Studies on Pyrazoles

Introduction

Five-membered ring systems containing two double bonds and two nitrogen atoms adjacent to each other are called pyrazoles. Previous chapters on pyrazoles have been presented covering the literature up to 1981\(^1\). During the last 10 years, more reports have appeared on the synthesis and reactivity of pyrazole ring systems. Furthermore, the medicinal chemistry applications of pyrazoles and fused-ring systems have found numerous applications in drug discovery. Survey of possible structures pyrazole is an aromatic molecule and, like its structural isomer imidazole, contains a pyrrole-like and a pyridine-like N atom, but in the 1- and 2-positions (1,2-diazole). Aromatic compounds with two double bonds include the core structures such as pyrazole (1), indazole (2), and isoindazole (3) along with their nonaromatic isomers, pyrazolenine or 3H-pyrazole (4), isopyrazole or 4H-pyrazole (5), and 1H-pyrazol-2-ium salts (6). Other pyrazole structures containing carbonyl groups include 1H-pyrazol-5(4H)-one (7), 1H-pyrazol-3(2H)-one (8), 3H-pyrazol-3-one (9), and 4,5-dihydro-3H-pyrazol-3-one (10). Pyrazolines such as 4,5-dihydro-3H-pyrazole or 1-pyrazoline (11), 4,5-dihydro-1H-pyrazole or 2-pyrazoline (12), and 2,3-dihydro-1H-pyrazole or 3-pyrazoline (13) are also represented. Pyrazolidine (14) and pyrazolidin-3-one (15) are representative structures with no ring double bonds. All of these structures can have substitution on any of the carbon atoms. Many other structures such as those with fused pyrazole rings are also possible.
**Theoretical Methods**

**Structure and Reactivity of Pyrazoles**

N-Unsubstituted pyrazoles can have N–H----N hydrogen bonds present in their crystals, which can lead to at least six motifs such as monomers, dimers, trimers, tetramers, hexamers, and catemers. Hydrogen-bonding motifs for pyrazoles have been examined in the Cambridge Structural Database (CSD). The accessible surface of the N-atoms has been found to be useful as a discriminator to divide structures into dimer and catemer motifs. Low accessibility favors dimers and tetramers and high values favor catemers and trimers. Empirical rules were successfully applied to predict the motifs of eight new structures in the subsequent release of the CSD. A search in the CSD for NH-pyrazoles lacking other hydrogen-bond donor and
acceptor sites identified compounds that crystallized in structures forming dimers, tetramers, trimers, a hexamer, and catemers using N–H---N hydrogen bonds. These structures were divided into two classes (dimers and tetramers vs. trimers and catemers) using the accessible surface to an atom with good results. The method has been extended to new pyrazoles by means of theoretical calculations of the geometry of the monomers. Aspects like the conformation of phenyl substituents, the additivity of substituent effects, and buttressing effects have been approached theoretically.

The supramolecular structure of 1H-pyrazoles in the solid state was investigated by crystallographic and ab initio studies. Harmonic force fields were calculated at the corresponding optimized geometry for pyrazole at the Hartree–Fock (HF), B₃LYP, MP₂, CCSD (coupled-cluster singles and doubles), and CCSD(T) (coupled cluster with
perturbative triples) levels using the 6-31G* basis set and at the HF and B3LYP levels using the ccp VTZ basis set. Ab initio coupled gauge-independent atomic orbital (GIAO) calculations were carried out on 21 1-substituted pyrazoles using four different ab initio methods which led to the final selection of the hybrid basis set. Comparison with experimental chemical shifts in solution (taking into account the calculated shielding of the corresponding references) showed an excellent agreement between both sets, allowing for a factor of proportionality of about 0.96. The infrared (IR) spectra and quantum-mechanical calculations of vibrational spectra and structure of pyrazole and 3,5-dimethylpyrazole in solution, gas phase, and solid state have been investigated over a wide range of concentrations and temperatures. It was found that in the gas phase, both pyrazole and 3,5-dimethylpyrazole exist in an equilibrium between monomers, dimers, and trimers. In solution, the equilibrium between monomers and trimers dominated and no bands which could be attributed to dimers were detected. 3,5-Dimethylpyrazole retained the trimer structure in the solid state, while in the case of pyrazole, formation of the crystal provided another type of association. Geometrical and spectral characteristics of dimers and trimers, obtained by ab initio calculations, were presented and compared with experimental data. Molecular dynamics of the self-organizing strong hydrogenbonded 3,5-dimethylpyrazole was studied by quasi-elastic neutron scattering (QENS).

Hindered pyramidal inversion and restricted rotation in N-propyl-N-(4-pyridyl)-1-amino-1H-pyrazoles (16) were studied by dynamic nuclear magnetic resonance (NMR) spectroscopy and molecular modeling methods. A coupled-cluster study of the structure and vibrational spectra of pyrazole has been reported. The structure of 5-tert-butyl-4-nitro-1H-pyrazol-3-ol (17) consisted of molecules that pack in a linear hydrogen-bonded ribbon motif. This hydrogen-bonding arrangement was constructed through two dimer formations, one that is atypical of pyrazoles (N–H---N) and the other
via an interaction from the hydroxyl group to one of the nitro oxygen atoms. The molecular structure of a novel monohydrated 3-p-nitrophenylpyrazole was found to exist as the 3-tautomer (18) rather than the corresponding 5-tautomer (19) using NMR spectroscopy, single crystal X-ray diffraction, and ab initio calculations\(^7\).

C–H and N–H bond-dissociation energies (BDEs) of pyrazole were calculated using composite ab initio CBS-Q, G\(_3\) and G\(_3B_3\) methods\(^8\). It was found that all these methods provided very similar BDEs, despite the fact that different geometries and different procedures in the extrapolation to complete incorporation of electron correlation and complete basis set limit were used. Bond dissociation energies of pyrazole (kcal mol\(^{-1}\)).
<table>
<thead>
<tr>
<th>Bond</th>
<th>CBS-Q</th>
<th>G3</th>
<th>G3B3</th>
<th>B3LYP</th>
<th>Charge</th>
<th>Spine</th>
<th>Bond Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)-H</td>
<td>112.0</td>
<td>111.3</td>
<td>109.2</td>
<td>107.6</td>
<td>0.401</td>
<td></td>
<td>113.3</td>
</tr>
<tr>
<td>C(3)-H</td>
<td>118.7</td>
<td>118.7</td>
<td>117.8</td>
<td>115.5</td>
<td>0.201</td>
<td>0.967</td>
<td>112.1</td>
</tr>
<tr>
<td>C(4)-H</td>
<td>122.6</td>
<td>122.2</td>
<td>121.0</td>
<td>118.9</td>
<td>0.221</td>
<td>0.953</td>
<td>104.5</td>
</tr>
<tr>
<td>C(5)-H</td>
<td>121.1</td>
<td>121.1</td>
<td>119.9</td>
<td>117.9</td>
<td>0.210</td>
<td>0.948</td>
<td>106.1</td>
</tr>
</tbody>
</table>

Structure and Reactivity of Indazoles Nuclear quadrupole resonance (NQR) frequencies were determined on the $^{35}$Cl isotope for several chloroindazoles and for two chloroindazole nucleosides at liquid nitrogen temperature\(^9\). The influence of the site of substitution and type of substituent on the resonance frequency was analyzed and the electron density distribution and electrostatic potential in the molecules were calculated by the B3LYP/6-31G*(p) method and the results were correlated with experimental data. The aqueous-phase physicochemical properties of some 3-substituted indazoles (H, Me, Br, Cl) were computed using semi-empirical methods and the results obtained were evaluated by searching for a possible correlation with the previously obtained experimental properties\(^{10}\). The aqueous-phase geometries, relative stabilities, acidity constants, tautomerism, proton affinities (PAs) and dipole moments for the tautomeric forms of some 3-substituted indazoles and their fixed forms (model compounds in which proton migration is eliminated by replacing the mobile hydrogen atom with a methyl group) were calculated with full geometry optimization using AM1, PM3, and modified neglect of diatomic overlap (MNDO) methods. The results of aqueous-phase semiempirical calculations indicate that 1H-form (20) of the studied molecules is more stable than the 2H-form (21).
Ab initio and density functional theory (DFT) methods have been used to study the five tautomeric forms of indazole in gaseous and aqueous phases. The tautomers in the gas phase were optimized at MP2/6-311G* (2d, 2p), B3LYP/6-311G* (2d, 2p), and B3PW91/6-311G* (2d, 2p) levels of theory. Computational studies on the three tautomeric forms of four 1,5,6,7-tetrahydro-4H-indazol-4-ones, 1,5,6,7-tetrahydro-4H-indazol-4-one, 6,6-dimethyl-1,5,6,7-tetrahydro-4H-indazol-4-one, 3-methyl-1,5,6,7-tetrahydro-4H-indazol-4-one, and 3,6,6-trimethyl-1,5,6,7-tetrahydro-4H-indazol-4-one, were performed at different levels, ranging from semi-empirical AM1, ab initio HF/6-31G* and HF/6-31G**, to B3LYP/6-31G** density functional calculations. These calculations were used to establish the most stable tautomer, which in all cases was in agreement with the experimental data.
Electrophilic Attack at Carbon

Nitration

A review has been written on the synthesis and reactions of the nitropyrazoles\(^{(11)}\). Pyrazole 1 on treatment with fuming nitric acid/trifluoroacetic anhydride gave 3,4-dinitropyrazole (22), while N-methylpyrazole under the same reaction conditions gave 3-nitropyrazole. 1-Methylpyrazole-3-ones were treated with aqueous nitric acid to give 1-methyl-4-nitropyrazol-3-ones, which could be reduced by catalytic hydrogenation with palladium on carbon to give 1-methyl-4-aminopyrazole-3-ones\(^{(12)}\). 1,4-Dimethylpyrazole (23) was converted into 3,5-dinitro-1,4-dimethylpyrazole (24) in the presence of 2 volumes of concentrated nitric acid and 20 volumes of sulfuric acid at reflux to ensure acceptably reproducible yields of the product. Pyrazole could be converted into 1-nitropyrazole (25) immediately with dinitrogen pentoxide, which can then slowly be transformed to 1,4-dinitropyrazole (26) in the presence of H-faujasite zeolite F-720\(^{(13)}\) or with nitrogen dioxide in ozone\(^{(14)}\). The nitration of 5-chloropyrazoles (27) with a mixture of 100% concentrated nitric acid and 65% oleum or a mixture of 60% nitric acid and polyphosphoric acid (PPA) gave substituted 5-chloro-4-nitropyrazoles (28). 4-Chloropyrazoles failed to undergo nitration under these conditions and the nitration of 3-aryl-5-halopyrazoles was accompanied by introduction of a nitro group into the benzenoid aromatic ring.
4-Keto-5-hydroxypyrazoles have been utilized as intermediates in the synthesis of fused pyrazole ring compounds. 4-Acetyl-5-
hydroxy-1-phenyl-1H-pyrazole (29) reacted with benzoyl chloride and lithium bis(trimethylsilyl)amide to give an intermediate diketone, which was cyclized in the presence of acid to yield 1,6-diphenyl-1H-pyrano[2,3-c]pyrazole-4-one (30)\(^{(15)}\). Similarly, Claisen condensation of 4-acetyl-5-hydroxypyrazoles with esters followed by acid-catalyzed ring closures provided a route to 1H-pyrano[2,3-c]pyrazol-4-ones. 4-Benzoyl-3-chloropyrazoles (31), prepared from 4-benzoyl-5-hydroxypyrazoles (32) with phosphorus oxychloride, were converted into oximes followed by intramolecular base-promoted cyclizations to give 3-phenyl-6H-pyrazolo[4,3-d]isoxazoles (33)\(^{(16)}\).

\[ \text{N} \quad \text{NOH} \quad \text{Ph} \]

\[ \text{O} \quad \text{Me} \]

\[ \text{O} \quad \text{Ph} \]

\[ \text{i, LiHMDS} \quad \text{ii, PhCOCl} \quad \text{iii, H}_2\text{SO}_4, \text{HOAc or EtOH} \]

\[ \text{29} \quad \text{30} \]

\[ \text{N} \quad \text{N} \quad \text{R}_1 \]

\[ \text{OH} \quad \text{Ph} \quad \text{R}_2 \]

\[ \text{O} \quad \text{Ph} \]

\[ \text{i, NH}_2\text{OH} \quad \text{ii, NaH, DMF} \]

\[ \text{R}_1 = \text{Me, Ph} \]

\[ \text{31} \quad \text{32} \quad \text{33} \]
Halogen Atoms

Nucleophilic substitution reactions

Many reactions have been reported in this area since the last report\(^\text{(17)}\). 5-Chloropyrazoles have been utilized in a myriad of nucleophilic substitution reactions. Various nucleophilic heteroaromatic substitutions on 5-chloropyrazoles \((34)\) occur readily in warm DMF to give 5-substituted pyrazoles \((35)\). Nucleophilic substitution reactions of 5-chloropyrazoles \((36)\) with amines and thiols under mild conditions provided 5-alkylamino- and 5-alkylthiopyrazoles \((37)\). Fluoride-mediated nucleophilic substitution reactions of 1-(4-methylsulfonyl(or sulfonamide)-2-pyridyl)-5-chloro-4-cyanopyrazoles with various amines and alcohols occurred under mild conditions to provide 5-alkylamino- and 5-alkoxypyrazoles in moderate to high yields. Substitution of 5-chloro-4-formyl-1-phenylpyrazole \((38)\) with prenyl thiolate gave chloropyrazole-4-carbaldehyde \((39)\), which is a synthon for the synthesis of polycyclic heterocycles\(^\text{(19)}\). Examples include the efficient synthesis of thiopyrano\([5,6-c]\) coumarin/\([6,5-c]\)chromones through intramolecular domino Knoevenagel hetero-Diels–Alder reactions with 4-hydroxycoumarin and its benzo analogs, and a rapid synthesis of mono- and bis-tetrahydropyrazolyl \([49, 39:5, 6]\) thiopyran\([4,3-b]\)quinolines via imino Diels–Alder reactions. The reaction of 5-chloro-1,3-dimethyl-4-nitropyrazole \((40)\) with ethyl cyanoacetate in DMSO in the presence of potassium carbonate led to ethyl 2-cyano-2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-yl)acetate \((41)\). 3-Chloro-5,7-dinitroindazoles underwent nucleophilic displacement with morpholine in refluxing 1,4-dioxane to give 3-morpholinoindazole\(^\text{(20)}\) 5-Aminopyrazoles were obtained by direct reaction of the ester with lithium arylamides\(^\text{(21)}\).
R = H, Me, Ph, 2-pyridyl
NuH = nitrogen heterocycles, (thio)phenol, secondary amines

