CHAPTER 2

REVIEW OF LITERATURE
2. REVIEW OF LITERATURE

2.1 CHEMISTRY OF VINYLAMIDINES AND ITS INTERMEDIATES

Functionlized vinylamidines are versatile intermediates for a variety of biologically active heterocycles. These include various pyrimidines and condensed pyrimidines in particular. Intermediates involved in the synthesis of vinylamidines, typically are functionalized ketene acetals, viz. ketene dithioacetals (S,S-acetal), ketene N,S-acetal and ketene N,O-acetal.

2.1.1 Chemistry of ketene dithioacetal (S,S-acetal)

The polarised ketene dithioacetals of the general formula \(90\)\(^{179}\), which may carry either one or two electron withdrawing groups at the \(\alpha\)-carbon atom (Table 3), belong to a class of intermediates, generally known as either polarised, push-pull or donor-acceptor ethylenes.

![Diagram of ketene dithioacetal](image)

Table 3: Acyclic polarized ketene dithioacetals

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>(R_1)</th>
<th>(R_2)</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-CHO</td>
<td>H, Me, Et, Ph</td>
<td>180, 181</td>
</tr>
<tr>
<td>2</td>
<td>COR(_3); (R_3 = \text{aryl, alkyl, cycloalkyl, 2-furyl, 2-thienyl, 2,3-pyridyl, styryl})</td>
<td>H, alkyl, aryl, benzyl, alkenyl, acyl, aroyl, CH(_2)CN, (\alpha)-pyridyl</td>
<td>182-187</td>
</tr>
<tr>
<td>3</td>
<td>CN</td>
<td>H, aryl, 3-indolyl, (\alpha)-pyridyl, aroyl, 2-furoyl, CN, 2-thienoyl</td>
<td>188-192</td>
</tr>
<tr>
<td>4</td>
<td>COOEt, COOMe, COOH</td>
<td>H, alkyl, benzyl, vinyl, aryl, MeCO, ArCO, CN, COOMe, COOEt, CONH(_2), CN</td>
<td>193-198</td>
</tr>
<tr>
<td>5</td>
<td>CONH(_2)</td>
<td>CN</td>
<td>198</td>
</tr>
<tr>
<td>6</td>
<td>NO(_2)</td>
<td>H, PhCO, COOEt</td>
<td>199-200</td>
</tr>
<tr>
<td>7</td>
<td>RSO(_2); (R = \text{Ph, alkyl})</td>
<td>H, CN, COMe, Ar, COOEt</td>
<td>201-204</td>
</tr>
</tbody>
</table>
2.1.1.1 Synthesis of ketene dithioacetals

Ketene dithioacetals (91) are easily prepared by reacting the corresponding active methylene compounds with carbon disulphide in the presence of a suitable base followed by alkylation, often in a one-pot reaction.

\[ R_1\,\text{C}\equiv\text{C}\,R_2 + \text{CS}_2 \xrightarrow{\text{i. Base/CS}_2} R_1\,\text{C}\equiv\text{C}\,\text{S}\,\text{S}\,R_2 \xrightarrow{\text{ii. CH}_3\text{I/(CH}_3\text{)}_2\text{SO}_4} \]

(91)

The alkali sensitive Meldrums acid (92) has been converted into the corresponding bisalkylthiolydine derivatives (93) in moderate to good yields by generating its enolate anion in the presence of triethylamine as base in dimethyl sulfoxide.\(^{205}\)

\[ \text{O} \quad \text{+ CS}_2 \xrightarrow{\text{i. Et}_3\text{N/DMSO/RT}} \text{SR} \quad \text{O} \xrightarrow{\text{ii. RX/DMSO/0°C}} \text{R} = \text{Me, Et, -(CH}_2\text{)}_2\text{, -(CH}_2\text{)}_3\text{,} \]

(92) (93)

Villemin D, et al, reported a convenient one-pot synthesis of ketene dithioacetals (94). The synthesis utilizes the following scheme.\(^{206}\)

\[ X + Y + \text{CS}_2 \xrightarrow{2\text{MeI/MeCN, KF/Al}_2\text{O}_3, \text{r.t.}} X\,\text{C}\equiv\text{C}\,Y \]

(94) \(X = Y = \text{CN, COOEt}\)

The bis(arylthio)derivatives (95), which could not be prepared through the corresponding dithiolate anions, have been prepared by nucleophilic displacement of \(\beta\)-dichloro groups by arylthiolate anions in the corresponding enoates.\(^{207,208}\)

\[ \text{Cl} \quad \text{COOEt} \quad \text{Cl} \quad \text{C}_6\text{H}_5\text{SH/ETOH/Na} \quad \text{Cl} \quad \text{COOEt} \]

(95) \(X = \text{CN}\)

