Chapter 1

General Introduction
1.1. Importance of heterocyclic compounds

Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. For more than a century, heterocyclic chemistry has constituted one of the largest areas of research in organic chemistry. This area has contributed to the development of society from a biological and industrial point of view as well as to the understanding of life processes and to the efforts to improve the quality of life.

The presence of heterocycles in all kinds of organic compounds of interest in various fields like electronics, biology, optics, pharmacology, material sciences and so on is very well known. Between them, sulfur, oxygen and nitrogen-containing heterocyclic compounds have maintained the interest of researchers. However, heterocycles with other heteroatoms such as phosphorus, boron, silicon, germanium, tellurium and selenium are also of interest.

Heterocyclic chemistry is an inexhaustible resource of novel compounds. Almost unlimited combinations of carbon, hydrogen and heteroatoms can be designed, making interesting compounds with the most diverse physical, chemical and biological properties. Heterocycles are of central importance to both academia and the chemical industry.

1.1.1. Naturally occurring heterocyclic compounds and their role in life processes

Heterocyclic compounds occur widely in nature and also in a variety of non-naturally occurring compounds. Naturally occurring heterocyclic compounds are extremely common. Many of the alkaloids [morphine 1 (Figure 1.1), reserpine and codeine], sugars, vitamins [thiamine, riboflavin, pyridoxine, nicotinamide and ascorbic acid], enzymic cofactors, components of coal tar, natural pigments [indigo, chlorophyll, haemoglobin, and the anthocyanins], antibiotics [penicillin 2 (Figure 1.1) and streptomycin], peptides [oxytocin], some of the essential amino acids [proline, tryptophan and histidine] and the hormones [serotonin 3 (Figure 1.1), melatonin and histidine] possess heterocyclic skeleton.

Coffee, tea and cocoa drinks contain heterocyclic compounds. Caffeine present in coffee and tea, is a central nervous system stimulant. Paraxantheine is the chief
metabolite of caffeine in the body. Cocoa contains theobromine. Some of the most important naturally occurring high polymers, including starch and cellulose are heterocycles. Dyes and ink are made up of substituted pyridines, quinophthalalones and tartrazines which are also heterocyclic compounds. Flowers and fruits contain heterocycles in the form of flavonoids and carotenoids. The colour of fruits and flowers are due to these heterocycles.

![Figure 1.1. Structures of some naturally occurring heterocycles.](image)

Fundamental manifestations of life such as the provision of energy, transmission of nerve impulses, sight, metabolism and the transfer of hereditary information are all based on chemical reactions involving the participation of many heterocyclic compounds such as vitamins, enzymes, coenzymes, ATP, DNA, RNA and serotonin.

The potential to think, intelligence, behavior and character of human beings depend on their gene. The basic skeleton of the genetic material DNA is pyrimidine (cytosine, uracil, and thymine) and purine (adenine and guanine) bases. In the DNA’s double helix, the C-G and A-T base pairs form the rungs of the ladder. The aromaticity, hydrogen bonding properties and catalytic activity of the pyrimidine and purine bases of RNA may explain why they were formed in prebiotic conditions and gave rise to the “RNA world”, which evolved later into life on earth.

Heterocycles play a major part in biochemical processes. Many heterocycles fulfill important physiological functions in plants and animals. Heterocycles are chemically more flexible and better able to respond to many demands of biochemical systems. Most coenzymes have aromatic heterocycles as major constituents. While enzymes possess purely protein structures, coenzymes consist of non-amino acid moieties, most of them being aromatic nitrogen heterocycles.
Coenzymes like Nicotinamide Adenine Dinucleotide (NAD) and Flavin Adenine Dinucleotide (FAD) are essential for the redox biochemical transformations. Thiamine pyrophosphate is a coenzyme that assists the decarboxylation of pyruvic acid, a very important biological reaction. B group vitamins viz thiamine, folic acid, riboflavin and cyanocobalamine are nitrogen-containing heterocycles and functioning either as coenzymes or their precursors. Vitamins such as ascorbic acid and tocidine, is a powerful vasodilator, which is released in allergic responses and stimulates acid secretion in the stomach, causing heartburn. Serotonin, formed from tryptophan, is an important neurotransmitter.

1.1.2. Heterocycles in Medicine

Majority of the medicine used nowadays are heterocyclic small molecules or have heterocyclic structural components. Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents. Around 80% of currently marketed drugs contain at least one heterocycle. One striking structural feature inherent to heterocycles, which continue to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in defined three dimensional representations. Synthesized nitrogen heterocycles in particular exhibit diverse biological and pharmacological activities due in part to the similarities with many natural molecules with known biological activity [1]. Furthermore, compounds that contain heterocyclic moieties often exhibit improved solubilities and can facilitate salt formation, both of which are known to be important for oral absorption and bioavailability.

Synthetic heterocycles have widespread therapeutic uses such as antibacterial, antifungal, antitubercular, antimalarial, herbicidal, anti-inflammatory, muscle relaxant, anticonvulsant, anticancer and lipid peroxidation inhibitor, hypnotics, antidepressant, antitumoral and anthelmintic [2-7]. Very many heterocyclic pharmaceutical products are mimics of natural products with biological activity. In the fight against disease, some of the most significant advances have been and are being made by designing and testing new structures, many of which are heterocyclic derivatives. The compounds we know as synthetic drugs such as diazepam 4, chlorpromazine,
isoniazid, metronidazole 5, azidothymidine, captopril, barbiturates, antipyrine and methotrexate are also heterocyclic.

1.1.3. Miscellaneous Use of Heterocyclic Compounds

Heterocyclic compounds are important components in dye chemistry. When applications in optical data storage are considered, it is evident that progresses such as CD-R and DVD/R would not be feasible without functional dyes [8]. Organic solar cells were first presented back in 1975 by Tang and Albrecht using microcrystalline chlorophyll-a sandwiched between two metal electrodes of different work functions [9].

