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Synthesis Strategies and Biological Value of Pyrrole and Pyrrolopyrimidine

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ABSTRACT

For several decades, interest in the synthesis pyrrole and pyrrolopyrimidine increases due to the importance of these heterocycles both from chemical and biological points of view. They possess several biological activities such as anti-microbial, analgesic, anti-inflammatory, anti-cancer, anti-viral, anti-convulsant, anti-hyperlipidemic, anti-depressant, anti-diabetic, anti-allergic activities. These findings motivated us to present this review which highlights different methods of the synthesis of pyrrole and pyrrolopyrimidine derivatives as well as their biological importance from the past to recent years.

Key Words: *Analgesic, Anti-allergic, Anti-cancer, Anti-convulsant, Anti-depressant, Anti-diabetic, Anti-hyperlipidemic, Anti-inflammatory, Anti-microbial, Anti-viral, 7-deazapurine, Knorr pyrrole synthesis, Paal Knorr, Pyrrole, Pyrrolopyrimidine, Synthesis.*

Literature survey indicated that pyrroles and pyrrolo[2,3-*d*]pyrimidines are of considerable interest in drug discovery. Pyrrole is one of the most important simple heterocycles, which is found in a broad range of natural products. It is the key structural fragment of heme and chlorophyll (two pigments essential for life), the chlorins, bacteriochlorins, corrins (vitamin B12) and some bile pigment (biliverdin and bilirubin). Pyrrolo [2,3-*d*]pyrimidines as 7-deazapurines exhibit remarkable biological activity due to their resemblance to cellular purines.

Owing to the importance of these systems, we introduce here the main aspects of the synthesis and the biological value of these heterocycles from the past to recent years.

1. Synthesis of pyrroles

Pyrrole derivatives could be synthesized by different methods which can be classified into two main categories:

1.1. Synthesis of pyrrole from non-heterocyclic molecules.

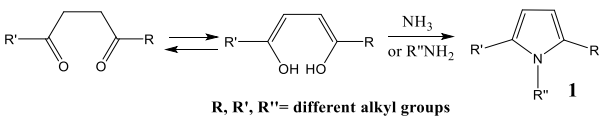
1.2. Ring transformation of other heterocyclic rings.

1.1. Synthesis of pyrrole from non-heterocyclic molecules

Generally, there are eight important strategies for synthesis pyrrole derivatives from non-heterocyclic starting materials, which can be summarized in the following:

1.1.1. Reaction of 1,4-dicarbonyl, 1,4-dihalo analogues, 1,3-dienes, 1,3-diyenes or 1,4-alkynediols with ammonia, amines or hydrazine derivatives

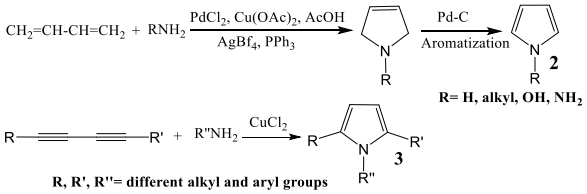
In 1885, Pall and Knorr[1] reported the synthesis of pyrroles **1** via reaction of 1,4-diketones with ammonia or primary amines.



R, R', R''= different alkyl groups **1**

Huisgen[2] then Potts *et al* [3,4] reported the synthesis of pyrroles **2, 3** by reaction of 1,3-diene or diyenes with primary amines.

In 1996, McLeod *et al.*[5] reported the reaction of 1,4-dicabonyl derivatives with hydrazides to afford pyrrole **4** which then treated with nBu4NF to give 1-amino-pyrrole **5**.



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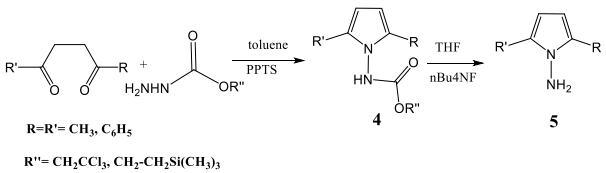
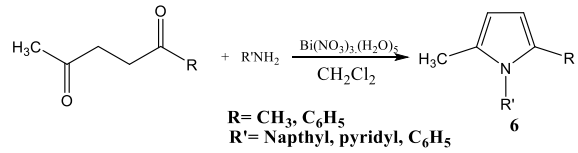
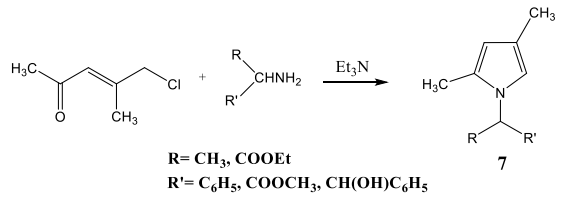


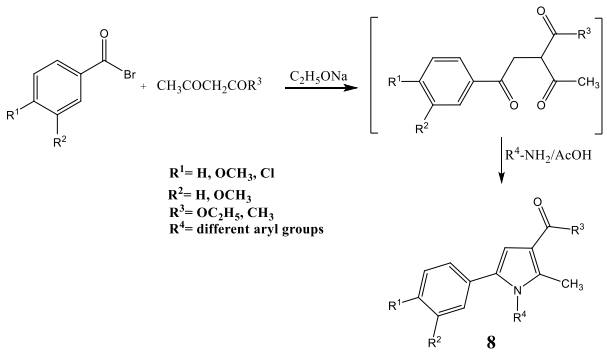
In 2005, Banik *et al.*[6] modified Paal-Knorr reaction using bismuth nitrate in the presence of dichloromethane with amine and ketone at room temperature to obtain pyrrole **6**.



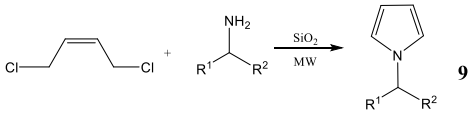
In the same year, Demir *et al.*[7] reported another Pall-Knorr modification via reaction of chloropentenones with amines, amino alcohols or esters of amino acids in presence of triethylamine.



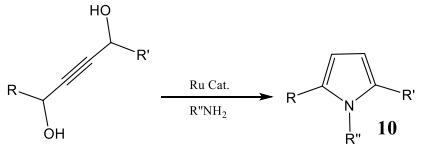
In 2006, Danchev *et al.*[8] applied Paal–Knorr cyclization between intermediately prepared 1,4-dicarbonyl compounds and different aryl amines to afford pyrrole **8**.



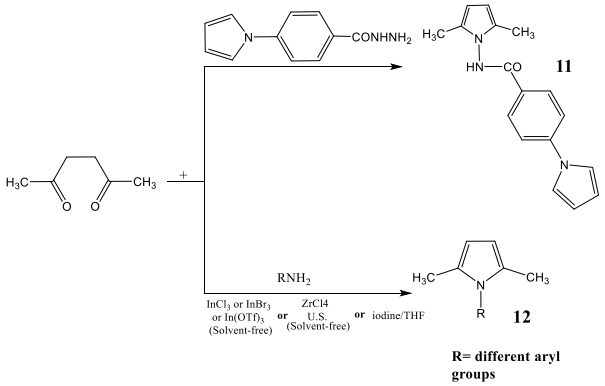
In 2007, Aydogan *et al.*[9] carried out the reaction of cis-1,4-dichloro-2-butene with various amines, amino alcohols or amino acid esters without solvent under microwave irradiation on silica gel to give pyrroles **9**.



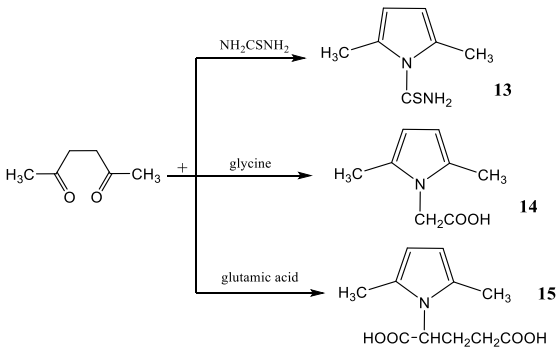
In the same year, Pridmore *et al.*[10] reported Ruthenium-catalysed conversion of 1,4-alkynediols into pyrroles **10**.



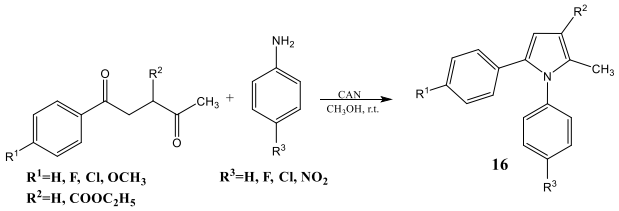
Many authors reported the reaction of acetonyl acetone either with benzoic acid hydrazide derivative[11] affording pyrrole **11** or with certain amines using indium(III) salts[12] under solvent-free conditions, zirconium chloride under ultrasound irradiation[13] or Iodine in tetrahydrofuran [14] affording pyrroles **12**.



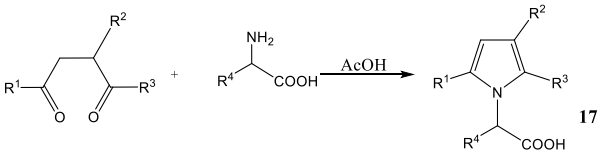
Acetonyl acetone was also utilized[15] for synthesis of pyrrole derivatives **13, 14** and **15** via reaction with thiourea, glycine or glutamic acid in 2010.



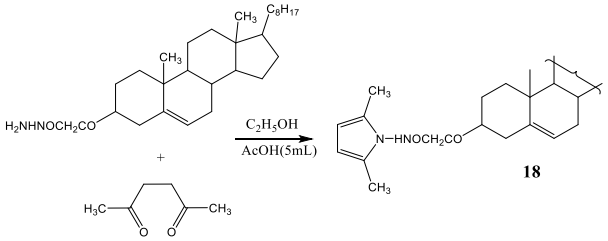
In 2013, Kamal *et al.*[16] reported CAN-catalyzed Paal-Knorr reaction of 1,4-diketones with various amines using cerium (IV) ammonium nitrate (CAN) as a catalyst to obtain pyrroles **16**.



In 2014, Pagadala *et al.*[17] reported the synthesis of highly substituted pyrrole-*N*-acetic derivatives **17** through the coupling of 1,4-diketones with amino acids following Paal-Knorr's approach.