The two-step method of alkylation was advantageously extended to prepare the important group of \(\alpha\)-oxo-\(\alpha\)-alkenyl dithioacetals in moderate to good yields.\(^{209}\) Thus the
dithioesters (96) underwent spontaneous thio-Claisen rearrangement during alkylation with allyl, crotyl or methacrylyl halides to afford first the rearranged dithioesters, which were further alkylated to afford the corresponding dithioacetals (97). The two step reaction sequence was achieved in one pot through adding alkenyl and alkyl halides sequentially to afford the corresponding dithioacetals (98) in identical yields.

\[
\begin{align*}
\text{(96)} & \quad \begin{array}{c}
\text{HO} \\
\text{S} \\
\text{C} \\
\text{S} \\
\text{R}_1 \\
\text{R}_2
\end{array} \\
\begin{array}{c}
\text{R}_3 \\
\text{R}_4
\end{array} \\
+ \\
\begin{array}{c}
\text{R}_1 \\
\text{R}_2
\end{array} \\
\begin{array}{c}
\text{H} \\
\text{Br}
\end{array} \\
\xrightarrow{K_2CO_3/\text{acetone}} \\
\begin{array}{c}
\text{O} \\
\text{S} \\
\text{C} \\
\text{C} \\
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{(97)} & \quad \begin{array}{c}
\text{O} \\
\text{S} \\
\text{C} \\
\text{C} \\
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4
\end{array}
\end{align*}
\]

R1 = Me, C6H5, 4-Me-C6H4, 4-Cl-C6H4, 4-MeO-C6H4; R2 = Me, Et; R3 = R4 = H
R1 = Me, C6H5, 4-Me-C6H4, 4-Cl-C6H4, 4-MeO-C6H4; R2 = Me; R3 = H; R4 = Me
R1 = 4-Cl-C6H4, R2 = Me; R3 = Me; R4 = H
2.1.1.2 Reactions of ketene dithioacetals: Synthesis of functionalized ketene N,S- and N,N-acetals

The doubly activated ketene dithioacetals (91) undergo an addition elimination sequence with primary and secondary amines to yield the corresponding N,S- and N,N-acetals (99, 100) in high yields.\textsuperscript{210,211} In these systems, the formation of N,S- and N,N-acetals can be controlled by the stoichiometric addition of amines.

\[
\text{R}_3\text{R}_4\text{NH} \quad \text{(1 eq)} \\
\text{R}_3\text{R}_4\text{NH} \quad \text{(2 eqv or more)}
\]

\[
\begin{array}{c}
\text{R}_1 = \text{CN}; \text{R}_2 = \text{CN}, \text{CONH}_2, \text{CO}_2\text{Alk} \\
\text{R}_1 = \text{CO}_2\text{Alk}, \text{R}_2 = \text{CO}_2\text{Alk}, \text{MeCO}, \text{ArCO} \\
\text{R}_1 = \text{MeCO}, \text{ArCO}; \text{R}_2 = \text{MeCO}, \text{ArCO}, \text{CN}, \text{SO}_2\text{Ar} \\
\text{R}_3 = \text{H}, \text{R}_4 = \text{alkyl}, \text{aryl}; \text{R}_3 = \text{R}_4 = \text{morpholino, pyrrolidino, piperidino, aziridino} \\
\text{R}_1 = \text{MeCO}, \text{ArCO}; \text{R}_2 = \text{H}; \text{R}_3 = \text{aryl, alkyl}; \text{R}_4 = \text{H}
\end{array}
\]

A convenient method of preparation of N,S-acetals (102) involves the reaction of enolate anion with isothiocyanates (101) followed by alkylation.\textsuperscript{212-217}

\[
\begin{array}{c}
\text{R}_1 + \text{R}_2\text{N}+\text{C}=\text{S} \\
\text{i. Base} \\
\text{ii. Mel}
\end{array}
\]

\[
\text{(101)}
\]

\[
\text{R}_1
\]

\[
\begin{array}{c}
\text{NHR}_3 \\
\text{(102)}
\end{array}
\]

The methylthio group of the ketene dithioacetal (103) has successfully been replaced by an amide.\textsuperscript{218}

\[
\text{MeS}\text{CN} + \text{MeS}\text{COOEt} \quad \text{NaH, benzene, r.t.} \\
\text{N,N-dimethylacetamide} \quad \text{40-76%}
\]

\[
\text{(103)}
\]

\[
\text{ROCHN} \quad \text{(104)}
\]

R = Me, phenyl, styryl, 4-NO\textsubscript{2}-phenyl, 4-Me-phenyl, 4-OCH\textsubscript{3}-phenyl
Zhang Q, et al. reported the first synthesis of single and mixed \( \alpha \)-oxoketene dithioacetals (105) from active methylene precursors.\(^{219}\)

\[
\begin{align*}
\text{EtONa} & \quad \text{EtOH} \\
\xrightarrow{\text{R}_3\text{X}} & \quad \xrightarrow{\text{K}_2\text{CO}_3, \text{R}_4\text{X}} \quad \text{DMF}
\end{align*}
\]

\[
\begin{align*}
\text{Me}_2\text{S} & \quad \text{CN} \\
\xrightarrow{\text{R}_2N-N\text{R}_1} & \quad \text{Me}_2\text{S} \quad \text{CN}
\end{align*}
\]