R¹ = H, CHO
R² = NR³R⁴, SR⁵
Syntheses Classified by Number of Ring Atoms in Each Compound

Ring Synthesis from Nonheterocycles: Formation of one bond

(i) Via hydrazones

(ii) Cyclization under basic conditions

The reaction of enolizable ketones with 1-alkyl-1-cyanohydrazine led to cyanohydrazones, which cyclized under mildly basic conditions to give the corresponding 5-aminopyrazoles\(^\text{22}\). Aminohydrazones underwent base-promoted heterocyclization at room temperature to produce 1-aminocarbonyl-1H-pyrazol-5(2H)-ones, which on thermal solvolytic cleavage afforded 1H-pyrazol-5(2H)-ones\(^\text{23}\). Base-mediated synthesis of 1,4-dihydrobenzopyranopyrazoles was achieved with bromovinyl hydrazones via \([2p3]\) intramolecular cycloaddition in a diazo intermediate\(^\text{24}\).

\[
\begin{align*}
\begin{array}{c}
\text{NH}_2 \\
R^1 \hspace{1cm} \text{Me} \hspace{1cm} O \hspace{1cm} COR^2
\end{array} + \begin{array}{c}
\text{Me} \\
\text{COR}^2
\end{array} & \xrightarrow{60^\circ C} \begin{array}{c}
\text{N} \\
\text{Me} \\
R^1 \hspace{1cm} \text{CN}
\end{array} \\
\begin{array}{c}
\text{KOH, EtOH} \\
25^\circ C
\end{array} & \xrightarrow{} \begin{array}{c}
\text{R}^2 \hspace{1cm} O \\
\text{Me}
\end{array}
\end{align*}
\]

\(R^1 = \text{CH}_3, \text{Bn}\)

\(R^2 = \text{CH}_3, \text{CF}_3, \text{OEt}, \text{Ph}\)

Cyclizations via acidic conditions

Hydrazone 1,4-adducts, prepared from thiocarboxylic acids and conjugated azoalkenes, reacted with trifluoroacetic acid in refluxing chloroform to give 1-alkoxycarbonyl-3-methyl-4-acylthio-5-alkoxypyrazoles\(^\text{25}\). Reactions with sodium hydride afforded pyrazolone-type products, while in acidic media hydrolysis products were observed. 1,4-Diazabicyclo[2,2,2]octane (DABCO)-catalyzedaza-Michael additions of hydrazones to activated alkenes gave products, which underwent cyclization to 4,5-dihydropyrazoles upon treatment
with acid. Cyclization of hydrazones with PPA gave substituted indazoles.

\[
\begin{align*}
\text{PPA, 80}^\circ\text{C} & \quad \text{R}^1 = \text{H, Me, Et, Pr}^n, \text{Bu}^n \quad \text{R}^2 = \text{H, OMe} \\
& \quad \text{R}^3 = \text{Me, Ar} \quad \text{R}^4 = \text{H, Me, Bn}
\end{align*}
\]

**Cyclizations via Vilsmeier–Haack Conditions**

Condensation of keto-ester hydrazones with the Vilsmeier reagent yielded a general synthesis of 1,3-diaryl-4-pyrazoleacetic acid esters. Regioselective addition of lithiated-hydrazonophosphino oxides to isocyanates afforded functionalized hydrazonoamides, which were then cyclized to 5-aminopyrazoles with phosphorus oxychloride in the presence of triethylamine\(^{26}\).

**Important Compounds and Applications**

**Pyrazoles in Supramolecular Chemistry**

A synthesis of novel 4-acylpyrazol-5-one-substituted crown ether metal-chelating reagents has been reported; crownether was found to be an effective and metal ion-selective extraction reagent\(^{27}\). A new diaza heteroaromatic crown of 3,5-disubstituted-1H-pyrazole which formed solid dinuclear complexes with lipophilic phenethylamines has been developed\(^{28}\). Bis-(3,5)pyrazolophanes (18-
to 24-membered rings annulated to pyrazole units) were synthesized by double cycloadditive macrocyclization of bis-hydrazonoyl chlorides with bis-allyl, bis-vinyl, and bis-propargyl ethers. 

**Pharmaceuticals and Agrochemicals**

Within the last 15 years or so, pyrazole-fused ring systems have found numerous applications in drug discovery efforts, and biological activities using these scaffolds have resulted in patented and approved drug candidates. For example, sildenafil is a selective inhibitor of phosphodiesterase 5 (PDE5) and is the first agent with this mode of action for the treatment of male erectile dysfunction. This new drug was approved for prescription use within the United States and the European Union during 1998 and has become one of the fastest-selling drugs of all time. Celecoxib has been approved for the inhibition of the COX-2 enzyme pathway for the treatment of rheumatoid arthritis. Rimonabant is a drug in clinical trials that shows high affinity for the CB1 cannabinoid receptor for the treatment of obesity.

Representative examples for various therapeutic areas show how pyrazole or fused pyrazole ring systems can have varied applications in drug discovery efforts. Only nonfused pyrazole ring examples will be shown in the examples below; fused pyrazole rings systems are presented.
Anti-inflammatory agents

Inhibition of p38 has become one of the major targets in developing anti-inflammatory drugs, due to its prominent role in regulating inflammatory cytokines such as tumor necrosis factor alpha (TNF) and interleukin (IL-1). Pyrazole-based inhibitors of the transforming growth factor beta (TGF) type I receptor kinase domain (T-R-I) included 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole analogues. Analogs of BIRB, a member of the N-pyrazole-N-naphthyl urea class of p38 nitrogen-activated protein kinase (MAPK) inhibitors, has been reported.

![Chemical structure of pyrazole-based inhibitors](image)

The COX enzymes, which catalyze the first step in arachidonic acid metabolism, were identified as the molecular targets of all nonsteroidal anti-inflammatory drugs (NSAIDs). SAR studies of the novel 2-[3-di and trifluoromethyl-5-alkylaminopyrazo-1-yl]-5-methanesulfonyl (SO₂Me)/sulfamoyl (SO₂NH₂)–pyridine derivatives for canine COX enzymes have been described; the 5-alkoxy and 5-alkylthio analogs and 5-heteroaryl-phenyl analogs have also been reported. 1,3-Diarylcycloalkanopyrazoles were identified as selective inhibitors of COX-2.
Cardiovascular agents

Thromboembolic diseases remain the leading cause of death and disability in developed countries. Factor IXa (fIXa) plays a key role in maintaining internal homeostasis in the intrinsic pathway of the clotting cascade. Inhibition of fIXa presents an alternative and viable way of treating thrombosis arising from both venous as well as arterial vascular injuries. Selective and efficacious factor IXa hydroxypyrazole inhibitors have been described\(^{(40)}\). Factor Xa has also become a major focus of pharmaceutical intervention in the past decade because of its central role in the blood coagulation cascade. A variety of P4 motifs have been examined to increase the binding affinity and in vitro anticoagulant potency of biphenyl 1-(2-naphthyl)-1H-pyrazole-5-carboxamide-based fXa inhibitors\(^{(41,42)}\). 1-(3-Amidinophenyl)-1H-pyrazole-4-carboxamides were found to be dual inhibitors of factors IXa and Xa\(^{(43)}\).
The renin–angiotensin system (RAS) plays a key role in regulating cardiovascular homeostasis and electrolyte/fluid balance in normotensive and hypertensive subjects. Activation of the rennin-angiotensin cascade begins with rennin secretion from the juxtaglomerular apparatus of the kidney and culminates in the formation of the octapeptide angiotensin II (AII), which then interacts with specific receptors present in different tissues. Two basic types of receptors, both having a broad distribution, have been characterized so far: the AT\(_1\) receptor, responsible for the majority of effects attributed to this peptide, and the AT\(_2\) receptor, with a functional role as yet uncertain. The synthesis and pharmacological activity of a new series of 5-\((\text{biphenyl-4-ylmethyl})\)pyrazoles as potent angiotensin II antagonists both in vitro (binding of \([3\text{H}]\text{AII}\)) and \textit{in vivo} (iv, inhibition of AII-induced increase in blood pressure, pithed rats; po, furosemide-treated sodium-depleted rats) are reported\(^{44}\).

\[
\begin{array}{c}
\text{HO}_2\text{C} \\
\text{R}_1 \\
\text{N} \\
\text{R}_2 \\
\text{N} \\
\text{N} \\
\text{NH} \\
\end{array}
\]

\textbf{CNS applications}

The dopamine D4 receptor subtype has received much attention as a pharmacological target for the treatment of schizophrenia, Parkinson’s disease, depression, and attention-deficit/hyperactivity disorder (ADHD). 4-N-linked heterocyclic piperidine derivatives with high affinity and selectivity for the human dopamine D\(_4\) receptors have been reported\(^{45}\). Aminomethyl-substituted biaryl bearing a
pyrazole moiety have been found to have dopaminergic partial agonism for the D4 receptor subtype.

\[
\begin{align*}
\text{Dopamine D}_2 \text{ receptor ligands have been designed for the treatment of schizophrenia. For example, 1-aryl-4-(piperazinylmethyl)-1H-pyrazoles have been found to be good ligands for the dopamine D}_2 \text{ receptor}^{(46)}.
\end{align*}
\]

**Infectious diseases**

A number of 1,5-disubstituted 4-[1H-imidazol-1-yl(phenyl)methyl]-1H-pyrazoles have been synthesized and evaluated for antibacterial activities in vitro against *Candida albicans*, *Cryptococcus neoformans*, and *Staphylococcus aureus*\(^{(47)}\). The antimicrobial activity of 1H-pyrazole carboxylates has been disclosed. The synthesis and antibacterial activity of 5-aryl- or 5-[(E)-2-arylvinyl]pyrazoles of DNA gyrase inhibitors has been disclosed\(^{(48)}\). 1,5-Diaryl-pyrazole-3-carboxylates have been found to have improved potency on bacterial methionyl-tRNA synthetase and selectivity over human methionyl-tRNA synthesis\(^{(49)}\). A number of 3-{(1-R-3(5)-methyl-4-nitroso-1H-5(3)-pyrazolyl)-5-methylisoxazoles were synthesized and tested for antibacterial and antifungal activity\(^{(50)}\). Carbon–carbon-linked (pyrazolylphenyl)-oxazolidinones with antibacterial activity against multiple drug-resistant Gram-positive and fastidious Gram-negative bacteria have been developed\(^{(51)}\) some pyrazoles prepared from pyrazole-4-carboxylic acid hydrazide showed antiviral activity.
Since the discovery of the chemokine receptor CCR5 as a co-receptor with CD4 for human immunodeficiency virus 1 (HIV-1) cell entry, there has been an intense interest to discover small-molecule CCR5 antagonists as potential agents for the treatment of HIV-1 infection. Antagonists of human CCR5 receptor containing 4-(pyrazolyl) piperidine side-chains as in 4-substituted pyrrolidines have been investigated intensely. 1,5-Diphenylpyrazole non-nucleoside HIV-1 reverse transcriptase inhibitors have been reported with enhanced activity against the HIV-1 virus. Malaria remains one of the most important diseases of humanity with over half of the world population at risk of infection. It affects mainly those living in tropical and subtropical areas with an incidence of 500 million cases per year globally. The antimalarial activity of 4-(5-trifluoromethyl-1H-pyrazol-1-yl) chloroquine analogues has been evaluated in vitro against a chloroquine-resistant Plasmodium falciparum clone.
**Metabolic diseases**

The physiological role of CB receptors is not yet completely understood, although they seem to be involved in certain pathophysiological processes such as asthma, pain, appetite modulation, multiple sclerosis, vomiting, immune and inflammatory diseases. In particular, selective CB₁ receptor ligands might produce potentially beneficial therapeutic effects including prevention of weight gain (treatment of obesity), mediated by interaction between CB₁ receptors, involved in the control of appetite. A series of 4,5-dihydro-1H-benzo[g]indazole-3-carboxamides showed high affinity for the CB₁ and CB₂ receptors\(^{(56)}\). A series of N-1- and C-5-substituted cycloalkyl and C-5 4-methylphenyl analogs of the N-(piperidin-1-yl)-4-methyl-1H-pyrazole-3-carboxamide class of cannabinoid ligands were synthesized\(^{(57)}\). Other 1,5-diarylpyrazole receptor ligands, close analogs to rimonabant, such as have been synthesized by various pharmaceutical companies. Novel 3,4-diarylpyrazolines as potent CB₁ receptor antagonists with lipophilicity are described.

![Chemical structures](image)

Another exciting drug target for the treatment of obesity is melanin-concentrating hormone receptor 1 (MCHR-1). Optimization of a high-throughput screening hit against MCHR-1 led to the discovery of 2-(4-benzyloxyphenyl)-N-[1-(2-pyrrolidin-1-ylethyl)-1H-indazol-6-yl] acetamide. This compound was found to be a high affinity ligand for MCHR-1 and a potent inhibitor of MCH-mediated Ca₂⁺ release; it
showed good plasma and central nervous system (CNS) exposure upon oral dosing in diet-induced obese mice, and is the first reported MCHR-1 antagonist that is efficacious upon oral dosing in a chronic model of weight. Urea-substituted variations of have also been tested for MCH-1 activity. The synthesis and biological evaluation of 3-aminoindazole MCHR-1 antagonists have been reported.

