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Recent synthetic methodologies for pyrimidine and its derivatives

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Abstract: Pyrimidine derivatives are well known due to their remarkable pharmacological potential in various fields of science, and they are also present in some natural substances like DNA and RNA. These scaffolds manifest diversified biological activities such as antimicrobial, antiinflammatory, anti-HIV, antitubercular, antitumor, antineoplastic, and antimalarial. A pyrimidine ring is constructed when chalcones, amidines, guanidine, nitriles, isocyanates, urea, thiourea, and aminopyrazoles undergo condensation, coupling, or cyclization reactions. In this context, the present review illustrates a variety of novel and efficient synthetic approaches towards the synthesis of pyrimidine and its derivatives that were reported recently.

Key words: Pyrimidine, synthesis, multicomponent, chalcones, guanidine, urea, thiourea

1. Introduction

Pyrimidine **1** is a six-membered heterocyclic compound containing two nitrogen atoms. Its synthetic derivatives demonstrate an essential role in modern medicines such as quinazoline alkaloids, which exhibit hypnotic activity.[1] Many simple fused pyrimidines such as purines and pteridines are biologically active. Some have bronchodilatory potential and act as antagonists of the human A_2A adenosine receptor and constitute some valuable naturally occurring substances such as nucleic acids.[2] Similarly, the presence of a pyrimidine base in cytosine, uracil, and thymine (building blocks of DNA and RNA) is one of the possible reasons for their activities. Some pteridine derivatives are also used as antileukemic drugs.[3] Moreover, a pyrimidine ring is also found in isoalloxazine, vitamin B2, flucytosine **2** (used as a nucleoside antifungal agent for the treatment of systemic severe infections), thiamine **3**, riboflavin (6,7-dimethyl-9-(D-1-ribityl) **4**, and folic acid **5** (Figure).[4] A few pyrimidine derivatives also show potassium-conserving diuretic and antimalarial activity.[5]

Condensed pyrimidine derivatives have also been reported as antimicrobial and hypnotic drugs for the nervous system,[6] with activities including antiinflammatory,[7] anti-HIV,[8] antiparasitic,[9] and antitumor and uses as calcium-sensing receptor antagonists,[10] antiulceratives,[11] antimalarial and cardiovascular agents,[12] and diuretic drugs.[13]

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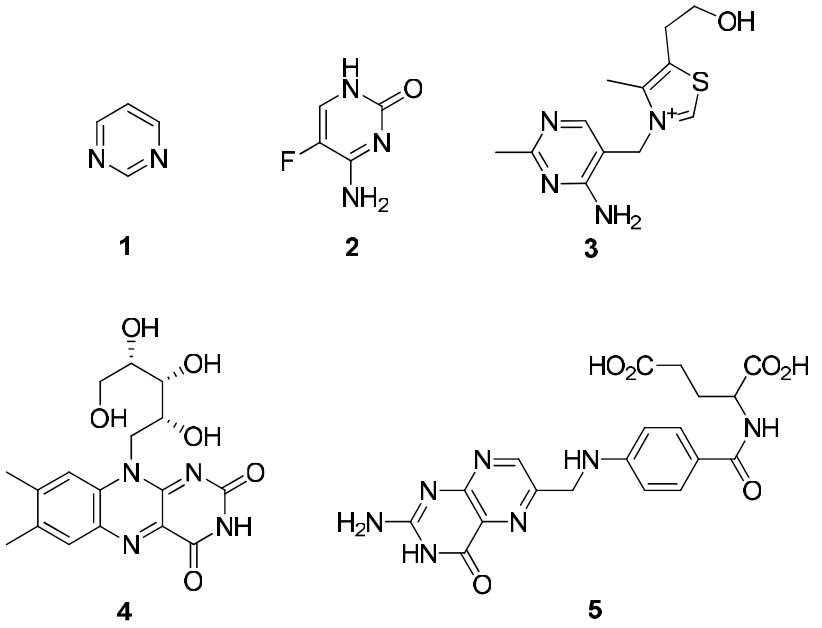
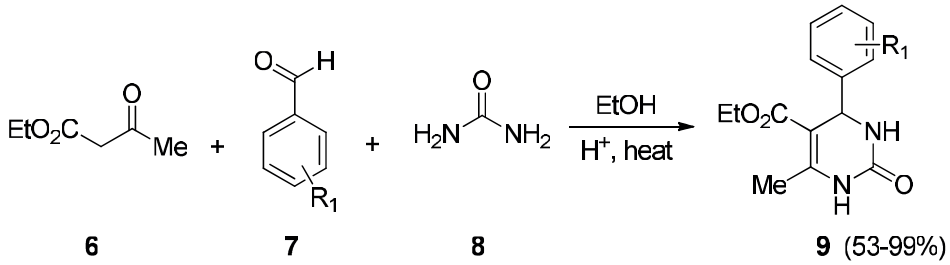


Figure. Structures of some biologically essential pyrimidines.

2. Review of the literature

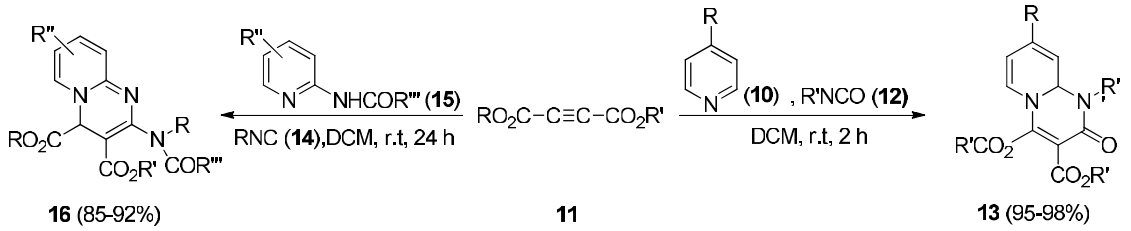
2.1. Multicomponent synthesis

In 2001, Falsone and Kappeexplored the Biginelli reaction conditions and reported the polyphosphate ester (PPE) mediated condensation between ethyl acetoacetate **6**, benzaldehydes **7**, and urea **8** to achieve pyrimidin-2-ones **9** in good to excellent yields (Scheme 1).[14] It was observed that the use of PPE in THF solvent stabilized the *N*-acyliminium ion intermediates produced during the Biginelli reaction.



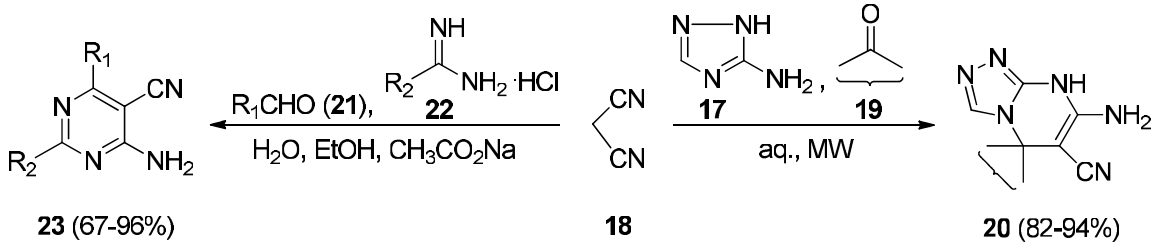
Scheme 1. Synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivatives.

Bicyclic 6-6 fused ring systems are well known due to their potent antipsychotic, analgesic, and anti-asthmatic properties. To target more efficient pharmacophores, Adib and colleagues synthesized 2-oxo-1,9a-dihydro-2*H*-pyrido[1,2-a]pyrimidines **13** in 95%–98% yield by the reaction of pyridines **10**, dialkyl acetylenedicarboxylates **11**, and isocyanates **12** (Scheme 2).[15] However, in another synthetic work, Adib et al. presented a concise synthetic route to achieve bicyclic 6-6 fused ring systems (2-amino-4*H*-pyrido[1,2-*a*]pyrimidine-3,4-dicarboxylates **16**) in 85%–92% yield via the coupling of dicarboxylates **11**, isocyanides **14**, and *N*-(2-heteroaryl)amides **15** under dry conditions (Scheme 2).[16]



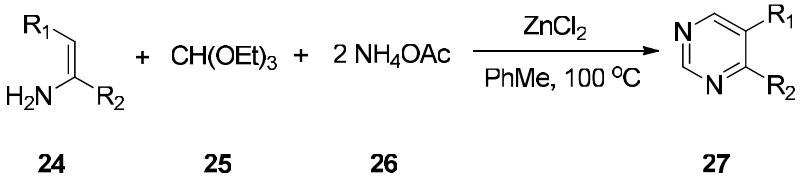
Scheme 2. Multicomponent synthesis of pyrimidine derivatives **13** and **16**.

For the first time, environmentally friendly microwave-mediated reaction between aminotriazole **17**, malononitrile **18**, and carbonyl compounds **19** under aqueous conditions resulted in the formation of triazolopyrimidines **20** (82%–94% yield) in the laboratories of Dandia and coworkers.[17] According to the mechanism, an alkenenitrile intermediate is produced by the reaction between malononitrile **18** and carbonyl compound **19**, which further reacts with aminotriazole **17** to afford final product **20** (Scheme 3). In the following year, Sheibani and colleagues condensed aromatic aldehydes **21**, malononitrile **18**, and amidines **22** to achieve 2-amino-5-pyrimidinecarbonitriles **23** (67%–96% yield) (Scheme 3).[18]



Scheme 3. Synthetic route to triazolopyrimidines **20** and 2-amino-5-pyrimidinecarbonitriles **23**.

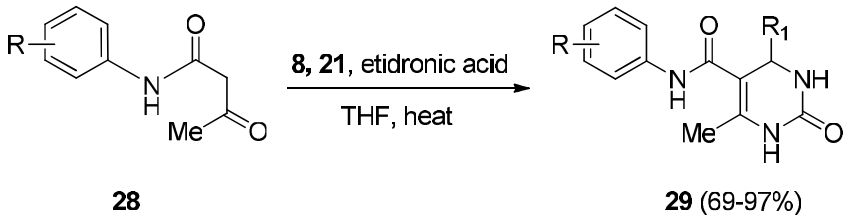
A [3+1+1+1] annulation process was employed for the synthesis of pyrimidine derivatives **27** by the condensation of aminoalkenes **24**, orthoester **25**, and ammonium acetate **26** in the presence of Lewis acid catalyst in the laboratories of Sasada and coworkers (Scheme 4).[19]



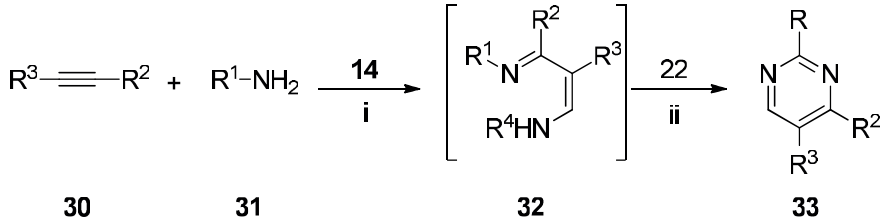
Scheme 4. Condensation between aminoalkenes, orthoester, and ammonium acetate.

Dihydropyrimidinones **29** (69%–97% yield) were achieved by Pansuriya and colleagues via the reaction of *N*-phenyl-3-oxobutanamides **28** with urea **8** and aldehydes **21** in the presence of etidronic acid (Scheme 5).[20] Etidronic acid was found suitable for all types of aldehydes and provided good to excellent yields of products compared to PPA and PPE.

In the same year, pyrimidine and its derivatives **33** (51% yield) were achieved by Majumder and Odom by treating amines **31**, alkynes **30**, and isonitrile **14** in the presence of $Ti(NMe_2)_2(dpma)$ or $Ti(dpm)(NMe_2)_2$ catalysts.[21] The resulting product was condensed with amidine **22** on heating in the presence of *tert*-amyl alcohol to provide the requisite pyrimidines (Scheme 6).

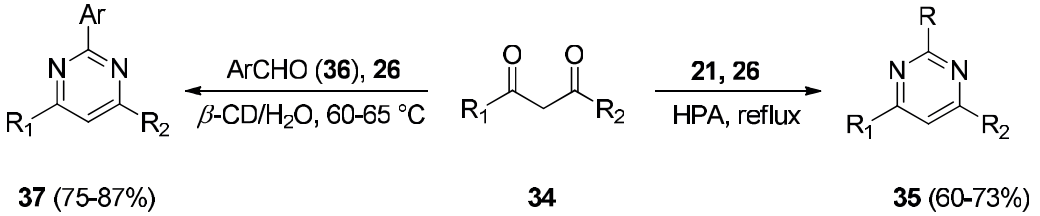


Scheme 5. Synthetic layout for the synthesis of 5-carboxanilide-4-substituted dihydropyrimidinones **29**.



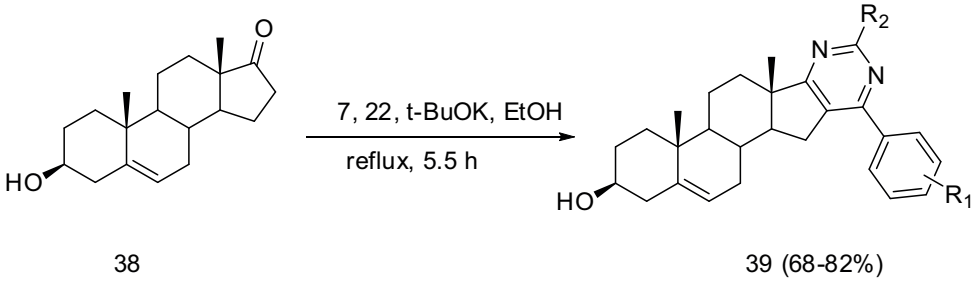
Scheme 6. Reaction conditions: (i) 10 mol% $Ti(NMe_2)_2$(dpma) or Ti(dpm)$(NMe_2)_2$, toluene, 100 °C; (ii) *tert*-amylalcohol, 150 °C.

Later, Heravi et al. employed the economic, less harmful, and recyclable Keggin-type heteropolyacids (HPAs) for the coupling of 1,3-diketones **34**, aldehydes **21**, and ammonium acetate **26** to achieve a variety of pyrimidine derivatives in good yields (60%–73%) (Scheme 7).[22] However, Chowrasia and coworkers executed similar coupling in the presence of β-cyclodextrin/H_2O to get the targeted pyrimides **35** in excellent yields (75%–87% yield) (Scheme 7).[23] Use of β-cyclodextrin/H_2O eliminated a few synthetic problems such as use of hazardous metals, acids, moisture-sensitive catalysts, and complicated reaction workups.



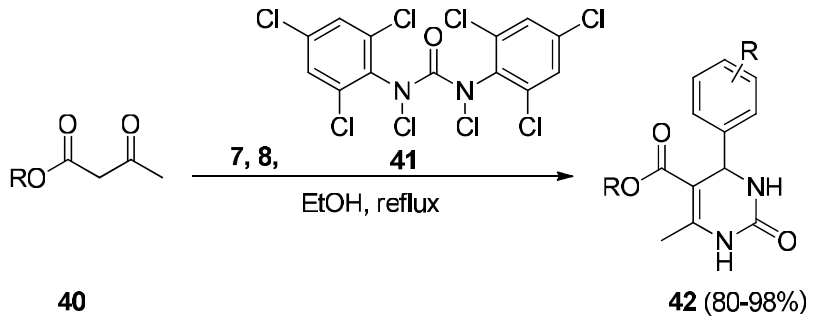
Scheme 7. Conversion of 1,3-diketones into pyrimidine derivatives.

Due to the tremendous biological potential associated with steroidal and nonsteroidal pyrimidine scaffolds, Saikia and coworkers synthesized novel steroidal/nonsteroidal pyrimidines **39** (68%–82% yield) in a one-pot multicomponent synthetic route from ketone **38**, aldehydes **7**, and amidine hydrochlorides **22** (Scheme 8).[24]



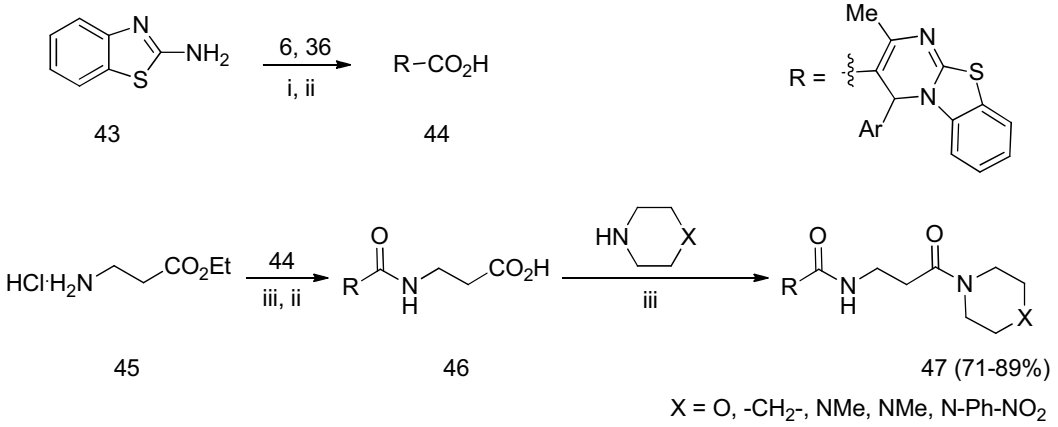
Scheme 8. Synthesis of steroidal/nonsteroidal pyrimidines.

Various reagents used in the Biginelli reaction for the synthesis of pyrimidine derivatives have limited applications. To overcome these limitations, Rao and colleagues incorporated $N,N'-$dichlorobis(2,4,6-trichlorophenyl)urea **41** in the Biginelli reaction between β-ketoesters **40**, arylaldehyde **7**, and urea **8** and achieved good to excellent yields of 3,4-dihydropyrimidin-2-(1*H*)ones **42** (80%–98% yield) (Scheme 9).[25] The $N,N'-$dichlorobis(2,4,6-trichlorophenyl)urea **41** is applied to a variety of reagents due to its high chlorine contents and harmless and stable character. The remarkable property of this reagent is that it releases positive chlorine, which participates in the reaction, while it itself transforms into an insoluble material that can easily be filtered off. However, treatment of this insoluble material with $AcOH/Cl_2/NaOH$ yields back $N,N'-$dichlorobis(2,4,6-trichlorophenyl)urea **41**.



