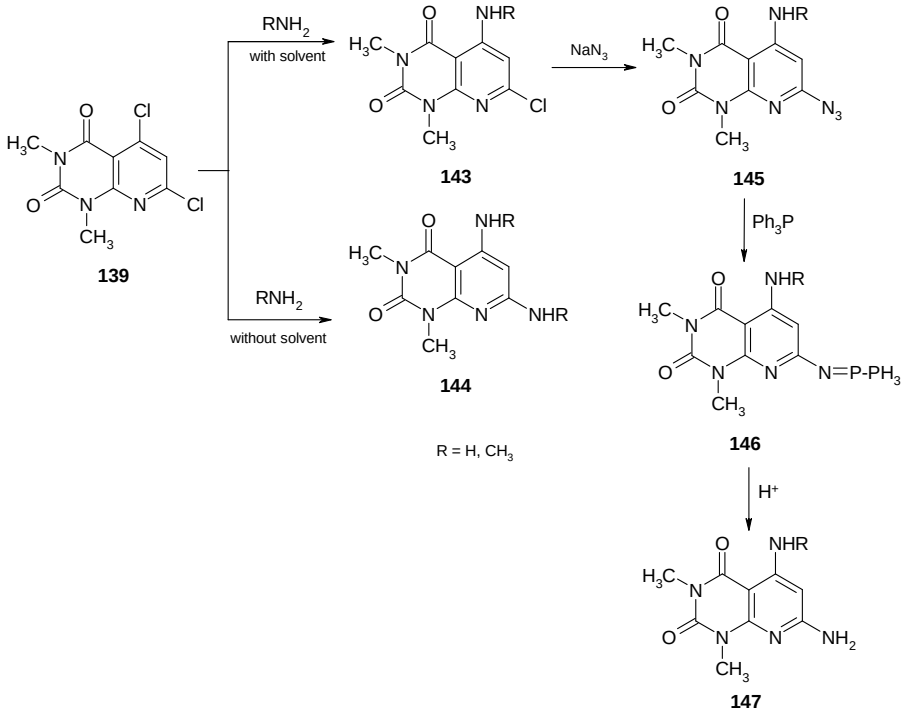
(ii) Reactions carried out on the pyridine rings

Chlorination of 5-hydroxy-pyrido[2,3-*d*]pyrimidine-2,4,7-triones **7** with phosphoryl chloride gave 5,7-dichloro-pyrido[2,3-*d*]pyrimidine-2,4-diones **139**.[145] While compound **7** (R = H) reacted with thionyl chloride in the presence of DMF to give trichloro derivatives **140**, chlorination at position 6 along with replacement of the hydroxyl groups at C(5) and C(7) with chlorine.[146] The nitration of **7** with fuming nitric acid in acetic acid gave 6-nitropyrido[2,3-*d*]pyrimidinetriones **141**. During chlorination of the latter compound, 5,7-dichloro- derivative **142** was obtained [147] .

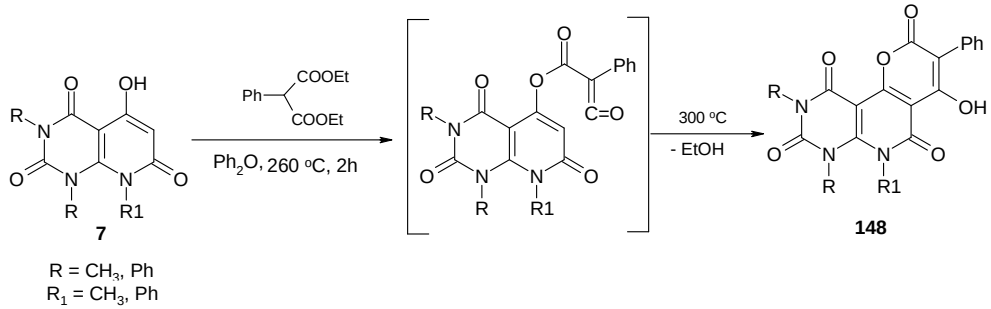


5-Amino- **143** and 5,7-diamino-pyrido[2,3-*d*]pyrimidine-2,4-diones **144** were prepared easily from the corresponding 5,7-dichloro-pyrido[2,3-*d*]pyrimidine-2,4-diones **139** with aliphatic and aromatic amines. The 7-

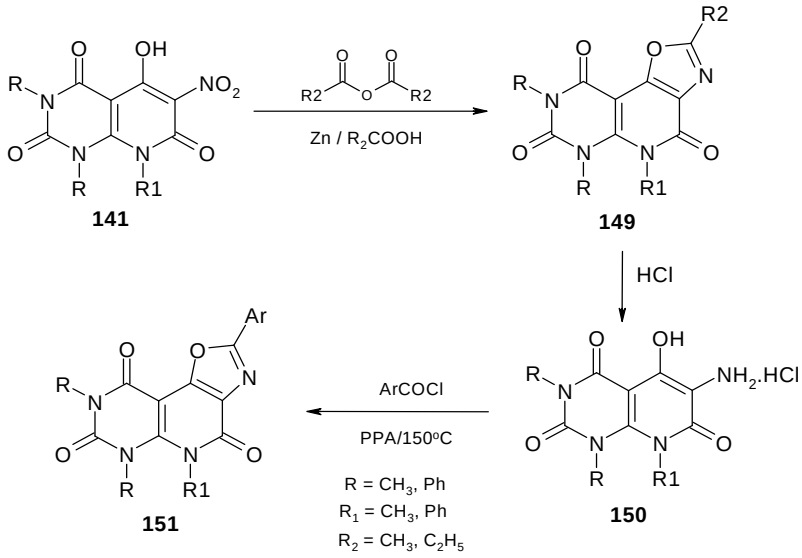
monoazides **145**, obtained by azidation of the chlorides **140**, were converted to iminophosphoranes **146** by reaction with triphenylphosphane. Hydrolysis produced in one step 7-amino-pyrido[2,3-*d*]pyrimidine-2,4-diones **147** [145] .



Substituents in position 5 and 6 of pyrido[2,3-*d*]pyrimidines give reactive synthons for cyclization reactions to polyheterocyclic systems. Thus, cyclocondensation of 5-hydroxy-pyrido[2,3-*d*]pyrimidines **7** with diethyl phenylmalonate gives pyrano[2',3':4,5]pyrido[2,3-*d*]pyrimidines **148** [147] .