Yang Y et al. have been synthesized pyrazoles derivatives from 3-arylsydrones and 2-aryl-1,1-dihalo-1-alkenes. 

\[
X = \text{Cl, Br}
\]
Wu J et al. have been prepared novel prazole derivatives and tested for their antifungal activity\textsuperscript{(59)}.

\[
\text{R}^1, \text{R}^2 = \text{H} \quad \text{R}^3 = 5\text{- chloro-1,3-dimethyl-1H-pyrazol-4-yl}
\]

Pattan SR and Co-workers have been synthesized a new series of pyrazole derivatives and screening for their anti-tubercular activity\textsuperscript{(60)}.

\[
\text{Rao RM and Co-workers have prepared some new pyrazole derivatives and tested for their antimicrobial activity}\textsuperscript{(61)}.
\]
The synthesis of following thiazole derivative have been discussed in part-I

Section-I:  (4-alkylacetamino-2,5-dimethyl-2H-pyrazol-3-yl)-cyano-acetamide

Section-II:  1-(4-alkylamino-2,5-dimethyl-2H-pyrazol-3-yl)-pyrrolidine-2-carboxylate

Spectroscopic analysis and biological activities of these compounds are discuss in chapter III
Section – I

Preparation of \((4\text{-alkylacetamino-2,5-dimethyl-2H-pyrazol-3-yl)}\)- cyano-acetamide

Where, \(R_1 = \text{Different Alkyl Amine}\)
Table: 1:- Physical Constant of (4-alkylacetamino-2,5-dimethyl-2H-pyrazol-3-yl)-cyanoacetamide

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>-R₁</th>
<th>-R₂</th>
<th>Molecular Formula</th>
<th>M.P. (°C)</th>
<th>Yield (%)</th>
<th>Elemental analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% C</td>
</tr>
<tr>
<td>1</td>
<td>-OH</td>
<td>-Me</td>
<td>C₁₀H₁₂N₄O₃</td>
<td>112-114</td>
<td>58</td>
<td>50.84</td>
</tr>
<tr>
<td>2</td>
<td>-OH</td>
<td>-Et</td>
<td>C₁₁H₁₄N₄O₃</td>
<td>119-122</td>
<td>52</td>
<td>52.79</td>
</tr>
<tr>
<td>3</td>
<td>-NH₂</td>
<td>-Me</td>
<td>C₁₀H₁₃N₅O₂</td>
<td>123-127</td>
<td>81</td>
<td>51.06</td>
</tr>
<tr>
<td>4</td>
<td>-NH₂</td>
<td>-Et</td>
<td>C₁₁H₁₅N₅O₂</td>
<td>131-133</td>
<td>70</td>
<td>53.00</td>
</tr>
<tr>
<td>5</td>
<td>-NHCH₃</td>
<td>-Me</td>
<td>C₁₁H₁₅N₅O₂</td>
<td>119-122</td>
<td>66</td>
<td>53.00</td>
</tr>
<tr>
<td>6</td>
<td>-NHCH₃</td>
<td>-Et</td>
<td>C₁₂H₁₇N₅O₂</td>
<td>141-143</td>
<td>71</td>
<td>54.74</td>
</tr>
<tr>
<td>7</td>
<td>-NHEt</td>
<td>-Me</td>
<td>C₁₂H₁₇N₅O₂</td>
<td>107-104</td>
<td>68</td>
<td>54.74</td>
</tr>
<tr>
<td>8</td>
<td>-NMe₂</td>
<td>-Me</td>
<td>C₁₂H₁₇N₅O₂</td>
<td>113-116</td>
<td>59</td>
<td>54.74</td>
</tr>
<tr>
<td>9</td>
<td>-NMe₂</td>
<td>-Et</td>
<td>C₁₃H₁₉N₅O₂</td>
<td>119-121</td>
<td>63</td>
<td>56.30</td>
</tr>
<tr>
<td>10</td>
<td>-NEt₂</td>
<td>-Me</td>
<td>C₁₄H₂₁N₅O₂</td>
<td>129-131</td>
<td>59</td>
<td>57.72</td>
</tr>
</tbody>
</table>
Experimental Procedure

**Preparation of cyano-(2,5-dimethyl-4-nitro-2H-pyrazol-3-yl)-acetic acid ethyl ester (I)**

To a mixture ethyl cyanoacetate (0.068 mmol) in DMF (20 ml) was added sodium hydride (0.123 mmol) portion wise at 0-5°C and stirred at rt for 30 min. 5-chloro-1,3-dimethyl-4-nitro-1H-pyrazole (0.057 mmol) in DMF (20 ml) was added to above reaction mass and stirred at room temperature for 4-5 h. Reaction mass was quenched with methanol (5 ml), water (100 ml) was added to reaction mass and stirred for 30 min. Solid product was separated by filtration and washed with water and suck dry to give Compound-I in 68% yield. Ana Obs.: C-47.67%, H-4.76%, N-22.26%; Calc. for C_{10}H_{12}N_{4}O_{4}: C-47.62%, H-4.80%, N-22.21%.

**Preparation of (4-amino-2,5-dimethyl-2H-pyrazol-3-yl)-cyano-acetic acid ethyl ester (II)**

A mixture cyano-(2,5-dimethyl-4-nitro-2H-pyrazol-3-yl)-acetic acid ethyl ester (I) (0.0388 mmol) and iron powder (5 g) was stirred in acetic acid (50 ml) at room temperature for 4 h. Reaction mixture was quenched with sat sodium carbonate solution and extracted with dichloromethane. Dichloromethane (100 ml), layer was washed with water (3x50 ml) and evaporated completely to give light brown color solid as Compound-II in 82% yield. Ana Obs.: C-54.09%, H-6.31%, N-25.26%; Calc. for C_{10}H_{14}N_{4}O_{2}: C-54.04%, H-6.35%, N-25.21%.

**Preparation of (4-Acetylamino-2,5-dimethyl-2H-pyrazol-3-yl)-cyano-acetic acid ethyl ester (III)**

A mixture (4-amino-2,5-dimethyl-2H-pyrazol-3-yl)-cyano-acetic acid ethyl ester (II) (0.0045 mmol) and TEA (0.0081 mmol) in dichloromethane (10 ml) was stirred at 0-5°C for 30 min. Acetyl chloride (0.0054 mmol) was added to above solution at 0-5°C and stirred for 1h. Reaction mixture was quenched with water and
extracted with ethyl acetate (20 ml), washed with water (10 ml) and dried. Solvent was evaporated completely to give solid residue to get crude Compound-III in 77% yield. Ana Obs.: C-54.60%, H-6.15%, N-21.14%; Calc. for C_{12}H_{16}N_{4}O_{3}: C-54.54%, H-6.10%, N-21.20%.

**Preparation of (4-acetylamino-2,5-dimethyl-2H-pyrazol-3-yl)-cyano-acetic acid (1)**

A mixture (4-amino-2,5-dimethyl-2H-pyrazol-3-yl)-cyano-acetic acid ethyl ester (III) (0.0034 mmol) in methanol (10 ml) was stirred at rt for 30 min. 50% aq. NaOH (0.0052 mmol) was added to above solution at rt and stirred for 2 h. Reaction mixture was quenched with dil HCl and stirred for 15 min to get solid precipitate. Solid was separated by filtration, washed with water and dried to get compound-1 in 58% yield. Ana Obs.: C-50.89%, H-5.08%, N-23.76%; Calc. for C_{10}H_{12}N_{4}O_{3}: C-50.84%, H-5.12%, N-23.72%.

**Preparation of N-(1,3-Dimethyl-5-phenoxy-1H-pyrazol-4-yl)-acetamide (2)**

A mixture (4-acetylamino-2,5-dimethyl-2H-pyrazol-3-yl)-cyano acetic acid (1) (0.00286 mmol) and thionyl chloride (0.0057 mmol) was heated at 60-65°C and stir for 2 h. Thionyl chloride was evaporated completely under vacuum. Residue was diluted with THF (10 ml) and aq. ammonia solution (1 ml) was added to above and stir for 1 h. Solid product separated was filtered and washed with water and dried to get crude compound. Solid was purified in 10% aq. ethanol to get pure compound-2 in 81% yield. Ana Obs.: C-51.01%, H-5.65%, N-29.84%; Calc. for C_{10}H_{13}N_{5}O_{2}: C-51.06%, H-5.57%, N-29.77%.

The monitoring of reaction and purity of compounds were checked on TLC aluminium sheet silica gel 60 F_{245} (E.Merck) using hexane-ethyl acetate (5:5 V/V) and methanol- chloroform (2:8 V/V ) as mobile phase and visualize under U.V light 254 nm.

Other compounds of the series (3 to 10) were prepared by using similar method and their physical data are recorded in Table-1.
Section-II
Preparation of 1-(4-alkylamino-2,5-dimethyl-2H-pyrazol-3-yl)-pyrrolidine-2-carboxylate derivative

Where, \( R_1 \) = Different Alkyl Amine
Table: 2:- Physical Constant Of 1-(4-alkylamino-2,5-dimethyl-2H-pyrazol-3-yl)-pyrrolidine-2-carboxylate derivative

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>-R$_1$</th>
<th>-R$_2$</th>
<th>Molecular formula</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Elemental analysis</th>
<th>% C</th>
<th>% H</th>
<th>% N</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>-OH</td>
<td>-Me</td>
<td>C$<em>{12}$H$</em>{18}$N$_4$O$_3$</td>
<td>141-143</td>
<td>83</td>
<td></td>
<td>54.12</td>
<td>54.09</td>
<td>6.81</td>
</tr>
<tr>
<td>12</td>
<td>-OH</td>
<td>-Et</td>
<td>C$<em>{13}$H$</em>{20}$N$_4$O$_3$</td>
<td>159-161</td>
<td>77</td>
<td></td>
<td>55.70</td>
<td>55.76</td>
<td>7.19</td>
</tr>
<tr>
<td>13</td>
<td>-OH</td>
<td>-n-Pr</td>
<td>C$<em>{14}$H$</em>{22}$N$_4$O$_3$</td>
<td>173-175</td>
<td>79</td>
<td></td>
<td>57.13</td>
<td>57.17</td>
<td>7.53</td>
</tr>
<tr>
<td>14</td>
<td>-NH$_2$</td>
<td>-Me</td>
<td>C$<em>{12}$H$</em>{19}$N$_5$O$_2$</td>
<td>201-203</td>
<td>56</td>
<td></td>
<td>54.33</td>
<td>54.39</td>
<td>7.22</td>
</tr>
<tr>
<td>15</td>
<td>-NH$_2$</td>
<td>-Et</td>
<td>C$<em>{13}$H$</em>{21}$N$_5$O$_2$</td>
<td>217-219</td>
<td>66</td>
<td></td>
<td>55.90</td>
<td>55.94</td>
<td>7.58</td>
</tr>
<tr>
<td>16</td>
<td>NHMe</td>
<td>-Me</td>
<td>C$<em>{13}$H$</em>{21}$N$_5$O$_2$</td>
<td>233-235</td>
<td>71</td>
<td></td>
<td>55.90</td>
<td>55.96</td>
<td>7.58</td>
</tr>
<tr>
<td>17</td>
<td>-NHEt</td>
<td>-Me</td>
<td>C$<em>{14}$H$</em>{23}$N$_5$O$_2$</td>
<td>241-144</td>
<td>85</td>
<td></td>
<td>57.32</td>
<td>57.38</td>
<td>7.90</td>
</tr>
<tr>
<td>18</td>
<td>-NMe$_2$</td>
<td>-Me</td>
<td>C$<em>{14}$H$</em>{23}$N$_5$O$_2$</td>
<td>231-234</td>
<td>76</td>
<td></td>
<td>57.32</td>
<td>57.38</td>
<td>7.90</td>
</tr>
<tr>
<td>19</td>
<td>-NMe$_2$</td>
<td>-Et</td>
<td>C$<em>{14}$H$</em>{23}$N$_5$O$_2$</td>
<td>247-249</td>
<td>83</td>
<td></td>
<td>57.32</td>
<td>57.28</td>
<td>7.90</td>
</tr>
<tr>
<td>20</td>
<td>-NEt$_2$</td>
<td>-Me</td>
<td>C$<em>{16}$H$</em>{27}$N$_5$O$_2$</td>
<td>222-225</td>
<td>79</td>
<td></td>
<td>59.79</td>
<td>59.81</td>
<td>8.47</td>
</tr>
</tbody>
</table>
Experimental Procedure

**Preparation of 1-(2,5-Dimethyl-4-nitro-2H-pyrazol-3-yl)-pyrrolidine-2-carboxylic acid ethyl ester (I)**

To a mixture proline ethyl ester (0.068 mmol) in DMF (20 ml) was added sodium hydride (0.103 mmol) portion wise at 0-5°C and stirred at rt for 30 min. 5-chloro-1,3-dimethyl-4-nitro-1H-pyrazole (0.057 mmol) in DMF (20 ml) was added to above reaction mass and stirred at room temperature for 3-4 h. Reaction mass was quenched with methanol (5 ml), water (100 ml) was added to reaction mass and stirred for 30 min. Solid product was separated by filtration and washed with water and suck dry to give compound-I in 73% yield. Ana Obs.: C-51.10%, H-6.38%, N-19.91%; Calc. C_{12}H_{18}N_{4}O_{4}: C-51.06%, H-6.43%, N-19.85%.

**Preparation of 1-(4-Amino-2,5-dimethyl-2H-pyrazol-3-yl)pyrrolidine-2-carboxylic acid ethyl ester (II)**

A mixture 1-(2,5-Dimethyl-4-nitro-2H-pyrazol-3-yl)-pyrrolidine-2-carboxylic acid ethyl ester (I) (0.041 mmol) and iron powder (5 g) was stirred in acetic acid (50 ml) at room temperature for 5 h. Reaction mixture was quenched with sat sodium carbonate solution and extracted with dichloromethane. Dichloromethane (100 ml), layer was washed with water (3x50 ml) and evaporated completely to give light brown color solid as compound-II in 76% yield. Ana Obs.: C-57.18%, H-7.91%, N-22.16%; Calc. for C_{12}H_{20}N_{4}O_{2}: C-57.12%, H-7.99%, N-22.20%.

**Preparation of 1-(4-acetylamino-2,5-dimethyl-2H-pyrazol-3-yl)pyrrolidine-2-carboxylic acid ethyl ester (II)**

A mixture (1-(4-amino-2,5-dimethyl-2H-pyrazol-3-yl)pyrrolidine-2-carboxylic acid ethyl ester (II) (0.0045 mmol) and TEA (0.0081 mmol) in dichloromethane (10 ml) was stirred at 0-5°C for 30 min. Acetyl chloride (0.0054 mmol) was added to above solution at 0-
5°C and stirred for 1h. Reaction mixture was quenched with water and extracted with ethyl acetate (20 ml), washed with water (10 ml) and dried. Solvent was evaporated completely to give solid residue to get crude compound-11 in 77% yield. Ana Obs.: C-57.17%, H-7.47%, N-19.10%; Calc. for C_{14}H_{22}N_{4}O_{3}: C-57.13%, H-7.53%, N-19.03%.

**Preparation of 1-(4-acetylamino-2,5-dimethyl-2H-pyrazol-3-yl)pyrrolidine-2-carboxylic acid (12)**

A mixture 1-(4-acetylamino-2,5-dimethyl-2H-pyrazol-3-yl)pyrrolidine-2-carboxylic acid ethyl ester (III) (0.0034 mmol) in methanol (10 ml) was stirred at rt for 30 min. 50% aq. NaOH (0.0052 mmol) was added to above solution at rt and stirred for 2 h. Reaction mixture was quenched with dil HCl and stirred for 15 min to get solid precipitate. Solid was separated by filtration, washed with water and dried to get compound-12 in 83% yield. Ana Obs.: C-54.16%, H-6.78%, N-21.10%; Calc. for C_{12}H_{18}N_{4}O_{3}: C-54.12%, H-6.81%, N-21.04%.