Scheme 9. Biginelli reaction between β-ketoesters, arylaldehydes, and urea.

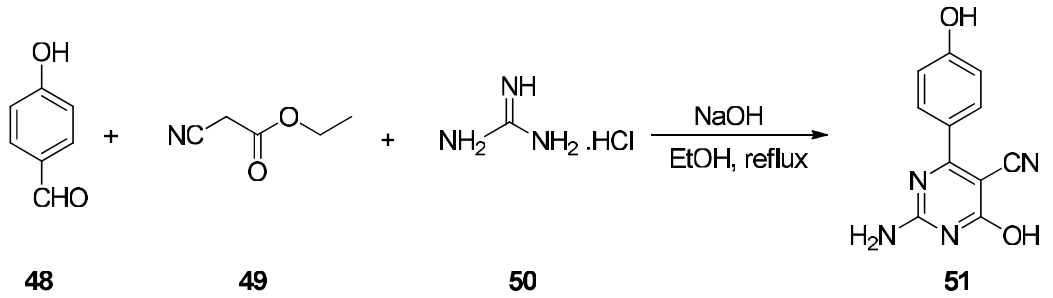
Later on, base-catalyzed condensation between benzaldehyde **36**, 3-amino-1*H*-pyrazole **43**, and ketoester **6** resulted in the formation of thiazolo[1,5-α]pyrimidines **44** in the laboratories of Nagarapu et al.[26] Furthermore, treatment of pyrimidine **44** with amino ester **45** followed by base hydrolysis furnished carboxylic acid **46**. Finally, the reaction between carboxylic acid **46** and a variety of secondary cyclic amines furnished the targeted pyrimidine derivatives **47** (71%–89% yield), which are associated with a wide spectrum of anticancer potential (Scheme 10).



Scheme 10. Reaction conditions: (i) $HOCH_2CH_2OH$, TBAHS, 120 °C; (ii) 1N KOH, EtOH, reflux; (iii) HOBt, EDC, HCl, Et_3N, DCM, r.t.

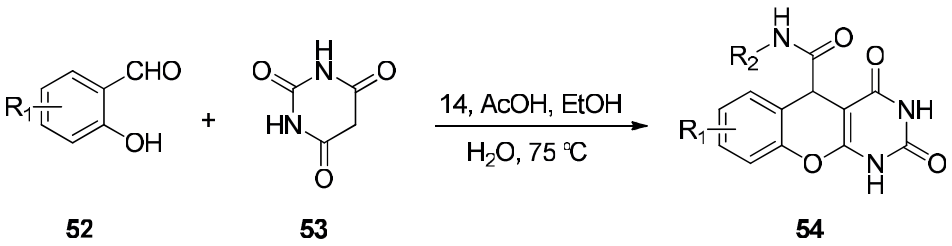
In another route, good yields of 2-amino-6-hydroxy-4-(4-hydroxyphenyl)-pyrimidine-5-carbonitrile **51**

were achieved by Suryawanshi and coworkers via the base-catalyzed reaction between aromatic aldehyde **48**, ethyl cyanoacetate **49**, and guanidine hydrochloride **50** (Scheme 11).[27]



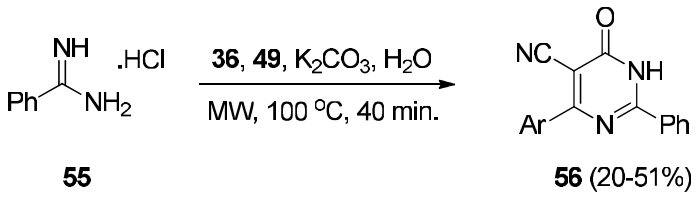
Scheme 11. Multicomponent synthesis of pyrimidine **51**.

In the same year, Soleimani and colleagues reported the synthesis of fused pyrimidine derivatives **54** by the reaction of salicylaldehydes **52**, barbituric acid **53**, and isocyanides **14** in acidic medium (Scheme 12).[28]



Scheme 12. Synthesis of fused pyrimidines **54**.

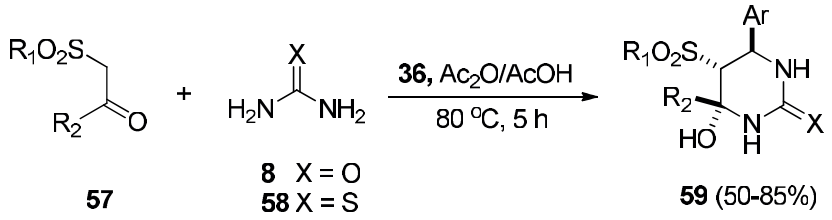
Later, Xavier et al. employed concise and environmentally friendly conditions for the coupling of aromatic aldehydes **36**, ethyl cyanoacetate **49**, and benzamidinehydrochloride **55** to afford pyrimidinones **56** (20%–51% yield), which possess significant analgesic potential (Scheme 13).[29]



Scheme 13. Microwave-mediated synthesis of pyrimidinones **56**.

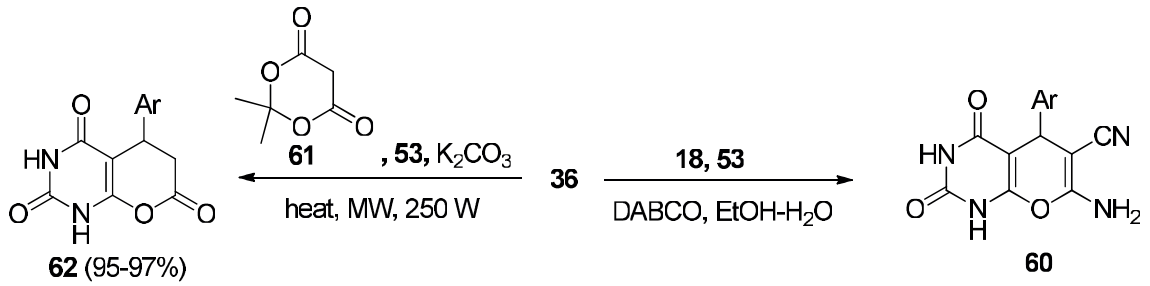
In the following year, a one-step synthetic route to tetrahydropyrimidinones **59** (50%–85% yield) was presented by Timoshenko and colleagues via the condensation of urea **8**/thiourea **58**, aryl aldehyde **36**, and a solution of ketosulfone/ketosulfamide **57** under acidic conditions (Scheme 14).[30]

Most of the pyrimidine synthetic routes are limited because of poisonous byproducts, use of metal triflates, excess amounts of bases, etc. Jain et al. synthesized pyrano[2,3-d]pyrimidines **60** by the coupling of 5-membered heteroaryl aldehydes **36**, malononitrile **18**, and dimethylcyclohexane-1,3-dione **53** in the presence of economic, cheaper, and nontoxic DABCO (diazabicyclo[2.2.2]octane) (Scheme 15).[31] Azzam and Pasha reported a solvent-free, rapid, facile, high-yielding multicomponent synthetic route to new pyrano[2,3-d]pyrimidine-2,4,7-triones



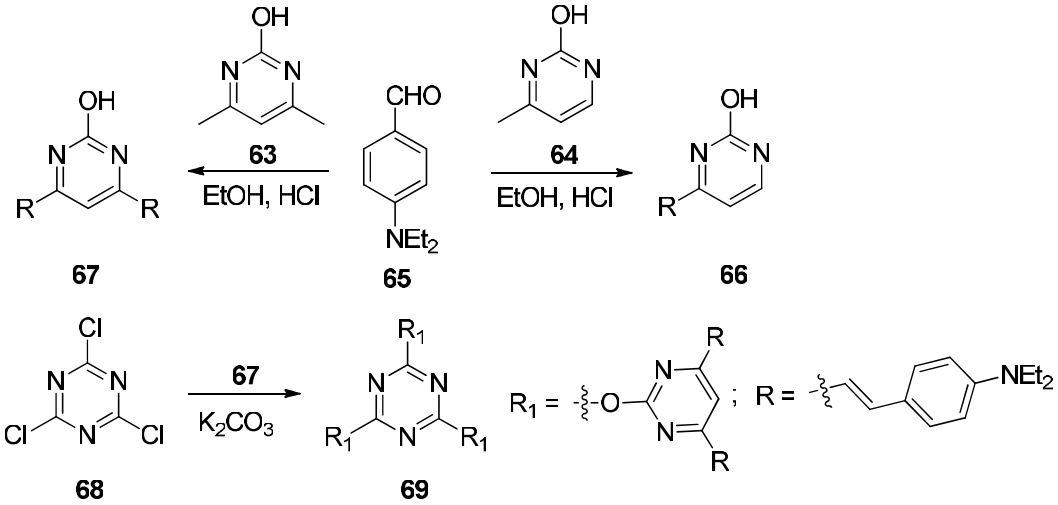
Scheme 14. One-step synthetic route to tetrahydropyrimidinones **59**.

62 (95%–97% yield) under solvent-free environment via the condensation of barbituric acid **53**, Meldrum's acid **61**, and diversified aldehydes **36** in the presence of efficient, cheaper, and readily available K_2CO_3 catalyst (Scheme 15).[32]



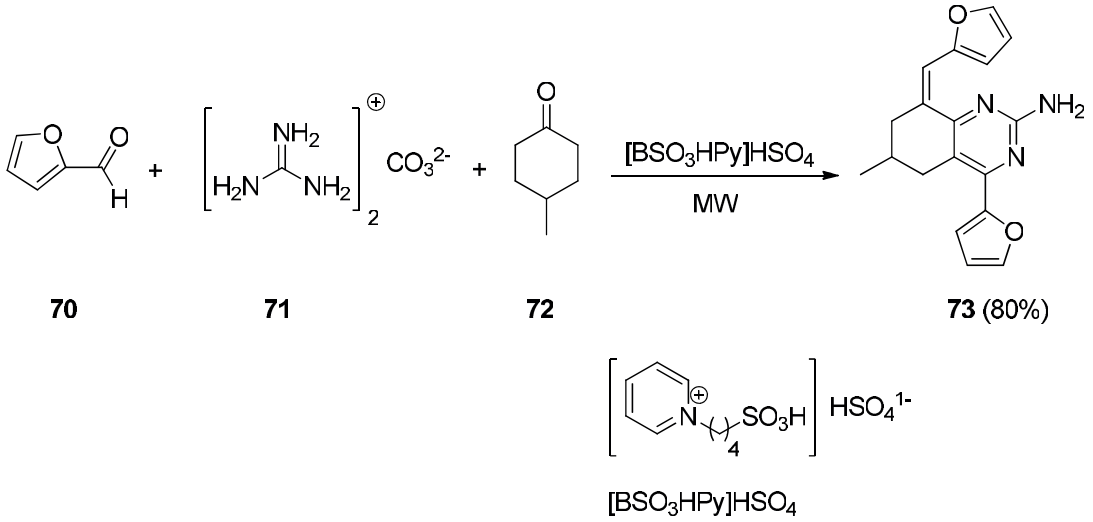
Scheme 15. Synthesis of pyrano[2,3-d]pyrimidine via condensation process.

In the next year, to achieve novel dyes, Wang and colleagues synthesized chromophores **66** and **67** by treating pyrimidines **63** and **64** and aldehyde **65**. After this, pyrimidine **67** was coupled with 2,4,6-trichloro-1,3,5-triazine **68** under basic conditions to afford another novel chromophore **65** (Scheme 16).[33]



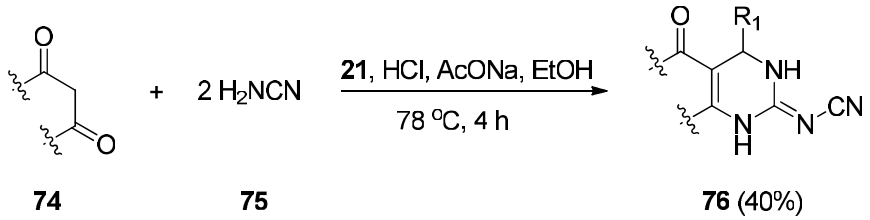
Scheme 16. Synthesis of novel chromophores.

Use of ionic liquids in synthetic chemistry is growing day by day because of their low pressure, thermal stability, recyclability, and ecofriendly nature. In this context, tetraquinazoline-2-amine **73** (80% yield) was achieved by Zakeri and colleagues by the condensation of furfural **70,** guanidine carbonate **71**, and 4-methyl cyclohexanone **72** under microwave irradiation using $[BSO_3HPy]HSO_4$ ionic liquid as catalyst (Scheme 17).[34]



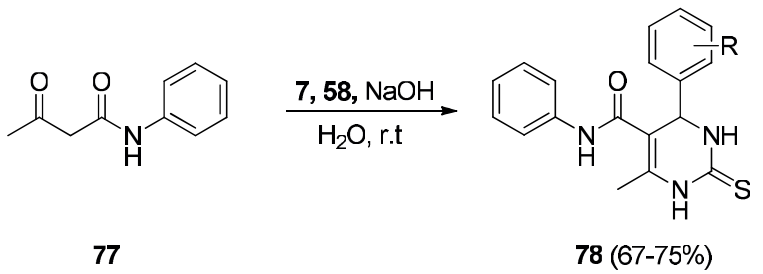
Scheme 17. Condensation between furfural, guanidine carbonate, and 4-methyl cyclohexanone.

Pyrimidines containing cyanoimino functionality possess various pharmacological activities. Considering this, in a multicomponent synthesis, Hulme and colleagues reacted 1,3-diketones **74**, aldehydes **21**, and cyanamide **75** to get good yields of pyrimidines **76** (40% yield) (Scheme 18).[35]



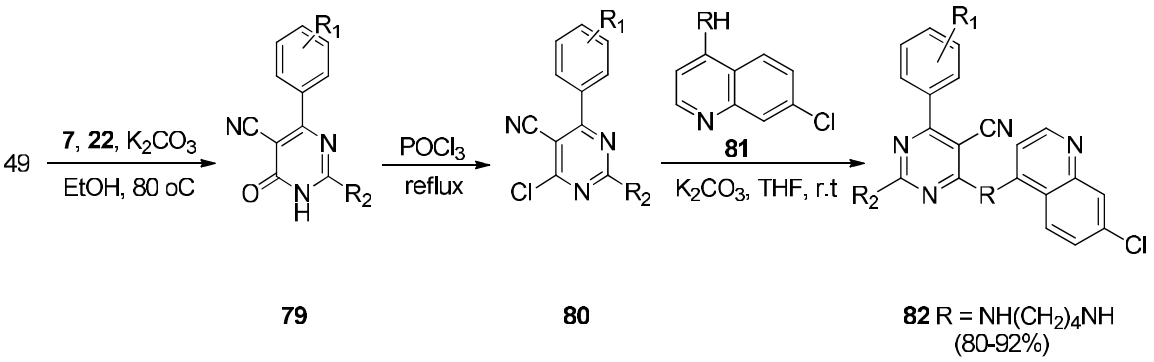
Scheme 18. Conversion of 1,3-diketones, aldehydes, and cyanamide into pyrimidine derivatives **76**.

For the further development in the field of more functionalized bioactive pyrimidine derivatives, ecofriendly base-catalyzed coupling between benzaldehyde **7**, thiourea **58**, and acetoacetanilide **77** was executed by Pagadala et al. to achieve pyrimidine derivatives **78** (67%–75% yield) (Scheme 19).[36]



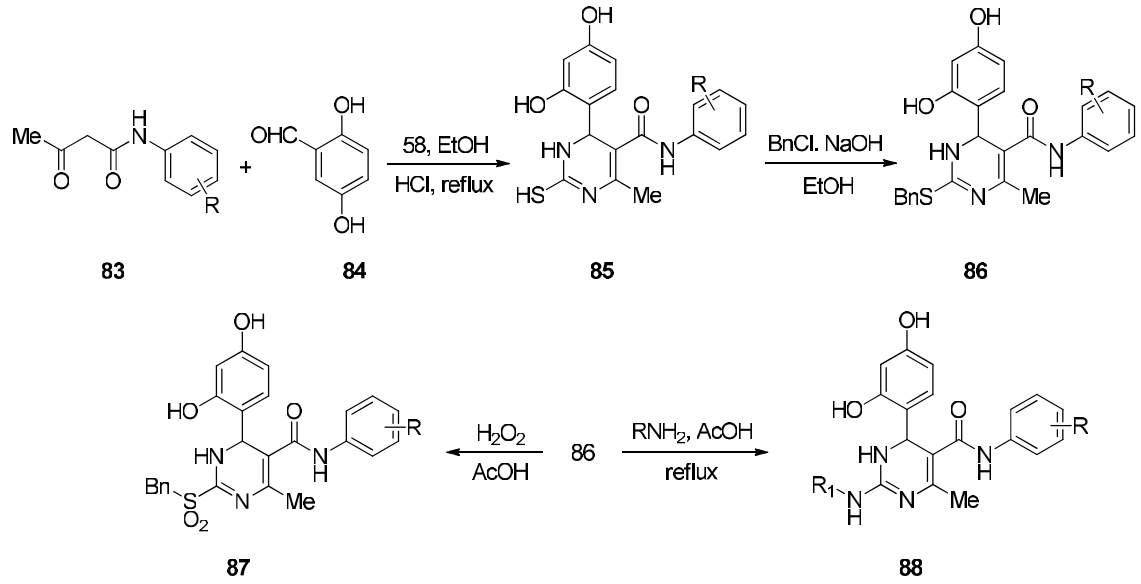
Scheme 19. Environmental friendly synthesis of pyrimidine derivatives **78**.

Versatility in the 4-aminoquinolines' framework enhances their antiplasmodial potential as reported by Kaur and colleagues. The authors condensed ethylcyanoacetate **49** with substituted benzaldehyde **7** and *S*-methylisothiourea hemisulfate salt **22** to afford pyrimidine **79**, which was further treated with $POCl_3$ and then converted to quinoline derivatives **82** (80%–92% yield) using 7-chloro-4-aminoquinoline **81** (Scheme 20).[37]



Scheme 20. Preparation of quinoline based pyrimidine derivatives **82**.