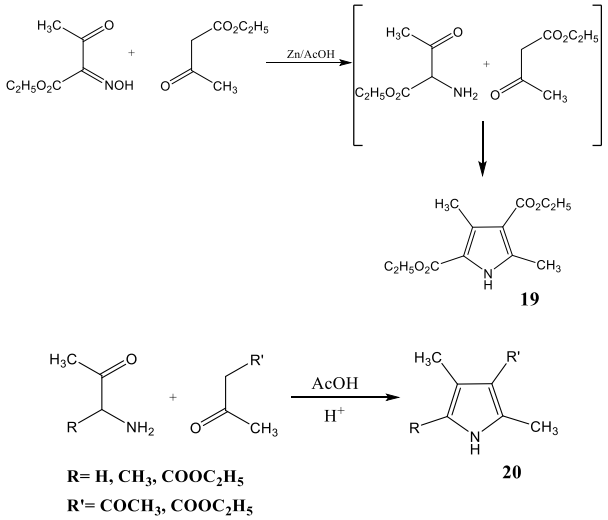
In 2015, Shamsuzzaman *et al.*[18] reported the synthesis of steroidal pyrrole **18** by reaction of cholest-5-en-3β-*O*-acetyl hydrazide with acetonyl acetone.



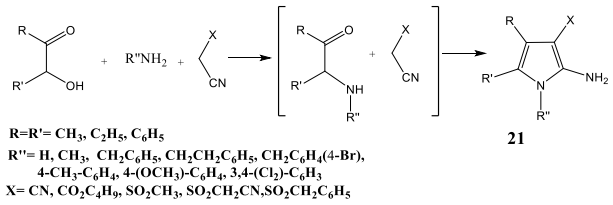
1.1.2. Reaction of α-aminocarbonyl compound with compound has active methylene group α-to carbonyl. (Knorr pyrrole synthesis)

It is the most widely used method for pyrrole synthesis. α-Aminocarbonyl compounds were readily dimerize to dihydropyrazines, one way to avoid this dimerization is to prepare and use them in the form of salts to be liberated for reaction by the base present in the reaction mixture. An alternative way was reported by L. Knorr[19] where the oximino precursor was converted to amino *in-situ.*

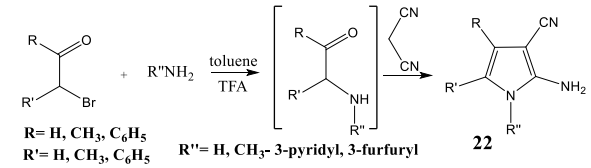
In 1955, Fischer[17] reported the condensation of certain α-amino ketones with β-diketones or β-ketoester in acidic medium to afford pyrroles **20**.



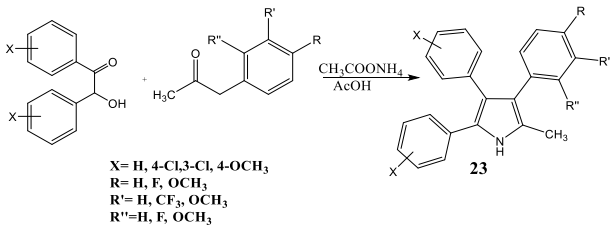
Many authors[21-28] reported the formation of α-aminoketones *in situ* via condensation of α-hydroxyketones with certain amines which then were reacted with malononitrile, alkylcyanoacetate or alkylsulphonyl acetonitrile giving 2-aminopyrroles **21**.



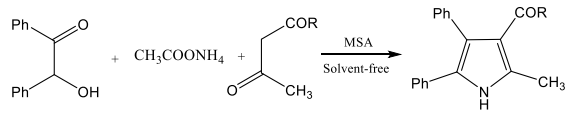
α-Aminoketones could be also obtained[29,30] *in situ* by the reaction of α-bromoketone with primary amines to be reacted with malononitrile giving 2-amino-3-cyano-pyrroles **22**.



Goel *et al.*[31] reported the reaction of benzoin, ketone and ammonium acetate in acetic acid to prepare 3,4,5-triaryl-1-H-pyrrole derivatives **23** in 2004.

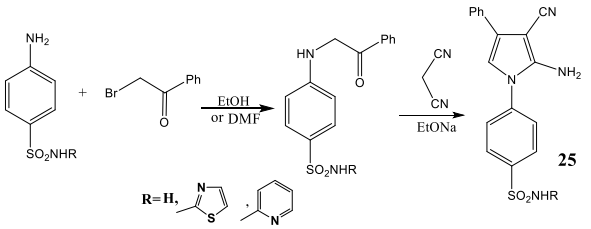


In 2012, Tamaddon *et al.*[32] reported the synthesis of other 2,3,4,5-tetrasubstituted pyrroles **24** via one-pot three component reaction of benzoin, 1,3-dicarbonyls, and ammonium acetate under solvent-free conditions using Molybdate Sulfuric Acid (MSA) as an efficient acid catalyst.



R= CH_3, OCH_3, OC_2H_5 **24**

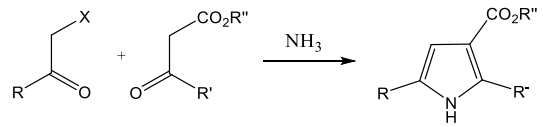
Ghorab *et al.*[33] reported the reaction of phenacyl bromide with certain sulfanilamides affording 4-(2-oxo-2-phenyl-ethylamino)-benzenesulfonamides which subsequently reacted with malononitrile in sodium ethoxide/ethanol to obtain 2-amino-3-cyano-pyrroles **25**.



25

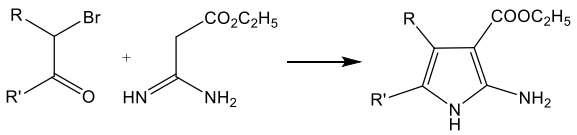
1.1.3. Reaction of α-halocarbonyl compounds, component with active methylene and ammonia derivatives.

This reaction was first reported by Hantzsch[34] in 1890 followed by Feist and Bénary[35] and then by Roomi and Macdonald[36] in 1970. They reported the reaction of α-haloketones with 1,3-dicarbonyl compounds in the presence of ammonia to give pyrroles **26**.



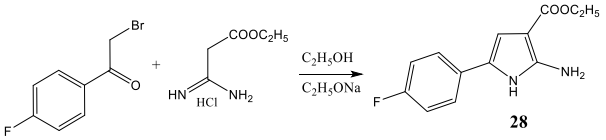
R, R', R''= different alkyl and aryl groups **26**

In 1986 Toja *et al.*[37] reported the condensation of ethoxycarbonyl acetamidine with α-haloketones to afford 2-aminopyrroles **27**.



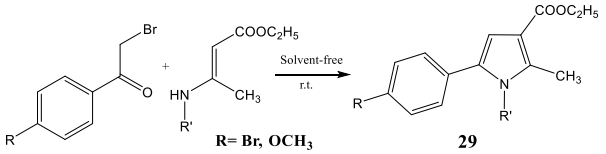
R, R'= H, CH_3, C_6H_5 **27**

In 2011, Kaspersen *et al.*[38] reported the synthesis of other 2-amino-pyrrole **28** via the reaction of 4-fluorophenacyl bromide with ethoxycarbonyl acetamidine salt in basic medium.



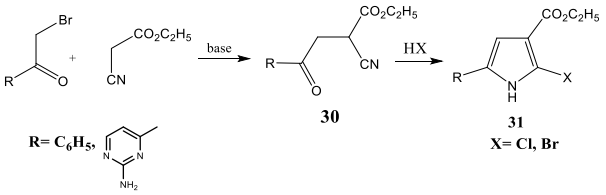
28

In the same year Yavari *et al.*[39] reported the reaction of other phenacyl bromide derivatives with certain enaminones under solvent-free conditions to afford 1,2,3,5-tetrasubstituted-pyrrole derivatives **29**.



R= Br, OCH_3
R'= n-butyl, cyclohexyl **29**

Menichincheri[40] *et al.* in 2010 and H. Nishida [41] *et al.* in 2012 reported a modification of Hantzsch pyrrole synthesis by condensation of α-halo ketones with ethylcyanoacetate affording α-cyano-γ-keto esters **30** which were cyclized to pyrroles **31** in acidic medium.

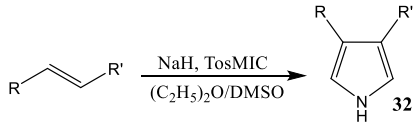


30 **31**

R= C_6H_5, **X= Cl, Br**

1.1.4. Reaction of tosylmethyl isocyanide with Michael acceptors.

This reaction was first reported[42] by Van Leusen *et al.* in 1972, where Tosylmethylisocyanide (TosMIC) was reacted under basic condition with α,β-unsaturated ketones, esters or nitriles to give, by concomitant loss of *p*-toluenesulfinic acid, 3-acylpyrrole, pyrrole-3-carboxylates or 3-cyanopyrroles **(32)**, respectively.

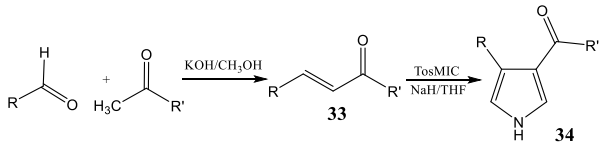


32

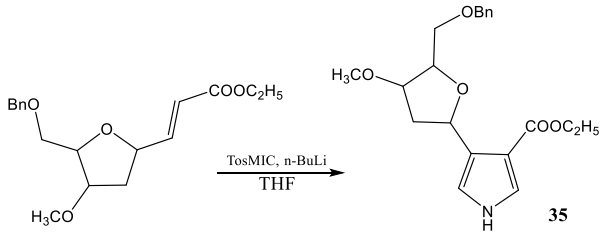
R= H, CH_3, C_6H_5, 2-furyl, COC_6H_5, $COOCH_3$
R'= $COCH_3$, COC_6H_5, $COOCH_3$, CN

Also, Dannhardt *et al.*[43] in 2000 reported the reaction of TosMIC with chalcones **33** to obtain pyrroles **34**.

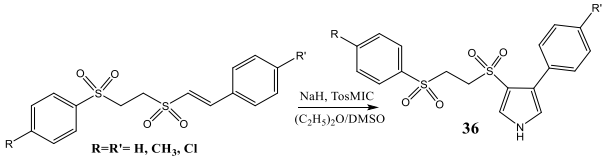
In 2007, Krishma *et al.*[44] reported the condensation reaction of 3-(2-tetrahydrofuranyl)-2-propenoate with TosMIC to afford pyrrole-carboxylate **35**.



R= C_6H_5, 4-F-C_6H_4, 2-OCH_3-C_6H_4, 4-CF_3-C_6H_4
R'= C_6H_5, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-OCH_3-C_6H_4

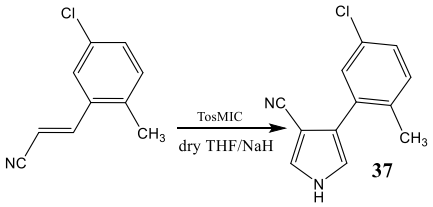


In 2012, Padmaja *et al.*[45] reported the reaction of 1-(arylsulfonylethylsulfonyl)-2-arylethene with TosMIC to obtain pyrrole derivatives **36**.