**Preparation of 1-(4-Acetylamino-2,5-dimethyl-2H-pyrazol-3-yl)pyrrolidine-2-carboxylic acid amide (13)**

A mixture (1-(4-acetylamino-2,5-dimethyl-2H-pyrazol-3-yl)pyrrolidine-2-carboxylic acid (12) (0.00286 mmol) and thionyl chloride (0.0057 mmol) was heated at 60-65°C and stir for 2 h. Thionyl chloride was evaporated completely under vacuum. Residue was diluted with THF (10 ml) and aq. ammonia solution (1 ml) was added to above and stir for 1 h. Solid product separated was filtered and washed with water and dried to get crude compound. Solid was purified in 10% aq. ethanol to get pure compound 13 in 56% yield. Ana Obs.: C-54.27%, H-7.27%, N-26.45%; Calc. for C_{12}H_{19}N_{5}O_{2}: C-54.33%, H-7.22%, N-26.40%.
The monitoring of reaction and purity of compounds were checked on TLC aluminium sheet silica gel 60 F_{245} (E.Merck) using hexane-ethyl acetate (5:5 V/V) and methanol- chloroform (2:8 V/V) as mobile phase and visualize under U.V light 254 nm.

Other compounds of the series (14 to 20) were prepared by using similar method and their physical data are recorded in Table-4.
References


Studies on Isoxazoles

Introduction

Isoxazoles, isoxazolines, and isoxazolidines are five-membered heterocyclic systems with one oxygen atom and one nitrogen atom at adjacent positions. The chemistry of isoxazole is associated with the name of Ludwig Claisen, who recognized in 1888 the cyclic structure of 3-methyl-5-phenylisoxazole, obtained by Ceresole in 1884 from hydroxylamine and benzoylacetonel. Claisen suggested for this nucleus the name of monoazole, then modified by Hantzsch to isoxazole, from the already-known isomeric ring oxazole. The parent isoxazole was synthesized by Claisen in 1903 by oximation of propargylaldehyde acetal. Between the three classes of dihydroderivatives, the 2-isoxazolines are by far the most easily prepared and widely studied. The preparation of the first derivative, 3,5-diphenyl-2-isoxazoline from chloro phenylpropiophenone and hydroxylamine, was reported in 1895; however, the synthesis of saturated compounds was not described until 1918 and isoxazolidine itself was prepared in 1942. Concerning bicyclic derivatives, the first 1,2-benzisoxazole, 3-phenyl-1,2-benzisoxazole, was synthesized by treatment of o-nitro benzophenone oxime with alkali in 1892 and the parent compound was obtained in 1908. In 1881, 5,6-dimethoxy-2,1-benzisoxazole was the first compound of this class to be prepared and in 1882 the unsubstituted system was synthesized by reduction of o-nitrobenzaldehyde with tin in acetic or hydrochloric acid. A very significant contribution to the development of isoxazole chemistry came in the period 1930–1946 from Quilico’s studies on synthetic approaches to the ring system from nitrile oxides and unsaturated compounds. However, the study of isoxazolidines began very much more recently being related to the availability of this nucleus and then to the discoveries of cyclo additions of nitrones to olefins and intramolecular cyclizations of
unsaturated nitrones\textsuperscript{(14)}. The great interest still nowadays associated with this class of compounds is certainly based on their versatility as synthetic building blocks: their latent functionalities as enaminones, 1,3-dicarbonyl compounds, amino alcohols, and hydroxy nitriles have been widely exploited for the synthesis of other heterocycles and complex molecules.

Moreover, many derivatives exhibit interesting applications in various fields such as agriculture, industry, and medicine. In particular, the wide spectrum of biological activities characteristic of these systems, including antithrombotic, platelet activating factor (PAF) antagonist, hypolipidemic, nootropic, immunomodulator, antiviral, antiobesity, and central nervous system (CNS) modulation, may reasonably be ascribed to the easy cleavage of the N-O bond with formation of more reactive species.

The literature concerning this topic has been presented in different series: Comprehensive Heterocyclic Chemistry\textsuperscript{(15,16)}. The chemistry of heterocyclic compounds\textsuperscript{(17-19)} and progress in heterocyclic chemistry\textsuperscript{(20-30)}. The following ring systems are discussed in this chapter, and Chemical Abstracts (CA) and common names are given as well as ring position numbering. Monocyclic species follow the normal numbering of the parent compound.
Structure

The evaluation of aromaticity is one of the most important aspects in chemistry, but the extent to which reactivity, energetic, magnetic, and geometric criteria are descriptions of a single, unifying property of molecules remains a matter of debate. In this context, a set of energetic, magnetic, and geometric indexes, such as aromatic stabilization energies (ASEs), (magnetic susceptibility exaltations), nucleus-independent chemical shifts (NICSs), and harmonic oscillator model of aromaticity (HOMA), have been determined for isoxazole and many other five-membered p-electron systems, choosing for the computations the highest, reasonable possible levels of theory\(^{31}\). Calculated energies and magnetic NICS indexes have also been reported for 2,1-benzisoxazole (anthranil) (1) and its isomers 1,2-benzisoxazole (2) and benzoxazole (3).
The negative values of the calculated NICS indexes (Restricted Hartree–Fock RHF) wave functions of the most stable geometries), examined as a magnetic criterion for aromaticity, indicate that all species have aromatic character. The NICS values for anthranil are remarkably different evidencing a loss of aromaticity in the six-membered ring and an increase in the aromaticity of the five-membered ring, suggesting that (1) is less benzenoid than its isomers (2) and (3). However, considering the sum of the NICS values for the five- and six-membered rings, there seem to be similar aromaticities for all the species\(^{(32)}\). Direct computation of the CTOCD-DZ/6-31G/RHF/6-31G p-current density, that is, the ring current, of anthranil (1) and 1,2-benzisoxazole (2) and benzoazole (3) reveals different patterns of current flow. Isomers (2) and (3) sustain strong benzene-like currents in the six-membered ring and bifurcated flow in the five-membered ring, whereas, in keeping with its lower thermodynamic stability (1) has only a perimeter circulation without separate monocycle currents. Although the ring current criterion does not offer a sharp distinction between (2) and (3), their difference in thermodynamic stability is identical to that between isoxazole and oxazole, suggesting an aromaticity order 1<2<3\(^{(33)}\).

As already reported in CHEC (1984) isoxazol-5-one can exist in different tautomeric forms. In particular, relative-stability energies (kcalmol\(^{-1}\) in brackets) for four forms consisting of three tautomers (4), (5) and (6) and a rotamer of 5-hydroxyisoxazole have been computed at the level. The stability order was found to be 7<6<5<4.
Ab initio and density functional theory (DFT) methods have been exploited to determine the structures and the interaction energies of 2H-isoxazol-5-one (5) and its dimer and trimer structures in the gas phase. For the cyclic trimer, the computed structural parameters resulted in excellent agreement with the X-ray determination of the supramolecular aggregate of 4-(2-methoxybenzyl)-3-phenyl-4H-isoxazol-5-one, involving very strong intermolecular H-bonds of the NH tautomeric form, interpreted in terms of the RAHB (resonance-assisted hydrogen bond) model\(^{[34]}\).

**Thermodynamic Aspects**

Stability Thermochemical experiments were performed to determine the standard molar enthalpy of formation of anthranil in the gaseous phase. A comparison of this value with that obtained from quantum-chemical calculations for 1,2-benzisoxazole showed that anthranil (1) is significantly less stable. This difference of about 42 kJ mol\(^{-1}\), even if significant, suggests that by thermochemical criteria, if aromatic character is ascribed to 1,2-benzisoxazole, a significant aromatic character must also be associated with anthranil.

**Tautomerism**

The tautomeric composition in solution of 4-(arylmethyl)-isoxazol-5-one derivatives has been determined on the basis of 1H NMR and infrared (IR) data. The CH form was predominant in chloroform solution, while the NH and OH forms are more common in polar solvents and in the solid state\(^{[35]}\). 5-Hydroxy- and 5-amino-2-isoxazolines show different tautomeric forms in solution. The presence
of cyclic hemiacetal or hemiaminal moieties in such molecules allows the easy cleavage of the C-5–O bond to form linear structures. Subsequent intramolecular addition of nucleophiles to the CTN bond gives rise to cyclic structures. Isoxazole exist, in the crystalline state, as the isoxazoline form (8). In solution, a ring-ring tautomeric equilibrium was observed between the isoxazoline form (9) and the pyrazoline form (10). The tautomeric ratio depended on steric factors and on the solvent used. The tautomeric equilibrium was established after several days\(^{36}\).

\[ R = \text{Me, Et, } i-\text{Pr} \]

More complex tautomeric equilibria have been observed for isoxazole involving the 1,2,4,5-tetrazin-3-thione (11). The equilibrium is strongly shifted toward the isoxazoline form (12) in solvents such as pyridine, acetone, dimethylsulfoxide (DMSO), and dimethylformamide (DMF), whereas the pyrazoline form (13) does not exceed 5–10\(\%\)\(^{37}\). The presence of the above tautomeric species has been demonstrated by NMR. 5-Hydroxy-3,3,5-trimethylisoxazolidine showed a similar behaviour\(^{38}\). The presence of a CF\(_3\) group such as in affects considerably the structure of these compounds, which exist only in the cyclic isoxazoline form (14)\(^{39}\).
**Isomerism**

Upon chromatographic purification on silica gel, aldehyde slowly epimerized to the all-trans substituted isoxazolidine via retro-Michael/Michael reactions\(^{40}\).

Silica gel catalyzed the cis-trans-isomerization of some 4-nitroisoxazolidines through a cycloreversion/cycloaddition process.
Thermal and Photochemical Reactions

Thermal isomerization of 4-nitro-3-phenylisoxazole derivatives to the corresponding 4-nitro-2-phenyloxazoles was performed in quite satisfactory yields by heating in xylene at 155°C in the presence of FeCl₃–SiO₂[41,42]. Flash vacuum thermolysis of isoxazolopyrimidinones gave rise to iminopropadienones observed in an Ar-matrix[43]. Alkylolithiums or Grignard reagents reacted at room temperature with 3-methylisoxazolo[5,4-b]pyridine and obtained through isoxazole ring opening. By contrast, sodium malonate and sodium borohydride were able to react only under ultraviolet (UV) irradiation, allowing selective trapping of ketenimine or azirine intermediates with formation of enaminopyridone and diastereomeric spiroaziridino pyridones respectively[44].

Electrophilic Attack at Nitrogen

5-Chloro-2-methylisoxazolium triflates were obtained in good yields from the corresponding chloroisoxazoles. Treatment with the sodium salt of 1,3-dioxo compounds, followed by addition of triethylamine, afforded isoxazolium anhydrobases[45]. Reactions of 3-hydroxyisoxazole derivatives with phosgene in toluene gave selectively
2-chlorocarbonyl-3(2H)-isoxazolones, converted in good yields with aniline derivatives into 2-carbamoyl-3(2H)-isoxazolones.

\[
\begin{align*}
\text{R}^1 &= \text{Ph} \\
\text{R}^2 &= \text{Me}
\end{align*}
\]

**Electrophilic Attack at Carbon**

A convenient C-4 halogenation of 3,5-diarylisoxazoles was performed with N-halosuccinimides in acetic acid, while the corresponding fluorination has been accomplished using N–F reagent Selectfluor\(^{46,47}\). A new one-pot nitration employing tetramethylammonium nitrate in dichloromethane at room temperature was efficiently applied to 3,5-dimethylisoxazole, leading to the corresponding 4-nitro derivative in high yield and purity\(^{48}\). Direct nitration of isoxazoles was also performed with nitric acid/trifluoroacetic anhydride affording mononitro derivatives in average yields of 60\(^\%\)\(^{49}\).

**Nucleophilic Attack at Carbon**

While 3-bromoisoxazoles were inert to SNAr reactions under thermal conditions, the employment of phosphazene bases under microwave irradiation facilitated the amination process, affording 3-aminoisoxazoles in moderate yields\(^{50}\).

**Nucleophilic Attack at Hydrogen**

Direct lithiation of 3-(BOC-amino)-5-methylisoxazole and 5-(BOC-amino)-3-methylisoxazole gave dianions that reacted with a variety of electrophiles to afford 4-substituted aminoisoxazoles in good
yields (BOC¼t-butoxycarbonyl)(51). A mechanistic investigation of reactions of 3-phenylisoxazole with alkylolithiums has been reported. Alkylolithiums gave 5-H abstraction followed either mainly by ring fragmentation to benzonitrile and ethynolate ion or by formation of alkylated enaminones(52).

**Ring Opening**

Base-induced or reductive cleavage of isoxazole rings followed by silylation of the resulting open-chain products gave rise to bis(siloxy)butadienes in high yields(53). The interaction of 3,5-disubstituted isoxazoles and isoxazolines with a low-valent titanium isopropoxide reagent, prepared from Ti(OPri)₄ and EtMgBr in diethyl ether, led to chemoselective reductive cleavage of the five-membered ring to afford enaminoketones and hydroxyketones respectively(54). Several enantiomerically pure 9-hydroxy-enaminoketones were synthesized by reductive cleavage of the corresponding isoxazole carbinols obtained in enantiopure form by enzymatic kinetic resolution (KR) of the racemic hydroxyisoxazoles using lipases(55). A convenient synthesis of substituted pyran-4-ones from isoxazoles through reaction with Mo(CO)₆ has been reported(56). Reductive cleavage of 3-, 4-, 5-silyl- and 5-silylmethylisoxazoles gave silyl-enaminones, useful synthons in the regioselective synthesis of silyl- and silylmethylpyrazoles, as well as pyrrole, pyrimidine and pyridine derivatives(57).
Hydrogenolysis and subsequent acidic hydrolysis of isoxazolyl-alcohols, synthesized via standard procedures, allowed a facile access to 3(2H)-furanones, useful intermediates for the synthesis of geiparvarin analogues\(^{58}\).

