The tetrahydrofuran backbone is a ubiquitous heterocyclic unit found in a number of biologically active natural products such as Annonaceae acetogenins and polyether antibiotics.

**Annonaceae acetogenins:**

The Annonaceous acetogenins are promising new antitumor and pesticidal agents that are found only in the plant family Annonaceae. Structurally, the Annonaceous acetogenins are a series of C-35/C-37 natural products derived from C-32/C-34 fatty acids that are combined with a 2-propanol unit. They are usually characterized by a long aliphatic chain bearing a terminal methyl-substituted α,β-unsaturated δ-lactone ring (sometimes rearranged to a ketolactone), with one, two, or three tetrahydrofuran rings located along the hydrocarbon chain and a number of oxygenated moieties (hydroxyls, acetoxyls, ketones, epoxides) and/or double bonds being present. The Annonaceous acetogenins are the most powerful of the known inhibitors of complex I (NADH: ubiquinone oxidoreductase) in mammalian and insect mitochondrial electron transport systems, in addition, they are potent inhibitors of NADH oxidase of the plasma membranes of cancer cells, these actions decrease oxidative, as well as, cytosolic ATP production. The consequence of such ATP deprivation is apoptosis (programmed cell death).


I. Annonaceous acetogenins

1) Murihexocin:

![Chemical Structure](image)

Biological activities (µg/mL): BST LC$_{50}$ 10, A-549 ED$_{50}$ 1.1, MCF-7 ED$_{50}$ 3.8, HT-29 ED$_{50}$ 1.3, A-498 ED$_{50}$ 2.5, PC-3 ED$_{50}$ 8.6 X 10$^{-1}$, PACA-2 ED$_{50}$ 4.9 X 10$^{-1}$.

Source: *Annona muricata*, leaves.

2) Glabracin B:

![Chemical Structure](image)

Biological activities (µg/mL): BST LC$_{50}$ 2.7 X 10$^{-1}$, A-549 ED$_{50}$ 1.3, MCF-7 ED$_{50}$ 5.2 X 10$^{-2}$, HT-29 ED$_{50}$ 8.7 X 10$^{-2}$, A-498 ED$_{50}$ 2.6, PC-3 ED$_{50}$ 5.6 X 10$^{-2}$, PACA-2 ED$_{50}$ 1.5 X 10$^{-2}$.

Source: *Annona glabra*, leaves.
3) Carolin B:

Polyether antibiotics:

The polyether antibiotics, a class of compounds isolated from fermentation cultures of *Streptomyces*, characteristically contain a carboxylate group and 2-5 oxygen atoms serving as ligands for the complexation of inorganic cations. Complexes generated from ionophores are exceptionally hydrophobic and facilitate translocation of ions across membrane barriers. The polyether antibiotics induce a range of biological responses that include ruminant growth promotion, anticoccidial activity, and mammalian cardiovascular effects.

II. Polyether antibiotics

1) Isolasalocid A:

Source: *Streptomyces lasaliensis*
2) Monensin A:

Source: *Streptomyces cinnamonensis*

3) Ionomycin:

Source: *Streptomyces congobatus*

The genus *Goniothalamus* (Annonaceae) is well-known as an interesting source of various bioactive compounds such as acetogenins, alkaloids, styryl lactones and flavanoids.
On the other hand, 2,3,4,5-tetrasubstituted tetrahydrofuran derivative, (+)-goniothalesdiol 7, was isolated from the bark of the Malaysian tree Goniothalamus borneensis (Annonaceae) and was revealed to have significant cytotoxicity against P388 mouse leukemia cells.\(^\text{10}\)

(+)-Goniothalesdiol

![Chemical structure of (+)-Goniothalesdiol]

The chemistry of 1,2,4-Triazole derivatives continues to draw the attention of synthetic organic chemists due to their varied biological activities. Among 1,2,4-triazoles the pyrimidine 1,2,4-triazoles have been found to be most active. Several general methods have been described in the literature for the synthesis of 1,2,4-triazoles.

Isoxazole, pyrazol and pyrimidine nucleus constitutes an important class of hetero cyclic compound possessing diverse biological activities. The Isoxazole, pyrazol and pyrimidines are heterocyclic of current interest due to their broad spectrum biological properties.
Ashry and co-workers\textsuperscript{11} reported the synthesis of 4-Amino-5(3-chlorobenzo[b]thien-2-yl)-3-mercapto 1,2,4-triazole \textsuperscript{11} under classical microwave conditions.

Hasim and Alioy\textsuperscript{12} have been reported the synthesis of 5-(4-Nitrophenyl)-4-phenyl-4H-1,2,4-trazole-3-thiol \textsuperscript{13} from substituted thio semicarbazide.