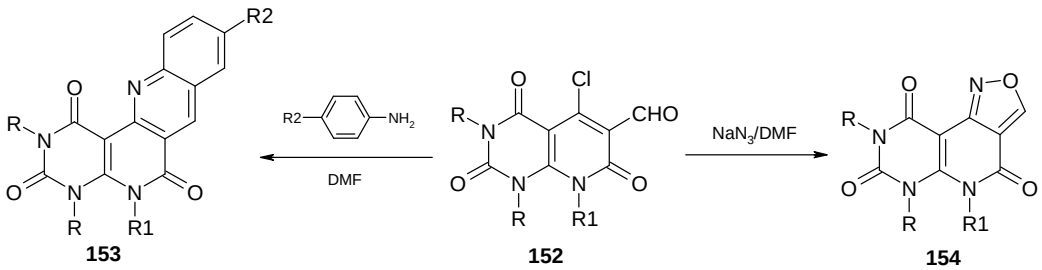


Also, 5-hydroxy-6-nitro derivatives **141** cyclized to 2-alkyloxazolo[5,4:4,5]pyrido[2,3-*d*]pyrimidinetriones **149** by reduction with zinc in the presence of alkanoates. Ring opening of the oxazole ring **149** with hydrochloric acid gave the 6-amino hydrochlorides **150**, which in turn could be cyclized again with benzoic acid chlorides in the presence of polyphosphoric acid to give 3-aryloxazolo[5,4:4,5]pyrido[2,3-*d*]pyrimidinetriones **151** [147] .



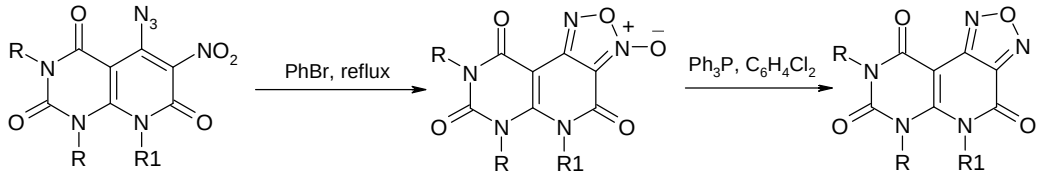
141 **149** **150** **151**

Furthermore, reaction of 5-chloro-6-formyl compounds **152** with aromatic amines gave a 1,6-naphthyridine derivatives **153**.[148] While, heating of the former compound with sodium azide in dimethylformamide gave isoxazolo[4,5:'4,'3]pyrido[2,3-*d*]- pyrimidines **154 [**149] **.**



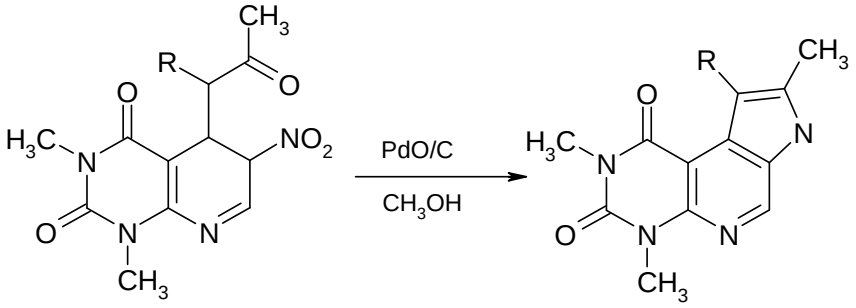
153 **152** **154**

Thermal decomposition of 5-azidopyrido[2,3-*d*]pyrimidines **155,** having reactive ortho-nitro group, in refluxing bromobenzene yielded furoxans **156**. Also, desoxygenation of *N*-oxides **156** by triphenylphosphane to oxadiazolo[4,5:'4,'3]pyrido[2,3-*d*]pyrimidines **157** was reported [149] .

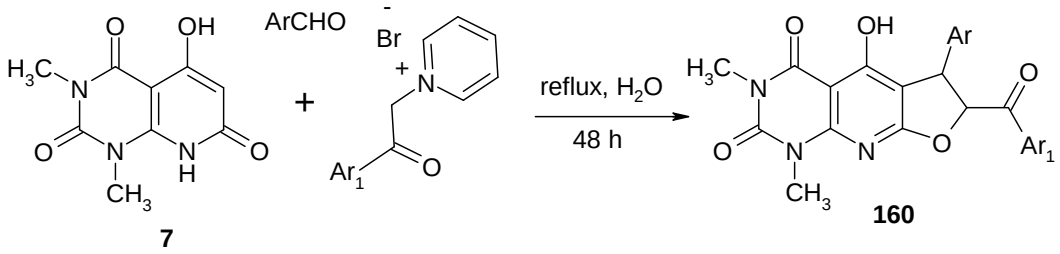


155 **156** **157**

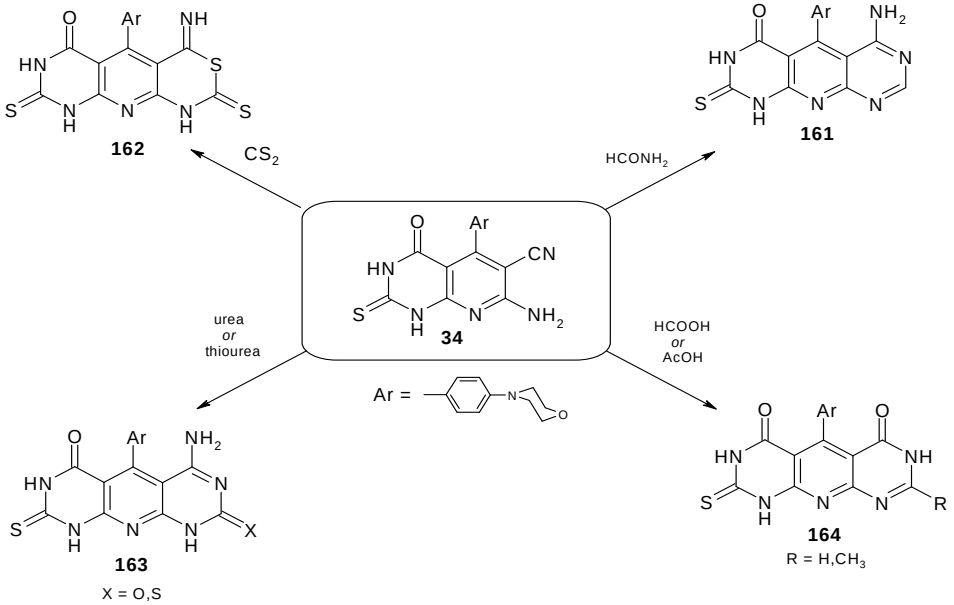
Reduction of 5-substituted 6-nitropyridol[2,3-*d*]pyrimidine-2,4-dione **158** under catalytic hydrogenation, not only was the nitro group reduced but intramolecular cyclization occurred forming pyrrolo[2',3':4,5]pyrido[2,3-*d*]pyrimidines **159** [150] .



