International Journal of Current Research in Applied Chemistry & Chemical Engineering
Vol. 2, Issue 1- 2018

REVIEW ON TO FREE RADICALS, ANTIOXIDANTS AND BRIEF OVERVIEW OF OXIMES

MOHAMMAD ASIF*

ABSTRACT

The present review gives the simple and convenient routes for the synthesis of various oxime derivatives. These compounds show promise regarding their applications as antioxidants. Oximes and oxime ethers have vital pharmaceutical and synthetic applications. The oxime/ oxime ether is incorporated into many organic medicinal agents, including some antibiotics, for example, gemifloxacin mesylate, pralidoxime chloride and obidoxime chloride are used in the treatment of poisoning by organophosphate insecticides like malathion and diazinon. The results obtained were very interesting, encouraging and it opens a new pathway for further investigation in this area. These aspects which promise us to have pharmaceutical, industrial and commercial applications.

KEYWORDS: Antioxidants, Applications, Biological Activities, Oximes, Synthesis.

FREE RADICALS

Nutrients that are commonly used by animal and plant cells in respiration include sugar, amino acids, fatty acids and a common oxidizing agent (electron acceptor) is molecular oxygen (O_2). The energy stored in ATP can then be used to drive processes requiring energy, including biosynthesis, locomotion or transportation of molecules across cell membranes. The ability to utilize oxygen has provided humans with the benefit of metabolizing nutrients. Oxygen is a highly reactive atom that is capable of becoming part of potentially damaging molecules commonly called “free radicals.” Free radicals can be defined as molecules or molecular fragments containing one or more unpaired electrons in atomic or molecular orbitals [1]. Free radicals may have positive, negative or zero charge, i.e., they have an unpaired electron on an open shell configuration, which causes them to seek out and capture electrons from other substances in order to neutralize themselves. Although the initial attack causes the free radical to become neutralized, another free radical is formed in the process, causing a chain reaction to occur and until subsequent free radicals are deactivated, thousands of free radical reactions can occur within seconds of the initial reaction. The formation of radicals may involve breaking of covalent bonds homolytically, radicals requiring more energy to form are less stable than those requiring less energy.

*Department of Pharmacy, GRD (PG) Institute of Management & Technology, Dehradun, 248009, (Uttarakhand), India. ***Correspondence E-mail Id:*** editor@eurekajournals.com

 ISSN: 2581-5385

Homolytic bond cleavage most often happens between two atoms of similar electro negativity. In organic chemistry this is often the O-O bond or O-N bonds. Radical ions do exist, most species are electrically neutral. Radicals may also be formed by single electron oxidation or reduction of an atom or molecule. An example is the production of superoxide by the electron transport chain. Free radicals are capable of attacking the healthy cells of the body, causing them to lose their structure and function. Cell damage caused by free radicals appears to be a major contributor to aging and to degenerative diseases of aging such as cancer, cardiovascular disease, cataracts, immune system decline and brain dysfunction. Overall, free radicals have been implicated in the pathogenesis of at least 50 diseases [1-3].

In-depth literature on oximes has induced us to synthesize several oxime derivatives and compared their antioxidant activities with standard antioxidants butylated hydroxyl anisole (BHA) and ascorbic acid (AA) by the following *in vitro* methods.

1. 2,2'-diphenyl-1-picrylhydrazyl (DPPH) assay,
2. 2,2'-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid (ABTS) assay,
3. Ferric reducing antioxidant power (FRAP) assay
4. Cupric ion reducing antioxidant capacity (CUPRAC) assay
5. Inhibition of microsomal lipid peroxidation

REACTIVE OXYGEN SPECIES

Reactive oxygen species (ROS) is a term which encompasses all highly reactive, oxygen-containing molecules, including free radicals. These include oxygen in its triplet state ($3O_2$) or singlet state ($1O_2$), superoxide anion (O_2^-), hydroxyl radical (·OH), nitric oxide (NO), peroxynitrite ($ONOO^-$), hypochlorous acid (HOCl), hydrogen peroxide (H_2O_2), alkoxyl radical (RO·) and the peroxyl radical ($RO\cdot^2$). Other free radicals are carbon-centered free radical ($CCl^3\cdot$) that arises from the attack of an oxidizing radical on an organic molecule. Hydrogen centered radicals result from attack of the H atom (H). Another form is the sulphur-centered radical produced in the oxidation of glutathione resulting in the thioyl radical (R-S·). A nitrogen-centered radical also exists, for example the phenyl diazine radical. All are capable of reacting with membrane lipids, nucleic acids, proteins and enzymes and other small molecules, resulting in cellular damage. ROS form as a natural byproduct of the normal metabolism of oxygen and have important roles in cell signaling. However, during times of environmental stress (e.g. UV or heat exposure) ROS levels can increase drastically, which can result in significant damage to cell structures. This cumulates into a situation known as oxidative stress. ROS are also generated by exogenous sources such as ionizing radiation. Exogenous ROS can be produced from pollutants, food additives, tobacco, smoke, drugs, xenobiotics and modern day lifestyles related stress is also a contributing factor to excess free radicals circulating in our body. Consequently, things like vigorous exercise, which accelerates cellular metabolism; chronic inflammation, infections and other illnesses; exposure to allergens and the presence of "leaky gut" syndrome; and exposure to drugs or toxins such as cigarette smoke, pollution, pesticides and insecticides may all contribute to an increase in the body's oxidant load.

CONCEPT OF OXIDATIVE STRESS

The term is used to describe the condition of oxidative damage resulting when the critical balance between free radical generation and antioxidant defenses is unfavorable [4]. Oxidative stress is associated with damage to a wide range of molecular species including lipids, proteins and nucleic acids [5]. Short-term oxidative stress may occur in tissues injured by

 ISSN: 2581-5385

trauma, infection, heat injury, hypertoxia, toxins and excessive exercise. These injured tissues produce increased radical generating enzymes (e.g., xanthine oxidase, lipogenase, cyclooxygenase) activation of phagocytes, release of free iron, copper ions or a disruption of the electron transport chains of oxidative phosphorylation, producing excess ROS. The initiation, promotion and progression of cancer, as well as the side-effects of radiation and chemotherapy, have been linked to the imbalance between ROS and the antioxidant defense system. ROS have been implicated in the induction and complications of diabetes mellitus, age-related eye disease and neurodegenerative diseases such as Parkinson's disease [6].

OXIDATIVE STRESS AND HUMAN DISEASES

A role of oxidative stress has been postulated in many conditions, including atherosclerosis, inflammatory condition, certain cancers and the process of aging. Oxidative stress is now thought to make a significant contribution to all inflammatory diseases (arthritis, vasculitis, glomerulonephritis, lupus erythematous, adult respiratory diseases syndrome), ischemic diseases (heart diseases, stroke, intestinal ischema), hemochromatosis, acquired immunodeficiency syndrome, emphysema, organ transplantation, gastric ulcers, hypertension and preeclampsia, neurological disorder (alzheimer's disease, parkinson's disease, muscular dystrophy), alcoholism, smokingrelated diseases and many others [7].

OXIDATIVE DAMAGE TO DNA

At high concentrations, ROS can be important mediators of damage to cell structures, nucleic acids, lipids and proteins [8]. The hydroxyl radical is known to react with all components of the DNA molecule, damaging both the purine and pyrimidine bases and also the deoxyribose backbone. The most extensively studied DNA lesion is the formation of 8-OH-G. Permanent modification of genetic material resulting from these “oxidative damage” incidents represents the first step involved in mutagenesis, carcinogenesis and ageing.

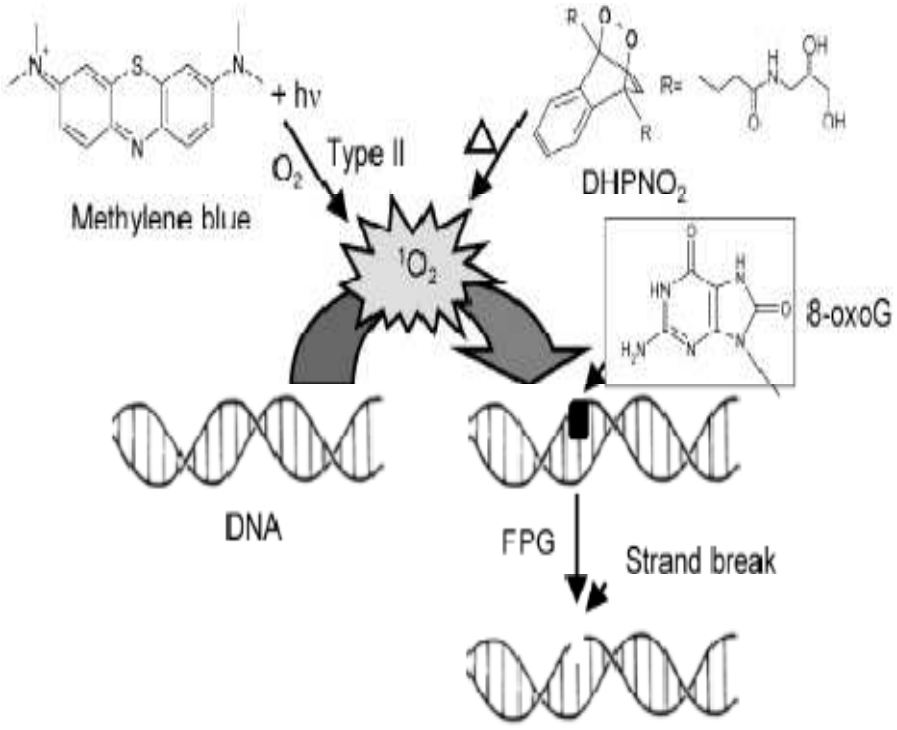


Figure 1.shows the schematic representation of singlet molecular oxygen

 ISSN: 2581-5385

Generation ($1O_2$) by methylene blue photosensitization (type II) or endoperoxide ($DHPNO_2$) thermolysis and DNA oxidation by $1O_2$ leading to the formation of base oxidation, as for example 8-oxoG, that is recognised by farmamido pyramidine DNA glycolase (FPG) enzyme that cleaves DNA in the site of the lesion. Mitochondria are unique organelles, as they are the main site of oxygen metabolism, accounting for about 85–90% of the oxygen consumed by the cell. Incomplete processing of oxygen and /or release of free electrons results in the production of oxygen radicals. Mitochondria constantly metabolize oxygen thereby producing ROS as a byproduct. These organelles have their own ROS scavenging mechanisms that are required for cell survival. It has been shown, however, that mitochondria produce ROS at a rate higher than their scavenging capacity, resulting in the incomplete metabolism of approximately 1–3% of the consumed oxygen. The byproducts of incomplete oxygen metabolism are superoxide (O^{2-}), hydrogen peroxide (H_2O_2), and hydroxyl radical (·OH). The formation of superoxide occurs via the transfer of a free electron to molecular oxygen. This reaction occurs at specific sites of the electron transport chain (ETC), which resides in the inner mitochondrial membrane (Figure 2). ETC complexes I (NADH dehydrogenase) and III (ubisemiquinone) produce most of the superoxide, which is then scavenged by the mitochondrial enzyme manganese superoxide dismutase (MnSOD) to produce H_2O_2.