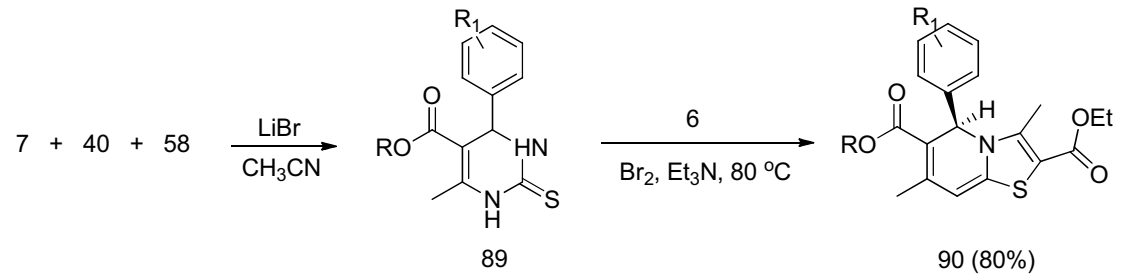
Ibrahim and El-Metwally synthesized pyrimidine derivatives by the treatment of acetoacetanilides **83**, 2,4-dihydroxy benzaldehyde **84**, and thiourea **58** in the presence of ethanol and conc. HCl. Benzylation of pyrimidine **85** followed by oxidation or reaction with primary amines afforded pyrimidine derivatives **87** and **88**, respectively (Scheme 21).[38] The synthesized derivatives proved to be good inhibitors of CDK2 and had anticancer potential.



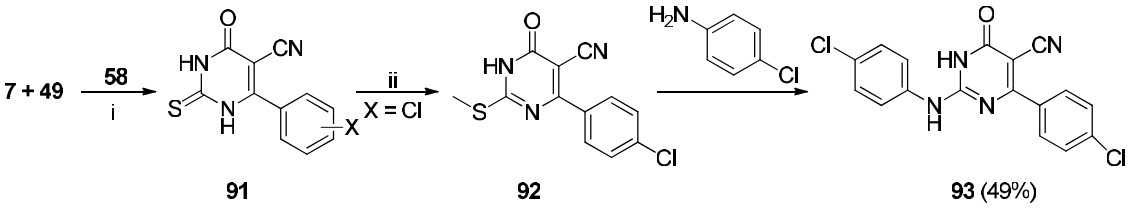
Scheme 21. Synthetic layout for the synthesis of pyrimidine derivatives **87** and **88**.

Later, Nagarajaiah and Begum coupled aromatic aldehydes **7**, alkyl acetoacetate **40**, and thiourea **58** to achieve dihydropyrimidine derivatives **89**.[39] Treatment of dihydropyrimidine derivatives **89** with ethyl acetoacetate **6** in the presence of bromine and triethylamine furnished the targeted fused pyrimidines **90** (95% yield) (Scheme 22).

Similarly, to investigate the immunosuppressive activity, Stella et al. coupled benzaldehyde **7**, ethyl-cyanoacetate **49**, and thiourea **58** in the presence of piperidine to achieve 2-thiouracil congeners **91**, which on further treatment with iodomethane and potassium carbonate produced thiomethyl derivative **92.**[40] Treatment of thiomethyl derivative **92** with *p*-chloroaniline under microwave irradiation produced 2-(4-chloroanilino)pyrimidine derivative **93** (49% yield) (Scheme 23).

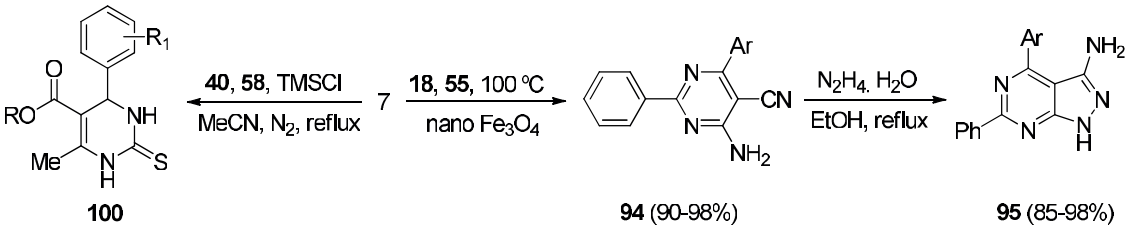


Scheme 22. Fused pyrimidines synthesis by Nagarajaiah and Begum.[39]



Scheme 23. Reaction conditions: (i) piperidine, EtOH, reflux, overnight; (ii) MeI, K_2CO_3, CH_3CN.

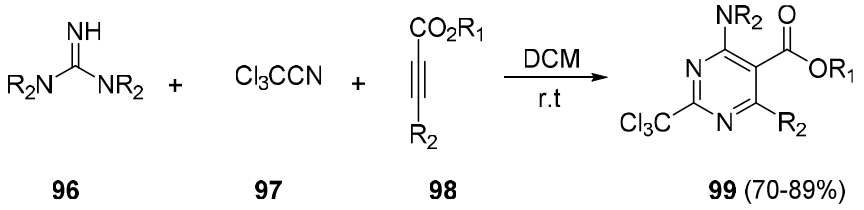
Condensation between aromatic aldehydes **7**, malononitrile **18**, and benzamidinehydrochloride **55** in the presence of magnetic Fe_3O_4 nanoparticles as a catalyst under solvent-free conditions furnished pyrimidine **94** (90%–98% yield). Rostamizadeh and coworkers also condensed pyrimidine **94** with hydrazine monohydrate to get the targeted fused pyrimidine derivatives **95** (85%–98% yield) (Scheme 24).[41] The present protocol is superior to the previously reported methodologies as it is consistent with high yields of products and easy workup, is ecofriendly, and includes fewer steps. Executing the microwave-mediated Biginelli reaction between arylaldehydes **7,** substituted β-ketoesters **40**, and thiourea **58**, Khan et al. achieved dihydropyrimidine-2-thiones **100** in good yields (Scheme 24).[42] The synthesized compounds were found to be good inhibitors of urease enzyme.



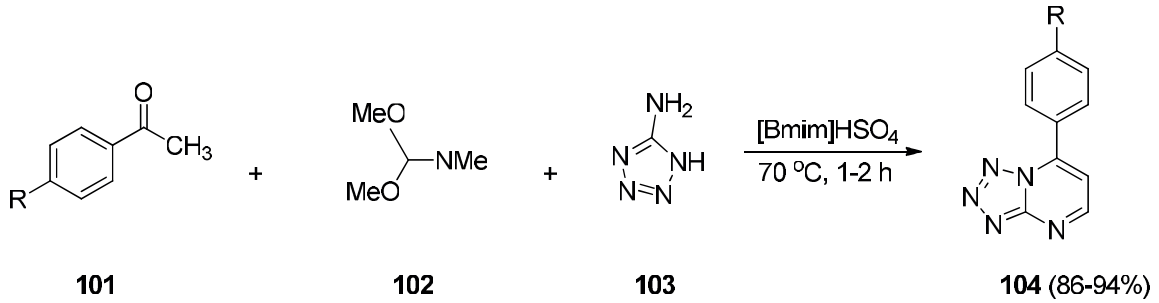
Scheme 24. Synthesis of novel pyrimidine derivatives.

The bioavailability, metabolic stability, and lipophilicity of organic scaffolds can be enhanced by the incorporation of the lipophilic trihalomethyl group, which is electron-withdrawing in character, and it can improve the therapeutic activity of biologically active substances. Yavari and colleagues reported the synthesis of trichloromethylated pyrimidine **99** (70%–89% yield) by the treatment of guanidine derivatives **96** with trichloroacetonitrile **97** and activated acetylenic esters **98** (Scheme 25).[43]

However, Suresh and colleagues condensed theacetophenones **101**, dimethylformamide dimethylacetal **102**, and 5-aminotetrazole **103** to obtain fused pyrimidines **104** (86%–94% yield) under optimal reaction conditions (Scheme 26).[44] The synthesized compounds were found to be potent inhibitors of α-glucosidase.

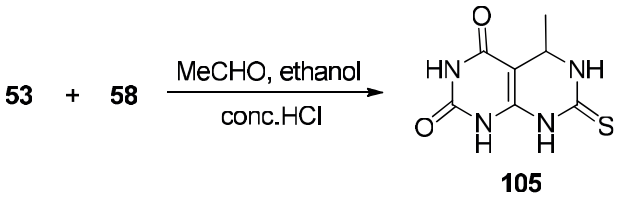


Scheme 25. Synthesis of trichloromethylated pyrimidines.



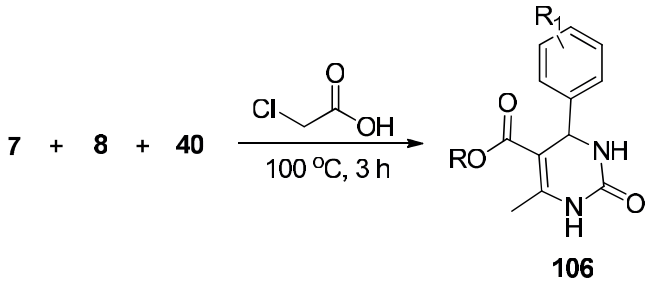
Scheme 26. Synthesis of tetrazolo[1,5-a]pyrimidine derivatives.

Devi and coworkers achieved 5,6,7,8-tetrahydro-5-methyl-7-thioxopyrimido [4,5-d] pyrimidine-2,4(1H, 3H)-dione **105** (58% yield) by the coupling of barbituric acid **53**, thiourea **58**, and acetaldehyde in the presence of ethanol (Scheme 27).[45]



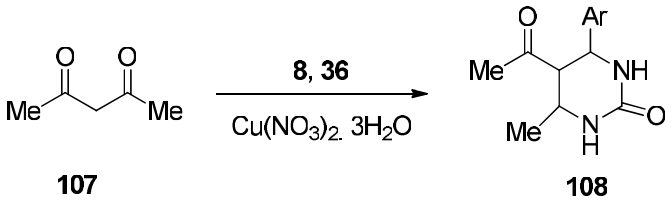
Scheme 27. Synthesis of fused pyrimidines.

Similarly, Murahari and coworkers synthesized pyrimidine derivatives **106** by the condensation of substituted benzaldehydes **7**, urea **8**, and ethyl acetoacetate **6** (Scheme 28).[46]



Scheme 28. Synthesis of pyrimidine derivatives **106**.

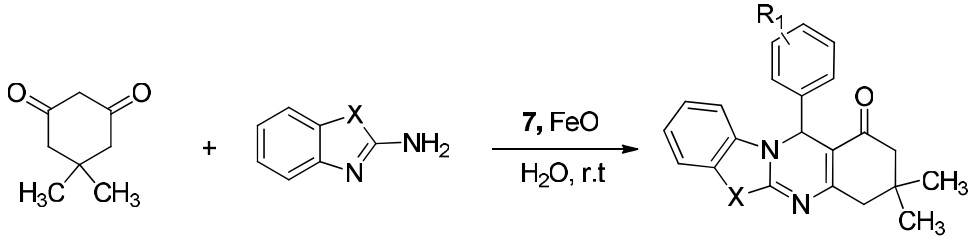
5-Acetyl-6-methyl-4-aryl-3,4-dihydropyrimidin-2(1H)-one derivatives **108** were prepared by Shamim and coworkers by treating urea **8**, acetyl acetone **107**, and aryl aldehyde **36** in the presence of $Cu(NO_3)_2.3H_2O$ catalyst (Scheme 29).[47]



107 108

Scheme 29. Condensation between urea **8**, acetylacetone **107**, and aryl aldehydes **36**.

Fe_3O_4-catalyzed condensation between benzaldehyde **7**, 5,5-dimethylcyclohexane-1,3-dione (dimedone) **109**, and 2-aminobenzimidazole **110** furnished imidazo(thiazolo)pyrimidines **111** in the laboratories of Maleki and Aghaei (Scheme 30).[48]

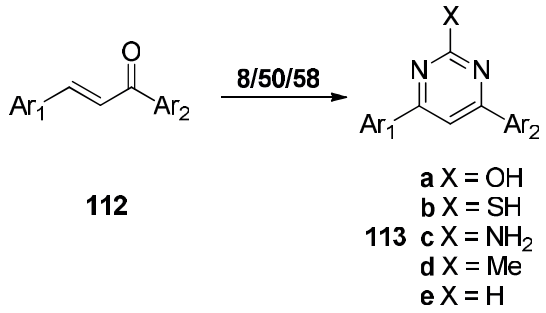


109 110 111

Scheme 30. Synthetic route to pyrimidine derivatives **111**.

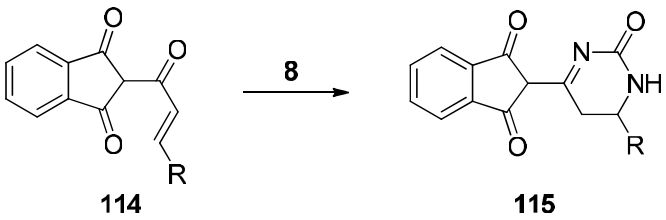
2.2. Synthesis from chalcones

Balaji et al. synthesized chalcones **112** and condensed them with urea **8** and thiourea **58** under basic conditions using NaOH to construct pyrimidine rings **113a** and **113b** (69%–91% yield), respectively (Scheme 31).[49] Protozoa of the genus *Leishmania* are responsible for leishmaniasis infection, which leads to some fatal diseases like visceral leishmaniasis, both mucocutaneous and cutaneous. Chandra et al. synthesized novel pyrimidine-based antileishmanial agent **113c** by the coupling of chalcones **112** with guanidine/morpholino guanidine **50** in the presence of silver oxide in isopropanol.[50] However, condensation between chalcones **112** and guanidine hydrochloride **50** in DMF under reflux for 5–7 h also resulted in the formation of pyrimidine derivative **113c** (52%–62% yield) in the laboratories of Kumar and coworkers (Scheme 31).[51] The obtained compounds exhibited good antiinflammatory and antimicrobial potential. In 2013, Mohsin condensed chalcones **112** with urea **8**, thiourea **58**, and guanidine **50** separately in the presence of 10% KOH to achieve pyrimidine derivatives **113a**–**113c**, respectively.[52] Similarly, condensation between chalcones **112** and guanidine hydrochloride **50** furnished the requisite pyrimidine derivative **113c** (60% yield) in the laboratories of Padarthi and colleagues.[53] In the following year, Kachroo et al. condensed chalcones **112** with urea **8** in ethanol, thiourea **58** (reflux in ethanolic KOH), and guanidine hydrochloride **50** in the presence of aqueous KOH to afford pyrimidine derivatives **113a**–**113c**, respectively.[54] In the same year, Gupta and colleagues achieved novel 4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidine-2-thiols via the coupling of chalcones **112** and thiourea **58**.[55] Kumar and coworkers synthesized pyrimidine derivatives **113c**–**113e** by the condensation of chalones **112** with guanidine **50**/acetamidine **22** and formamidine in the presence of anhydrous sodium carbonate in acetonitrile (Scheme 31).[56]



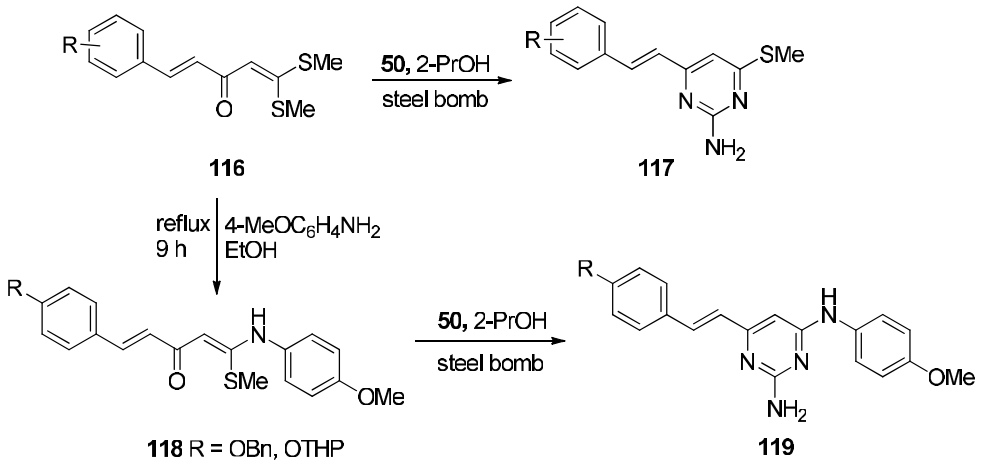
Scheme 31. Condensation of chalcones with urea/guanidine/thiourea.

Later, Giles et al. synthesized pyrimidine derivatives **115** in good yield by treating chalcones **114** with urea **8** (Scheme 32).[57]



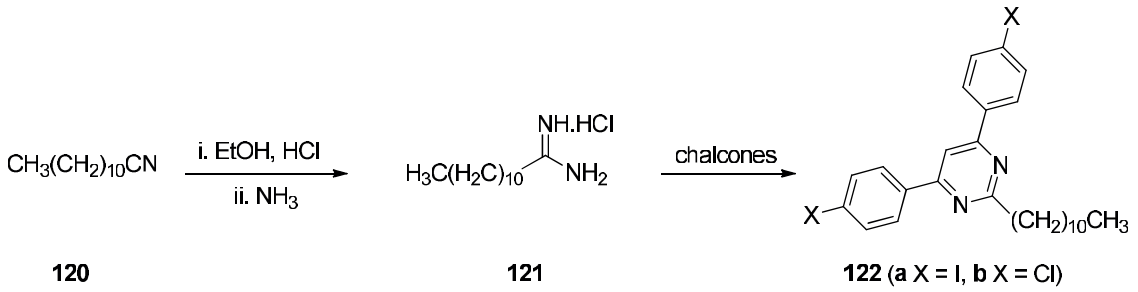
Scheme 32. Synthesis of pyrimidine derivatives **115**.