Recently, a green method for the synthesis of dihydrofuropyrido[2,3-*d*]pyrimidines **160** *via* the reaction of pyrido[2,3-*d*]pyrimidine **7**, aldehydes and 1-(2-oxo-2-phenylethyl)pyridin-1-ium bromides as a pyridinium ylide base is investigated [151] .

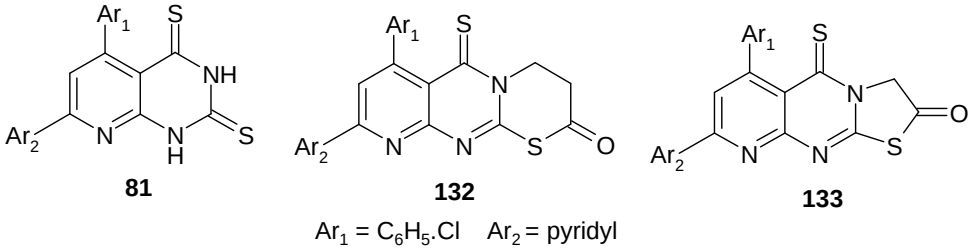


7-Amino-6-cyano-5-sbstituted-2-thioxopyrido[2,3-*d*]pyrimidin-4-one **34a** as a typical β-enaminonitrile derivative, reacted with different reagents such as formamide, carbon disulfide, urea, thiourea, formic and acetic acids to give the corresponding tricyclic derivatives **161-164**, respectively [77] .

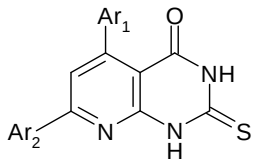


5- Contributions of our Laboratory

The chemistry of pyridopyrimidine derivatives has prompted many authors in the National Research Centre to study the synthesis and reactions of such compounds. Particularly, our research group gave a considerable attention for construction of new derivatives of pyrido[2,3-*d*]pyrimidines on the account of their reported biological activities. Thus, Rashad *et al*,[124] prepared compound **81**, from β-enaminonitrile derivative of pyridine with carbon disulfide, which in turn reacted with β-bromopropionic acid or chloroacetic acid to afford **132** and **133**, respectively.



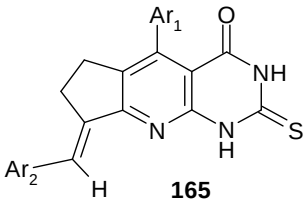
Also, El-Gazzar *et al*, has prepared a series of pyrido[2,3-*d*]pyrimidine derivatives such as: compounds **18**, [75] **165,** [152] and **166** [153] *via* cyclo-condensation of α,β-unsaturated ketones and 6-aminothiouracil. While, compounds **34** [95] were prepared either by the one-pot reaction of aldehydes, malononitrile and 6-aminothiouracil or by cycloaddition of arylidenemalononitriles with 6-aminothiouracil. Moreover, the reactivity of pyridopyrimidines **34** was studied toward hydarzonoyl halides and formic acid or acetic acid to give polynuclear pyrido[2,3-*d*][1,2,4]triazole- [4,3-*a*]pyrimidin-5-ones **130** and pyrimido[4`,5`:4,5]pyrido[2,3-*d*]pyrimidine-4,8-diones **164** respectively [95] .



18

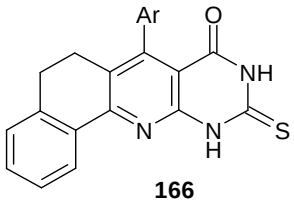
Ar_1 = phenyl, thienyl

Ar_2 = chlorophenyl



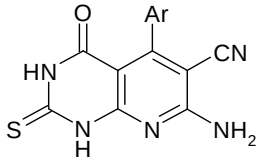
165

Ar_1 = 4-chlorophenyl, Ar_2 = 4-methoxyphenyl



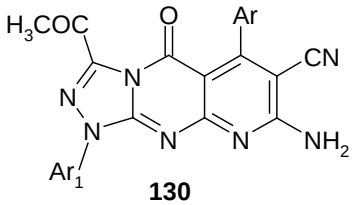
166

Ar = 4-chlorophenyl

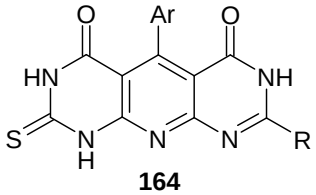


34

Ar = $C_6H_4.Cl(p)$, $C_6H_4.CH_3$, $C_6H_4.N(CH_3)_2$



130



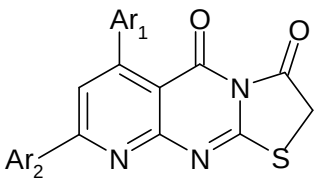
164

R = H,CH_3

Ar = $C_6H_4.Cl(p)$, $C_6H_4.CH_3$, $C_6H_4.N(CH_3)_2$

Ar_1 = C_6H_5, $C_6H_4.Cl(p)$, $C_6H_4.OCH_3$, $C_6H_4.NO_2$

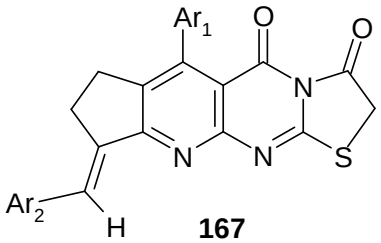
While, refluxing of compounds **18** or **165** in a mixture of acetic acid, acetic anhydride, and anhydrous sodium acetate afforded the corresponding pyrido[2,3-*d*]thiazolo[3,2-*a*]pyrimidines **131** and **167**, respectively [75, 152] .



131

Ar_1 = phenyl, thienyl

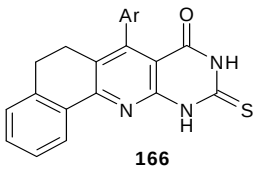
Ar_2 = chlorophenyl



167

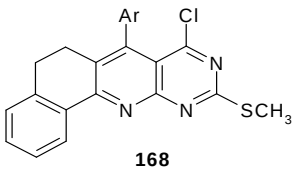
Ar_1 = 4-chlorophenyl, Ar_2 = 4-methoxyphenyl

Furthermore, alkylation of compound **166** with methyl iodide followed by chlorination with $POCl_3$ give 4-chloro-2-methylthio derivatives **169**. The latter product treated with hydrazine hydrate to give 2,4-dihydrazino **169** which in turn annulated to polycyclic compound **170** under effect of formic acid [153] .