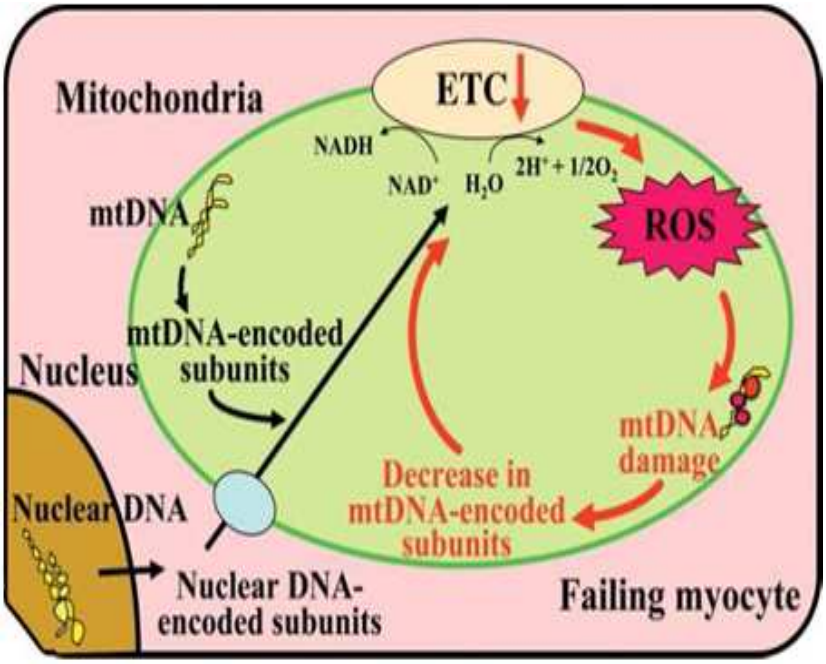


Figure 2.Generation of ROS in electron transport chain

LIPID PEROXIDATION

Lipid peroxidation is a free radical process involving a source of secondary free radical, which further can act as second messenger or can directly react with other biomolecule, enhancing biochemical lesions. Lipid peroxidation occurs on poly saturated fatty acid located on the cell membranes and it further proceeds with radical chain reaction. Hydroxyl radical is thought to initiate ROS and remove hydrogen atom, thus producing lipid radical and further converted into diene conjugate. Further, by addition of oxygen it forms peroxyl radical; this highly reactive radical attacks another fatty acid forming lipid hydroperoxide (LOOH) and a new radical. Thus, lipid peroxidation is propagated. Due to lipid

 ISSN: 2581-5385

peroxidation, a number of compounds are formed, for example, alkanes, malanoaldehyde and isoprotanes. These compounds are used as markers in lipid peroxidation assay and have been verified in many diseases such as neurogenerative diseases, ischemic reperfusion injury and diabetes [9].

OXIDATIVE DAMAGE TO PROTEIN

Proteins can be oxidatively modified in three ways: oxidative modification of specific amino acid, free radical mediated peptide cleavage and formation of protein cross-linkage due to reaction with lipid peroxidation products. Protein containing amino acids such as methionine, cystein, arginine, and histidine seem to be the most vulnerable to oxidation [10]. Free radical mediated protein modification increases susceptibility to enzyme proteolysis. Oxidative damage to protein products may affect the activity of enzymes, receptors and membrane transport. Oxidatively damaged protein products may contain very reactive groups that may contribute to damage to membrane and many cellular functions. Peroxyl radical is usually considered to be free radical species for the oxidation of proteins. ROS can damage proteins and produce carbonyls and other amino acids modification including formation of methionine sulfoxide and protein carbonyls and other amino acids modification including formation of methionine sulfoxide and protein peroxide.

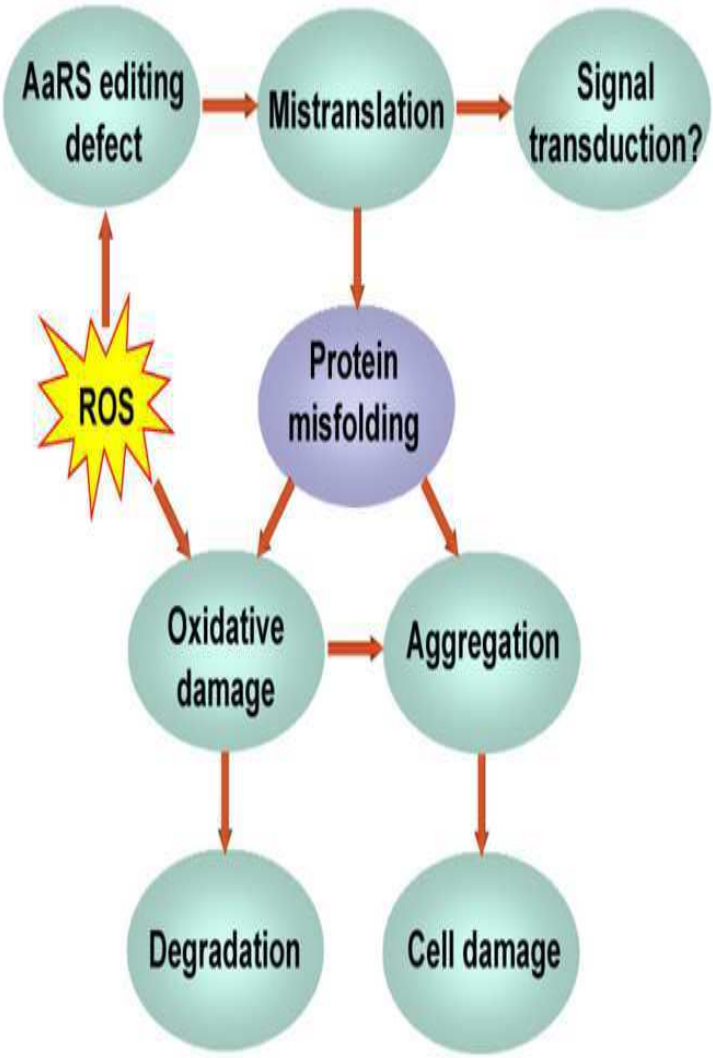


Figure 3.Protein oxidation by ROS

 ISSN: 2581-5385

Protein oxidation (Figure 3) affects the alteration of signal transduction mechanism, enzyme activity, heat stability and proteolysis susceptibility, which leads to aging.

ANTIOXIDANT

Antioxidant means "against oxidation. Antioxidants are effective because they are willing to give up their own electrons to free radicals. When a free radical gains the electron from an antioxidant it no longer needs to attack the cell and the chain reaction of oxidation is broken. After donating an electron an antioxidant becomes a free radical by definition. Antioxidants in this state are not harmful because they have the ability to accommodate the change in electrons without becoming reactive [11]. Antioxidants are capable of stabilizing or deactivating, free radicals before they attack cells. Antioxidants are absolutely critical for maintaining optimal cellular and systemic health and well-being.

THE CHEMISTRY OF ANTIOXIDANTS

It involves the mechanism of action of antioxidant. Two principle mechanisms of action have been proposed for antioxidants. The first is a chain-breaking mechanism by which the primary antioxidants donate electrons to the free radicals present in the system, example lipid radicals. The second mechanism involves removal of ROS and RNS (reactive nitrogen species) initiator by quenching chain initiator catalyst.

CHAIN REACTIONS OF FREE RADICALS

Initiation stage	**Propagation stage**	**Termination stage**
(a) $RH \longrightarrow R^{\cdot}+H^{\cdot}$	(a) $R^{\cdot}+O_2 \longrightarrow ROO^{\cdot}$	(a) $R^{\cdot}+R^{\cdot} \longrightarrow R-R$
(b) $2R^{\cdot}+O_2 \longrightarrow 2ROO^{\cdot}$	(b) $ROO^{\cdot}+RH \longrightarrow ROOH+R^{\cdot}$	(b) $R^{\cdot}+ROO^{\cdot} \longrightarrow ROOR$
(c) $2ROOH \longrightarrow ROO^{\cdot}+RO^{\cdot}+H_2O$	(c) $RO^{\cdot}+RH \longrightarrow ROH + R^{\cdot}$	(c) $ROO^{\cdot}+ROO^{\cdot} \longrightarrow ROOR+ O_2$
		(d)Antioxidants+$O_2 \longrightarrow$ oxidized antioxidants

Further, in free radical chain reactions, when fats are in contact with oxygen, it forms unsaturated fatty acids which give rise to free radicals. Also hydro peroxide which exist in trace quantities prior to oxidation reaction, break down to yield radicals which abstract hydrogen atom from another molecule and become a hydroperoxide producing further radicals. The antioxidants added to it, will neutralize the free radicals by donating one of their own electrons ending the reactions. These occur generally in the body.

TYPES OF ANTIOXIDANTS

Antioxidants have been classified based on their occurrence, mode of action, kinetics and solubility.

BASED ON THEIR OCCURRENCE

There are two types (a) Natural antioxidants (b) Synthetic antioxidants

NATURAL ANTIOXIDANTS

They are the chain breaking antioxidants which react with radicals and convert them into more stable products. Antioxidants of this group are mainly phenolic in structures and include the following [12]:

1. Antioxidants minerals-These are co factor of antioxidants enzymes. Their absence will definitely affect metabolism of many macromolecules such as carbohydrates. Examples include selenium, copper, iron, zinc and manganese.

 ISSN: 2581-5385

2. Antioxidants vitamins-These are needed for most body metabolic functions includes - vitamin C, vitamin E, vitamin B.
3. Phytochemicals-These are phenolic compounds that are neither vitamins nor minerals. These includes: Flavonoids, catechins, carotenoids, beta carotene, lycopene, herbs and spices-source include diterpene, rosmariquinone, thyme, nutmeg, clove, black pepper, ginger, garlic and curcumin and derivatives.

SYNTHETIC ANTIOXIDANTS

These are phenolic compounds that perform the function of capturing free radicals and stopping the chain reactions, the compounds includes: butylated hydroxyl anisole (BHA), butylated hydroxyl toluene (BHT), propyl gallate (PG), metal chelating agent (EDTA), tertiary butyl hydroquinone (TBHQ) and nordihydro guaretic acid (NDGA).

BASED ON THEIR MODE OF ACTION

There are two types (a) Primary antioxidants (b) Secondary antioxidants

PRIMARY ANTIOXIDANTS

These interrupt the primary oxidation cycle by removing the propagating radicals. Such compounds are also called chain breaking antioxidants. They have reactive OH or NH groups (Hindered phenols and secondary aromatic amines). Inhibition occurs via a transfer of a proton to the free radical species. The resulting radical is stable and does not abstract a proton from the polymer chain. Examples: BHA, BHT, TBHQ, PG, NDGA, hydroquinone, auxomers, olive oil, carotenoids, steroids, ethoxy quins.

SECONDARY ANTIOXIDANTS

These compounds are also called preventative antioxidants as they interrupt the oxidative cycle by preventing or inhibiting the formation of free radicals. Phosphites or phosphonites, organic sulphur containing compounds and dithiophosphonates are widely used to achieve this, acting as peroxide decomposers. Secondary antioxidants frequently referred to as hydroperoxide decomposers; decompose hydroperoxides into non-radical, non-reactive and thermally stable products.

