Synthesis Strategies and Biological Value of Pyrrole and Pyrrolopyrimidine

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Submitted on: 23-10-2016; Revised on: 04-11-2016; Accepted on: 05-11-2016

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-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 pyroles 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, corins (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 pyroles

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

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

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

Huisgen then Potts et al. reported the synthesis of pyroles by reaction of 1,3-diene or diynes with primary amines.

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

1.2. Ring transformation of other heterocyclic rings

In 1996, McLeod et al.\textsuperscript{5} reported the reaction of 1,4-dicarbonyl derivatives with hydrazides to afford pyrrole 4 which then treated with nBu4NF to give 1-amino-pyrrole 5.

\[
\begin{align*}
R & = \text{H, alkyl, OH, NH}_2 \\
R', R'' & = \text{different alkyl and aryl groups}
\end{align*}
\]

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

\[
\begin{align*}
R & = \text{CH}_3, \text{C}_2\text{H}_5 \\
R'' & = \text{Naphthyl, pyridyl, C}_6\text{H}_5
\end{align*}
\]

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

\[
\begin{align*}
R & = \text{CH}_3, \text{COOH}_2 \\
R'' & = \text{C}_3\text{H}_5, \text{COOCH}_3, \text{CH(OH)}\text{C}_3\text{H}_7
\end{align*}
\]

In 2006, Danchev et al.\textsuperscript{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.\textsuperscript{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.

\[
\begin{align*}
R & = \text{Naphthyl, pyridyl, C}_6\text{H}_5 \\
R'' & = \text{different aryl groups}
\end{align*}
\]

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

Acetonyl acetone was also utilized\textsuperscript{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.\textsuperscript{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 \textsuperscript{16}.

![Chemical structure of pyrrole (16)](image)

In 2014, Pagadala et al.\textsuperscript{17} reported the synthesis of highly substituted pyrrole-N-acetic derivatives \textsuperscript{17} through the coupling of 1,4-diketones with amino acids following Paal-Knorr’s approach.

![Chemical structure of pyrrole-N-acetic derivative (17)](image)

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

![Chemical structure of steroidal pyrrole (18)](image)

1.1.2. Reaction of \(\alpha\)-aminocarbonyl compound with compound has active methylene group \(\alpha\)-to carbonyl.

(\textit{Knorr pyrrole synthesis})

It is the most widely used method for pyrrole synthesis. \(\alpha\)-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\textsuperscript{19} where the oximino precursor was converted to amino \textit{in situ}.

In 1955, Fischer\textsuperscript{17} reported the condensation of certain \(\alpha\)-amino ketones with \(\beta\)-diketones or \(\beta\)-ketoester in acidic medium to afford pyrroles \textsuperscript{20}.

Many authors\textsuperscript{21-28} reported the formation of \(\alpha\)-aminoketones \textit{in situ} via condensation of \(\alpha\)-hydroxyketones with certain amines which then were reacted with malononitrile, alkylcyanooacetate or alkylsulphonyl acetonitrile giving 2-aminopyrroles \textsuperscript{21}.

<Chemical reaction for \(\alpha\)-aminoketones synthesis (21)>

Goel et al.\textsuperscript{31} reported the reaction of benzoin, ketone and ammonium acetate in acetic acid to prepare 3,4,5-triaryl-1-H-pyrrole derivatives \textsuperscript{23} in 2004.
In 2012, Tamaddon et al.\textsuperscript{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.

![Chemical structure 24](image)

Ghorab et al.\textsuperscript{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-pyroles 25.

In 2011, Kaspersen et al.\textsuperscript{38} reported the synthesis of other 2-amino-pyrole 28 via the reaction of 4-fluorophenacyl bromide with ethoxycarbonyl acetamide salt in basic medium.

![Chemical structure 28](image)

In the same year Yavari et al.\textsuperscript{39} reported the reaction of other phenacyl bromide derivatives with certain enamiones under solvent-free conditions to afford 1,2,3,5-tetrasubstituted-pyrole derivatives 29.

Menichincheri\textsuperscript{40} et al. in 2010 and H. Nishida\textsuperscript{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.