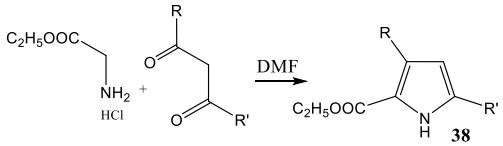
R=R'= H, CH_3, Cl

Similarly, in 2015, Brasca *et al.*[46] reported the synthesis of pyrrole **37** by treatment of 3-(5-chloro-2-methylphenyl)-acrylonitrile with TosMIC.



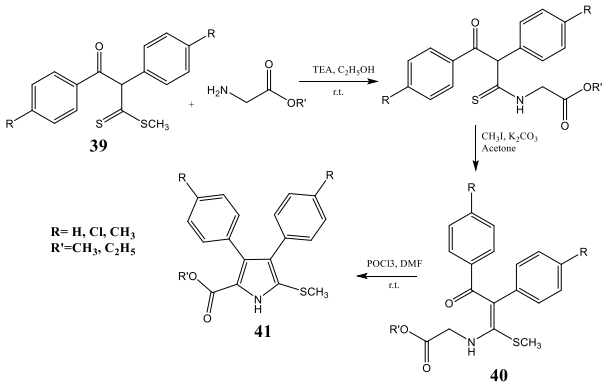
1.1.5. Reaction of 1,3-dicarbonyl with amino component containing active methylene.

In 1982, Mataka *et al.*[47] reported the reaction of certain 1,3-dicarbonyl compounds with ethyl glycinate HCl to give ethyl pyrrole-2-carboxylates **38**.



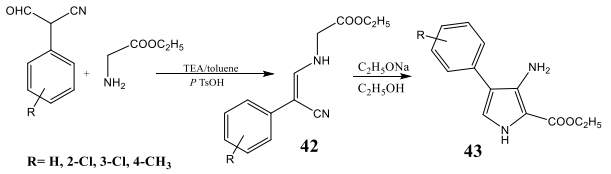
R, R'= CH_3, C_6H_5

In 2005, Mathew[48] reported that α-oxoketene-*N*,*S*-acetals **40**, prepared by the reaction of alkyl glycinates with β-oxodithiocarboxylates **39** followed by alkylation, smoothly underwent cyclization to afford alkyl 3,4-diaryl-pyrrole-2-carboxylates **41**.



R= H, Cl, CH_3
R'=CH_3, C_2H_5

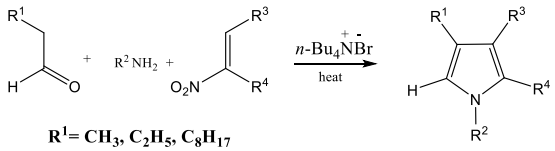
In 2011, Pittala *et al.*[49] reported a modification of this reaction through the condensation of ethyl glycinate with α-formyl-substitutedbenzeneacetonitriles affording N-[2-cyano-2-(substitutedphenyl)ethenyl] glycine ethyl esters **42** which then cyclized in sodium ethoxide/ethanol mixture to give pyrrole aminoesters **43**.



R= H, 2-Cl, 3-Cl, 4-CH_3

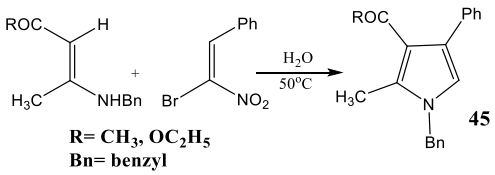
1.1.6. Reaction of nitroalkenes with carbonyl compounds.

In 2003, Ranu and Dey[50] reported an efficient synthesis of substituted pyrroles **44** through one-pot, three-component condensation of a carbonyl compound, amine and nitroalkene using tetrabutyl-ammonium bromide.



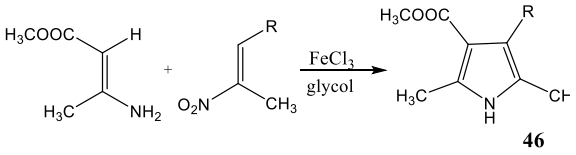
R^1= CH_3, C_2H_5, C_8H_{17}
R^2= cyclohexyl, $(CH_2)_3CH_3$, $CH_2C_6H_5$
R^3= C_6H_5, 4-NO_2-C_6H_4, 4-Cl-C_6H_4
R^4= CH_3, C_2H_5

In 2010, Rueping and A. Parra[51] reported the synthesis of pyrroles **45** via reaction of β-bromonitrostyrenes with enaminones in water.



R= CH_3, OC_2H_5
Bn= benzyl

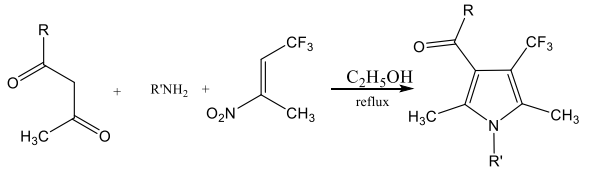
In 2012, Li *et al.*[52] reported $FeCl_3$-catalyzed addition and cyclization of enamino esters with nitroalkenes to obtain tetrasubstituted pyrroles **46**.



46

R= 3-Cl-C_6H_4, 4-$(CH_3)_2$N-C_6H_4, 2,4-diCl-C_6H_3

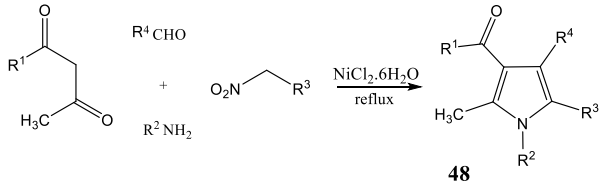
In the same year, Korotaev *et al.*[53] reported one-pot, three-component cyclization of 1,1,1-trifluoro-3-nitrobut-2-ene with 1,3-dicarbonyls (ethyl acetoacetate, acetylacetone, benzoylacetone) and ammonia or primary aliphatic amines to obtain pyrrole derivatives **47**.



47

R= CH_3, OC_2H_5, C_6H_5
R'= H, CH_3, C_2H_5

One-pot four-component condensation reaction of nitroalkanes, aromatic aldehydes, β-ketoesters, and amines in the presence of 10 mol % $NiCl_2.6H_2O$ afforded substituted pyrrole derivatives **48** in good yields. This reaction was reported[54] by A. T. Khan *et al*.



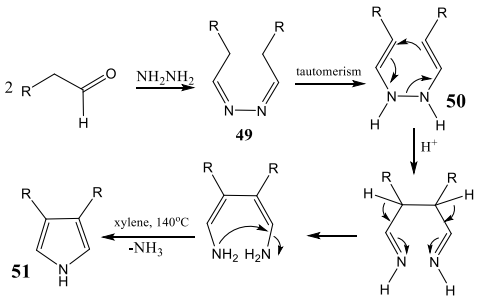
48

R^1= CH_3, OCH_3, OC_2H_5, $OC(CH_3)_3$, O-allyl
R^2= C_6H_5, $CH_2C_6H_5$, cyclohexyl, furfuryl
R^3= H, CH_3
R^4= C_6H_5, 4-Cl-C_6H_4, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 4-NO_2-C_6H_4

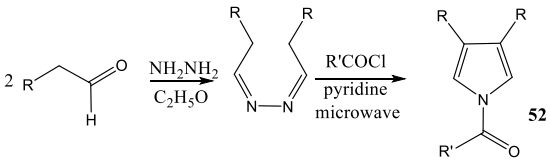
1.1.7. Piloty-Robinson pyrrole synthesis

Piloty and Robinson reported[55] the reaction of 2 equivalents of an aldehyde and hydrazine to produce ketazine **49** which by treating with strong acid gives pyrroles **51** through sigmatropic rearrangement of divinyl hydrazine **50**.

In 2007, B. C. Milgram *et al.*[56] reported Microwave-Assisted Piloty-Robinson synthesis of pyrroles **52** by treating aldehyde first with hydrazine and then with aroyl chloride.



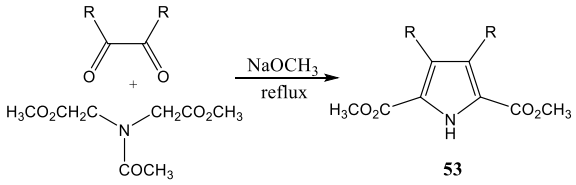
R= different alkyl and aryl groups



R= C_2H_5, C_3H_7, C_4H_9, CH_2-$CH(CH_3)_2$, $(CH_2)_2$-C_6H_5
R'= C_6H_5, 4-CH_3-C_6H_4, 4-Cl-C_6H_4, 4-OCH_3-C_6H_4

1.1.8. Reaction of α-dicarbonyl compound with secondary or tertiary amine having two active methylene groups.

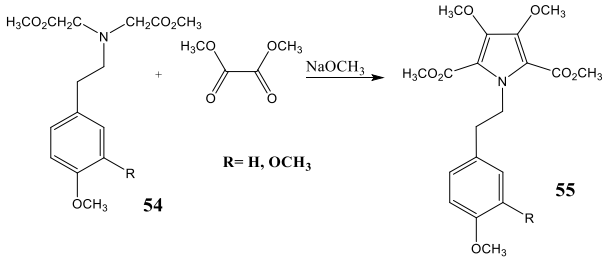
In 1965, Friedman[57] reported the reaction of benzils with dimethyl N-acetyliminodiacetate in the presence of sodium methoxide to afford 3,4-diaryl-pyrrole **53**.



53

R= C_6H_5, 2-CH_3-C_6H_4, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4

In 2003, Iwao *et al.*[58] reported the condensation of dimethyl oxalate with iminodiacetates **54** to afford 3,4-dimethoxypyrrole-2,5-dicarboxylates **55**.



