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Synthesis and applications of 2-aminopyrimidine derivatives as key intermediates in chemical synthesis of biomolecules

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Abstract. Published data on the main approaches to the formation of the heterocyclic 2-aminopyrimidine system, which is one of important pharmacophores responsible for the biological properties of its derivatives, are described systematically. Main chemical transformations of functionalized 2-aminopyrimidines and their application in the synthesis of modern pharmaceuticals are considered. The bibliography includes 147 references.

I. Introduction

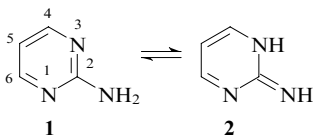
The pyrimidine ring is responsible for the properties of many natural and synthetic biomolecules. The pyrimidine ring is a key structural moiety of life-supporting substances, such as vitamins, coenzymes, and uric acid, as well as of drugs, such as Veronal, Sulfadiazine, Fluorouracil, Glivec, and Rosuvastatin. Since the aminopyrimidine ring is a fragment of nucleotide bases in DNA and RNA, which are the most important components of living cells, the significance of these compounds in the nature can scarcely be overestimated.

Since derivatives prepared based on 2-aminopyrimidine have a broad spectrum of activities, the organic synthesis of these compounds has attracted attention for many decades, and the development of new methods for the synthesis of these compounds is of great interest. The search for specific kinase inhibitors among 2-aminopyrimidines has culminated in the discovery of the drug Glivec in 1995 and inspired a renewed interest in the directed synthesis of these derivatives as potential antitumour compounds.

The previous review [1] on pyrimidines included the data published before 1960 and summarized information on various derivatives, including isomeric mono-, di-, and triaminopyrimidines. Since that time no comprehensive reviews on this subject were published, although numerous original studies on the synthesis and application of 2-aminopyrimidines have been carried out. In the monographs [2, 3] published in 1987 and 1994, 2-aminopyrimidines were considered in separate sections; however, only methods for the synthesis of these compounds based on the intramolecular cyclization with the involvement of nitrile and amino groups were described in the former monograph, whereas the brief survey of bibliographic information was presented in the latter monograph. The present review covers the results of research into the synthesis and chemical properties of 2-aminopyrimidine derivatives and their application in the synthesis of biologically active compounds published in the last two decades.

Due to the mobility of the protons of the amino group, 2-aminopyrimidine can exist in two tautomeric forms. In the present review, 2-aminopyrimidines are considered according to the IUPAC nomenclature as derivatives of the aromatic pyrimidine ring with the arrangement of the double bonds and the atomic numbering scheme corresponding to structure **1**. In some cases, hydrogenated atoms and/or substituents in dihydro derivatives of 2-aminopyrimidine have different numbers because of the equivalence of the symmetrical positions 4 and 6 in the molecule.

Isomeric 2-iminohydroxypyrimidine (**2**) and its derivatives are considered if they are formed in the reactions and were presented in original publications in this aspect.



1 **2**

II. Modern methodology for the synthesis of 2-aminopyrimidines

The methodology for the synthesis of substituted pyrimidines is based on two general approaches. One approach involves the construction of the heterocycle by the condensation of moieties containing required substituents. Another approach is based on the introduction of the amino group

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into the pyrimidine ring by the replacement of the substituent in position 2. The latter approach is less efficient and gives target products in low yields, particularly, in the reactions with arylamines, which require a large excess of nucleophiles.

1. Condensation reactions

The pyrimidine ring can be formed by condensation reactions, which differ in the nature of the moieties involved in the condensation (variants *a*–*e* in Fig. 1).

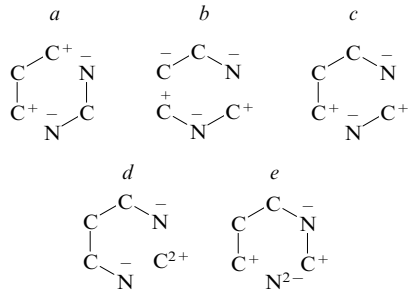


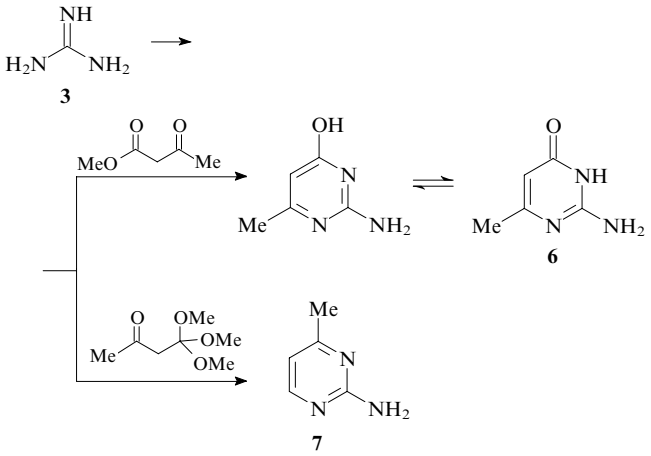
Figure 1. Variants of the condensation of the reagents giving rise to the pyrimidine ring.

The preparation of 2-aminopyrimidines is most often based on the convergent synthesis (method *a*), which is often called the conventional synthesis.[4] The method *a* (see Fig. 1) is based on the condensation of dielectrophiles containing the three-carbon chain and the carbonyl, ester, or nitrile group with dinucleophiles containing the N–C–N moiety. If guanidine serves as the dinucleophilic component, the formation of the pyrimidine ring is accompanied by the introduction of the amino group in position 2. 2-Aminopyrimidines substituted at the amino group are formed in the reactions with alkyl-, aryl-, or arylsulfonylguanidines, as well as with dicyanodiamide.

β-Dicarbonyl compounds and their derivatives (β-keto esters, β-keto nitriles, and acid chlorides, whose terminal functional fragments can react with nucleophiles), serve as the dielectrophilic component. The condensation is performed in polar solvents with heating in the presence of a condensing agent; in some cases, the reactions are performed by the fusion. The yields of 2-aminopyrimidines containing various substituents in the ring (Alk, Ar, Het, CF_3, CHF_2, OH, CO_2Et, CN, NHCOAr) are 60%–95%.[2,3]

In the study of the reactions of acetylacetone and dimethyl malonate with guanidine (**3**), it was found that the 1,2-addition of amine to the most reactive carbonyl group is the rate-determining step. 2-Aminopyrimidine derivatives **4** and **5** are formed as a result of the elimination of water or methanol (Scheme 1).[5] Apparently, the reactions of guanidine with methyl acetoacetate and 4,4,4-trimethoxybutan-2-one occur in a similar way to give compounds **6** and **7**, respectively (Scheme 2). The experimental details for tens of these reactions with the involvement of various amidines were published in the literature, and these data were summarized in the review.[3]

Scheme 2

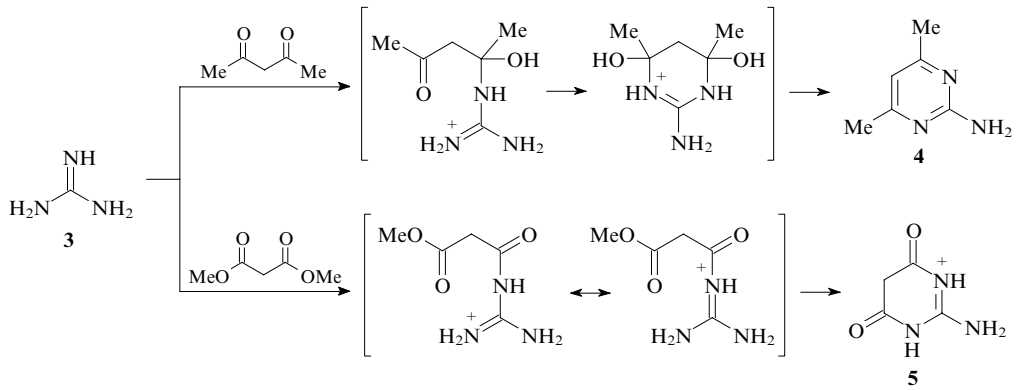


The preparative synthesis of fluorine-substituted 2-aminopyrimidines, which are analogues of the known antitumour drugs Fluorouracil and Ftorafur, was performed based on fluorinated β-diketones.[6–11]

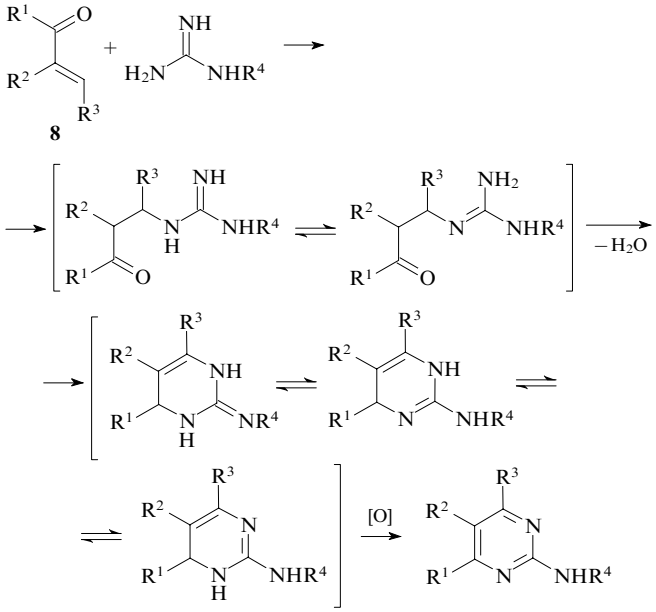
Synthetic equivalents of β-dicarbonyl compounds, *viz*., α,β-unsaturated aldehydes, ketones, nitriles, carboxylic acids, and/or their latent forms (alkoxides of hydroxy enones, acetals, and β-sulfanyl- and β-dimethylamino derivatives of α,β-unsaturated ketones), are often used as dielectrophiles.[7,12–16]

The reactions of guanidine with α,β-unsaturated ketones, aldehydes, or nitriles involve the nucleophilic attack of the NH_2 group on the activated double bond (the Michael addition) as the first step followed by the ring closure and dehydration. In the last step, the resulting dihydropyrimidine should be oxidized. To facilitate the dehydrogenation of dihydro-2-aminopyrimidines, the condensation of α,β-unsaturated carbonyl compounds **8** with guanidines or their salts (hydrochlorides or carbonates) is

Scheme 1



carried out under a dry air flow in dimethyl sulfoxide with oxidizing properties in the presence of zeolites as catalysts and dehydrating agents.[15]

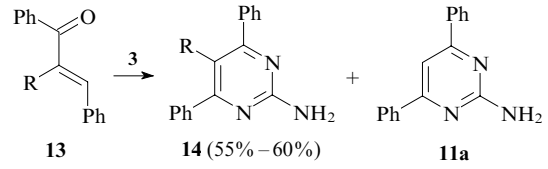


R^1 = Me, Ph; R^2, R^3 = H, Me, Ph; R^2–R^3 = $(CH_2)_4$; R^4 = H, Ac.

Chalcones **9** react with guanidinium carbonate in a similar way through the 1,2- or 1,4-addition of guanidine (**3**) to chalcone followed by the cyclization and dehydration of intermediates to give dihydropyrimidines **10**. The latter undergoes the hydride shift to form aromatic 2-amino-4,6-diarylpyrimidines **11**.[13,17,18] It should be noted that the preparative syntheses based on the condensation of guanidine (**3**) with chalcones and/or their heterocyclic (thienyl, furyl) analogues generally afford dihydropyrimidines **10**, whereas aromatic products are formed only when the reagents are used in microamounts as a result of the oxidation of intermediates by atmospheric oxygen. For this reason, the synthesis of (het)aryl-substituted 2-aminopyrimidines is generally performed with the use of an oxidizing agent (hydrogen peroxide), and compounds **11** are obtained in 60% yield (Scheme 3).[12,14,17,19–21]

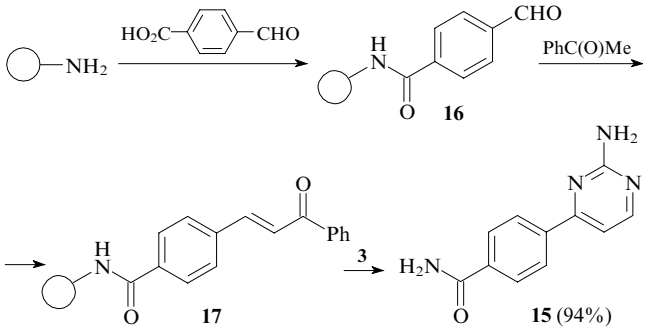
The reactions of 4-methoxy-, 4- and 2-hydroxychalcones **9** (X = 4-MeO, 4-OH, 2-OH) with guanidine (**3**) immediately afford 4,6-diaryl-substituted 2-aminopyrimidine **11** (X = 4-MeO, 4-OH, 2-OH). Under these conditions, 4-halogen-substituted chalcones **9** (X = Cl, Br) give only the corresponding dihydro derivatives **10** stabilized as salts. The heating of **9** in dimethylformamide leads to their aromatization and the formation of 2-amino-4,6-diarylpyrimidines as a results of oxidation by atmospheric oxygen. In addition to dihydropyrimidines, 4-chloro- and 4-bromochalcones form 2,4,6,8-tetraaryl-1,6-dihydro-4*H*-pyrimido[1,2-*a*]pyrimidines **12**.[12] In the case of X = Cl and X = Br, the ratio of the products **11** : **12** is 3 : 2 and 25 : 1, respectively.

The reactions of 2-substituted chalcones **13** with guanidine (**3**) afford both 5-substituted pyrimidines **14** and 2-amino-4,6-diphenylpyrimidine unsubstituted at position 5 (**11**, $Ar^1 = Ar^2 = Ph$).[14]



R = SPh, OPh.

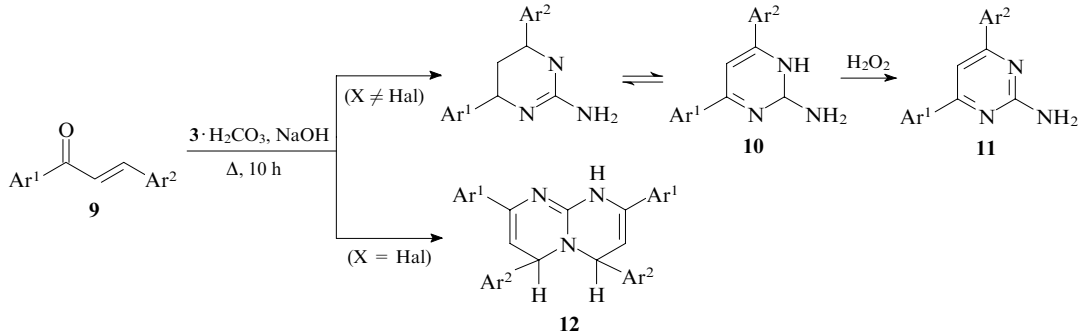
In the condensation of guanidine with α,β-unsaturated ketones (or their precursors), the quantitative yields of 2-aminopyrimidines are achieved with the use of the reagents immobilized on solid-phase polymer and resin supports. Thus, in the synthesis of 4-(2-aminopyrimidin-4-yl)benzamide (**15**), key formylbenzamide **16** is formed by the aminolysis of 4-formylbenzoic acid by a support amino group. The reaction of formylbenzamide **16** with acetophenone gives α,β-unsaturated ketone **17**, which is fused to guanidine to form aminopyrimidine **15**.[22,23]



○ is polymer.

In spite of the high yield and the purity of the reaction products, the solid-phase synthesis is rarely used for the preparation of 2-aminopyrimidines, because these processes

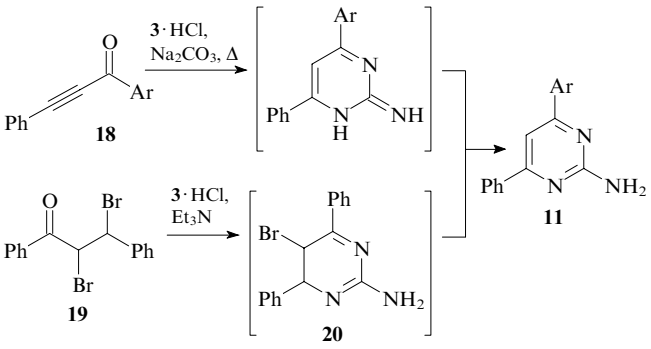
Scheme 3



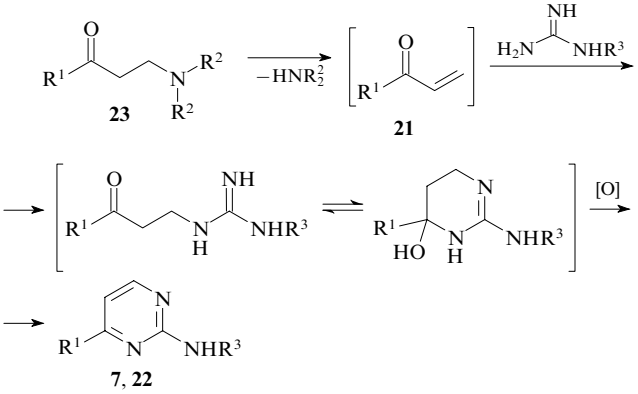
Ar^1, Ar^2 = XC_6H_4 (X = H, 2-OH, 4-OH, 4-Cl, 4-Br, 4-OMe), 2-thienyl (Th), 2-furyl (Fu).

are labour-consuming and require complex apparatus and expensive supports.

The heating of aroylphenylacetylenes **18** with guanidine resulted in the formation of 2-amino-4-aryl-6-phenylpyrimidines **11**. 2-Amino-4,6-diphenylpyrimidine (**11a**) was synthesized also by the condensation of guanidine with chalcone dibromide **19** in the presence of Et_3N; the initially formed 2-amino-5-bromo-4,6-diphenyl-5,6-dihydropyrimidine **20** is unstable under the reaction conditions and is stabilized by the elimination of HBr.[24]

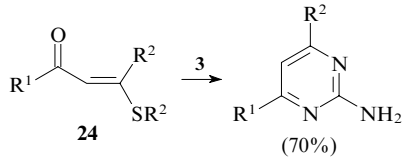


Attempts to perform the condensation of methyl and phenyl vinyl ketones **21** with guanidine failed because the reactions were accompanied by the polymerization; hence, aminopyrimidines **7** (R^1 = Me, R^3 = H) and **22** were synthesized with the use of Mannich keto bases **23** as precursors of vinyl ketones.[25]



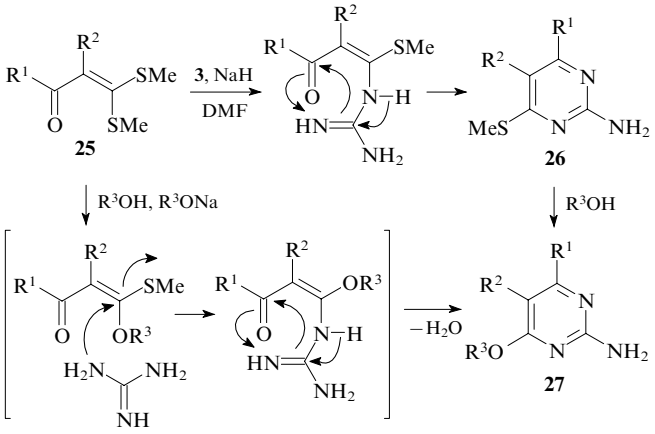
R^1 = Me, Ph; R^2 = Me, Et; R^3 = H, Ac.