Examples: Thiodipropioncacid, ascorbic acid, dilauryl, sulphates, erythorbic acid, polyphosphates, EDTA, phytic acid, lecithin, distearyl ester, nitrates, amino acids, flavanoids, β-carotene, tea extracts, zinc, selenium, vitamin-C, spice, tartaric acid.

There are several enzyme systems that catalyze reactions to neutralize free radicals and reactive oxygen species. These form the body's endogenous defense mechanisms to help protect against free radical-induced cell damage. The antioxidant metabolizes oxidative toxic intermediates. These enzymes include:

GLUTATHIONE ENZYMES AND SYSTEM

Glutathione, an important water-soluble antioxidant, is synthesized from the amino acids glycine, glutamate and cysteine. Glutathione can directly neutralize ROS such as lipid peroxides, and also plays a major role in xenobiotic metabolism. The glutathione system includes glutathione, glutathione reductase, glutathione peroxidases and glutathione ''S''-transferases.

LIPOIC ACID

This is another important endogenous antioxidant. It is categorized as "thiol" or "biothiol". These are sulfur-containing molecules that catalyze the oxidative decarboxylation of alpha-keto acids, such as pyruvate and alphaketoglutarate, in the Krebs cycle. Lipoic acid and its reduced form, dihydrolipoic acid (DHLA), neutralize the free

 ISSN: 2581-5385

radicals in both lipid and aqueous domains and as such has been called a "universal antioxidant."

SUPEROXIDE DISMUTASE

Superoxide dismutase (SOD) is a class of enzymes that catalyse the breakdown of the superoxide anion into oxygen and hydrogen peroxide. These enzymes are present in almost all aerobic cells and in extracellular fluids.

CATALASES

Catalases are enzymes that catalyze the conversion of hydrogen peroxide to water and oxygen, using either an iron or manganese cofactor. This is found in peroxisomes in most eukaryotic cells. Its only substrate is hydrogen peroxide. It follows a ping-pong mechanism. Here, its cofactor is oxidized by one molecule of hydrogen peroxide and then regenerated by transferring the bound oxygen to a second molecule of substrate.

Kinetically antioxidants can be classified into six categories as below:

1. Antioxidants that break chains by reacting with peroxyl radicals having weak O-H or N-H bonds; phenol, napthol, hydroquinone, aromatic amines and aminophenols.
2. Antioxidants that break chains by reacting with alkyl radicals: quinones, nitrones, iminoquinones.
3. Hydro peroxide decomposing antioxidants; sulphide, phosphide, thiophosphate.
4. Metal deactivating antioxidants: diamines, hydroxyl acids and bifunctional compounds.
5. Cyclic chain termination by antioxidants: aromatic amines, nitroxyl radical, variable valence metal compounds.
6. Synergism of action of several antioxidants: phenol sulphide in which phenolic group reacts with peroxyl radical and sulphide group with hydro peroxide.

BASED ON THEIR SOLUBILITY

Antioxidants are classified into two broad divisions

WATER SOLUBLE ANTIOXIDANTS

In general, water-soluble antioxidants react with oxidants in the cell cytosol and the blood plasma. The water soluble antioxidants include vitamin-C, glutathione peroxidase, superoxide dismutase, and catalase [13].

LIPID SOLUBLE ANTIOXIDANTS

While lipid-soluble antioxidants protect cell membranes from lipid peroxidation. These compounds may be synthesized in the body or obtained from the diet [14]. The lipid soluble antioxidants are vitamin-E, beta-carotene, and coenzyme Q [15] of these, vitamin-E is considered the most potent chain breaking antioxidant within the membrane of the cell.

EPIDEMIOLOGY OF ANTIOXIDANTS

Investigators conducting epidemiologic studies of antioxidant nutrients typically estimate intake of the nutrient from foods and supplements using questionnaire or foodrecord techniques and/or rely upon a biochemical measure of exposure to the nutrient of interest.16 Moreover oxidised LDLs show cytotoxic potential which is probably responsible for endothelial cell damage and macrophage degeneration in the atherosclerotic human plaque. Following the oxidation hypothesis of atherosclerosis the role of natural antioxidants, i.e. vitamin-C, vitamin-E and carotenoids, has been investigated in a large number of epidemiological, clinical and experimental studies. Animal studies indicate that dietary antioxidants may reduce atherosclerosis progression, and observational data in humans suggest that antioxidant vitamin ingestion is associated with reduced cardiovascular disease, but the results of

 ISSN: 2581-5385

randomised controlled trials are mainly disappointing. It has been suggested that natural antioxidants may be effective only in selected subgroups of patients with high levels of oxidative stress or depletion of natural antioxidant defence systems [17]. The favourable effects shown by some studies relating antioxidant dietary intake and cardiovascular disease, may have been exerted by other chemicals present in foods. Flavonoids are the ideal candidates, since they are plentiful in foods containing antioxidant vitamins (i.e. fruits and vegetables) and are potent antioxidants. Tea and wine, rich in flavonoids, seem to have beneficial effects on multiple mechanisms involved in atherosclerosis.

Table 1.1.Epidemiological studies on antioxidants

Disease	**Antioxidant**
Cancer	
Gastric cancer	Vit E, β-carotene, Selenium
Lung cancer in smokers	Vit E, β-carotene both together
Prostate cancer	Vit E
Lung cancer in workers exposed to asbestos	Vit A + β-carotene
Lung cancer	α,β-carotene, lutein, lycopene and β-crypto-xanthine in diet for 10 years
CARDIOVASCULAR DISEASES	
Myocardial infarction	Aspirin
Coronary heart disease	Vit E
Atherosclerosis	Vit E
Stroke and myocardial infarction N-3	PUFA , Vit E And both together
Cardiovascular disease	Catechin, Quercetin
Coronary heart disease	Vit C
Hypertension	Vit C
Heart failure	Carvedilol (25 mg bid) Metoprolol (50 mg bid) for 4, 8, 12 weeks.
Neurodegenerative diseases	
Parkinson's disease	Vit E. (2000 UI/day), Deprenyl (10 mg/day)and in combination for 14 months
Alzheimer's disease	Selegiline (10mg/day), Vit E (2000 UI/day) and in combination for 2 yrs
OTHERS	
Diabetes/hyperglycemia	Vit C (24 mg/min) intra arterially for 10 min
Type 2 diabetes	Vit E
Renal dysfunction	Acetylcysteine (600 mg bid) i.v.
Subarachnoid hemorrhage in mice	Transgenic Cu-Zn SOD (22.7 U/mg protein) as compared to 7.9 in non transgenic mice
Pre-eclampsia	Vit C (1000 mg) + Vit E (400 mg) during pregnancy

 ISSN: 2581-5385

USES OF ANTIOXIDANTS IN TECHNOLOGY

FOOD PRESERVATIVES

Antioxidants are used as food additives to help guard against food deterioration. Exposure to oxygen and sunlight are the two main factors in the oxidation of food, so food is preserved by keeping in the dark and sealing it in containers or even coating it in wax, as with cucumbers. However, as oxygen is also important for plant respiration, storing plant materials in anaerobic conditions produces unpleasant flavors and unappealing colors [18]. Consequently, packaging of fresh fruits and vegetables contains an ~8% oxygen atmosphere. Antioxidants are an especially important class of preservatives as, unlike bacterial or fungal spoilage, oxidation reactions still occur relatively rapidly in frozen or refrigerated food [19]. These preservatives include natural antioxidants such as ascorbic acid and tocopherols, as well as synthetic antioxidants such as PG, TBHQ, BHA and BHT [20]. The most common molecules attacked by oxidation are unsaturated fats; oxidation causes them to turn rancid [21,22]. Antioxidant preservatives are also added to fat-based cosmetics such as lipstick and moisturizers to prevent rancidity.

INDUSTRIAL USES

Antioxidants are frequently added to industrial products. A common use is as stabilizers in fuels and lubricants to prevent oxidation, and in gasoline's to prevent the polymerization that leads to the formation of engine-fouling residues [23].

HETEROCYCLIC COMPOUNDS

Of the more than 20 million chemical compounds currently registered about one half contains heterocyclic systems. Heterocycles are important, not only because of their abundance, but due to their chemical, biological and technical significance. Heterocycles count among their number many natural products, such as vitamins, products of technical importance (corrosion, inhibitors, anti aging drugs, sensitizers, stabilizing agents etc.). The heterocyclic compounds is an evergreen field in the branch of organic and medicinal chemistry this always attracts the attention of scientists working not only in the area of natural products but also synthetic organic, bio-organic and medicinal chemistry. Many useful drugs have emerged from the successful investigations carried out in this branch. More over spectacular advances have been made to furtherance the knowledge of relationship between chemical structure and biological activity this tendency is in fact reflected by the voluminous data available in literature on hetero cyclic chemistry. Thus the successful application in various fields ensures a limitless scope for the development of structurally novel compounds with a wide range of physicochemical and biological properties. Heterocyclic ring systems have emerged as powerful scaffolds for many biological evaluations [24]. Heterocyclic compounds provide scaffolds on which pharmacophores can arrange to yield potent and selective drugs [25]. Heterocyclic compounds carrying piperidine skeleton are attractive targets of organic synthesis owing to their pharmacological activity and their wide occurrence in nature.

OXIMES

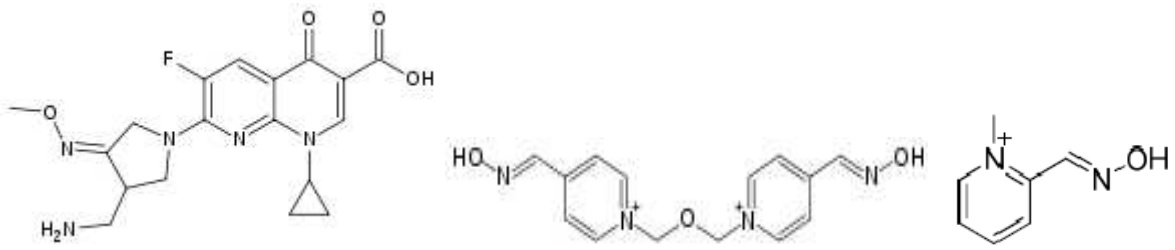
Oximes (R_1R_2C=N-OH) are a major class of hydroxylamines (R_1R_2NOH), where R_1 represents an organic side chain (i.e., alkyl, cycloalkyl or an aromatic moiety) and R_2 is either hydrogen, forming aldoxime, or another aromatic group, forming ketoxime [26]. The oxime functional groups can be transformed into such important groups as carbonyl, amino,

 ISSN: 2581-5385

nitro and cyano functions and can also serve as a convenient protective group in synthetic chemistry applications [27].

BIOLOGICAL SIGNIFICANCE OF OXIME DERIVATIVES

Oximes and oxime ethers (RRC=N-OR) have important pharmaceutical and synthetic applications. The oxime (and oxime ether) functional group is incorporated into many organic medicinal agents, including some antibiotics, for example, gemifloxacin mesylate, pralidoxime chloride and obidoxime chloride (Figure 4) are used in the treatment of poisoning by organophosphate insecticides like malathion and diazinon.