Azo dyes having heterocyclic moieties have gained very strong position in the colourant market and textile industry [10-13]. Heterocyclic azo compounds tend to be more strongly affected by solvents than azobenzene based dyes. This is a consequence of the increased polarity of the system, especially in the excited state. Isoxazoline Azo Dyes (IADs) were synthesized and dyed on synthetic fabrics.

Alpha-terthienyl 6 is an interesting thiophene trimer found in the roots of marigold. Alpha-terthienyl is a member of phototoxic compounds, having great potential as a pest control agent and is a potent insecticide/ larvicide [14]. Polymers incorporating thiophene units and fused systems such as dithienothiophene 7 have interesting electromagnetic properties, and show promise as organic metal like conductors and photovoltaic materials. The charge transfer complex formed by tetrathiofulvalene 8 and tetracyanoquinodimethane 9 has been shown to have the highest electrical conductivities reported for an organic solid.
Polythiophene and polypyrrole derivatives are very useful materials for fabricating electro optical display devices [15]. Organic electronics such as organic photoconductors (OPCs), organic light-emitting devices (OLEDs), organic photovoltaics (OPVs) and organic thin film transistors (OTFTs) attract increasing attention as they are flexible, printable, micro-buildable and multiple designable.

There are a larger number of other synthetic applications of heterocyclic compounds that include fungicides, herbicides, insecticides, anticorrosive agents, photostabilizers, agrochemicals, photographic developers, fluorescent whiteners, sensitizers, booster agents, antioxidants and vulcanization accelerators in rubber industry and flavouring agents.

1.2. Organoselenium Compounds

1.2.1. General aspects of the organoselenium compounds

Selenium (Se) is a non-metal element, occurring in varying degrees in the environment. Selenium was predicted to be hazardous causing livestock poisoning [16] until it was recognized as an essential nutrient of animals and humans found in some selenoproteins in 1950s [16-18]. Selenium, an essential micronutrient whose absence causes skeletal and cardiac muscle dysfunction [19, 20], is required for the proper function of the immune system and for cellular defense against oxidative damage, thus playing a role in the prevention of cancer and premature aging [21]. Brazil nuts are unique in that they are the highest known food source of selenium. Brazil nuts with high selenium levels slow the aging process, stimulate the immune system and protect against heart disease and certain forms of cancer. Brazil nuts exhibit antioxidant and antiproliferative activities. Epidemiological studies revealed an inverse relationship between nut intakes and chronic diseases such as cardiovascular diseases and cancers [22].

Garlic is one of the several vegetables containing elevated levels of selenium. Furthermore, animal studies have shown that selenium-enriched garlic possesses
cancer preventive properties [23]. In 1964, Finnish Nobel Laureate A. I. Virtanen, reported on the basis of radioisotope studies, that onion contained the selenoamino acids selenocystine and selenomethionine.

The first report on the synthesis of an organoselenium compound, diethyl selenide, was in 1836. Organoselenium compounds have substantially greater bioavailability and less toxicity than that of inorganic selenium compounds. The pharmacology of synthetic organoselenium compounds that have been subjected to more than just a biological screen was critically evaluated in a review by Parnham and Graf [24]. There were also reports and reviews on the prospective practical applications of organoselenium compounds as reagents and catalysts [25], pharmaceuticals [26] and electroconducting materials [27].

Above two hundred different selenium containing saturated, unsaturated and aromatic ring systems are known. Majority of these compounds have the five and six-membered rings and generally they are thermodynamically stable. Developments in the field of selenaheterocyclics are of recent interest.

1.2.2. Selenaheterocyclic compounds

The structures of selenaheterocyclic compounds are closely related to those of analogous sulphur compounds, but their properties often present marked difference. In these compounds the selenium atom is mainly bivalent. The representatives are common cyclic selenides 10, diselenides 11 and selenosulfides. In tetravalent selenium compounds such as cyclic selenoxides 12, selenonium salts and selenuranes, a tetragonal structure arises from sp^3 hybridization of the selenium atom. When three different substituents are bonded to selenium (12, R≠H) the selenium atom is a stereogenic center. In most selenaheterocyclic rings the selenium atom is bounded to carbon or to the heteroatom, like selenium, oxygen, nitrogen or sulphur resulting in compounds of the type 11, 13, 14 and 15. Some of the selenaheterocyclic systems containing Se-P, Se-B and Se-Sn bonds (16-18) are also known (Figure 1.2). A number of macrocyclic compounds containing one or more selenium atoms and also other heteroatoms like N, P, O and S are known. The ring size varies from seven to eighteen atoms.
The best known selenaaromatic compounds have a five-membered ring containing only selenium or selenium and adjacent or nonadjacent nitrogen atoms. Some important selenaaromatic compounds such as selenophene 19, selenazoles 20, 21 and selenadiazoles 22, 23 are presented in Figure 1.3.

Bicyclic heteroaromatic selenium containing systems with ring junction sulphur or selenium atom are less common. The cationic forms such as 24 and 25 (Figure 1.4) are also possible, existing as stable selenonylium salts. Selenaaromatic six-membered ring systems are known only in the ionic seleninium form 26, like the pyrylium cation.
1.2.3. Organoselenium polymers

There are a number of organoselenium polymers but the ones of interest for their transport properties are poly(phenylene selenide), poly(thiophene selenide), poly(selenophene) and poly carbon diselenide [28].