In the 1980s mono- and di-β-sulfanyl derivatives of α,β-unsaturated ketones found use as efficient synthons for the synthesis of 2-aminopyrimidines. These compounds contain two reaction centres for the nucleophilic attack [the C(1) and C(3) atoms] and have a weak tendency to undergo polymerization. The reactions of sulfanyl α,β-enones **24** with guanidine afford the corresponding 2-aminopyrimidines.[26]



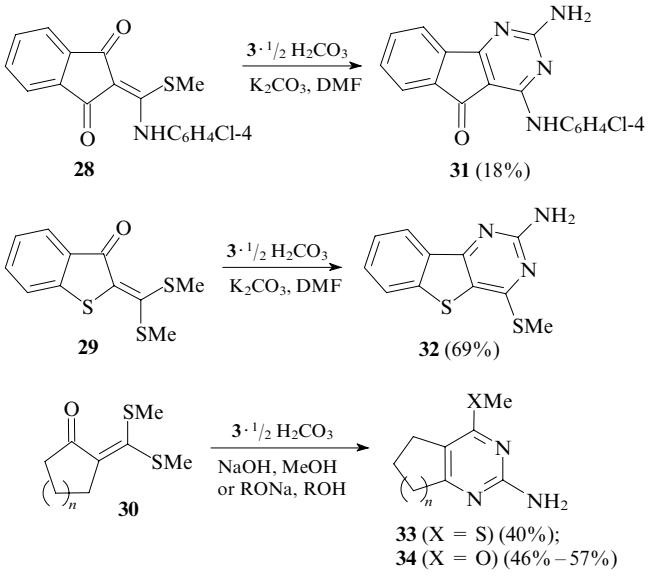
R^1 = Me, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$; R^2 = Me, Ph.

The condensation of acylketene *S*,*S*-acetals **25** with guanidine occurs in a similar way, 4-methylthio- (**26**) or 4-alkoxy-2-aminopyrimidines (**27**) being obtained in 35%–50% yields depending on the nature of the base and the solvent (the NaH–DMF or RONa–ROH system).[26]



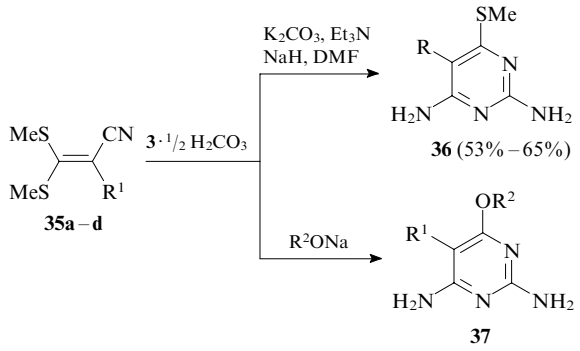
R^1 = Me, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$; R^2 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$; R^3 = Me, Et, Pr^i.

The condensation of mono- and dithioacetals of cyclic ketones (for example, of compounds **28**–**30**) with guanidine in the presence of potassium carbonate affords 2-aminopyrimidines **31**–**34** fused to the indene, thiophene, or aliphatic ring. Cycloalkanedione *S*,*S*-acetals **30** give 4-methylthiopyrimidines **33** in a methanolic NaOH solution at room temperature and form 4-alkoxy-2-aminopyrimidines **34** upon heating in aliphatic alcohols in the presence of sodium alkoxide.[26,27]

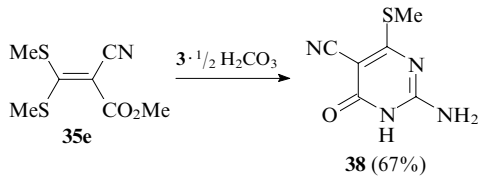


n = 1–3; R = Me, Et.

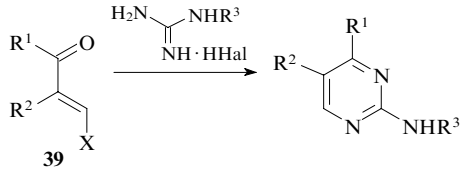
The condensation of α-cyanoketene *S*,*S*-acetals **35a**–**d** with guanidine in the presence of potassium carbonate affords 2,4-diaminopyrimidines **36** with a sulfur-containing substituent in the ring. This reaction with the use of sodium alkoxides as bases gives 6-alkoxy-2,4-diaminopyrimidines **37**, because the nucleophilic substitution of the methylthio group with alkoxide ions can occurs both in the starting thioacetal and in the resulting pyrimidine. The condensation of guanidine hydrochloride with ketene dithioacetal **35e** affords multifunctional 2-amino-5-oxopyrimidine **38** due to the involvement of the ester group of the starting compound in the formation of the heterocycle.[26–28]



R^1 = CN (**a**), Ph (**b**), 4-ClC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**); R^2 = Et, Pr^i.



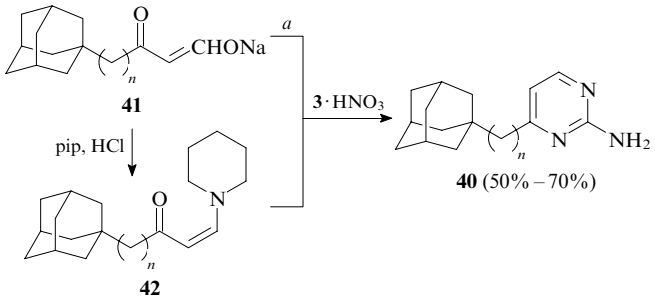
Dimethylamino and alkoxy derivatives of α,β-unsaturated ketones **39**, *viz*., vinylogues of amides (X = NMe_2) and enol ethers (X = OAlk), also serve as efficient dielectrophiles in the synthesis of 2-aminopyrimidines. The condensation of derivatives **39** with alkyl(aryl)guanidines under reflux in ethanol affords the corresponding alkyl-, aryl-, or hetaryl-substituted 2-aminopyrimidines.[29] In this condensation, cyclic ketones give carbo- (C_5 – C_{12}) or heterocycle-fused 2-aminopyrimidines in 35% – 75% yields.



X = NMe_2, OAlk; R^1, R^2 = Alk, Ar, SO_2Ph, Het; R^3 = Alk, Ar.

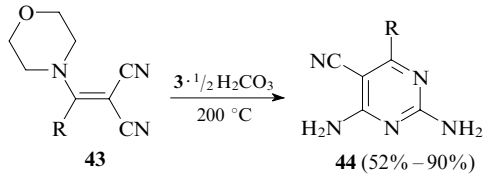
A versatile method for the synthesis of a wide range of 2-arylaminopyrimidines was developed based on the reaction of arylguanidine derivatives with dimethylaminopropenones containing a hetaryl substituent.[30 – 33]

The synthesis of adamantyl derivatives of 2-aminopyrimidine **40** is an example of the application of enol derivatives stabilized as salts. The reaction of guanidine with an equimolar amount of the sodium salt of 3-(1-adamantyl)-1-hydroxyprop-1-en-3-one **41** (n = 1) occurs under reflux in 50% aqueous ethanol.[34] A similar product can be synthesized through the formation of piperidine derivative **42**.



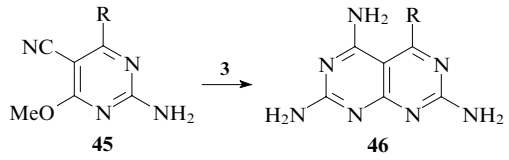
(*a*) EtOH, Δ; n = 0, 1; pip is piperidine.

Dinitriles activated with enol or enamine derivatives of ketones can be used as dielectrophiles. Thus, enamino dinitriles **43** react with guanidinium carbonate at 200 °C to form 2,4-diaminopyrimidine-5-carbonitriles **44**.[27]



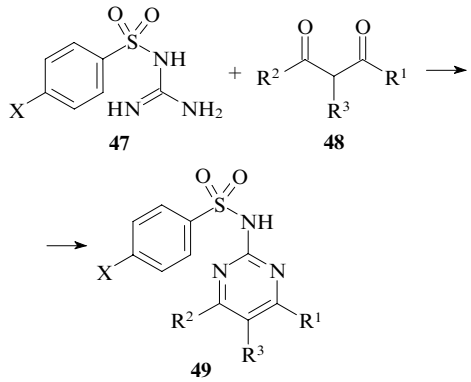
R = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-$MeOC_6H_4$, 2-Th, Bn.

4-Alkoxy-substituted pyrimidinecarbonitriles synthesized in a similar way can serve as dielectrophiles in the reactions with guanidine to form pyrimido[4,5-*d*]pyrimidine derivatives. For example, the condensation of 2-amino-4-aryl(alkyl)-6-methoxypyrimidine-5-carbonitrile **45** with compound **3** affords 2,5,7-triamino-4-R-pyrimido[4,5-*d*]-pyrimidine **46** in good yield. This reaction lies at the basis of the efficient method for the synthesis of drugs containing the pyrimido[4,5-*d*]pyrimidine ring.[35]



R = Alk, Ar.

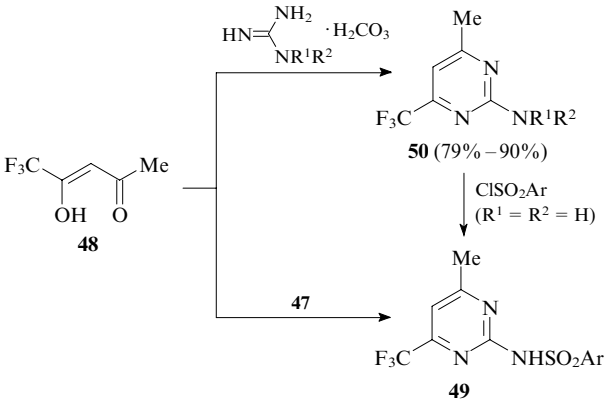
Arylsulfonylguanidines **47** react with fluorine-containing dicarbonyl derivatives **48** to form 2-arylsulfonylamino-pyrimidines **49** in preparative yields.



R^1 = CF_3, 4-FC_6H_4; R^2 = Me, Et, Pr^i, Bu^t, iso-C_5H_{11}, C_mF_{2m+1} (m = 1 – 7); R^3 = H, Alk; X = H, Me.

This method was used to synthesize compounds **49** (R^1 = Me, R^2 = CF_3, R^3 = H), which are biologically active fluorinated analogues of the known drug Sulfamethazine, from trifluoroacetylacetone **48** (R^1 = Me, R^2 = CF_3, R^3 = H) and arylsulfonylguanidines **47**.[7]

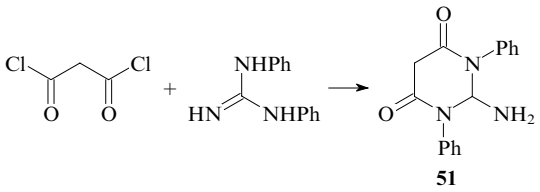
2-Amino-4-trifluoromethylpyrimidines **50** were synthesized by the fusion of trifluoroacetylacetone with guanidinium carbonate, 4-tolylguanidinium carbonate, or *N*-(2-hydroxyethyl)-*N*-methylguanidinium sulfate or by heating ethanolic solutions of these reagents.[8, 9, 11] Compound **50a** (R^1 = R^2 = H) was transformed into pyrimidine **49** (R^1 = Me, R^2 = CF_3, R^3 = H) in the reaction with arenesulfonyl chloride.

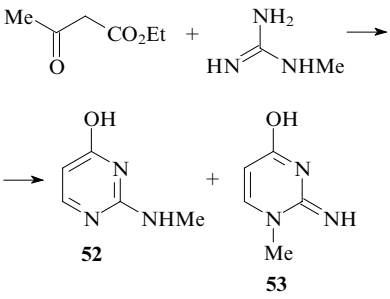


R^1 = H: R^2 = H, 4-MeC_6H_4; R^1 = Me, R^2 = $HO(CH_2)_2$.

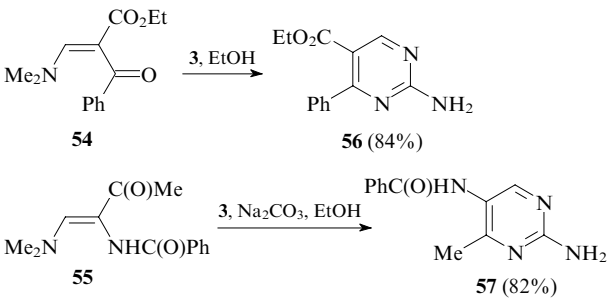
α,β-Unsaturated ketones and/or Mannich keto bases react with sodium salts of sulfonylguanidines to form the corresponding 2-sulfonylaminopyrimidines in low yields (12% – 17%).[36]

The condensation of *N,N′*-diphenylguanidine with malonic acid dichloride affords 2-amino-1,3-diphenylhexahydropyrimidine-4,6-dione (**51**), and the reaction of methylguanidine with acetoacetic ester gives 2-methylaminopyrimidine **52** along with isomeric *N*-methylated compound **53** (the yields and the ratio of the reaction products were not reported in the original study).[1]

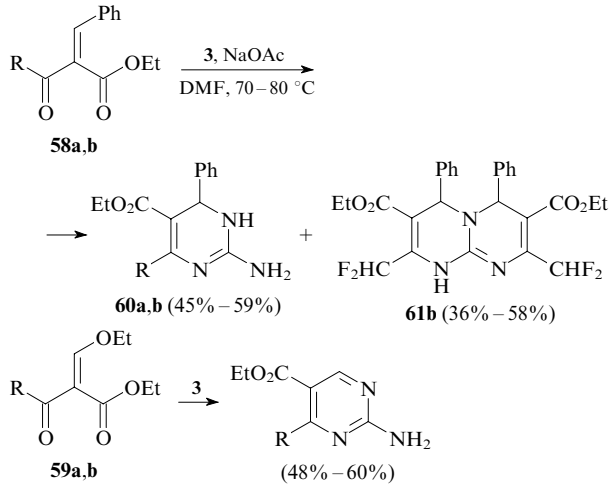




The reactions of guanidine with ethyl 2-benzoyl-3-(dimethylamino)acrylate (**54**) and (*Z*)-3-benzoylamino-4-dimethylaminobut-3-en-2-one (**55**) give the corresponding ethoxycarbonyl- (**56**) and benzoylamido-2-aminopyrimidines (**57**). In benzoylacrylate **54**, the ester group, as the less reactive group compared to the carbonyl group of the ketone, is not involved in the formation of the pyrimidine ring and is introduced as the substituent at the C(5) atom.[37]

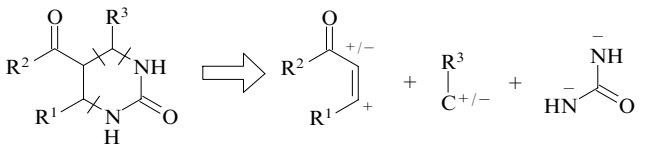


The reactions of guanidine with 2-benzylidene- (**58a**,**b**) and 2-ethoxymethylidene-3-oxo-3-(fluoroalkyl)propionates (**59a**,**b**) provide an approach to the synthesis of 2-aminopyrimidines containing the fluoroalkyl substituent along with the ester group. The reactions of benzylidene derivatives **58a**,**b** stop at the formation of ethyl 2-amino-4-fluoroalkyl-6-phenyl-1,6-dihydropyrimidine-5-carboxylates **60a**,**b**. Apparently, the phenyl substituent in the resulting dihydropyrimidine ring hinders the oxidation. The reaction of ester **58b** containing the difluoromethyl substituent gives diethyl 2,8-bis(difluoromethyl)-4,6-diphenyl-1,6-dihydro-4*H*-pyrimido[1,2-*a*]pyrimidine-3,7-dicarboxylate (**61b**) as the by-product formed in the reaction of primary condensation product **60b** with the starting keto ester **58b** that is present in the reaction mixture.[38]

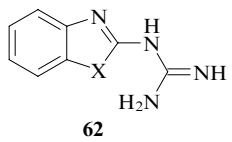


R = CF_3 (**a**), HCF_2 (**b**).

2-Aminopyrimidines can be synthesized also by the three-component condensation of amines, aldehydes, and CH-acids, which has been developed in recent years.[39,40] This method for the construction of the pyrimidine ring based on the use of β-dicarbonyl compounds as a source of the two-carbon moiety (see the retrosynthetic scheme given below, in which one of the carbonyl groups remains intact) is known as the Biginelli reaction.[4]



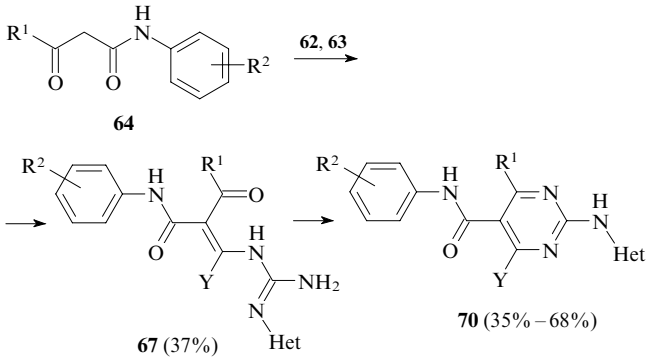
In this reaction with CH-acids and orthoesters, benzoxazolyl- and benzothiazolylguanidines **62** were examined (Schemes 4 and 5).[41]



X = O, S.

Orthoesters $YC(OEt)_3$ (**63**) react with CH-acids **64** – **66** followed by the addition of guanidine **62** to the double bond of the enone that formed (enedione, unsaturated keto ester) to give intermediate linear addition products **67** – **69** (see

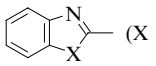
Scheme 4

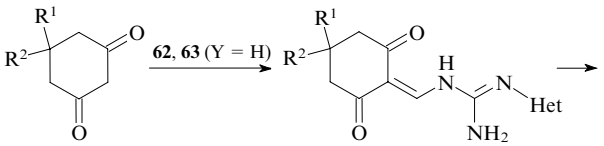


64

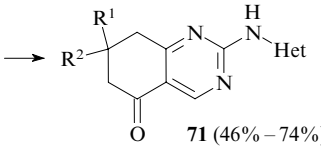
67 (37%) **70** (35%–68%)

R^1 = Alk; R^2 = 2-Me, 4-Me, 3-CF_3, 2-MeO; Y = H, Me;

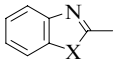
Het =  (X = O, S).

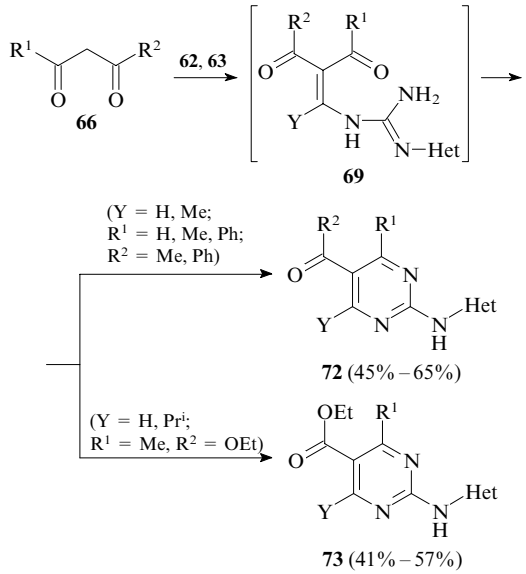


65 **68** (58%–62%)

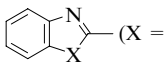


71 (46%–74%)

R^1 = R^2 = H, Me; Het =  (X = O, S).

