1.1. INTRODUCTION

The efficiency of benzophenone analogues as chemotherapeutic agent especially as inhibitors of HIV-1 reverse transcriptase RT,\textsuperscript{1-3} cancer\textsuperscript{4-8} and anti-inflammatory\textsuperscript{9,10} is well established and their chemistry has been extensively studied. Benzophenones and their analogues are usually obtained from natural products\textsuperscript{11-14} or by synthetic methods.\textsuperscript{1, 4-7, 15} The importance of these substances is fundamentally due to the diverse biological\textsuperscript{1-10} and chemical\textsuperscript{17,18} properties that they possess. Subsequently, benzophenone analogues are frequently used in medicine\textsuperscript{19,20} and industry.\textsuperscript{21-23}

1.2. ANTI HIV AGENTS

HIV is etiological agent responsible for the onset of AIDS.\textsuperscript{24} Since two decades, AIDS was first reported by US CDC and the retrovirus called HIV is the causative agent in AIDS.\textsuperscript{25, 26} In short time, AIDS increased to epidemic proportions throughout the world with more than 40 million causalities and claiming more than 22 million lives till now.\textsuperscript{27}

The search for safe and effective treatments for HIV infection has become a major focus for drug discovery groups world wide. Investigations into molecular biology of HIV have identified a number of vital targets for drug design, such as RT, protease and integrase enzymes and regulatory proteins. RT, an essential enzyme in the replication cycle of HIV has been frequently targeted as a site for possible drug design.\textsuperscript{1} The majority of drugs under clinical use are inhibitors of such enzyme.\textsuperscript{28} These inhibitors are classified into two groups, NRTIs and NNRTIs. The NRTIs viz., AZT, DDI and DDC are used in the treatment of HIV. However, its usage is compromised by side effects, which are attributed to inhibition of cellular DNA polymerases.\textsuperscript{29} The toxicity of NRTIs has stimulated considerable interest into alternative approaches in search for effective NNRTIs, which are structurally diverse group of compounds that inhibit the enzyme. In contrast to the former group, NNRTIs present low toxicity and high selectivity.\textsuperscript{30} Two NNRTIs which focused upon are nevirapine (dipyridodiacepinone)\textsuperscript{31} and benzophenone derivatives,\textsuperscript{1} these drugs inhibit RT by structurally blocking the active sites and are non-competitive inhibitors.\textsuperscript{31} Each NNRTIs has its own unique structural characteristic allowing it to interact with the surrounding active site. This induces the formation of unfavorable contacts between the enzymes. In addition, NNRTIs have been shown to bind RT without changing its structure, while still displaying inhibition of its polymerizing ability.
Based on these explorations, Wyatt et al\textsuperscript{1} have synthesized a series of benzophenone derivatives and evaluated them as inhibitor of HIV-1 RT and the growth of HIV-1 in MT-4 cells. Besides they have proposed a binding conformation through the use of SAR and computational chemistry techniques.

The SAR indicated that major interactions of benzophenone analogue 1 with the RT enzyme are through hydrogen bonding of the amide and benzophenone carboxyls and π-orbital interactions with the benzophenone nucleus and an aromatic function separated from the benzophenone by a suitable spacer group.

Anti HIV activity has been detected in an extract of *Calophyllum lanigerum* (Guttiferae).\textsuperscript{2} Organic extracts from four other members of the Guttiferae—*Symphonia globulifera, Garcinia livingstonei, Garcinia ovalifolia* and *Clusia rosea* were also found active to the primary screen. Extensive phytochemical studies have shown Garcinia to be a rich source of benzophenones.\textsuperscript{32, 33}

Bioessay and guided fractionation of the *Symphonia globulifera* extract tracked the HIV inhibitory activity to a series of new isoprenylated benzophenone derivatives, named as guttiferones (2a-c and 3).
Fractionation of the *Garcinia livingstonei* extract provided guttiferone 2a as the primary anti HIV active constituent, while two benzophenone compounds, guttiferone 4 and the known metabolite isoxanthochymol 5 were obtained from *Garcinia ovalifolia*. *Clusia rosea* extracts were found to contain guttiferone 4 and xanthochymol 5. All of these analogues showed a similar level of activity, except for compound 5, which was inactive. The active compounds inhibited the cytopathic effects of in vitro HIV infection in human lymphoblastic leukemia cells with EC$_{50}$ values of 1-10 µg/ml, while cytotoxicity occurred at concentration greater than 50 µg/ml.