Two series of active pyrimidine derivatives (leishmanicidal agents) were introduced by Suryawanshi and coworkers, who coupled ketene dithioacetal **116** and guanidine in dry isopropanol to achieve terphenyl pyrimidines **117**.[58,59] Similarly, treatment of ketene dithioacetal **116** with 4-methoxyaniline followed by reaction with guanidine hydrochloride **50** provided the targeted pyrimidine derivatives **119** (Scheme 33).



Scheme 33. Synthetic route to pyrimidine derivatives.

Condensation between amidine **121** and a variety of chalcones furnished pyrimidines **122a** and **122b** in 72% and 63% yield, respectively. Katritzky and colleagues achieved amidine **121** from alkyl nitrile **120** (Scheme 34).[60]



120 **121** **122** (**a** X = I, **b** X = Cl)

Scheme 34. Conversion of alkyl nitrile into pyrimidine derivatives.

Later, cyclization of chalcones **124** with guanidines **22** furnished pyrimidine derivative **125** under basic conditions**.** Alternatively, palladium-catalyzed coupling between Boc-protected amines **126** and dichloropyrimidines **127** followed by reaction with aryl boronic acids **129** furnished pyrimidines **130**. Deprotection, reaction with oxone, and finally treatment with a variety of amines also furnished targeted amines **124**. Similarly, Lin and colleagues also coupled chalcones **132** with urea followed by chlorination with $POCl_3$ to achieve choropyrimidine derivatives **133**, which on reaction with different boronic acids **130** in the presence of palladium catalyst yielded final pyrimidine derivatives **133** (Scheme 35).[61]

There are numerous citations in the literature highlighting the pharmacological potential of pyrimidines and coumarins. In this regard, Chaudhary and colleagues treated salicylaldehyde **134** with ethyl acetoacetate **6** to produce 3-acetyl-6-bromo-2*H*-chromen-2-one **135**, which on condensation with diversified benzaldehydes **36** provided chalcones **136**.[62] Coupling of chalcones **136** with guanidine carbonate **71** furnished the pyrimidine derivative **137**, which was further derivatized by treatment with piperidine and formaldehyde to get the final products **138** (Scheme 36). These hybrid scaffolds exhibited good analgesic potential with less ulcerogenicity.

Chalcones **139** were coupled with urea **8**, guanidine hydrochloride **50** (using NaOH/EtOH), and thiourea **58** in the presence of sodium ethoxide in the laboratories of Al-Sabawi to afford pyrimidines **140a**–**140c**, respectively (Scheme 37).[63]

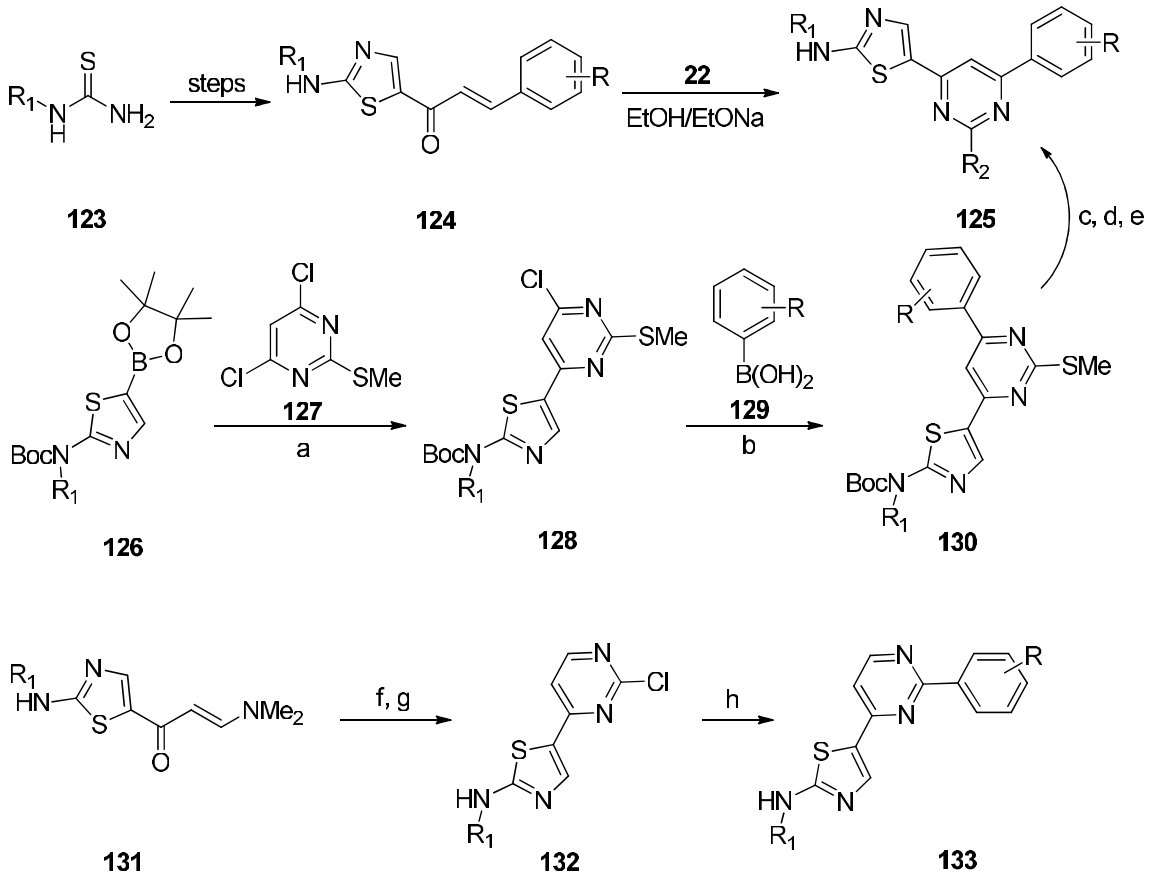
Solankee et al. synthesized aminopyrimidines **142** by treating chalcones **141** with guanidine hydrochloride **50** in the presence of NaH (Scheme 38).[64]

Among the synthesized series, a few derivatives exhibited potent antiinflammatory, antitubercular, and antioxidant activity. Sharma and coworkers treated oxo- and amino linked chalcones **143** with guanidine hydrochloride **50** in the presence of NaH in DMF to afford oxo- and amino linked pyrimidine derivatives **144** (Scheme 39).[65]

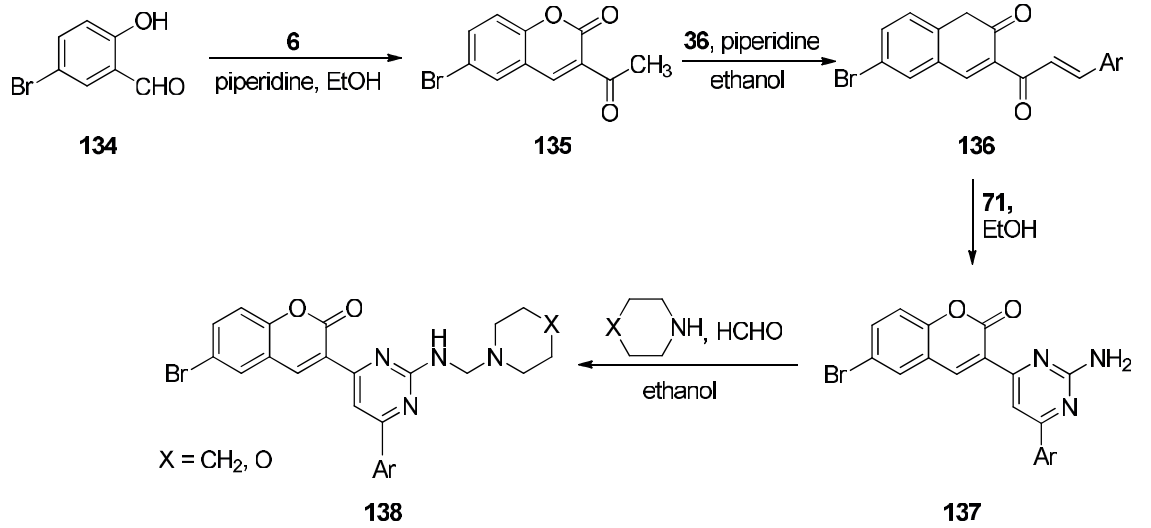
Recently, base-catalyzed condensation between benzamidine hydrochloride and cinnamaldehyde **145** under an oxygen atmosphere in DMSO by Guo et al. resulted in the formation of new pyrimidine derivatives **146** (64% yield) (Scheme 40).[66] The main feature of this protocol is the use of ecofriendly, inexpensive, and natural oxidant oxygen.

However, El-Gaby and colleagues elaborated the condensation between chalcones **147** and guanidine **50** to furnish fused pyrimidines **148** (Scheme 41).[67]

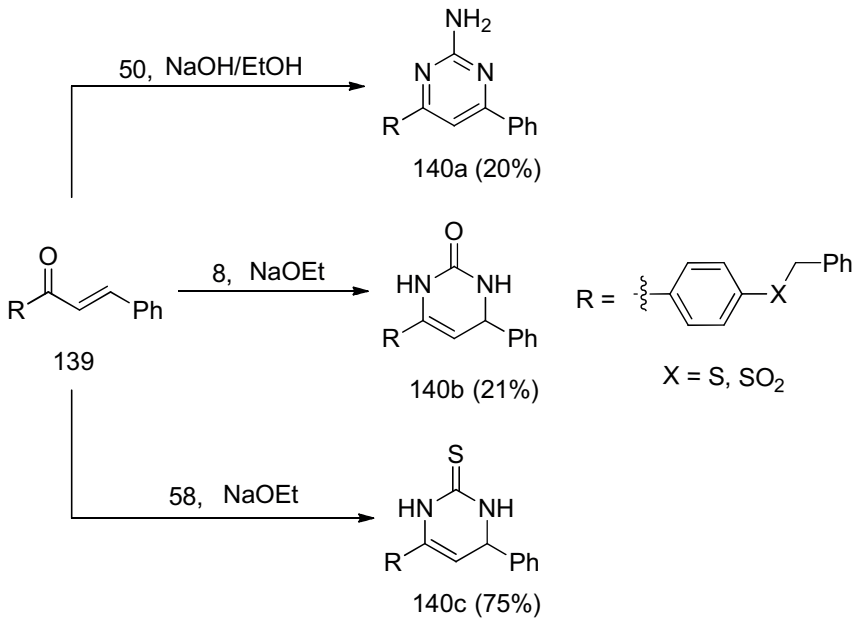
There are only a few reports about the synthesis of pyrazolo[1,5-*a*]pyrimidines from chalcones. In this context, Kaswan and colleagues elaborated on the synthesis of 5,7-diarylpyrazolo[1,5-*a*]pyrimidine **150** from chalcone **112** and 1*H*-pyrazol-3-amine **149** in the presence of catalytic amounts of KOH (Scheme 42).[68]



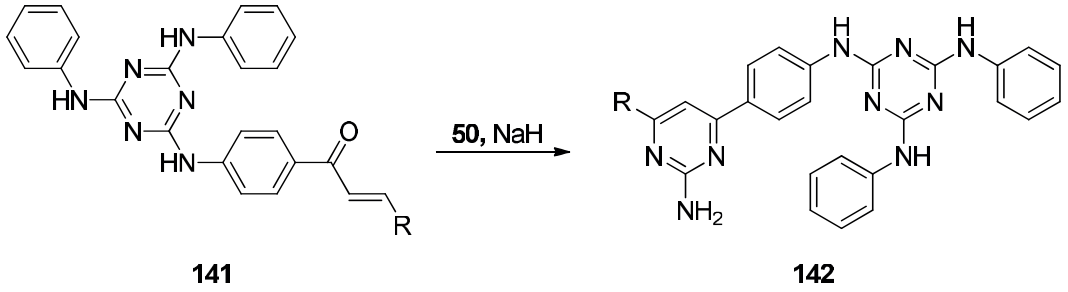
Scheme 35. Reaction conditions: (a) $Pd(PPh_3)_4$, K_3PO_4, EtOH, toluene; (b) $Pd(PPh_3)_4$, K_3PO_4, EtOH, toluene; (c) TFA, quant.; (d) oxone, aq. MeOH; (e) amines, *i*-PrOH, 120 °C; (f) NaH, urea; (g) $POCl_3$, toluene, 110 °C; (h) aryl boronic acid **129**, $Pd(PPh_3)_4$, EtOH, toluene.



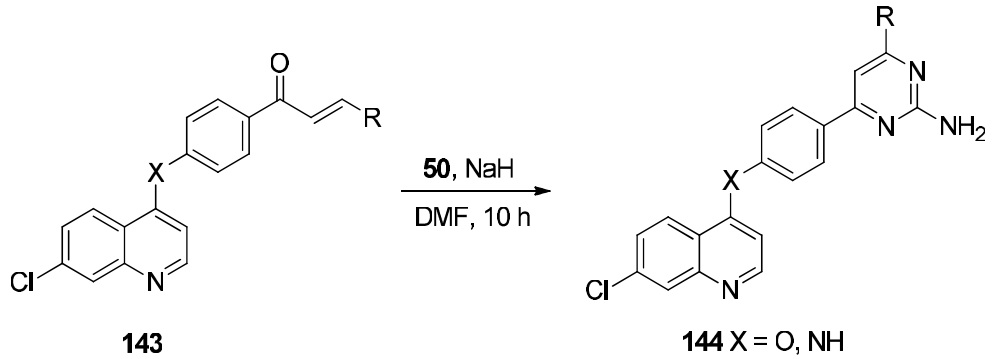
Scheme 36. Schematic layout for the preparation of pyrimidine derivatives **138**.



Scheme 37. Coupling of chalcones with guanidine hydrochloride, urea, and thiourea.

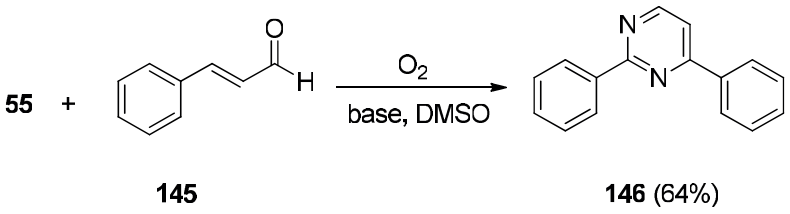


Scheme 38. Condensation between chalcones and guanidine hydrochloride.

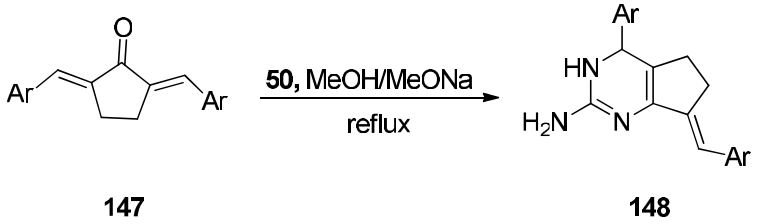


Scheme 39. Synthesis of oxo- and amino linked pyrimidine derivatives.

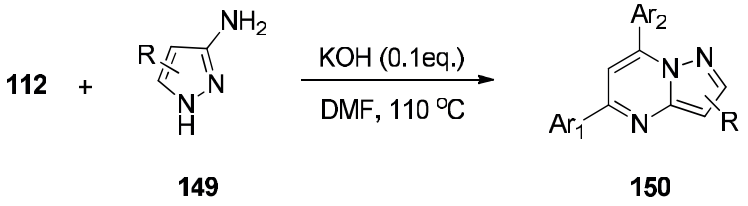
In the same year, condensation of bis-chalcones **151** with imidine hydrochlorides **152** in the presence of sodium isopropoxide furnished the 2,4,6-trisubstituted bis-pyrimidine derivatives **153a** and **153b** in the laboratories of Parveen and coworkers (Scheme 43).[69]



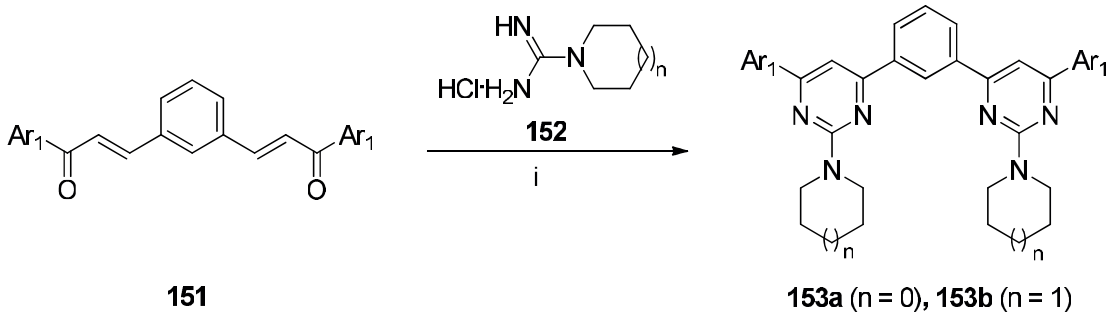
Scheme 40. Condensation between benzamidine hydrochloride and cinnamaldehyde.



Scheme 41. Condensation between chalcones **147** and guanidine **50**.



Scheme 42. Synthesis route to 5,7-diarylpyrazolo[1,5-a]pyrimidines.

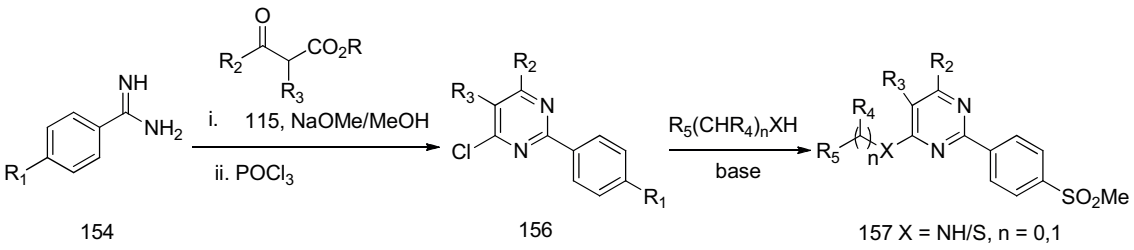


Scheme 43. Reaction conditions: (i): isopropoxide, isopropanol, reflux, 8 h.