Gemifloxacin **Pralidoxime** **Obidoxime**

Figure 4.Structure of some antibiotics

Oximes are generally used as chemical building blocks for the synthesis of agrochemicals and pharmaceuticals [28]. Oximes exhibited a protective role during *invitro* Cu^{2+}-induced oxidation of LDL and serum [29]. Flavanone oxime derivatives (ethers) have been shown to modulate the growth of Yoshida Sarcoma cells *in vivo* and to induce apoptosis, but compared to anticancer drugs (doxorubicin, aclarubicin and mitoxantrone), flavanone oximes displayed cytotoxicity at considerably higher concentrations [30]. In inorganic chemistry, oximes act as a versatile ligand. The stability of oxime complexes with various metals has been shown to result in promising compounds with antitumor activity, such as cis and trans platinum complexes [31] and homo and heteronuclear Cu(II) and Mn(II) oxime complexes [32]. A complex of technetium with hexamethylpropyleneamine oxime was also used to monitor photodynamic therapy of prostate tumors [33]. Some oxime complexes has reported remarkable DNA binding, antioxidant, antimicrobial activities [34]. Recently, pyrazole oxime derivatives have attracted considerable attention in chemical and medicinal research because of their diverse bioactivities. They are widely used as fungicide, insecticide, acaricide, and antitumor agents [35-39]. Fenpyroximate is currently used for the control of mites on various crops [40,41]. However, several field populations of *T. urticae* have already develops high levels of Fenpyroximate resistance despite its short-term use and chemists have begun to study cross-resistance patterns of Fenpyroximate-resistant *T. urticae*, structural modification of Fenpyroximate and corresponding effects on the biological activities [42-45].

There are a large number of pharmaceuticals containing an oximino group attached to a variable structure, frequently a heterocyclic one [46]. Some oxime derivatives present a fungitoxic and herbicide effect [47,48] or act as growth regulators for plants. Some α-oximinoketones are known to be important intermediates for the synthesis of aminoacids [49] nitrosopyrazoles [50], 2-vinylimidazoles [51], and so on. Oxime moiety offers a convenient structural moiety for probing an element of the pharmacophore which had proven to be of considerable importance in the bezimidazole-isatin oximes and profiled as inhibitors of respiratory syncytial virus (RSV) replication in cell culture [52]. 3-keto-

 ISSN: 2581-5385

clarithromycin 9-O-(3- aryl-E-2-propenyl) oxime derivatives exhibited improved antibacterial activities against erythromycinsusceptible *Staphylococcus aureus* and *Streptococcus pneumonia* and greatly enhanced activities against the resistant strains encoded by erm and mef genes, as compared to clarithromycin and azithromycin [53]. One of the structurally distinct class of antiepileptic drugs are (arylalkyl) imidazoles, Nafimidone and denzimole. Anticonvulsant properties of this group are associated with the presence of a small oxygen functional group (such as carbonyl, ethylene dioxy, methoxy, acyloxy and hydroxy substituents) in the alkylene bridge in addition to imidazole ring [54] and lipophilic aryl portion facilitating penetration of the blood–brain barrier. The introduction of oxime and oxime ether groups to the alkylene bridge of (arylalkyl) imidazoles as a small oxygen functional group led to oxime and some oxime ether derivatives of nafimidone was reported as potential anticonvulsant compounds [55]. A series of bis-pyridinium oximes connected by xylene linker were evaluated for their *in-vitro* reactivation potential against acetylcholinesterase (AChE) inhibited by nerve agent, sarin [56]. A series of novel (Z)- and (E)-2-imidazolo-2-triazolo-methyl tetrahydro-naphthyl oxime ethers conformationally rigid analogues of oxiconazole (Figure 5) has been reported as potent antimicrobial agents [57].

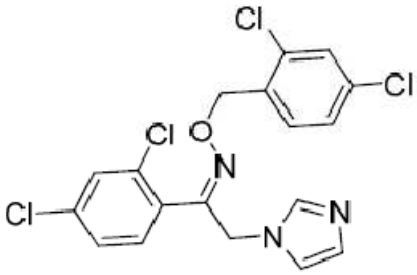


Figure 5.Structures of oxime derived drug oxiconazole

A series of bis-pyridinium oximes bearing (E) and (Z)-but-2-ene linkers, which showed promising reactivation ability against chlorpyriphos and paraxon inhibited AChE [58]. Such bis-pyridinium oximes (Figure 6) have shown promising reactivation profile against organo phosphorus (OP)-inhibited AChE. In the past, reactive oxime moiety was incorporated into the variety of micelle forming molecules, resulting in significant enhancement of hydrolysis of OP compounds [59].

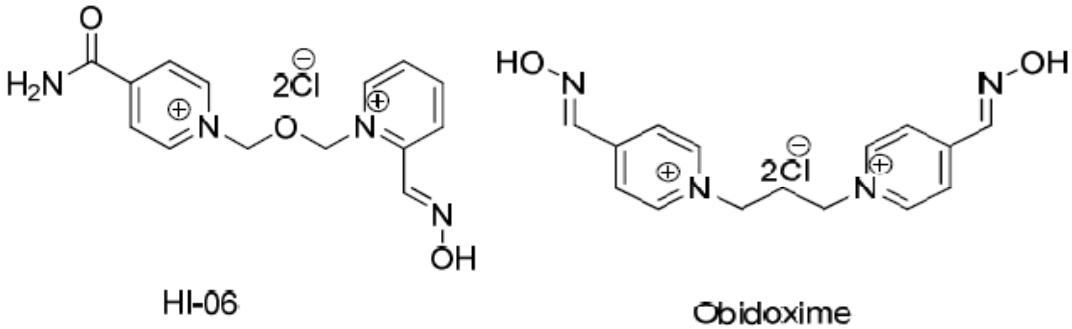


**Figure 6.Bis-pyridinium oximes used as reactivators of OP-inhibited AChE **

Quinolinone oxime sulffmic acid compounds are novel diuretics, clearly different from conventional diuretics in chemical structure but possessing functional groups essential to interact with the cotransporter [60].

 ISSN: 2581-5385

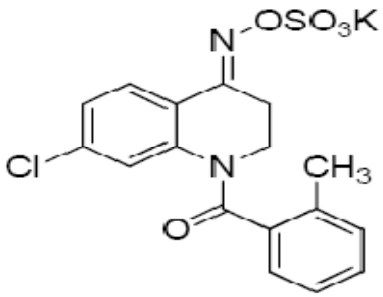
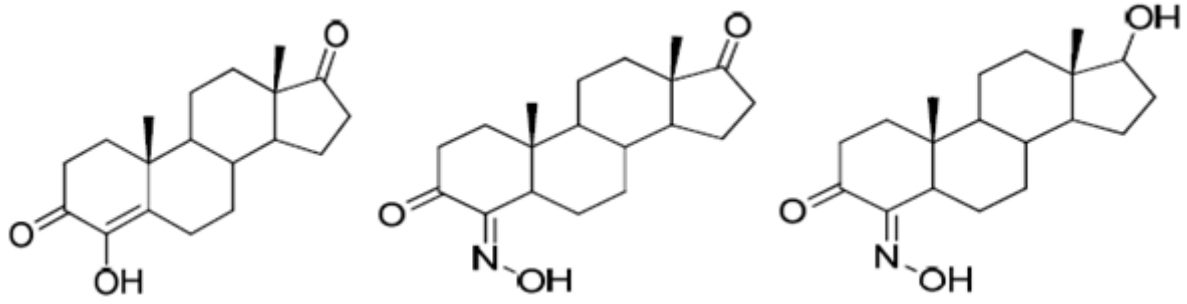


Figure 7.Structure of potent diuretic quinolinone oxime sulffmic acid

Structure of potent diuretic quinolinone oxime sulffmic acid are shown in Figure 7.

OXIMES AS ANTICANCER AGENTS

Besides to this oxime-containing molecules caught attention, as they appear to be amenable to biotransformation and conjugations with organic and inorganic molecules. The properties of these classes of compounds have been recently exploited with the aim to design and develop novel therapeutic agents that can display acyl group transfer capabilities and serve for the evaluation of novel candidate drugs for the treatment of various diseases. For example, furan oximes were found to inhibit DNA, RNA and protein synthesis in lipoid leukemia cells [61] Derivatives of quinoline oximes were also shown to possess antitumor activity [62] and glucosinolates were suggested as cancer preventive agents. There are several approaches for the therapy of breast cancer but the most effective way to treat hormone-dependent breast cancer is to inhibit the key enzyme in oestrogen biosynthesis i.e. aromatase cytochrome P450 (P450 arom) by making use of aromatase inhibitors. Among steroidal aromatase inhibitors, (Figure 8) 4-hydroxy androstenedione (4-OHA, Formestane) (a) has been approved for clinical use in the treatment of breast cancer in several countries. Oximino derivatives, 6-hydroxiimino-4-en-3-ones (b) and (c) also show a high affinity for human placental aromatase and function as competitive inhibitors of this enzyme [63].



a **b** **c**

Figure 8.Structures of steroidal aromatase inhibitors (a) Formestane, (b,c) 6-Hydroxiimino-4-en-3-ones

Anthracenone-based oxime ethers and esters (Figure 9) are considered to contribute to the development of novel antiproliferative drugs, based on tubulin interaction. Several investigated compounds displayed strong antiproliferative activity against K562 leukemia cells and proved to be strong inhibitors of tubulin polymerization [64].

 ISSN: 2581-5385

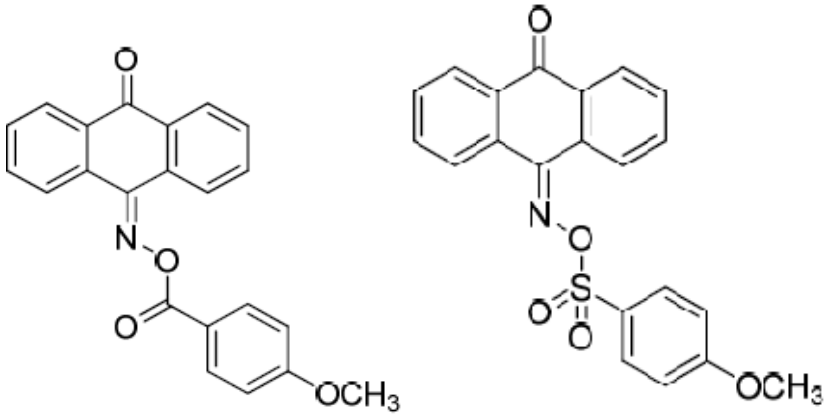


Figure 9.Structure of Anthracenone-based oxime ether and ester derived Antiproliferative agents

OXIME CHEMISTRY

The synthesis of conjugate vaccines can be a complex and expensive process involving the preparation of the individual components, the chemical activation of the polysaccharide and protein, a conjugation step and the purification of the conjugate from its components [65]. Applications of oxime chemistry are described for the efficient bioconjugation of proteins and polysaccharides for the preparation of conjugate vaccines. In this process, aldehyde or ketone carbonyls are reacted with the highly nucleophilic aminooxy (AO) group to form oximes. Either the protein or the carbohydrate moiety can be functionalized with aminooxy groups. In contrast to reductive amination, which yields an unstable Schiff base, aminooxy groups rapidly condense with aldehydes or ketones to form stable oximes, as indicated in Eq.(1).