Recently benzophenone analogue 6 has been reported as anti HIV agent. It has shown anti HIV activity in the range IC$_{50}$ = 1-1000 nM against wild type mutant viruses.

1.3. ANTICANCER AGENTS

Cancer is caused by stepwise accumulation of mutations that effect growth control, differentiation and cell survival. The term cancer refers to more than 100 forms of diseases. Almost every tissue in the body can spawn malignancies. In order to discover novel antitumor compounds with different pharmacophores from currently used antitumor drugs and to develop them as antitumor agents with potent activity and low toxicity, 2500 compounds from Tokyo institute’s chemical library were randomly screened for cytotoxic activity. Chemoprevention is the attempt to use natural and
synthetic compounds to intervene in the early pre-cancerous stages of carcinogenesis, before invasive disease begins.\textsuperscript{37}

Inhibition of the enzyme, farnesyltransferase has become a major strategy for the development of novel potential anticancer drugs.\textsuperscript{38, 39} Farnesyltransferase, catalyzes the transfer of a farnesyl residue from farnesylpyrophosphate to thiol of cysteine side chain of proteins bearing C-terminal the CAAX-tetrapeptide sequence (C, cysteine, AA, aliphatic amino acid and X, serine or methionine).\textsuperscript{40} Farnesylation is a prerequisite for transforming activity of oncogenic Ras which is found in approximately 30\% of all cancers in humans. The SAR of novel class of CAAX peptidomimetic farnesyltransferase inhibitors based on benzophenone scaffold has been described.\textsuperscript{41, 42} For instance, Schlitzer \textit{et al}\textsuperscript{6} have developed benzophenone analogues 7\textsubscript{a} and 7\textsubscript{b} as farnesyltransferase inhibitors.

\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}

Compound 7\textsubscript{a} exhibited significant activity, on the other hand when a sequence of the two elements of amide moiety connecting the alkyl chain in 7\textsubscript{a} is inverted from amide nitrogen-carbonyl group to carbonyl group-amide nitrogen as in 7\textsubscript{b} displayed 2.5 fold times more activity than 7\textsubscript{a}. The binding model of compound 7\textsubscript{a} suggests that the 2-acylamino benzophenone moiety occupies the peptide-binding site of the farnesyltransferase while the alkyl chain of the terminal palmitoyl residue (lipophilic moiety) is located in the farnesyl binding cleft.

Nitro substituted benzophenone analogues exhibit significant invivo antitumor activity and they have been reported to show activity as immunomodulators.\textsuperscript{42, 43} Based on these reports, invitro and invivo studies of novel nitro and amino substituted benzophenones have been investigated as potential anticancer agents.\textsuperscript{44} Nitro benzophenone derivative 8 (\textit{GI}_{50} = 16.8 \text{ ng/ml for P388 and GI}_{50} = 1.26 \text{ ng/ml for PC-6}) and 9 (\textit{GI}_{50} = 23 \text{ ng/ml for P388 and GI}_{50} = 4.89 \text{ ng/ml for PC-6}) showed strong cytotoxic activity while the corresponding aminobenzophenone derivatives showed weak activity. The nitro and carbonyl moieties in this skeleton are considered to be essential for
cytotoxic activity. Also compound 8 and 9 were tested against murine P388 leukemia by intraperitontial administration. Increase in life span (ILS) was calculated and it was found to be 6 and 36% for compounds 8 and 9 respectively.

8

To evaluate the intensity of the side effects of compounds, the body weight loss (BWL) was utilized as a parameter of toxicity. The maximum rate of body weight loss (BWL_{max}) values for 8 and 9 were found to be 1.2 and 7.9% respectively in two days for 600x2 dose mg/kg. Compound 9 showed moderate effect but compound 8 was only slightly active in spite of showing potent cytotoxic activity in vitro. No correlation between in vitro cytotoxic activity and in vivo antitumor activity has been reported.