Reductive ring opening was exploited for the synthesis of pyrido-condensed heterocycles, containing from five to eight atoms in the fused ring. 4-Substituted isoxazolo[4,5-c]pyridines were easily converted into derivatives with Mo(CO)\(_6\) in refluxing methanol. The same ring-opening/ring-closure strategy was also applied to 4-substituted isoxazolo[5,4-b]pyridine systems\(^{59}\).
Aryl groups

A series of iridium-based complexes formed in situ have been used to mediate ortho-exchange of hydrogen with deuterium in model substrates such as 3-phenyl-5-acetylisoxazole\(^{60}\). 4,5-Diarylisoxazoles were exploited in the synthesis of phenanthro[9,10-d] isoxazoles. For instance, compound was prepared by intramolecular Stille–Kelly stannylation/biaryl coupling of 9-diiodo 4,5-diarylisoxazole and by nonphenolic oxidative coupling of the corresponding nonhalogenated substrate with phenyliodine(III) bis(trifluoroacetate) (PIFA)\(^{61}\).

\[
\begin{align*}
\text{X}_1 & = \text{H, PIFA, BF}_3\text{OEt}_2, \text{CH}_2\text{Cl}_2, -40^\circ\text{C}, \\
\text{X}_2 & = \text{Me}_6\text{Sn}_2\text{PdCl}_2\text{(PPh}_3\text{)}_2, \text{dioxane, 140}^\circ\text{C}
\end{align*}
\]

Aldehydes and Baylis–Hillman adducts

The Baylis–Hillman (BH) reaction is one of the most studied carbon–carbon bond-forming reactions of recent years, now considered a standard synthetic methodology, where an aldehyde and an electron-deficient alkene are allowed to react in the presence of a tertiary amine or Lewis acid. This process was extensively studied by Batra and co-workers on isoxazolecarbaldehydes. In particular, 3-arylisoxazolecarbaldehydes undergo extremely fast BH reactions by treatment with a mixture of DABCO and activated alkenes: the reactions went to completion within 10–15 min, leading to adducts, suitable for further synthetic elaborations\(^{62}\). On the other hand, the reaction with cycloalkenones in the presence of TiCl\(_4\), as Lewis acid, at
lower temperature followed a different reaction pathway, leading to other products in addition to BH adducts\(^{(63)}\).

\[
\begin{align*}
\text{Ar}^- & \quad \text{N} \quad \text{H} \quad \text{EWG} \\
\text{N} & \quad \text{H} \\
\text{Ar}^- & \quad \text{N} \quad \text{H} \quad \text{EWG}
\end{align*}
\]

\[
\begin{align*}
\text{Ar} & = 4-\text{BnOC}_6\text{H}_4, \ 4-\text{MeC}_6\text{H}_4, \ 2-\text{ClC}_6\text{H}_4, \ -\text{C}_6\text{H}_5, \ 2-\text{ClC}_6\text{H}_4, \ 3-\text{O}_2\text{NC}_6\text{H}_4, \\
\text{EWG} & = \text{CO}_2\text{Me}, \ \text{CO}_2\text{Et}, \ \text{CO}_2n-\text{Bu}, \ \text{CO}_2t-\text{Bu}, \ \text{CN}, \ \text{COMe}
\end{align*}
\]

5-Isoxazolecarbaldehydes are among the fastest-reacting substrates for BH reactions, and comparative studies on 4-isoxazolecarbaldehydes showed that for these regioisomers a lower reactivity led to poorer yields (10–89%) and longer reaction times (2–7 h). The proposed rationale for this different behavior involves the proton abstraction step in the intermediate I: the proximity of the oxygen atom in the 5-substituted isoxazole derivative perhaps could assist the deprotonation and thus the elimination of the base, with a consequent acceleration of the process\(^{(64)}\). This hypothesis was corroborated by the fast and facile BH reactions in substituted 3-isoxazole carbaldehydes, having a proximal nitrogen atom in the corresponding intermediate (product yields: 77–95%, reaction times: 15–30 min)\(^{(65)}\).

\[
\begin{align*}
\text{Ar}^- & \quad \text{N} \quad \text{H} \quad \text{EWG} \\
\text{N} & \quad \text{H} \\
\text{Ar}^- & \quad \text{N} \quad \text{H} \quad \text{EWG}
\end{align*}
\]

BH reactions of substituted 3-, 4-, and 5-isoxazolecarbaldehydes were even performed on solid phase, in
general through immobilization of acrylic acid on the resin. In particular, using solid-phase methods, 3-aryl-5-isoxazolcarbaldehydes were exploited as building blocks for the generation of combinatorial libraries through BH reactions, Wittig reactions, nitroalldol condensations, imine and oxime formation, Michael additions, reductive aminations, and alklylation reactions. A sequence of BH reactions/Michael additions of primary amines, followed by cleavage from the solid support, gave substituted amino propionic acid derivatives as diastereomeric mixtures in excellent yields and purity; other synthetic strategies involving reductive amination and alklylation of the NH group led to highly functionalized isoxazoles\(^{66,67}\).

\[
\begin{align*}
\text{i} &= \text{DABCO, DMSO, 3h;} \\
\text{ii} &= \text{RNH}_2, \text{DMSO, 5h;} \\
\text{iii} &= \text{5% THF/DCM 20 min}
\end{align*}
\]

BH adducts coming from 3-, 4-, and 5-isoxazolcarbaldehydes, as well as the corresponding acetates, were subjected to catalytic hydrogenation in the presence of Raney-Ni or Pd–C. Adducts (EWG-CO\(_2\text{Me}\)) and diastereoselectively converted into enamminones by the former reagent, while the latter afforded derivatives through reduction of the double bond and retention of the isoxazole ring\(^{68}\). Treatment of
esters with NaBH₄ even allowed reduction of the ester function, assisted by the secondary hydroxyl group in the position, with formation of 1,3-diol systems\(^{(69)}\). Moreover, operating in aqueous media in the presence of DABCO, the corresponding acetates were easily transformed in excellent yields into azides by treatment with NaN₃, while reactions with unsaturated ketones, esters, and nitriles afforded 1,4-pentadienes\(^{(70,71)}\). Acetates were respectively reduced to regioisomers by treatment with DABCO and NaBH₄ or NaBH₄ alone. Further synthetic elaborations of the above BH adducts leading to different heterocyclic systems have also been reported\(^{(72-74)}\).

**Carboxylic acids and derivatives**

3-Methylisoxazole-5-carboxylic acid was converted into the corresponding 5-carboxamides and 5-(1H-pyrazol-1-ylcarbonyl) derivatives in satisfactory yields by treatment with thionyl chloride and amines or pyrazoles\(^{(75)}\). A three-component assembly of isoxazole-5-carboxylic acid chloride, 1,1-dimethylallene, and bispinacolatodiboron, catalyzed by a phosphine-free palladium complex, gave 2-acylallylboronate derivatives regioselectively\(^{(76)}\). On the other hand, a mild procedure allowed the preparation of unsaturated ketones by simple reaction of 3-aryl-5-methylisoxazole-4-carboxylic acid chlorides with allyl bromide and indium in DMF\(^{(77)}\).
In contrast to 4-nitrobenzonitrile, cyano groups on 3,5-dicyanoisoxazoles were found to be highly reactive to nucleophilic addition of alcohols (or amines) leading to imidates (or amidines); the use of 1,2-diamines, such as ethylenediamine, afforded 3,5-bis(imidazolinyl)isoxazoles. The solvent-sensitive decarboxylation of 3-carboxy-1,2-benzisoxazoles was catalyzed by monoclonal antibodies, generated against a 3-phenyl-1,2-benzisoxazole derivative.

**N-Linked substituents**

3-Methyl-5-aminoisoxazole was allowed to react with 4,4,4-trifluoro-3-oxobutanoates in refluxing HOAc to give isoxazolopyridines in satisfactory yields. N-(1-Chloro-2,2,2-trihaloethylidene)-O-methylurethanes underwent cyclization with 3-amino-5-methylisoxazole and 5-amino-3-methylisoxazole to give isoxazolotriazinones and pyrimidones, respectively, through amidine
intermediates\(^{(81)}\). Compound 5-t-butyl derivative, reacted with diimidoyl dichlorides in a new and efficient anionic domino process, leading to biologically relevant imidazo[4,5-b]quinoxalines\(^{(82)}\). The same 3-aminoisoxazole systems were efficiently transformed into the corresponding salicyldimines by solvent-free microwave-assisted condensation with salicylaldehyde\(^{(83)}\) and were even exploited in the catalytic amination of 5-iodouracil derivatives\(^{(84)}\). Isoxazol-3-yl methylenecyclopropyl amide underwent alkylative ring expansion with aryl aldehydes (and aryl aldmines) in the presence of MgI\(_2\), leading to the exclusive formation of hydroxy-alkylated (and amino-alkylated) pyrrol-2-ones. The amide nitrogen atom, generally considered non-nucleophilic, was incorporated into the newly formed ring under neutral conditions\(^{(85)}\).

\[
\begin{align*}
R^1 &= \text{NH}_2, \text{Me} \\
R^2 &= \text{Me, NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{Ar} &= \text{Ph, 2-CF}_3\text{C}_6\text{H}_4, 4-\text{CF}_3\text{C}_6\text{H}_4, 3,4-\text{OCH}_2\text{OC}_6\text{H}_3, 4-\text{MeOC}_6\text{H}_4
\end{align*}
\]
O-Linked substituents

The synthesis of 3-hydroxyisoxazoles (3-isoxazolols), as well as annulated analogues, has been exhaustively reviewed\(^{86}\). The regioselective O-versus N-alkylation of 5-carbomethoxy-3-hydroxyisoxazole was studied: 3-o-alkyl products were highly favored with benzyl, benzhydryl, and allyl bromide (91:9), while methylation with diazomethane or methyl iodide gave mixtures of both regioisomers (73:27 and 58:42, respectively). On reduction with DIBAL-H, the esters afforded 3-o-protected carbaldehydes, versatile key intermediates in the synthesis of pharmacologically interesting 3-hydroxyisoxazoles\(^{87}\).

![Chemical structure](image)

Halogen atoms

Palladium-catalyzed coupling reactions of 2-(5-iodoisoxazol-3-yl)pyridine with a variety of organometallic compounds led to derivatives through Sonogashira, Suzuki, Negishi, and Stille reactions, respectively\(^{88}\).
Isoxazolines

Substituents of 4,5-dihydroisoxazole rings have been manipulated with a variety of reagents exploiting the stability of the ring. Chiral isoxazoline was treated with LiB(Et)₃H to remove the D-glucose-derived auxiliary R*OH, which was recovered in high yields. Both the methyl ester groups of isoxazoline were reduced with sodium borohydride, giving in 89% yield following reaction of the diol with methanesulfonyl chloride. Further reduction of the nitro group and subsequent cyclization by intramolecular nucleophilic substitution of the amino group afforded.

\[
\begin{align*}
\text{LiB(Et)}_3\text{H} & \rightarrow \text{THF, rt} \\
\text{LiB(Et)}_3\text{H} & \rightarrow \text{R}^*\text{OH}
\end{align*}
\]

Ring Syntheses Classified by Number of Ring Atoms Contributed by Each Component Ring synthesis was previously discussed in CHEC(1984) and CHEC-II(1996). This section is an update of the previous work with particular attention toward new reagents, processes, and products. Synthetic approaches have been classified on the basis of the number and arrangement of ring atoms present in each component.
Synthesis of Isoxazoles

Isoxazoles can be easily prepared from isoxazoline precursors through dehydrogenation or elimination processes. This aspect is not discussed in detail in this section.

Isoxazoles From atom fragment: C–C–C–N–O

This kind of reaction refers to cyclization of synthons containing all five atoms of the isoxazole ring. In some cases, these acyclic species are stable and isolable, but often they are only transient or supposed intermediates coming from C–C–C and N–O fragments. Many synthetic routes involve cyclocondensations of hydroxylamine with 1,3-bielectrophiles. In this context, three-carbon 1,3-difunctionalized units bearing sp or sp² carbons have been widely exploited. Condensation of silylalkynones with NH₂OH.HCl allowed the synthesis of 5-silylisoxazoles\(^{91}\).

Analogously, using the alkenyl ketone functionality of ynone, coming from protected L-aspartic acid, nonproteinogenic heterocyclic substituted amino acids were synthesized. Reaction with hydroxylamine hydrochloride in EtOH afforded exclusively the 3-substituted isoxazole in 62% yield, while operating in the presence of pyridine a 1:3 mixture of 3- and 5-substituted regioisomers was obtained in 51% yield\(^{92}\). Starting from ynones, electrophilic cyclization allowed an easy access to a variety of 3,5-disubstituted-4-halo- or 4-selenoisoxazoles under mild reaction conditions, by treatment of the o-methyl oximes with ICl, I₂, Br₂ or PhSeBr\(^{93}\).
Various unsaturated ketones were used as versatile synthons in heterocyclizations with hydroxylamine hydrochloride, probably through oxime intermediates, \((R= \text{alkyl, aryl, furyl})\), affording 3-substituted 5-bromomethylisoxazoles\(^\text{(94)}\) and 1-bis(methoxy)-4-bis(methylthio)-3-buten-2-one led to isoxazoles with a masked aldehyde functionality. A regioselective method affording directly 3-phenyl-5-substituted isoxazoles, without isolation of isoxazoline intermediates, exploited reactions of \(\text{NH}_2\text{OH}\) and benzotriazolyl, unsaturated ketones, stereoselectively generated from benzotriazolylacetophenone and aldehydes in the presence of piperidine\(^\text{(95)}\). Treatment of lithiated benzotriazolyvinyl ethyl ether with acid chlorides followed by cyclocondensation with hydroxylamine hydrochloride gave 4-benzotriazolyl-substituted isoxazoles. A convenient one-pot preparation of 4,5-diarylisoxazoles was performed from enaminones under standard oximation conditions \((\text{NH}_2\text{OH.HCl, MeOH–AcOH, Na}_2\text{CO}_3, \text{reflux})\). The regiochemistry of the final products unequivocally supports a reaction mechanism involving a tandem amine exchange/heterocyclization process. This procedure allowed the synthesis of 4,5-bis(o-haloaryl)isoxazoles, which were efficiently
converted via intramolecular Stille-type biaryl coupling to phenanthro[9,10-d]isoxazoles in high overall yields\(^{96}\). In a similar way, reactions of alkoxyvinyl trichloromethyl ketones with hydroxylamine in hydrochloric or sulfuric acid gave 5-carboxyisoxazoles, exploiting the reactivity of the trichloromethyl group as a carboxyl group precursor.

Although the synthesis of 3-isoxazolols from keto esters and hydroxylamine suffers from the formation of 5-isoxazolones as major products, treatment of acyl chlorides with Meldrum’s acid and subsequent aminolysis gave rise to protected keto hydroxamic acid derivatives that cyclized to the corresponding 5-substituted-3-isoxazolols without formation of any by-product\(^{97}\). 5-Amino-3-(pyrrol-2-yl)isoxazoles were selectively prepared by treatment of cyanoethylthio-ethenylpyrroles with hydroxylamine in methanol, probably through replacement of their SEt group with a hydroxylamino moiety.
With carbamoyl derivatives ($R^3=\text{CONH}_2$), minor amounts of regioisomers were also isolated and their formation was increased (12–48%) operating in the presence of aqueous NaOH$^{98}$. Various 3-acyl-lactams were reacted with NH$_2$OH.HCl in boiling EtOH to give 3-substituted 4-aminoalkyl-5(2H)-isoxazolones as single regioisomers in satisfactory yields, through oxime intermediates. Cyclodehydration of N-substituted salicylhydroxamic acids under Mitsunobu conditions was the key step in the synthesis of N-substituted 1,2-benz-3(2H)-isoxazolones$^{99}$.

\[
\begin{align*}
\text{R} &= \text{Ph}, 3-\text{BrC}_6\text{H}_4, 3-\text{py}, 4-\text{py} \\
\end{align*}
\]

SPS using the ‘catch and release’ approach allowed the efficient preparation of libraries of substituted isoxazoles. Starting from aniline–cellulose as solid support, N-formylimidazole dimethyl acetal, and different ketoesters or ketoamides ($X = \text{O, NH, NEt}$), the one-pot generation of cellulose-bound enaminones was performed in quantitative yields. Following treatment with hydroxylamine hydrochloride, pure isoxazoles were obtained in high yields directly in
solution, with recovery of the starting resin\textsuperscript{(100)}. Microwave-assisted synthesis was also reported.