2.3. Synthesis from imidamide/guanidine

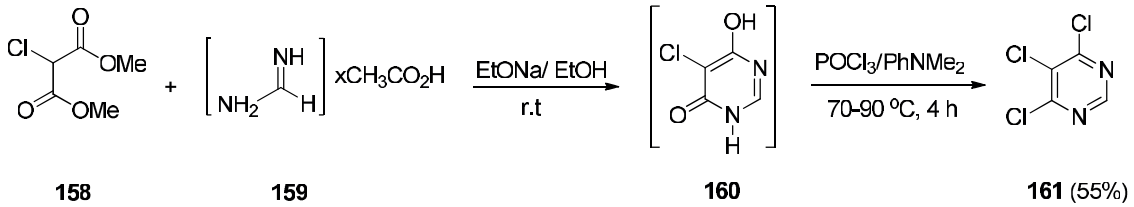
Chloropyrimidines **156** were synthesized by the condensation of amidine **154** with appropriate acetoacetate or malonate derivative **155** in the presence of a base followed by chlorination with $POCl_3$. Finally, Orjales and coworkers substituted the chlorine atom in pyrimidines **156** with N- or S-nucleophiles to get the targeted pyrimidine derivatives **157** (99% yield) that exhibited specific and potent COX-2 inhibition (Scheme 44).[70]

A short transformation to achieve more substituted pyrimidines is always an intense need for synthetic chemists as these templates can be used as intermediates for further valuable compounds. Considering this fact, Ostrowski et al. synthesized 4,6-dihydroxy-5-chloropyrimidine **160** by reacting dimethyl chloromalonate **158** with formamidine acetate **159**. In the next step, N,N-dimethylaniline was reacted with pyrimidine **160**



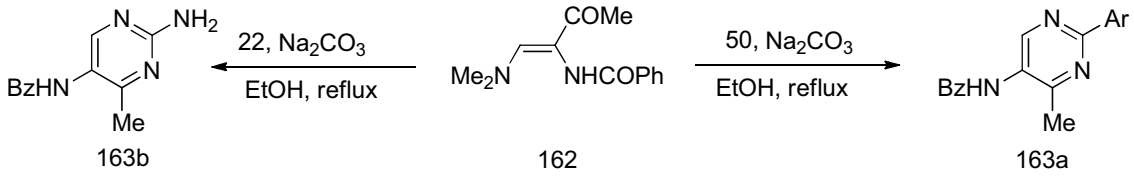
Scheme 44. Conversion of amidine into pyrimidine derivatives.

in the presence of phosphorus oxychloride to afford 4,5,6-trichloropyrimidine **161** (55% yield), a substantially important diazine ring system that can easily be converted into a variety of valuable products only by the S_NAr process (Scheme 45).[71]



Scheme 45. Preparation of 4,5,6-trichloropyrimidine.

Later, in an efficient one-step protocol, Bratusek and colleagues treated enaminone **162** with different amidines and guanidine hydrochloride **50** to afford 2-aryl-5-benzoylamino-4-methylpyrimidines **163a** and 2-aminopyrimidine derivative **163b**, respectively (Scheme 46).[72]

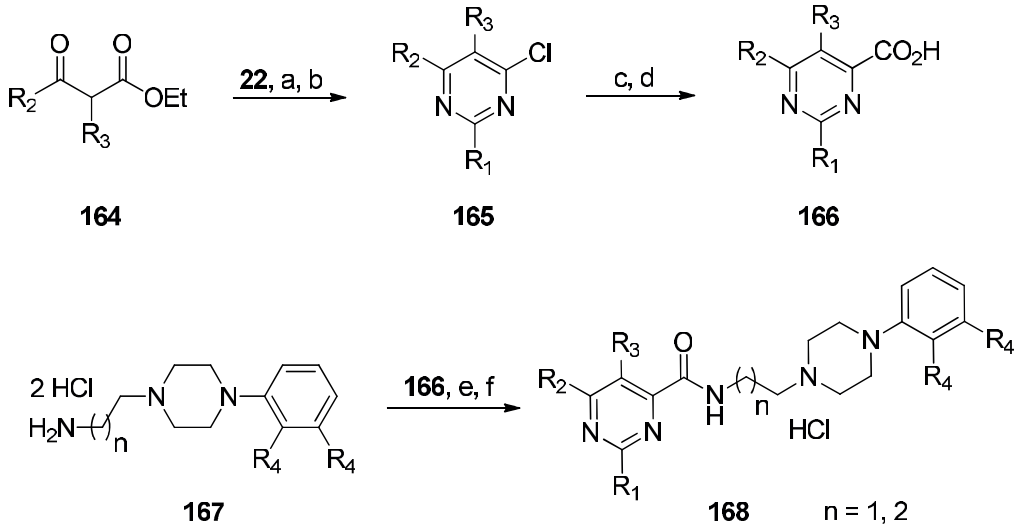


Scheme 46. Synthetic layout to achieve pyrimidine derivatives **163a** and **163b**.

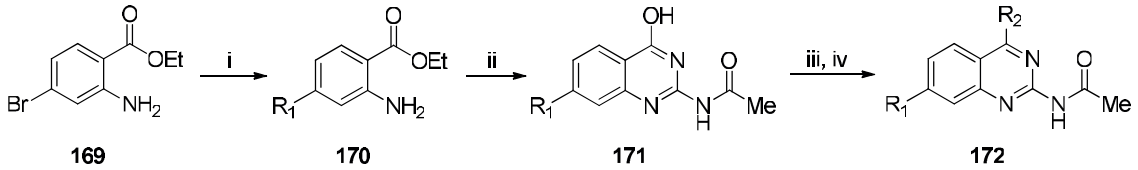
Similarly, pyrimidine derivatives **168** were achieved starting from the reaction of amidine acid salt **22** with keto-ester **164** followed by chlorination with $POCl_3$. Microwave-mediated reaction of obtained pyrimidine **165** with zinc cyanide in the presence of $Pd(PPh_3)_4$ followed by hydrolysis furnished pyrimidine derivatives **166**. Finally, Kim and colleagues obtained the requisite pyrimidine derivatives **168** (antidepressant agents) via the coupling of pyrimidines **166** with a variety of primary amines **167** (Scheme 47).[73]

In another novel route, Andaloussi and colleagues coupled ester **170** with chloroformamidine hydrochloride to afford pyrimidine **171** (Scheme 48).[74] Tosylation of pyrimidine **171** followed by the addition of amines furnished pyrimidine derivatives **172**, which were found as good antagonists of histamine H_4 receptor.

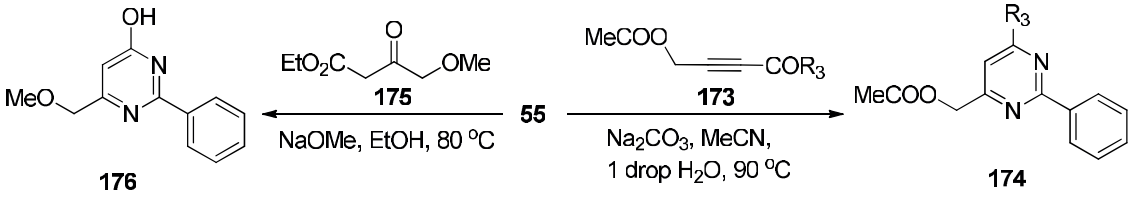
In 2014, Caroff and coworkers achieved pyrimidine templates **174** and **175** via condensation of benzamidine **55** with keto-alkynes **173** (produced by the treatment of different acid chlorides with prop-2-yn-1-yl acetate and ester **175**.[75] The authors also further derivatized these pyrimidines to achieve a variety of novel pyrimidine-based derivatives in their synthetic work (Scheme 49).



Scheme 47. Reaction conditions: (a) NaOEt, EtOH, 100 °C; (b) $POCl_3$, 110 °C; (c) $Zn(CN)_2$, $Pd(PPh_3)_4$, THF, microwave reaction, 165 °C, 30 min; (d) NaOH, EtOH, water, reflux; (e) EDCI, HOBt, NMM, DCM, or DMF, r.t; (f) HCl, MeOH, 0 °C.



Scheme 48. Reaction conditions: (i) (a) isopropenylboronic acid pinacol ester, $Pd(PPh_3)_4$, K_2CO_3, $PhCH_3$, EtOH, MW, 130 °C, or (b) cyclopropylboronic acid, PCy_3, $Pd(OAc)_2$, KF, THF, r.t, (c) H_2, Pd/C 5%, EtOH, r.t; (ii) (a) chloroformamidine hydrochloride, dimethyl sulfone, sulfolane, 160 °C, (b) acetic anhydride, reflux; (iii) TsCl, K_2CO_3, CH_3CN, Δ; (iv) (a) various amines (Boc-protected), DIPEA, 1,4-dioxane, r.t, (b) dioxane/HCl, r.t.



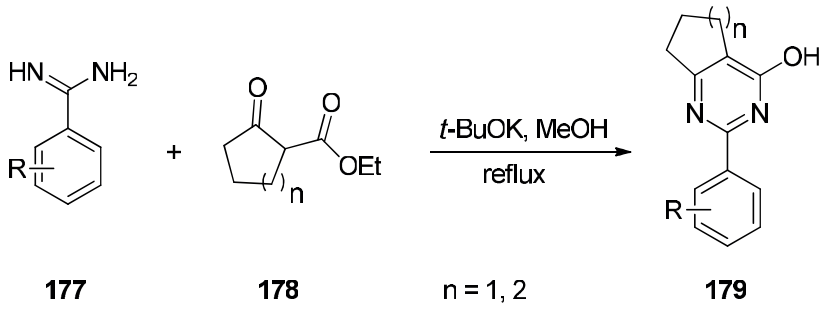
Scheme 49. Synthesis of pyrimidine derivatives **174** and **176**.

Searching for novel and more effective pyrimidine derivatives to cure pain, sigma-1 (σ_1) receptor antagonists, Lan and coworkers coupled 4-substituted benzimidamide **177** with ethyl 2-oxocyclopentanecarboxylate **178** to achieve novel pyrimidine derivatives **179** (Scheme 50).[76]

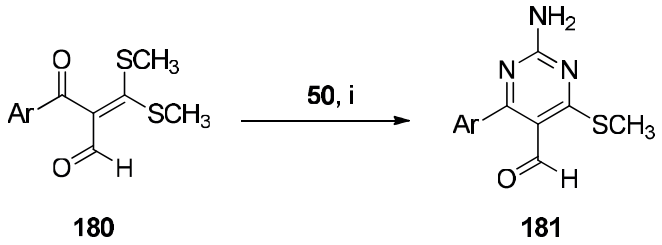
Mathews and Asoka reported the synthesis of pyrimidine carbaldehyde **181** by the reaction of 2-aroyl-3,3-bis(alkylsulfanyl)acrylaldehyde **180** with guanidine hydrochloride **50** (Scheme 51).[77]

Later, Xie et al. described the synthesis of different pyrimidine derivatives **183** (anticancer agents) by treating ketones **183** with acetamidines **22**/guanidine **50** (Scheme 52).[78]

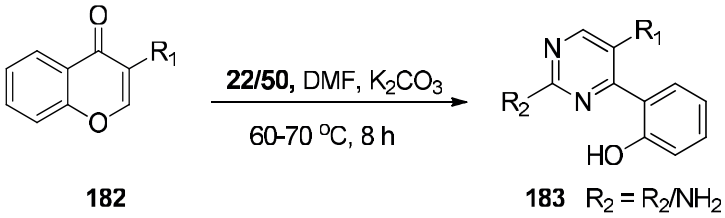
In light of the drug resistance of *Plasmodium falciparum*, like against quinines, there is an urgent need to develop more effective drugs. In this context, Deng et al. coupled dichloro-pyrimidines **185** with imidazol-



Scheme 50. Coupling between benzimidamide and cyclopentanecarboxylate.

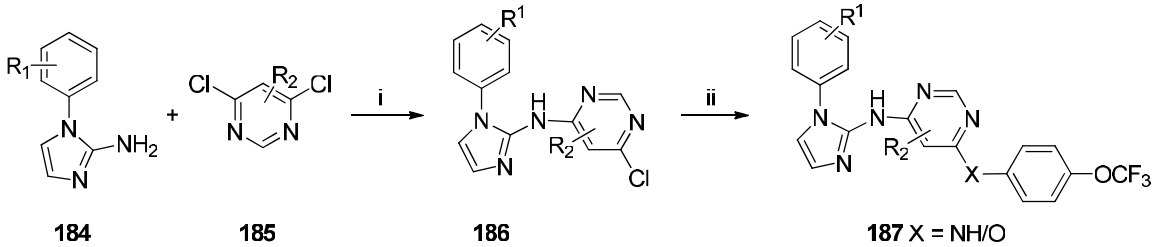


Scheme 51. Reaction conditions: (i) K_2CO_3, DMF, CH_3CN, water bath, 20 h.



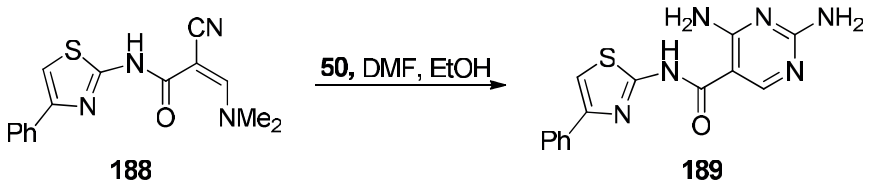
Scheme 52. Preparations of pyrimidine derivatives.

2-amine guanidine **184** to achieve phenyl-1*H*-imidazol-2-yl-pyrimidinediamines **186** (Scheme 53).[79] Moreover, treatment of pyrimidines **186** with 4-substituted benzenamine/phenols afforded the targeted pyrimidine derivatives **187** that exhibited good antimalarial potential.



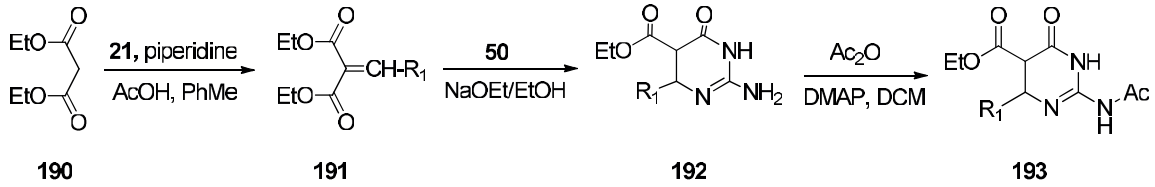
Scheme 53. Reaction conditions: (i) DIEA, dioxane, 100 °C; (ii) 4-(trifluoromethoxy)benzenamines, TFA, 2-PrOH, 80 °C, NaH, dioxane or 4-(trifluoromethoxy)phenols, NaH, dioxane, r.t to 80 °C.

Heteroaromatics, which are not obtainable from simple precursors, can easily be achieved from enaminonitriles, which highlighted their significance in heterocycle chemistry. Similarly, thiazoles linked with various heterocycles via carboxamide linkage are found to possess remarkable medicinal activities. Bondock and coworkers synthesized 2,4-diamino-*N*-(4-phenylthiazole-2-yl)pyrimidine-5-carboxamide **189** by the reaction of enaminonitrile **188** with guanidine hydrochloride **50** (Scheme 54).[80]



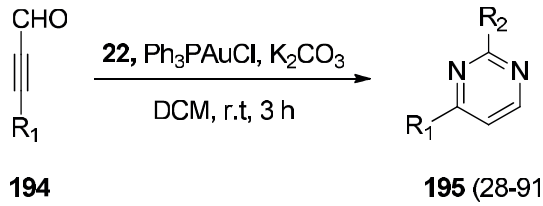
Scheme 54. Synthesis of 2,4-diamino-*N*-(4-phenylthiazole-2-yl)pyrimidine-5-carboxamide.

Lou et al. treated diethyl malonate **190** with different aldehydes **21** to afford intermediates **191**, which were transformed into pyrimidine derivative **192** on treatment with guanidine hydrochloride **50**.[81] Finally, compounds **193** (neuraminidase inhibitors) were obtained in good yield by the reaction of pyrimidine **192** with acetic anhydride (Scheme 55).



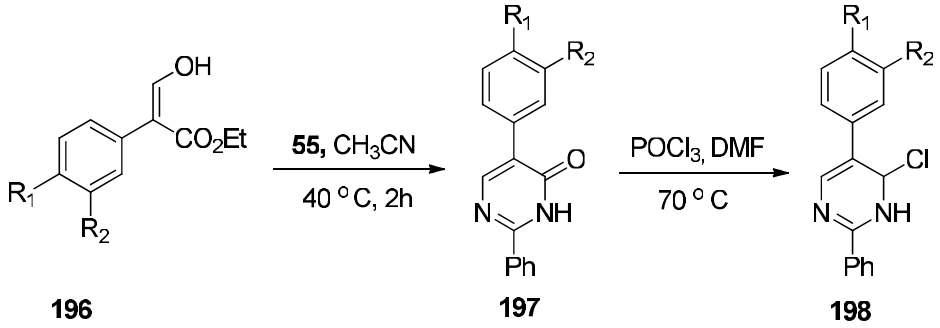
Scheme 55. Synthetic layout for the synthesis of pyrimidine derivatives **193**.

In a one-step protocol, pyrimidines **195** (28%–91% yield) were achieved by the synergism of aldehydes **194** and diversified amidines **22** in the presence of a gold catalyst under basic conditions in the laboratories of Zhan and colleagues (Scheme 56).[82]



Scheme 56. Palladium-catalyzed synthesis of pyrimidine derivatives.