Natural products of plant origin also offer a wide variety of bioactive compounds that meets the demand for base compound drugs.\textsuperscript{45} Combrestatin A-4, isolated from \textit{Combretum caffrum}\textsuperscript{12} and cryptophycins isolated from blue green algae (Nostoc),\textsuperscript{46} are potent tumor selective class of tubulin-binding antimitotic agents that show excellent activity against MDR, cancer cell lines and against mammary derived tumors.\textsuperscript{47}

Based on the findings phenstatin, a benzophenone type combretastatin A-4 analogue 10a has been synthesized and investigated as a very strong cytotoxic agent comparable to combretastatin A-4.\textsuperscript{12} In view of this, Hsieh \textit{et al}\textsuperscript{4} investigated cytotoxic potential of benzophenone analogues 10b, 11a and 11b, based on a panel of human cancer cell lines. Compounds 10b with methoxy and 11b with amino and methoxy substituents showed more potent cytotoxicity than 10a and slightly less potent than combretastatin A-4.
Compound 11a with amino and chloro substituents showed good activity against various drug resistant cell lines although less active than combretastatin A-4. These cytotoxic activity results conclude that, the introduction of amino group at ortho position enhances cytotoxicity. Besides SAR information revealed that the introduction of an amino group at the ortho position of the benzophenone ring plays an integral role for increased cytotoxic activity.\(^7\)

Cryptophycins interacts in a manner different from those of other tubulin binding anti mitotic agents. For the development of Cryptophycin into useful chemotherapeutic agent, detailed information about the binding domain of the Cryptophycin is essential.

Therefore β- benzophenone analogue of Cryptophycin analogue 12 bearing a photo affinity label for tubulin labeling studies were synthesized.\(^{13}\) In tubulin assembly assay, compound 12 exhibited activity twice that of Cryptophycin and in cytotoxic studies it has reduced activity against breast and HCT-116 cancer cell lines compared to that of Cryptophycin, but was still active in pM or low nM range. This suggests that the addition of benzophenone moiety in Cryptophycin makes the compound a better substrate for the P-gp multi-drug transporter.

In propolis, a resin produced from floral parts of \textit{Clusia rosea}, by the honey bees, contains nemarosone 13, the most abundant poly isoprenylated benzophenone. It
has cytotoxic activity against epitheloid carcinoma, epidermoid carcinoma, PC-3 and CNS cancer\textsuperscript{14} and it is active with IC\textsubscript{50} < 4\textmu g/ml.

\begin{center}
\includegraphics[width=\textwidth]{chapter-1.png}
\end{center}

Matsumoto \textit{et al}\textsuperscript{45} examined the invitro effects of the poly isoprenylated benzophenone analogue isogarcinol 14 isolated from guttifereous plants on cell growth in human leukemia cell lines and it has shown potential growth inhibitory effect.

According to findings, resistance of neoplastic cells towards chemotherapeutic agents is a major obstacle in clinical cancer treatment. A large number of cancer cells are intrinsically resistant to chemotherapy, while others initially respond to treatment but progressively acquire resistance to the drugs used. The best studied mechanism of drug resistance is the over expression of the MDR-1 gene produce P-gp that rejects chemotherapeutic drugs out of the cell using ATP hydrolysis as an energetic source.\textsuperscript{48} P-gp is composed of two homologues halves, each comprising of a membrane domain and a cytosolic domain. The site of ATP binding is present on the cytosolic domain. The presence of carbonyl and hydroxyl groups is required for ATP mimicry. Benzophenones possess this structural requirement for interaction with cytosolic moiety through binding to both steroid and ATP binding sites within NBD\textsubscript{2}, the C-terminal cytoplasmic domain of mouse P-gp. As a result, benzophenone analogues have been isolated from \textit{Davallia solida} and reported as modulators of P-gp.\textsuperscript{49} For instance, 2,4,6-trihydroxy-4'-methoxy benzophenone and 2,4-dihydroxy benzophenone showed high apparent affinity for quenching(K\textsubscript{D} = 1.27).

PKC is a family of phospholipids dependent serine/threonine-specific protein kinases, which plays an important in the control of cell growth, cellular proliferation and gene expression.\textsuperscript{50} As this enzyme has been implicated in the progression of numerous diseases, a selective inhibitor of this, PKC-\beta-II isoenzyme is currently under trial for
treatment of diabetic retinopathy. The usage of PKC inhibitors has been suggested in the treatment of many more diseases ranging from psoriasis to cancer. Benzophenone analogue, balanol 15 has been discovered as PKC-inhibitory fungal metabolite. The novelty of the balanol structure has PKC inhibitors has resulted in a development of synthetic approaches to the natural material.