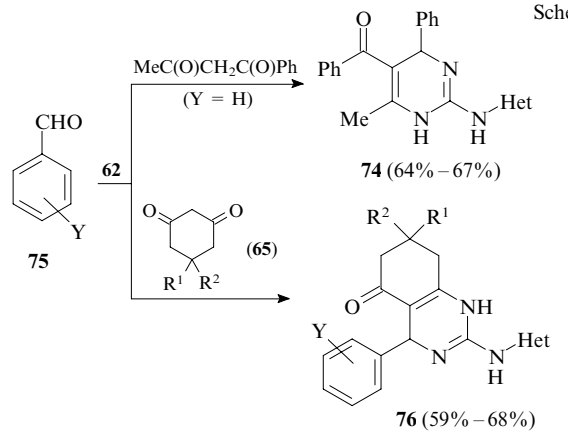


66 **69** **72** (45%–65%) **73** (41%–57%)

Het =  (X = O, S).

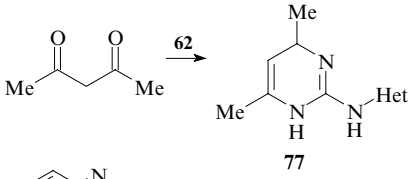
Scheme 4). The latter undergo cyclization to hetaryl-substituted 2-aminopyrimidines **70**–**73** with the involvement of the carbonyl group of the CH-acidic component and the second amino group of the dinucleophile. The condensation of linear β-diketones **66** (R = Me, Ph) with hetarylguanidines **62** and orthoesters occurs under reflux of the reactant mixture in an excess of the orthoester for 20–40 min.

Scheme 5

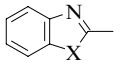


74 (64%–67%) **76** (59%–68%)

Y = H, Cl; R^1 = H, Me; R^2 = H, Me, 4-FC_6H_4.



77

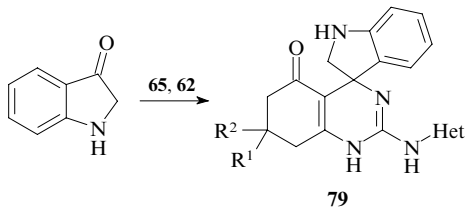
Het =  (X = O, S);

Cyclic diketones **65** cause a large steric hindrance to the condensation. Hence, in the case of less reactive benzoxazolylguanidine **62** (X = O), intermediates **68** (X = O) were isolated in the individual state, and their cyclization was performed by heating in acetic acid in the presence of sodium acetate. More reactive benzothiazolylguanidine **62** (X = S) immediately gave cyclic products **71** (see Scheme 4).[41]

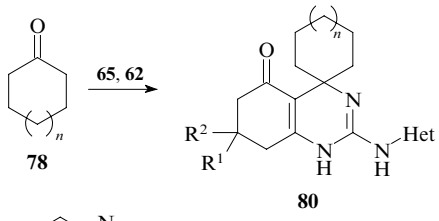
The reactions of hetarylguanidines **62** and orthoesters **63** with β-keto esters **66** (R^2 = OEt), which can give two intermediates, afford the only cyclization product, *viz*., 5-ethoxycarbonylpyrimidine **73**. Evidently, intermediate **69** containing the closely spaced amino and carbonyl (rather than ester!) groups undergoes intramolecular cyclization.[41–43] It should be noted that, unlike the classical Biginelli reaction, which is performed with the use of (thio)ureas and gives 3,4-dihydro(thio)oxopyrimidines, the condensation of hetarylguanidines with orthoesters and CH-acids is accompanied by the aromatization of the dihydropyrimidine ring.

1,4-Dihydropyrimidine derivatives **74** can be synthesized also by the three-component condensation of hetarylguanidines **62** with benzoylacetone and benzaldehydes **75** (Scheme 5). The three-component condensation of hetarylguanidines **62**, cyclic β-diketones **65**, and aromatic aldehydes **75** affords cyclohexane-fused 2-hetarylamino-1,4-dihydropyrimidines **76**, *viz*., arylhetaryl-substituted hexahydroquinazolinones.[42] The reactions with more reactive acetylacetone, which is easily involved in the two-component condensation with guanidine **62** in the absence of the third component (aldehyde), give 2-benzoxa(thia)zolylamino-4,6-dimethylpyrimidines **77** (see Scheme 5).[43]

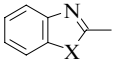
The reactions of hetarylguanidines **62** and cyclic β-diketones **65** with cyclic ketones **78** or isatin instead of benzaldehydes afford the corresponding spiro-fused compounds **79** and **80** containing 2-amino-1,4-dihydropyrimidine moieties.[43]



79

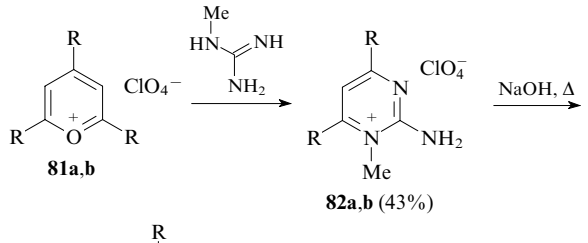


78 **80**

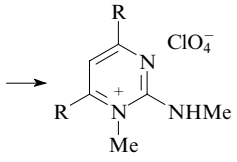
Het =  (X = O, S);

R^1 = H, Me; R^2 = H, Me, 4-FC_6H_4; n = 0, 1.

Several examples of the synthesis of 2-aminopyrimidines based on the recyclization of latent forms of α,β-unsaturated carbonyl compounds, *viz*., pyrylium salts and 5-(silylmethyl)isoxazoles, were reported. For example, 2,4,6-triarylpyrylium perchlorates (**81a**,**b**) react with methylguanidine under reflux in ethanol to give 2-amino-4,6-diaryl-1-methylpyrimidinium perchlorates (**82a**,**b**). The Dimroth rearrangement of these salts affords 4,6-diaryl-2-methyliminopyrimidine perchlorates (**83a**,**b**).[44]



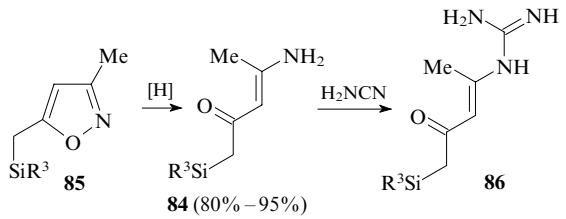
81a,**b** **82a**,**b** (43%)



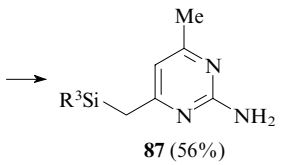
83a,**b** (35%)

R = Ph (**a**), 4-$MeOC_6H_4$ (**b**).

Silyl-substituted β-amino enones **84**, which were synthesized by the catalytic hydrogenolysis of 3-methyl-5-(silylmethyl)isoxazoles **85**, have different stability depending on the nature of the silyl group. Compounds **84** containing a nucleofuge[45] group (for example, the dimethylphenyl, methyldiphenyl, or *tert*-butyldiphenylsilyl group) react with cyanamide to give guanidines **86**, which undergo cyclization to pyrimidines **87**, with the silyl group remaining intact.[46]



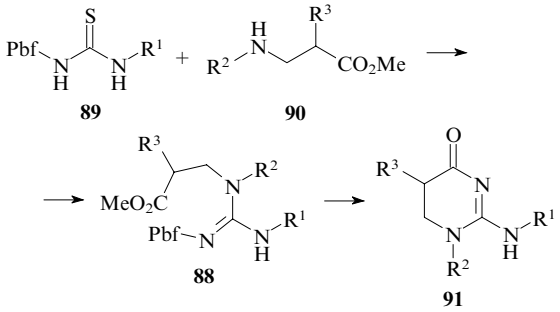
85 **84** (80%–95%) **86**



87 (56%)

R_3 = Me_3, $PhMe_2$, $MePh_2$, Bu^tPh_2.

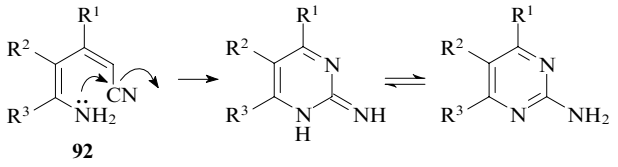
The analogous cyclization of guanidines **88**, which were synthesized from substituted thioureas **89** and N-alkylated amino acids **90**, is stimulated by the elimination of the good leaving 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfanyl group (Pbf) in the presence of trifluoroacetic acid. Since the starting amino acids are readily available and the reaction proceeds under mild conditions, this reaction provides an efficient approach to the synthesis of a wide range of 1,5-dialkyl-2-(*N*-alkylamino)tetrahydropyrimidin-4-ones **91**.[47]



89 **90** **88** **91**

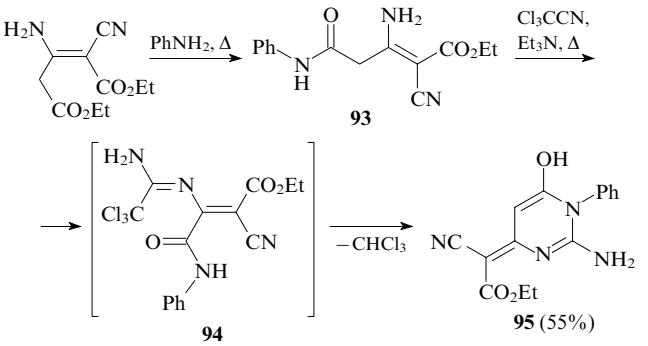
R^1 = Bu^n, Bn, Ph; R^2 = Bu^n, Bu^i, Bn; R^3 = H, Me, Ph.

Methods for the synthesis of 2-aminopyrimidines based on the intramolecular cyclization of dienes **92** containing the three-carbon moiety with terminal amino and nitrile groups can be considered as a special group. Compounds **92** undergo cyclization to the corresponding 2-iminopyrimidines followed by the isomerization to 2-aminopyrimidines upon heating and/or in the presence of bases.[2]



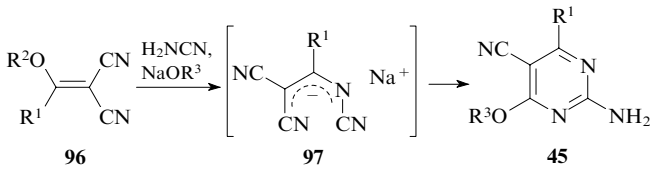
92

The condensation of trichloroacetonitrile and enamine **93** (type *c*, see Fig. 1) affords intermediate **94**, whose intramolecular cyclization accompanied by the elimination of the trichloromethylene group affords 2-aminopyrimidine **95**.[48]



93 **94** **95** (55%)

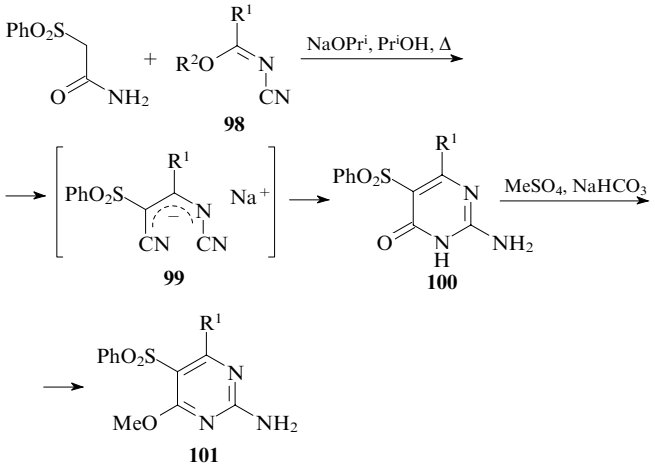
The cyclization of salt **97**, which is an intermediate in the reaction of cyanamide with alkoxyalkylidenemalononitrile **96**, in the presence of sodium alkoxides afforded 6-alkoxy-2-amino-4-aryl(alkyl)pyrimidine-5-carbonitriles **45**.[35]



96 **97** **45**

R^1 = Alk, Ar; R^2, R^3 = Me, Et.

The reactions of alkyl *N*-cyanoimidates **98** with 2-(phenylsulfonyl)acetamide through the intermediate cyclization of the salt of cyanoaminosulfonylnitrile **99** accompanied by the elimination of the alkoxy group give substituted 2-amino-5-phenylsulfonylpyrimidin-4-ones **100**. The methylation of the latter compounds affords sulfur-containing 2-amino-4-methoxypyrimidines **101**.[49] This method is an example of the condensation of the type *b* (see Fig. 1); sulfonylamide acts as the dinucleophile.

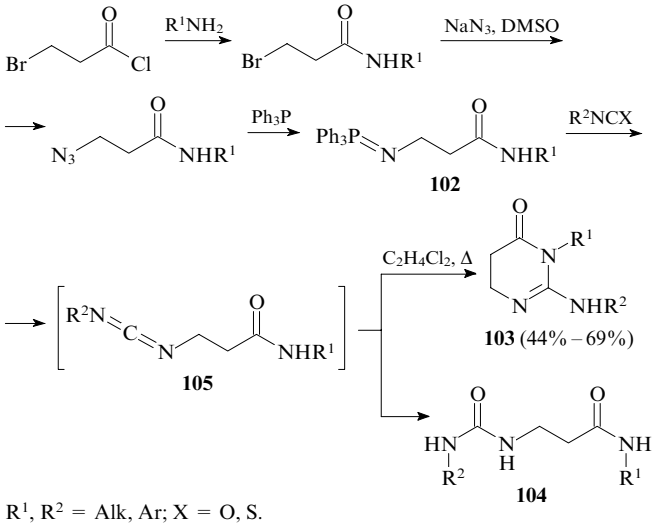


98 **99** **100** **101**

R^1 = H, Me, Ph, 4-MeC_6H_4; R^2 = Me, Et.

The cyclization of 3-cyanoiminopropionitriles in the presence of hydrogen halides affords isomeric 2- and 4-aminopyrimidines. The variations of the reaction conditions made it possible to change the reaction pathway. The cyclization of *N*-cyanoamidines in the presence of hydrogen iodide in acetic acid even in the absence of Lewis acids affords 6-amino-4-iodopyrimidine as the major product.[50]

In the last decades, the aza-Wittig reaction with the use of iminophosphoranes has found great significance in the design of heterocyclic systems. A preparative method for the synthesis of 3-substituted 2-alkylamino-5,6-dihydropyrimidin-4(3*H*)-ones **103** was developed based on the condensation of [2-(*N*-R^1-carbamoyl)ethyl]triphenyliminophosphoranes **102** with heterocumulenes (isocyanates and isothiocyanates). The synthesis involves the amination of bromopropionic acid chloride, the nucleophilic substitution of the bromine atom in the corresponding amide with the azide ion, and the Staudinger transformation of the resulting azides into iminophosphoranes **102** in the presence of triphenylphosphine. The last step involves the condensation of compounds **102** with isocyanates and isothiocyanates according to the path *c* (see Fig. 1) with the simultaneous involvement of the amide group:



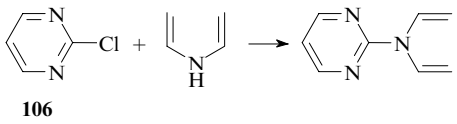
102 **105** **103** (44% – 69%) **104**

R^1, R^2 = Alk, Ar; X = O, S.

It should be noted that the reactions with the use of aromatic heterocumulenes (R^2 = Ar) give dihydropyrimidines **103** as the major products, whereas the reactions with aliphatic derivatives (R^2 = Alk) afford unsymmetrical ureas **104** as a result of the hydrolysis of intermediate carbodiimides **105**.[51]

2. Substitution reactions

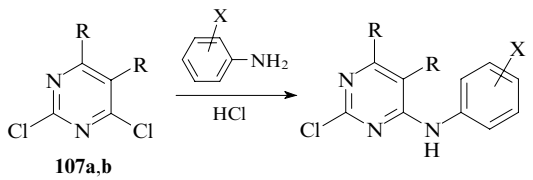
The synthesis of 2-aminopyrimidines by the replacement of the halogen atom in mono- (**106**) and dichloropyrimidine (**107**) was performed most often with the use of ammonia, primary aliphatic and aromatic amines, as well as of secondary acyclic and cyclic amines, for example:



106

This method, which was modified by the use of modern reagents (bases and catalysts), is widely used in the synthesis of biologically active arylaminopyrimidines providing a diversity of structures for the screening.

However, dichlorides **107a**,**b** are aminated by aromatic amines predominantly at position 4 rather than at position 2.[52 – 56]

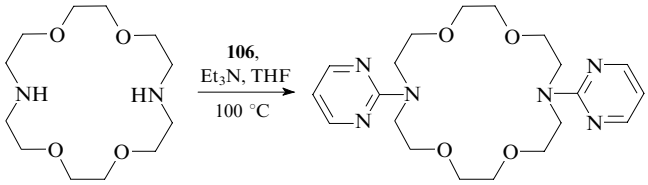


107a,**b**

R = H (**a**), Me (**b**); X = H, 4-NO_2, 2-Cl, 3-Cl, 4-Cl, 4-Br, 4-NH_2SO_2, 4-Me, 4-MeO, 4-Ac, 4-OH.

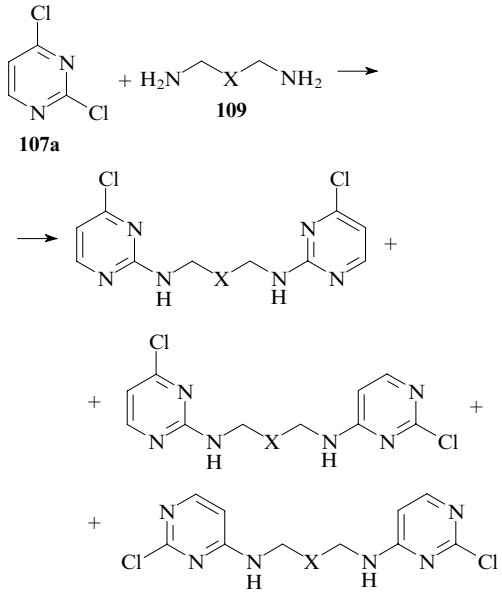
The amination of 2-chloropyrimidines is often carried out in the presence of a palladium catalyst;[53] microwave radiation and high pressure are also used for this purpose.[57 – 59] Recently, an efficient method has been developed for the synthesis of pyrimidine-substituted diazacrown ether

108 by heating 2-chloropyrimidine (**106**) with diaza-18-crown-6 at 100 °C under high pressure in the presence of triethylamine.[58]



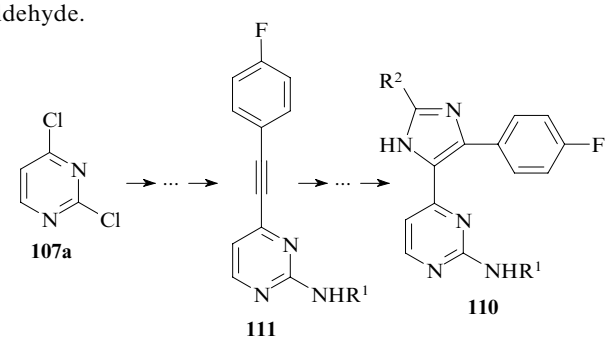
108 (100%)

The reactions of 2,4-dichloropyrimidine **107a** with di-, tri-, and tetramines **109** give mixtures of three possible diarylated derivatives.[58]



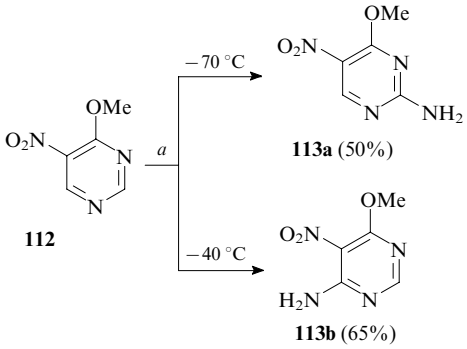
X = CH_2, $(CH_2)_2NH(CH_2)_2$, $(CH_2)_2NH(CH_2)_2NH(CH_2)_2$.