Ketene dithioacetals (106) have been also reacted with cyclic amines to afford corresponding N,S-acetals (107).\(^{220}\)

\[
\begin{align*}
\text{Me}_2\text{S} & \quad \text{CN} \\
\xrightarrow{\text{C}_2\text{H}_5\text{OH}} & \quad \text{Me}_2\text{S} \quad \text{CN}
\end{align*}
\]

\[
\begin{align*}
\text{Me}_2\text{S} & \quad \text{CN} \\
\xrightarrow{\text{C}_2\text{H}_5\text{OH}} & \quad \text{Me}_2\text{S} \quad \text{CN}
\end{align*}
\]
Shishoo C.J., et al reported the first isolation of vinylamidine intermediate (109) while synthesizing pyrimidines from functionalized ketene N,S-acetals (108).  

\[
\text{EtOOC-CN} + \text{NH}_2 \rightarrow \text{EtOOC-CN-NH}_2 \\
\text{ArHN-SMe} \quad \text{ArHN} \quad \text{ArHN}
\]

(108)

\[
\text{Ar} = \text{phenyl, 4-Me-phenyl, 4-Cl-phenyl} \\
\text{R} = \text{H, Me, Ph}
\]

Ketene dithioacetals (110, 112) have been condensed with amidines under different conditions to afford pyrimidine (111, 113) derivatives.  

\[
\text{HCl/dioxane} \\
\text{NaOEt/EtOH} \\
\text{p-TSA benzene}
\]

(109)
2.2 BIOLOGICAL SIGNIFICANCE OF AMIDINES

Amidine derivatives have been reported to possess varied pharmacological activities.  

2.2.1 Amidines as orally active anticoagulants  

Mack H., et al. reported a series of amidine derivatives as orally active thrombin inhibitors. The most potent compound 114 exhibited an IC₅₀ value of 0.98 nM in a chromogenic substrate assay.

\[ \text{(114)} \]

Separately, Cui J., et al. reported a new series of amidine-substituted bis-cycloketones as Factor Xa inhibitors. Compound 115 emerged out as the best with Ki value of 42 nM against FXa with strong selectivity against thrombin (1000-fold), trypsin (300-fold) and plasmin (900-fold).

\[ \text{(115)} \]

Dange V., et al. reported a series of hydroxyl pyrazole based Factor IXa inhibitors. Authors concluded that the amidine substituent is essential for the potency and selectivity. Compound 116 showed Ki value of 50 nM along with selectivity over thrombin (813-fold), FVIIa (36-fold), FXa (96-fold) and trypsin (44-fold).
Sielecki T. M., et al. demonstrated the effect of benzamidine substitution on the duration of antiplatelet efficacy in dog. Most of the compounds (117) displayed modest IC\textsubscript{50} values in the range of 16-82 nM in an \textit{in vitro} hPRP assay.\textsuperscript{226}

![Chemical structure](image)

(116)

\[R = \text{H, Et, n-butyl, 2-OMe-benzyl, 3-F-benzyl}
\]
\[R_1 = \text{-NHCOO(n-butyl), -NHSO_2-m-tolyl, -NHSO_2-o-tolyl}
\]

2.2.2 Amidines as antibacterial and antifungal agents

A series of 1,3-diazabuta-1,3-dienes were synthesized and reported as potential antibacterial and antifungal agents.\textsuperscript{227} Compounds (118) displayed potent antibacterial activity against \textit{E. coli}, \textit{S. aureus}, \textit{P. aeruginosa}, \textit{B. cereus} and \textit{B. subtilis}. Compounds also showed good antifungal activity against \textit{C. albicans} and \textit{A. niger} strains.

![Chemical structure](image)

(118)

\[R_1 = \text{H, Me, Cl}
\]
\[R_2 = \text{Me, Et, i-Pr}
\]
Özden S., et al. reported a series of 1H-benzimidazole-5-carboxylates derivatives carrying amidine groups as potential antibacterials.\textsuperscript{228} Results showed that aromatic amidine derivatives (119) exhibited the best inhibitory activity with 1.56-0.39 μg/mL MIC values against methicillin-resistant \textit{S. aureus} (MRSA) and methicillin-resistant \textit{S. epidermis} (MRSE) strains.

\begin{equation}
R_1 = \text{benzyl, 2,4-dichlorobenzyl} \\
R_2 = \text{4-chlorobenzyl, 3,4-dichlorobenzyl} \\
R_3 = \text{H, 3,4-dichlorobenzyl}
\end{equation}

Wiedner-wells, M. A., et al. reported some amidino benzimidazoles as inhibitors or bacterial two-component systems.\textsuperscript{229} The most potent compound 120 exhibited MIC values of 1, 0.5, 1 and 0.5 μg/mL against \textit{S. aureus}, MRSA, \textit{E. faecalis} and \textit{E. faecium} strains.