For example, replacement of the benzophenone carboxylate group in 15 with biosteric equivalents leads to analogue 16 with PKC inhibitory potencies(IC$_{50}$ = 50µM) similar to that of balanol and with modestly enhanced activity in cellular assays. It has been suggested that the balanol might serve as a protein structure used to develop selective kinase inhibitors.

Cathepsin, a soluble lysosomal enzyme, is an aspartyl endopeptidase, that is a member of the pepsin family. Cathepsin has been implicated in a number of disease processes including Alzheimer disease, tumour invention, metastasis and destruction of joint. Cathepsin is overproduced and hypersecreted by breast cancer cells and in vivo studies in mice suggest that the over expression of Cathepsin many be responsible for metastasis in breast cancer. This enzyme may also be involved in the progression of other neoplastic diseases. Cathepsin has been shown to be fibrinolytic and may possess a role in the regulation of celllar insulin-like growth factor actioned by altering the structure or function of insulin like growth factor-binding protein and in regulation of cysteine protease activity. In retrospect of the above observations, Whitesitt et al
have designed and synthesized benzophenone analogue 17 (IC\textsubscript{50} = 210 nM) as the potent and selective non peptide inhibitors of cathepsin to study the role of enzyme in human disease states.

Steroid sulphatase (estrone sulphatase) regulates the local production of estrogens from systemic precursors, such as estrone sulphatase and dehydroepiandrosterone sulphate in normal and malignant breast tissues. There is increasing evidence that in breast and endomaterial tissues the steroid sulphatase pathway is the major source of estrogens, which support the growth of endocrine-dependent tumors. Inhibition of steroid sulphatase is therefore considered as potential new therapeutic agents for the treatment of estrogen-dependent cancers.\textsuperscript{63} Both irreversible and reversible inhibitors of human steroid sulphatase have been reported.\textsuperscript{64} The reversible inhibitors are less potent due to lack of the 3-D structures of steroid sulphatase. Based on the findings, Nussbaumer \textit{et al}\textsuperscript{8} envisaged the design and synthesis of photo labeling ligands for steroid sulphatase to enhance the inhibitory potency. Incorporation of benzophenone substituent in photolabeling substrates has proven to have several advantages.\textsuperscript{65}

![Benzophenone Substrate](image)

To estimate the magnitude of binding affinity of benzophenone based ligands, sulphamates were prepared and tested for their inhibitory potencies, analogously to the successful search for a new steroid sulphatase substrate. Following this approach, 4,4'-benzophenone-o,o'-disulfamate 18 discovered as potent inhibitor of human steroid sulphatase (IC\textsubscript{50} = 0.19\textmu M).\textsuperscript{8}

### 1.4. ANTIMALARIAL AGENTS

Malaria is one of the most threatening tropical diseases which cause between 1.5 and 2.7 million fatal cases per year, particularly among children, primarily in Africa and Asia.\textsuperscript{66} Nearly all fatal cases are caused by \textit{plasmodium falciparum}, the causative agent of \textit{malaria tropica} strains resistant to presently available drugs. Therfore, there is an
urgent need for new agents active against multi-resistant *plasmodium* strains. 2,5-diamino-benzophenone analogue 19a has been investigated as an active agent against multi-resistant strains of *plasmodium* (IC$_{50}$ = 340 nM).$^{67}$

![Chemical Structure of 19a](image)

Wiesner *et al* $^{68}$ have replaced the tolylacetyl residue at the amino group of compound 19a by para-trifluoromethyl phenyl acyl group as in compound 19b resulting in a three fold improvement in antimalarial activity (IC$_{50}$ = 120 nM). This benzophenone analogue is an important compound in the development of novel and potential antimalarial agent.