1.2.4. Selenaporphyrins

The porphyrins are called “pigments of life” and occur broadly in nature. They fulfil many roles ranging from oxygen transportation (haemoglobin), electron transfer (cytochromes), oxidations and reductions (peroxidase, catalase, cytochrome, oxidase), light harvesting and photosynthesis (chlorophylls). Although naturally occurring porphyrins have no chalcogen atoms in the macrocycle ring, many efforts have been made to synthesize modified and expanded porphyrins. Among these have been the porphyrins and analogs modified by introduction of selenium atoms. Synthetic porphyrins have been investigated for numerous applications, including the
production of molecular wires, oxidation catalysts, novel optical materials, components of molecular based information storage systems and photosensitizers in photodynamic therapy. The porphyrins containing one or two selenium atoms in the macrocyclic ring as well as core-modified expanded selenaporphyrins have been obtained by the acid-catalyzed condensation of appropriate pyrrole with bis(phenylhydroxymethyl)selenophene. For example, 5,20-diphenyl-10,15-bis(p-tolyl)-21-selenaporphyrin 27 was obtained by a [3 + 1] condensation reaction [29].

1.2.5. Organoselenium compounds of practical importance

(i) Reagents, catalysts and intermediates in synthesis

Many organoselenium compounds are found to be useful intermediates in a great variety of reactions since they often react regio and/or stereoselectively [30]. The reactions can be divided into two groups: (i) those which proceed through extrusion of the selenium in thermal or reductive conditions, or under treatment with a nucleophile (photochemical extrusion of the selenium is of minor importance for use in synthesis) and (ii) those where selenium plays a role as oxygen-transfer agent.

The ready thermal and photochemical decomposition of 1,2,3-selenadiazoles resulting in extrusion of nitrogen and selenium or nitrogen alone has been exploited widely in synthesis for more than thirty years. The valuable synthetic intermediates are benzo-2,1,3-selenadiazoles. They were used to prepare N-alkyl-1,2-benzene diamines, 3-nitro-1,2-benzenediamines, 3,4-diamino-2-nitrophenols, and 5-nitro quinoxalines.
Selenazole and the 1,2,4- and 1,2,5-selenadiazoles serve as heterodienes in the Diels-Alder reaction. [1,4]-Cycloaddition of the active dienophiles to these selenaheterocyclic compounds, followed by deselenation, is a convenient route for the synthesis of a nonselenium azaaromatic ring. Cycloaddition of 2,4-disubstituted 1,3-selenazole 28 with DMAD forms a bicyclic intermediate 29 that undergoes extrusion of elemental selenium liberating the pyridine derivative 30 [31].

The methyl selenienyl salt 31, readily obtained from dibenzoselenophene, is a powerful methylating agent even in water as a solvent. For many reactions, benzisoselenazol-3(2H)-one and ebselen 32, used in 5% molar amount (related to the substrate), were found to be the most versatile oxygen-transfer catalysts among organoselenium compounds.

Selective oxidation of sulfides to sulfoxides 33 [32], oxidation of oximes in the presence of primary or secondary alcohols to esters 34 [33], oxidative conversion of N,N-dimethylhydrazones or benzylamines into nitriles 35 [34, 35], regeneration of the parent ketones 36 from azines, dehydrogenation of tetrahydroisoquinoline to isoquinoline 37, oxidation of cyclooctene to epoxide 38 [36], and oxidation of aromatic aldehydes to arenecarboxylic acids 39 avoiding the Baeyer-Villiger rearrangement [37] are the reactions catalysed by ebselen 32 (Scheme 1.1).
(ii) Electroconducting Materials

Selenium compounds show broad similarities with the corresponding sulfur analogues, but, remarkable differences are known between selenium and sulfur compounds. Because of the larger size of the selenium atom, selenium compounds show an increased polarizability and, therefore, they are, in general, less stable than the sulphur analogues. Their physical properties make selenaheterocycles attractive materials in the development of organoelectric or organo-optic materials. Various types of conductors having a selenaheterocyclic ring system have been obtained and characterized. The conductive properties of selenium contribute to the design and function of photoelectric cells, light meters, solar cells and photocopiers. Compounds exhibiting such behaviour include tetramethyl tetraselefulvalene (TMTSF) 40,
bis(ethylenedithio) tetrathiafulvalene (BETS) and poly(3-alkylselenophenes) [38-40].

Interest in the selenafulvalenes culminated in 1980 when superconductivity in an organic selenium compound was discovered for the first time in salts of tetramethyltetrathiafulvalene (TMTSF)$_2$X, where X = PF$_6$, AsF$_6$, SbF$_6$, TaF$_6$, ReO$_4$, FSO$_3$, ClO$_4$ [38]. While using bis(ethylenedithio)tetrathiafulvalene BETS molecules and typical magnetic anions such as [FeCl$_4$]$^-$ and [FeBr$_4$]$^-$ various types of new magnetic conductors were discovered, including the first antiferromagnetic and metamagnetic organic metals and antiferromagnetic organic superconductors.

Conjugated polymers have been the subject of many investigations [41]. The most notable property of polyselenophenes (PSs) and their derivatives is the electrical conductivity. Since the mid 1980s, more than 60 patents concerning selenophene derivatives have been filed. They generally deal with polyselenophenes that can be used as electro conducting films and photosensitive materials. Selenophene oligomers such as 43 and 44 are promising compounds applicable to organic field effect transistors, photodiodes, light-emitting diodes and their integrated devices.

Several charge-transfer salts of sulphur and selenium containing heterofulvalenes with 7,7',8,8'-tetracyano-p-quinodimethane (TCNQ) have been shown to possess unique solid state properties [42-46]. Of the tetrathiafulvalenes prepared so far, HMTSF 45 has been of particular interest because HMTSF-TCNQ [45] is the first example of an organic compound which retains high electrical conductivity at very low temperatures ($\sigma_{0.03K} \sim 600(\Omega\text{cm})^{-1}$).
Di-(2,5-dihydrothieno)-{3,4-b;3,4-h}-1,4,5,8-tetraselenafulvalene, DTTSF 46, was synthesized in order to investigate the effect of introducing a polarisable heteroatom into the exocyclic rings, while retaining the overall size and symmetry, and thereby probably the packing properties of the congener (HMTSF). 1,2,3-Thiadiazoles are known to react with a 1,3-dipolarophile such as CS₂ to give 1,3-dithiole-2-thiones in low to moderate yields [47]. Recently, it was shown that 1,2,3-selenadiazoles can react in an analogous manner to form 1,3-thiaselenole-2-thiones, which in turn were converted to dithiadielenafulvalenes [48]. Berg et al. reported the reaction of 4,6-dihydro-(3,4-d)-thieno-1,2,3-selenadiazole 47 with CSe₂ [49] to yield 1,3-diselenole-2-selone 48. 48 was treated with triethylphosphite to give DTTSF (II), which formed a highly conducting 1:1 charge-transfer salt with TCNQ.