\begin{equation}
\end{equation}

\textbf{2.2.3 Amidines as anticancer agents}

Stolic, I. et al. reported a series of bisbenzimidazole amidines as potential anticancer agents.\textsuperscript{230} Compound 121 displayed the best inhibitory potential and in equitoxic concentration (IC\textsubscript{50} = 1 μM) induced accumulation of cells in G2/M phase after 48 h of incubation. Fluorescence microscopy showed that 121 entered into live HeLa cells within 30 min, but did not accumulate in nuclei even after 2.5 h. It inhibited the growth of \textit{Trypanosoma cruzi} epimastigotes (IC\textsubscript{50} = 4.3 μM).
A novel amidine analogue of melphalan (AB4, 122) was compared to its parent drug, melphalan, in respect to cytotoxicity, DNA and collagen biosynthesis in MDA-MB-231 and MCF-7 human breast cancer cells. It was found that AB4 was more active inhibitor of DNA and collagen synthesis as well more cytotoxic agent than melphalan. The topoisomerase I/II inhibition assay indicated that AB4 is a potent catalytic inhibitor of topoisomerase II. Data from the ethidium displacement assay showed that AB4 intercalated into the minor-groove at AT sequences of DNA.

Recently, Letari, et al. filed a patent claiming some benzamidine derivatives for treatment and prevention of cancer therapy induced mucositis. The most potent compound 123 displayed IC$_{50}$ values of 30, 63 and 54 μM for interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α in an lipopolysaccharide (LPS)-induced cytokine release in rat peritoneal macrophages, respectively.
2.2.4 Amidines as antiviral agents

Tucker, J. A. et al. reported a series of acyloxyamidine derivatives as cytomegalovirus DNA polymerase inhibitors. The compounds (124) displayed very good inhibition of cytomegalovirus (CMV) replication in human foreskin fibroblast (HFF) cells ($IC_{50} = 0.7-73 \mu M$).

![Chemical Structure](image)

A series of piperazine amidines has recently been patented claiming the compounds as potential antiretroviral agents. Most of the compounds (125) displayed $EC_{50}$ values less than 0.5 \( \mu M \) against human epithelial cell lines (HeLa) expressing the HIV-1 receptor CD4.

![Chemical Structure](image)

Kraska, A. R. et al. patented a series of aromatic amidines as antiviral agents. Compound (126) was found to be the most potent with $ED_{50}$ value of 2.8 mg/kg for encephalomyocarditis virus.

![Chemical Structure](image)
2.2.5 Amidines as Nitric Oxide Synthase (NOS) inhibitors

A series substituted amidines was identified as NOS inhibitors by Moore, W. M. et al.\textsuperscript{236} 2-Methylthioacetamide (127) and 2-thienylcarbamidine (128) were found to be the most potent of the series with IC\textsubscript{50} values of 3.9 and 2.9 μM for human neuronal constitutive (hnc)-NOS. 2-Thienylcarbamidine (128) and cyclopropylcarbamidine (129) were the most potent inhibitors for human inducible (hi)-NOS with IC\textsubscript{50} values of 5.2 and 6.5 μM, respectively. These substituted amidines represented a new class of NOS inhibitors and provided a foundation for potential therapeutic agents.

\[
\begin{align*}
\text{(127)} & \quad \text{S} \quad \text{NH} \quad \text{NH}_2 \\
\text{(128)} & \quad \text{S} \quad \text{S} \quad \text{NH} \quad \text{NH}_2 \\
\text{(129)} & \quad \text{N} \quad \text{NH} \quad \text{NH}_2
\end{align*}
\]

The potency and selectivity of a series of heterocyclic amidine derivatives were examined as inhibitors of the three human NOS isoforms.\textsuperscript{237} Potencies for these inhibitors (130) were found to be in the low micromolar range (IC\textsubscript{50} = 0.15-14.03) for hi-NOS with some examples exhibiting a 500-fold selectivity versus e-NOS.

\[
\begin{align*}
\text{(130)} & \quad X = \text{CH}_2, \text{NCH}_3, \text{O}, \text{S}, (\text{CH}_2)_2 \\
& \quad R = \text{H}, \text{COOEt}, \text{n-butyl}, \text{nitropropyl}, \text{aminopropyl}
\end{align*}
\]

Harnett, J. J. et al. reported some novel lipoic acid analogs containing amidino group as NOS inhibitors.\textsuperscript{238} Most potent compounds (131, 132) inhibited nNOS with IC\textsubscript{50} values of 1.04 and 1.15 μM, respectively.

\[
\begin{align*}
\text{(131)} & \quad m = 3; \quad \text{(132)} & \quad m = 0
\end{align*}
\]

2.2.6 Amidines for the treatment of CNS disorders

Burnett, D. A. et al. patented a series of substituted N-aryl amidines as selective dopamine D\textsubscript{1}-receptor antagonists.\textsuperscript{239} Compound 133 emerged out as the most potent compound with IC\textsubscript{50} value of 0.9 nM with D\textsubscript{2}/D\textsubscript{1} ratio of 1258.5.
A series of \( N^1 \)-(benzyl)cinnamamidine derived N-methyl-D-aspartate (NMDA) receptor 2B (NR2B) subtype-selective NMDA receptor antagonists have been reported.\(^{240}\) Compound 134 has 1000-fold lower IC\(_{50}\) in NR2B than NR2A-containing cells (IC\(_{50}\), NR2B = 0.7 nM).