1.5. ANTIINFLAMMATORY AGENTS

PGs, which are produced by the action of COX enzyme on arachidonic acid, are mediators in the process of inflammation, pain and swelling. COX is the principal target of NSAIDs and metabolites of the COX pathway are widely accepted as mediators of the inflammatory response. Recent studies have shown that COX exists in two isoforms COX-1 and COX-2.$^{69}$ NSAIDs block the formation of PGs and have anti-inflammatory, analgesic and antipyretic activity.$^{70}$ Several attempts to derive COX selective inhibitors from the non-selective NSAIDs like ketoprofen [2-(3-benzoyl-phenyl)-propionic acid], a benzophenone analogue$^{9}$ has been published and is indicated in the treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis at a daily dose of 150-3000 mg. At 150 mg/d its clinical efficacy is comparable to a similar dose of indomethacin (1-(p-chlorobenzoyl)-5-methoxy-2-methylindoile-3-acetic acid), but fewer and less severe adverse effects are observed. Based on these findings, Palomer *et al*,$^{10}$ have synthesized benzophenone analogue 20 having sulphonylvinyl substituent and tested against COX.
It was able to significantly inhibit the COX-1 and COX-2, in the human whole blood assay (IC$_{50}^{\text{COX-2}} = 12.0 \pm 0.7$ µM and IC$_{50}^{\text{COX-1}} = 100 \pm 3.3$ µM).

IL is a protein made by the body. T-helper cells, a kind of white blood cell, produce IL when they are stimulated by an infection. IL makes infection-fighting cells multiply and mature. Patients who use IL have been large increases in their T-cell counts. IL is called as an immune modulator. IL has been described as a pro-inflammatory and anti-inflammatory molecule, a modulator of bone resorption, a promoter of hematopoiesis, and an inducer of plasma cell development.$^{71}$ Aminobenzophenone$^{72}$ and halo aminobenzophenones$^{73}$ are IL and TNF-α inhibitors.

The former are also cytokine inhibitors and are used as in the prophylaxis of asthma, allergy, rheumatoid arthritis, spondylarthrits, gout atherosclerosis, chronic inflammatory bowel diseases, proliferative and inflammatory skin disorders, such as psoriasis and atopic dermatitis. The latter are MAP kinase inhibitors and are useful pharmaceutically for treating TNF-α and IL-1β mediated diseases such as rheumatoid arthritis and disease of bone metabolism example osteoporosis. Based on these reports benzophenone analogues were synthesized as inhibitors of IL. For instance, analogue 21 inhibit IL and TNF-α and useful in the therapy of inflammatory diseases and conditions.
It showed IC$_{50}$ of 31 nM, 5.0 nM, 15 nM and 12.8 nM against IL, TNF-α, PMN-superoxide production in vitro and against p38α MAP kinase, respectively. Nevertheless benzophenone analogue 22 was prepared as AP-1 inhibitors for the treatment of autoimmune diseases and chronic articular rheumatism (IC$_{50}$=110 mM).

Elastin is a connective tissue component that provides elasticity to lung connective tissue, yellow tendon and cartilage of joints. The rate of elastin degradation is greatly enhanced in pulmonary emphysems and rheumatoid arthritis eventually destroying the connective tissue of the lung and joints. Elastase also accelerates inflammation indirectly and contributes to the pathology of rheumatoid factor. Other disease states in which elastase can be implicated are gingivitis and cancer metastasis.

Based on these findings, benzophenones, which are excellent of HLE, were investigated. The topological relationship of these new inhibitors and a substrate for HLE is shown in Figure 1. According to SAR benzophenone analogue 23 (IC$_{50}$ = 1.2x10$^{-7}$ M) is potent inhibitor of HLE and also chemically stable.

LTB$_4$ is a dihydroxylated lipid formed as a product of the 5-lipoxygenase pathway of arachidonic acid metabolism. LTB$_4$ is a potential mediator of inflammation. Elevated amounts of LTB$_4$ have been found in human psoriatic plaque in colonic mucosa of patients with inflammatory bowel disease, in the synovial fluid of arthritic joints and in the sputum of cystic fibrosis patients. A potent and selective
antagonist of LTB\(_4\) would greatly aid in the evaluation of the role of these leukotriene in human disease. Therefore studies and these derivatives have been found to possess potent LTB\(_4\) antagonist activity.\(^{88}\)

\[
\begin{align*}
\text{HOOC} & \quad \text{O} & \quad \text{CH}_2\text{COOH} \\
\text{A} & \quad \text{B} & \quad \text{OC}_{10}\text{H}_{21} \\
\end{align*}
\]