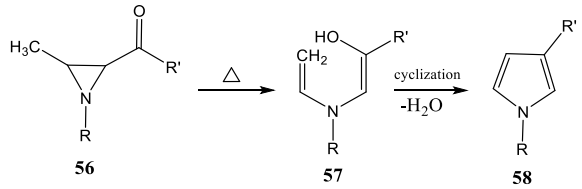
54 **R= H, OCH_3** **55**

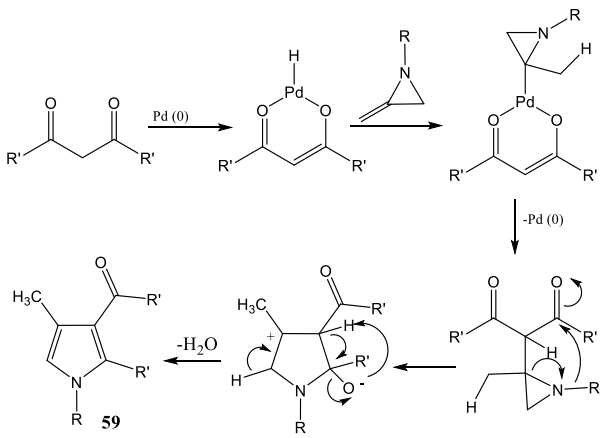
1.2. Synthesis of pyrrole via ring transformation

1.2.1. From aziridine and azirine derivatives

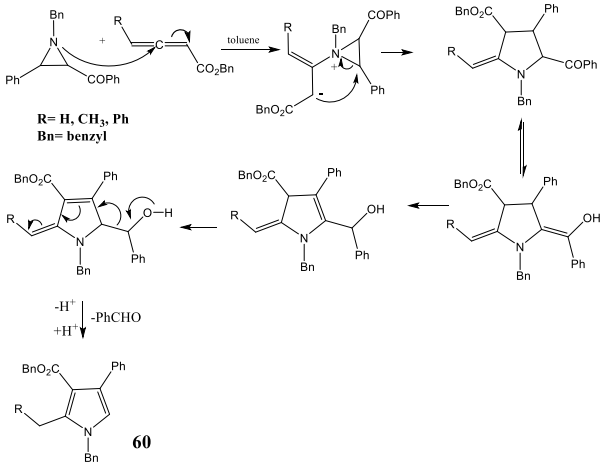
In 1977, Lukac *et al.*[59] reported that 2-acylaziridines **56** were transformed to pyrrole derivatives **58** by ring expansion involving ring-opened dipolar intermediate **57**.

In 2007, Kathriarachchi *et al.*[60] reported the synthesis of pyrrole derivative **59** via palladium-catalyzed reaction of methyleneaziridines with 1,3-diketones.

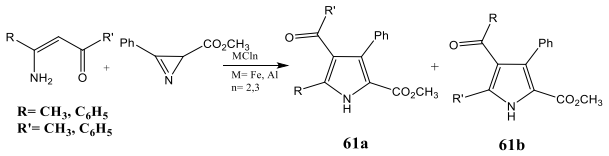




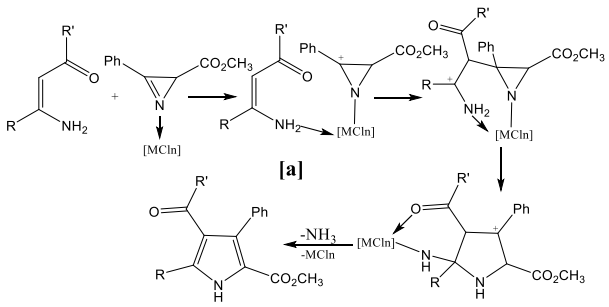
In 2010, Ribeiro Laia *et al.*[61], reported the formation of pyrroles **60** via thermolysis of aziridine in the presence of benzyl buta-2,3-dienoate derivatives in refluxing toluene.

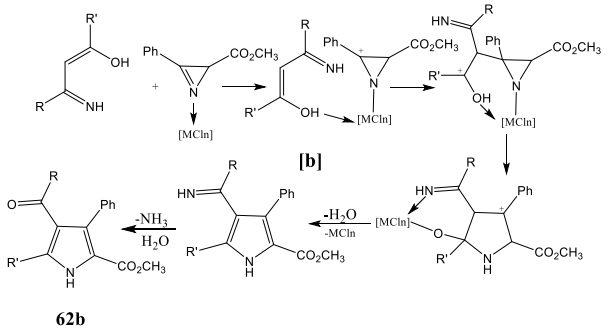


In 2012, S. Auricchio *et al.* reported[62] the synthesis of pyrrole derivatives **61a,b** by reaction of 2*H*-azirines with enaminones and enaminoesters in the presence of metal salts that act as Lewis acids.



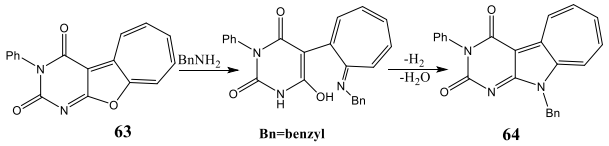
Authors suggested[62] that the azirine complex undergoes nucleophilic attack by the enaminic double bond to give intermediates, which can afford the different products depending upon the different intramolecular linkage with nitrogen (route a) or oxygen (route b).





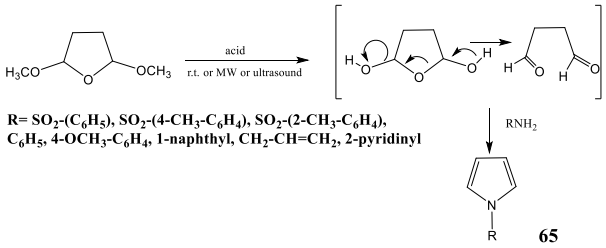
1.2.2. From furan derivatives

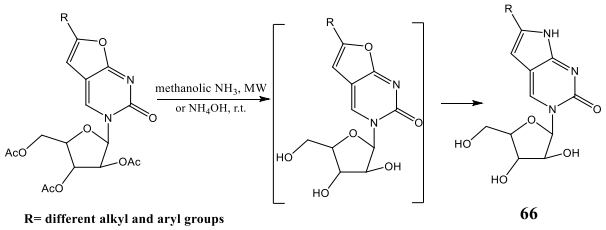
Shin-ichi Naya *et al.*[63] reported the condensation of furano[2,3-*d*]pyrimidine **63** with benzyl amine to afford pyrrolo[2,3-*d*] pyrimidines **64**.



Many authors[64-67] reported another approach to transformation of 2,5-dimethoxytetrahydrofuran to pyrrole derivatives **65** in presence of acid either by stirring at room temperature[64], using microwav[65,66] or ultrasound conditions[67]. According to the authors, the methoxy groups can be deprotected under acidic conditions. The intermediate can easily form the reactive dialdhyde which on reaction with amines can lead to pyrroles.

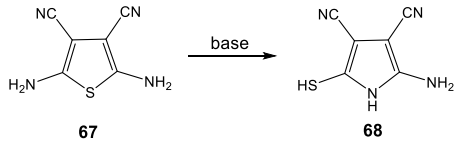
Similarly, in 2015, Mieczkowski *et al.*[68] reported the reaction of 6-substituted furo[2,3-*d*]pyrimidin-2(3*H*)-one arabinosides either with ammonium hydroxide at room temperature or with ammonia under microwave condition led to the fast removal of the acetyl groups followed by rather slow conversion of the deprotected furo[2,3-*d*]pyrimidin-2(3*H*)-one nucleosides to the 3*H*-pyrrolo[2,3-*d*]pyrimidin-2(7*H*)-one nucleosides **66**.





1.2.3. From thiophene derivative

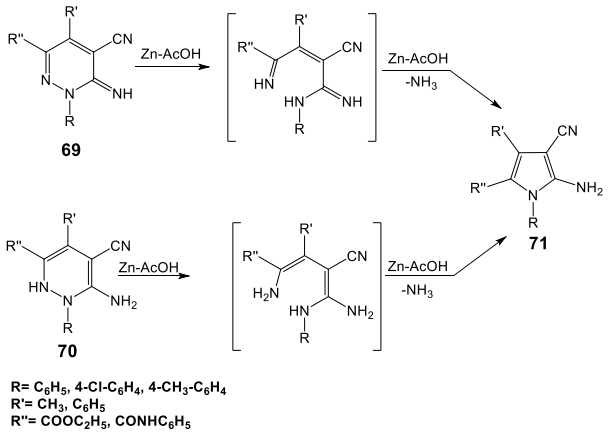
Middleton et al.[69] in 1958 and Taylor *et al.*[21a] in 1964 reported the transformation of 2,5-diaminothiophene-3,4-dicarbonitrile (**67)** in alkaline medium to 5-amino-2-mercaptopyrrole-3,4-dicarbonitrile (**68)**.

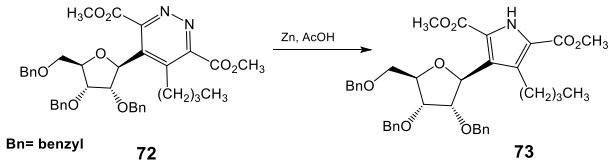


1.2.4. From pyridazine derivatives

2-Aminopyrrole-3-carbonitriles **71** were produced via reduction of iminopyridazine **69** or dihydro-pyridazines **70**. These reactions were reported by Gewald *et al.*[70] and Abd-Elhamid *et al.*[71].

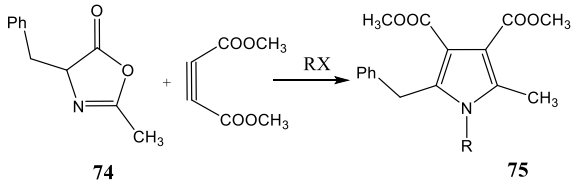
Analogously, in 2004, Joshi *et al.*[72] reported the transformation of pyridazine C-nucleoside **72** to the corresponding pyrrole **73**.



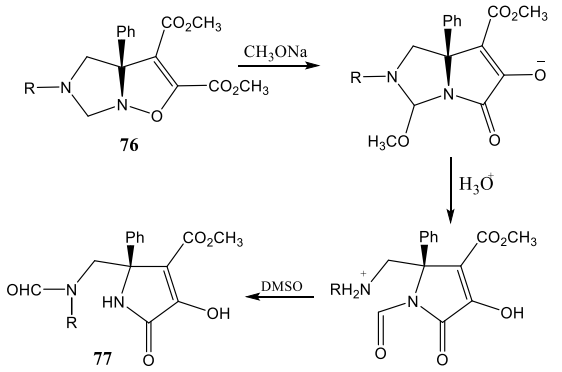


1.2.5. From oxazole derivatives

Hershenson and Pavia reported[73] the use of azalactone (2-oxazolin-5-one) **74** in 1,3-dipolar cycloaddition provided a synthetic route to pyrroles **75**, Where in *situ* alkylation of **74** with highly reactive alkylating agents, such as methyl trifluoromethanesulfonate or triethyloxoniumtetra-fluoroborate in the presence of dimethylacetylene-dicarboxylate (DMAD) as the dipolarophile offered pyrroles **75.**



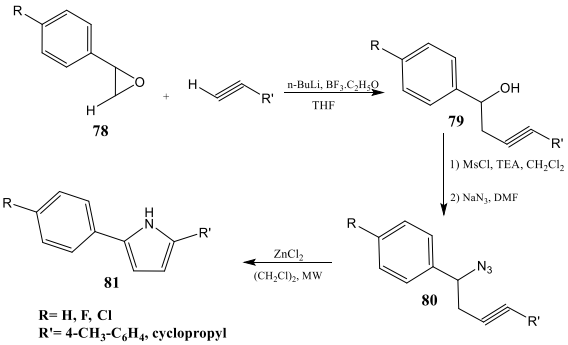
Also, in 2009, Coşkun and Çetin reported[74] the methoxide-induced diastereoselective rearrangement of isoxazolines **76** into 3-methoxy-7-(methoxycarbonyl)-2,7a-diaryl-5-oxo-2,3,5,7a-tetrahydro-*1H*-pyrrolo[1,2-*e*] imidazol-6-olates, that on reacting with H_3O^+, it is converted to the corresponding methyl-1-formyl-4-hydroxy-5-oxo-2-phenyl-2-((arylamino) methyl)-2,5-dihydro-*1H*-pyrrole-3-carboxylates **77**.