Further optimization of the series discovered compound 135 as a potent and selective NR2B antagonist.\(^{241}\) Efficacy of 135 was measured by scoring behavioral responses to noxious stimuli in a carageenan-induced hyperalgesia assay in the rat.\(^{242}\) The compound showed ED\(_{50}\) value of 5.5 mg/kg. Non-selective NMDA antagonists produce significant locomotor effects in the rotarod assay, and virtually no separation exists between efficacy and loss of motor coordination.\(^{242}\) In contrast, dosed orally at 10, 30 and 100 mg/kg, compound 135 exhibited significant block of the hyperalgesic response with no measurable effect on motor function.

\[ \text{(135)} \]

### 2.2.7 Amidines as anti-inflammatory and analgesic agents

Recently, Giordani, A. et al. patented a series of amidine derivatives of 2-heteroaryl-quinazolines and quinolines as potent analgesics and anti-inflammatory agents.\(^{243}\) Compounds (136 and 137) showed 50 and 45% inhibition of IL-1 and 65 and 78% inhibition of IL-6, respectively.
Sondhi, S. M. et al. reported analgesic and anti-inflammatory activity of some amidine and hydrazone derivatives. Compounds 138 and 139 showed 52 and 36% inhibition of carrageenan induced rat paw edema, respectively at 50 mg/kg dose. Compounds 138 and 139 also displayed 50 and 60% inhibition of acetic-acid induced writhing, respectively at 50 mg/kg dose.

A series of naphthamidine based urokinase inhibitors has been patented by Bruncko, M. et al. Compounds 140 showed a wide range of activity (Ki = 0.010-1.44 μM) against urokinase enzyme, Abbokinase (Abbott Laboratories, Abbott Park III).

R₁ = H, X, alkyl, alkenyl, alkynyl, alkoxyalkyl, aryl, heteroaryl, cycloalkyl
R₂ = substituted phenyl
R₃ = H, OH
2.2.8 Other biological uses of amidines

Nakamura, H. et al. reported a series of benzamidines as selective inhibitors of vascular endothelial growth factor receptor (VEGFR) tyrosine kinases. The most potent compound 141 exhibited 44% inhibition of KDR catalytic domain of VEGFR2 protein tyrosine kinase at a dose of 10μM.

\[
\text{HN} \quad \text{HN} \quad \text{CF}_3
\]
\[
\text{NH} \quad \text{NH}
\]
\[
\text{N} \quad \text{N}
\]
\[
(141)
\]

Complement activation has been implicated in disease states such as hereditary angioedema, ischemia-reperfusion injury, acute respiratory distress syndrome, and acute transplant rejection. Travins, J. M. et al. reported a series of biphenylsulfonylthiophene-carboxamidine derivatives as inhibitors of complement component C1s where compound 142 displayed potent activity (Ki = 20 nM).

\[
\text{MeS} \quad \text{HN} \quad \text{NH}_2
\]
\[
\text{HN} = \text{NH}_2
\]
\[
(142)
\]

A series of azaterphenyl diamidines was reported as potential antileishmanial agents by Hu, L. et al. Compound 143 displayed IC₅₀ value of 63 nM in an axenic assay with L. donovani amastigote-like parasites.

\[
\text{H}_2\text{N} \quad \text{HN} \quad \text{NH}
\]
\[
\text{NH}_2
\]
\[
(143)
\]
Aslanian, R. et al. reported a series of novel 4-[(1H)-imidazol-4-yl)methyl] benzamidines and benzylamidines as potent Histamine H3-receptor antagonists. The most potent compound 144 exhibited potent activity (Ki = 7.2 nM) on histamine H3 receptor of guinea pig brain using N°-methylhistamine as a ligand.

![Structure 144](image)

Ojo, B. et al. reported some novel amidine derivatives as M1-muscarinic receptor agonists. Compound 145 was found to be the most potent (IC₅₀ = 3.3 μM) showing 230% inhibition of ³H-(R)-quinuclidinyl benzilate (QNB) binding to rat brain membrane at a dose of 100 μM.

![Structure 145](image)
2.3 CHEMISTRY OF 1,2,4-TRIAZOLES

2.3.1 Introduction

1,2,4-Triazoles (those not forming part of a fused polynuclear system) are cyclic hydrazidines with H or some other substituent on either a hydrazide nitrogen as in 146 or an amide nitrogen as in 147. The prefixes 1H and 4H are used to distinguish 146 and 147, respectively.

A few trivial names for 1,2,4-triazoles are in common use: 3,4-dioxo-1,2,4-triazolidines (148) are called urazoles, and the corresponding 3,5-diamino compounds (149) guanazoles.