(1) $R_1CHO + NH_2OR_2 \rightarrow RCHNOR_2$

Coupling using oxime chemistry is efficient and can be effected over a wide pH range. Furthermore, by limiting the number of cross-links between the protein and polysaccharide, control can be exerted over the degree of cross-linking. The approaches described are compatible and complementary to a number of chemistries currently used in conjugate vaccine synthesis. Oxime chemistry can be used to both simplify the synthesis of and increase yields of conjugate vaccines. Mice immunized with pneumococcal type 14 conjugates that were made using oxime chemistry mounted significant anti-polysaccharide immune responses. The primary immune response could be boosted, indicating that the polysaccharide conjugate had characteristics of a T cell dependent antigen.

OXIMES AS ANTIOXIDANT

The antiradical and antioxidant activities of four biologically active *N,N*diethyloaminoethyl ethers of flavanone oximes were investigated and these compounds were shown to be promising antioxidants and radioprotectors comparable to rutin activities, rendering them useful under oxidative stress conditions [66]. Because of the important potential uses of oximes, especially of flavonone oximes, The antioxidant properties of naringenin oxime has been identified by using the cupric ion reducing antioxidant capacity (CUPRAC) method [67]. Naringenin (4,5,7-trihydroxyflavanone) is a member of the flavonoid family (flavanone) that is considered to have various bioactivities on human health as antioxidant, ROS scavenger, monoamine oxidase inhibitor, and especially a most investigated cancer preventive agent. Naringenin is a naturally available antioxidant that can be used as starting material for the synthesis of other novel antioxidants with enhanced antioxidant

 ISSN: 2581-5385

activity. A naringenin-derivatized compound, naringenin-2-hydroxy benzoyl hydrazone, and this compound was found to possess higher antioxidant activity than simple naringenin. Because of the important potential uses of oximes, especially of flavonone oximes, naringenin was derivatized as naringenin oxime (**Figure 10**) and their antioxidant activity was evaluated [68,69].

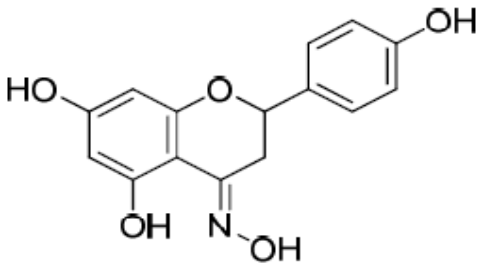


Figure 10.Structure of naringenin oxime

NATURAL OCCURRENCE OF OXIME IN PLANTS

Sponges of the family Verongidae provide a series of closely related compounds which may be considered as metabolites of 3, 5-dibromotyrosine, including aerothionin (1), homoaerothionin and the nitrile aeroplysinin (2).The spiro system in (1) and (2) could arise in various ways, including nucleophilic attack by an oxime function on an arene oxide (Figure 11). It has been speculated that the oxime (i) could be also a likely precursor of the nitrile aeroplysinin-1. There was a report on the isolation of 4-hydroxyphenylpyruvic acid oxime (ii) (oximinopyruvic acid) from a marine sponge, *Hymeniacidon sanguinea* [70].

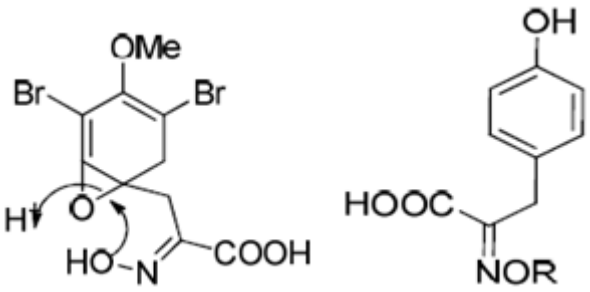


Figure 11.Structure of 4-hydroxyphenylpyruvic acid oxime isolated from a marine sponge *Hymeniacidon sanguinea*

Since the discovery that indolyl-3-acetonitrile (IAN) occurs naturally and shows auxin activity in certain plant species. Other oximes and particularly a-keto acid oximes, have, however, been isolated from natural sources [71] and the formation of indolyl-3-acetaldoxime from indolyl-3-acetaldehyde and hydroxylamine is a tenable supposition, since indirect evidence for the occurrence of both these substances in plants is available [72]. There was report on the chemical and chromatographic properties of synthetic indolyl-3-pyruvic acid oxime and have found them to be very similar to those of the IAN precursor. A new hypothesis has been there for the biosynthesis of IAN with indolyl-3-pyruvic acid oxime as the key intermediate (Figure 12).

 ISSN: 2581-5385

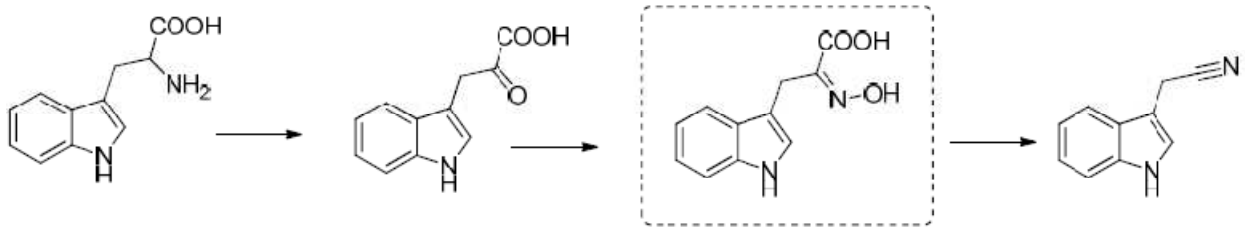
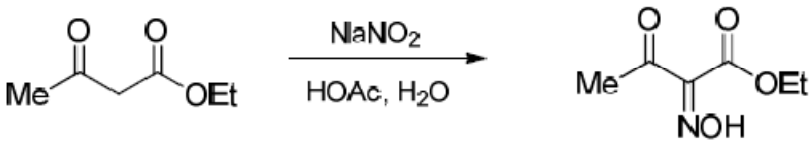


Figure 12.Biosynthesis of IAN with indolyl-3-pyruvic acid oxime as the key intermediate

SYNTHESIS OF OXIMES

Synthesis of oximes is an important reaction in organic chemistry, because these versatile oximes are used for protection, purification and characterization of carbonyl compounds. Nitriles, amides via Beckmann rearrangement, nitro compounds, nitrones, amines, and azaheterocycles can be synthesised from oximes. They also find applications for selective *α*-activation. Numerous functional group transformations of oximes make them very important in synthetic organic chemistry. Among other synthesis applications, these compounds were successfully transformed into amides [73], amines [74], hydroxylamines [75], hydroxylamine *O*-ethers [76], nitroalkanes [77], 1,3-oxazoles, thiazoles, and diazoles [78] etc. Therefore, synthetic organic chemists are interested in a facilitation of oxime synthesis. Although alternative methods exist [79] reaction of carbonyl compounds with hydroxylamine hydrochloride remains still the most important route. The classical method involves refluxing of an alcoholic solution of these reactants in the presence of sodium acetate or hydroxide [80]. Many improvements of this methodology have been described. Thus, treatment of ketones with hydroxylamine hydrochloride in the presence of an ion-exchange resin (Amberlyst A-21) as the catalyst in ethanol gave oximes in high yields at room temperature and with a simple work-up procedure [81].

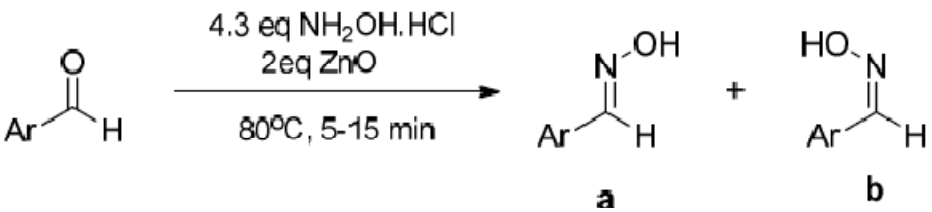
FROM ETHYL ACETOACETATE



Scheme 1

To the solution of ethyl acetoacetate and glacial acetic acid 95 per cent sodium nitrite in water was added. The mixture is stirred for one and half hour longer and then allowed to stand for four hours to get desired oxime [82].

FROM ALDEHYDE

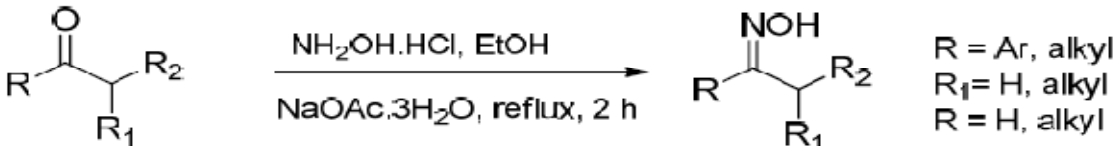


Scheme 2

 ISSN: 2581-5385

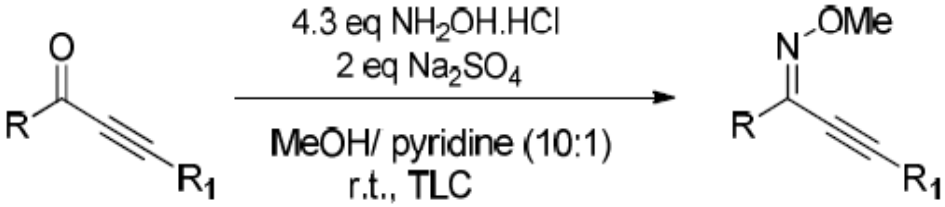
In the presence of zinc oxide and without any additional organic solvents, Beckmann rearrangement of several ketones and aldehydes were performed in good yields [83].

FROM KETONE



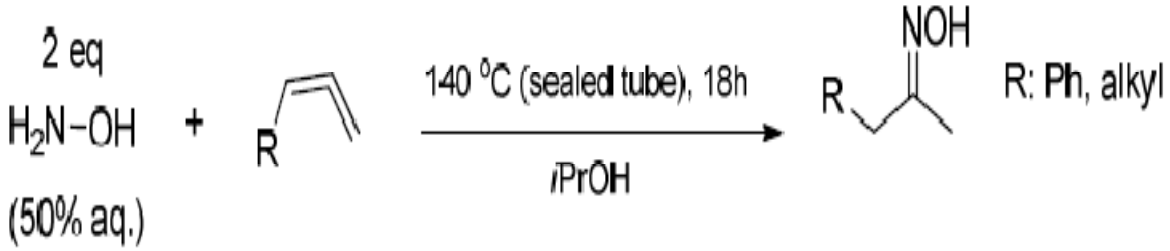
Scheme 3

The synthesis of oximes from ketones involves a reaction with hydroxylamine hydrochloride and sodium acetate/sodium sulphate resulting oximes are isolated in excellent purity [84].