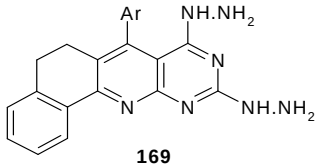


166

Ar = 4-chlorophenyl



168



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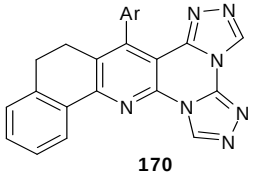
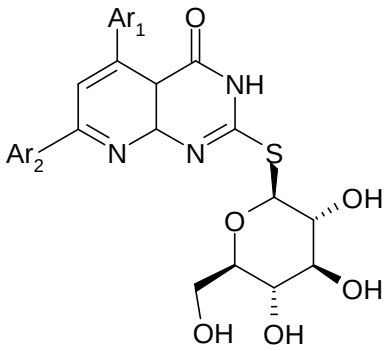
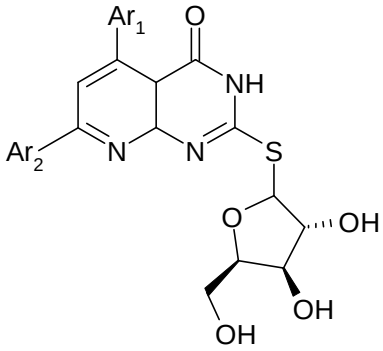


170

Also 2-*S*-nucleosides analogous of pyrido[2,3-*d*]pyrimidines **171** and **172** was synthesized according to reported method from compound **18** [16] .



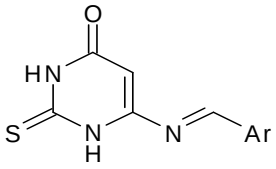
171



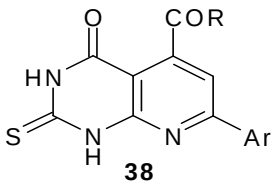
172

Compounds **34**, **171** and **172** exhibited anti-inflammatory and analgesic activities with superior gastrointestinal safety profile. Interestingly these compounds showed one-third of ulcer index of the reference Aspirin and Diclofenac [16,77] .

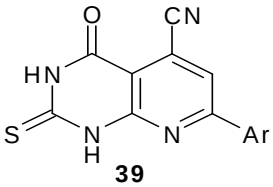
On the other hand, Mohamed *et al*,[81] synthesized compounds **38** and **39** *via* [4+2] cycloaddition of azomethine derivatives **35** with enaminones or enaminonitrile whereas, the in vivo antitumor activity of compound **38** (R = 2-thienyl, Ar = phenyl) showed moderate activity against lung carcinoma cell line (H460). Moreover, heterocyclic steroid **86[**15] was prepared and studied as a central antioxidant and anti-inflammatory agent.



35



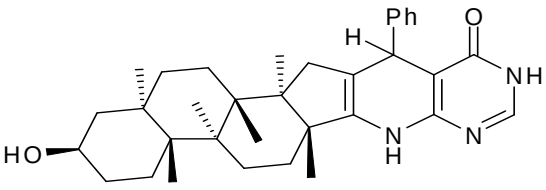
38



39

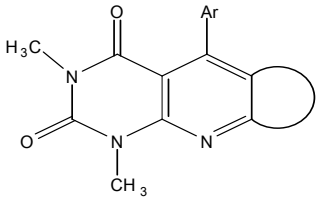
Ar = C_6H_5, $C_6H_4.OCH_3$(p)

R = 2-thienyl, 2-furyl, 2-naphthyl

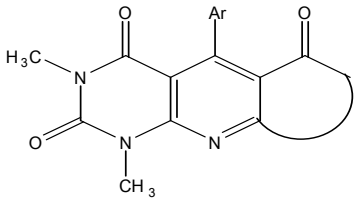


86

Moreover, Hassan *et al*,[97] prepared a series of polycyclic pyrido[2,3-*d*]pyrimidines **173-176** (linear structures) *via* three component one pot reaction of 6-amino-1,3-dimethyluracil and 6-amino-2-methylthiouracil with an appropriate aldehydes and a cyclic ketones or cyclic 1,3-diketones.



173



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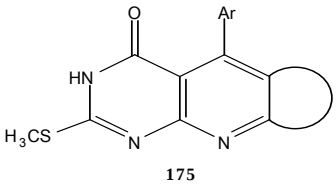

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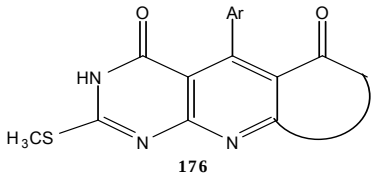
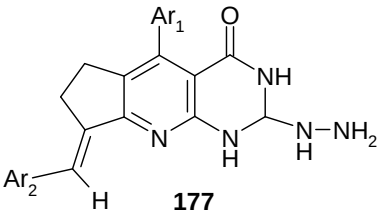


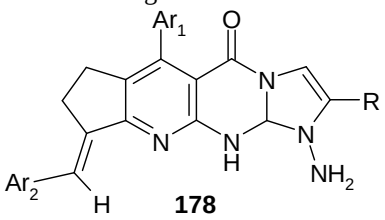
176

Also, Hafez *et al*,[143] prepared polynuclear heterocycles such as pyridoimidazolopyrimidines **178** and pyridotriazolopyrimidines **179** from the reaction of 2-hydrazino-pyrido[2,3-*d*]pyrimidines **177**, which obtained from hydrazinolysis of pyridopyrimidin-2-thiones **165,** with one carbon donors such as formic acid, acetic acid, potassium isothiocyanate or benzoyl chloride. Besides the evaluation of pyrazolyl pyrido[2,3-*d*]pyrimidine derivatives **180** as analgesic and anti-inflammatory agent where compound **180** (R = OH, R_1 = NH_2, X = H) revealed higher anti-inflammatory activity (82.8%) than ibuprofen (79.5%) and lower ulcerogenic effect.