An efficient approach to the synthesis of biologically active 4-aryl-5-(2-aminopyrimidin-4-yl)imidazoles **110** starting from 2,4-dichloropyrimidine **107a** was described.[59] The successive regioselective replacement of the chlorine atoms in positions 4 and 2 lead to the formation of 2-alkylamino-4-alkynylpyrimidines **111**. Compounds **111** are oxidized to the corresponding 1,2-diketones, which are subjected to the condensation with ammonium acetate and aldehyde.



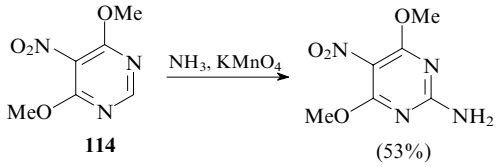
Due to the low electron density at positions 2, 4, and 6 of the pyrimidine molecule, the hydrogen atoms in these positions can be replaced by amino groups (Chichibabin amination) in the reactions with nucleophilic reagents, such as sodium or potassium amide in liquid ammonia.

The direct amination of unsubstituted pyrimidine (**1**) in the MNH_2-NH_3 system (M = K, Na) affords a complex mixture of products.[60] The amination of 4-phenylpyrimidine with the KNH_2-NH_3 system gives a mixture of 2-amino- and 6-amino-4-phenylpyrimidines. The reactions of substituted pyrimidines are performed in the presence of potassium permanganate. For example, 5-nitropyrimidine can be aminated with the NH_3-KMnO_4 mixture at low temperature; the yield of 2-amino-5-nitropyrimidine is 45%. The analogous reaction of 4-methoxy-5-nitropyrimidine **112** gives 2-amino- (**113a**) or 6-amino-4-methoxy-5-nitropyrimidine (**113b**) depending on the temperature.



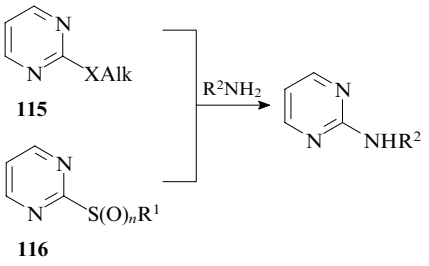
(*a*) NH_3, $KMnO_4$.

The amination of 2,4-dimethoxy-5-nitropyrimidine (**114**) affords the corresponding 2-aminopyrimidine in moderate yield.[60, 61]



The replacement of the hydrogen atom in position 2 of the pyrimidine ring by the amino group occurs by the ANRORC mechanism (addition of the nucleophile, ring opening, and ring closure), whereas the amination at position 4 occurs without the closure of the pyrimidine ring. The replacement of the chlorine atom in 2-chloro-4-phenylpyrimidine in the KNH_2-NH_3 system at −33 °C also occurs by the ANRORC mechanism.[62]

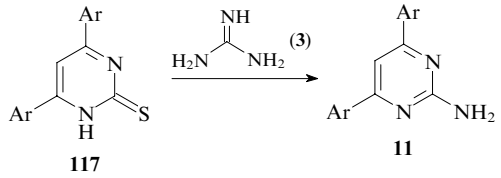
2-Alkylaminopyrimidines can be synthesized by the aminolysis (with ammonia, butyl-, pentyl-, and cyclohexylamines) of 2-alkoxy-, 2-alkylthio- (**115**), methyl(phenyl)sulfinyl-, or -sulfonylpyrimidines (**116**).



X = O, S; R^1 = Me, Ph; n = 1, 2; R^2 = Bu^n, n-C_5H_{11}, cyclo-C_6H_{11}.

Sulfoxides and sulfones proved to be slightly more reactive and alkoxy and alkylthio derivatives are much more reactive in amination reactions compared to the corresponding chloropyrimidines. However, it is reasonable

to use these compounds as the starting reagents when halogen derivatives are unavailable or unstable on storage.[63] 4,6-Diarylpyrimidine-2-thiones **117** react with guanidine to form 2-aminopyrimidines **11**.[18]



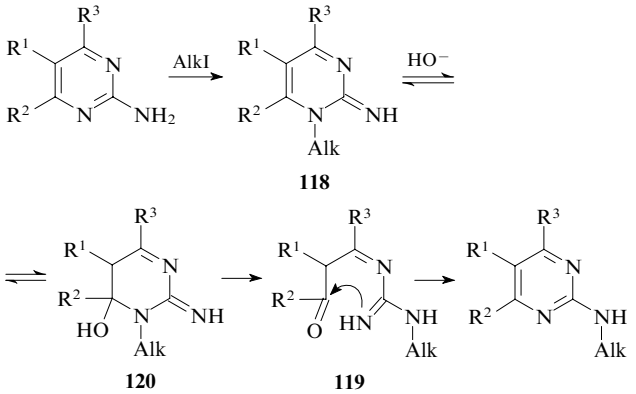
117 **11**

The method for the synthesis of aminopyrimidines substituted at the exocyclic nitrogen atom from available 2-(or 4-, 6-)-aminopyrimidines by heating salts of the starting substrates with amines did not gain acceptance because the transamination virtually does not occur at position 2 of the ring.[3] 2-R-Substituted aminopyrimidines can be synthesized by the direct alkylation of 2-aminopyrimidine after prolonged heating.

III. Chemical properties of 2-aminopyrimidine derivatives

The chemical properties of 2-aminopyrimidine derivatives are determined by the presence of the amino group, the amidine moiety, and the aromatic character of the pyrimidine ring. Formally, pyrimidine is a cyclic amidine, which is responsible for the behaviour of certain functional pyrimidine derivatives in chemical reactions. The carbon atoms in positions 2, 4, and 6 have similar reactivities, but their reactivity differs from that of the C atom in position 5.

The reaction of 2-aminopyrimidine (**1**) with alkyl halides proceeds through the intermediate formation of imine **118**, its decomposition in the presence of bases, and the recyclization (the Dimroth rearrangement). In the absence of bases, the direct alkylation of 2-aminopyrimidine by heating the reactants during a long period of time affords products in low yields. The reaction mechanism was confirmed by the isolation of oxime generated from aldehyde **119** (Alk = Me, $R^1 = R^2 = R^3 = H$), which is the product of the ring opening in compound **120**.[64]

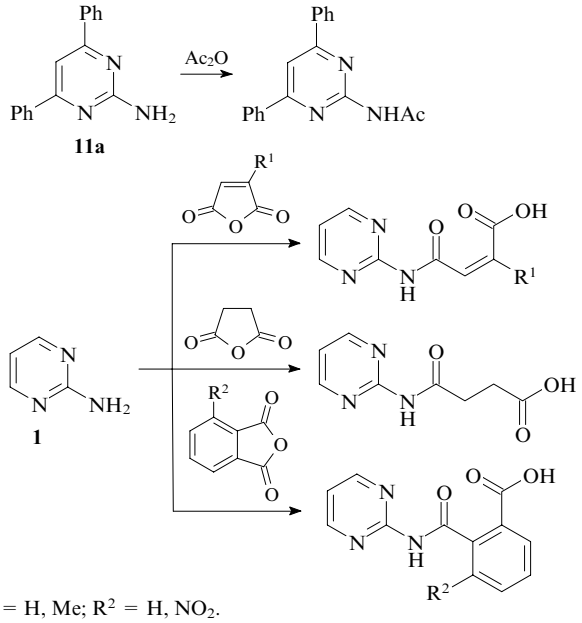


118 **120** **119**

R^1 = H, OMe, Ph, 4-$O_2NC_6H_4$, 4-$Me_2NC_6H_4$, Hal;
R^2 = H, Me, Cl; R^3 = H, Me.

The arylation of 2-aminopyrimidine with phenyllithium under reflux in toluene affords 2-amino-4-phenylpyrimidine.[62]

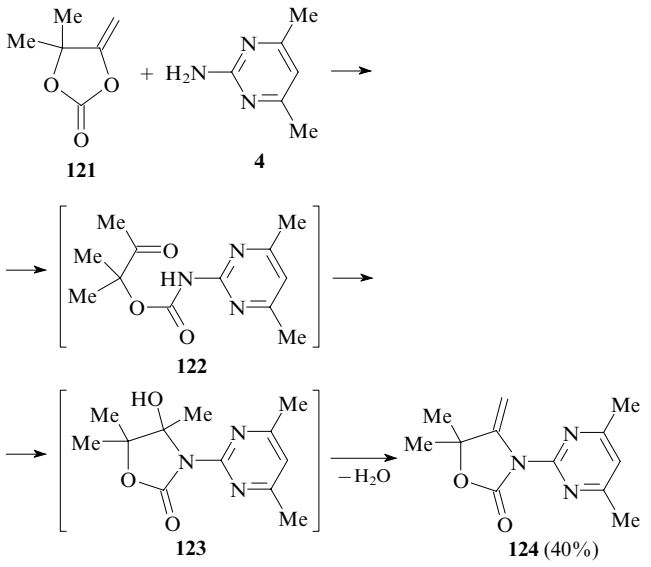
2-Amino-4,6-diphenylpyrimidine (**11a**) and 2-aminopyrimidine (**1**) are acylated at the exocyclic nitrogen atom by acetic anhydride and dicarboxylic acid (maleic, succinic, phthalic, nitrophthalic, and citraconic) anhydrides at room temperature to form the corresponding *N*-acyl derivatives.[65]



11a **1**

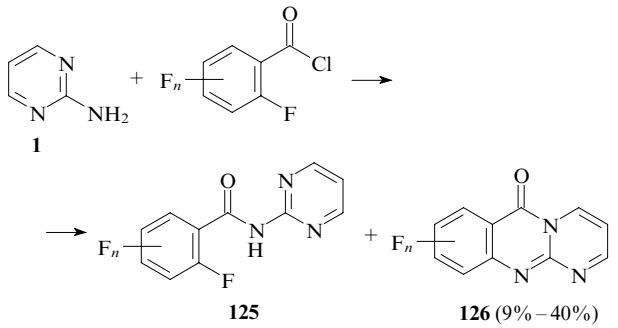
R^1 = H, Me; R^2 = H, NO_2.

2-Amino-4,6-dimethylpyrimidine (**4**) reacts with 4,4-dimethyl-5-methylidene-1,3-dioxolan-2-one (**121**) as a usual primary amine. The reaction proceeds at 150 °C for 46 h through the formation of linear carbamate **122** and cyclic hydroxyoxazolidinone **123** to give pyrimidinyloxazolidinone **124** as the final product.[66]



121 **4** **122** **123** **124** (40%)

The acylation of pyrimidines is often accompanied by the cyclization of the resulting acyl derivatives as a result of the interaction between the peripheral group and one of the nitrogen atoms of the ring. For example, 2-aminopyrimidine (**1**) reacts with fluorine-substituted benzoyl chlorides to give amides **125** along with 4(3*H*)-quinazolinones **126** as by-products.[67]

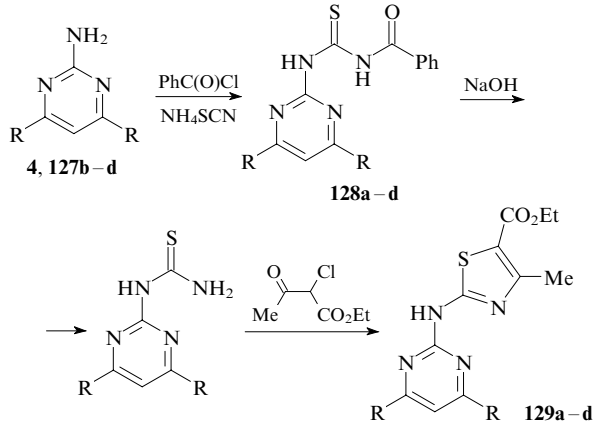


$n = 0-4$.

It should be noted that polyfluorine-substituted quinazolinones **126** feature *in vitro* a broad spectrum of activities against particular tumours.[67]

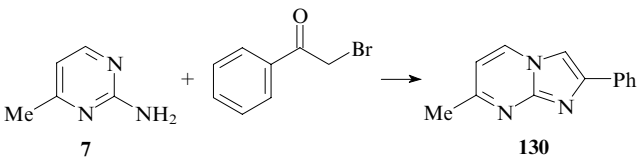
This reaction of 2-aminopyrimidines with benzoyl halides containing the halogen atom in the *ortho* position with respect to the carbonyl group is common for 2-aminoazaheterocycles (2-aminopyrimidine, 2-aminopyridine, and 2-aminothiazole) and provides an approach to the synthesis of azaheterocycles containing the bridging nitrogen atom.[67]

The treatment of 2-aminopyrimidines **4**, **127b–d** with a mixture of benzoyl chloride and ammonium thiocyanate affords *N*-benzoyl-*N*-(pyrimidin-2-yl)thioureas **128a–d**. After the debenzoylation in the presence of bases, compounds **128** undergo cyclization with α-chloroacetic ester to give pyrimidinylamino-substituted thiazole carboxylates **129a–d**.[68]



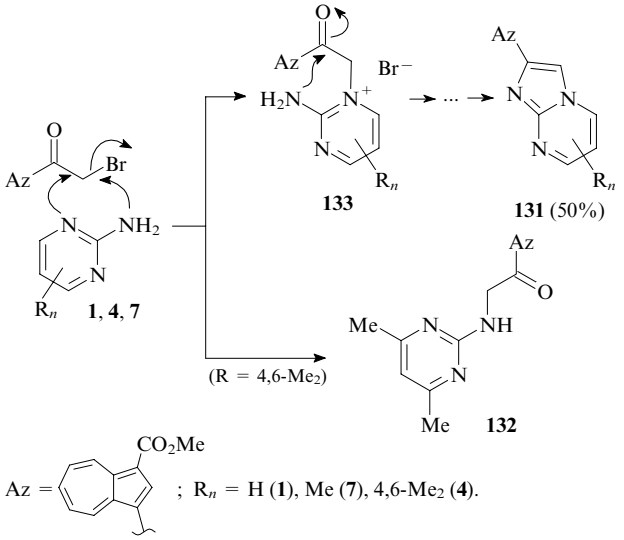
R = Me (**4**, **a**), OMe (**b**), NHEt (**c**), NHPr^i (**d**).

The reaction of 2-aminopyrimidines with phenacyl halides affords bicylic 2(het)arylimidazo[1,2-*a*]pyrimidines. This reaction was described for the first time as a method for the synthesis of 7-methyl-2-phenylarylimidazo[1,2-*a*]-pyrimidine (**130**) from 2-amino-4-methylpyrimidine (**7**) and phenacyl bromide.[69]

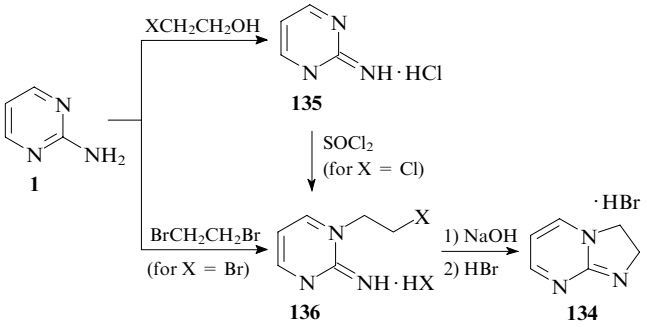


Nowadays, this reaction is widely used for the synthesis of imidazopyrimidines. Fused imidazopyrimidines with the bridging nitrogen atom are present as important structural moieties in many natural and synthetic compounds exhibiting high antiviral, antibacterial, antifungal, *etc.*, activities.[70–73]

The reactions of unsubstituted 2-aminopyrimidine (**1**) and its methyl derivatives **4** and **7** with methyl 3-(2-bromoacetyl)azulene-1-carboxylate under reflux in ethanol for 4–26 h give 3-(imidazo[1,2-*a*]pyrimidin-2-yl)azulenecarboxylates **131**.[71] In the case of 2-amino-4,6-dimethylpyrimidine (**4**), derivative **132** was also isolated. The mechanism of the formation of imidazopyrimidines **131** involves the nucleophilic attack of the cyclic nitrogen atom of pyrimidine on the bromo-substituted methylene group. The subsequent intramolecular cyclization of iminium intermediate **133** occurs due to the interaction between the amino and carbonyl groups. The yield of the reaction products decreases in the series of compounds **1** > **7** > **4** evidently due to the inhibition of the nucleophilic attack of both the cyclic nitrogen atom and the nitrogen atom of the amino group by the methyl groups.



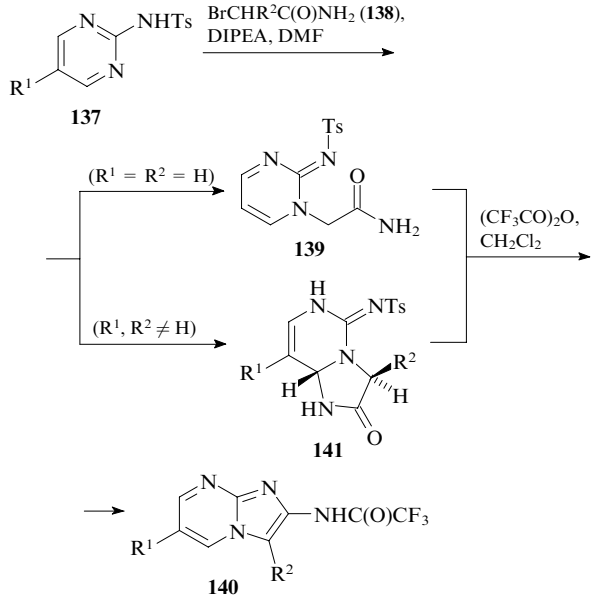
2,3-Dihydroimidazo[1,2-*a*]pyrimidine (**134**) was synthesized from 2-aminopyrimidine (**1**) according to two methods.[74] In one method, the reaction of compound **1** with ethylenechloro(bromo)hydrin gives 1-(β-hydroxyethyl)-2-imino-1,2-dihydropyrimidine **135**, whose treatment with thionyl chloride affords 1-(β-chloroethyl)-2-imino-1,2-dihydropyrimidine (**136**, X = Cl). Related compound **136** (X = Br) can be synthesized by the reaction of 2-aminopyrimidine (**1**) with 1,2-dibromoethane. The cyclization of intermediates **136** occurs in the presence of sodium hydroxide.

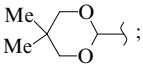


X = Cl, Br.