24

\[
\begin{align*}
\text{N} & \quad \text{NH} & \quad \\
\text{N} & \quad \text{N} & \quad \text{H} & \quad \text{NNH} \\
\text{N} & \quad \text{N} & \quad \text{A} & \quad \text{B} \\
\end{align*}
\]

25

The benzophenone analogue 24 with carboxylic acid showed activity in the LTB\(_4\) binding assay (LTB\(_4\) = 27\times10^{-6}\text{M})). On the other hand removal of carboxylic acid residue of 24 reduced the activity. Similarly substitution of the carboxylic acid residue with the acidic tetrazole group gave compound 25 of similar activity (LTB\(_4\) = 20\times10^{-6}\text{M})). This reflects the importance of the acidic group for the inhibition of LTB\(_4\) binding.

1.6. ANTIMICROBIAL AGENTS

Over the past several years the emergence of organisms resistant to nearly all the class of antimicrobial agents has become a serious public concern.\(^9^9\) Since two decades there has been significant increase in the frequency of systematic fungal infection in man. Fungi can produce allergic reactions and also toxins. In view of this, isoprenylated benzophenones, has been isolated from the stem bark of \textit{Garcinia huillensis} grown in Zaire, used in central-African traditional medicine and it has been shown to exhibit chemotherapeutical activity against gram-positive and gram-negative cocci, mycobacteria and fungi.\(^{90}\) Besides isoprenylated benzophenones, at its lower concentration of 500 to 1000 ppm inhibits aflatoxin production in \textit{Aspergillus flavus}, relatively greater than inhibition growth of the fungus.\(^{91}\) Benzophenone analogues suppress \textit{Bacillus bravis} in water waste.\(^{92}\) Encouraged by these findings, Thomas \textit{et al}\(^9^3\) have synthesized 2',3'-dichloro-4,5,6-trimethoxy-2,6'-benzophenone and investigated for controlling phyto pathogenic fungi. At 4 ppm and 16 ppm it showed 100% control of \textit{Erysiphe graminis forma specialis tritici}. Correspondingly 2',3'-dichloro-4,5,6-trimethoxy-2,6'-benzophenone showed 100% control against \textit{Erysiphe graminis forma specialis tritici} at 100 ppm.\(^{94}\)
Recently benzophenone analogues 26 showed 30-60 times more activity than natifine and clotrimazole against *Sporotrichu schenckii*, 2-4 times as active as naftifine and 30-60 times more active than clotrimazole against *Epidermophyton flocassum*.95

Benzophenones were also explored as herbicides and insecticides. For example, 4-methoxy-3,3'-dimethylbenzophenone is a synergistic herbicide which is highly selective for sugar beets and pre-emergence spraying of 6 kg/ha, controlled mono and dicotyledonous weeds by 94% without injuring sugar beets.96 In addition, it exhibits the dechlorination in soil at a 0.5 ppm level.97 On the other hand, 2-chloro-4-methoxy-2'-trifluoroethylbenzophenone have herbicidal activity at 0.3-10 kg/ha with no damage to soyabean, corn or cotton.98 An additional nitro group at meta position showed herbicidal activity against lowland weeds eg., *Flatsedge monochoria* without damage to rice plants.99 Further, hydroxybenzophenones act as insecticides against flies and mosquitoes.100

Recently benzophenone analogue 27 exhibited advantageous pesticidal properties and it is especially suitable for controlling parasites in warm-blooded animals (also humans). It showed a 100% reduction in trichostrongylus infestation at 32 mg/kg101 Benzophenone were evaluated as spermicides at 1% concentration102 and as inhibitors of *coccida* in chickens.103 The polyisoprenylated benzophenone analogue isogarcinol 14 is also reported as antibacterial agents against methicillin-resistant *Staphylococcus aureus*.45
1.7. ANTIOXIDANT AGENTS

Reactive oxygen species, example superoxide, hydrogen peroxide and hydroxyl radicals produced by the sources such as bioreductively activated xenobiotics or by low molecular-weight complexes of transition metals such as iron and copper via the Fenton reagent are byproducts of normal metabolic processes in aerobic environments. These species can exert cytotoxicity by damaging critical cellular components necessary for viability. These oxidants are eliminated by enzymatic and non-enzymatic mechanisms. Imbalances in the detoxification of reactive oxygen species leads to oxidative stress which plays a role in the progression of many neurodegenerative pathologies of the central nervous system, including Parkinson and Alzheimer disease. Phenolic compounds have been found to be among the more active inhibitors in the antioxidants, in this context, exifone or adlone (2,3,4,3',4',5'-hexahydroxybenzophenone) was launched in France, in 1988, for the treatment of cognitive problems and reported to have a number of pharmacological properties. Furthermore, exifone demonstrated remarkable scavenger properties against free radicals. Unfortunately, after reports of severe hepatotoxicity with exifone, in 1990, it was withdrawn from the market.