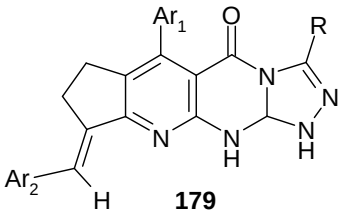
177

Ar_1 = 4-chlorophenyl, Ar_2 = 4-methoxyphenyl



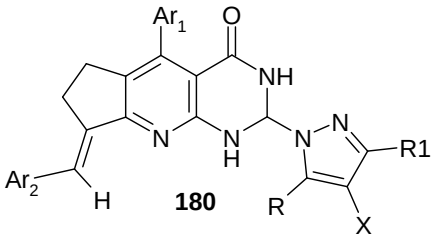
178

R = CH_3, C_6H_5



179

R = H, CH_3, C_6H_5, NH_2



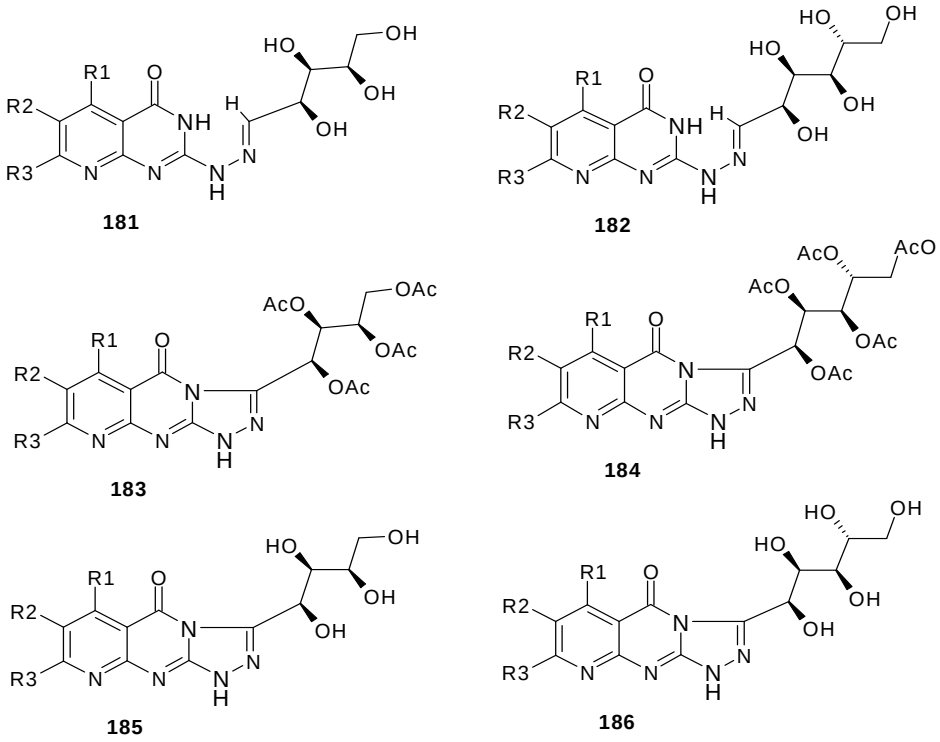
180

R = OH, R_1 = NH_2, X = H

R = R_1 = CH_3, X = H

R = R_1 = CH_3, X =Cl

On the other hand, Abu-Zied *et al*, [154] treateed the 2-hydrazino derivatives **129** (R_1 = C_6H_5, R_2 = H, R_3 = C_6H_4.Cl) with D-xylose or D-glucose to afford the acyclic *N*-nucleoside **181**, **182** which were converted into tetra/penta O-acetate acyclic *C*-nucleoside **183**, **184** in acetic anhydride/pyridine. De-acetylation of compounds **183**, **184** afforded *C*-nucleosides **185**, **186**.

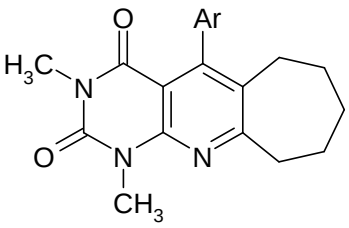


181 **182**

183 **184**

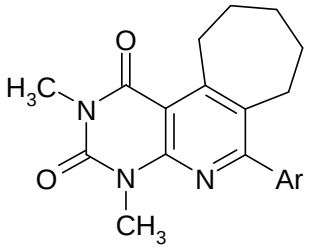
185 **186**

Finally, Hegab *et al*, [96] isolated hexahydrocyclohepta[5,6]pyrido[2,3-*d*]pyrimidine-2,4-dione **63** (linear structure) and hexahydrocyclohepta[4,5]pyrido[2,3-*d*]pyrimidine-2,4-dione **64** (angular structure) *via* a three-component one pot reaction of cycloheptanone, 6-amino-1,3-dimethyluracil, and aromatic aldehydes. Compound **63** was presumably formed *via* the initial formation of the α,β-unsaturated ketone, with a subsequent nucleophilic attack by the amino group of the uracil derivative on the carbonyl carbon of the α,β-unsaturated ketone intermediate, followed by cyclization. While the formation of compound **64** might be *via* the nucleophilic attack by the amino group of the uracil derivative on the methylenic carbon of the α,β -unsaturated ketone intermediate (Skraup and Doebner-Miller synthesis of pyridines), followed by cyclization. The structures of products were verified by single crystal X-ray diffraction.



63

Ar = C_6H_4.Cl(p), C_6H_4.Br(p)



64

Ar = C_6H_4.CN(p), C_6H_4.OCH_3(p)

6-Applications

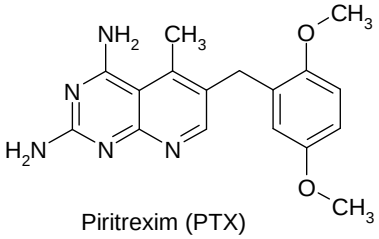
Biological and Medicinal Applications

Pyrido[2,3-*d*]pyrimidine derivatives received considerable attention due to their pharmaceutical importance [1,9-11,104,144] . In the last few decades, the synthesis of pyrido[2,3-*d*]pyrimidine derivatives had reported as a way to develop new simple route for synthesis of functionally substituted heterocyclic of anticipated biological activity as potential therapeutic agents. Some examples of the biological activity of pyrido[2,3-*d*]pyrimidine are displayed.

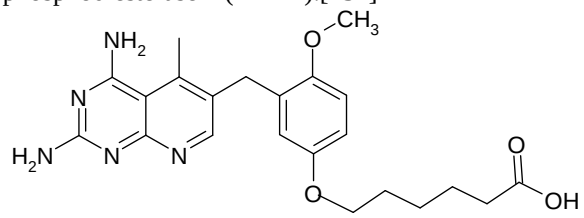
(i) As Antitumor agents

Cancer is a major health problem worldwide and the discovery of new compounds with antitumor activity has become one of the most important goals in medicinal chemistry. Chemotherapy, is one of the most commonly used treatment, aims to destroy the cancer cells with various types of chemicals. The substances used are supposed to target mainly the cancer cells, and doses are calculated to minimize the collateral damage to surrounding tissues, which does not happen. Several literatures enlightening the anticancer nature of pyrido[2,3-*d*]pyrimidines such as piritrexim (PTX), piritrexim analogs and isopiritrexim, which exhibited their antitumor activity by inhibiting