The synthesis, electrochemical and optical properties of two newly designed donor/acceptor-type polymers, namely poly[4,7-di(1H-pyrrol-2-yl)benzo[c][1,2,5]thiadiazole] 49 and poly[4,7-di(1H-pyrrol-2-yl)benzo[c][1,2,5]selenadiazole] 50 have been reported [50].
(iii) Bioactive compounds

During last few years, a tremendous effort has been directed toward the synthesis of stable organoselenium compounds that could be used as antioxidants, enzyme modulators, antitumours, antivirals, antimicrobials, antihypertensive agents and cytokine inducers.

a) Antioxidants and anti-inflammatory agents

Ebselen has undergone Phase III clinical trials as a neuroprotective agent and is soon to become the first synthetic organoselenium therapeautic released in the market. Ebselen acts as glutathione peroxidase (GPx) mimic by reducing hydroperoxides to water or the corresponding alcohol. Lipoxygenases (LOX) is an inflammatory enzyme. The capacity for ebselen to act as LOX inhibitor is critical to its anti-inflammatory activity. The camphor-derived cyclic selenenamide 51 and selenenamides 52, 53 having supplementary tetrahedral carbon in the ring display appreciable GPx mimetic activity. Other representative selenaheterocyclic compounds which mimic the biological activity of GPx are 54, 55 and 56.

4,5-Diaryl isoselenazoles as multiple target non-steroidal anti-inflammatory drugs (MTNSAIDs) was investigated by M Scholz et al. [51]. They described the synthesis of COX/LOX inhibitors which additionally reduce the level of reactive oxygen species, such as hydroxyl radicals which are well known for supporting inflammation processes in Parkinson’s disease, Alzheimer’s disease and rheumatoid arthritis.

Synthesis, anti-inflammatory, analgesic and antimicrobial activities of some new 4-cyanopyridazine-3(2H)selenone derivatives were described [52]. It is well established that selenium has a key role in redox regulation and antioxidant function, and hence in membrane integrity, energy metabolism and protection against DNA damage.

These and other functions are mediated through a small number of approximately 50 different selenoproteins encoded by 25 separate genes, which require adequate selenium availability for their regular biosynthesis and expression. Selenoproteins include several forms of the enzymes glutathione peroxidase (GPx), thioredoxin reductase, iodothyronine deiodinase and most importantly selenocysteine [53].
b) Enzyme inhibitors

Organoselenium compounds, which are known to inhibit a variety of enzymes such as nitric oxide synthase (NOS), inosine monophosphate dehydrogenase (IMPDH) and lipoxygenases (LOX) are considered as potential pharmaceuticals. Ebselen and related organoselenium compounds, among them carboxylated analog 57, have been reported to be inhibitors of constitutive endothelial NOS. Since the activity of IMPDH increases significantly in proliferating cells, the IMPDH inhibitors are expected to be promising antitumor and immunosuppressive agents and have been considered as potentiators of the anti-HIV activity of retroviral drugs such as 2',3' -dideoxyinosine. Selenazofurin 58 and selenophenfurin 59 are potent IMPDH inhibitors and have pronounced antitumor activity in animals and broad spectrum antiviral as well as maturation-inducing activities [54].
c) Antitumor agents

The search for novel antitumor agents resulted in the successful development of two clinically useful agents, 6-phenyl-7(6H)-isoselenazolo-[4,3-d]pyrimidine 60 and 4,5-dihydro-4-methyl-6-oxo-5-phenyl-6H-pyrazolo[4,5-c]isoselenazole 61 that were tested against tumor growth in a mouse model. The organoselenium compounds 60 and 61 markedly inhibited the growth of P388 mouse leukemia at a dose of 100 µg/mouse/day without exhibiting any toxicity.

2,4-Disubstituted selenazoles 62 and 63, were evaluated for their antitumor activity. A number 1,3-selenazine and selenazole derivatives have been reported as antiproliferative agents. Selenazines 64 and 65 are the most active against human fibrosarcoma HT-1080 cells. Alkyl aryl and diaryl selenides can also act as antitumor agents.

\[
\begin{align*}
60 & \quad 61 \\
62 \text{ R=CH}_2\text{Cl} & \quad 63 \text{ R=SCN} \\
64 \text{ R=Et} & \quad 65 \text{ R=n-Pr}
\end{align*}
\]

d) Anti-infecitve Drugs

Studies of the anti-infecitve organoselenium compounds started as early as 1950, when the selenium analogues of sulfonamides were tested. Compounds such as 66 show in vitro activity against HIV at nanomolar concentrations and below this level toxicity is observed. Selenazofurin 58 exhibits antiviral action in addition to its antitumor activity.

The 7-azabenziisoselenazol-3(2H)-ones 67 substituted at 2-position with phenyl or alkyl groups and the methiodides 68 were found to be strong inhibitors of cytopathic activity of herpes simplex type 1 virus (HSV-1) and encephalomyocarditis.
virus (EMCV), more potent than ebselen. The antibacterial activities of ebselen and several other benzisoselenazo-3(2H)-ones against gram-positive and gram-negative bacteria have been reported. Ebselen as well as the p-chloro analogue 69 exhibited strong inhibitory activity against the growth of fungi *Saccharomyces cerevisiae* and *Candida albicans* strains [55]. Several benzisoselenazo-3(2H)-ones were tested *in vitro* against pathogenic bacteria, yeasts and filamentous fungi *Aspergillus niger*, *Penicillium chrysogenum* and *Penicillium citrinum*. The broadest spectrum of activity was observed for the 2-methyl-7-azabenzisoselenazol-3(2H)-one (67, R = Me).