Scheme 4

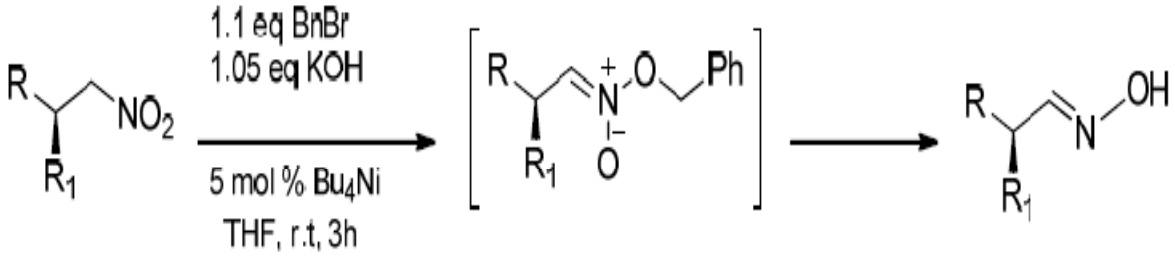
FROM ALLENES



Scheme 5

The reaction of monosubstituted allenes with aqueous hydroxylamine gives oximes [85]

FROM NITRO ALKANES



Scheme 6

A convenient, environmentally friendly method for the synthesis of optically active aldoximes and nitriles starting from chiral nitroalkanes was developed [86].

REACTIONS OF OXIME DERIVATIVES

The Beckman rearrangement is well known as the most characteristic reaction of oxime derivatives and using this reaction, amides are

 ISSN: 2581-5385

produced when oximes or their derivatives react with either acid or base. This rearrangement reaction is used not only for synthesis of amides but also for synthesis of various heterocyclic compounds using *N*-alkyl nitrilium ion intermediates. Thus, substitution on the nitrogen atom of the oxime can be easily achieved via the Beckman rearrangement (**Figure 13**), oxime derivatives can be widely used as electrophilic amination reagents for synthesis of amines and heterocyclic compounds containing nitrogen atoms.

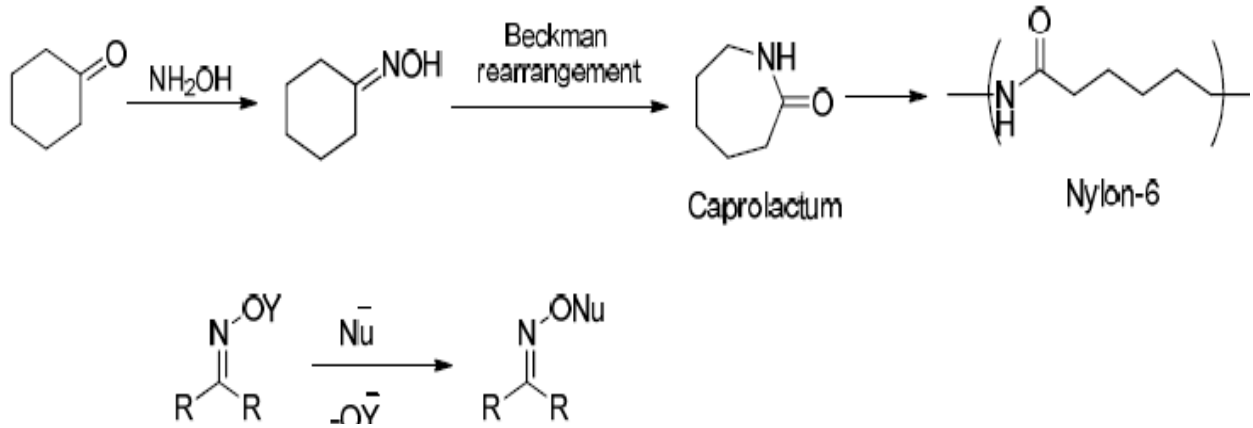
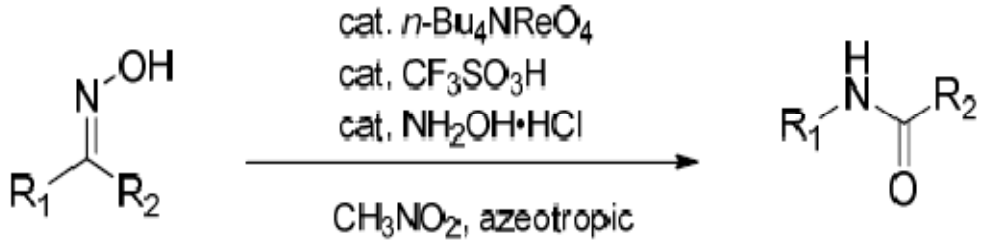


Figure 13.Reactions of oximes

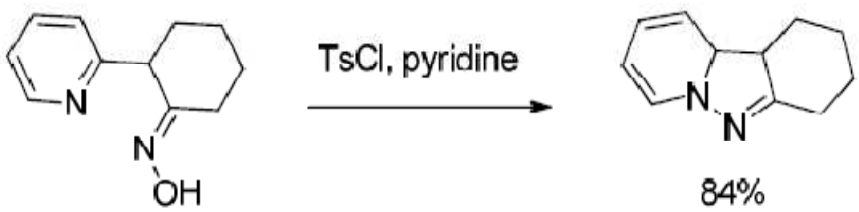
SUBSTITUTION ON OXIME NITROGEN ATOMS BY SN2 TYPE NUCLEOPHILIC REACTION

It is possible to catalytically induce a Beckmann rearrangement when n-Bu4NReO$_4$ and sulphonic acid were reacted with different oximes, resulting in the generation of various perrhenic acid esters of oximes. Indeed, the Beckmann rearrangement occurred and amides were produced when oximes were reacted with n-Bu4NReO$_4$ and trifluoromethane sulfonic acid (CF3SO3H) in a highly polar solvent such as nitromethane [87] (Scheme 7).



Scheme 7

On the other hand, there are several reports in which N-N or N-S bond formation took place at the nitrogen atom of oxime. For instance, it has been reported that when an oxime having pyridyl group was reacted with tosyl chloride and pyridine (Scheme 8), a cyclic compound was produced from anti-isomer of the oxime, while no cyclization occurred when the syn-isomer was used [88].

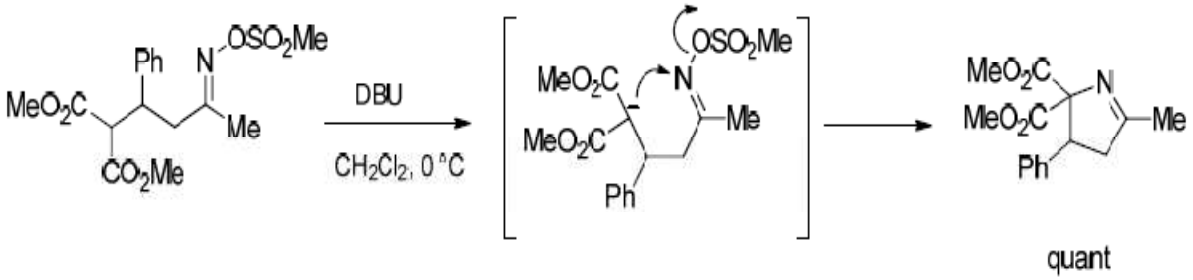


 ISSN: 2581-5385

Scheme 8

SYNTHESIS OF CYCLIC IMINES USING NUCLEOPHILIC SUBSTITUTION REACTION OF OXIMES

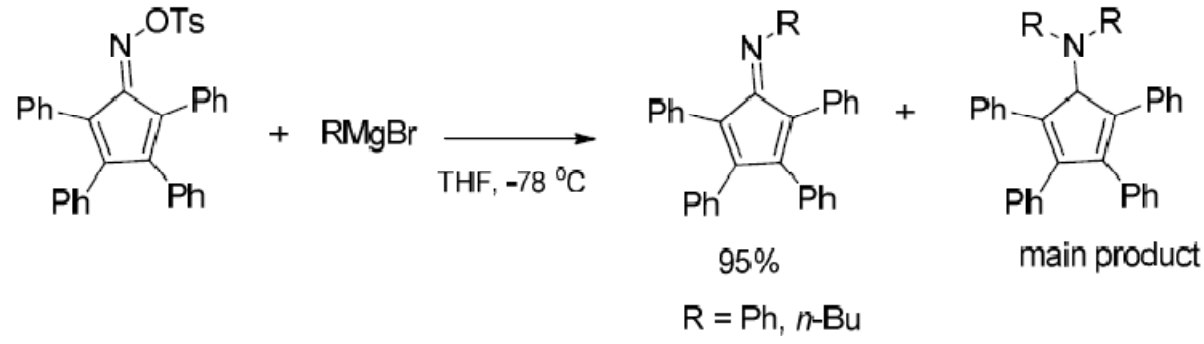
When (E)-*O*-methylsulfonyloximes of ketones having active methylene moieties at the γ and δ positions, were treated with DBU, an intramolecular nucleophilic substitution took place, resulting in the quantitative production of five and six membered cyclic imines (Scheme 9). However, when the corresponding Z isomers were used, no cyclic compounds were obtained at all. Moreover, when reaction conditions were set for being more restricted, various reaction products such as Neber reaction products were yielded.



Scheme 9

ALKYLATION OF OXIME DERIVATIVES BY GRIGNARD REAGENTS: SYNTHESIS OF THE PRIMARY AMINES

Nucleophilic species can attack on the oxime nitrogen atoms indicates that Nalkylation can be undertaken by organometallic compounds using oxime derivatives that rarely undergo the Beckmann Rearrangement. A report, in which a similar attempt was made using *O*-tolylsulfonyl oxime derived from tetraphenylcyclopenta dienone as described below. However, it was reported that the reaction mechanism was through addition/elimination but not substitution reactions (Scheme 10) In this method, large excess amounts of Grignard reagents were required to make the reaction take place. Moreover, mono *N*-alkylation could dominantly occur only when an aromatic Grignard reagent was used, while dialkylated compound was a major reaction product in cases involving an alkyl Grignard reagent. This is because *N*-alkylimines formed by monoalky lation are far more easily susceptible to addition reactions than *O*methylsulfonyl oxime.