Recently, a new rearrangement of imidazo[1,2-*c*]pyrimidines into imidazo[1,2-*a*]pyrimidines has been found.[75] The alkylation of 2-tosylaminopyrimidine **137** (R^1 = H) by bromoacetamide **138** (R^1 = H) affords *N*-tosyliminodihydropyrimidine **139**, whose heating in trifluoroacetic anhydride

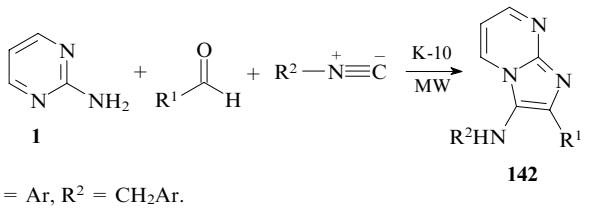
leads to the transformation into imidazo[1,2-*a*]pyrimidine **140**. However, in the presence of a substituent in position 5 of the pyrimidine ring and with the use of substituted bromoacetamides **138** ($R^2 \neq H$), the first step of the reaction affords imidazo[1,2-*c*]pyrimidine **141**. Apparently, the cyclization of tosyliminopyrimidine **139** occurs through the intramolecular Michael addition of the amino group to the α,β-unsaturated imine moiety of the ring. In this reaction, the amide group acts as the nucleophile, and the exocyclic C=N bonds serves as the electrophile. The reaction of imidazo[1,2-*c*]pyrimidines **141** with trifluoroacetic anhydride under reflux in dichlormethane in the presence of a catalytic amount of TsOH gives imidazo[1,2-*a*]pyrimidines **140** (the mechanism of the rearrangement was described in the study [75]).



R^1 = H, Br,  ; R^2 = H, Ph, 4-BrC_6H_4, 2-ClC_6H_4, 4-FC_6H_4, 2.5-$F_2C_6H_3$; Ts is *p*-toluenesulfonyl (tosyl); DIPEA is diisopropylethylamine.

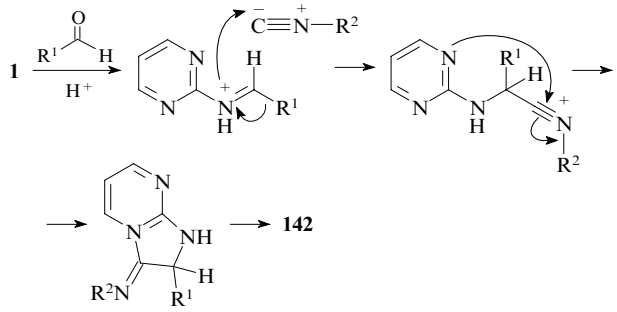
This approach to the synthesis of fused bicyclic structures based on 2-aminopyrimidine, in which the N-acylation(alkylation) product serves as the starting compound, has found wide use. An alternative approach is based on the reaction of derivatives **45** containing two reactive functional substituents, due to which they act as dielectrophiles and are involved in the cyclocondensation with guanidine to give pyrimido[4,5-*d*]pyrimidines **46**.[35] In addition, 2-aminodihydropyrimidine can serve as a dinucleophilic substrate in the condensation with dicarbonyl compounds to give pyrimido[1,2-*a*]pyrimidines, for example, dicarboxylate **61b**. The latter was synthesized from keto ester **58b** and dihydropyrimidine **60b** serving as a source of the guanidine moiety (see above).[38]

The modern methodology for the synthesis of bi- and polynuclear heterocycles containing the 2-aminopyrimidine moiety is based on the three-component condensation, where 2-aminopyrimidine serves as the amino component. Thus, the reactions of 2-aminopyrimidine (**1**) with aldehydes and isonitriles under acidic catalysis or with the use of microwave irradiation of the reactants adsorbed on montmorillonite K-10 give the dinuclear heterocycles, *viz*., 3-aminoimidazo[1,2-*a*]pyrimidines **142**.[76–78]

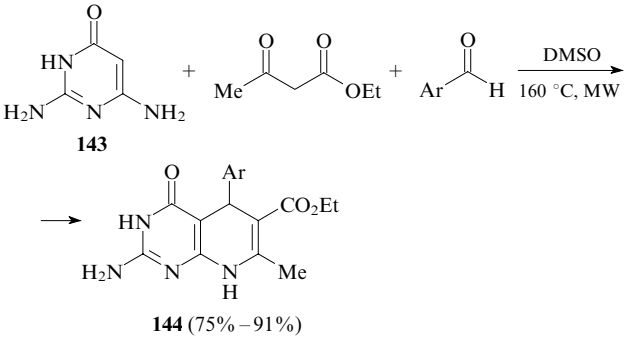


R^1 = Ar, R^2 = CH_2Ar.

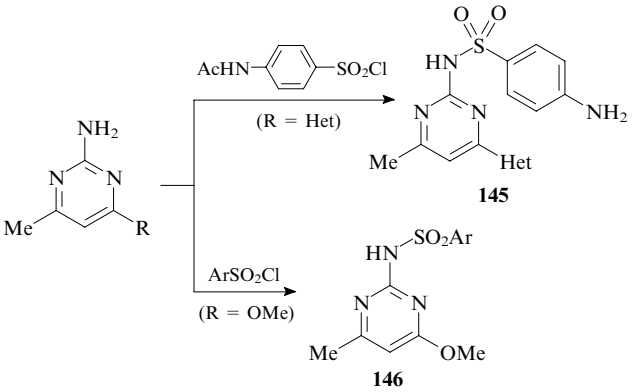
The mechanism of this reaction can be represented by the following scheme:



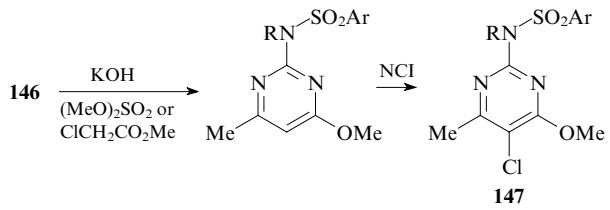
The reaction of 2,6-diaminopyrimidinone **143** with aromatic aldehydes and acetoacetic ester affords deazadihydropteridines **144**.[79]



The sulfonylation of 2-aminopyrimidines with derivatives of benzenesulfonic acids is widely used in the synthesis of sulfanilamide drugs and their biologically active analogues. The alkylation of functionalized pyrimidines **145** and **146** thus synthesized followed by the halogenation can be used for the synthesis of polysubstituted pyrimidinesulfamides, for example, of compounds **147**.[3, 80, 81]

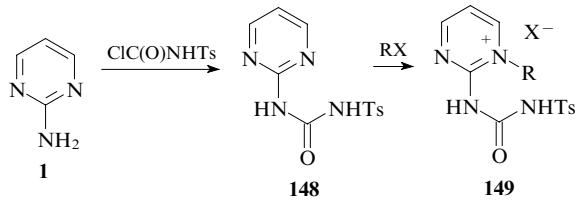


Ar = Ph, 4-MeC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4; Het = 2-Fu, 2-Th, 2-Py, 3-Py, 4-Py.



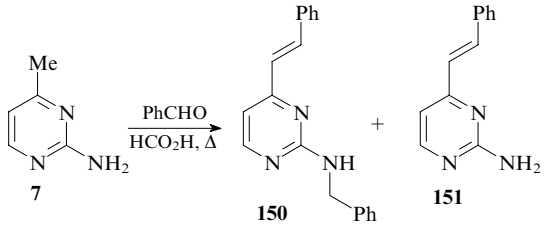
R = Me, CH_2CO_2Me; NCl is *N*-chlorosuccinimide.

The monoalkylation of 2-(*N*-tosylureido)pyrimidine **148**, which was prepared by acylation of 2-aminopyrimidine, with methyl iodide or *p*-nitrobenzyl bromide occurs at the nitrogen atom of the pyrimidine ring to form quaternary pyrimidinium salts **149**.[82]

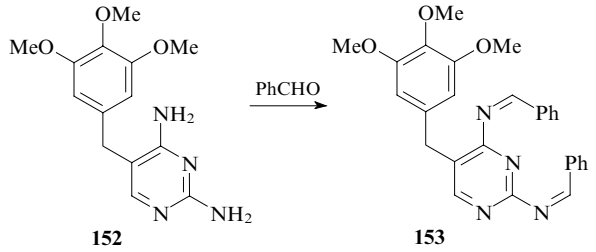


R = $CH_2C_6H_4NO_2$-4, X = Br; R = Me, X = I.

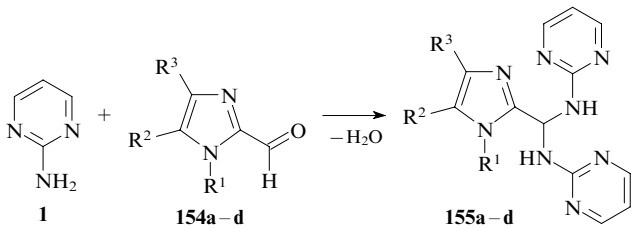
Examples of the reactions of 2-aminopyrimidines with the involvement of substituents were given in the literature. Thus, the reaction of 2-amino-4-methylpyrimidine (**7**) with benzaldehyde in boiling formic acid involves two types of processes. The direct reductive alkylation results in the transformation of the primary amino group into the secondary (benzylamino) group.[83] In addition, the methyl group, which has CH-acidity due to the effect of the nitrogen atom of pyrimidine ring, is fused to aldehyde to form 4-styrylpyrimidines **150** and **151** in a ratio of 1 : 5.[84]



2,4-Diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine (**152**) (the active substance of Trimethoprim) reacts with benzaldehyde to form bis-azomethine **153**.[85]

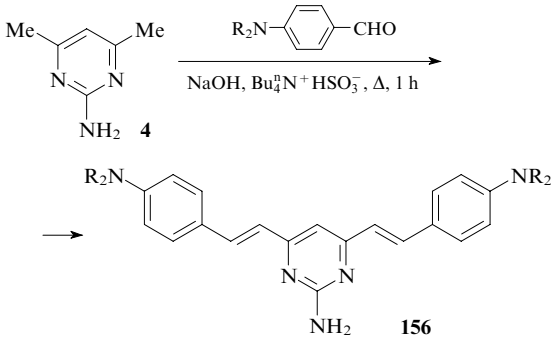


The reaction of 2-aminopyrimidine (**1**) with 2-formylimidazole derivatives **154a–d** gives heteroaldehyde aminals **155a–d**.[86]



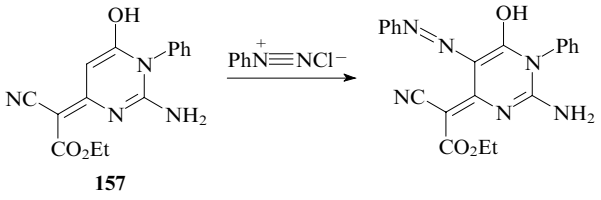
$R^2 = R^3 = H$: $R^1 = CH{=}CH_2$ (**a**), Et (**b**);
$R^2–R^3$ = benzo: $R^1 = CH{=}CH_2$ (**c**), Et (**d**).

Under phase-transfer catalysis conditions, the reaction of *p*-(*N*-dialkyl)aminobenzaldehydes with 2-amino-4,6-dimethylpyrimidine (**4**) occurs as the selective aldol condensation; in the presence of an alkali and tetrabutylammonium hydrosulfate, the reaction gives bis-styryl derivatives **156**.[87]



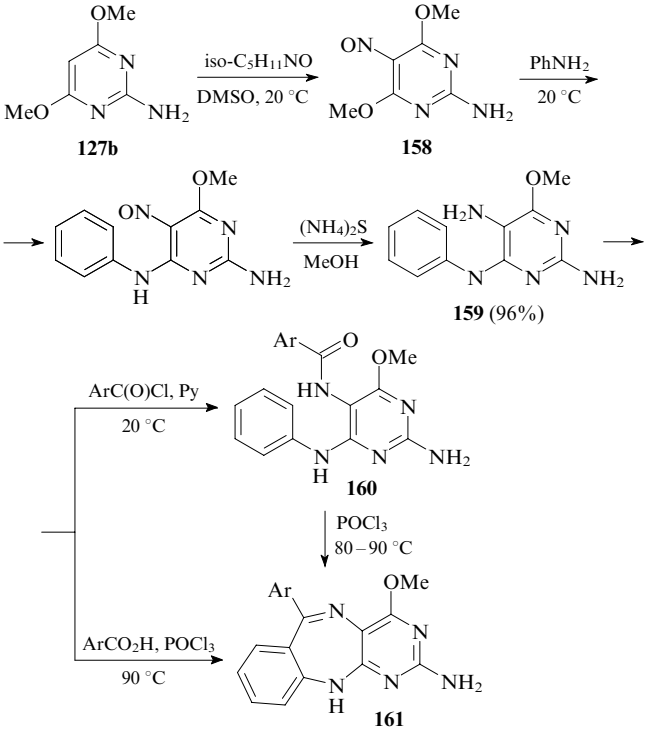
R = Alk.

The azo coupling of compound **157** with phenyldiazonium salt occurs at position 5 of the heterocycle.[48]

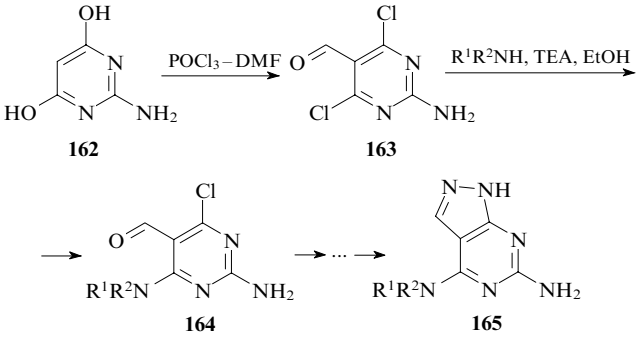


The electrophilic substitution is not typical for pyrimidines because of the presence of two electron-withdrawing nitrogen atoms in the pyrimidine ring. Data on these processes are scarce.[80, 88, 89] However, due to the presence of the amino group and activating substituents in the molecule (for example, methyl or amino groups in positions 4 and 6), the halogenation, nitration, and nitrosation at the least deactivated position 5 of pyrimidine can be performed.

The nitrosation of 2-amino-4,6-dimethoxypyrimidine **127b** with isoamyl nitrite at room temperature affords 5-nitroso derivative **158**, which is transformed into 2,5-diamino-6-anilino-4-methoxypyrimidine (**159**) by the selective aminolysis of one of the methoxy groups followed by the reduction of the nitroso group.[88] The Bischler–Napieralski cyclization of benzoyl derivative **160** or the direct cyclocondensation with arylbenzoic acids gave new representatives of arylpyrimido[4,5-*b*][1,4]benzazepines **161**. These compounds exhibit analgesic, immunostimulating, antiulcer, *etc.* activities. An analogous strategy for the synthesis of pyrimidobenzazepines is applicable to 4-chloropyrimidines.

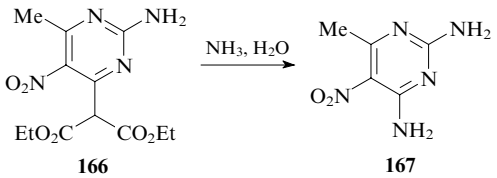


The Vilsmeier reaction of 2-amino-4,6-dihydroxypyrimidine **162** with phosphorus oxychloride and DMF involves the replacement of the hydroxy groups by chlorine atoms along with the formylation at position 5 of the pyrimidine ring to give 2-amino-4,6-dichloropyrimidine-5-carbaldehyde (**163**). The latter is a key compound in the synthesis of *N*-substituted 2,4-diamino-6-chloropyrimidine-5-carbaldehydes **164** and bicyclic pyrazolo[3,4-*d*]pyrimidines **165** related to purines.[89]



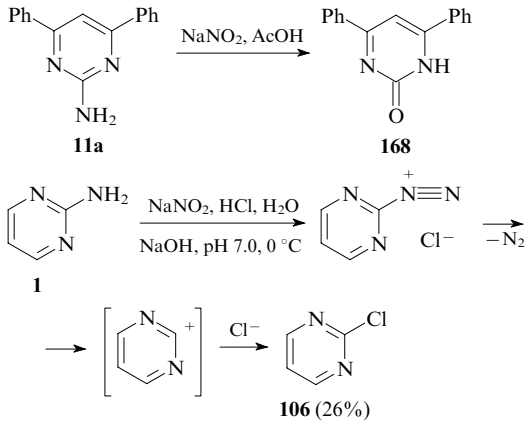
R^1, R^2 = H, Me, Et, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$;
TEA is triethylamine.

The nucleophilic substitution in 2-aminopyrimidines occurs at positions 4 and 6 of the ring in the presence of good leaving groups (halogen atoms, alkoxy, alkythiol, methylsulfo, *etc.* groups) in these positions.[53, 54, 58, 76] For example, in the case of the heating of substituted (2-aminopyrimidin-4-yl)malonic ester **166** with aqueous ammonia,

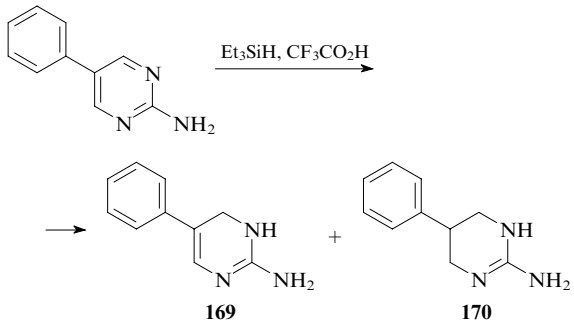


the malonate moiety is the leaving group and the substitution amination affords compound **167**.[90]

2-Amino-4,6-diphenylpyrimidine (**11a**) is oxidized by sodium nitrite in acetic acid to give 4,6-diphenylpyrimidin-2-one (**168**).[91] The reaction of 2-aminopyrimidine (**1**) with concentrated HCl and sodium nitrite proceeds through the formation of the corresponding diazonium ion, the elimination of nitrogen, and the stabilization of the carbocation to form 2-chloropyrimidine (**106**). This reaction is of practical importance for the synthesis of 2-chloropyrimidine.[92]



In spite of the fact that 2-amino-3,4-dihydro- and -3,4,5,6-tetrahydropyrimidines are often formed as stable primary products in cyclization reactions, the hydrogenation reactions of 2-aminopyrimidines deserve mention. These reactions can be used for the synthesis of compounds structurally similar to natural physiologically active substances. For example, the moiety of completely hydrogenated 2-aminopyrimidine is present in the polycyclic system of the marine hepatotoxin *Cylindrospermopsin*.[93] The reduction of 2-amino-5-phenylpyrimidine with triethylsilane in trifluoroacetic acid affords 2-aminodihydro- (**169**) and 2-aminotetrahydropyrimidines (**170**) (60%–90% yields).[94] The selectivity of the reduction is achieved by the control of the amount of the reducing agent and the temperature.



IV. Drugs based on 2-aminopyrimidine derivatives and examples of their synthesis

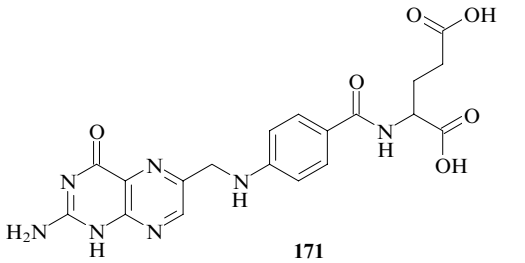
Since pyrimidines are involved in vital processes, synthetic derivatives of this heterocyclic compound can found use as drugs in medicine and veterinary medicine. Due to high and diverse biological activities of natural and synthetic 2-aminopyrimidine derivatives, these compounds can be considered as potential pharmaceuticals with a broad spectrum of therapeutic activity.