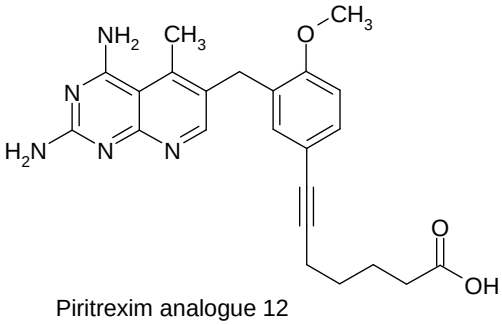
different types of enzymes such as cyclin-dependent kinase 4 (CDK4),[4] tyrosine kinase (TKI-28),[23,24] non-nucleoside adenosine kinase (ABT-702 dihydrochloride),[155] mammalian target of rapamycin (mTOR) kinase inhibitors,[156] dihydrofolate reductase (DHFR),[21] phosphodiesterase 2 (PDE 2).[157]



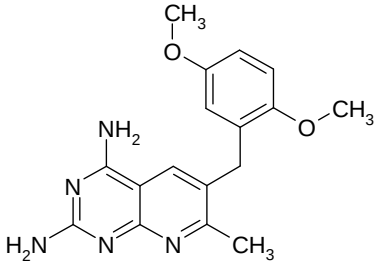
Piritrexim (PTX)



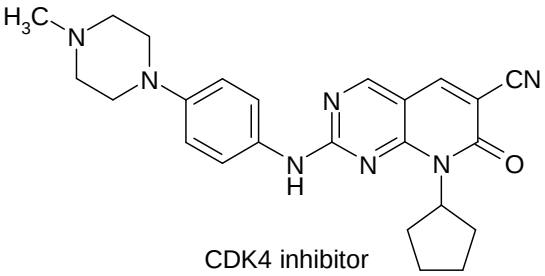
Piritrexim analogue 8



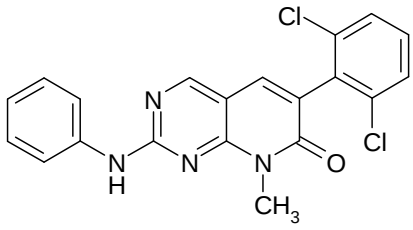
Piritrexim analogue 12



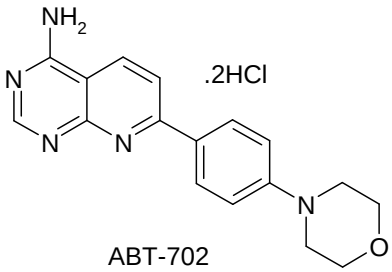
Iso-piritrexim



CDK4 inhibitor

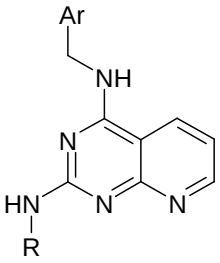


TKI-28



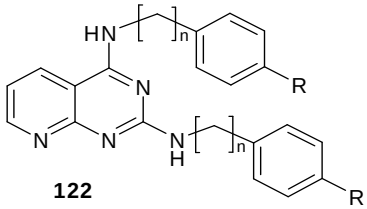
ABT-702

adenosine kinase inhibitor



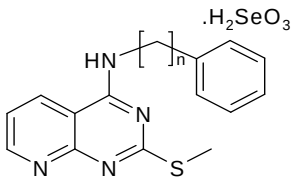
PDE 2 inhibitors

In 2014, Palop *et al*,[9] prepared a series of pyrido[2,3-*d*]pyrimidines and their hydroselenite salts with the aim of evaluating *in vitro* their cytotoxicity against a human prostate cancer cell line (PC-3) as well as their antioxidant activity with the free radical (1,1-diphenyl-2-picrylhydrazylradical) DPPH. Compounds **122** and **187** exhibited strong cytotoxic and antioxidant activities in comparison to the positive controls.



122

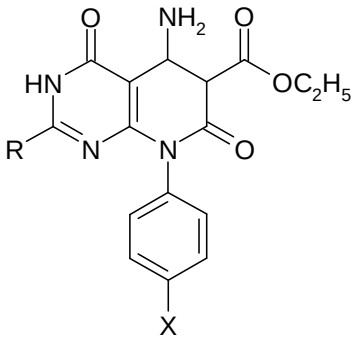
n = 1, R = SCH_3



187

n = 4

Also, the synthesis of pyrido[2,3-*d*]pyrimidine carboxylates **188** was reported and the anticancer activities of the pyrido[2,3-*d*]pyrimidine derivatives were evaluated using three human cancer cell lines, colon cancer (HT29), Liver cancer (HepG2) and cervical cancer (Hela) with MTT assay showed significant activity. The LC50 of the evaluated derivatives was found to be > 100 μg/ml for all these cell lines [1] .

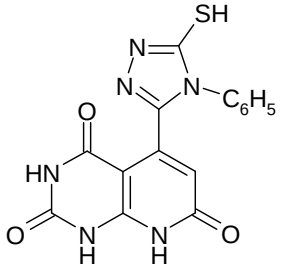


188

X = F, Cl, Br

R = OCH_3, CO_2CH_3

Gineinah *et al* Synthesized pyrido[2,3-*d*]pyramidine derivatives and screened for antitumor activity which possess high and potential efficiency with minimal side effects. As a result, interaction of antitumor agents with DNA should produce as little DNA damage as possible. The prepared compounds had been subjected to bleomycin-dependant DNA damage assay to screen their antitumor activity and the degree of DNA damage caused by these compounds. The antitumor activity of synthesized compounds is evaluated in terms of sample absorbance (A). As sample absorbance (A) increases, DNA damage increases and the sample efficiency as antitumor agent decreases. Compound **189** showed the lowest absorbance (0.052), and hence exhibited the highest antitumor activity [10] .

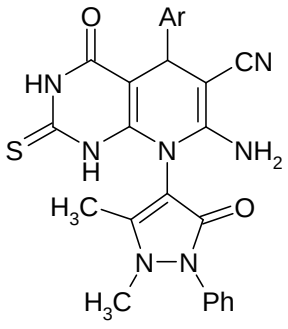


189

(ii) As Antimicrobial Agents

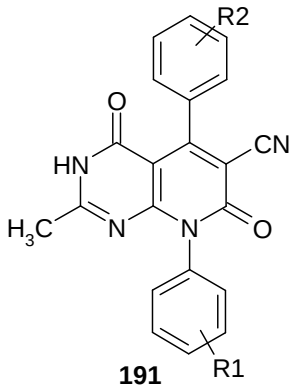
In 2014, Zaki *et al*, [158] prepared Fused pyrido[2,3-*d*]pyrimidines incorporating Egyptian natural products visnagin and khellin and the obtained products were tested against various microorganisms.