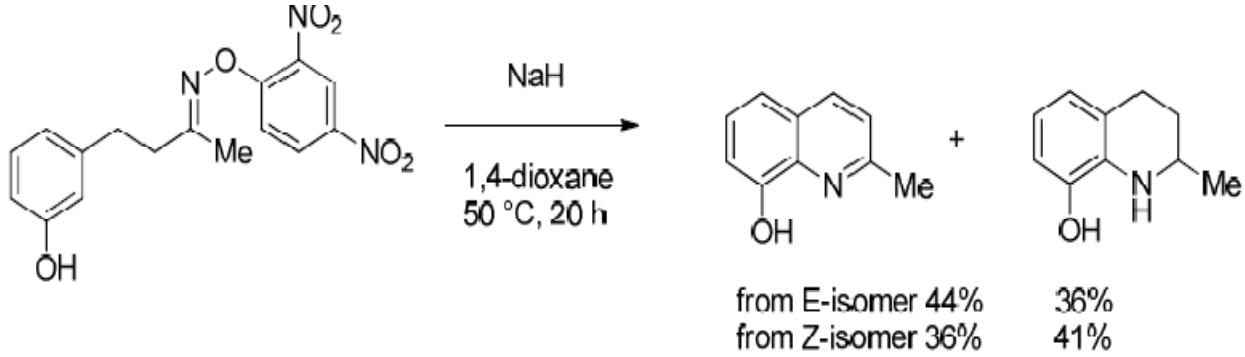
Scheme 10

RADICAL CYCLIZATION REACTION OF OXIMES BY ONE ELECTRON REDUCTION

SYNTHESIS OF 8-QUINOLINOL DERIVATIVES

 ISSN: 2581-5385

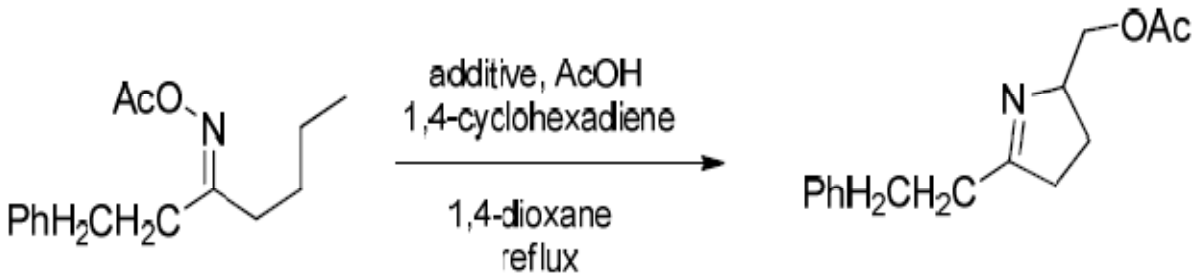
In the nucleophilic substitution reactions described above, it was considered to be important to maintain a good balance between nucleophiles and leaving groups on the oxime N atoms. Therefore, we attempted substitution using oxime derivatives possessing various leaving groups. During this process, we found that 8-quinolinol and its tetrahydro derivative were formed when *m*-hydroxyphenethyl ketone *O*-2,4-dinitrophenyloxime was treated with sodium hydride (NaH). However, it was also found that no 6-quinolinol, one of the position isomers, was produced at all. Moreover, it was also demonstrated that both E- and Z-isomers of *O*-2,4-dinitrophenyloxime exerted a similar reactivity (Scheme 11) [89].



Scheme 11

CATALYTIC RADICAL CYCLIZATION REACTION OF OXIME DERIVATIVES

Oxime was treated with acetic acid in the presence of 1,4-cyclohexadiene to yield an acetoxy substituted dihydropyrrole as a product of the nucleophilic substitution reaction, and its hydrogenated compound were produced (Scheme 12) [90].

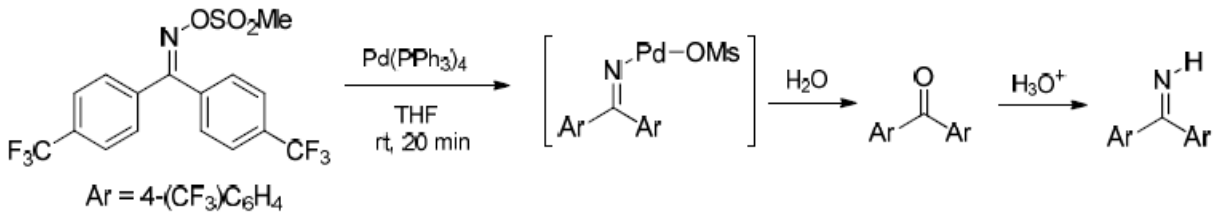


Scheme 12

OXIDATIVE ADDITION REACTION OF OXIMES TO PALLADIUM CATALYSTS

Since, low valent transition metal complexes are good electron donors, it was expected that alkylideneamino metal complexes can be formed when *O*-substituted oximes are oxidatively added to low valent transition metal complexes. In fact, when benzophenone *O*-mesyloxime was reacted with an equimolar amount of $Pd(PPh_3)_4$, followed by addition of water to the reaction mixture, imine was quantitatively obtained (Scheme 13). This result showed that an alkylideneaminopalladium complex was formed as an intermediate [91].

 ISSN: 2581-5385



Scheme 13

CONCLUSION

Free radicals are responsible for causing a large number of diseases including cancer [92], cardiovascular disease [93], neural disorders [94], alzheimer's disease [95], mild cognitive impairment [96], Parkinson's disease [97], alcohol induced liver disease [98], ulcerative colitis [99], aging [100] and atherosclerosis [101].

Protection against free radicals can be enhanced by ample intake of dietary antioxidants. Antioxidants are of great benefit in improving the quality of life by preventing or postponing the onset of degenerative diseases. In addition, they have a potential for substantial savings in the cost of health care delivery. It is reasonable to assume that compounds functionalized with groups endowed with potential antioxidant properties could be useful as new drugs for chemoprevention and chemotherapy.

There is, however, a growing consensus among scientists about the synthetic antioxidants. In connection to this oxime-containing molecules caught our attention, as they appear to be amenable to biotransformation and conjugations with organic and inorganic molecules. They have important pharmaceutical and synthetic applications. Oxime moiety offers a convenient structural moiety for probing an element of the pharmacophore which had proven to be of considerable importance in the medicinal chemistry. The properties of these classes of compounds have been recently exploited with the aim to design and develop novel therapeutic agents that can serve for the evaluation of novel candidate drugs for the treatment of various diseases. For example, furan oximes were found to inhibit DNA, RNA, and protein synthesis in lipoid leukemia cells [102,103] Naringenin oximes were also shown to possess antioxidant activity [104].

REFERENCES

[1]. Halliwell, B.; Gutteridge, J. M. C. 1999, *Free radicals in biology and medicine* (3rd ed.). Oxford University Press.
[2]. Langseth, L. From the Editor: 1993, *Antioxidants and Diseases of the Brain. Antioxidant Vitamins Newsletter*.
[3]. Halliwell, B. *Lancet.* 1994, 344, 721.
[4]. Rock, C. L.; Jacob, R. A.; Bowen, P. E. *J. Am. Diet. Assoc.* 1996, 96, 693.
[5]. Mc Cord, J. M. *Am J Med.* 2000, 108, 652.
[6]. Rao, A. L.; Bharani, M.; Pallavi, V. *Adv. Pharmacol. Toxicol.* 2006, 7, 29.
[7]. Stefanis, L.; Burke, R. E.; Greene, L. A. *Curr Opin Neurol.* 1997, 10, 299.
[8]. Valko, M.; Rhodes, C. J.; Moncol, J.; Izakovic, M.; Mazur, M. *Chem. Biol. Interact.* 2006, 160, 1.
[9]. Lovell, M. A.; Ehmann, W. D.; Buffer, B. M.; Markesberry, W. R. *Neurology.*1995, 45,1594.
[10]. Freeman, B. A.; Crapo, J. D. *Lab. Invest.* 1982, 47, 412.
[11]. Sies, H. *Exp.Physiol.,* 1997, 82, 291.
[12]. Hurrell, R. *J. Nutr.* 2003, 133, 2973.
[13]. Vertuani, S.; Angusti, A.; Manfredini, S. *Curr. Pharm. Des.* 2004, 10, 1677.

 ISSN: 2581-5385

[14]. Kaczmarski, M. J.; Wojicicki, L.; Samochowiee, T.; Dutkiewicz, Z. *Pharmazie*. 1999, 54, 303.

[15]. Dekkers, J. C.; van Doornen, L. J. P.; Han, C.G. K. *Sports. Med.* 1996, 21, 213.

[16]. Flagg, E.W.; Coates, R. J.; Greenberg, R. S. *J Am Coll Nutr*. 1995, 14, 419.

[17]. Cherubini, A.; Vigna, G. B.; Zuliani, G.; Ruggiero, C.; Senin, U.; Fellin, R. *Curr Pharm Des.* 2005, 11, 2017.

[18]. Kader, A.; Zagory, D.; Kerbel, E. *Crit. Rev. Food Sci. Nutr.* 1989, 28, 1.

[19]. Zallen, E.; Hitchcock, M.; Goertz, G. *J. Am. Diet. Assoc.* 1975, 67, 552.

[20]. Iverson, F. *Cancer. Lett.* 1995, 93, 49.

[21]. Robards, K.; Kerr, A.; Patsalides, E. *Analyst.* 1988, 113, 213.

[22]. Del Carlo, M.; Sacchetti, G.; Di Mattia, C.; Compagnone, D.; Mastrocola, D.; Liberatore, L.; Cichelli, A. *J. Agric. Food. Chem.* 2004, 52, 4072.

[23]. Boozer, C. E.; Hammond, G. S.; Hamilton, C. E. *J. Amer. Chem. Soc.* 1955, 35, 3233.

[24]. Eren, G.; Unlu, S.; Nunez, M. T.; Labeaga, L.; Ledo, F.; Entrena, A.; Lu, E. B.; Costantino, G.; Sahin, M. F. *Bioorg. Med. Chem.* 2010, 18, 6367.

[25]. Gordon, E.; Barrett, R. W.; Dower, W. J.; Foder, S. P. *J. Med. Chem.* 1994, 37, 1485.

[26]. Sayin, U.; Yuksel, H.; Ozmen, A.; Birey, M. *Radiat. Phys. Chem.* 2010, 79, 1220.

[27]. Mikhaleva, A. I.; Zaitsev, A. B.; Trofimov, B. A. *Russ. Chem. Rev.* 2006, 75, 797.

[28]. Sayin, U.; Yuksel, H.; Ozmen, A.; Birey, M. *Radiat. Phys. Chem.* 79, 2010, 1220.

[29]. Mikhaleva, A. I.; Zaitsev, A. B.; Trofimov, B. A. *Russ. Chem. Rev.* 2006, 75, 797.

[30]. Lorke, D. E.; Kalasz, H.; Petroianu, G. A.; Tekes, K. *Curr. Med. Chem.* 2008, 15, 743.

[31]. De L. P. R.; Barcelos, R. P.; De Bem, V. S.; Carratu, A. F.; Bresolin, L.; Da Rocha, J. B. T.; Soares, F. A. A. *Life Sci.* 2008, 83, 878.

[32]. Quiroga, A. G.; Cubo, L.; de Blas, E.; Aller, P.; Navarro- Ranninger, C. *J. Inorg. Biochem.* 2007, 101, 104.

[33]. Saglam, N.; Colak, A.; Serbest, K.; Dulger, S.; Guner, S.; Karabocek, S.; Belduz, A. O. *BioMetals.* 2002, 15, 357.

[34]. Moore, R. B.; Chapman, J. D.; Mokrzanowski, A. D.; Arnfield, M. R.; McPhee, M. S.; McEwen, A. J. *Br. J. Cancer.* 1992, 65, 491.

[35]. Colak, A,; Terzi, Ü,; Col, M,; Karaoglu, Ş. A.; Karaböcek, S.; Küçükdumlu, A.; Ayaz, F. A. *Eur. J. Med. Chem.* 2010, 45, 5169.