2-Aminopyrimidine (**1**) is not present in the pure state in the nature. The 2-aminopyrimidine derivative, *viz*., 4-(2-amino-2-carboxyethyl)-2-aminopyrimidine, was isolated from seeds of *Lathyrus tingitanus* in 1961 and was then synthesized according to several procedures starting from 2-amino-4-methylpyrimidine and 2-amino-4-chloromethylpyrimidine.[3]

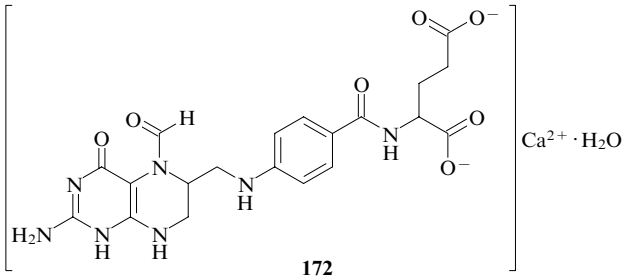
2-Amino-4-hydroxypyrimidine fused to the pyrazine ring (aminohydroxypteridine) is the main structural moiety of folic, or pteroyl-L-glutamic (*N*-{4-[(2-amino-4-oxo-1,4-dihydropteridin-6-yl)methyl]amino}benzoyl-L-(+)-glutamic), acid (**171**). This acid belongs to vitamins B; it is isolated from spinach leaves and some other plants and is used for the treatment of anemia.[95]

The physiological activity of folic acid is similar to that of folinate **172**.[96,97] Free folinic acid, or citrovorum factor, was isolated from liver.

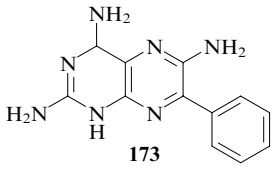
2,4,7-Triamino-6-phenylpteridine **173** (Triamterene, Triampur compositum, which is a potassium-sparing diuretic) and 4-amino-N^{10}-methylpteroylglutamic acid, or deoxy-4-amino-N^{10}-methylfolic acid, **174** (Methotrexate inhibiting the growth of malignant neoplasms)[96,97] are the most well-known synthetic drugs, analogues of folic acid.



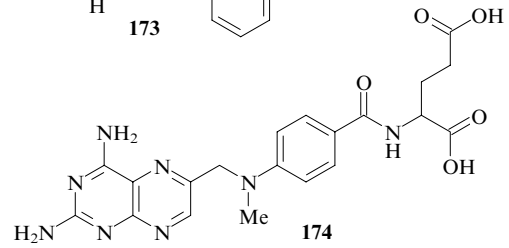
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172

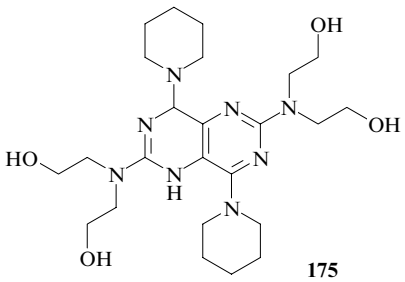


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174

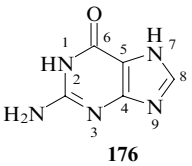
These bicyclic compounds belong to pteridines containing the pyrimidino[4,5-*b*]pyrazine (tetraazanaphthalene) system as the structural base. The isomeric tetraazanaphthalene moiety is present in compound **175**, which is the well-known antithrombotic vasodilator Dipyridamole (Kurantil).[98]



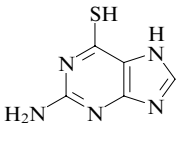
175

Pharmaceuticals of this series can be prepared using the methodology for the synthesis of pteridines, pyrimidines, and pyrazines. In particular, the tetraazanaphthalene skeleton of pyrimido[4,5-*d*]pyrimidines **46** can be constructed in good yield by the condensation of functionalized 2-aminopyrimidines **45** with guanidine (see above).[35]

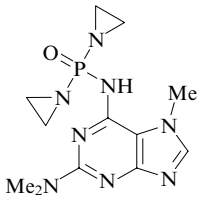
Another group of pharmaceuticals with a bicyclic structure containing the 2-amino-6-hydroxypyrimidine (isocytosine) moiety fused to the imidazole ring belongs to purines, *viz*., guanine analogues [2-amino-6-hydroxypurine (**176**)] involved in DNA and RNA.[95]



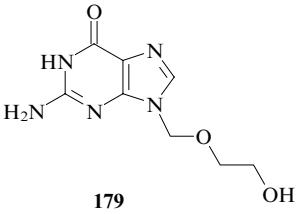
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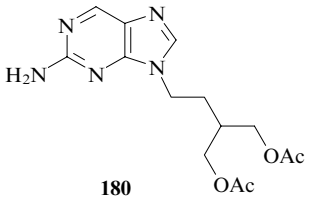
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179



180

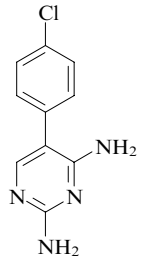
Thioguanine (2-amino-6-mercaptopurine) (**177**) and Phopurinum (2-dimethylamino-6-diethyleneiminophosphamido-7-methylpurine) (**178**) are used for the treatment of chronic myelogenous leukemia, exhibit cytostatic activity, and inhibit the growth in proliferating tissues.[96,97]

Acyclovir [Zovirax, Virolex, 9-(2-hydroxy)ethoxymethylguanine (**179**)] and its analogues Gancyclovir (sodium salt of 9-(1,3-dihydroxy-2-propoxy)guanine) and Famcyclovir {2-[2-(2-amino-9*H*-purin-9-yl)ethyl]propane-1,1-diol diacetate (**180**)} are the well-known antiviral agents particularly effective against herpes simplex and herpes zoster viruses.[96,97] Acyclovir is the analogue of the purine nucleoside deoxyguanidine, which is a component of DNA. Due to the structural similarity of Acyclovir and deoxyguanidine, the former can interact with virus enzymes, resulting in the inhibition of viral replication.

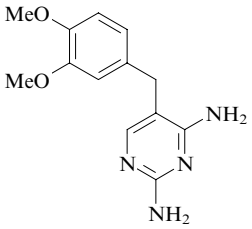
At least three compounds of the aminopyrimidine series are currently widely used as antimicrobial agents: 2,4-diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine (Pyrimethamine, Daraprim, Chloridine; **181**), 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine (Trimethoprim, **152**), and 2,4-diamino-5-(3,4-dimethoxybenzyl)pyrimidine (Diaveridine, **182**).[99] Daraprim (**181**) is the powerful dihydrofolate reductase inhibitor, exhibits the antiprotozoic activity, and, in particular doses, is useful as the prophylactic agent against

the malaria parasites *Plasmodium falciparum* and *P. vivax*.[96,97]

Trimethoprim (**152**) was initially considered as the antimalarial drug. More recently, it appeared that this substance is highly effective against bacterial infections, particularly, in a synergistic combination with the antibacterial agent 5-methyl-3-sulfanylamidoisoxazole (Sulfamethoxazole). This drug is manufactured by different pharmaceutical companies under the names Bactrim, Septrin, Biseptol, Oriprim, *etc*.[96,97]



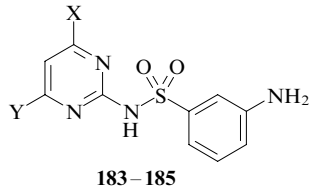
181



182

The success of Trimethoprim (**152**) as the antibacterial agent has stimulated extensive investigations on the optimization of the methods for the synthesis of its analogues, some of which exhibit antimicrobial activity.[55] The closest analogue of Trimethoprim, Diaveridine (**182**), proved to be the effective synergist of sulfonamides against infections in birds caused by coccidia (microscopic parasites).

Of ~5000 sulfonamides, which were synthesized and tested for antibacterial activity, more than a dozen of sulfanylamidopyrimidines were implemented into the clinical practice. Most of these compounds are not currently used because antibiotics are more easily available. 2-Sulfonylamidopyrimidine (**183**) (Sulfadiazine, Sulfazine) is the only pyrimidine, which is still used almost all through the world for the treatment of infections caused by hemolytic streptococcus, pneumococcus, and colibacillus. Mixtures containing this compound, as well as 4-methyl-2-sulfonylamidopyrimidine (**184**) (Sulfamerazine) and 4,6-dimethyl-2-sulfonylamidopyrimidine (**185**) (Sulfamethazine), are also employed. Due to high solubility of acetylated metabolites of these pharmaceuticals in urine, the degree of precipitation of the pharmaceuticals in organs and tissues and the risk of kidney obstruction were minimized.[96,97]



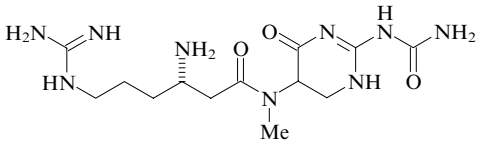
183–185

X = Y = H (**183**); X = Me: Y = H (**184**), Me (**185**).

General approaches to the synthesis of sulfonylamidopyrimidines are based on the condensation of β-dicarbonyl compounds with *p*-aminobenzenesulfoguanidine or the acylation of 2-aminopyrimidine with *p*-acetamidobenzenesulfonyl chloride followed by the deacetylation.[3,7,80,81]

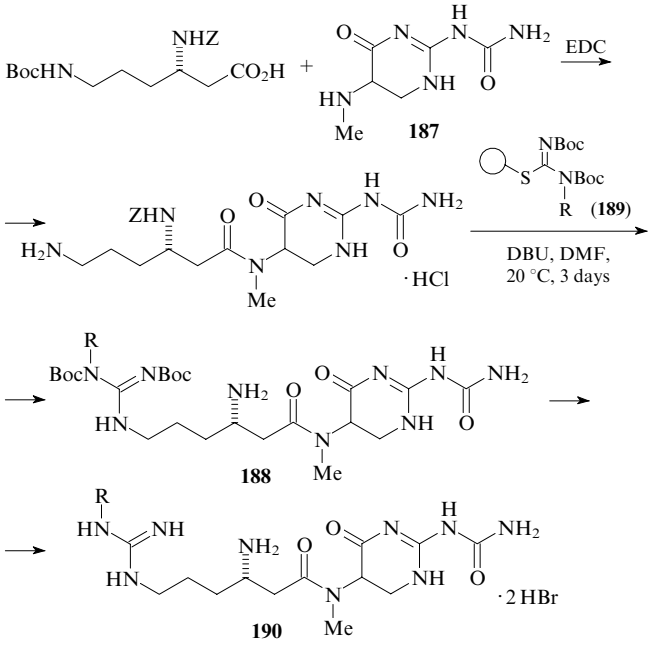
Vasodilators and potassium-channel modulators were found among 2-aminopyrimidine derivatives. Thus, 2,6-diamino-6-piperidinopyrimidine 3-oxide (Minoxidil) is the vasodilator for resistant hypertension, reduces arterial hypertension, and is the potassium channel agonist in vessel smooth muscles.[96,97] Nowadays, this medicine attracts attention as the agent promoting the hair growth. *N*-Tosylcarbamide derivatives of 2-pyrimidinium **149** acting as potassium channel inhibitors were synthesized to correct potassium ion currents in cells for the treatment of heart failure.[82]

The dipeptide antibiotic TAN-1057 A,B (**186**) is the natural substance isolated from a filtrate of gram-negative marine bacteria *Flexibacter sp*. PK-74 (the known fish pathogen). Its structure was determined in 1993.[100]



186

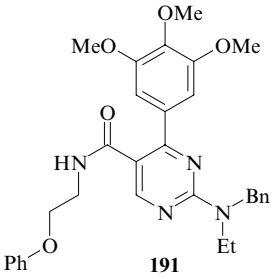
More recently, compound **186** was synthesized from 5-methylaminodihydropyrimidin-4-one **187**.[101] This antibiotic shows high efficacy *in vivo* and *in vitro* against staphylococcus infections but it is highly toxic (LD_{50} = 50 mg kg^{-1}), which limits its use in the therapy. For this reason, the strategy was developed for the synthesis of analogues of TAN-1057 A,B (**186**) containing the modified arginine side chain and different substituents in the guanidine moiety. The convergent synthesis of amine **188** involves the amidation of dihydropyrimidinone **187** with Boc-protected lysine as the key step. The guanidine moiety is introduced by the solid-phase method with the use of immobilized substituted isothioureas **189**. After the deprotection of derivatives **188**, target compounds **190** were obtained in 20% – 32% yields.[101]



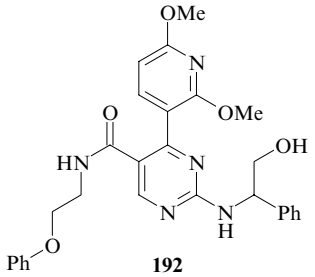
187 **188** **190** **(189)**

R = Ph, 2-Py, $AcOCH_2CH_2$, $MeOCH_2CH_2$, $BocHNCH_2CH_2$, cyclo-C_3H_5; Boc is *tert*-butyloxycarbonyl, Z is benzyloxycarbonyl, EDC is *N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide, DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene.

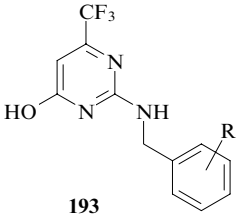
In recent years, numerous 2-aminopyrimidine derivatives have been synthesized and tested as various receptor antagonists. Thus, 2,4,5-trisubstituted 2-aminopyrimidines **191** and **192** proved to be selective calcium-sensitive receptor antagonists (CaSR),[102] 2-(*N*-benzylamino)-6-trifluoromethylpyrimidines **193** act as antigen-binding receptor antagonists,[103] 4-[2-amino-6-(4-methylpiperazin-1-yl)pyrimidin-4-yl]benzonitrile (**194a**), 2-amino-4-*tert*-butyl-6-(4-methylpiperazin-1-yl)pyrimidine (**194b**), and tricyclic aminopyrimidine **195** are histamine receptor H_4 antagonists,[104] hetaryl-substituted bipyrimidineamine (LAS 38069) **196** has properties of adenosine receptor A_{2B} antagonist,[105] [(2,4-dichlorophenyl)amino]pyrimidine-5-carboxamide **197** is cannabinoid CB_2[106] and histamine receptor antagonist,[107] and polyazaheterocycle **198** exhibits properties of adenosine receptor A_3 antagonist.[108–110]



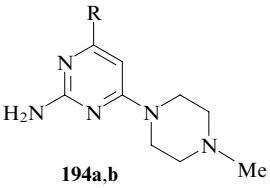
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192

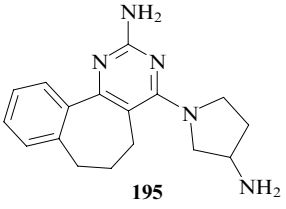


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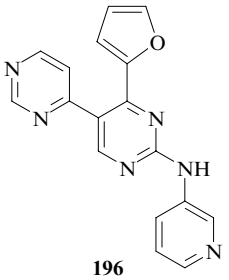


194a,**b**

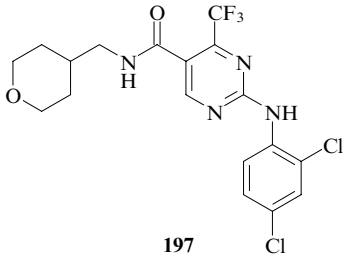
R = 4-NCC$_6$H$_4$ (**a**), Bu^t (**b**).



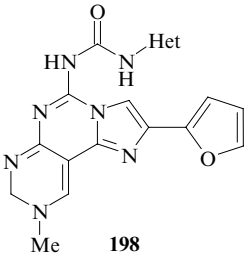
195



196



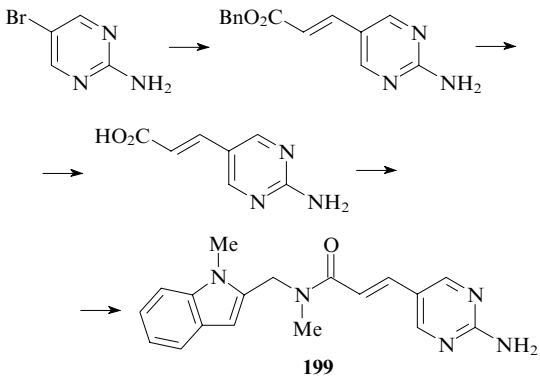
197



198

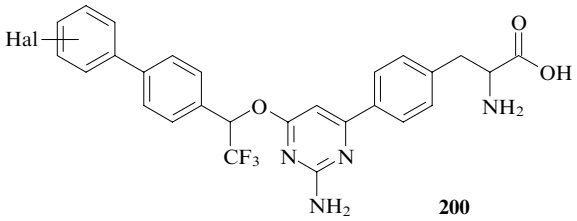
Het = 2(3,4)-Py, 2(3)-Fu, 2(3)-Th, 4-Qui (Qui is quinolyl).

Among aminopyrimidine derivatives, 3-(2-aminopyrimidin-5-yl)-*N*-methyl-*N*-(1-methylindol-2-ylmethyl)acrylamide (**199**) was found to be the synthetic inhibitor of bacterial acetyl-carrier protein (ACP) reductase involved in the bacterial fatty acid biosynthesis. This compound was synthesized in several steps starting from 2-amino-5-bromopyrimidine.[111]



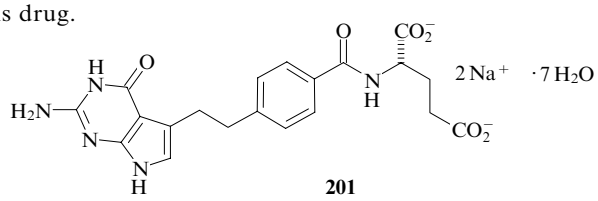
199

Recently, new potent tryptophan hydroxylase inhibitors, *viz*., 4,6-disubstituted 2-aminopyrimidines **200**, have been synthesized.[112]



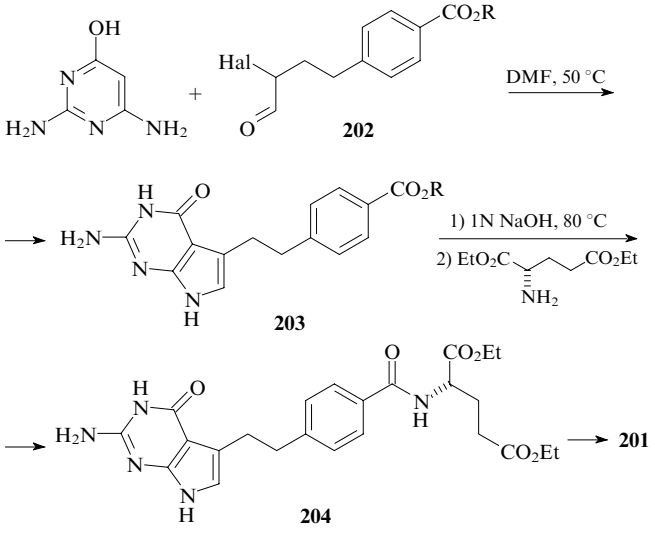
200

Compounds exhibiting antifolate activity are effective antitumour agents. Pemetrexed (Alimta manufactured by EliLilly) is the modern antifolate agent against different types of tumours. The salt of pyrrolo[2,3-*d*]pyrimidine-substituted L-glutamic acid **201** is the active component of this drug.