![Chemical structures](image)

Many selenophene derivatives act bacteriostatically *in vitro* on acid resistant bacteria and fungi. The most active compounds were found to be 70, 71 and 72.
e) Cytokine inducers and immunomodulators

Several benzisoselenazol-3(2H)-ones were studied for their immunological activities in mouse, rat cells and chickens. Among the benzisoselenazol-3(2H)-ones the highest activity is exhibited by ebselen and compounds 73 and 74 [56-58].

\[
\begin{align*}
\text{R} & = \text{H, Me, t-Bu, C}_{12}\text{H}_{25}, \text{C}_{18}\text{H}_{37} \\
\text{73} & \\
\text{R} & = \text{NO}_2, \text{Cl} \\
\text{74} &
\end{align*}
\]

f) Organoselenium compounds for cancer therapy

The trace element selenium appears to have cancer preventive properties, as evidenced by a converging body of evidence from epidemiologic, clinical and experimental studies [59-62]. Selenium is present in 25 human selenoproteins and many of them are involved in anti-oxidant defense systems and in cancer prevention [63]. Selenoproteins include enzymes, such as the glutathione peroxidases (GPx), thioredoxin reductases (TrxR) and iodothyronine deiodinases (ID) [64]. It is well established that these Selenium enzymes play a key role in redox regulation as modulators of reactive oxygen species (ROS). As a constituent of the small group of selenocysteine-containing selenoproteins, selenium elicits important structural and enzymatic functions.

A new series of benzo- and dibenzoselenadiazoles and selenadiazolepyridines had been synthesized and their antiproliferative and cytotoxic activities were evaluated against four cancer cell lines and two non-malignant cell lines. A novel series of fourteen substituted selenadiazoles has been synthesized and the compounds tested for their \textit{in vitro} antiproliferative and cytotoxic activities [65].

Mammalian thioredoxin reductase (TrxR), together with thioredoxin (Trx) and NADPH, constitutes a critical system for many cellular pathways. Mammalian TrxRs are large selenoproteins acting as catalytically active sites. Trx system is involved in many aspects of tumour physiology such as proliferation, apoptosis and metastasis. Until 2011, only three anticancer drugs targeting Trx system were under clinical
trials: (1) Motexafin gadolinium17 (MGd) - phase III; (2) PX-1218 (1-methylpropyl-2-imidazolyl disulfide) - phase II; (3) Ethaselen (1,2-[bis-1,2-benziselenazol-3(2H)-one]ethane), also named BBSKE - phase I. Ethaselen which is an organoselenium drug was demonstrated to be a potent inhibitor of TrxR in rats showing remarkable anticancer activity in both \textit{in vitro} and \textit{in vivo} experiments [66].

Several forms of organoselenium compounds have been studied for their cancer preventive activities. The dietary $p$-methoxybenzeneselenol, a synthetic organoselenium compound was found to inhibit azoxymethane-induced hepato carcinogenesis in female F 344 rats without clinical signs of toxicity. Jibril \textit{et al.} [67] cited that El-Bayoumy in 1997 found that two newly synthesized selenium compounds, $p$-methoxybenzyl selenocyanate and 1,4-phenylenebis(methylene) selenocyanate prevented both precancerous cell growth and tumor growth in animals after being treated with a colorectal cancer inducing agent with no side effects.

Desai \textit{et al.} [68] demonstrated that substitution of sulfur with selenium in known iNOS inhibitor increases the compound's potency by several folds in a variety of cancer cell lines tested. Hence, this can be used as a strategy to increase the efficacy of the anticancer agents. Cytogenetic effects of cyclopentadienyldicarbonyliron selenoterephthalic acid in cultured rat bone marrow cells was examined by Jacob \textit{et al.} [69]. Certain photoactive organoselenium compounds have been used as sensitizers in photodynamic therapy (PDT) [70-72]. PDT is a promising approach to the treatment of cancer in which a tumour specific dye is irradiated to produce a cytotoxic species or reaction in or around the cancer cell.

\subsection*{1.3. Nitrones}

The name “nitrone” was coined by Pfeiffer to designate substances having the linkage as shown in \ref{fig:75} because they behave like ketones in some respects. Pfeiffer had in mind the similarity between C=O and N→O in coining the name.

\begin{equation}
\begin{align*}
\text{R} & \quad \text{N} \quad \text{O} \\
\text{75}
\end{align*}
\end{equation}
For the last five decades many scientists have drawn special attention to nitrones due to their successful application as building blocks in the synthesis of various natural and biologically active compounds. They are employed in generating stable nitroxyl radicals and of other important products for special purposes. They are used as spin traps to study radical processes including those which take place in biological systems. They also find application as modifiers and regulators of molecular weight in radical polymerization.

### 1.3.1. Synthesis

The most popular method of preparing nitrones is the condensation of aldehydes or ketones with \( N \)-monosubstituted hydroxylamines. Direct oxidation of secondary amines to the corresponding nitrones was also studied in these two decades and was found to be another useful method for the preparation of nitrones. Yet another method for the preparation of nitrones is the oxidation of \( N,N \)-disubstituted hydroxylamines.

#### i) By oxidation of \( N,N \)-disubstituted hydroxylamines

The mildest oxidation method of nitrone formation seems to be \textit{via} oxidation of the corresponding hydroxylamines containing one or more protons at \( \alpha \)-C. The preparation of cyclic and acyclic nitrones from the corresponding \( N,N \)-disubstituted hydroxylamines has been achieved by a variety of oxidizing agents such as molecular oxygen, yellow mercuric oxide, "active" lead oxide, potassium ferricyanide, potassium permanganate, \( t \)-butyl hydroperoxide and hydrogen peroxide. The air oxidation of secondary hydroxylamines has been known for a long time. Aqueous cupric salt solutions were shown to accelerate markedly the uptake of oxygen [73]. 5-Ethyl-l-hydroxy-2,2-dimethylpyrrolidine in aqueous ethanol containing cupric acetate and some ammonia yielded 90\% of the nitrone when air was bubbled through the solution for a few hours [74]. This method has been found to be useful for the preparation of cyclic nitrones [74,75].