Moreover, in 2014, Aly *et al*, [14] synthesized hexahydropyrido[2,3-*d*]pyrimidines containing 8-(1,5-dimethyl-3-oxo-2-phenyl)pyrazole **190** and screened their antimicrobial activity against two fungal species, namely *Aspergillus flavus* and *Candida albicans* as well as two bacteria species, namely *Pseudomonas aeruginosa* and *Staphylococcus aureus*. by the disc diffusion method. In general, the novel synthesized compounds showed a good antimicrobial activity against microorganisms.



190

Recently, Khokhani *et al*, [126] prepared a series of pyrido[2,3-*d*]pyrimidines **191** and tested for their antimicrobial activities using three fungal species *Candida albicans*, *Aspergillus niger*, *Aspergillus clavatus*, two gram positive bacterial species, *Staphylococcus aureus*, *Streptococcus pyogenes* and two gram negative bacterial species *Escherichia coli*, *Pseudomonas aeruginosa*. The results revealed that all compounds exhibited considerable inhibition action against Gram positive and Gram negative but found inactive against all the fungal species.

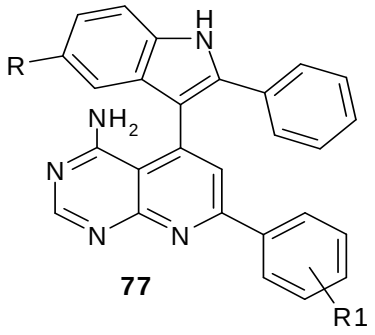


191

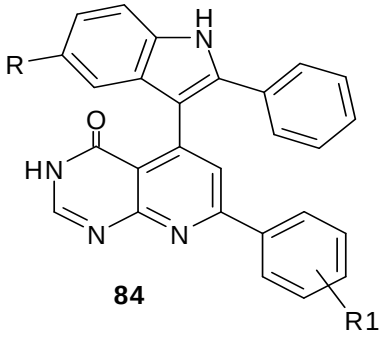
R_1 = 3-F, 4-Cl, 3,4-diCl

R_2 = H, 4-OCH_3, 4-NO_2, 4-CH_4

Also, a series of 4-amino-pyrido[2,3-*d*]pyrimidines **77** and pyrido[2,3-*d*]pyrimidin-4-(3*H*)-ones **84** have been synthesized and evaluated for their antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella penumoniae* and *Pseudomonas aeruginosa* and antifungal activity against *Aspergillus nizer*, *Aspergillus oryzae*, *Aspergillus terrus* and *Aspergillus flavus* by cup-plate method.[118] Generally, the majority of synthesized compounds having chloro substitution exhibited maximum growth inhibitory activity. The electronegative nature of the chloro group may be responsible to inhibit the growth of the microbes.



77

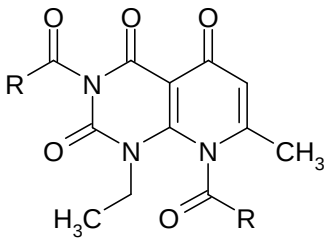


84

R = Cl, CH_3, H

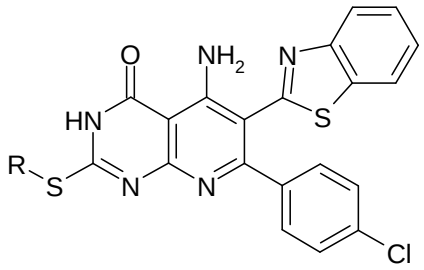
R_1 = Cl, CH_3, H

Kumaran *et al*, [67] prepared a series of 3,8-diacyl-1-ethyl-7-methylpyrido[2,3-*d*] pyrimidine-2,4,5- triones **192**. Antibacterial activity of all the synthesized derivatives was evaluated against pathogenic bacterial strains *viz*., *E.Coli*, Staphylococcus aureus, Pseudomonas aeruginosa, also Anti fungal activity of these derivatives are evaluated against fungal strains viz., *Aspergillus flavus*, *Cryptococcus neoformans*, *Candida albicans* using well diffusion methods. The results obtained showed that most of the compounds possess high activity of Cryptococcus neoformans.



192

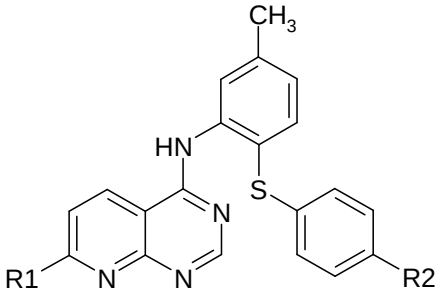
Suresh *et al*,[78] reported the synthesis of 2-(4-substitutedbenzylthio)-5-amino-6-(benzo[*d*]thiazol-2-yl)-7-(4-chlorophenyl)pyrido[2,3-*d*]pyrimidine-4(3*H*)ones **193** and tested their antimicrobial activity using Gram-positive and Gram negative bacteria by disc diffusion method. MIC was calculated using Ciprofloxazin as standard. Antifungal activity was studied in Sabourard's agar media using various strains of fungus using Amphotericin as standard [13] .



193

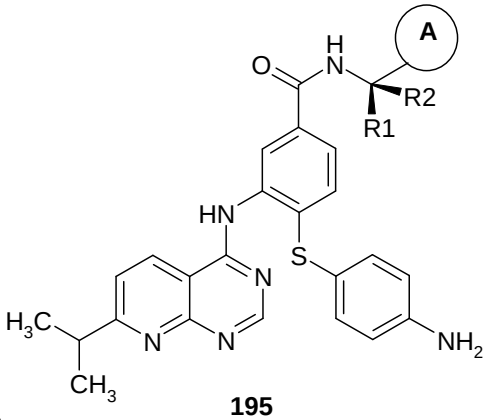
(iii) As Antiviral Agents

Hepatitis C virus (HCV) is a common pathogen that can lead to cirrhosis, hepatocellular carcinoma (HCC) and liver failure. There is still an urgent need for new HCV drugs with diverse modes of action. Thus, Krueger *et al*.[159] synthesized a group of pyrido[2,3-*d*]pyrimidines **194** and tested them for cytotoxicity in Huh-7 cells (a cell line of epithelial-like tumorigenic cells) and inhibitory potency in genotype 1a and 1b HCV replicon assays. Although compound **194** (R_1 = isopropyl, R_2 = OH) displayed improved potency, it lacked sufficient metabolic stability and oral pharmacokinetics.