Extensive literature exists that covers the first 70 years of the chemistry of 1,2,4-triazoles that deals with the mono and polynuclear triazoles.\textsuperscript{251,252}

2.3.2 Molecular geometry and dimensions

On the evidence of X-ray diffraction analysis, the solid parent triazole has a planar structure with hydrogen bridges between N-1 and N-4 of neighboring rings. Of the two N-H bond lengths implied, only that leading to N-1 is of the order required by covalent bonding.\textsuperscript{253} Confirmation from similar studies carried out at \(-160^\circ\text{C}\) proves the molecular dimensions as shown in Table 4 for one unit of a pleated sheet linked by hydrogen bridges.\textsuperscript{254}
Table 4: Molecular geometry of 1,2,4-triazole at -160°C

<table>
<thead>
<tr>
<th>Angle</th>
<th>Bond</th>
<th>Bond length (pm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-1-4</td>
<td>1-2</td>
<td>135.9</td>
</tr>
<tr>
<td>1-2-3</td>
<td>2-3</td>
<td>132.3</td>
</tr>
<tr>
<td>2-3-4</td>
<td>3-4</td>
<td>135.9</td>
</tr>
<tr>
<td>3-4-5</td>
<td>4-5</td>
<td>132.4</td>
</tr>
<tr>
<td>4-5-1</td>
<td>5-1</td>
<td>133.1</td>
</tr>
<tr>
<td>N(1)-H</td>
<td></td>
<td>103.0</td>
</tr>
<tr>
<td>C(3)-H</td>
<td></td>
<td>93.0</td>
</tr>
<tr>
<td>C(5)-H</td>
<td></td>
<td>93.0</td>
</tr>
</tbody>
</table>

2.3.3 Synthesis of substituted 1,2,4-triazoles

2.3.3.1 Synthesis of 1,2,4-triazoles from hydrazine derivatives

The ease of forming C-N and C=N bonds as compared with the difficulty of N-N formation practically prescribes the use of hydrazines in the synthesis of 1,2,4-triazole (146). Following scheme illustrates synthetic schemes that use one of the following: (a) hydrazine, (b) an acylhydrazine, (c) amidrazone or (d) acylamidrazone.
Although 1,2,4-triazole (150) can be prepared by heating hydrazine with two (preferably more) equivalents of formamide, the reaction presumably occurs in steps, e.g. as in the following scheme. Syntheses corresponding to step 3 are well known, but occur in poor yields or not at all.

\[
\text{H}_2\text{NNH}_2 + \text{HCONH}_2 \rightarrow \text{H}_2\text{NNNN}_2 \rightarrow \text{H}_2\text{NNNH}_2 \rightarrow \text{H}_2\text{NNNH}_2 + \text{NH}_3
\]

Following scheme illustrates extensions of these methods proceeding from or through hydrazidines, amidrazones or acylamidrazones to syntheses of 1,2,4-triazoles (147) with substituents on N-4.

Unsubstituted hydrazine can react with an amide derivative (151) to yield the amidrazone (152) which then either reacts with more 151 or undergoes self-condensation to 153 which then cyclizes to the triazole (154) on heating.
Conversion of the amidrazone (155) into the triazole (156) takes place in basic solution, while the oxadiazole (157) is obtained in the presence of acid.\textsuperscript{256}

The formation of alternative heterocycles can be the main reaction with semicarbazides or thiosemicarbazides which are used extensively in the preparations of triazolinones and triazolinethiones. Aminoguanidines can give rise to isomeric triazoles. The preferred formation of thiadiazole (158) from the 1-acylthiosemicarbazide is explained by the protonation of N-4 in strong acid with accompanying loss of nucleophilicity, while in the presence of base its nucleophilic character is enhanced and 159 is obtained.\textsuperscript{257}
Many convenient triazole syntheses proceed through amidrazones derived from formic acid. Thus DMF, thionyl chloride and hydrazine react to give the bisamidrazone (160) which is then cyclized by transamination:

\[
\begin{align*}
\text{H}_2\text{NNNH}_2 & \xrightarrow{\text{SOCl}_2} \text{N} & \text{N} & \xrightarrow{\text{RNH}_2} \text{N} & \text{N} \\
& & \text{(160)} & & \text{(161)} \\
\end{align*}
\]

One can use s-triazine (161) as a source of formamidrazones that react with more triazine or undergo self-condensation in the presence of acid. In the absence of acid, the acyclic dihydrazone (162) is formed and can be cyclized to 4-aminotriazole (163). Following schemes illustrates some applications of the triazine (161) and trichloros-triazine (167) methods.