![Chemical Reaction Diagram]

Direct interaction of a nitro substituent with electron-rich and electron-poor side-chains in ortho-substituted nitroaromatic and nitro-heteroaromatic compounds is a well-documented and fruitful source of novel heterocyclization reactions. In this context, efficient solution-phase pyrolytic transformations of 4-nitro-1H-imidazol-5-ylethanoates and 3-nitropyridinyl- and 5-nitropyrimidinyl-ethanoates gave 3,4-fused isoxazoles, plausibly through ketene intermediates\textsuperscript{(101)}. 

\[ X = \text{O, NH, NEt} \]
\[ R_1 = \text{Me, } i-\text{Pr; } R_2 = \text{Me, Et, Bn, Ph(CH}_2)\text{)}_2 \]
5-Aminoisoaxazoles were obtained from (Z)-3-alkyl-3-nitro-2-phenylpropenenitriles using baker’s yeast. Reductive cyclizations of 2-nitroacylarenes allowed the synthesis of anthranil derivatives. For example, a series of 5-substituted 2,1-benzisoxazoles where prepared by reduction with SnCl₂ and subsequent cyclization of 5-substituted-2-nitrobenzaldehydes. Analogous processes were performed in the presence of 2-bromo-2-nitropropane/Zn in methanolic solution or by controlled cathodic electrolysis reactions. The use of 2-bromo-2-nitropropane and indium in aqueous media solution gave 2,1-benzisoxazoles in excellent yields. Moreover, an efficient Me₃SiCl/base-mediated dehydration allowed the synthesis of 3-substituted anthranils from 2-nitrobenzyl derivatives and from reactions of nitroarenes with arylmethylene compounds.
Synthesis of Isoxazolidinones and Isoxazolidinediones

Diazoketones underwent Wolff rearrangement in the presence of PhCO$_2$Ag and Et$_3$N at 78°C to give 5-substituted isoxazolidin-3-ones. The ketene intermediate was trapped by the oxy-amide moiety even in the presence of H$_2$O or MeOH.$^{105}$

\[
\begin{align*}
\text{R}^1 &= i - \text{Pr}, \text{CH}_2\text{CHMe}_2; \text{R}^2 = \text{Cbz}, \text{EtOCO}
\end{align*}
\]

Intramolecular halocyclization of butenohydroxamic acids with iodine monochloride, N-bromo- or N-chlorosuccinimide afforded 5-halomethylisoxazolidin-3-ones in high yields.$^{106}$

\[
\begin{align*}
\text{X} &= \text{Cl, Br, I}
\end{align*}
\]

Natural Products

Both ibotenic acid and muscimol (a structural analogue of aminobutyric acid, GABA) have been isolated from several fungal species including Amanita muscaria and are active CNS agents of the N-methyl-D-aspartate (NMDA) and GABA receptor systems respectively. Their presence in macromycetes and their biological activities have been recently reviewed.$^{107}$ The decarboxylation observed in certain circumstances, has been studied in DMSO with 3H$_2$O or D$_2$O.$^{108}$
A family of cis-cyclopent[c]isoxazolidine alkaloids named pyrinodemins was isolated from the marine sponge Amphimedon sp. These compounds, which show potent cytotoxicity, were synthesized in racemic form by different groups in order to clarify their structures. The asymmetric total synthesis of pyrinodemin A was also accomplished. Both the enantiomers of cycloserine (4-amino-3-isoxazolidinone) act as alanine racemase inhibitors and the mechanism of inactivation has been studied.
Karabasana gouda T et al. have been synthesis and described some new isoxazole derivatives and screening for their anti inflammatory activity\(^{(110)}\).

![Chemical structure](image1)

\[ \text{Ar} = 4,4'-\text{biphenyl, 2-amino-3-pyridyl} \]

Tirlapur VK and Co-workers have been prepared some new isoxazole derivatives and tested for their biological activities\(^{(111)}\).

![Chemical structure](image2)

\[ \text{R} = \text{C}_6\text{H}_5, \text{C}_6\text{H}_4\text{OH(p) etc.} \]

Solankie A et al. have been synthesized some novel isoxazole derivatives and evaluated for their antibacterial activity\(^{(112)}\).

![Chemical structure](image3)
Magar BK and Co-workers have been prepared some isoxazole and tested for their antimicrobial activity\textsuperscript{(113)}.

\[
\begin{array}{c}
\text{R} \\
\text{N} \quad \text{S} \quad \text{NH} \quad \text{N} \\
\text{O} \\
\text{CH}_3
\end{array}
\]

Joshi VD et al. have been synthesized some novel isoxazole derivatives and evaluated biological activity\textsuperscript{(114)}.

\[
\begin{array}{c}
\text{R} \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{R}
\end{array}
\]
The synthesis of following isoxazoles derivatives have been discussed in part III

**Section-I:** Preparation of \( N-(5\text{-tetrazol-1-yl}-\text{benzo}[d]\text{isoxazol-3-yl})-(\text{aryl})\text{amide} \)

**Section-II:** \( N-(3\text{-pyrrol-1-yl}-\text{benzo}[d]\text{isoxazol-5-yl})-(\text{aryl})\text{amide} \)

Spectroscopic analysis and biological activities of these compounds are discuss in chapter III
Section – I
Preparation of N-(5-tetrazol-1-yl-benzo[d]isoxazol-3-yl)-(aryl)amide

Where, Ar = Aryl / Hetero Aryl Groups
## Table: 3- Physical Constant of N-(5-tetrazol-1-yl-benzo[d]isoxazol-3-yl)-(aryl)amide

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>-Ar</th>
<th>Molecular formula</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Elemental analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% C</td>
</tr>
<tr>
<td>21</td>
<td>-Ph</td>
<td>C₁₅H₁₀N₆O₂</td>
<td>161-</td>
<td>72</td>
<td>58.8</td>
</tr>
<tr>
<td>22</td>
<td>-4-Ph-Cl</td>
<td>C₁₅H₉ClN₆O₂</td>
<td>175-</td>
<td>61</td>
<td>52.8</td>
</tr>
<tr>
<td>23</td>
<td>-4-Ph-F</td>
<td>C₁₅H₉FN₆O₂</td>
<td>177-</td>
<td>65</td>
<td>55.5</td>
</tr>
<tr>
<td>24</td>
<td>-4-Ph-OMe</td>
<td>C₁₆H₁₂N₆O₃</td>
<td>155-</td>
<td>71</td>
<td>57.1</td>
</tr>
<tr>
<td>25</td>
<td>-4-Ph-Me</td>
<td>C₁₆H₁₂N₆O₂</td>
<td>153-</td>
<td>81</td>
<td>60.0</td>
</tr>
<tr>
<td>26</td>
<td>-4-Ph-Et</td>
<td>C₁₇H₁₄N₆O₂</td>
<td>166-</td>
<td>73</td>
<td>61.0</td>
</tr>
<tr>
<td>27</td>
<td>-4-Py</td>
<td>C₁₄H₉N₇O₂</td>
<td>143-</td>
<td>59</td>
<td>54.7</td>
</tr>
<tr>
<td>28</td>
<td>-1-Naph</td>
<td>C₁₉H₁₂N₆O₂</td>
<td>155-</td>
<td>70</td>
<td>64.0</td>
</tr>
<tr>
<td>29</td>
<td>2,4-Cl₂-Ph</td>
<td>C₁₅H₈Cl₂N₆O</td>
<td>181-</td>
<td>73</td>
<td>48.0</td>
</tr>
<tr>
<td>30</td>
<td>-4-Ph-Br</td>
<td>C₁₅H₉BrN₆O₂</td>
<td>161-</td>
<td>61</td>
<td>46.7</td>
</tr>
</tbody>
</table>
Experimental Procedure

Preparation of 5-nitro-benzo[d]isoxazol-3-ylamine (I)

A solution of acetoxime (0.144 mol) in DMF (100 ml) was stirred at rt, then t-BuOK (0.180 mol) was added and the solution stirred for another 30 min. at rt. 2-fluoro-5-nitro-benzonitrile (0.120 mol) was added drop wise and the reaction mixture stirred for another hour at rt. The reaction mixture was poured out in a solution of isopropylether (200 ml) and saturated NH₄Cl (200 ml) solution and stirred vigorously for 10 minutes. After completion, the organic layer was separated, washed with water, dried over sodium sulphate, filtered off and the solvent was evaporated dry. The residue was dissolved in ethanol (200 ml). A solution of 2N HCl (100 ml) was added and the reaction mixture refluxed for 1 hour. After completion the solvent was evaporated, the aqueous residue basifies with a solution of K₂CO₃ and extracted with EtOAc (200 ml). The organic layer was separated, washed with water (100 ml), dried over sodium sulphate, filtered off and the solvent was evaporated to get pale yellow solid as Compound-I in yield 81.0%. Ana Obs.: C-46.99%, H-2.87%, N-23.39%. Calc. for C₇H₅N₃O₃: C-46.94%, H-2.81%, N-23.46%.

Preparation of N-(5-nitro-benzo[d]isoxazol-3-yl)-acetamide (II)

To a solution of 5-nitro-benzo[d]isoxazol-3-ylamine (I) (0.094 mol) and triethyl amine (0.188 mol) in dichloromethane (200 ml) was added acetyl chloride (0.112 mol) at 5-10°C and reaction mixture was stirred at 10-15°C for 2 h. Water (500 ml) and dichloromethane (200 ml) was added to reaction mixture and stir for 15 min at rt. Organic layer was separated, washed with water (2x100 ml) and brine (100 ml). Solvent was evaporated under vacuum to get pale yellow solid as compound-II in yield 71%. Ana Obs.: C-48.82%, H-3.24%, N-19.05%; Calc. for C₉H₇N₃O₄: C-48.88%, H-3.19%, N-19.00%.
Preparation of N-(5-amino-benzo[d]isoxazol-3-yl)-acetamide (III)

To a solution of N-(5-nitro-benzo[d]isoxazol-3-yl)-acetamide (II) (0.063 mol) and iron powder (7.0 g) in acetic acid (100 ml) was stirred at RT for 4 h. Water (500 ml) was added to reaction mass and neutralized with 1N sodium hydroxide solution. Extracted with dichloromethane (3 x 200 ml), combined dichloromethane layer washed with water (3 x 200 ml). Solvent was evaporated under vacuum to get pale yellow solid as compound-III in yield 70%. Ana Obs.: C-56.50%, H-4.79%, N-21.93%; Calc. for C₉H₉N₃O₂: C-56.54%, H-4.74%, N-21.98%.

Preparation of N-(5-tetrazol-1-yl-benzo[d]isoxazol-3-yl)-acetamide (IV)

A solution of N-(5-amino-benzo[d]isoxazol-3-yl)-acetamide (III) (0.041 mol), sodium azide (0.041 mol) and triethyl orthoformate (20 ml) was stirred at 100°C for 4 h. After completion the reaction mixture was diluted with cold water (100 ml) and extracted with ethyl acetate (3×100 ml) and the combined organic layers were washed with brine (2×100 ml) and dried over the anhydrous sodium sulphate. After evaporation of solvent under vacuum get light brown as compound-IV in yield 84%. Ana Obs.: C-49.12%, H-3.37%, N-34.48%; Calc. for C₁₀H₈N₆O₂: C-49.18%, H-3.30%, N-34.41%.

Preparation of 5-tetrazol-1-yl-benzo[d]isoxazol-3-ylamine (V)

A mixture of N-(5-tetrazol-1-yl-benzo[d]isoxazol-3-yl)-acetamide (IV) (0.032 mol) and 1N HCl (10 ml) in methanol was reflux for 5 h. Solvent was evaporated completely under vacuum and water was added to residue. Aqueous solution was neutralized with saturated sodium bicarbonate to get solid precipitate. Solid separated by filtration, washed with water to get yellowish solid as compound-V in yield 79%. Ana Obs.: C-47.59%, H-2.93%, N-41.54%; Calc. for C₈H₆N₆O : C-47.53%, H-2.99%, N-41.57%.
Preparation of N-(5-tetrazol-1-yl-benzo[d]isoxazol-3-yl)-benzamide (21)

A solution of 5-tetrazol-1-yl-benzo[d]isoxazol-3-ylamine (V) (0.9 mmol), benzoic acid (1.2 mmol) and EDC (1.5 mmol) in THF (10 ml) was stirred at rt. Solvent was evaporated completely and water was added to residue. Solid separated by filtration and re-crystalized from 10% aq. ethanol giving off white solid as Compound-21 in yield 72%. Ana Obs.: C-58.82%, H-3.29%, N-27.44%; Calc. for C₁₅H₁₀N₆O₂: C-58.88%, H-3.24%, N-27.495%.

The monitoring of reaction and purity of compounds were checked on TLC aluminium sheet silica gel 60 F₂₄₅ (E.Merck) using hexane-ethyl acetate (5:5 V/V) and methanol-chloroform (2:8 V/V) as mobile phase and visualize under U.V light 254 nm.