201

The synthesis of compound **201** involves the condensation of 2,4-diamino-6-hydroxypyrimidine with benzoic acid derivatives **202**, the aminolysis of pyrrolopyrimidine **203** with L-glutamic acid ester, and the saponification of the product.[113,114]



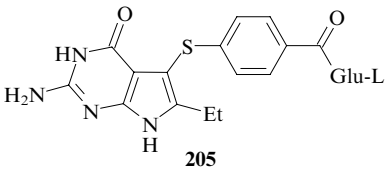
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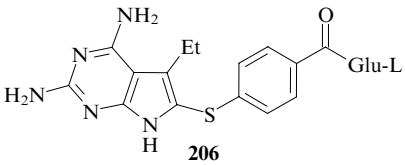
204

R = H, Me.

Pyrrolopyrimidines **205** and **206**, which are analogues of Pemetrexed (**201**), act as dihydrofolate reductase (DHFR) inhibitors.[115, 116]

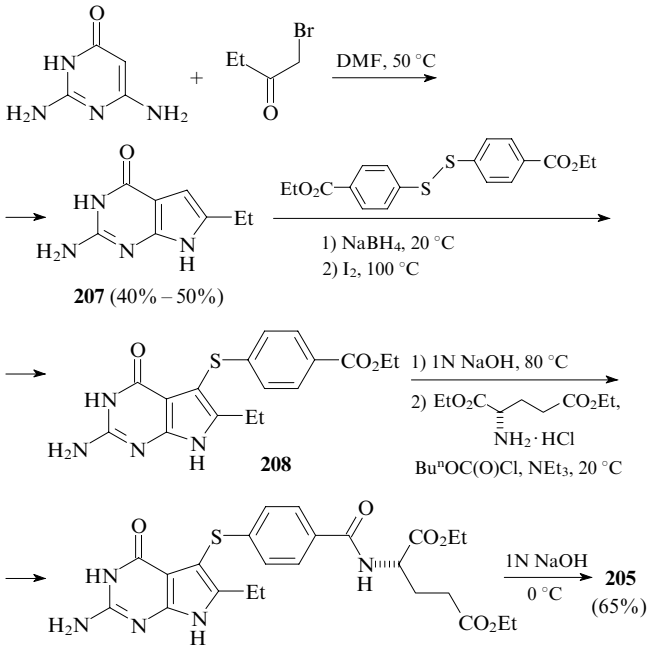


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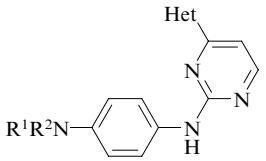


206

Compound **205** was synthesized from 2-aminopyrrolopyrimidine **207**, which was prepared by the cyclization of 2,4-diamino-6-hydroxypyrimidine and 1-bromobutan-2-one. The oxidative addition of diethyl 2,2′-dithiodibenzoate to compound **207** affords compound **208**. The ester function was transformed into the amide group by the mixed anhydride method based on the reaction with L-glutamic acid diethyl ester in the presence of isobutyl chloroformate and triethylamine.

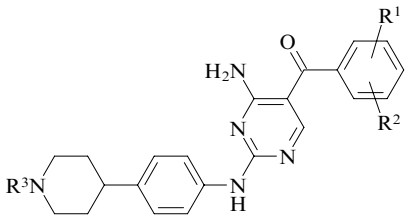


In recent years, the synthesis of 2-aminopyrimidines has attracted increasing interest because specific kinase inhibitors were found in this series of compounds. Basic research on the pharmacological activity of 2-aminopyrimidine derivatives gave rise to a new direction of the design of antitumour agents based on synthetic tyrosine kinase blockers of growth factor receptors. Starting from 1990s, dozens of 2-arylaminopyrimidine derivatives, *viz*., compounds **209** and **210** and their analogues, were tested as potent kinase inhibitors for antitumour activity, and a new class of agents blocking pathogenic mechanisms of tumour growth was found.[30, 117]



209

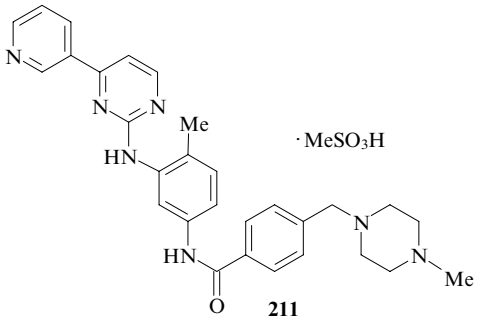
R^1, R^2 = H, Me, Et, Ac, CF_3, *etc.*



210

R^1, R^2 = Hal, OAlk, $NAlk_2$; R^3 = Alk.

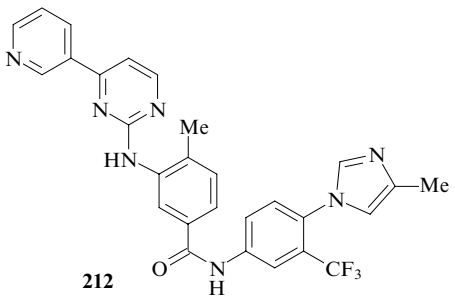
In 1995, first results of investigation on the activity of compound **211** as the active component of the drug Glivec designed by Novartis were presented at the Annual Meeting of the American Society of Hematology.



211

After this report, Glivec has attracted rapidly increasing interest. The efficacy of Glivec against Ph-positive (Ph is the Philadelphia chromosome) leukemia was so impressive that the agent was quickly approved in the USA as the drug. The clinical practice confirmed that Glivec outperforms all other pharmaceuticals used for the drug therapy of chronic myelogenous leukemia (CML). Glivec, which was initially discovered as the Abl-tyrosine kinase inhibitor, proved to be the effective blocker of at least two other types of tyrosine kinase receptors (c-kit and PDGF-R). This is why Glivec is effective in the treatment of gastrointestinal stromal tumours, prostate cancer, and high differential glioma.

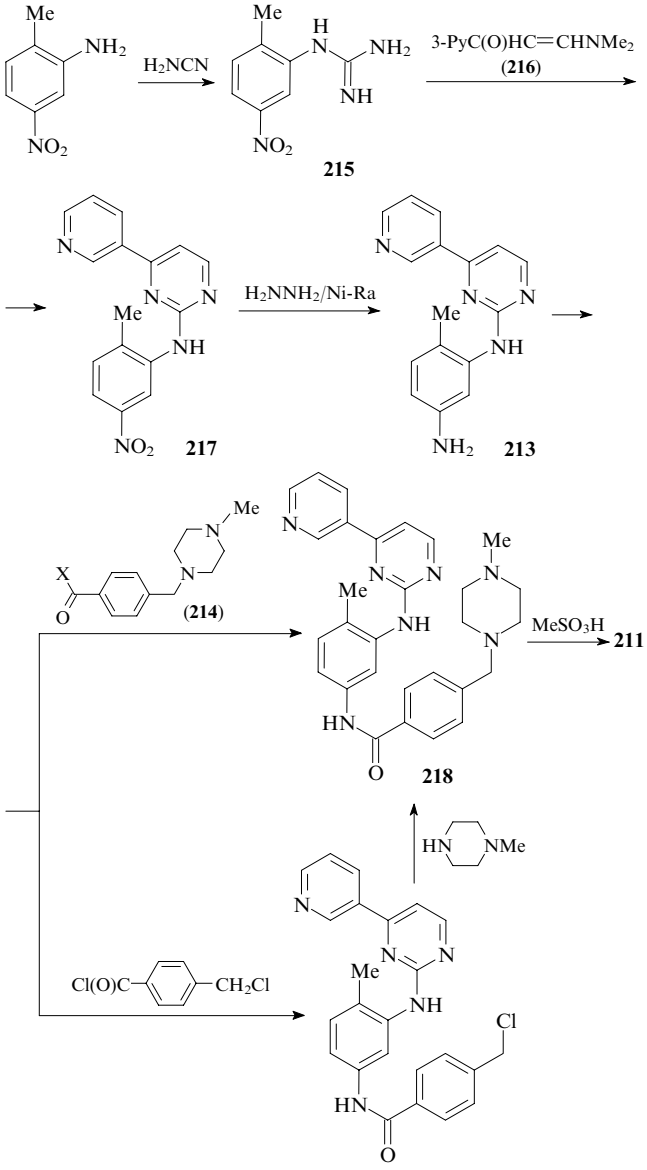
However, patients taking Glivec for several years develop resistance to this drug. This forces pharmaceutical companies to spend heavily on the design of Glivec analogues. Thus, Glivec analogues were already synthesized, among which is Nilotinib **212** (Novartis Tasigna) capable of increasing the efficacy of prolonged therapy for CML.



212

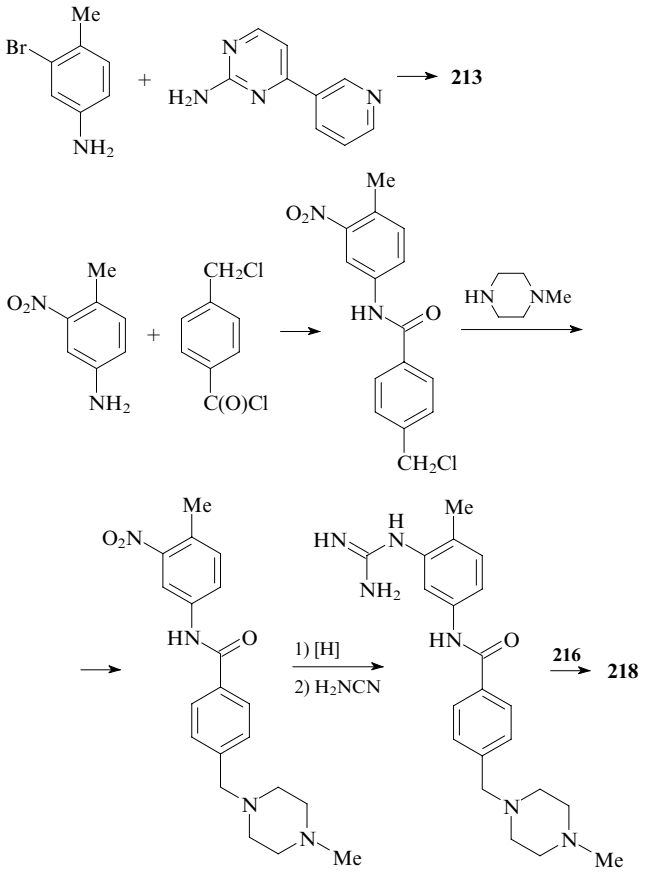
The scheme for the synthesis of the active component of Glivec, *viz*., compound **211**, is the multistep convergent synthesis (Scheme 6). 2-Aminopyrimidine **213** and 4-(4-methylpiperazin-1-ylmethyl)benzoic acid derivative **214** are the key starting compounds. The synthesis of compound **213** involves the reaction of 2-methyl-5-nitroaniline with cyanamide followed by the condensation of derivative **215** with unsaturated ketone **216** and the reduction of the nitro group in intermediate **217**. Aminopyrimidine **213** is acylated with acid or acid chloride (**214**, X = Cl) to prepare the basic form, *viz*., compound **218** (Imatinib).[118–120] Another pathway involves the acylation of aminopyrimidine **213** with 4-(chloromethyl)benzoyl chloride followed by the reaction of the resulting chloride with 1-methylpiperazine and other amines giving not only target product **218** but also its analogues (see Scheme 6).[121,122]

Scheme 6

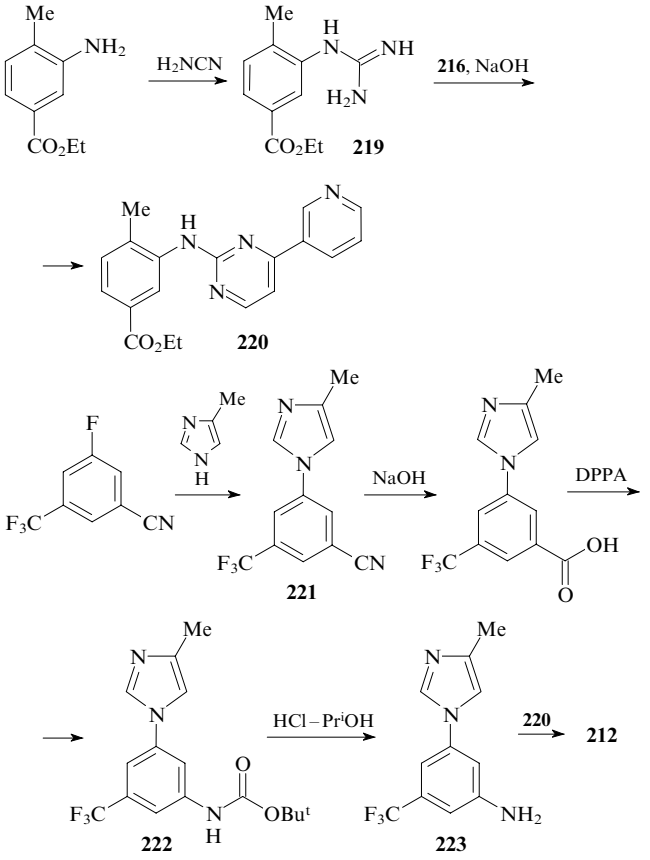


X = Cl, HO.

An alternative approach to the synthesis of compound **211** is based on the successive addition of aromatic and heterocyclic fragments to bromo- or nitrotoluidines.[123,124]



Scheme 7



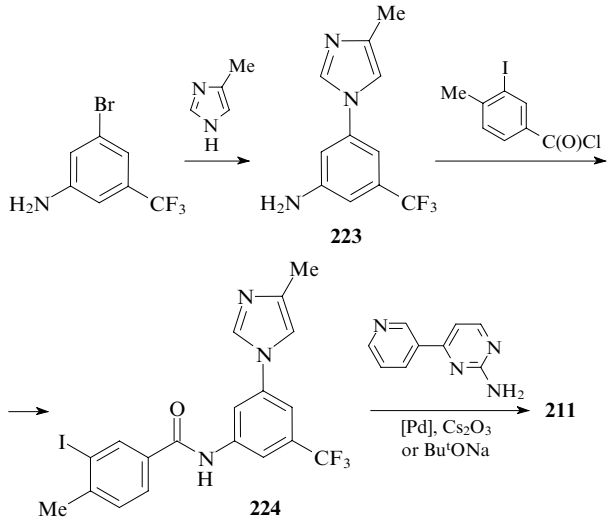
DPPA is diphenylphosphoryl azide.

Other functionalized 2-aminopyrimidine derivatives can also be used as key compounds in the synthesis of Glivec analogues (see, for example, the study [125]).

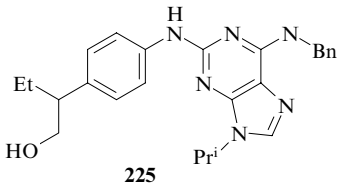
Two alternative procedures were developed for the synthesis of Nilotinib (**212**).[32, 126] The eight-step scheme (Scheme 7) covered by the Novartis patent involves the condensation of guanidine **219** with compound **216** giving 2-aminopyrimidine **220** followed by the reaction of 4-methylimidazole with 3-fluoro-5-trifluoromethylbenzonitrile and the transformation of the nitrile function in compound **221** into the amino group through the formation of protected carbamate **222**. In the final step, the amide bond is formed between compounds **223** and **220** to give target product **212**.[126]

The four-step scheme of the synthesis of Nilotinib (Scheme 8) has been described recently in the study.[32] 4-Methylimidazole is arylated with 3-bromo-5-trifluoromethylaniline, and reaction product **223** is acylated with 3-iodo-4-methylbenzoyl chloride followed by the reaction of the resulting amide **224** with 2-amino-4-(3-pyridyl)pyrimidine (heating in a dioxane – butanol mixture at 100 °C in the presence of catalysts).

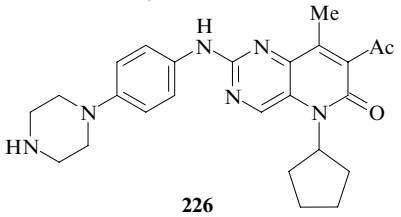
Scheme 8



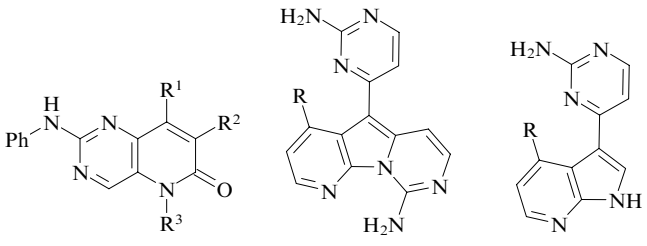
Certain 2-aminopyrimidines are effective inhibitors of cyclin-dependent kinases (CDK), which are key regulators of the cell cycle, such as Roscovitin (CYC202, **225**) and PD0332991 (**226**).[127, 128] These compounds are currently under clinical testing. 2-Anilino-8*H*-pyrido[2,3-*d*]pyrimidin-7-ones **227**,[129] variolin (**228**) isolated from marine organisms, and its structural synthetic analogue meriolin (**229**) [130, 131] exhibit similar inhibitory activity.



225



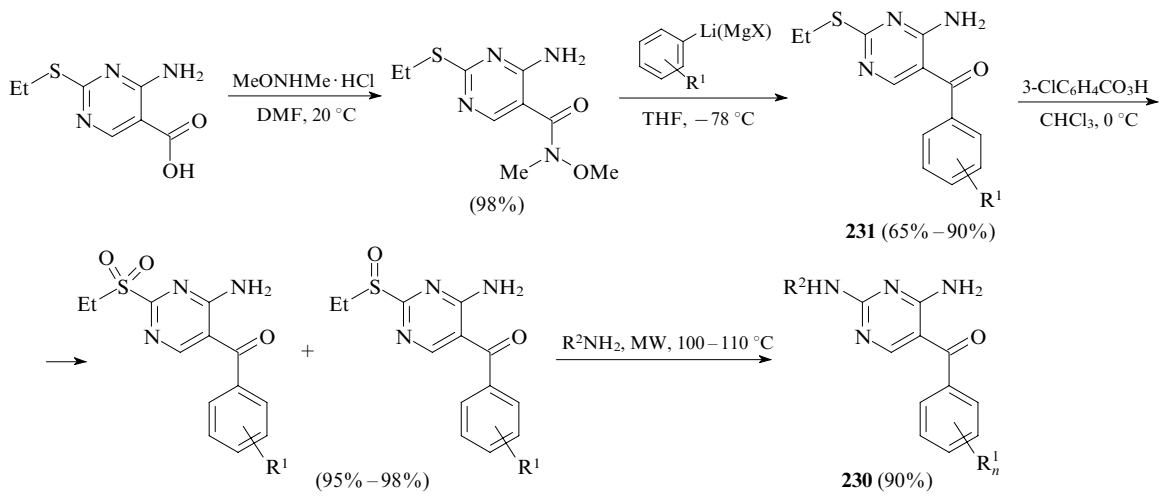
226



R = H, Alk, OH.