R= C_6H_5, 4-C_6H_4, 4-OCH_3-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4

1.2.6. From oxirane derivative

In 2009, Wyrębek *et al.*[75] reported the transformation of oxirane derivatives **78** to pyrroles **81**. This transformation was carried out by the reaction of oxirane derivatives with alkyne affording alkynols **79** which then transformed to mesylates followed up by in situ SN^2 reaction with sodium azide forming azides **80** which finally cyclized in the presence of zinc chloride and dichloroethane to pyrroles **81**.



R= H, F, Cl
R'= 4-CH_3-C_6H_4, cyclopropyl

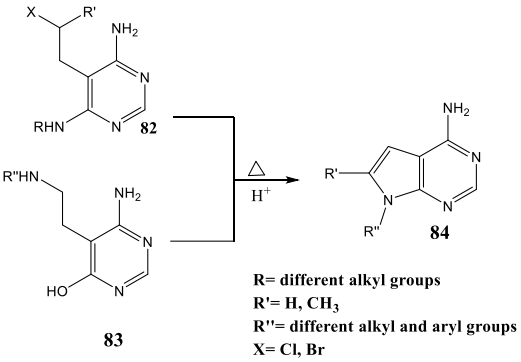
2. Synthesis of pyrrolo[2,3-*d*]pyrimidines

Pyrrolo[2,3-*d*]pyrimidine derivatives could be synthesized from:
2.1. Pyrimidine derivatives.
2.2. Pyrrole derivatives.

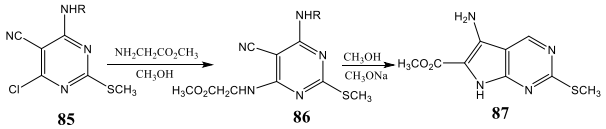
2.1. Synthesis of pyrrolopyrimidines from pyrimidines

Many authors reported[76-78] the acidic cyclization of pyrimidine derivatives **82** or **83** to afford 4-amino-pyrrolopyrimidine derivatives **84**.

Also, Tumkevicius *et al.* described the reaction[79,80] of 6-chloro-pyrimidine derivatives **85** with methyl glycinate affording pyrimidines **86** which underwent ring closure to obtain pyrrolo[2,3-*d*]pyrimidines **87**.

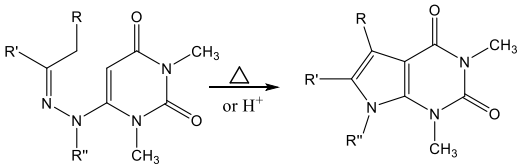


R= different alkyl groups
R'= H, CH_3
R"= different alkyl and aryl groups
X= Cl, Br



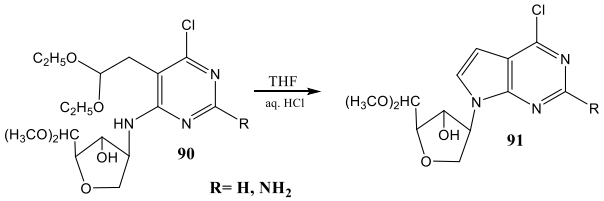
R=CH_3, butyl, 2-Cl-C_6H_4

Pyrrolo[2,3-*d*]pyrimidines **89** could be obtained via thermal [81] or acid catalyzed[82] cyclization of 6-pyrimidylhydrazones **88.** This reaction was reported [81] by Senda and Hirota in 1972, then[82] Duffy and Wibberley in 1974.



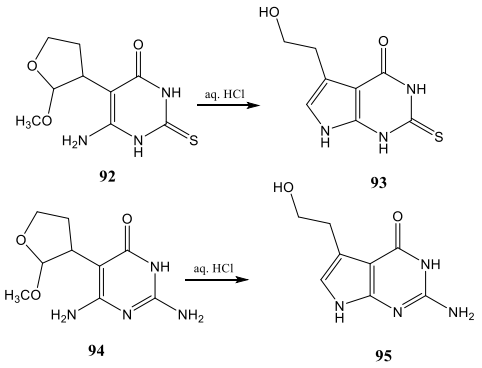
R= H, CH_3, C_6H_5
R'= H, CH_3
R"= H, CH_3

In 1997, Talekar and Wightman reported[83] the reaction of 4-chloro-pyrimidine derivatives **90** to give the corresponding pyrrolo[2,3-*d*]pyrimidines **91** in acidic medium.



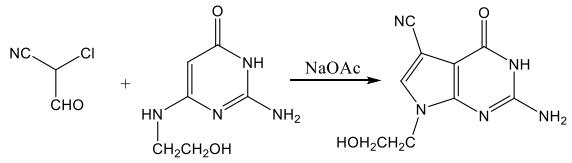
R= H, NH_2

In the same year, Williams *et al.*[84] reported the formation of pyrrolo[2,3-*d*]pyrimidines **93**, **95** through cyclization of pyrimidine derivatives **92, 94,** respectively, in acidic medium. The reaction proceeds via deprotection of the acetal followed by condensation of the carbonyl with the ortho amino group.



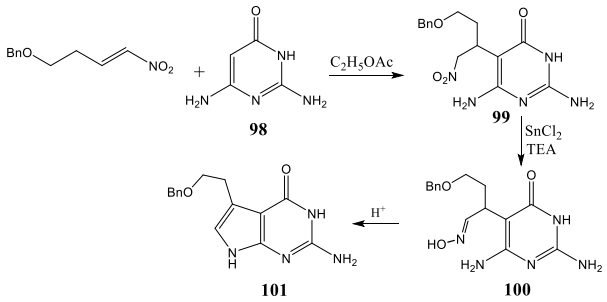
92 **93** **94** **95**

In 1998, Gibson *et al.* reported[85] the preparation of pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile **97** through the reaction of 2-amino-6-(2-hydroxyethylamino) pyrimidin-4(3*H*)-one (**96**) with chloro(formyl)-acetonitrile.



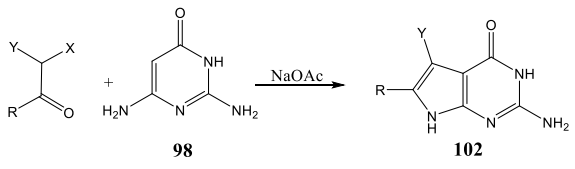
96 **97**

In 2000, Edmont and Williams reported[86] the synthesis of pyrrolo[2,3-*d*]pyrimidine derivative **101** via Michael addition of 2,6-diamino-4(3*H*)-pyrimidinone (**98)** to a nitro olefin followed by reduction and acid cyclization**.**



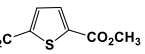
98 **99** **100** **101**

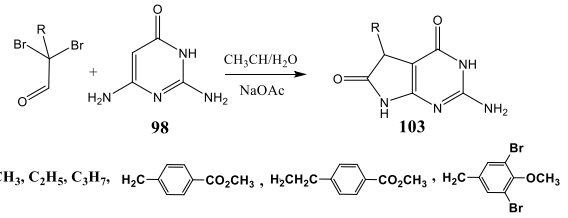
Many reports[87-92] used also 2,6-diamino-4(3*H*)-pyrimidinone (**98)** to be condensed with α-halocarbonyl compounds affording pyrrolo[2,3-*d*]pyrimidine-4-ones **102**. On the other hand, N. M. Sekhar *et al.* reported[93] that the condensation of **98** with α,α-dihalocarbonyl compound afforded pyrrolo[2,3-*d*]pyrimidine-4,6-diones **103**.



98 **102**

R= H, CH_3, C_6H_5, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-OCH_3-C_6H_4 , 4-CN-C_6H_4, 4-Br-C_6H_4, $CH_2CO_2C_2H_5$

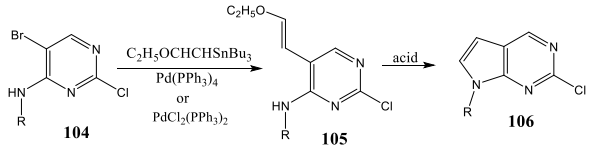
X= Cl, Br **Y= H, CH_2OBn,** 



98 **103**

R= CH_3, C_2H_5, C_3H_7,

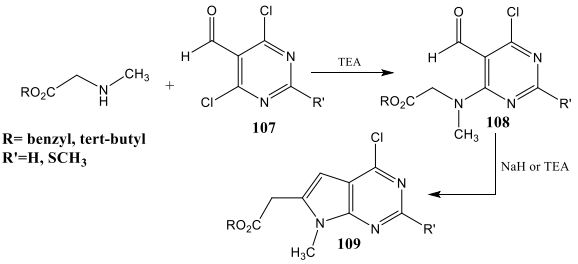
In 2006, H.-S. Choi *et al.* and K. J. Moriarty *et al.* described[94,95] the Palladium-catalyzed cross coupling of the pyrimidines **104** with tributyl(2-ethoxyvinyl) stannane giving the corresponding vinyl ether **105**, which was cyclized to furnish pyrrolopyrimidines **106** upon treatment with acid. This reaction was also reported[96] by S. Nagashima *et al.* in 2009.



104 **105** **106**

R= H, cyclohexyl, 2-(SO_2NHPr)-C_6H_4

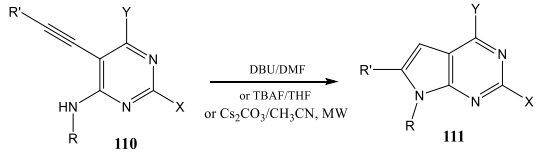
Pyrrolo[2,3-*d*]pyrimidines **109** were prepared by the reaction of pyrimidine-5-carbaldehyde **107** with sarcosine esters followed by base induced cyclization of the resulting aminoaldehydes **108**. This reaction was reported[97] by Clark *et al.* in 2007 and Wang *et al.*[98] in 2016.



R= benzyl, tert-butyl
R'=H, SCH_3

107 **108** **109**

A group of researchers reported[99-101] the formation of pyrrolo[2,3-*d*]pyrimidines **111** via cyclization of 5-alkynylpyrimidine derivatives **110** using either 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[99,100] or tetrabutylammonium flouride (TBAF)[101]. While V. Prieur *et al.* reported the same reaction in the presence of cesium carbonate (Cs_2CO_3) under microwave irradiation[102] in 2014 and 2015.