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

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

![Chemical structure 26](image)

1.1.4. Reaction of tosylmethyl isocyanide with Michael acceptors.

This reaction was first reported\textsuperscript{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.

![Chemical structure 32](image)

Also, Dannhardt et al.\textsuperscript{43} in 2000 reported the reaction of TosMIC with chalcones 33 to obtain pyrroles 34.

In 2007, Krishna et al.\textsuperscript{44} reported the condensation reaction of 3-(2-tetrahydrofuranyl)-2-propenoate with TosMIC to afford pyrrole-carboxylate 35.
In 2012, Padmaja et al.\textsuperscript{45} reported the reaction of 1-(arylsulfonylethylsulfonylethyl)-2-arylethene with TosMIC to obtain pyrrole derivatives \textsuperscript{36}.

Similarly, in 2015, Brasca et al.\textsuperscript{46} reported the synthesis of pyrrole \textsuperscript{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.\textsuperscript{47} reported the reaction of certain 1,3-dicarbonyl compounds with ethyl glycinate HCl to give ethyl pyrrole-2-carboxylates \textsuperscript{38}.

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

In 2011, Pittala et al.\textsuperscript{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 \textsuperscript{42} which then cyclized in sodium ethoxide/ethanol mixture to give pyrrole aminoesters \textsuperscript{43}.

1.1.6. Reaction of nitroalkenes with carbonyl compounds.

In 2003, Ranu and Dey\textsuperscript{50} reported an efficient synthesis of substituted pyroles \textsuperscript{44} through one-pot, three-component condensation of a carbonyl compound, amine and nitroalkene using tetrabutyl-ammonium bromide.

In 2010, Rueping and A. Parra\textsuperscript{51} reported the synthesis of pyroles \textsuperscript{45} via reaction of β-bromonitrostyrenes with enaminoes in water.
In 2012, Li et al.\textsuperscript{52} reported FeCl\textsubscript{3}-catalyzed addition and cyclization of enamino esters with nitroalkenes to obtain tetrasubstituted pyrroles \textsuperscript{46}.

\[
\begin{align*}
\text{H}_2\text{C}=&\text{C}-\text{OOC}
\quad \text{FeCl}_3
\quad \text{O}_2\text{N}
\quad \text{N}=\text{N}
\quad \text{H}_2\text{C}=&\text{C}-\text{OOC} \\
\text{R}=3\text{-Cl-C}_6\text{H}_4, 4\text{-}(\text{CH}_3)\text{N}-\text{C}_6\text{H}_4, 2,4\text{-diCl-C}_6\text{H}_3
\end{align*}
\]

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

One-pot four-component condensation reaction of nitroalkanes, aromatic aldehydes, \(\beta\)-ketoesters, and amines in the presence of 10 mol \% NiCl\textsubscript{2} \cdot 6H\textsubscript{2}O afforded substituted pyrrole derivatives \textsuperscript{48} in good yields. This reaction was reported\textsuperscript{54} by A. T. Khan et al.

\[
\begin{align*}
\text{RCOOH} + \text{RNH}_2 + \text{CF}_3 + \text{C}_6\text{H}_5\text{OH} \rightarrow & \quad \text{R}^1\text{CH}=\text{O} - \text{OCH}_2\text{CHO} \\
\text{R}=&\text{H}, \text{CH}_3, \text{C}_6\text{H}_5
\end{align*}
\]

1.1.7. Piloty-Robinson pyrrole synthesis

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

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

1.1.8. Reaction of \(\alpha\)-dicarbonyl compound with secondary or tertiary amine having two active methylene groups.

In 1965, Friedman\textsuperscript{57} reported the reaction of benzils with dimethyl N-acetyliminodiacetate in the presence of sodium methoxide to afford 3,4-diarylpyrrole \textsuperscript{53}.

In 2003, Iwao et al.\textsuperscript{58} reported the condensation of dimethyl oxalate with iminodiacetates \textsuperscript{54} to afford 3,4-dimethoxypyrrole-2,5-dicarboxylates \textsuperscript{55}.