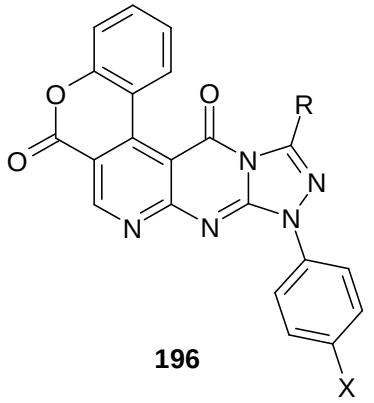
194

In 2013, studying the structure–activity relationships SAR on the latter system revealed that the introduction of amides bearing an additional 'A' ring provided compounds **195** with improved potency and pharmacokinetics. Introduction of a chiral center on the amide portion resulted in the observation of a stereochemical dependence for replicon potency and provided a site for the attachment of functional groups useful for improving the solubility of the series.[17] Besides, Quantum-chemical modeling has been reported in an attempt to find the relationship between the the electronic structure of pyrido[2,3-*d*]pyrimidines **194** and the variation of their inhibitory potencies [18] .



195

Also, Farghaly *et al*,[19] prepared a series of polynuclear heterocycles such as benzo[5',6']pyrano[4',3':4,5]pyrido[2,3-*d*]triazolo[4,3-a]pyrimidine-7,13(3*H*)-diones **196**. The tested compounds showed promising activities against HCV, H1N1, and could also be used as antiandrogenic agents.

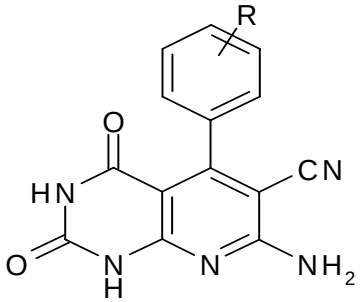


196

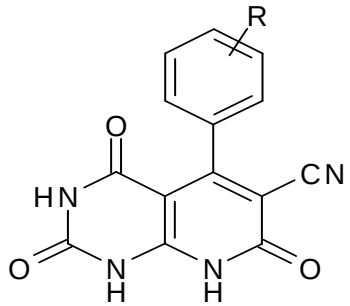
R = CH_3CO, EtOCO, PhNHCO

X = H, 4-CH_3, 4-Cl, 4-NO_2

A series of 7-amino- and 7-oxo-5-aryl-6-cyanopyrido[2,3-*d*]pyrimidines **69** and **197**, respectively has been synthesized and subjected to antiviral screeing against herpes simplex virus (HSV) where some of them show good activities [160] .



69

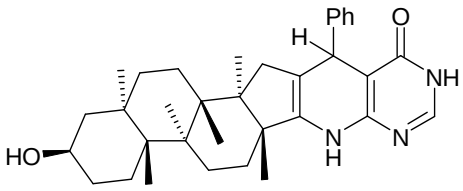


197

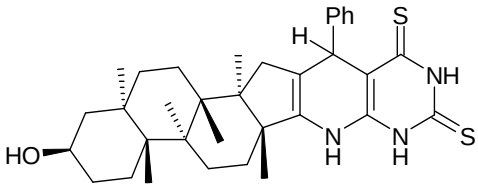
R = 4-Cl, 2-Br, 4-Br, 3-OH, 3-NO_2, 2,4-$(OCH_3)_2$,

(iv) As Analgesic and Anti-inflammatory Agents

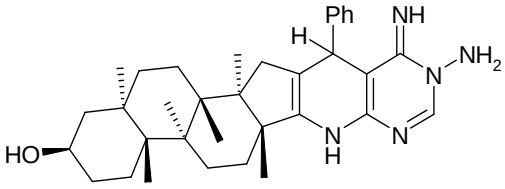
In the last few years, our research group evaluated the inflammatory activity for a series of pyrido[2,3-*d*]pyrimidine derivatives such as: Mohamed *et al*, [15] prepared a series of heterocyclic steroids via incorporating heterocylic moiety to the steroid nucleus and studied their activity as a central antioxidant and anti-inflammatory agent. It was found that compounds **86, 198** and **199** showed anti-neuroinflammatory and antioxidant activities with various intensities.



86

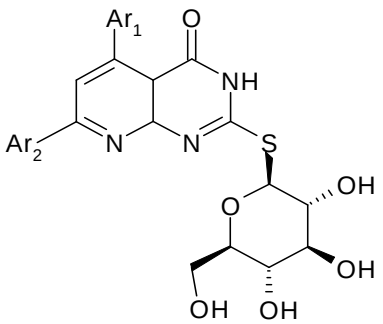


198

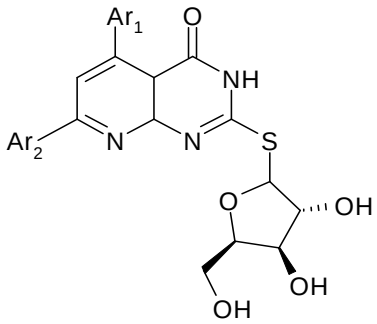


199

El-Gazzar and co-workers reported the synthesis of 2-S-nucleosides analogous of pyrido[2,3-*d*]pyrimidines **171** and **172** which evaluated for their anti-inflammatory and analgesic activity. It has been found that these compounds exhibited the dual pharmacological activities with gastrointestinal safety when compared to Indomethacin [16] .

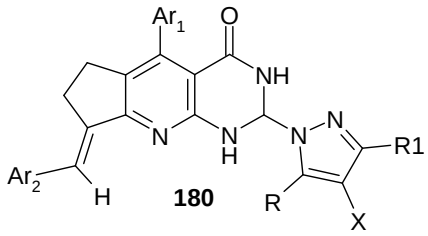


171



172

Also, Hafez *et al*,[143] evaluated a series of pyrazolyl pyrido[2,3-*d*]pyrimidine derivatives **180** as analgesic and anti-inflammatory agent where compound **180** (R = OH, R_1 = NH_2, X = H) revealed higher anti-inflammatory activity (82.8%) than ibuprofen (79.5%) with lower ulcerogenic effect.



180

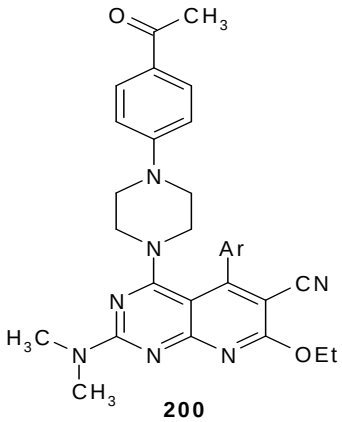
R = OH, R_1 = NH_2, X = H

R = R_1 = CH_3, X = H

R = R_1 = CH_3, X =Cl

(v) Activities for Antihistamine

Several pyrido[2,3-d]pyrimidines are prepared and their action on the release of histamine by mast cells examined under immunological and chemical stimulus, with and without pre-incubation. Pyrido[2,3-*d*]pyrimidine derivative **200** (Ar = 4-Cl-C_6H_4) is the more active of all, inhibiting the release of histamine in all the conditions tested [25] .



200

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