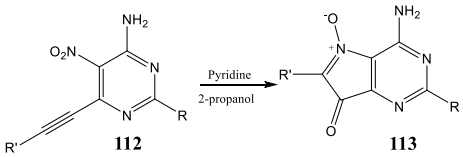


110 **111**

R= CH_3, CH_2CH_2-cyclohexyl, neopentyl, cyclopentyl , X= CN, Cl, H , Y= H, Cl

R'= CH_2OH,  ,  **, C_6H_5, 4-OCH_3-C_6H_4, 4-CF_3-C_6H_4**

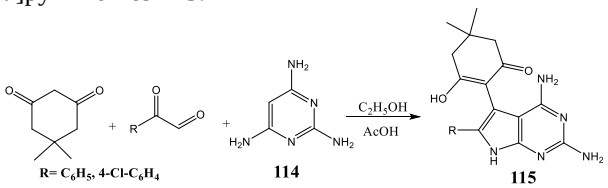
In 2009, E. Pudziuvelyte *et al.* described[103] the synthesis of pyrrolo[3,2-*d*]pyrimidin-5-oxides **113** via pyridine initiated smooth cycloisomerization of 5-nitro-6-arylethynylpyrimidines **112**.



112 **113**

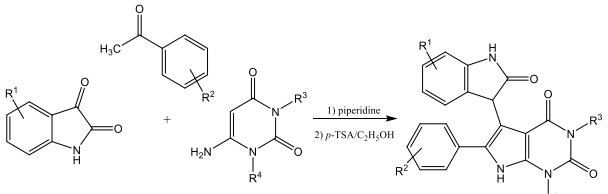
R= H, SCH_3
R'=C_6H_5, 4-CH_3-C_6H_4, 4-C_2H_5-C_6H_4

In 2010, J. Quiroga *et al.* reported[104] the three-component reaction of 2,4,6-tri-aminopyrimidine **114**, dimedone, and arylglyoxal to prepare pyrrolo[2,3-*d*]pyrimidines **115**.



R= C_6H_5, 4-Cl-C_6H_4 **114** **115**

In 2012, Rad-Moghadam and Azimi reported[105] another one-pot three-component reaction of 6-amino-uracil derivatives **116a,b**, isatins, and acetophenones to give pyrrolo[2,3-*d*]pyrimidines **117** through nucleophilic addition of acetophenones onto isatins followed by Michael addition.

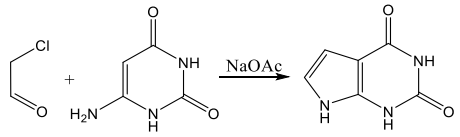


R^1= H, Cl,
R^2= H, Cl, F, OCH_3

116 a, R^3, R^4= H
116 b, R^3, R^4=CH_3

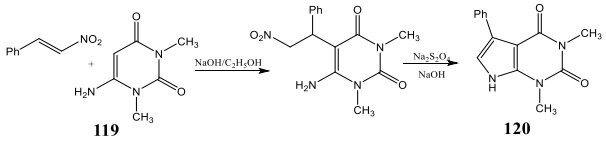
117

Analogous to the previously reports[87-92], N. J. O'Brien *et al.* reported[106] the condensation reaction of 6-amino-uracil (**116a**) with α-chloroacetaldehyde affording pyrrolopyrimidine **118** in 2014.



116 a **118**

Similar to what was reported[86] by Edmont and Williams in 2000, L. Saikia *et al.* described [107] Michael addition of 6-amino-1,3-dimethyluracil (**119**) to (2-nitrovinyl)benzene affording pyrrolo[2,3-*d*]pyrimidine **120** in 2016.

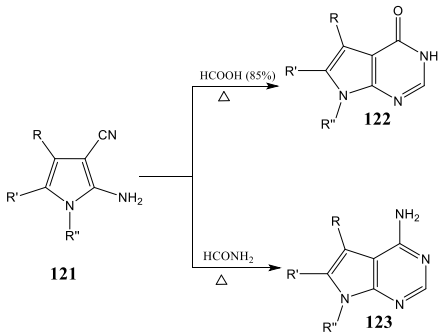


119 **120**

2.2. Synthesis of pyrrolopyrimidines from pyrrole derivatives

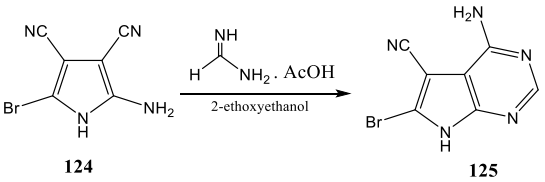
Many reports[108-112] mentioned that condensation reaction of 2-amino-pyrrole-3-carbonitriles **121** with formic acid or formamide afforded the corresponding pyrrolo[2,3-*d*]pyrimidines **122** or **123,** respectively. In 2016, H. Suh *et al.* used formamidine acetate[113] instead of formamide to be condensed with 2-amino-5-bromo-3,4-dicyanopyrrole (**124**) in 2-ethoxyethanol giving 4-amino-pyrrolo[2,3-*d*]pyrimidine **125**.

Alternatively, treatment[38,114] of ethyl 2-amino-pyrrole-3-carboxylates **126** with formamide gave pyrrolo[2,3-*d*]pyrimidine-4-ones **127.**

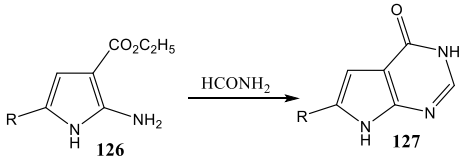


121 **122** **123**

R= H, CH_3, C_6H_5, 4-OCH_3-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4
R'= H, CH_3, C_6H_5, 4-CH_3-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4
R''= $CH(CH_3)C_6H_5$, C_6H_5, 4-OCH_3-C_6H_4, 4-Br-C_6H_4, 4-CH_3-C_6H_4, 4-I-C_6H_4, 4-F-C_6H_4



124 **125**

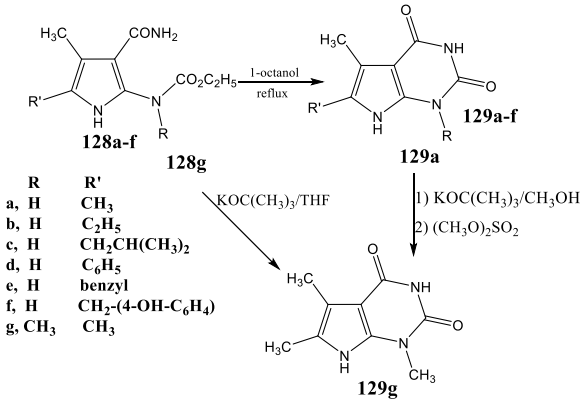


126 **127**

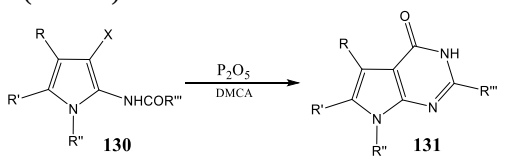
R= C_6H_5, 4-OCH_3-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4, 4-CN-C_6H_4, CH_2-(2-CH_3-C_6H_4), CH_2-(2,4-diCl-C_6H_3), CH_2-(2,5-diOCH_3-C_6H_3

In 1979, Etson *et al.* reported [115] that refluxing a suspension of 2-carbethoxyamido-3-carbamoyl-pyrroles **128a-f** in 1-octanol afforded pyrrolo[2,3-*d*]pyrimidin-2,4-diones **129a-f.** Reaction of **129a** with potassium *t*-butoxide in absolute methanol followed by

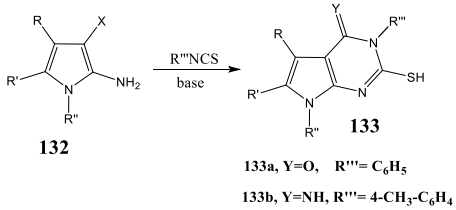
alkylation with dimethylsulfate gave **129g** which was prepared unambiguously by cyclization of **128g** with potassium t-butoxide in anhydrous tetrahydrofuran.



In 1985, N. S. Girgis *et al.* reported the synthesis of Pyrrolo[2,3-*d*]pyrimidin-4-ones **131** via treatment of the acylpyrrole derivatives **130** with phosphorus pentoxide and *N,N*- dimethylcyclohexyl amine (DMCA)[116].



Reaction[33c,116] of the 2-amino-pyrroles **132** with aryl isothiocyanate gave pyrrolo[2,3-*d*]pyrimidine derivatives **133.**

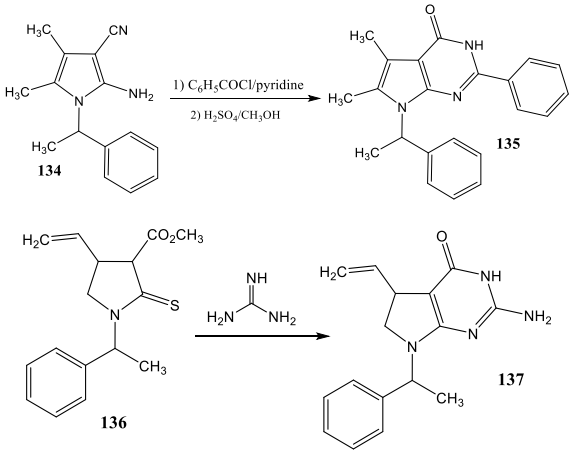


132a, X= CO_2tBu, R,R'= CH_3, R''= pyridylmethyl,

132b. X= CN, R= 4-Br-C_6H_4, R'= H, R''= 4-NH_2SO_2-C_6H_4

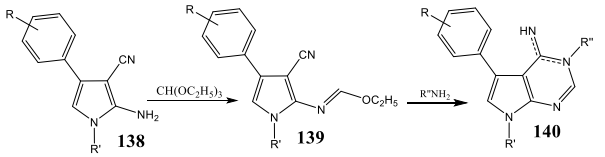
In 1999, Campbell *et al.* reported[117] the formation of pyrrolo[2,3-*d*]pyrimidin-4-one **135** by the reaction of pyrrole **134** with benzoyl chloride followed by subsequent cyclization in acid medium.

In the same year, Taylor et al. described[118] the reaction of 2-thioxo-4-vinylpyrrolidine-3-carboxylate **136** with guanidine affording 2-amino-5,6-dihydro-pyrrolo[2,3-*d*]pyrimidin-4-one **137**.



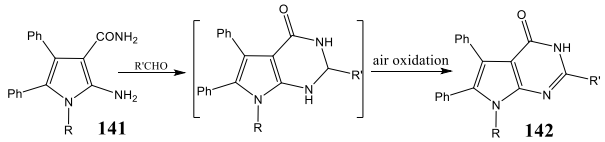
Treatment[119-121] of 2-amino-pyrrole-3-carbonitriles **138** with triethylorthoformate afforded the amidines **139** which were reacted with ammonia, hydrazine hydrate or amines to furnish pyrrolo[2,3-*d*]pyrimidines **140**.