1.2. Synthesis of pyrrole via ring transformation

1.2.1. From aziridine and azirine derivatives

In 1977, Lukac et al.\textsuperscript{59} reported that 2-acylaziridines \textsuperscript{56} were transformed to pyrrole derivatives \textsuperscript{58} by ring expansion involving ring-opened dipolar intermediate \textsuperscript{57}.
In 2007, Kathriarachchi et al.\textsuperscript{60} reported the synthesis of pyrrole derivative 59 via palladium-catalyzed reaction of methyleneaziridines with 1,3-diketones.

![Diagram of pyrrole derivative synthesis](image)

R, R'~ different alkyl groups

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

![Diagram of pyrrole formation](image)

Authors suggested\textsuperscript{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).

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

![Diagram of pyrrole derivative synthesis](image)

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![Diagram of pyrrole formation](image)

Authors suggested\textsuperscript{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.\textsuperscript{63} reported the condensation of furano[2,3-d]pyrimidine 63 with benzyl amine to afford pyrrolo[2,3-d] pyrimidines 64.

![Diagram of furan derivative condensation](image)

Many authors\textsuperscript{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\textsuperscript{64}, using microwave\textsuperscript{65,66} or ultrasound conditions\textsuperscript{67}. According to the authors, the methoxy groups can be deprotected under acidic conditions. The intermediate can easily form the reactive dialdehyde which on reaction with amines can lead to pyroles.
Similarly, in 2015, Mieczkowski et al.\textsuperscript{68} reported the reaction of 6-substituted furo[2,3-d]pyrimidin-2(3H)-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(3H)-one nucleosides to the 3H-pyrolo[2,3-d]pyrimidin-2(7H)-one nucleosides \textsuperscript{66}.

![Chemical structure](image1)

R= SO\textsubscript{2}(C\textsubscript{6}H\textsubscript{5}), SO\textsubscript{2}(4-CH\textsubscript{3}C\textsubscript{6}H\textsubscript{4}H\textsubscript{2}), SO\textsubscript{2}(2-CH\textsubscript{2}C\textsubscript{6}H\textsubscript{4}), C\textsubscript{6}H\textsubscript{5}, 4-OCH\textsubscript{3}C\textsubscript{6}H\textsubscript{4}H\textsubscript{2}, 1-ethylpropyl, CH\textsubscript{2}=CHR=CH\textsubscript{2}, 2-pyridinyl

1.2.3. From thiophene derivative

Middleton et al.\textsuperscript{69} in 1958 and Taylor et al.\textsuperscript{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).

![Chemical structure](image2)

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.\textsuperscript{70} and Abd-Elhamid et al.\textsuperscript{71}.

Analogously, in 2004, Joshi et al.\textsuperscript{72} reported the transformation of pyridazine C-nucleoside 72 to the corresponding pyrrole 73.

![Chemical structure](image3)

1.2.5. From oxazole derivatives

Hershenson and Pavia reported\textsuperscript{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 triethylxoniumtetrafluoroborate in the presence of dimethylacetylene-dicarboxylate (DMAD) as the dipolarophile offered pyrroles 75.

Also, in 2009, Coşkun and Çetin reported\textsuperscript{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\textsubscript{2}O\textsuperscript{+}, 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.
1.2.6. From oxirane derivative

In 2009, Wyrębek et al.\(^75\) reported the transformation of oxirane derivatives 78 to pyroles 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 pyroles 81.

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.

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.

In 1997, Talekar and Wightman reported\(^83\) the formation of pyrrolo[2,3-d]pyrimidines 93 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.

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

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

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

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

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

A group of researchers reported the formation of pyrrolo[2,3-d]pyrimidines via cyclization of 5-alkynylpyrimidine derivatives using either 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or tetrabutylammonium fluoride (TBAF). While V. Prieur et al. reported the same reaction in the presence of cesium carbonate under microwave irradiation in 2014 and 2015.
In 2009, E. Pudziuvelyte et al. described\(^\text{103}\) the synthesis of pyrrolo[3,2-\(d\)]pyrimidin-5-oxides \(^\text{113}\) via pyridine initiated smooth cycloisomerization of 5-nitro-6-arylethynylpyrimidines \(^\text{112}\).