Alkaline solution of potassium ferricyanide was employed to prepare \( \alpha \)-methyl-\( N \)-phenyl nitrone [76,77] and other nitrones from the corresponding hydroxylamines, often in high yields. The preparation of \( \alpha \)-phenyl-\( N \)-benzyl nitrone [78,79] was
achieved by reacting the corresponding hydroxylamines with yellow mercuric oxide in anhydrous chloroform.

Mercury(II) oxide oxidation of \(N,N\)-disubstituted hydroxylamines 76 with the \(\alpha\) and \(\alpha'\) carbon atoms containing one and two hydrogen atoms, respectively, gave aldinitrones 77 and 78 in a highly regioselective manner [80].

Though the most widely used oxidant for this transformation is yellow \(\text{HgO}\), its high toxicity together with the large excess that is needed to ensure complete oxidation, raised severe concerns regarding its use and disposal. \(\text{MnO}_2\) was proposed as a valid non-toxic substitute of \(\text{HgO}\) for the oxidation of \(N,N\)-dialkylhydroxylamines [81]. The oxidation of several structurally differentiated hydroxylamines with commercial \(\text{MnO}_2\) ('activated', 90% purity) gave nitrones in good to excellent yield.

A cold alkaline solution of potassium permanganate in acetone was employed to prepare \(\alpha,N\)-diphenylnitrone in 60% yield from the hydroxylamine [82]. \(t\)-Butyl hydroperoxide oxidized \(N,N\)-dibenzylhydroxylamine to the corresponding nitrone in 90% yield. Hydrogen peroxide was employed as the oxidizing agent for the preparation of \(\alpha,N\)-diphenylnitrone [82], \(\alpha\)-(\(o\)-nitrophenyl)-\(N\)-phenylnitrone [82], and \(\alpha\)-benzyl-\(N\)-phenylnitrone [83] from the corresponding hydroxylamines.

A convenient method for the synthesis of nitrones 80 by the oxidation of \(N,N\)-disubstituted hydroxylamines 79 with \(N\)-\(t\)-butylbenzenesulfinimidoyl chloride and DBU was developed [84]. Intermolecular 1,3-dipolar cycloaddition of thus formed nitrones with certain kinds of olefins was also performed by one-pot procedure.
ii) From $N$-substituted hydroxylamines

The condensation of aldehydes or ketones 81 with $N$-monosubstituted hydroxylamines 82 proceeded smoothly and in high yields when R is an alkyl or aryl group and if R' and R" are of small size. When R' and R" are bulky groups the reaction did not proceed to any extent [85].

\[ 
\text{R} + \text{R'} + \text{R"} \rightarrow \text{R} + \text{R'} + \text{R"} 
\]

$N$-Phenylhydroxylamine was treated with a variety of aldehydes and ketones [86-89]. $N$-(p-Tolyl)hydroxylamine and $N$-diphenylmethylhydroxylamine were also used. The bisulfite addition compounds of aldehydes and ketones 84 have been reported to react with $N$-substituted hydroxylamines 85, yielding nitrones 86 quantitatively.

\[ 
\text{R} \text{R}' \text{R}" + \text{R} \text{R}' \text{R}" \rightarrow \text{R} \text{R}' \text{R}" + \text{R} \text{R}' \text{R}" + \text{R} \text{R}' \text{R}" 
\]

Various C-aryl and C-alkyl-nitrones were synthesized within 0.5-2 hours via condensation of an equimolar amount of aldehydes and $N$-substituted hydroxylamines under solvent free conditions in a ball mill apparatus [90]. For example nitrone 89 was prepared by the reaction between benaldehyde 87 and $N$-methylhydroxylamine 88.
Nitrones have also been prepared by the generation *in situ* of the hydroxylamine in the presence of a carbonyl compound. Nitrobenzene, benzaldehyde, and zinc dust in a mixture of water, ethanol, and acetic acid at -8°C for 2 hours yielded 90% of α,N-diphenylnitrone [91]. Aliphatic nitro compounds behave similarly.

### iii) From oximes

Oximes undergo Michael addition with electronegative alkenes to generate nitrones. Alkylation of oximes 90 with alkyl halide 91 gave a mixture of oxime ethers 92 and nitrones 93, since alkylation may occur on either oxygen or nitrogen [92-94]. Dimethyl sulfate was employed in the alkylation of various ketoximes. Heptanal oxime when treated with benzyl chloride in a solution of ethanol and sodium ethoxide yielded 77% of α-hexyl-N-benzylnitrone [95].

![Diagram of electron-withdrawing groups in p,p'-disubstituted benzenophenone oxime salts](image)

Nitrones can be generated from oximes, which are ambivalent nucleophiles, either the N or the O acting as the reactive site, depending on the reaction conditions. Grigg *et al.* recently described the halogen and phenylselenyl halide induced inter- and intramolecular formation of nitrones from oximes and alkenes [96, 97].