Other compounds of the series (22 to 30) were prepared by using similar method and their physical data are recorded in Table-3.
Section-II

Preparation of N-[4-(3-oxo-3H-benzo[d]isoxazole-2-carbonyl)-phenyl]-{aryl}amide

\[
\begin{align*}
\text{OH} & \quad \text{O} & \quad \text{OH} \\
\text{OMe} & \quad \text{O} & \quad \text{OH} \\
\text{NH} & \quad \text{O} & \quad \text{OH} \\
\end{align*}
\]

SoCl₂ / MeOH  \quad \text{Reflux}

\[
\begin{align*}
\text{NH₂OH} / \text{NaOH} & \quad \text{RT} \\
\end{align*}
\]

CDI, THF  \quad \text{RT}

\[
\begin{align*}
\text{NO₂} & \quad \text{NO₂} \\
\end{align*}
\]

TEA / MDC  \quad \text{RT}

Fe / AcOH  \quad \text{RT}

\[
\begin{align*}
\text{NH₂} & \quad \text{Ar-COOH} \\
\end{align*}
\]

Where, Ar = Aryl / Hetero Aryl Groups
Table: 4:- Physical constant of N-[4-(3-oxo-3H-benzo[d]isoxazole-2-carbonyl)-phenyl]-(aryl)amide

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>-Ar</th>
<th>Molecular formula</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>% C</th>
<th>% H</th>
<th>% N</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>-Ph</td>
<td>C_{21}H_{14}N_{2}O_{4}</td>
<td>141-143</td>
<td>61</td>
<td>70.39</td>
<td>70.32</td>
<td>3.94</td>
</tr>
<tr>
<td>32</td>
<td>-4-Ph-Cl</td>
<td>C_{21}H_{13}ClN_{2}O_{4}</td>
<td>161-163</td>
<td>73</td>
<td>64.21</td>
<td>64.27</td>
<td>3.34</td>
</tr>
<tr>
<td>33</td>
<td>-4-Ph-F</td>
<td>C_{21}H_{13}FN_{2}O_{4}</td>
<td>158-159</td>
<td>59</td>
<td>67.02</td>
<td>67.06</td>
<td>3.48</td>
</tr>
<tr>
<td>34</td>
<td>-4-Ph-OMe</td>
<td>C_{22}H_{16}N_{2}O_{5}</td>
<td>155-157</td>
<td>81</td>
<td>68.04</td>
<td>68.09</td>
<td>4.15</td>
</tr>
<tr>
<td>35</td>
<td>-4-Ph-Me</td>
<td>C_{22}H_{16}N_{2}O_{4}</td>
<td>165-167</td>
<td>73</td>
<td>70.96</td>
<td>70.92</td>
<td>4.33</td>
</tr>
<tr>
<td>36</td>
<td>-4-Ph-Et</td>
<td>C_{23}H_{18}N_{2}O_{4}</td>
<td>171-173</td>
<td>66</td>
<td>71.49</td>
<td>71.42</td>
<td>4.70</td>
</tr>
<tr>
<td>37</td>
<td>-4-Py</td>
<td>C_{20}H_{13}N_{3}O_{4}</td>
<td>143-146</td>
<td>58</td>
<td>66.85</td>
<td>66.80</td>
<td>3.65</td>
</tr>
<tr>
<td>38</td>
<td>-1-Naph</td>
<td>C_{25}H_{16}N_{2}O_{4}</td>
<td>181-183</td>
<td>67</td>
<td>73.52</td>
<td>73.58</td>
<td>3.95</td>
</tr>
<tr>
<td>39</td>
<td>2,4-Cl_{2}-Ph</td>
<td>C_{21}H_{12}Cl_{2}N_{2}O_{4}</td>
<td>178-180</td>
<td>73</td>
<td>59.04</td>
<td>59.00</td>
<td>2.83</td>
</tr>
<tr>
<td>40</td>
<td>-4-Ph-Br</td>
<td>C_{21}H_{12}BrN_{2}O_{4}</td>
<td>177-179</td>
<td>61</td>
<td>53.47</td>
<td>53.41</td>
<td>2.56</td>
</tr>
</tbody>
</table>
Experimental Procedure

**Preparation of 2-hydroxy-benzoic acid methyl ester (I)**

A solution of 2-hydroxy-benzoic acid (0.144 mol) and methanol (100 ml) was stirred at 0-5°C. Thionyl chloride (0.289 mol) was added slowly and reflux under stirring for 3 h. Solvent was evaporated completely, hexane (100 ml) was added to residue and filtered to give compound-I in yield 81%. Ana Obs.: C-63.19%, H-5.23%; Calc. for C₈H₈O₃: C-63.15%, H-5.30%.

**Preparation of N,2-dihydroxy-benzamide (II)**

A solution of hydroxylamine hydrochloride (0.222 mol) was stirred at rt under N₂ atmosphere, then NaOH (0.444 mol) in 240 ml water and 2-hydroxy-benzoic acid methyl ester (I) (0.111 mol) in 170 ml dioxane were added dropwise and the reaction mixture was stirred for 12 hours at rt. After completion, the reaction solvent was evaporated, the remaining residue cooled and acidified with 12N HCl. The mixture was stirred for 30 min. at 10-15°C and the resulting precipitate filtrated, washed with ice-water and dried under reduced pressure at 90°C to get solid compound-II in yield 75%. Ana Obs.: C-54.96%, H-4.56%, N-9.19%; Calc. for C₇H₇NO₃: C-54.90%, H-4.61%, N-9.15%.

**Preparation of benzo[d]isoxazol-3-ol (III)**

A solution of N,2-dihydroxy-benzamide (II) (0.081 mol) in THF(120 ml) was stirred at 60°C. A solution of CDI (0.162 mol) in THF (50 ml) was added over 30 min. under reflux to the aforementioned solution and refluxed for another 2 hours at 60°C. The reaction mixture was cooled to 40°C and the solvent evaporated. After completion, the remaining residue was quenched with water and acidified with 12N HCl to pH 2. The mixture was stirred for 30 min at 10-15°C and the resulting precipitate filtrated, washed with ice-water and dried under reduced pressure at 90°C to give compound-III in
yield 83%. Ana Obs.: C-62.28%, H-3.67%, N-10.32%; Calc. for C\textsubscript{7}H\textsubscript{5}NO\textsubscript{2} : C-62.22%, H-3.73%, N-10.37%.

**Preparation of 2-(4-nitro-benzoyl)-benzo[d]isoxazol-3-one (IV)**

Triethylamine (0.10 mol) was added to a solution of benzo[d]isoxazol-3-ol (III) (0.066 mole) in dichloromethane (100 ml). The reaction mixture was stirred at rt and then p-nitro benzoylchloride (0.072 mol) was added dropwise. The reaction mixture was stirred overnight at rt. The mixture was diluted with dichloromethane (200 ml), washed with water (200 ml). The organic layer was separated, dried over magnesium sulphate and the solvent was evaporated dry. The residue was purified by 10% aq. ethanol and resulting off-white solid separated by filtration giving pure compound (IV) in yield 69.0%. Ana Obs.: C-59.11%, H-2.89%, N-9.81%; Calc. for C\textsubscript{14}H\textsubscript{8}N\textsubscript{2}O\textsubscript{5} : C-59.16%, H-2.84%, N-9.86%.

**Preparation of 2-(4-amino-benzoyl)-benzo[d]isoxazol-3-one (V)**

To a solution of 2-(4-nitro-benzoyl)-benzo[d]isoxazol-3-one (IV) (0.046 mol) and iron powder (7.0 g) in acetic acid (130 ml) was stirred for 2-3 h. Reaction diluted with water (500 ml) and basify to pH 7.0-8.0 by adding 10% NaOH and extracted with ethyl acetate (500 ml). Ethyl acetate layer was washed with water (200 ml), dried and evaporated under vacuum giving light brown solid as compound-V in yield 79%. Ana Obs.: C-66.19%, H-3.91%, N-11.09%; Calc. for C\textsubscript{14}H\textsubscript{10}N\textsubscript{2}O\textsubscript{3} : C-66.14%, H-3.96%, N-11.02%.

**Preparation N-[4-(3-oxo-3H-benzo[d]isoxazole-2-carbonyl)-phenyl]-benzamide (31)**

A solution of 2-(4-amino-benzoyl)-benzo[d]isoxazol-3-one (V) (1.4 mmol) and benzoic acid (1.54 mmol) in THF was stirred at rt for 15 min. EDC was added to reaction mixture and stirred at rt for 3-4 h. Solvent was evaporated completely from the reaction mass and water was added to residue. Residue was recrystalized from 10% aq. ethanol
giving off white solid as compound-31 in yield 61%. Ana Obs.: C-70.32%, H-3.99%, N-7.87%; Calc. for C_{21}H_{14}N_{2}O_{4}: C-70.39%, H-3.94%, N-7.87%.

The monitoring of reaction and purity of compounds were checked on TLC aluminium sheet silica gel 60 F_{245} (E.Merck) using hexane-ethyl acetate (5:5 V/V) and methanol-chloroform (2:8 V/V) as mobile phase and visualize under U.V light 254 nm.

Other compounds of the series (32 to 40) were prepared by using similar method and their physical data are recorded in Table-4.
References

64. Roy AK, Batra S, Synthesis, 2003, 9, 1347.


Studies on Triazoles

Introduction:

Many of the azoles comprise the ring system of several natural and synthetic compounds which are important for living system and also for synthesis of important drugs, dyes and agricultural chemicals. Triazoles is less than a century old and starts with work of Bladin who synthesized the first representatives and coined the name for this class of compounds. Although most triazoles are readily prepared and stored, expensive starting materials or sensitive intermediates appear to have discouraged industrial synthesis and wide applications. The first studies of triazole were concerned with structural isomerism. Modern instrumental and theoretical methods achieved much success in dealing with tautomeric problems, the complexity of which is one of the enduring charms of the chemistry of triazoles. However, some structural and many tautomeric problems require further study, kinetic and other quantitative mechanistic studies are scarce, the stereochemistry and photochemistry of triazole are virtually unexplored.

Azoles and its derivatives are associated with various biological activities as antifungal, antibacterial\cite{1-4}, anti-inflammatory\cite{5-7}, herbicida\cite{8}, anthelmintic\cite{9-11}, CNS depressant\cite{12-14}, antitumor agent\cite{15}, anticancer\cite{16-18}, antiparasitic\cite{19}, analgesic\cite{20-21}, anticonvulsant\cite{22}, antipyretic and antihypertensive activity\cite{23}. Itoh Manabu et al.\cite{24} proved that 3-arylamino-1,2,4-triazole (1) derivative is remarkably stable in a human serum and is a highly promising pharmaceutical agent.

\begin{center}
\includegraphics[width=0.2\textwidth]{1.png}
\end{center}
The triazoles are numbered to indicate the relative positions of the nitrogen atoms, tetrazole and pentazole are unambiguous names. 1,2,3-triazoles are surprisingly stable, when one considers that they contain three directly-linked nitrogen atoms, but on flash vacuum pyrolysis at 500°C they do lose nitrogen to give 2H-azirines, probably via the 1H-isomers\(^{25,26}\).

![Diagram of triazole tautomerism](image)

The additional hetero atoms make these systems less basic but more acidic than comparable 1,2- and 1,3-azoles. Each is subject to the same kind of tautomerism as discussed for the 1,2- and 1,3-azoles, in which the tautomers are equivalent but also, in these systems, to tautomerism which generates different arrangements.
Different Routes for Synthesis of Triazoles

(i) Methods Employing Hydrazine Derivatives

The ease of forming C-N and C=N bonds as compared with difficulty of N-N formation practically prescribes the use of hydrazines in the synthesis of 1,2,4-triazoles. In addition to hydrazine, acylhydrazine, amidrazone or acylamidrazone can also be used for the synthesis of triazole analogues.

(ii) Nitrilimine Methods

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. Nitrilimines (5) formed by dehydrohalogenation of C-halobenzylidenephenylhydrazones (4) react with C=N, C=N (as in CNO) to afford triazoles and triazolines.
Synthesis of Triazole Rings From Other Heterocyclic Systems

Transformation of other heterocycles into triazoles implies one or more of the following operations:

- Destruction of Non-Triazole Rings

Methods of this type are best considered as reactions of the fused ring systems. The example illustrated in the given scheme is of potential interest in pharmacology. The conversion of the 1-aminoadenosine (9) into the imidazolyltriazole (10) amounts to triazole formation from an amidrazone intermediate and a formyl group derived from the pyrimidine moiety.
Nitrilimines Derived From Non-Triazole Rings

Nitrilimines for the preparation of triazoles are often generated from tetrazoles or from 1,3,4-oxadiazoline (11) derivatives, which themselves are obtainable by thermolysis of tetrazoles.

Intra Molecular Condensations\(^{(27)}\)

(i) Ring Closures in Alkaline Media

Ring closure of acyl derivatives of semicarbazides, thiosemicarbazides, or aminoguanidines in alkaline solutions is a method widely applied for the preparation of s-triazoles. Gehlen\(^{(28)}\) reported that 3-hydroxy-5-alkyl–s-triazoles (12) are produced in 40-50% yield by this method.
(ii) Ring Closures in Acidic Media

In concentrated hydrochloric acid, thiourazole (13) has been obtained from carbamylthiosemicarbazide (14, R=H), but phenylcarbamyl-thiosemicarbazide (14, R=C₆H₅) apparently is changed into 2-amino-5-hydroxythiadiazoles (30). From (15) in concentrated hydrochloric acid, 4-aminodithiourazole is obtained (31).

(iii) Oxidative Ring Closures in the Presence of Peroxide

From the S-methylthiosemicarbazone of benzaldehyde, 3-phenyl-5-methyl-thio-1,2,4-triazole is obtained in an unspecified good yield by peroxide oxidation (32).

(iv) Thermally Induced Ring Closure

Several acyl derivatives of semicarbazides, thiosemicarbazides, and aminoguanidines change into s-triazoles when heated.

➤ Molecular Rearrangements

Hydroxy-s-triazoles are obtained on pyrolysis of hydrazones of pyruvylhydroxamic acids, the Gastaldi reaction (33). In an illustration of the reaction, 1-phenyl-3-methyl-5-hydroxy-1,2,4-triazole is obtained.
from the phenylhydrazone of pyruvylhydroxamic acid in prop ionic anhydride.

![Chemical Structure](image)

**Biological Activity of 1,2,4-triazoles**

Shirodkar PY *et al.*\(^{(34)}\) synthesized different kinds of 1,2,4-triazole derivatives and screened for their antitumor activity and found to be weakly cytotoxic. Haydar Yuksek *et al.*\(^{(35)}\) synthesized 4-arylamino-4,5-dihydro-1H-1,2,4-triazole-5-one derivatives and checked acidic properties of these new potential biologically active compounds.

Gadaginamath GS *et al.*\(^{(36)}\) synthesized triazoles (20) and were found to exhibit a wide spectrum of biological activities\(^{(37-43)}\). They have synthesized some bio-dynamic heterocyclic systems at position-5 linked through methoxy bridge with a view to prepare bi heterocycles to enhance biological activities.

![Chemical Structure](image)

Jingde Wu *et al.*\(^{(44)}\) synthesized novel derivatives of 4-amino-3-(2-furyl)-5-mercapto-1,2,4-triazole (21) as potential HIV-1.
Hardtmann GE et al.\(^{(45)}\) have prepared tricyclic 1,2,4-triazoloquinazolines (22) and tested them for antibacterial activity. The synthesized compounds were also tested for anti-inflammatory activity.