\[
\begin{align*}
\text{R}^e\text{H}, \text{SCH}_3 &
\text{Pyridine} \\
\text{Pyrolo[3,2-\(d\)]pyrimidin-5-oxide} & \\
\text{R}^e\text{C}_\text{H}_2, 4\text{-CH}_2\text{C}_\text{H}_3, 4\text{-CH}_2\text{C}_\text{H}_3\text{C}_\text{H}_3
\end{align*}
\]

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

\[
\begin{align*}
\text{R}^e\text{C}_\text{H}_3, 4\text{-CH}_2\text{C}_\text{H}_3, 4\text{-CH}_2\text{C}_\text{H}_3
\end{align*}
\]

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

\[
\begin{align*}
\text{R}^e\text{H}, \text{Cl} &
\text{R}^e\text{H}, \text{Cl}, \text{F}, \text{OCH}_3 \\
\text{6-amino-uracil} & \\
\text{isatins} & \\
\text{acetophenones} & \\
\text{pyrrolo[2,3-\(d\)]pyrimidines} \end{align*}
\]

Analogous to the previously reported\(^\text{87-92}\), N. J. O’Brien et al. reported\(^\text{106}\) the condensation reaction of 6-amino-uracil \(^\text{116a}\) with α-chloroacetaldehyde affording pyrrolopyrimidine \(^\text{118}\) in 2014.

\[
\begin{align*}
\text{6-amino-uracil} & \\
\alpha\text{-chloroacetaldehyde} & \\
\text{pyrrolopyrimidine} \end{align*}
\]

Similar to what was reported\(^\text{87-92}\) by Edmont and Williams in 2000, L. Saikia et al. described\(^\text{107}\) Michael addition of 6-amino-1,3-dimethyluracil \(^\text{119}\) to (2-nitrovinyl)benzene affording pyrrolo[2,3-\(d\)]pyrimidine \(^\text{120}\) in 2016.

\[
\begin{align*}
\text{6-amino-1,3-dimethyluracil} & \\
\text{(2-nitrovinyl)benzene} & \\
\text{pyrrolo[2,3-\(d\)]pyrimidine} \end{align*}
\]

2.2. Synthesis of pyrrolopyrimidines from pyrrole derivatives

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

Alternatively, treatment\(^\text{108,114}\) of ethyl 2-amino-pyrrole-3-carboxylates \(^\text{126}\) with formamide gave pyrrolo[2,3-\(d\)]pyrimidine-4-ones \(^\text{127}\).
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)\(^{116}\).

\[
\text{R} \quad \text{DMCA} \quad \text{P}_{2}O_{5}
\]

\[
\text{X} = \text{CN, CONH}_{2} \\
\text{R}, \text{R}', \text{R''} = \text{different alkyl and aryl groups}
\]

Reaction\(^{33c,116}\) of the 2-aminopyrroles \(132\) with aryl isothiocyanate gave pyrrolo[2,3-d]pyrimidine derivatives \(133\).

\[
\text{R}^+\text{NCS}
\]

\[
\text{X} = \text{CN, CONH}_{2} \\
\text{R}, \text{R}', \text{R''} = \text{different alkyl and aryl groups}
\]

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-dihydropyrrolo[2,3-d]pyrimidin-4-one \(137\).

M. M. Ghorab et al. reported that fusion of 2-amino-pyrrole-3-carbonitriles \(132b\) and \(143\) with urea or thiourea afforded\(^{33c,119}\) 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\(^\text{(124-126)}\). For example, the pyrrolomycin A (150a) had distinguished antibiotic activity\(^\text{(127)}\), natural product dispacamide B (150b) and its derivatives isolated from sponge had evident antibacterial activities\(^\text{(126,128,129)}\). Also, monodeoxy-
pyoluteorin (150c) and 2-(2-hydroxy benzoyl) pyrrole bromine (150d)\(^\text{(130,131)}\) are pyrrole derivatives having antimicrobial activity against \textit{Staphylococcus aureus}, \textit{Bacillus subtilis} and \textit{Escherichia coli}, added to antifungal activity against \textit{Candida albicans}.