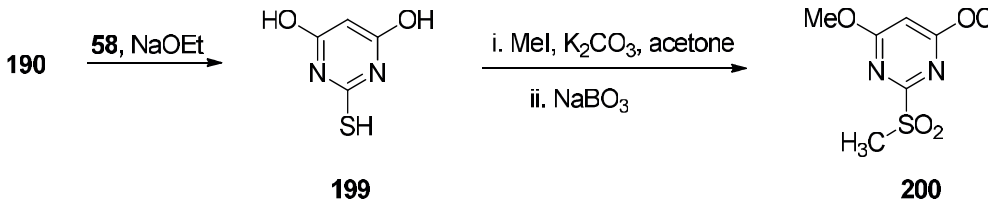
Shestakov et al. treated ester **196** with benzamidine **55** to afford intermediates **197**, which were transformed into pyrimidine derivative **198** on treatment with $POCl_3$ in DMF (Scheme 57).[83]



Scheme 57. Preparation of pyrimidine derivatives **198**.

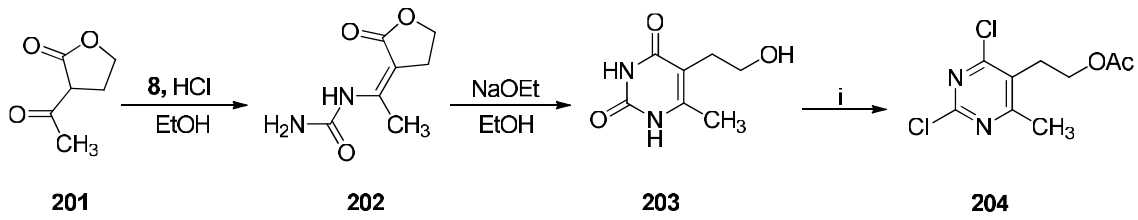
2.4. Synthesis from urea/thiourea

To synthesize novel antiinflammatory agents, Venu and coworkers achieved 2-mercapto-pyrimidine-4,6-diol **199** by the coupling of thiourea **58** and diethylmalonate **190**. $S-$Alkylation of pyrimidine **199** followed by oxidation with perborate furnished the pyrimidine sulfone **200** (Scheme 58).[84]



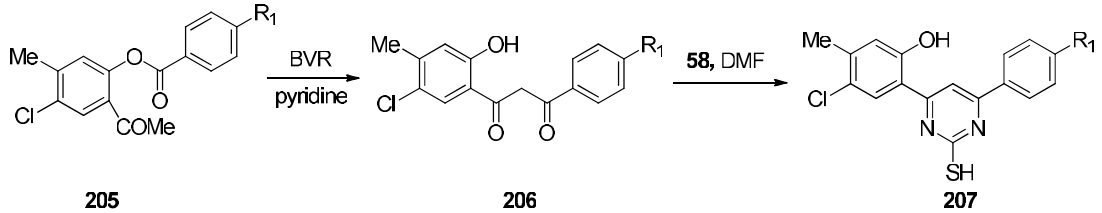
Scheme 58. Coupling between thiourea and diethylmalonate.

Base-catalyzed cyclization of α-(1-carbamyliminomethylene)-γ-butyrolactone **202** (prepared by the condensation of α-acetyl-γ-butyrolactone **201**) with urea **8** by Kraljevic and colleagues resulted in the formation of antitumor pyrimidine derivative **203** in good yield (Scheme 59).[85] Acylation of pyrimidine **203** followed by reaction with $POCl_3$ in the presence of N,N-diethylaniline furnished the targeted product **204**.



Scheme 59. Reaction conditions: (i) a) acetic anhydride, pyridine, b) $POCl_3$, N,N-diethylaniline, pyridine.

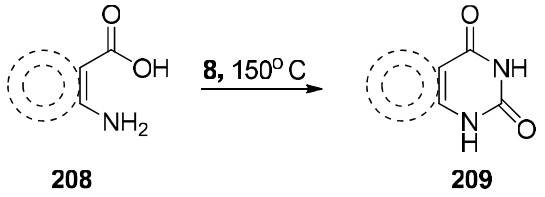
Binani and colleagues executed the Baker–Venkataraman rearrangement (BVR) of ketoester **205** to get 1,3-diketone **206**, which on treatment with thiourea **58** yielded antimicrobial pyrimidine derivatives **207** (Scheme 60).[86]



Scheme 60. Application of BVR in the synthesis of pyrimidine derivatives.

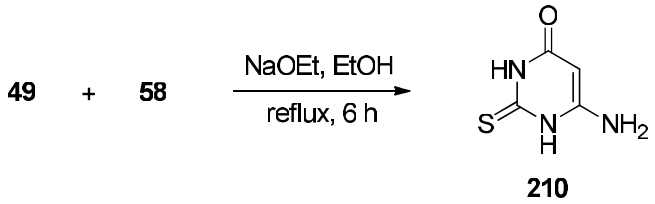
In 2012, Li et al. achieved aromatic fused pyrimidine-2,4(1H,3H)-diones **209** in 80%–95% yield by the reaction of aromatic 3-amine-2-carboxylic acid **208** with urea **8** (Scheme 61).[87]

Recently, the coupling of thiourea **58** and ethyl cyanoacetate **49** in the presence of sodium ethoxide resulted in the synthesis of 6-amino-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one **210** in the laboratories of Abdelgawad and coworkers (Scheme 62).[88]



208 209

Scheme 61. Condensation between 3-amine-2-carboxylic acid and urea.

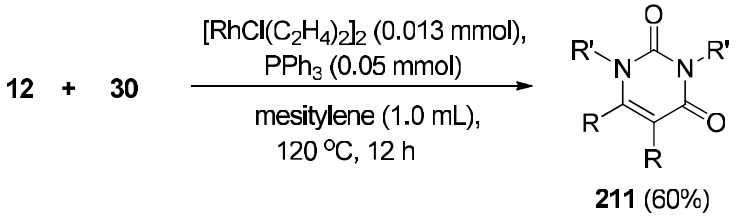


210

Scheme 62. Coupling between thiourea **58** and ethyl cyanoacetate **49**.

2.5. Synthesis from isocyanates/nitriles

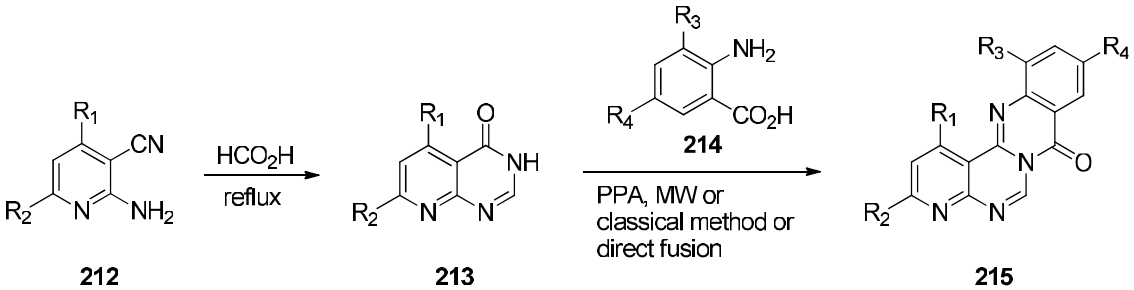
Pyrimidine-2,4-diones **211** (60% yield) were synthesized by Kondo and colleagues via rhodium-catalyzed coupling of alkyne **30** and isocyanates **12** (Scheme 63).[89] The cyclotrimerization reaction was carried out selectively and the present catalyst was found stable compared to previously reported metallic catalysts.



211 (60%)

Scheme 63. Ruthenium-catalyzed synthesis of pyrimidine-2,4-diones **211**.

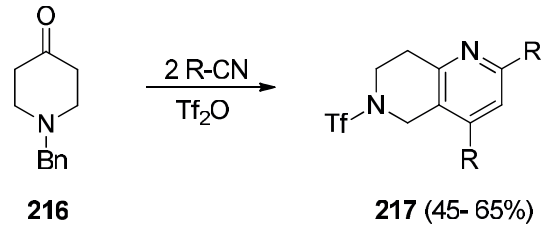
Laddha and Bhatnagar achieved 3*H*-pyrido[2,3-*d*]pyrimidin-4-ones **213** by the coupling of 2-amino-4,6-disubstituted-nicotinonitriles **212** with formic acid.[90] However, efficient Niementowski reaction via microwave irradiation in the presence of PPA or under a classical method or direct fusion of pyrimidines **213** with substituted 2-aminobenzoic acids **214** furnished the fused pyrimidines **215** (Scheme 64).



212 213 214 215

Scheme 64. Synthesis of fused pyrimidine derivatives **215**.

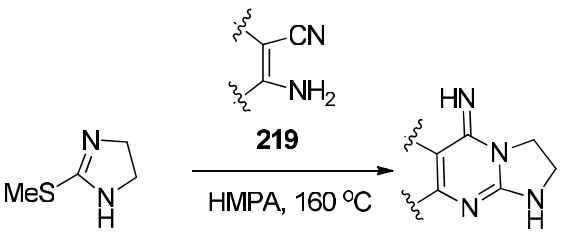
In the same year, Herrera and colleagues achieved 2,4-disubstituted-*N* trifluoromethylsulfonyltetrahydropyrido[4,3-*d*]-pyrimidines **217** (45%–65% yield) in a facile one-pot synthetic route from 1-benzylpiperidin-4-one **216** and a variety of nitriles in the presence of Tf_2O under mild reaction conditions (Scheme 65).[91]



216 **217** (45- 65%)

Scheme 65. Coupling between 1-benzylpiperidin-4-one and nitriles.

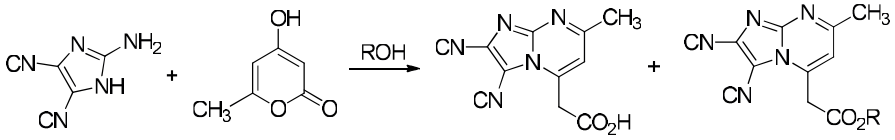
Similarly, Frohlich et al. treated 2-(methylthio)-2-imidazoline **218** (by dissolving it in hexamethylphosphoric acid triamide) with different aminonitriles **219** to afford pyrimidine derivatives **220** (Scheme 66).[92]



218 **220**

Scheme 66. Synthetic route to pyrimidine derivative 2**20**.

In the following year, Otmani and coworkers treated imidazole **221** with 4-hydroxy-6-methylpyran-2-ones **222** to achieve 2,3-dicyanoimidazo[1,2-*a*]pyrimidines **223** in 24–48 h along with the side product **224** (Scheme 67).[93]

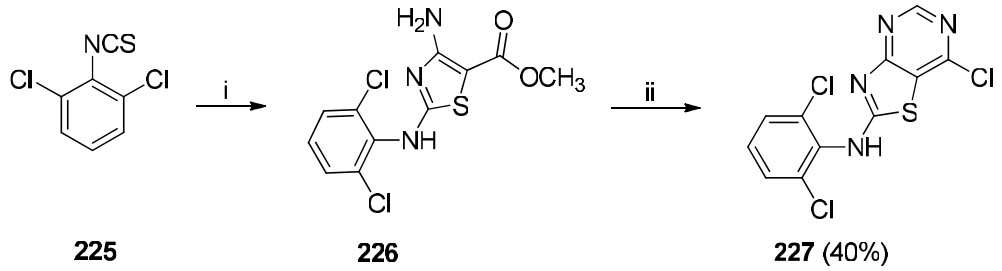


221 **222** **223** (90%) **224**

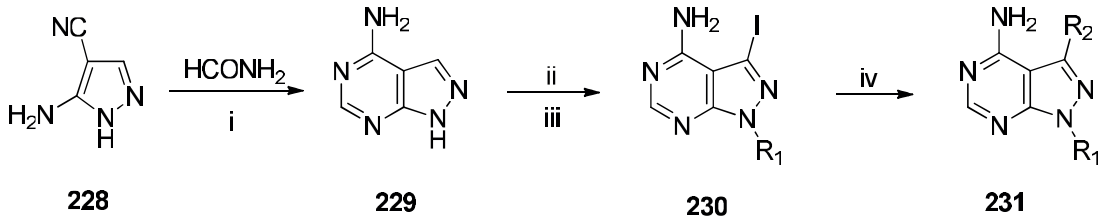
Scheme 67. Synthetic layout for the synthesis of 2,3-dicyanoimidazo[1,2-*a*]pyrimidines.

In 2009, Lebsack and colleagues executed the cyclization of 2,6-dichlorophenyl isothiocyanate **225** to get 4-amino-thiazole-5-methyl ester **226.** Finally, condensation of ester **226** with formamide in the presence of $POCl_3$ and acetic anhydride (cat.) furnished the targeted pyrimidine **227** (40% yield), which showed good potential to inhibit the capsaicin-induced influx of Ca^{2+} in cells (HEK293) expressing human and rat TRPV1 (Scheme 68).[94]

In another route, Todorovic and Awuah executed the microwave-mediated condensation between 5-amino-1*H*-pyrazole-4-carbonitrile **228** and formamide to achieve pyrimidine **229**.[95] The authors also carried out the iodination with *N*-iodosuccinimide and *N*-alkylation of pyrimidine **229** with an alcohol in the presence of PPh_3 and DIAD to achieve pyrimidine **230**. Pyrimidine **230** was transformed into N1- and C3-substituted pyrazolo[3,4-*d*]pyrimidines **231** by reaction with diversified boronic acids using Pd_2dba_3 catalyst and PA-Ph ligand under microwave irradiation (Scheme 69).

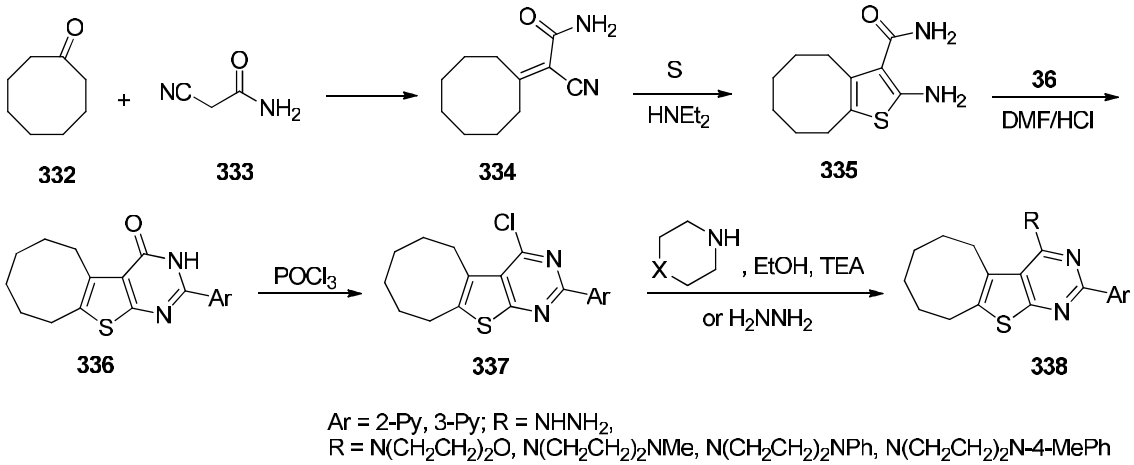


Scheme 68. Reaction conditions**:** i: (a) NH_2CN, sodium methoxide, r.t; (b) chloroacetic acid, methyl ester, 50 °C, 24 h; (ii) (a) formamide, Ac_2O (cat), 170 °C, 18 h; (b) $POCl_3$, 90 °C, 6 h.



Scheme 69. Reaction conditions: (i) MW, 200 °C, 30 min; (ii) N-iodosuccinimide, MW, 90 °C, 10 min; (iii) R_1-OH, DIAD, PPh_3 or R_1-X, K_2CO_3; (iv) R_2-$B(OH)_2$; (iv) R-$B(OH)_2$, Pd_2dba_3, PA-Ph, MW, 70 °C, 30 min.

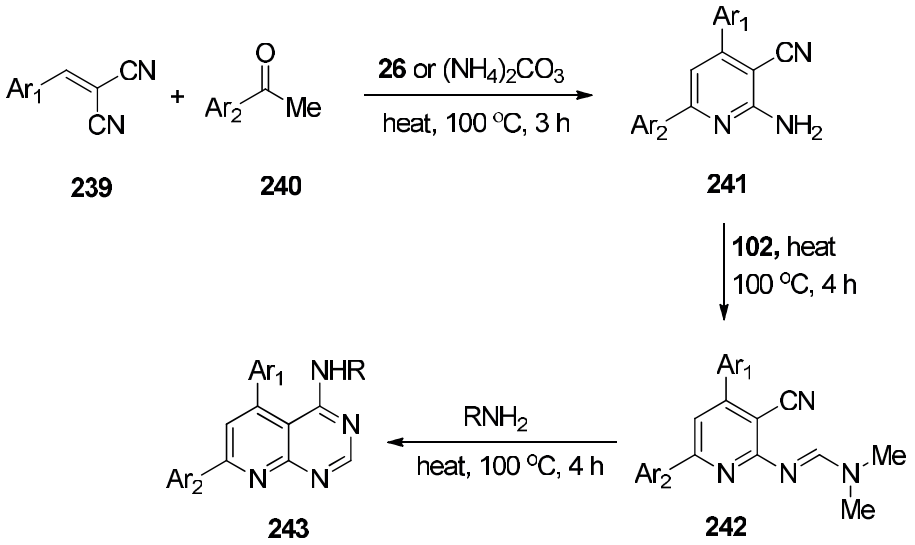
Kassab and coworkers coupled cyclooctanone **232** with cyanoacetamide **233** to achieve cyanoacetamide **234**, which on further reaction with sulfur in the presence of diethylamine produced carboxamide **235**.[96] Finally, carboxamide **235** was reacted with pyridine carboxaldehyde in the presence of DMF and HCl to produce pyrimidine **236.** After that, reaction with $POCl_3$ followed by nucleophilic displacement of chlorine with cyclic secondary amines afforded final anticancer pyrimidine derivatives **238** (76% yield) (Scheme 70).



Scheme 70. Synthesis of fused pyrimidine derivatives.