Mernyák *et al.* reported the electrophile-induced cyclization of 13α- and 13β-estrone oximes to form cyclic nitrones, and intermolecular 1,3-dipolar cycloadditions of the steroidal nitrone dipoles with N-phenylmaleimide (NPM). Additionally, hydride reduction of the initially formed cyclic nitrones, yielded substituted aza-D-homo-estrones and dimeric derivatives [98].
iv) By oxidation of secondary amines

Among the methods for the synthesis of nitrones, the catalytic oxidation of secondary amines with hydrogen peroxide is the most simple and effective method. However, the disadvantage of this method is that the oxidation of unsymmetrical secondary amines often gives a mixture of regioisomeric nitrones. Oxidation of secondary amines catalysed by methyl trioxorhenium (MTO) with H₂O₂ or urea–hydrogen peroxide complex (UHP) at room temperature gave the corresponding nitrones in good yield as described by Goti and Nannelli [99]. Recently it has been shown that nitrones can be prepared from secondary amines with selenium dioxide [100] or sodium tungstate [101] as catalysts and hydrogen peroxide as oxygen donor. Molybdenum oxide/bipyridine hybrid material {{[MoO₃(bipy)][MoO₃(H₂O)]}} was shown to catalyse the oxidation of secondary amines to nitrones [102].

v) Oxidation of imines

Oxidation of imines with peracids leads to oxaziridines, with the possibility of their successive rearrangement into nitrones, depending on their structure and the employed oxidant. Oxidation of N-alkyl imines with dimethyldioxirane (DMD) in a solution of dichloromethane-acetone gives nitrones without the apparent formation of oxaziridines [103]. Diaryl diselenides and benzisoselenazole-3(2H)-ones are used as efficient catalysts in the process of imine oxidation with hydrogen peroxide and t-butylhydroperoxide [30]. A series of imines have been oxidised to nitrones in reasonable yields with permanganate ion under phase transfer conditions [104]. Also, nitrones can be formed by photochemical oxidation (λ350 nm) of aldimines in acetonitrile, in the presence of O₂ over a TiO₂ suspension [105].

vi) From diazo compounds

This reaction involves the introduction of a diazo compound into a solution of an aromatic nitroso compound, causing a vigorous reaction to take place. α,α-Ν-triphenylnitrone 96 was formed in 77% yield from the reaction between nitrosobenzene 94 and diphenyldiazomethane 95 [106,107] while nitrosobenzene and phenyldiazomethane yielded α,N-diphenylnitrone.
vii) From nitroso compounds

Aryl nitroso compounds react easily with dimethyl bromomalonate in the presence of alkali to give the corresponding \(N\)-aryl-\(C,C\)-dimethoxycarbonyl nitrones [108]. Synthesis of nitrones utilizing nitroso compounds as reagents with a variety of substrates have been developed [109,110]. The reaction of nitrosobenzene 97 with a readily available substrate series, the phenylhydrazones of aromatic aldehydes (98, \(R = H\)) and ketones (98, \(R = \text{Ar}\)), takes place under mild conditions to give good yields of the corresponding nitrones 99 [111].

1.3.2. Reactions

The wide breadth of reactivity is due to the structure of the nitrone functionality. Nitrones are isoelectronic with allyl anions and enolates, but the presence of the \(C=\text{N}\) moiety provides an iminium-type character which is responsible for its reactivity as an electrophile. Accordingly, in addition to their 1,3-dipolar character, nitrones react with nucleophiles at the carbon atom and with electrophiles at the oxygen atom (Scheme 1.2).
i) Cycloaddition Reactions

Nitrones undergo 1,3-dipolar cycloaddition reactions with a wide variety of dipolarophiles including alkenes, alkynes, cumulenes, thiocarboxyls, phosphoranes, isocyanates and nitriles. This powerful reaction can be utilised to create multiple chiral centres in a single step providing excellent synthetic routes to complex systems. 1,3-Dipolar [2+3] cycloadditions (1,3-DCA) are reactions involving a 1,3-dipole and a dipolarophile. The dipole is a 4π-system (an ylide) and the dipolarophile is a 2π-system, usually a CC or CX double bond or triple bond. 1,3-Dipolar cycloaddition reactions involving nitrones as dipole have met a recent growing interest [112-118] especially in their diastereoselective and enantioselective versions [119,120]. 1,3-Dipolar cycloaddition reactions are among the most important synthetic manipulations allowing the construction of five-membered ring carbocycles and heterocycles. Nitrones have been shown to be effective 1,3-dipoles and they undergo smooth reactions with different dipolarophiles.

The 1,3-dipolar reaction of alkenes with nitrones gave substituted isoxazolidines, which are versatile intermediates for the synthesis of natural products and biologically active compounds [121]. Simple alkenes appear to react considerably slower than conjugated systems. Usually, electron-rich alkenes were reported to react with nitrones to give exo selectivity, while endo selectivity is favoured for electron-deficient alkenes. Lewis acid catalysis has been used to enhance reaction rates with a strict control on regio-, diastero- and enantioselectivity.

Cyclopentene, cyclohexene, norbornene, bicyclopentadiene, and other bicycloalkenes have been treated with a variety of nitrones. Norbornene 100 and α,N-diphenylnitrene 101 yielded 99% of a mixture of two isomers, presumably epimeric at the 3-position 102. The isomers yielded identical β-aminoalcohols 103 when treated with hydrogen and Raney nickel [122].

![Diagram of cycloaddition reaction]
1,3-Dipolar cycloadditions of nitrones with alkenes afforded the corresponding isoxazolidines in ionic liquid in the presence of Er(OTf)$_3$ [123]. With the aim of obtaining $\alpha,\beta$-unsaturated aldehydes, cycloaddition under thermal conditions of a variety of ($Z$)-nitrones with vinylsilanes was carried out by DeShong et al. to produce 5-(trimethylsilyl)-substituted isoxazolidines [124, 125].

Tetrachloroethylene 105 reacts smoothly in refluxing benzene with nitrone 104a (R=(CH$_2$)$_4$OH), generated *in situ* from dihydropyrane and $N$-cyclohexyl hydroxylamine, to afford 4,4,5,5-tetrachloroisoxazidine 106a in 34% yield [126]. More recently, the related cycloaddition of tetrachloroethylene 105 and nitrone 104b (R = NMe$_2$) was performed in water at room temperature to give adduct 106b in 77% yield [127].