Diguanido 1-methyl-2,5-diaryl-1H-pyrrole derivatives 151 have antifungal activity against Candida species\(^\text{(132)}\). The antifungal activity of compound 151 (R=CH\(_3\)) was better than that of fluconazole on \textit{Candida albicans}, \textit{Candida krusei}, and \textit{Candida parapsilosis}.

Tubercidin, Toyocamycin and Sangivamycin 152 are naturally occurring pyrrolo[2,3-d]pyrimidine antibiotics\(^\text{(133-137)}\) having significant activity against \textit{Mycobacterium tuberculosis}, \textit{Candida albicans} and \textit{Streptococcus neoformans}.

2-Methyl-1,3,5-trisubstituted pyroles 153 have significant activity against \textit{Mycobacterium tuberculosis}\(^\text{(138,139)}\).

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

Pyrrolo[2,3-d]pyrimidine-6-carboxylic acid esters \( \text{87} \) possess fungicidal properties against *Fusarium nivale*, *Septoria nodorum* and *Pythium al tinum* \(^{79}\).

Several pyroles \( \text{155a-c} \) and pyrrolopyrimidine containing sulfonamide \( \text{156} \) are proved to exhibit a remarkable antifungal activity \(^{144}\) compared with the standard fungicide mycostatine.

### 3.2. Analgesic and Anti-inflammatory activity

Pyrole derivatives, tolmetin (Rumatol \(^{©}\) \( \text{157} \)) and ketorolac (Ketolac \(^{©}\) \( \text{158} \)) are non-steroidal anti-inflammatory drugs \(^{142,143}\) which block prostaglandin synthesis by nonselective inhibition of cyclooxygenase (COX-1 and COX-2).

Pyrrolo[2,3-d]pyrimidine \( \text{159} \) is a potent carbocyclic nucleoside adenosine kinase (AK) inhibitor \(^{144}\), has analgesic and anti-inflammatory activity. Also pyrrole derivatives \( \text{8} \) were proved to have high analgesic activity \(^{9}\).

2-(4-Ethoxyphenyl)-4-methyl-1-(4-sulfamoyl phenyl)-1\(H\)-pyrrole \( \text{160} \) 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.

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

3-(4-Chlorophenyl)-4-(5-chlorothien-2-oyl) 1\(H\)-pyrrole \( \text{163} \) 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 \(^{147}\).
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).

Pyrole derivatives 25 are reported\(^{33a}\) to possess potent anticancer activity against liver and breast cancer cell lines (HEPG2 and MCF7).

3-\{1-Methyl-4-phenylacetyl-1H-pyrrol-2-yl\}-N-hydroxy-2-propenamide (164) showed antiproliferative and cytodifferentiating effect in erythroleukemia\(^{149}\).

MCS-C2 (165), a sangivamycin analogue, has high activity as anti-proliferative\(^{150}\) in human promyelocytic leukemia.

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\(^{16}\); Eli Lilly) 167 is illustrative example for clinically used thymidylate synthetase inhibitor and potent antimetabolite\(^{152}\).

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).

Pyrrole derivatives 171-173 possess a significant anti-viral activity against human immunodeficiency virus (HIV)\(^{158-160}\).

Pyrrolo[2,3-d]pyrimidine derivatives 174-176 can inhibit the viral replication of herpes simplex virus\(^{161}\).
Pyrrolo[2,3-d]pyrimidine derivatives 177, carbocyclic analogs Toyocamycin and sangivamycin, are proven to have anti-viral activity against hepatitis B virus (HBV)\textsuperscript{162}.

A series\textsuperscript{165-167} of 4-substituted toyocamycin and sangivamycin analogs 178 and triciribine\textsuperscript{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\textsuperscript{169}.

Also, we introduced\textsuperscript{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.\textsuperscript{14} reported that two pyrrole derivatives 12a,b have potential anti-convulsant activity.

3.6. Anti-hyperlipidemic activity
Lipitor\textsuperscript{183} (atorvastatin calcium)\textsuperscript{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\textsuperscript{172}.

3.8. Anti-diabetic activity
2-Methyl-4,5-diphenyl-3-substituted-phenyl-1H-pyroles 23 have significant hepatic glucose lowering properties by acting as inhibitors of glucagon receptor\textsuperscript{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\textsuperscript{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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