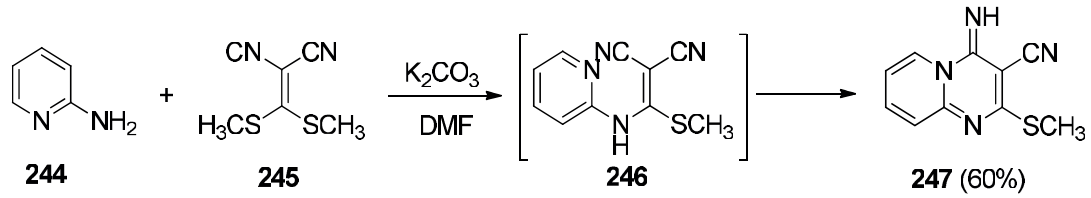
Aminopyrido[2,3-d]pyrimidines **243** were achieved in three synthetic steps, initiating from the coupling of arylethylidenemalononitriles **239** with different acetophenones **240** in the presence of ammonium acetate or ammonium carbonate under solvent-free conditions to achieve 3-cyano-2-aminopyridines **241**. After that, Belhadj and colleagues condensed aminopyridine **240** with dimethylformamide dimethyl acetal (DMFDMA)

102 without using any solvent, yielding N,N-dimethyl-N -(pyridin-2-yl)formamides **242**, which on treatment with primary amines under the same reaction conditions provided the targeted pyrimidine derivatives **243** (73% yield) (Scheme 71). The present protocol required mild reaction conditions and a short reaction time and provided high yields of products.[97]



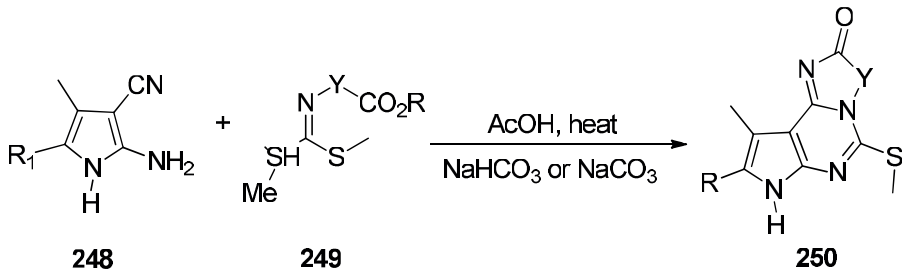
Scheme 71. Schematic layout for the synthesis of pyrimidine derivatives.

In 2012, Vartaleand coworkers treated 2-aminopyridine **244** with bis-(methylthio) methylene malononitrile **245** to achieve fused pyrimidine **247** (60% yield) via intermediate **246** (Scheme 72).[98]



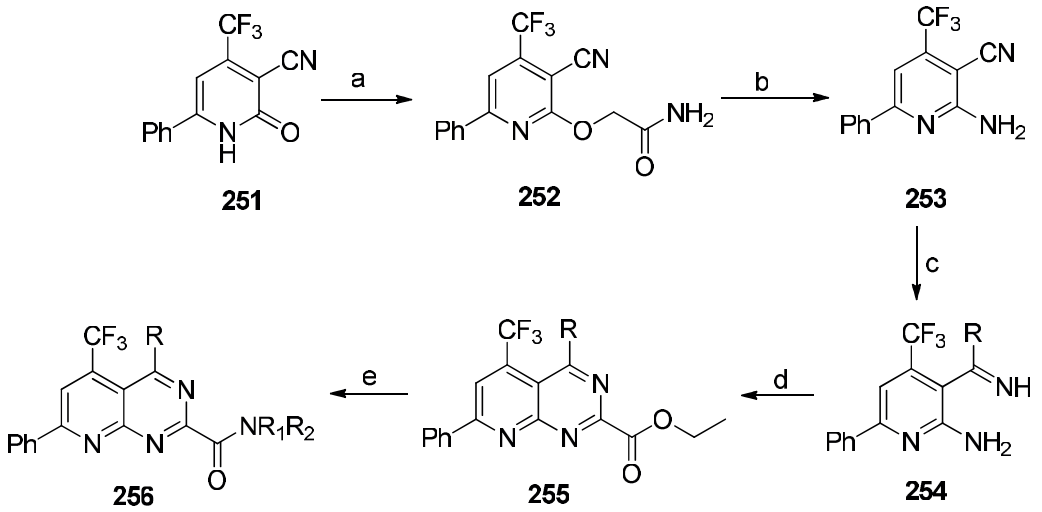
Scheme 72. Condensation between 2-aminopyridine and bis-(methylthio)methylene malononitrile.

Recently, Lauria et al. treated 2-amino-3-cyanopyrroles **248** with N-[bis(methylthio)methylene]amino moiety (BMMA) **249** to get antitumor fused pyrimidines **250** in good yield (Scheme 73).[99]



Scheme 73. Coupling of 2-amino-3-cyanopyrrole with BMMA.

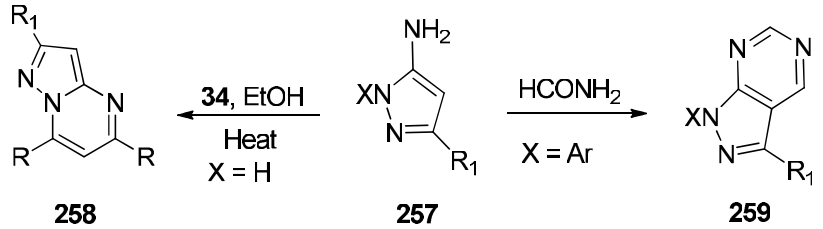
Veeraswamy and colleagues treated compound **251** with 2-chloroacetamide to achieve amide 2**52**, which on further heating in DMF and in the presence of potassium carbonate afforded 2-amino-3-cyano-4-trifluoromethyl-6-phenyl pyridine **253**.[100] Product **254** was produced by the coupling of pyridine derivative **253** and aryl magnesium bromide in the presence of diethyl ether. The reaction of pyridine derivative **254** with ethyl-2-chloro-oxo-acetate furnished ester **255**. Finally, the condensation between ester **255** and diversified amines yielded final amides **256** (Scheme 74).



Scheme 74. Reaction conditions: (a) 2-chloroacetamide, NaI, acetone, K_2CO_3, reflux, 6 h; (b) K_2CO_3, DMF, 110-120 °C, 2 h; (c) RMgX, Et_2O, r.t, 1 h; (d) ethyl-2-chloro-oxo-acetate, Et_3N, DCM, r.t, 1 h; (e) amines, 50–60 °C, 2–3 h.

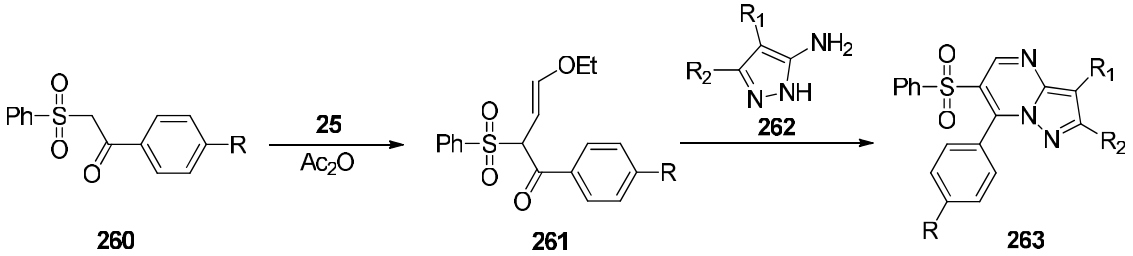
2.6. Synthesis from pyrazole

In 2006, Rao et al. executed the condensation between aminopyrazoles **257** and 1,3-dicarbonyl compounds **34** to afford pyrazolopyrimidines **258** (Scheme 75).[101] Similarly, the reaction between 5-amino-1,3-disubstituted pyrazoles **257** with formamide in the presence of PBr_3 (coupling agent) yielded anticancer pyrimidine derivative **259** in the laboratories of Huang and coworkers.[102] However, for this Vilsmeier heterocyclization, Chang et al. employed $POCl_3$ and 80–90 °C temperature (Scheme 75).[103]



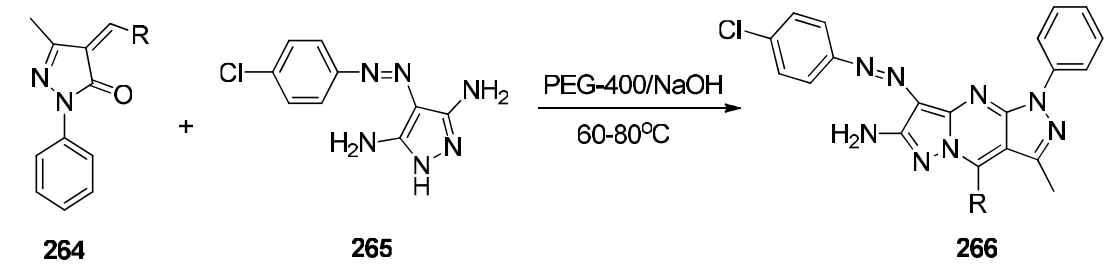
Scheme 75. Preparation of pyrazolopyrimidine derivatives.

Later, Shaaban and colleagues also conducted cyclization between 1-aryl-3-ethoxy-2-(phenylsulfonyl)prop-2-ene-1-ones **261** and 5-aminopyrazole derivatives **262** to achieve anticancer pyrimidine derivatives **263**.[104] However, the authors achieved compound **261** by the reaction of compound **260** with orthoester **25** in the presence of acetic anhydride (Scheme 76).



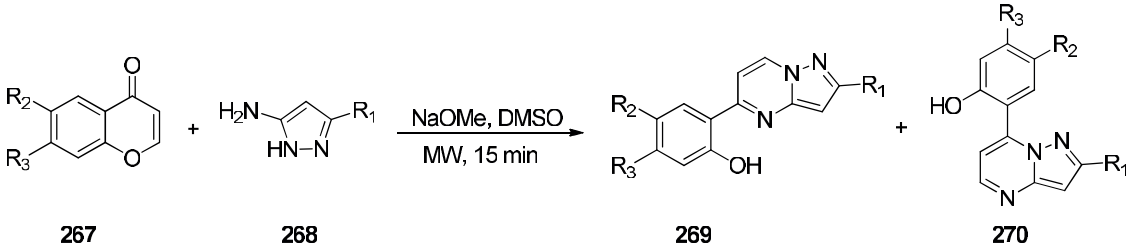
Scheme 76. Synthetic layout for the synthesis of pyrimidine derivatives.

Chobe and colleagues employed environmentally friendly conditions for the coupling of 4-substituted benzylidene-3-methyl-1H-pyrazol-5(4H)-ones **264** and 5-aminopyrazole **265** in the presence of PEG-400 to afford pyrazolo[1,5-a]pyrimidines **266** (Scheme 77).[105]



Scheme 77. Green synthetic route to pyrazolo[1,5-a]pyrimidines.

Zhang and colleagues explored the green chemistry and carried out the microwave-mediated condensation reaction between diversified chromones **267** and 3-aminopyrazoles **268** in the presence of sodium methoxide to achieve a variety of antifungal fused pyrimidine isomers **269** and **270** in good yield (Scheme 78).[106]

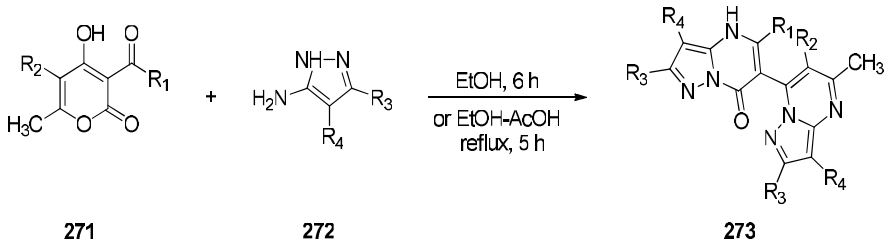


Scheme 78. Microwave-mediated condensation between chromones and 3-aminopyrazoles.

Later, Aggarwal and colleagues achieved antifungal pyrimidine derivatives **273** by the condensation of ketones **271** with pyrazoles **272** (Scheme 79).[107]

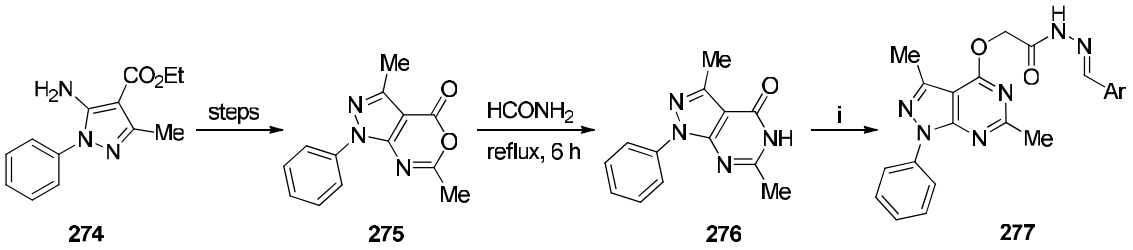
In order to enhance the cytotoxic activities, Abdelgawad et al. synthesized a new series of pyrazolo[3,4-d]pyrimidine derivatives **277** by treating 3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d][1,3]oxazin-4-one **275** with formamide under reflux. After that, O-alkylation of pyrimidine **276**, hydrazinolysis, and coupling with aromatic aldehydes afforded targeted Schiff bases **276** (Scheme 80).[108]

5-Aminopyrazole **278** was condensed with diethyl malonate to afford pyrazolopyrimidine **279**, which on reaction with $POCl_3$ furnished the dichloropyrazolopyrimidine **280**. Tian and colleagues also treated pyrimidine **281** with a variety of phenols followed by palladium-catalyzed Buchwald–Hartwig reaction with diversified



271 272 273

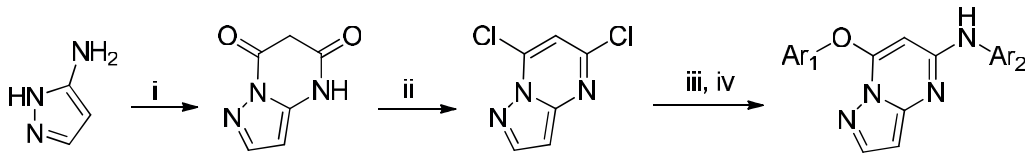
Scheme 79. Synthesis route to fused pyrimidine derivatives.



274 275 276 277

Scheme 80. Reaction conditions: (i) (a) $ClCH_2CO_2Et$, acetone, K_2CO_3, reflux, 6 h; (b) NH_2NH_2, EtOH, reflux, 4 h; (c) ArCHO, AcOH, 10 h.

anilines to achieve the requisite anti-HIV pyrimidine derivatives **282** (98% yield) (Scheme 81).[109]

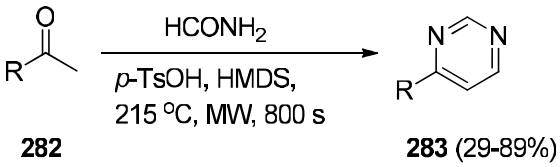


278 279 280 281

Scheme 81. Reaction conditions: (i) diethyl malonate, Na, EtOH; (ii) $POCl_3$, dimethylaniline; (iii) ArOH, K_2CO_3, DMF; (iv) $ArNH_2$, $Pd(OAc)_2$, xantphos, Cs_2CO_3, 1,4-dioxane.

2.7. Miscellaneous

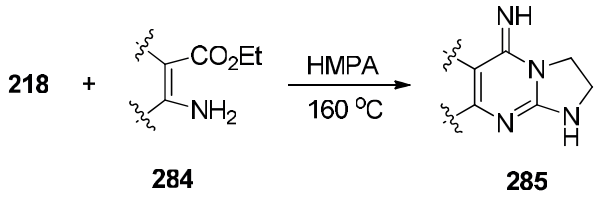
Tyagarajan and Chakravarty achieved 4-phenylpyrimidine **283** (29%–89% yield) by the reaction of various acetophenones **282** with formamide in the presence of 1,1,1,3,3,3,-hexamethyldisilazane (HMDS) and $p-$TsOH (cat.) under microwave irradiations (Scheme 82).[110]



282 283 (29-89%)

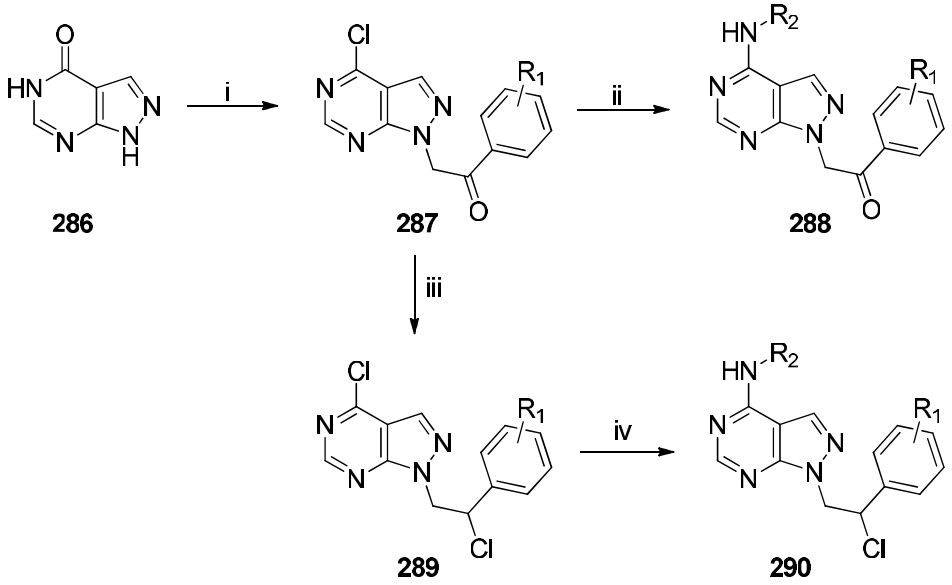
Scheme 82. Microwave-mediated synthesis of 4-phenylpyrimidine.