There were several reports on the 1,3-dipolar cycloaddition of the acyclic nitrones with fluoro-substituted alkenes [128, 129]. 1,3-Dipolar cycloaddition of $N$-alkynitrones with diphenyl(vinyl)phosphine were reported [130, 131]. There are two reviews on 1,3-dipolar cycloadditions of nitrones to heterosubstituted alkenes, bearing an oxygen, nitrogen, sulfur, halogen, phosphorous or silicon atom [132, 133].

The addition of various substituted alkynes to 3,4-dihydroisoquinoline $N$-oxide has been described [134]. There are only two significant routes to $\Delta^4$-isoxazolines. The most general and widely used one is due to Huisgen and his co-workers, the cycloaddition of nitrones 107 and alkynes 108 [135]. In general, unsymmetrical terminal acetylenes would be expected to yield 5-substituted isoxazolines 109.
Styrene and α,N-diphenyl nitrone 101 yielded two isomeric adducts 110a and 110b, presumably diastereoisomers. The products of the hydrogenolysis 111 were found to be identical [136].

![Chemical structure](image)

**ii) Reduction**

Nitrones upon treatment with either lithium aluminium hydride or sodium borohydride yielded the corresponding hydroxylamines, generally in high yields, presumably by a 1,3-addition mechanism. α-Phenyl-N-methylnitrite or α,α-diphenyl-N-methylnitrite for instance form the corresponding hydroxylamines in yields of 94 and 91%, respectively, when treated with lithium aluminium hydride [137, 138].

Treatment of α-hexyl-N-benzyl nitrite with sodium and alcohol yielded N-heptyl-N-benzylamine. Deoxygenation of nitrones has been accomplished by zinc, tin or iron dust, phosphines, sulfur dioxide, sulfur, and catalytic hydrogenation. α,N-Diphenyl nitrite and other nitrones were successfully deoxygenated by sulfur. Phosphines, especially triphenylphosphines were found to act as efficient deoxygenating agents towards acyclic [139] and cyclic nitrones [140].

**iii) Hydrolysis**

Nitrones generally hydrolyze readily, forming an aldehyde or ketone and an N-substituted hydroxylamine. Arylnitrones are far less susceptible to hydrolysis than alkynitrones. For example, α,α,α-triphenyl nitrite upon treatment with dilute sulphuric acid yielded benzophenone and N-phenylhydroxylamine.

**iv) Photolysis**

Irradiation of nitrones 112 led to the formation of isomeric oxaziranes 113 [141-143], which were found to rearrange further thermally to the nitrones, or thermally and photochemically to amides 114.
In 1957 Krohnke [144] reported that N-aryl-α-benzoynitrones rearrange to N-aryl-N-formylbenzamides on irradiation. In some cases, particularly when the substituent on nitrogen is alkyl, oxaziridines are the products isolated when nitrones are irradiated. The product of photolysis of N-methyl-α-(4-bromo-2,6-dimethylphenyl)nitrone 115 is the trans form of the oxaziridine 116 [145], the structure of which has been proven by X-ray analysis [146]. Similarly, the structure of the photo product from the corresponding chloro compound was examined by X-ray analysis and thereby shown also to be the trans form of the expected oxaziridine [147].

1.3.3. Uses

The principal use of nitrones appears to be that of a synthetic intermediate. Five-membered heterocyclic systems may be prepared by 1,3-cycloaddition reactions, as discussed in detail in the previous section. Reductive cleavage of the five-membered ring 1,3-DCA product of nitrone with alkene (i.e an isoxazolidine derivative) furnishes amino alcohols whose functional groups can be found in many natural products. Amino alcohols have also been used as chiral ligands in asymmetric catalytic reactions.

The most common reagents for the cleavage of the five-membered rings include Zn/acetic acid, Raney Ni/ H₂, H2/Pd/C and LiAlH₄, but other methods exist as well. Hydrolysis of appropriate nitrones gave a variety of carbonyl compounds such as aldehydes, ketones, glyoxals, α,β-unsaturated aldehydes, dialdehydes and α-ketocarboxylic acids. The cortisone-21-aldehyde, hydrocortisone-21-aldehyde and
dihydrocortisone have been prepared from the corresponding methyl compounds by employing the King reaction followed by nitrone formation and hydrolysis [148, 149].

Nitrones have been used for the synthesis of neocyanine dyes, as supersensitizers of 2,2'- cyanines, and in photographic plates. An efficient approach to the synthesis of a carbohydrate moiety of an antifungal agent, has been demonstrated by Hoveyda et al. [150]. (-)-5-epi-Shikimic acid and (-)-Shikimic acid were synthesized by Jiang et al. via an intramolecular nitrone cycloaddition as one of the key steps [151].

During the course of a study on the cycloaddition of nitrones with vinylsilanes, DeShong et al. found that 5-sila-isoxazolidines adducts 117 could undergo a HF-induced ring-opening pathway to lead to the formation of α,β-unsaturated aldehydes 119 as a result of protonation fragmentation of the isoxazolidine 117 followed by β-elimination of the amino moiety 118 [125]. This method, for the homologation of aldehydes to α,β-unsaturated aldehydes, is an excellent alternative to Wittig chemistry.

In the area of 1,3-DCA involving nitrones as dipoles as field of reaction, using heterosubstituted alkenes are of importance for the following reasons. First, the 5-heterosubstituted isoxazolidines so obtained in these series display specific interest as key intermediates for some valuable bioactive compounds like deoxy sugars, amino sugars [152], amino prolines, amino polyols [153] and natural products benzoxocin, [154] sedridine [155, 156]. Moreover, the polyfunctionalized 3-carbon units included in the isoxazolidine pattern allow to envision direct access to promising targets in the field of aminoacids chemistry, especially α,α-disubstituted α-amino acid derivatives, carbo-differentiated aspartate derivatives, dipeptides and β-lactams proved that a high level of stereoselectivities can be achieved during the cycloaddition process.
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References