Svensson et al.\(^{(46)}\) synthesized 2,4-dihydro-[1,2,4]triazole-3-thione (23). These compounds are inhibitors of the enzyme myeloperoxidase (MPO) and are thereby particularly useful in the treatment of prophylaxis of neuro inflammatory disorders.
Udupi RH et al.(47-49) synthesized different kinds of 1,2,4-triazole derivatives by treating acid hydroxide with alcoholic KOH/CS₂ and further with acid hydroxide and tested them for anti-inflammatory and analgesic activities.

Kane JM et al.(50) synthesized 1,2,4-triazole derivatives (24) as potential anti-tumor agents.

\[
\begin{align*}
\text{R} &= \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_3\text{H}_7, \text{etc}... \\
\end{align*}
\]

Mhasalkar MY et al.(51) synthesized some 5-substituted, 4-(substituted aryl), 3-mercapto 1,2,4-triazoles (25) which showed antifungal activity. Similarly 5(p-sec-amylphenyl)methoxy-3-mercapto1,2,4-triazole (26) showed good antifungal activity(52).

\[
\begin{align*}
\text{R} &= \text{Aryl groups} \\
\text{R}’ &= \text{Alkyl groups} \\
\end{align*}
\]
Goknur Aktay et al.\(^{53}\) have synthesized 3-(1-(4-(2-methylpropyl)phenyl)ethyl)-1,2,4-triazole-5-thione (27) and demonstrated that they possess moderate anti-inflammatory activity.

![Chemical structure of 3-(1-(4-(2-methylpropyl)phenyl)ethyl)-1,2,4-triazole-5-thione (27)](image)

Xu LZ et al.\(^{54}\) have synthesized novel triazole compounds (28) containing N,N-dialkylthio-carbamate and tested for their biological activity.

![Chemical structure of novel triazole compounds (28)](image)

\[ R = \text{p-Cl-Ph} \quad R' = \text{CH}_3, \text{C}_2\text{H}_5, \text{i-C}_3\text{H}_7, \text{etc.} \]  

Demirbas N et al.\(^{55}\) have been synthesized a series of 1,2,4-triazole derivatives (29) and screened for their anti cancer activity. It showed a potent therapeutic activity for the treatment of breast cancer.

![Chemical structure of 1,2,4-triazole derivatives (29)](image)
El-Sayed R\textsuperscript{(56)} have prepared a series of new 1,2,4-triazole derivatives (30) and have been screened for anti microbial activity.

Udupi RH \textit{et al.}\textsuperscript{(57)} have been synthesized new derivatives of 1,2,4-triazole (31) from potassium dithio carbazinates and tested for their antibacterial, anti fungal, anti inflammatory and analgesic properties.
Kumar H et al.\(^{(58)}\) have studied a series of 3-mercepto-(4H)-1,2,4-triazole derivatives (32) and tested for the analgesic activity.

![Chemical Structure 32](image)

Somani RR\(^{(59)}\) have prepared 1,2,4-triazole compounds (33). These compounds were subjected to anti fungal and anti-TB activities.

![Chemical Structure 33](image)

1,2,4-triazole-3-thione (34) which were obtained by intramolecular cyclization have synthesized by Cretu OD et al.\(^{(60)}\).

![Chemical Structure 34](image)
A series of 5-substituted-4-amino-1,2,4-triazole-3-thioesters (35) was synthesized by Hasan A et al.\textsuperscript{(61)} The synthesized compounds were evaluated for their \textit{in-vitro} antifungal activity.

![Chemical Structure 35](image)

$$35 \quad \begin{align*}
R^1 &= 4\text{-NO}_2\text{-C}_6\text{H}_4, \ 2\text{-NO}_2\text{-C}_6\text{H}_4; \\
R^2 &= -\text{C}_6\text{H}_5
\end{align*}$$

Pattan S et al.\textsuperscript{(62)} have been synthesized 1,2,4-triazole compounds (36) and all obtained compounds were evaluated for their antimicrobial, antituberculer and anti inflammatory activity.

![Chemical Structure 36](image)
The synthesis of following triazole derivatives have been discussed in part II

**Section-I:** \((S)-3-(4\text{-}(\text{alkoxy})\text{-}\text{phenyl})\text{-}N\text{-}(\text{alkyl})\text{-}2\text{-}(5\text{-}\text{phenyl}\text{-}2\text{H}\text{-}[1,2,4]\text{triazol}\text{-}3\text{-}\text{ylamino})\text{-}\text{propionamide}\)

Spectroscopic analysis and biological activities of these compounds are discuss in chapter III.
Section – I

Preparation of (s)-3-(4-(alkoxy)-phenyl)-N-(alkyl)-2-(5-phenyl-2H- [1,2,4]triazol-3-ylamino)-propionamide

Where, R1 = Alkyl Groups; R2 = Hetero Alkyl Groups
Table: 5:- Physical Constant of (S)-3-(4-(alkoxy)-phenyl)-N-(alkyl)-2-(5-phenyl-2H-[1,2,4]triazol-3-ylamino)-propionamide

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>-R1</th>
<th>-R2</th>
<th>Molecular formula</th>
<th>M.P. °C</th>
<th>Yield %</th>
<th>Elemental analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% C</td>
</tr>
<tr>
<td>41</td>
<td>-Me</td>
<td>-OH</td>
<td>C_{18}H_{18}N_{4}O_{3}</td>
<td>232-235</td>
<td>81</td>
<td>63.89</td>
</tr>
<tr>
<td>42</td>
<td>-Me</td>
<td>-NH_{2}</td>
<td>C_{18}H_{19}N_{5}O_{2}</td>
<td>215-217</td>
<td>72</td>
<td>64.08</td>
</tr>
<tr>
<td>43</td>
<td>-Me</td>
<td>-NHMe</td>
<td>C_{19}H_{21}N_{5}O_{2}</td>
<td>201-203</td>
<td>81</td>
<td>64.94</td>
</tr>
<tr>
<td>44</td>
<td>-Me</td>
<td>-N(Me)_{2}</td>
<td>C_{20}H_{23}N_{5}O_{2}</td>
<td>185-187</td>
<td>71</td>
<td>65.74</td>
</tr>
<tr>
<td>45</td>
<td>-Me</td>
<td>-N(Et)_{2}</td>
<td>C_{22}H_{27}N_{5}O_{2}</td>
<td>180-183</td>
<td>67</td>
<td>67.15</td>
</tr>
<tr>
<td>46</td>
<td>-Et</td>
<td>-NHMe</td>
<td>C_{20}H_{23}N_{5}O_{2}</td>
<td>191-194</td>
<td>77</td>
<td>65.74</td>
</tr>
<tr>
<td>47</td>
<td>-Et</td>
<td>-N(Me)_{2}</td>
<td>C_{21}H_{25}N_{5}O_{2}</td>
<td>177-179</td>
<td>63</td>
<td>66.47</td>
</tr>
<tr>
<td>48</td>
<td>-Et</td>
<td>-N(Et)_{2}</td>
<td>C_{23}H_{29}N_{5}O_{2}</td>
<td>169-171</td>
<td>81</td>
<td>67.79</td>
</tr>
<tr>
<td>49</td>
<td>-Pr C_{6}H_{5}OH</td>
<td>-N(Me)_{2}</td>
<td>C_{22}H_{27}N_{5}O_{2}</td>
<td>177-181</td>
<td>63</td>
<td>67.15</td>
</tr>
<tr>
<td>50</td>
<td>-Pr C_{6}H_{5}OH</td>
<td>-N(Et)_{2}</td>
<td>C_{24}H_{31}N_{3}O_{2}</td>
<td>167-169</td>
<td>71</td>
<td>68.38</td>
</tr>
</tbody>
</table>
Experimental Procedure

**Preparation of (S)-2-amino-3-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-propionic acid ethyl ester (I)**

To a solution of (S)-2-amino-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (0.095 mol) in dichloromethane (200 ml) was added imidazole (0.114 mol), DMAP (0.009 mol), and TBDMSCl (0.104 mol) sequentially. The reaction mixture was stirred at room temperature for 20 h. The reaction mixture diluted by dichloromethane (300 ml) and washed with water (300 ml x 2). Organic layer dried over sodium sulphate and distilled out under vacuum to get Compound-I in yield 85.0%. Ana Obs.: C-63.18%, H-9.09%, N-4.28%. Calc. for C_{17}H_{29}NO_{3}Si: C-63.12%, H-9.04%, N-4.33%.

**Preparation of (S)-2-(3-benzoyl-thioureido)-3-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl] -propionic acid ethyl ester (II)**

To a solution of NH_{4}SCN (0.12 mol) in acetone (100 ml) was added slowly benzoyl chloride (0.096 mol) under dry condition within 10 min. After completion of addition reaction mixture was refluxed for 15 min. A solution of (S)-2-amino-3-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-propionic acid ethyl ester (I) (0.08 mol) in acetone (100 ml) was added to above stirred suspension at such a rate that refluxes gently. After completion of addition reaction mixture was refluxed further for 30 min. Reaction was cooled and poured in water, and resulting off white solid separated by filtration. Solid was recrystallized in ethanol giving pure Compound-II in yield 79%. Ana Obs.: C-61.75%, H-7.09%, N-5.70%; Calc. for C_{25}H_{34}N_{2}O_{4}SSi : C-61.70%, H-7.04%, N-5.76%.
Preparation of (S)-2-[(benzoylamino-methylsulfanyl-methyl)amino]-3-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-propionic acid ethyl ester (III)

A mixture of (S)-2-(3-benzoyl-thioureido)-3-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-propionic acid ethyl ester (II) (0.061 mol), methyl iodide (0.09 mol) and anhydrous K$_2$CO$_3$ (0.122 mol) in DMF (150 ml) was stirred at rt for 1 h. Reaction mixture was poured in water (500 ml) with stirring. The resulting off-white solid was filtered, washed with water and dried to give compound-III in yield 77%. Ana Obs.: C-66.69%, H-7.70%, N-5.94%.; Calc. for C$_{26}$H$_{36}$N$_2$O$_4$Si : C-66.63%, H-7.74%, N-5.98%.

Preparation of (S)-3-[4-(tert-Butyl-dimethyl-silanyloxy)-phenyl]-2-(5-phenyl-2H-[1,2,4]triazol-3-ylamino)-propionic acid ethyl ester (IV)

To a solution of (S)-2-[(benzoylamino-methylsulfanyl-methyl)amino]-3-[4-(tert-butyl-dimethyl-silanyloxy)-phenyl]-propionic acid ethyl ester (III) (0.04 mol ) and Hydrazine hydrate (5 ml) in ethanol (200 ml) was refluxed for 2 h. Reaction was cooled and poured in water, and resulting off-white solid separated by filtration giving pure Compound-IV. in yield 83%. Ana Obs.: C-64.30%, H-7.39%, N-12.08%.; Calc. for C$_{25}$H$_{34}$N$_4$O$_3$Si: C-64.35%, H-7.34%, N-12.01%.

Preparation of (S)-2-[(5-4-amino-phenyl)-2H-[1,2,4]triazol-3-ylamino]-3-phenyl-propionic acid ethyl ester (V)

To a solution of (S)-3-[4-(tert-Butyl-dimethyl-silanyloxy)-phenyl]-2-(5-phenyl-2H-[1,2,4]triazol-3-ylamino)-propionic acid ethyl ester (IV) (0.1 mol ) in methanol (50 ml) was added 2N HCl solution (20 ml) was added. Reaction mass stirred at 40-45°C for 1 h. Solvent was evaporated completely and water (1000 ml) was added to residue and stir for 1 h. Solid separated by filtration, washed with water and dried giving yellowish solid as compound-V in yield 85%. Ana Obs.: C-
Preparation (S)-3-(4-methoxy-phenyl)-2-(5-phenyl-2H-[1,2,4]triazol-3-yl-amino)-propionic acid ethyl ester (VI)

To a solution of (S)-3-(4-hydroxy-phenyl)-2-(5-phenyl-2H-[1,2,4]triazol-3-ylamino)-propionic acid ethyl ester (V) (8.52 mmol) and DMF (10 ml) was added K₂CO₃ (12.7 mmol) was stir at rt. Methyl iodide (10.22 mmol) was added to above and stir for 1 h. Water was added to reaction mixture and stir for 30 min. Solid separated by filtration and washed with water and dried to get off white solid as compound-VI in yield 84%. Ana Obs.: C-65.62%, H-6.11%, N-15.21%; Calc. for C₂₀H₂₄N₄O₃: C-65.56%, H-6.05%, N-15.29%.

Preparation (S)-3-(4-methoxy-phenyl)-2-(5-phenyl-2H-[1,2,4]triazol-3-yl-amino)-propionic acid (41)

A solution of (S)-3-(4-methoxy-phenyl)-2-(5-phenyl-2H-[1,2,4]triazol-3-ylamino)-propionic acid ethyl ester (VI) (0.008 mol) in methanol (5 ml) and THF (5 ml) was stirred at rt. 1N aq. NaOH (2 ml) was added to above and stir for 2 h. Reaction mixture was diluted with water and acidified to pH 5 by addition of dil. HCl. Solid separated by filtration and washed with water (20 ml), suck dried. Solid was dried to giving off white solid as compound-41 in yield 81%. Ana Obs.: C-63.94%, H-5.40%, N-16.50%; Calc. for C₁₈H₁₈N₄O₃: C-63.89%, H-5.36%, N-16.56%.

Preparation (S)-3-(4-methoxy-phenyl)-N,N-dimethyl-2-(5-phenyl-2H-[1,2,4]triazol-3-yl-amino)-propionamide (42)

A solution of (S)-3-(4-methoxy-phenyl)-2-(5-phenyl-2H-[1,2,4]triazol-3-ylamino)-propionic acid (41) (0.59 mmol), aq. ammonia (0.2 ml) and EDC (0.1 g) in THF (10 ml) was stirred at rt. Solvent was evaporated completely and water was added to residue. Solid separated by filtration and dried to giving off white solid as
compound-42 in yield 72%. Ana Obs.: C-65.79%, H-6.28%, N-19.21%;
Calc. for C_{20}H_{23}N_{5}O_{2} : C-65.74%, H-6.34%, N-19.16%.

The monitoring of reaction and purity of compounds were checked on TLC aluminium sheet silica gel 60 F_{254} (E. Merck) using hexane-ethyl acetate (5:5 V/V) and methanol-chloroform (2:8 V/V) as mobile phase and visualize under U.V light 254 nm.

Other compounds of the series (43 to 50) were prepared by using similar method and their physical data are recorded in Table-5.
References

27. Boyer JH, Heterocyclic compounds, Depa. of Chem., Tulane University.