Similarly, Frohlich et al. treated 2-(methylthio)-2-imidazoline **218** (by dissolving it in hexamethylphosphoric acid triamide) with different aminoesters **284** to afford pyrimidine derivatives **285** (Scheme 83).[92]



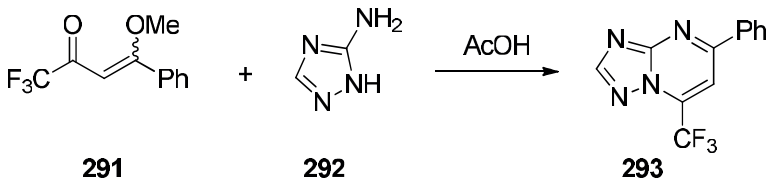
Scheme 83. Condensation between 2-(methylthio)-2-imadazoline and aminoesters.

Antitumor pyrazolo[3,4-*d*]pyrimidines **287** were achieved via the chlorination of pyrimidine **286** followed by reaction with a variety of benzoyl bromides. Reduction of derivatives **287** and subsequent treatment with $POCl_3$ yielded compounds **289**. Radi et al. achieved targeted products **290** by reacting compounds **289** with various amines under microwave irradiations.[111] The authors also treated compounds **287** with amines to get another series of novel pyrimidine derivatives **288** (Scheme 84).



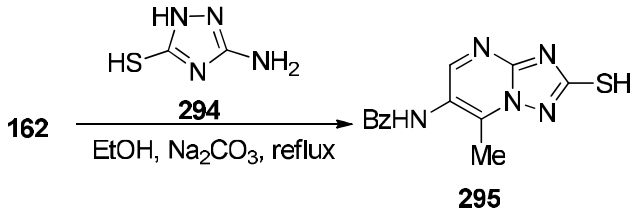
Scheme 84. Reaction conditions: i. (a) $POCl_3$/DMF, reflux, 12h; (b) $R_1C_6H_4COCH_2Br$, TBAF, THF, r.t, 16 h; ii. R_2NH_2, AcOH, dioxane, MW, 180 °C, 10 min; iii. (a) $NaBH_4$, THF, r.t, 1 h, (b) $POCl_3$/DMF, reflux, 5 h; iv. R_2NH_2, AcOH, dioxane, MW, 150 °C, 5 min.

Frizzo and colleagues elaborated the synthesis of pyrimidine derivative **293** (84% yield) by the coupling of 1,1,1-trifluoro-4-methoxy-4-phenyl-3-alken-2-one **291** with aminotriazole **292** under ultrasonic irradiations (Scheme 85).[112]



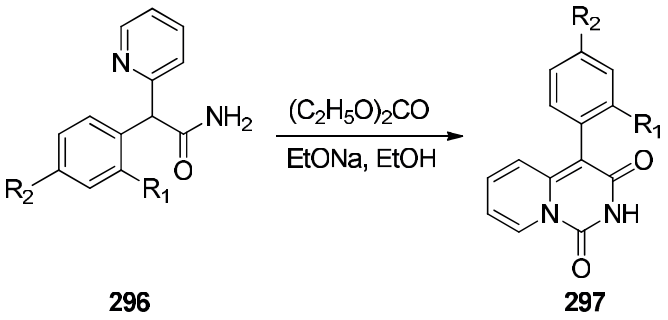
Scheme 85. Synthesis of pyrimidine derivatives under ultrasonic irradiations.

Bratusek and colleagues treated enaminone **162** with 3-amino-5-mercapto-1*H*-1,2,4-triazole **294** to afford fused pyrimidine **295** (Scheme 86).[72]



Scheme 86. Synthesis of fused pyrimidine.

In the following year, Gomolka and colleagues performed the cyclocondensation of amides **296** with diethyl carbonate to achieve 4-aryl-pyrido[1,2-c]pyrimidines **297** (Scheme 87), which were found to be serotonin transporter (SERT) and 5-HT$_{1A}$, 5-HT$_{2A}$ receptors.[113]



Scheme 87. Cyclocondensation of amides with diethyl carbonate.

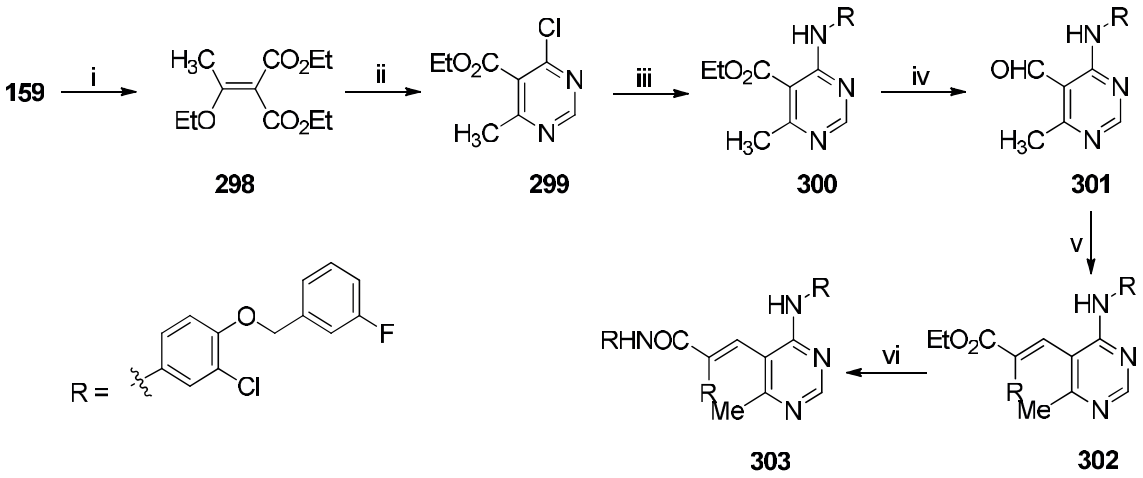
In the same year, the reaction between ester **298** and formamidine acetate **159** furnished pyrimidine derivative **299**. After this, chlorination with $POCl_3$ followed by the addition of 3-chloro-4-((3-fluorobenzyl)oxy)aniline yielded product **300**. Suzuki and coworkers also carried out the reduction of pyrimidine derivative **300** with $LiAlH_4$ followed by the Horner–Wadsworth–Emmons reaction with phosphonates to afford acrylate **302** (Scheme 88). Finally, alkaline hydrolysis of **302** and condensation with amines provided acrylamide analogues **303** that were found to be EGFR/Her-2 dual inhibitors.[114]

Thieno-pyrimidines are well known due to their exceptional pharmacological activities, which encouraged Davoodnia and colleagues to condense thiophene **304** and different aryl isocyanates **305** under a basic environment to achieve fused thieno-pyrimidines **306** (66% yield) (Scheme 89).[115]

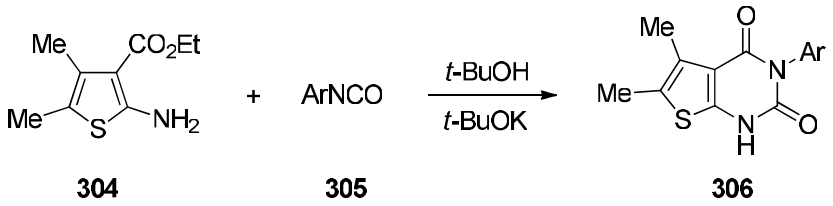
Fused pyrimidine **309b** was achieved via reaction of pyrimidine **307** with bromine in CCl_4 followed by cyclization of intermediate **308** in the laboratories of Studzinska and coworkers. However, treatment of pyrimidine **307** with excess bromine in methanol furnished both pyrimidines **309a** and **309b** simultaneously (Scheme 90).[116]

Yu et al. achieved 5-amino-1-methylpyridin-2(1*H*)-one **311** by the alkylation and reduction of 5-nitropyridin-2(1*H*)-one **310**. Amine **311** was treated with pyrimidine **312** under microwave irradiations and afforded ester **313a**, which on hydrolysis and treatment with ammonia produced carboxylic acid **313b** and amide **313c**, respectively (Scheme 91).[117]

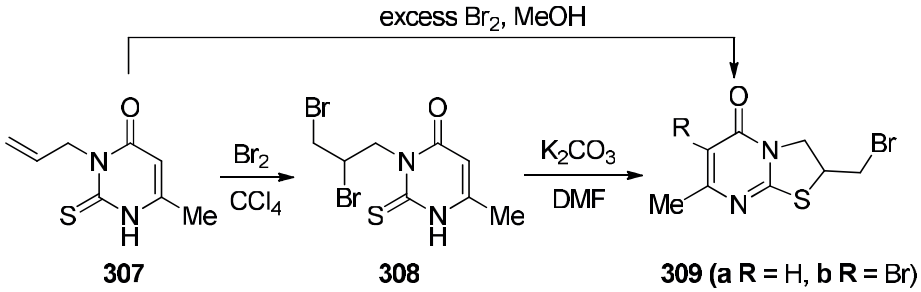
Hou and coworkers described the synthesis of pyrimidine **316** by the cyclization of 2-amino-5-bromonicotinic acid **315** in the presence of formamide (Scheme 92).[118]



Scheme 88. Reaction conditions: i. (a) acetyl chloride, Et_3N, $MgCl_2$, MeCN, 0 °C; (b) Et_2SO_4, K_2CO_3, DMF, 60 °C; ii. (a) formamidine acetate **159**, *t*-BuOK, EtOH, r.t; (b) $POCl_3$, toluene, 120 °C; iii. $ArNH_2$, DIPEA, toluene, reflux; iv. (a) $LiAlH_4$, THF, r.t; (b) $(COCl)_2$, DMSO, Et_3N, DCM, 78 °C to r.t; v. phosphonate, NaH, DMF, r.t; vi. (a) 2 N NaOH, THF, MeOH, 60 °C; (b) amine, HOBt, WSCD, HCl, Et_3N, DCM, r.t.



Scheme 89. Coupling between thiophene and isocyanates.

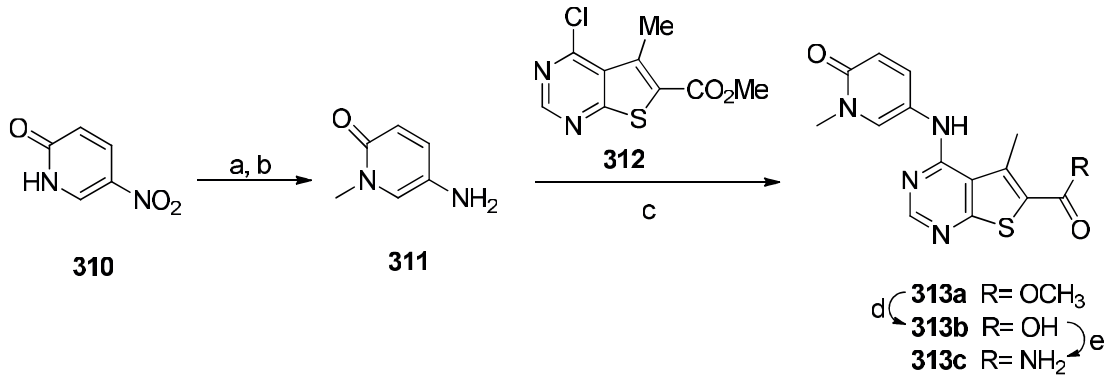


Scheme 90. Two different routes to achieve fused pyrimidines **309**.

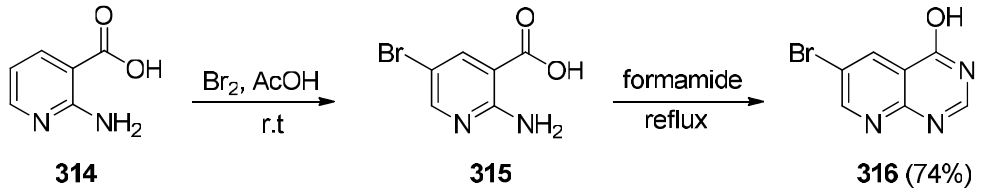
Recently, the reaction between ester **317** and hydrazine hydrate resulted in the formation of cyclized product **318**. In this work, Guo and coworkers also condensed a variety of aromatic aldehydes with pyrimidine **318** to yield Schiff bases **319** (Scheme 93), which were treated with dialkyl phosphite in an inert atmosphere to achieve the targeted α-aminophosphonate thieno-pyrimidine derivatives **320** found as good antitumor agents.[119]

Sankarganesh and coworkers reported the synthesis of pyrimidine derivative **323** by the coupling of 4-morpholinoacetophenone **321** and 4-amino-5-pyrimidinecarbonitrile **322** in ethanol (Scheme 94).[120]

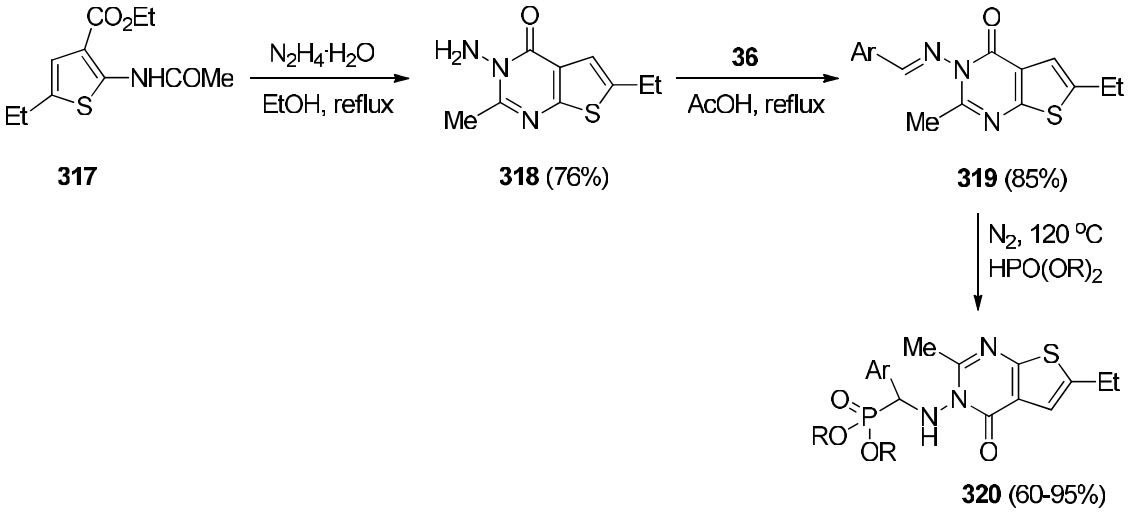
However, Sun and coworkers synthesized pyrimidine derivatives **326** from the condensation of chalcones **324** with 2,4-dichloropyrimidine **325** in the presence of acetone and sodium hydroxide, which on further treatment with amines produced substituted pyrimidines **327** (Scheme 95).[121]



Scheme 91. Reaction conditions: (a) CH_3I, K_2CO_3, DMF, 0 °C to r.t, (b) H_2, 10% Pd/C, CH_3OH, r.t; (c) TsOH-H_2O, 1,4-dioxane, microwave 200–300 W, 150 °C, 30 min; (d) 2 M NaOH, CH_3OH, r.t, 48 h; (e) NH_3, HATU, DIPEA, DMF, 0 °C to r.t.



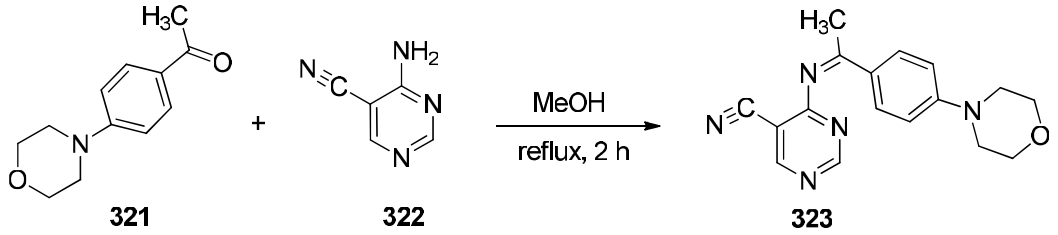
Scheme 92. Conversion of carboxylic acid **314** into pyrimidine **316**.



Scheme 93. Synthetic route to pyrimidine-based Schiff bases.

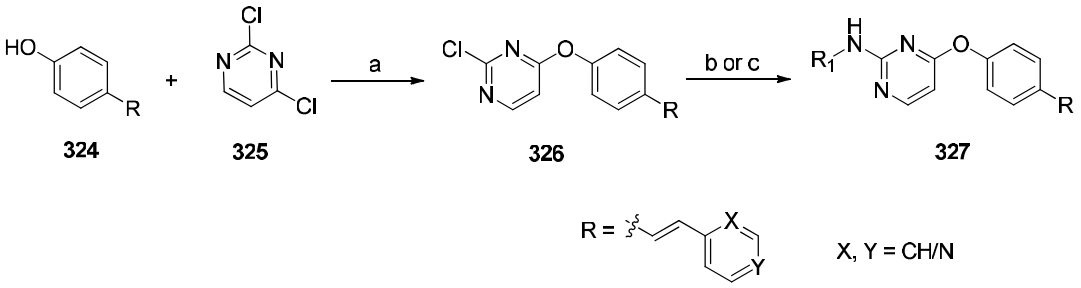
3. Conclusion

A pyrimidine ring is present in many critical molecules that constitute biological systems. Pyrimidine and its derivatives possess a wide range of biological potentials. In this context, we have elaborated a number of synthetic routes to synthesize the pyrimidine ring and its derivatives, which include multicomponent synthesis, condensation of chalcones with urea/thiourea, coupling of imidamide/guanidine with various reagents, cyclization of nitrile/isocyanate derivatives, condensation of urea/thiourea with orthoesters, and reaction of aminopyrazoles with different moieties. All these synthetic routes are simple, straightforward, and high-yielding and are executed under mild reaction conditions. Moreover,



321 322 323

Scheme 94. Coupling between acetophenone **321** and pyrimidine **322**.



324 325 326 327

Scheme 95. Reaction conditions: a) NaOH, acetone, reflux; b) amines, DMF, microwave, 130 °C; c) amines, conc. HCl, *i*-PrOH, reflux.

in some cases, environmentally friendly conditions like microwaves, PEG-400, etc. have also been employed. We hope this review will lead the researchers to explore pyrimidine chemistry in a better way.

Acknowledgment

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