In 2010, A. Davoodnia *et al.* reported the formation[122] of 2-aryl-pyrrolo[2,3-*d*]pyrimidin-4-ones **142** by cyclocondensation reacttion of 2-amino-pyrrole-3-carboxamides **141** with aromatic aldehydes followed by air oxidation.



R= H, 4-OCH_3, 3-OCH_3, 4-OH, 3-OH, 4-Cl
R'=H, C_6H_5, 4-Cl-C_6H_4, 4-OCH_3-C_6H_4

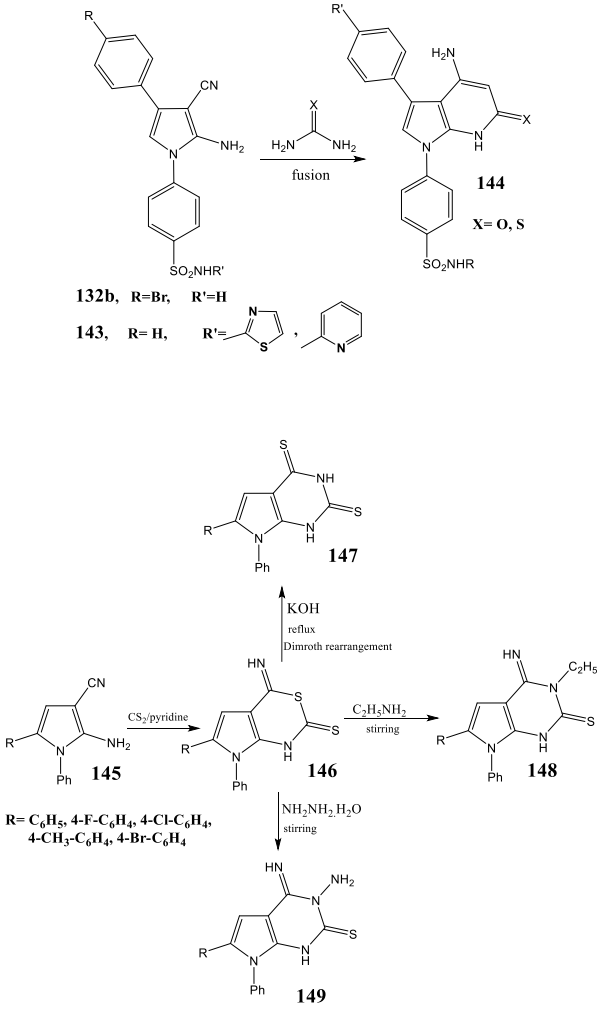
R''= H, NH_2, CH_3, C_2H_5, $(CH_2)_2CH_3$, $(CH_2)_2OH$, $(CH_2)_3OH$, Bn

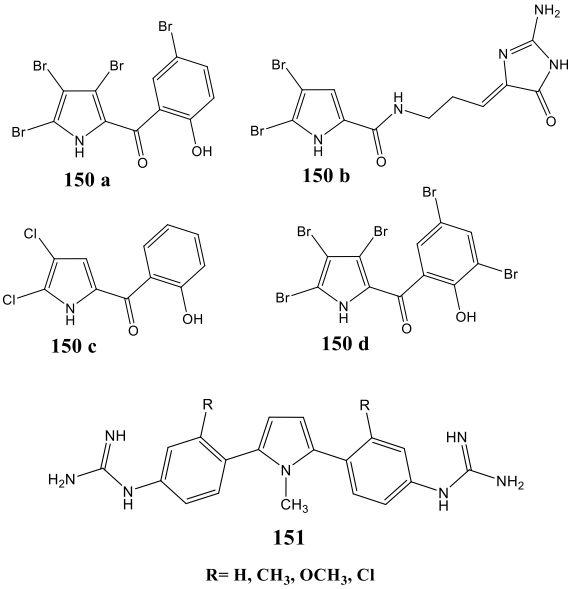


R= benzyl, cyclohexyl
R'= 3-Cl-C_6H_4, 4-Cl-C_6H_4, 3-CH_3-C_6H_4, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4

M. M. Ghorab *et al.* reported that fusion of 2-amino-pyrrole-3-carbonitriles **132b** and **143** with urea or thiourea afforded[33a,c] 4-amino-pyrrolo[2,3-*d*]pyrimidin-2-ones (or 2-thiones) **144**.

In 2014, K. M. H. Hilmy *et al.* reported the reaction of 2-amino-pyrrole-3-carbonitriles **145** with carbon disulfide in pyridine[123] to afford the corresponding pyrrolothiazine-2-thiones **146** which could be converted to pyrrolopyrimidine derivatives **147**, **148** and **149** via treatment with KOH, ethylamine or hydrazine hydrate, independently.





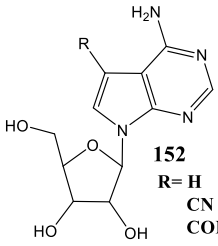
3. Biological value of pyrrole and pyrrolopyrimidine

3.1. Anti-microbial activity

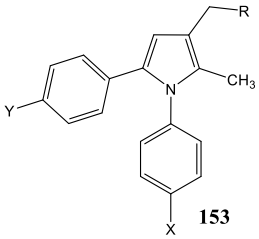
It was commonly assumed that many bromopyrrole alkaloid metabolites were served as antibacterial and antifungal agents[124-126]. For example, the pyrrolomycin A **(150a)** had distinguished antibiotic activity[127], natural product dispacamide B **(150b)** and its derivatives isolated from sponge had evident antibacterial activities[126,128,129]. Also, monodeoxy-pyoluteorin **(150c)** and 2-(2′-hydroxy benzoyl) pyrrole bromine **(150d)**[130, 131] are pyrrole derivatives having antimicrobial activity against *Staphylococcus aureus, Bacillus subtilis* and *Escherichia coli*, added to antifungal activity against *Candida albicans*.

Diguanido 1-methyl-2,5-diaryl-1H-pyrrole derivatives **151** have antifungal activity against Candida species.[132] The antifungal activity of compound **151** (R=CH_3) was better than that of fluconazole on *Candida albicans, Candida krusei,* and *Candida parapsilosis.*

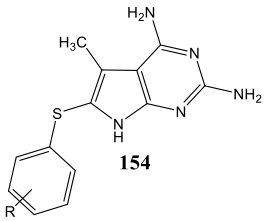
Tubercidin, Toyocamycin and Sangivamycin **152** are naturally occurring pyrrolo[2,3-*d*]pyrimidine antibiotics[133-137] having significant activity against *Mycobacterium tuberculosis, Candida albicans* and *Streptococcus neoformans*



2-Methyl-1,3,5-trisubstituted pyrroles **153** have significant activity against *Mycobacterium tuberculosis*[138,139].



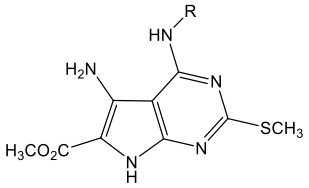
2,4-Diamino-5-methyl-6-substituted pyrrolo [2,3-*d*]pyrimidines **154** are potent and selective dihydrofolate reductase (DHFR) inhibitors[140] against *Pneumocystis carinii, Toxoplasma gondii* and *Mycobacterium avium.*



154

R=3-Cl, 4-Cl, 2,4-Cl_2, 2-OCH_3, 3-OCH_3, 4-OCH_3

Pyrrolo[2,3-*d*]pyrimidine-6-carboxylic acid esters **87** possess fungicidal properties against *Fusarium nivale*, *Septoria nodorum* and *Pythium altinum* [79].



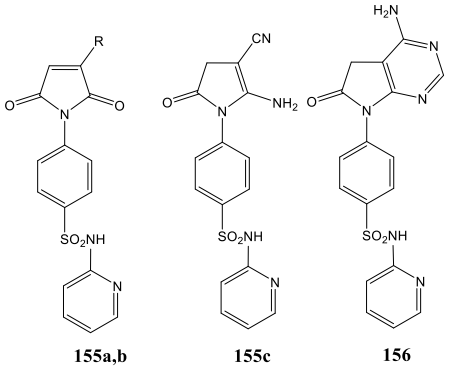
87

R=CH_3, butyl, 2-Cl-C_6H_4

Several pyrroles **155 a-c** and pyrrolopyrimidine containing sulfonamide **156** are proved to exhibit a remarkable antifungal activity[141] compared with the standard fungicide mycostatine.

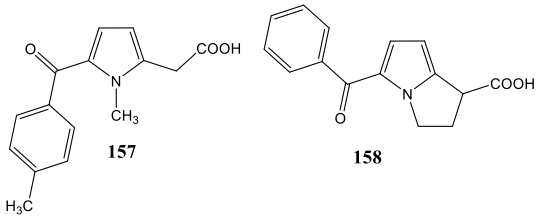
3.2. Analgesic and Anti-inflammatory activity

Pyrrole derivatives, tolmetin (Rumatol ®) **157** and ketorolac (Ketolac ®) **158** are non-steroidal anti-inflammatory drugs[142,143] which block prostaglandin synthesis by nonselective inhibition of cyclooxygenase (COX-1 and COX-2).



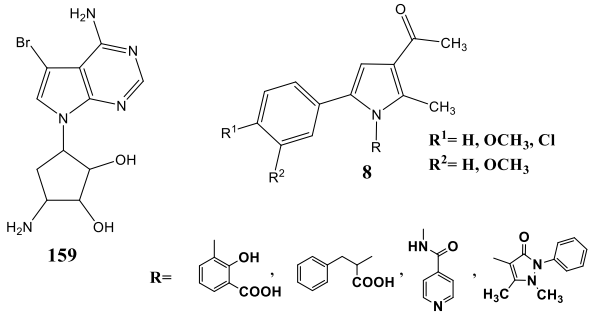
155a,b **155c** **156**

R= CN, $COCH_3$



157 **158**

Pyrrolo[2,3-*d*]pyrimidine **159** is a potent carbocyclic nucleoside adenosine kinase (AK) inhibitor[144], has analgesic and anti-inflammatory activity. Also pyrrole derivatives **8** were proved to have high analgesic activity[8].

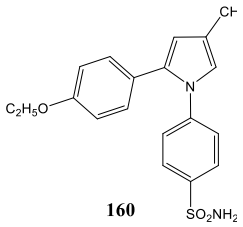


159 **8**

R=

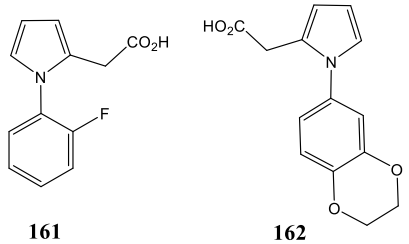
R^1= H, OCH_3, Cl
R^2= H, OCH_3

2-(4-Ethoxyphenyl)-4-methyl-1-(4-sulfamoyl phenyl)-1*H*-pyrrole (**160)** is known as selective cyclooxygenase-2 (COX-2) inhibitor[145]. The selectivity ratio of this pyrrole derivative was higher than those of the conventional non-steroidal anti-inflammatory drugs naproxen, indomethacin, and sodium diclofenate.