[36]. Obata, T.; Fujii, K.; Fukuda, Y.; Tsutsumiuchi, K. *Jpn. Patent.* 1991, 03240775.

[37]. Drabek, Offen J. G. D. E. *Jpn. Patent.* 1992, 4200742.

[38]. Hamaguchi, H.; Kajihara, O.; Katoh, M. *J. Pestic. Sci.* 1995, 20, 173.

[39]. Park, H. J.; Lee, K.; Park, S. J.; Ahn, B.; Lee, J. C.; Cho, H. Y.; Lee, K. I. *Bioorg. Med. Chem. Lett*. 2005, 15, 3307.

[40]. Li, Y.; Zhang, H. Q.; Liu, J.; Yang, X. P.; Liu, Z. J. *J. Agric. Food Chem.* 2006, 54, 3636.

[41]. Swanson, M. B.; Ivancic, W. A.; Saxena, A. M.; Allton, J. D.; O'Brien, G. K.; Suzuki, T.; Nishizawa, H.; Nokata, M. *J. Agric. Food Chem.* 1995, 43, 513.

[42]. Motoba, K.; Nishizawa, H.; Suzuki, T.; Hamaguchi, H.; Uchida, M.; Funayama, S. *Pestic. Biochem. Physiol.* 2000, 67, 73.

[43]. Cho, J. R.; Kim, Y. J.; Ahn, Y. J.; Yoo, J. K.; Lee, J. O. *J. Appl. Entomol.* 1995, 31, 40.

[44]. Watanabe, M.; Kuwata, T.; Okada, T.; Ohita, S.; Asahara, T.; Noritake, T.; Fukuda, Y. *Jpn. Patent.* 2001, 2001233861.

[45]. Kim, Y. J.; Lee, S. H.; Lee, S. W.; Ahn, Y. J. *Pest Manage. Sci.* 2004, 60, 1001.

[46]. Chen, L.; Ou, X. M.; Mao, C. H.; Shang, J.; Huang, R. Q.; Bi, F. C.; Wang, Q. M. *Bioorg. Med. Chem.* 2007, 15, 3678.

[47]. R. Plate, *"Eur Pat Appl EP"* 1993, 559, 279.

[48]. Lauer, M.; Zipperer, B.; Goetz, N. *Eur. Pat. Appl.* 1991, EP 409,077.

 ISSN: 2581-5385

[49]. Benoit, R.; Sauter H.; Kirstgen, R. *Eur Pat Appl* 1992, EP 498,188.

[50]. Lazonova, K.; Vasilev, G.; Kalcheva, V.; Nauk, D. B. *Eur. J. Med. Chem.* 1992, 44, 115.

[51]. McOmie, J. F. W.; "Protective Groups in Organic Chemistry", Plenum Press, London and New York, 1973, 46.

[52]. Cameron, M.; Gowenlock, B. G.; Boyed, A. S. F. *J. Chem. Soc. Perkin Trans.* 1996, 2, 2271.

[53]. Veronese, A. C.; Vecchiati, G.; Sferra S.; Orlandini, P. *Synthesis* 1985, 3, 300.

[54]. Ny Sin,; Brian, L.; Venables,; Keith, D.; Combrink, H. B.; Gulgeze,; Yu K. L.; Rita L. C.; Thuring, J.; Wanga, X. A.; Yang, Z.; Zadjura, L.; Marino, A.; Kadow, K. F.; Cianci, C. W.; Clarke, J.; Genovesi, E. V.; Medina, I.; Lamb, L.; Krystal, M.; Meanwell, N. A. *Bioorg. Med. Chem. Lett.* 2009, 19, 4857.

[55]. Liang, J. H.; Dong, L. J.; Wang, H.; An K.; Li X. L.; Yang, L.; Yao G. W.; Xu, Y. C. *Eur. J. Med. Chem.* 2010, 45, 3627.

[56]. Robertson, D.W.; Krushinski, J. H.; Beedle, E.E.; Leander, J. D.; Wong, D.T.; Rathbun, R. C. *J. Med. Chem.* 1986. 29, 1577.

[57]. Karakurta, A.; Dalkaraa, S.; zalpb, M. O.; zbeyc, S. O.; Stables, E. K. P. *Eur. J. Med. Chem.* 2001, 36, 421.

[58]. Acharya, J.; Gupta, A. K.; Mazumder, A.; Dubey, D. K. *Eur. J. Med. Chem.* 2009, 44, 1326.

[59]. Bhandari, K.; Srinivas, N.; Shiva Keshava, G. B.; Shukla P. K. *Eur. J. Med. Chem.* 2009, 44, 437.

[60]. Musilek, K.; Holas, O.; Kuca, K.; Jun, D.; Dohnal, V.; Opletalova, V.; Dolezal, M. *Bioorg. Med. Chem. Lett.* 2007, 17, 3172.

[61]. Bunton, C. A.; Robinson, L.; Stam, M. J. *J. Am. Chem. Soc.* 1970, 92, 7393.

[62]. Nishijimaa, K.; Shinkawaa, T.; Yamashita, Y.; Satoa, N.; Nishidaa, H.; Kato K.; Onukia, Y.; Mizota, M.; Ohtomob, K.; Miyanoc, S. *Eur J. Med. Chem.* 1998, 33, 267.

[63]. Holland, H.L.; Kumaresan, S.; Tan, L.; Nzar, V. C. O. *J. Chem. Soc.* 1992, 113, 585.

[64]. Lees, A.; Sen, G.; Acosta A. L. *Vaccine* 2006, 24, 716.

[65]. Metodiewa, D.; Koceva-Chyla, A.; Kochman, A.; Skolimowski, J.; Joswiak, Z. *Anti-cancer Res.* 1999, 99, 1255.

[66]. Metodiewa, D.; Kochman, A.; Karolczak, S. *Biochem. Mol. Biol. Int.*1997, 41, 1067.

[67]. Abele, E.; Lukevics, E. *Chem. Heterocycl. Compd.* 2001, 37, 141.

[68]. Abele, E.; Abele, R.; Rubina, K.; Lukevics, E. *Chem. Heterocycl. Compd.* 2005, 41, 137.

[69]. Türkkana, B.; Özyürekb, M.; Benerb, M.; Güc, K. *Spectrochim. Acta Part A.* 2012, 85, 235.

[70]. Stowe, B. B. F. *Chem. org. Nat. Stoffe.* 1959, 17, 248.

[71]. Virtanen, A. I.; Saris. N. E. *Acta Chem. Scand.* 1955, 9, 337.

[72]. N. Rautanen. In Encyclopedia of plant physiology. Editor, I . Wlothes. Springer, Berlin. 1958, 8, 212. P. W. Wilson. In Encyclopedia of plant physiology. Editor, I. Mothes. Springer, Berlin. 1958, 8, 9.

[73]. Frutos, R. P.; Spero, D. M. *Tetrahedron Lett.* 1998, 39, 2475.

[74]. Sasatani, S.; Miyazak, T.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* 1983, 24, 4711.

[75]. Das, M. K.; Bhaumik, A. *Indian J Chem. Sect. B*. 1997, 36, 1020.

[76]. Miyabe, H.; Ushiro, C.; Naito, T. *Chem. Commun.* 1997, 21, 1789.

[77]. Bose, D. S.; Vanajatha, G. *Synth. Commun.* 1998, 28, 4531.

[78]. Bougrin, K.; Loupy, A.; Souaoui, M. *Tetrahedron.* 1998, 54, 8055.

[79]. Hwu, J.R.; Tseng, W. N.; Patel, H. V.; Wong, F.F.; Horng, D. N.; Liaw, B. R.; Lin, L. C. *J. Org. Chem.* 1999, 64, 2211.

 ISSN: 2581-5385

[80]. Beckman, E. *Chem. Ber.* 1890, 23, 1680.
[81]. Beckman, E. Liebigs. *Ann. Chem.* 1909, 365, 200.
[82]. Ballini, R.; Barboni, L.; Filippone, P. *Chem. Lett.* 1997, 26, 475.
[83]. Sharghi, H.; Hosseini, M. *Synthesis,* 2002, 1057.
[84]. Zhao, H.; Vandenbossche, C. P.; Koenig, S. G.; Singh, S.P.; Bakale, R. P. *Org. Lett.* 2008, 10, 505.
[85]. Moran, J.; Pfeiffer, J. Y.; Gorelsky, S. I.; Beauchemin, A. M. *Org. Lett.* 2009, 11, 895.
[86]. Czekelius, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* 2005, 44, 612.
[87]. Kusama, H.; Yamashita, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* 1995, 68, 373.
[88]. Ishida, Y.; Sasatani, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* 1983, 24, 255.
[89]. Uchiyama, Y.; Hayashi, K.; Narasaka. *Synlett.* 1997, 12, 445.
[90]. Yoshida, M.; Kitamura, M.; Narasaka, K. *Chem. Lett*. 2002, 10, 144
[91]. Tsutsui, H.; Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* 2002, 75, 1451.
[92]. Kinnula, V. L.; Crapo, J. D. *Free Radic. Biol. Med.* 2004, 36, 718.
[93]. Singh, U.; Jialal, I. *Pathophysiology.* 2006, 13, 129.
[94]. Sas, K.; Robotka, H.; Toldi, J.; Vecsei, L. *J. Neurol. Sci.* 2007, 257, 221.
[95]. Smith, M. A.; Rottkamp, C. A.; Nunomura, A.; Raina, A. K.; Perry, G. *Biochim Biophys. Acta.* 2000, 1502, 139.
[96]. Guidi, I.; Galimberti, D.; Lonati, S.; Novembrino, C.; Bamonti, F.; Tiriticco, M.; Fenoglio, C.; Venturelli, E.; Baron, P.; Bresolin, N. *Neurobiol. Aging.* 2006, 27, 262.
[97]. Bolton, J.L.; Trush, M. A.; Penning, T. M.; Dryhurst, G.; Monks, T.J. *Chem. Res. Toxicol.* 2000, 13, 135.
[98]. Arteel, G.E. *Gastroenterol.* 2003, 124, 778.
[99]. Ramakrishna, B.S.; Varghese, R.; Jayakumar, S.; Mathan, M.; Balasubramanian, K.A. *J. Gastroenterol. Hepatol.* 1997, 12, 490.
[100]. Hyun, D.H.; Hernandez, J. O.; Mattson, M. P.; De Cabo, R. *Aging Res. Rev.* 2006, 5, 209.
[101]. Upston, J. M.; Kritharides, L.; Stocker, R. *Prog. Lipid Res.* 2003, 42, 405.
[102]. Abele, E.; Lukevics, E. *Chem. Heterocycl. Compd.* 2001, 37, 141.
[103]. Abele, E.; Abele, R.; Dzenitis, O.; Lukevics, E. *Chem. Heterocycl. Compd.* 2003, 39, 3.
[104]. Türkkan, B.; Ozyurek, M.; Bener, M.; Guclu, K.; Apak, R. *Spectrochimica Acta Part A.* 2012, 85, 235.

 ISSN: 2581-5385