\[
\begin{align*}
\text{H}_2\text{NN} & \xrightarrow{\text{NH}_2\text{NH}_2} \text{NN} & \xrightarrow{\text{H}^+} \text{N} & \text{N} & \text{N} \\
& & \text{(162)} & & \text{(163)} \\
\text{(161)} & \xrightarrow{\text{NH}_2\text{NH}_2\text{HCl}} \left( \begin{array}{c}
\text{NH}_2 \\
\text{NNH}_2 \text{HCl}
\end{array} \right) & \xrightarrow{\text{H}^+} \text{H}_2\text{NN} & \xrightarrow{\text{H}^+} \text{N} & \text{N} & \text{N} \\
& & \text{(166)} & & \text{(150)} \\
\text{X} = \text{O, S} & \xrightarrow{\text{RNH}_2\text{NH}_2\text{HCl}} \text{X} = \text{NH, NR} & \xrightarrow{\text{H}^+} \\
& & \text{(164)} & & \text{(165)} \\
\text{(167)} & \xrightarrow{\text{MeNCHO}} \left( \begin{array}{c}
\text{N} & \text{N} & \text{N} \\
\text{Cl} & \text{Cl} & \text{Cl}
\end{array} \right) & \xrightarrow{\text{RNH}_2\text{NH}_2} \text{R} \\
& & \text{(166)} & & \text{(166)}
\end{align*}
\]
2.3.3.2 Synthesis of 1,2,4-triazoles from nitrilimines

Huisgen's studies of 1,3-dipolar cycloadditions leading to a great variety of heterocyclic systems are applicable to the synthesis of triazoles and derivatives.\textsuperscript{263,264} Nitrilimines (168) formed by dehydrohalogenation of C-halobenzylidene phenylhydrazones (169) react with \( \text{C} \equiv \text{N}, \text{C}=\text{N} \) (as in CNO) to afford triazoles (170) and triazolines (171, 172) in yields of 50-75\%, respectively.

\[
\begin{align*}
\text{Cl} & \quad \text{HN} \quad \text{Ph} \\
\text{Ph} & \quad \text{HN} \quad \text{Ph} \\
\text{Et}_3\text{N} & \\
\text{Ph} & \quad \text{N}^+ \quad \text{N} \quad \text{Ph}
\end{align*}
\]

Examples depicted in the following scheme indicate the caution required when a nitrilimine intermediate favors the formation of a heterocycle other than triazole. The bromo derivative (173) of the semicarbazone (174) is formally analogous to (169); the nitrilimine (175) is formed even in the presence of such weak bases as sodium acetate or water and undergoes ring closure to the 1,3,4-oxadiazole (176). In anhydrous acetic acid the tirazolinone (177, \( R = \text{H} \)) is formed.\textsuperscript{265} A similar reaction occurs on teating the N-methyl homolog of (174) with bromine in acetic acid to obtain (177, \( R = \text{Me} \)).
Another example of ambiguity arises out of the addition of phenylisocyanate in the presence of aluminum oxide to the nitrilimine (1681) that affords a triazolinone (178) with some oxadiazoline (179) as byproduct\textsuperscript{266}, while the addition of phenylcyanate affords the expected triazole (180).

71
2.3.3.3 Synthesis of 1,2,4-triazoles from other heterocyclic systems

Following scheme summarizes the overall reaction much used for the conversion of 1,3,4-oxadiazoles (181, X = O) and thiadiazoles (181, X = S) to triazoles (182 and 183). Intermediates such as 184 and 185 have been isolated in some cases and have been reasonably assumed in others, especially when such amidrazones could be converted either into 182 or 183 according to the reaction conditions.267

\[
\begin{align*}
\text{R}_1'-(X)-\text{R}_2 & \text{R}_3\text{NH}_2 \\
\text{N-N} & (181) \\
X = \text{O, S}; \text{R}_1, \text{R}_2 = \text{H, Alk, Ar}
\end{align*}
\]

The action of alkali on aminooxadiazole (181, X = O; R₁ = H, alkyl, aryl; R₂ = NH₂) affords the acylsemicarbazone intermediate (186) that cyclizes to the triazolinone (187). Ethanolic alkali reacts by ethanolysis to give (188) which cyclizes the ethoxytriazole (189).
The rearrangement of 2-methylamino-1,3,4-thiadiazole (190) to the triazolinethione (191) occurs in good yield at 160°C, while a similar reaction of 192 to 193 occurs only to the extent of 30% in boiling methanol with the formation of an equal amount of 194. However, the reaction of 190 with hydrazine in methanol gives 4-amino-1,2,4-triazole-5-thione (195) in good yield in a reaction proceeding through nucleophilic displacement of the halogen and ring opening to formyl thiocarbohydrazide.

\[
\text{MeNH}_2, 160^\circ\text{C} \quad \begin{array}{c}
\text{H}_2\text{N}_2\text{S} \\
\text{N} \\
\text{N}
\end{array} \quad \begin{array}{c}
\text{H} \\
\text{N} \\
\text{N}
\end{array}
\]

(190) \quad (191)

The same kind of ambiguity besets the reaction of (196) with aniline that leads to a mixture of triazolethione (197) and aminoanilinothiadiazole (198), the later rearranges to (197) in ethanolic potassium hydroxide.

\[
\begin{array}{c}
\text{H}_2\text{N}_2\text{S} \\
\text{N} \\
\text{N}
\end{array} \quad \begin{array}{c}
\text{H} \\
\text{N} \\
\text{N}
\end{array}
\]

(196) \quad (197)

An efficient one-pot, three-component synthesis of substituted 1,2,4-triazoles (147) was reported utilizing a wide range of substituted primary amines and acyl hydrazides.
2.4 ANTIHYPERLIPIDEMIC ACTIVITY OF TRIAZOLE AND LIKE COMPOUNDS

2.4.1 Triazoles as lipid lowering agents

A series of triazole derivatives have been patented as inhibitors of lipid peroxidation. The most potent compound showed 85.8% inhibition of lipid peroxidation at a dose of 5 μM while the standard drug Vitamine E showed only 30.5% inhibition at a dose of 100 μM.