A novel synthesis of substituted pyridine 1,2,4-triazole have been reported by Ramesh Krishna\textsuperscript{13}. 
Askar et al.\textsuperscript{14} reported an efficient synthesis of 1,2,4-triazole[4,3-b] benzoxazole-1-(2H)thione \textsuperscript{20} from 2-mercapto benzoxazole \textsuperscript{18}.

\[
\begin{align*}
&\text{18} \xrightarrow{N\text{H}_2} \text{19} \xrightarrow{\text{CS}_2/\text{NaOH}} \text{20} \\
&\text{O} \quad \text{N} \quad \text{SH} \quad \text{N} \quad \text{H} \\
&\text{4} \\
&\text{O} \quad \text{N} \\
&\text{N} \quad \text{NH} \\
&\text{2} \quad \text{NH}_2 \\
&\text{H} \\
&\text{S} \quad \text{H} \\
&\text{CS}_2 \\
&\text{2} \quad \text{CS} \\
&\text{2} \quad \text{CS} \\
&\text{2} \quad \text{CS} \\
&\text{2} \quad \text{CS} \\
&\text{2} \quad \text{CS} \\
&\text{2} \quad \text{CS} \\
&\text{2} \quad \text{CS} \\
&\text{2} \quad \text{CS} \\
&\text{2} \quad \text{CS} \\
\end{align*}
\]

Godhani et al.\textsuperscript{15} reported a new approach to synthesis of 1,2,4-triazole derivative \textsuperscript{24} from 3-methoxy benzoylchloride.

\[
\begin{align*}
&\text{Cl} \quad \text{O} \quad \text{OMe} \\
&\text{O} \quad \text{NMe} \quad \text{NH}_2 \\
&\text{OMe} \quad \text{OMe} \\
&\text{O} \quad \text{NMe} \quad \text{NH}_2 \\
&\text{OMe} \\
&\text{HCHO} \\
&\text{Ar} \\
&\text{21} \xrightarrow{\text{NH}_2\text{SCN}} \text{22} \xrightarrow{\text{OMe}} \text{23} \xrightarrow{\text{OMe}} \text{24} \\
&\text{Cl} \quad \text{O} \quad \text{OMe} \\
&\text{O} \quad \text{NMe} \quad \text{NH}_2 \\
&\text{OMe} \quad \text{OMe} \\
&\text{O} \quad \text{NMe} \quad \text{NH}_2 \\
&\text{OMe} \\
&\text{HCHO} \\
&\text{Ar} \\
\end{align*}
\]

The chemistry of barbituric acid and its derivatives has been studied for over 100 years. The parent compound barbituric acid was prepared by Von Baeyer in 1864\textsuperscript{16} by the reaction of malonic ester with urea in the presence of sodium ethoxide\textsuperscript{17}.
Peter\textsuperscript{23} and Gerrit \textit{et al.}\textsuperscript{18} reported the formation of pyrazolidine-3,5-dione by the cyclization of hydrazide derivative of malonic ester in the presence of sodium methoxide. However, low yield (27\%) was obtained by this method.

Ross and Scott\textsuperscript{19} reported that the reaction between hydroxylamine and ethyl acetoacetate produced methyl isoxazolone. Later, Nripendra Nath and Paresh Chandra\textsuperscript{20} however, repeated the same reaction and found that the compound was dimethyldiisoxazolone which exist in tautomeric form.
The reaction of acetone oxime with dialkylmalonyl chlorides in the presence of triethylamine gave 2-(2-propenyl)-4,4-dialkyl isoxazolidine-3,5-diones and 2,2-bis[2-(4,4-dialkylisoxazolidine-3,5-dione)]propanes\(^{21}\).

\[
\begin{align*}
\text{Cl} & \quad \text{O} & \quad \text{Cl} \\
\text{O} & \quad \text{R} & \quad \text{R} \\
\quad & \quad \text{Me} & \quad \text{Me} \\
\quad & \quad \text{OH} & \\
\text{Et}_{3} & \quad \text{N} & \quad \text{ON} \\
\text{Me} & \quad \text{C} & \quad \text{H} \\
& \quad \text{2} & \quad \text{3} \\
\text{O} & \quad \text{R} & \quad \text{R} \\
\quad & \quad \text{ON} & \quad \text{O} \\
\text{R} & \quad \text{R} & \quad \text{O} \\
\quad & \quad \text{N} & \quad \text{O} \\
\text{Me} & \quad \text{Me} & \quad \text{3} \quad \text{5} \\
\end{align*}
\]

The chemistry of 1,2,3-Triazde derivatives continues to draw the attention of Synthetic organic chemistry due to their varied biological activities.

The 1,2,3-triazole ring system has been the subject of considerable research mainly due to its because of the pharmalogical properties shown by some of it’s derivatives.

Over the past few years, 1,2,3-trizoles have attracted the attention of organic and medicinal chemistry because of their varied biological properties, anti-HIV, anticonvulsant, anti-inflammatory, anti-tubercular and anticancer activates\(^{22}\). The favourable properties of 1,2,3-triazole ring like moderate dipole character, hydrogen bonding capability, rigidity and stability under in vivo conditions are evidently responsible for their enhanced biological activities\(^{23}\).