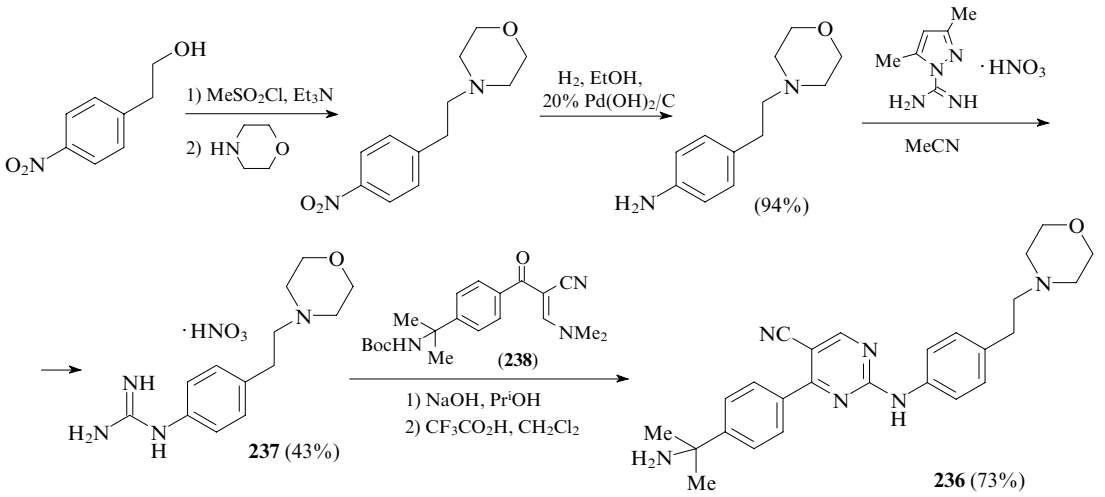
Biologically active 2,4-diamino-5-benzoylpyrimidines **230** were synthesized starting from 4-amino-2-ethylsulfanylpyrimidine-5-carboxylic acid (Scheme 9).[132] The amidation of the starting sulfanylpyrimidine with *N*,*O*-dimethylhydroxylamine followed by the treatment with the corresponding lithium derivative or Grignard reagents gave ketone **231**. After the oxidation of the sulfanyl substituent in compound **231** by *m*-chloroperoxybenzoic acid, the sulfonic or sulfoxide group was replaced by the amino group. Among the compounds thus synthesized, derivative **230** (R^1_n = 2-OMe-5,6-F_2, R^2 is *N*-methylsulfanylpiperidin-4-yl) has the highest activity and it is the potent selective

Scheme 9



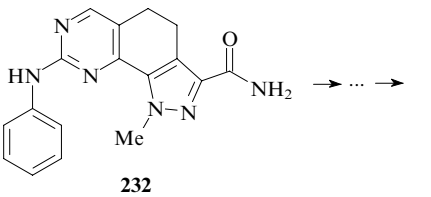
R^1_n = H, Hal, Hal_2, OAlk, *etc.*; R^2 = Alk.

Scheme 10

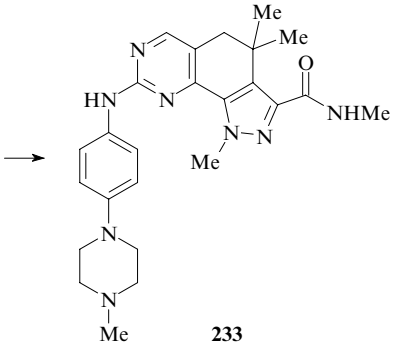


inhibitor of cyclin-dependent kinases. This compound inhibited the tumour cell growth in *in vivo* experiments.[132]

4,5-Dihydro-1*H*-pyrazolo[4,3-*h*]quinazoline-3-carboxamide **233** (PHA-848125) was synthesized starting from tricyclic compound **232**, which is the active but nonselective CDK inhibitor. In preclinical tests, compound **233** exhibited activity on an ovarian carcinoma model and is currently under clinical testing as the new antitumour agent.[133]

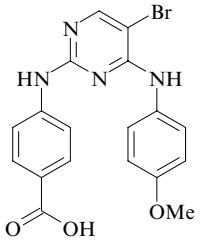


232

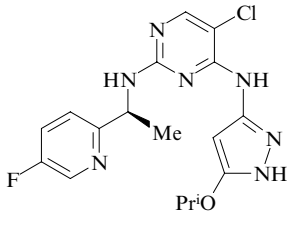


233

More than a hundred of synthetic 2,4-diaminopyrimidine derivatives **234** and **235** from the Astra Zeneca collection were screened to found effective inhibitors of cyclin-dependent kinases Chk-1 and Trk.[134, 135]



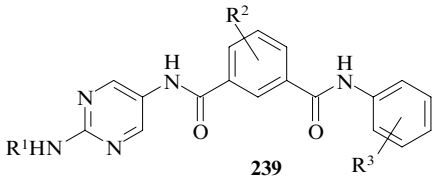
234



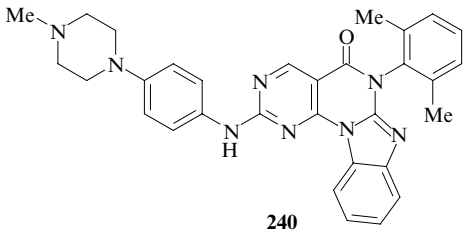
235

2-Arylaminopyrimidine-5-carbonitrile **236** (JNS-17029259), the inhibitor of tyrosine kinase VEGFR2, was synthesized by the condensation of guanidine **237** with enamino keto nitrile **238** by heating in propan-2-ol in the presence of sodium hydroxide (Scheme 10).[136]

New synthetic 2-aminopyrimidine amide derivatives, *viz*., compounds **239**–**241**, were studied *in vivo* as inhibitors of lymphocyte-specific kinase Lcl of the cytoplasmic tyrosine kinase family Src.[137–139]

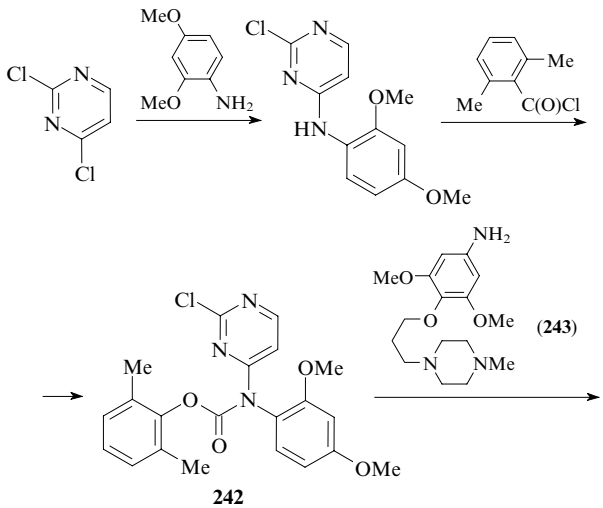


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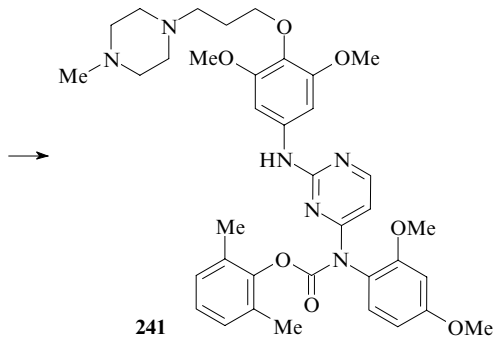


240

Compound **241** was synthesized by the nucleophilic substitution of the chlorine atom in derivative **242** with arylamine **243**. In turn, pyrimidine **242** was synthesized by the alkylation of 2,4-dimethoxyaniline with 2,4-dichloro-



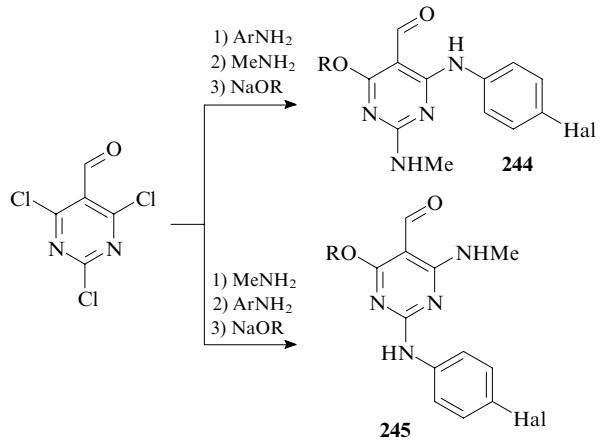
242



241

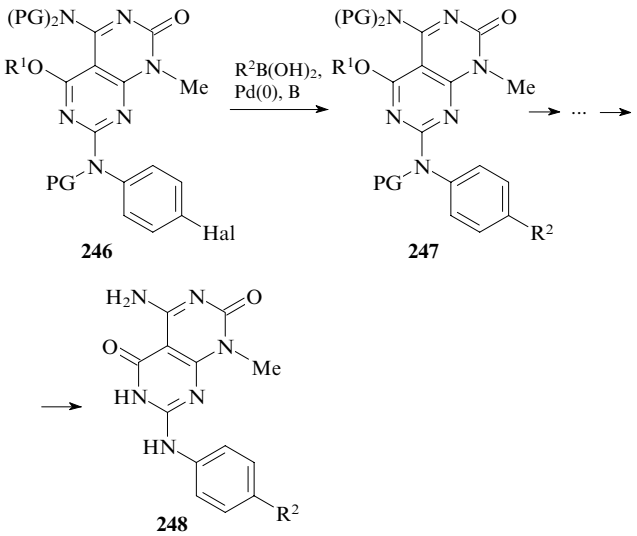
pyrimidine followed by the acylation of the corresponding intermediate with 2,6-dimethylbenzoyl chloride.[139]

A method was developed for the regioselective synthesis of trisubstituted 2(or 6)-arylaminopyrimidine-5-carbaldehydes **244** and **245** starting from 2,4,6-trichloropyrimidine-5-carbaldehyde. The nucleophilic substitution of the chlorine atom by the aniline or methylamine residue was carried out both under conventional conditions and under phase-transfer catalysis conditions.



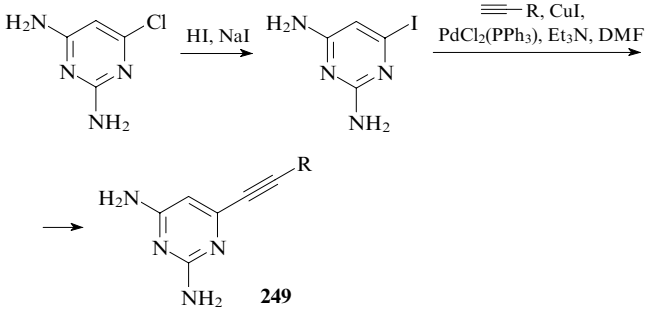
R = Me, Et; Ar = C_6H_4Hal-4.

Compounds **246** and **247**, which are structural precursors of guanine cytosine base pair **248**, were synthesized based on functionalized 2-arylaminopyrimidine-5-carbaldehyde derivatives **245**.[140]



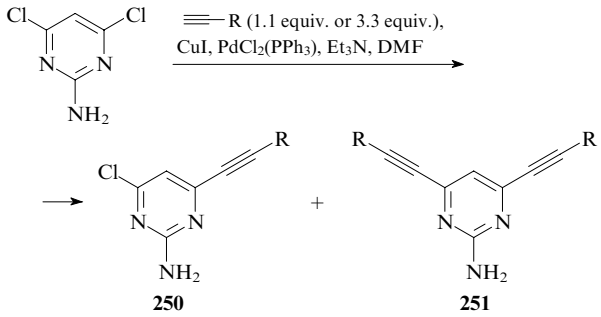
B is a base, PG is a protecting group.

6-Alkynyl-2,4-diaminopyrimidine derivatives **249** containing different substituents in the alkynyl moiety were synthesized by the Sonogashira cross-coupling reaction from 2,4-diamino-6-iodopyrimidine.



R = H, Ph, Bu^n, $SiMe_3$, CH_2OH, CH(Ph)OH, CH(Me)OH, $(CH_2)_2OH$.

This reaction with the use of 2-amino-4,6-dichloropyrimidine and 1 equiv. of alkyne affords 6-alkynyl-2-amino-4-chloropyrimidine **250** as the major product. The reaction with the use of 3 equiv. of alkyne gives, in addition, 4,6-bis(alkynyl)-2-aminopyrimidine **251**.[141] The subsequent oxidation of alkynylpyrimidines **250** and **251** to the corresponding 1,2-diketones provides a route to a wide range of hetarylpyrimidines.[59, 141]

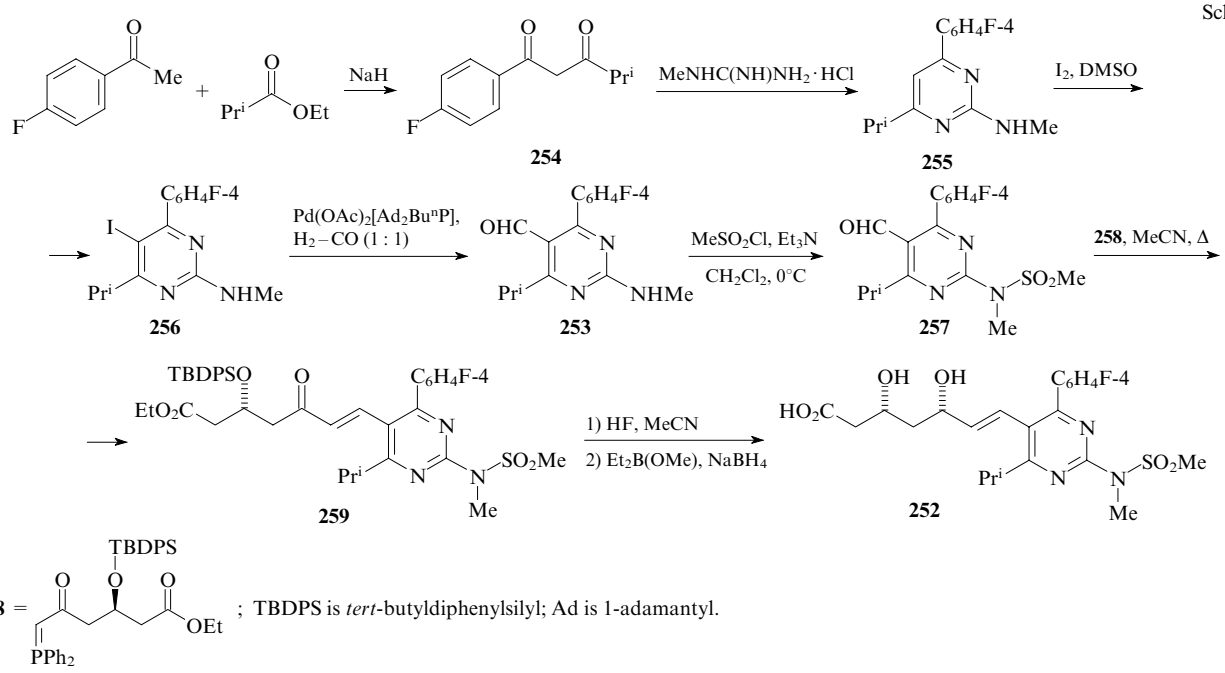


R = H, Ph, $SiMe_3$, CH_2OH.

Potassium salt of acid **252** (the active component of the drug Rosuvastatin) is the effective inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA). This compound is one of the most powerful pharmaceuticals used to decrease the cholesterol level. Recently, the rational scheme for the synthesis of compound **252** was developed (Scheme 11).[142] 6-Isopropyl-4-(4-fluorophenyl)-2-methylaminopyrimidine-5-carbaldehyde (**253**) is employed as the key intermediate. Aldehyde **253** can be synthesized in several steps. The condensation of fluoroacetophenone with isopropyl acetate affords product **254**, which reacts with methylguanidine to give 2-methylaminopyrimidine derivative **255**. The iodination of the latter followed by the catalytic formylation of compound **256** gives derivative **253.** The subsequent Wittig olefination of aldehyde **257** with ylide **258** and the stereospecific reduction of the second carbonyl group in compound **259** affords the active component of the drug Rosuvastatin.

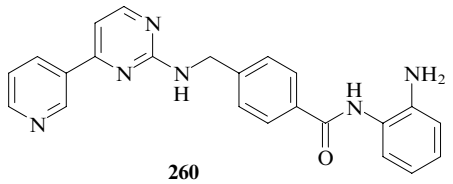
Compound **260** (MGCD0103) was synthesized and tested for the biological activity. Compound **260** selectively inhibits *in vitro* histone deacetylase HDAC at a submicromolar concentration, inhibits the tumour cell proliferation, and induces the histone acetylation and tumour cell apoptosis. The observed activity *in vivo* stimulated the design of a new antitumour agent based on this compound.[143] It should

Scheme 11

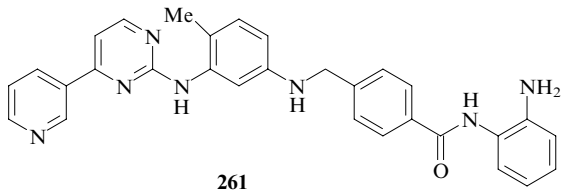


258 = ; TBDPS is *tert*-butyldiphenylsilyl; Ad is 1-adamantyl.

be noted that structurally similar compound **261**, which is also the Glivec analogue, was constructed as a chimeric hybrid of the inhibitor of histone deacetylase PDGT-Rβ and tyrosine kinase BCR-ABL. It is speculated that compound **261** is the inhibitor of these enzymes with the additive synergistic effect.[144]



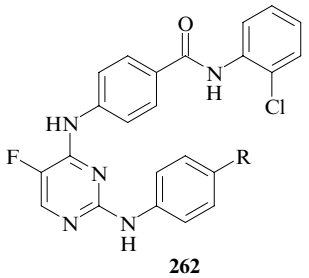
260



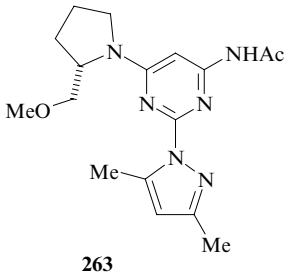
261

2,4-Diarylaminopyrimidines **262** are highly effective as inhibitors of kinase Aurora B and are currently under clinical testing.[145]

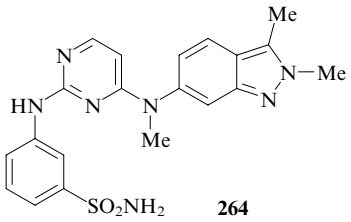
The biological activity of 2-aminopyrimidine derivatives is enhanced when the hydrogen atom at positions 4 and/or 6 of the heterocycle is replaced by the amino group (compounds **263** and **264**).[146, 147]



262



263



264

* * *

The consideration and analysis of the structures of biologically active synthetic 2-aminopyrimidine derivatives showed that the presence of the aniline moiety, the amide bond, and halogen atoms, as well as heterocyclic substituents (piperazine, pyridine, imidazole), in their molecules plays an important role. Evidently, 2-aminopyrimidine is the most significant moiety responsible for the biological activity of its derivatives. This is true not only for substituted 2-aminopyrimidines but also for derivatives with fused rings, including pteridines, pyridopyrimidines, imidazopyrimidines, purines, *etc*.

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