Zhu, Y. et al. recently filed a patent claiming a series of triazole derivatives as potent hypolipidemic and hypoglycemic agents. The most potent compound inhibited peroxisome proliferator activated receptor (PPAR) α, δ and γ with EC₅₀ ≤ 10 μM in a transactivation assay.
A series of 1,2,4-triazole derivatives were reported as potent inhibitors of Apolipoprotein B. Compounds (201 and 202) stood out as the most potent derivatives with IC$_{50}$ value of 15 nM.

![Chemical Structure](image1)

(201) $R = H$; (202) $R = \text{CH}_3$

Janssen, C.G.M. et al. patented a series of triazolone derivatives claiming the compounds to be lowering lipid levels. Most potent compound 203 showed potent inhibition of Apolipoprotein B (IC$_{50} = 61$ nM).

![Chemical Structure](image2)

(203)

A series of substituted triazole derivatives has been reported as potent modulators of PPAR. Compound 204 showed a modest EC$_{50}$ value of $< 10 \mu M$ in a transactivation assay.

![Chemical Structure](image3)

(204)
Recently, a series of triazole disulfide derivatives (205) has been patented as potential PPAR modulators. Typically, most of the compounds displayed good potency (IC_{50} \leq 100 \text{nM}). Compounds also elevated HDL (≥ 25%) and reduced triglycerides (≥ 30%) in a high fat diet model in hamsters.

\[
\text{R1, R2 = alkyl, aryl, halo, nitro, hydroxy, cyano}
\]

Izydore, R. A. et al, patented a series of triazolidinedione derivatives (206) as potential antihyperlipidemic agents. Most of the compounds reduced triglycerides and cholesterol levels by 40-90% in high-cholesterol diet fed mouse model.

\[
\text{R1 = R2 = H, alkylcarbonyl, alkoxy carbonyl, aryl carbamoyl}
\]

\[
\text{R3 = phenyl, substituted-phenyl, alkyl}
\]

### 2.4.2 Other heterocycles as lipid lowering agents

A wide range of chemical scaffolds exists in the literature which act on many targets of hyperlipidemia and atherosclerosis. Only those structurally similar to the target compounds are reviewed.

A series of 3,5-dialkyl-4,6-diaryl-tetrahydro-2H-1,3,5-thiadiazine-2-thiones (207) were synthesized and reported as potent antihyperlipidemic agents. Compounds significantly reduced triglycerides (13-52%) and elevated HDL (6-99%). The most potent compound (R= CH₃, R₁ = 4-methyl-phenyl) showed 49% reduction in triglycerides and 99% elevation of HDL.
Wright, J. J. et al. patented a series of tetrazole derivatives as potent hypolipidemic agents where compound 208 had \( \text{ED}_{50} \) value comparable to that of lovastatin.\(^{281}\)

Commons, T. J. et al. patented a series of open chain hydrazino thioamides as potent HDL elevators.\(^{282}\) Compound 209 showed 87% increase in HDL at a dose of 50 mg/kg in a high-fat diet model in male Sprague-Dawley rats.

A series of tetrahydro-pyrimidine-2-(1\(H\))-thione derivatives were reported as potent HDL elevators.\(^{283}\) The most potent compound 210 showed as high as 183% increase in HDL levels in a high-fat diet model in male Sprague-Dawley rats.
A series of triazine-diones were synthesized and reported as potent lipid lowering agents. Compounds 211 and 212 significantly reduced total cholesterol (63%) and triglycerides (51% and 55%, respectively) in a high-fat diet fed mouse model.

Recently, Momose, Y. et al. patented some five membered heterocycles as potential hypolipidemic and hypoglycemic agents. Compound 213 stood out as the most potent compound with EC₅₀ value of 0.38 nM for PPARδ-RXRα heterodimer ligand activity assay. It also showed significant reduction of triglycerides (82%) along with modest reduction in total cholesterol levels (22%) in a high-fat diet model in mice.

A series of pyrimidoimidazoles were patented as potent antihyperlipidemic agents. Claimed compounds showed very good range of reduction in lipid parameters. The most potent compound 214 produced 34% decrease in total cholesterol, 31% decrease in triglycerides and 19% increase in HDL levels in a high-fat diet model in male S.D. rats.
A Series of five-membered heterocycles have been reported as PPARγ agonists. Compound 215 was found to be the most potent ($IC_{50} = 3.6 \text{ nM}$) in a radioligand assay.