Kumar et al.,\(^{24}\) have been reported an azide alkyne cycloaddition en route to novel 1H-1,2,3-triazole tethered isatin conjugates with in vitro cy to toxic evaluation.
Awad, Abdel-wahab and Khidre have been reported the design and synthesis of 1,2,3-triazol imidazothiazoles as antimicrobial agents.

Isoxazole is a five membered heterocyclic ring system containing an oxygen and a nitrogen in the adjacent positions. Isoxazole name was introduced by Hantzsch as a modification of the term monoazole coined earlier by Claisen to differentiate it from the already known isomeric oxazole. The chemistry of isoxazoles has been reviewed thoroughly from time to time.
Isoxazoles are unique in their chemical behavior not only among other heterocyclic compounds in general but also among related azoles. This is because isoxazole possesses the typical properties of the aromatic system in their derivatives, together with lability of the nucleus under high temperatures, photochemical and mass spectral conditions. Besides, the ring undergoes cleavage with some reagents. All these cleavage reactions are mainly occurs at the site of N-O bond of the ring.

A characteristic peculiarity of isoxazole derivatives is the relatively facile ring cleavage under suitable conditions, and this is a severe limitation on reactions of substitution in the isoxazole series. It is interesting to investigate the reaction of isoxazole derivatives in which the heterocyclic nucleus remains intact.

1,3-Benzoxazines play an important role for their diverse biological properties. A large number of synthetic derivatives of these nuclei are well documented in the literature. Isoxazole derivatives possess a wide variety of biological activities. Introduction of benzoxazine moiety on to isoxazole nucleus may enhance the activity.
Billmann and Dorman\textsuperscript{34} have reported that the paraformaldehyde underwent a bimolecular condensation with $N,N'$-bis(o-hydroxybenzyl)-ethylenediamines \textsuperscript{47} in benzene to form 1,2-bis-[3(3,4-dihydro-1,3,2\textit{H}-benzoxazino]-ethane \textsuperscript{48}. The compounds \textsuperscript{2} showed bacteriostatic and fungistatic activities.

The reaction of substituted salicylylanilide-isothiocyanates \textsuperscript{49} with ethyl chloroformate in alcohol afforded 2,4-dioxobenzoxazines \textsuperscript{50} in quantitative yields\textsuperscript{35}. The compounds \textsuperscript{50} were tested against antihelmintic activity.

Murthy \textit{et al.}\textsuperscript{36} reported the synthesis of naphtha [1,2-\textit{e}] [1,3]-oxazines \textsuperscript{52} by interaction of 3-benzalamino-5-methylisoxazoles \textsuperscript{51} with $\beta$-naphthol in acetic acid.
The synthesis and spermicidal activity of 1,3-benzoazines 54 have been reported by Dwivedi and co-workers\textsuperscript{37}. The reaction of thymol 53 with paraformaldehyde and isoproplamine in propanol furnished the title compounds 54.

The chemistry of 1,2,4-oxadiazole derivatives continues to draw the attention of synthetic organic chemists due to their varied biological activities. Among 1,2,4-oxadiazoles the spiro-1,2,4-oxadiazoles have been found to be most active. Several general methods have been described in the literature for the synthesis of 1,2,4-oxadiazoles.

A variety of substituted 1,2,4-oxadiazolines 55 have been readily obtained by the interaction of nitrile oxides with a number of aromatic Schiff bases\textsuperscript{38}. Diverse heterocyclic Schiff bases have also been utilized\textsuperscript{39}. 
Rajanarendar et al.\textsuperscript{40} reported the synthesis of isoxazoles substituted spiro[3H-indole-3,5',3'-phenyl-1',2',4'-oxadiazoline]-2(1H)-ones \textsuperscript{57} from isoxazoyl imino-2-indolinones \textsuperscript{56} by cycloaddition of benzonitrile oxide.

Present work

The tetrahydrofuran backbone is a ubiquitous heterocyclic unit found in a number of biologically active natural products such as \textit{Annonaceae} acetogenins and polyether antibiotics. Heterocyclic compounds containing oxygen-nitrogen atoms have been focus of considerable interest because of their potential biological and pharmacological application. As a result, the
development of a new series of bioactive nitrogen heterocycles has been actively perused. Such class of important heterocyclic compounds are triazoles, isoxazoles, oxazines, pyridines.

Chapter II deals with the stereo selective synthesis of (+) - Goniothalesdiol from commercially available D-Glucose.

Synthesis of new route synthesis of pyridine & pyrimidine based 1,2,4-triazoless and substituted thioxopyrimidines, pyrazolidines and isoxozolidines are presented in chapter III.

Chapter IV describes the synthesis of 1,2,3-Triazoles & 1,3-benzoaxazines and it’s derivatives

Synthesis of novel 9-(3,5-dimethyl-4-isoxazolyl)-3,4-diaryl-(1-oxa-6-thia)/(1,6-dioxa)-2,4,9-triaza spiro[4,4] non-2-ene-8-ones are discussed in chapter V.
References


27. Claisen L & Lawmann O, Ber, 21, 1880, 1150.