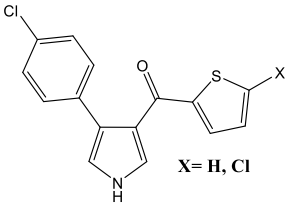
160

Also, 2-(N-(2-fluorophenyl)pyrrol-2-yl) acetic acid **(161)** and 2-[N-(2,3-dihydro-1,4-benzodioxin-6-yl)-pyrrol-2-yl] acetic acid **(162)** showed[146] more anti-inflammatory activity than the known classical anti-inflammatory agent ibuprofen.



161 **162**

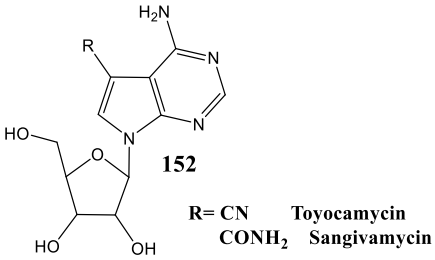
3-(4-Chlorophenyl)-4-(5-chlorothien-2-oyl) 1*H*-pyrrole **(163)** and its 4-(thien-2-oyl) analogue are templates for anti-inflammatory drugs, which show a balanced inhibition of the COX-isoenzymes and enhancing patient compliance[43].



163

3.3. Anti-cancer activity

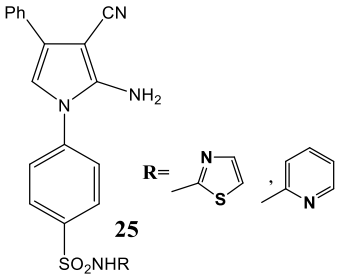
Toyocamycin and sangivamycin **152** are reported[147,148] as inhibitors of protein kinase C (PKC) and/or protein kinase A (PKA).



152

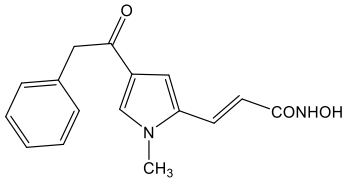
R= CN Toyocamycin
$CONH_2$ Sangivamycin

Pyrrole derivatives **25** are reported[33a] to possess potent anticancer activity against liver and breast cancer cell lines (HEPG2 and MCF7).



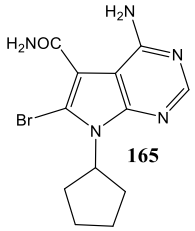
25

3-[1-Methyl-4-phenylacetyl-1*H*-pyrrol-2-yl]-N-hydroxy-2-propenamide **(164)** showed antiproliferative and cytodifferentiating effect in erythroleukemia[149].



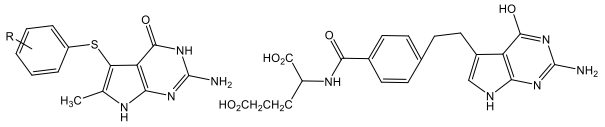
164

MCS-C2 (**165**), a sangivamycin analogue, has high activity as anti-proliferative[150] in human promyelocytic leukemia.



165

A series of novel 2-amino-4-oxo-5-[(substitutedphenyl)thio]pyrrolo[2,3-*d*]pyrimidines **166** are reported as potential inhibitors of thymidylate synthetase (TS) and dihydrofolate reductase (DHFR)[151]. Pemetrexed (Alimta®; Eli Lilly) **167** is illustrative example for clinically used thymidylate synthetase inhibitor and potent antimetabolite[152].

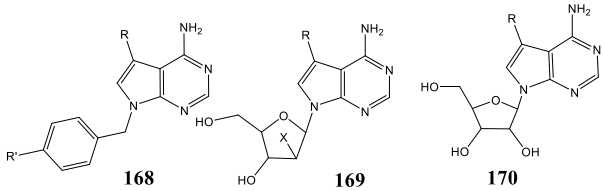


166 **167**

R= H, CH_3, OCH_3

3.4. Anti-viral activity

Some pyrrolo[2,3-*d*]pyrimidine derivatives **168-170** are found to have a significant anti-viral activity[153-157] against human cytomegalovirus (CMV).



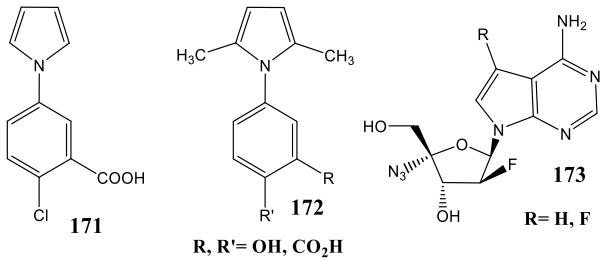
168 **169** **170**

R=CN, $CSNH_2$
R'= CH_3, OCH_3

R= CN, $CONH_2$
X= NH_2, N_3

R= I (5-Iodotubercidin)
= Cl (5-Chlorotubercidin)
= Br (5-Bromotubercidin)

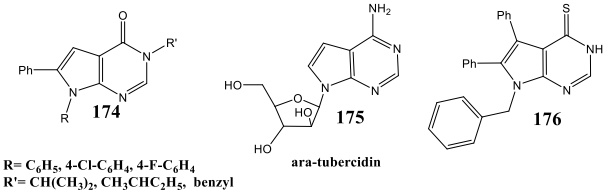
Pyrrole derivatives **171-173** possess a significant anti-viral activity against human immunodeficiency virus (HIV)[158-160].



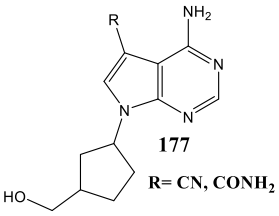
171 **172** **173**

R, R'= OH, CO_2H **R= H, F**

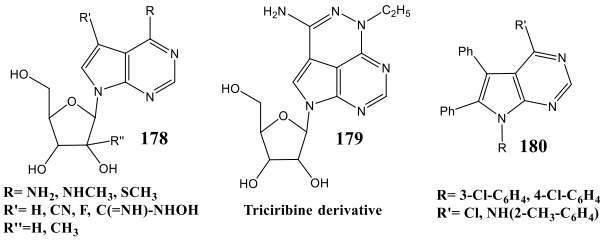
Pyrrolo[2,3-*d*]pyrimidine derivatives **174-176** can inhibit the viral replication of *herps simplex* virus[161-163].



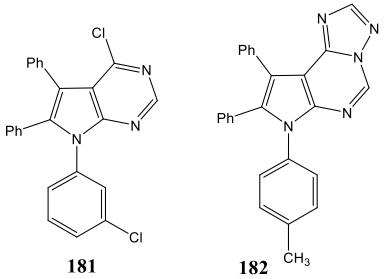
Pyrrolo[2,3-*d*]pyrimidine derivatives **177**, carbocyclic analogs Toyocamycin and sangivamycin, are proven to have anti-viral activity against hepatitis B virus (HBV)[164].



A series[165-167] of 4-substituted toyocamycin and sangivamycin analogs **178** and triciribine[168] derivative **179** show excellent anti-HCV activity due to their ability to inhibit HCV-RNA replication. Moreover, we reported pyrrolo[2,3-*d*]pyrimidine **180** as anti-HCV through inhibition of the viral NS5B RNA-dependent RNA polymerase enzyme[169].

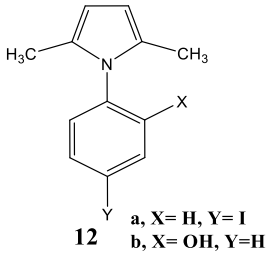


Also, we introduced[170] Pyrrolo[2,3-*d*] pyrimidine **181** and pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*c*] pyrimidine **182** to be significant anti-viral agents against *Coxsackievirus B4*, the later has also activity against *Rotavirus Wa strain.*



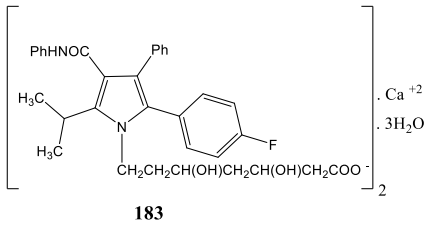
3.5. Anti-convulsant activity

V. M. Patil *et al.*[14] reported that two pyrrole derivatives **12a,b** have potential anti-convulsant activity.



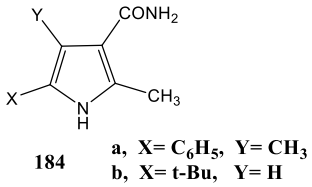
3.6. Anti-hyperlipidemic activity

Lipitor® **183** (atorvastatin calcium)[171], a pyrrole derivative, is a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor so it is a lipid-lowering agent.



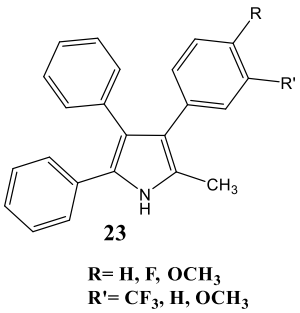
3.7. Anti-depressant activity

Both pyrrole derivatives **184a,b** exhibit favorable in vitro and in vivo antidepressant activities as they are targeting serotonin 5-HT2A, 5-HT2C, and serotonin transporter[172].



3.8. Anti-diabetic activity

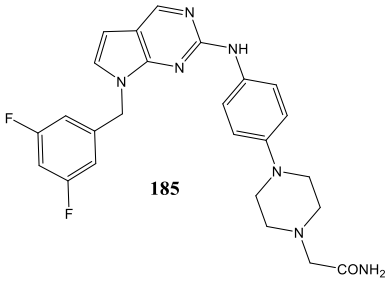
2-Methyl-4,5-diphenyl-3-substituted-phenyl-1H-pyrroles **23** have significant hepatic glucose lowering properties by acting as inhibitors of glucagon receptor[31].



3.9. Anti-allergic activity

Pyrrolo[2,3-*d*]pyrimidine derivative **185** is reported to be a potent Signal Transducers and Activators of Transcription 6 (STAT6) inhibitor[96]. STAT6 is an

important transcription factor in interleukin (IL)-4 signaling pathway and a key regulator of the type 2 helper T (Th2) cell immune response. Therefore, STAT6 is considered as an excellent therapeutic target for allergic conditions, including asthma and atopic diseases.



Conflict of Interest: The authors declare that they don't have any conflict of interest

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