On the basis of previous results, Sun et al have investigated the antioxidative capacity of six sunscreen benzophenone compounds and they have also shown significant free radical scavenging effect. Garcinia, which is a rich source of benzophenones, also exhibited 60 and 78% free radical scavenging activity at 25 and 50 ppm concentration respectively. This activity garcinia is attributed to their hydrogen donating ability. The antifungal and scavenging reports of garcinia can be commercially exploited and applied to food systems. Further, isogarcinol has also shown antioxidant activity.

1.8. ANTIDIABETIC AGENTS

More than 200 million people afflicted worldwide, diabetes mellitus is the most common of the endocrine diseases. About 90% of the patients are suffering from type 2 diabetes, the non-insulin-dependent diabetes mellitus (NIDDM). Recent studies suggest, controlling hypoglycemia in NIDDM is often not possible, not even by intensive pharmacological intervention with insulin or common antidiabetic agents. Therefore the search for new improved therapeutic approaches represents an extremely important goal.
Inhibition of enzyme, glucose-6-phosphate translocase (G6P-TI) are of interest as potential drugs for the treatment of diabetes type 2 by regulating hepatic glucose production. G6P-TI is a part of the glucose-6-phosphatase (G6Pase) enzyme complex, which catalyzes the cleavage of G6P to liberate glucose in both pathways of endogenous hepatic glucose production and transport protein, which mediates the entry of G6P through the membrane into the endoplasmic reticulum. Natural products of plant origin also offer a wide variety of bioactive compounds that meets the demand for base compound drugs.

Mumbaistatin, 28 isolated from cultures of Streptomyces sp. DSM 11641 is the most powerful natural inhibitor of G6P-TI with IC\textsubscript{50} = 5 nM. (115) In view of this, Kaiser et al\textsuperscript{116} focused on the exploitation of the developed synthetic strategies and building blocks both for the total synthesis of mumbaistatin\textsuperscript{117} itself and for the synthesis of new analogues.

1.9. INDUSTRIAL APPLICATIONS

Benzophenone is an UV absorbing agent that has been used in industry and medicine for more than 30 years.\textsuperscript{118} They exhibit structural, chemical and biological properties of great interest and one of their most important properties is the ability to absorb and dissipate UV radiation.\textsuperscript{19} Benzophenones absorbs radiations in between 200 to 400 nm with maximum absorbance at 288-290 and 325 nm.\textsuperscript{119} The harmful UV radiations having wave lengths of 280 and 400 nm causes most of the skin cancers.\textsuperscript{20} Benzophenones twelve derivatives designated as benzophenone-1 through benzophenone-12, specially benzophenone-3 also known as 2-hydroxy-4-methoxy benzophenone are widely used today in cosmetic products as photostabilizer, as a sunscreen in lotions and hair sprays to protect the skin and hair from UV irradiation, as
they have the ability to absorb photons and rapidly return to the ground state by vibrational relaxation. After returning to their ground state the active molecules in the sunscreen agents can absorb additional photons and repeat the process, thereby protecting the skin from damage by UV radiation.\textsuperscript{120} It is also used as a photostabilizer for agricultural films and paints and is used clinically as a treatment for photodermatoses. Besides benzophenones occurs naturally in food such as Muscat grape and mango. The US food and drug administration has also approved benzophenone-3 for use as an indirect food additive.\textsuperscript{20} Millions of consumers are exposed to benzophenones on a daily basis owing to the widespread use of these compounds in many of the products in the market such as lipsticks, hair spray, hair dye, shampoo and detergent, bars and sunscreen lotions. Based on these investigations Masashi \textit{et al.}\textsuperscript{22} have formulated cosmetics, like eye liners, eye shadows, mascaras, lipstick etc., with good resistance to water and sebum and UV-shielding effect containing the silyl benzophenone derivatives 29.

![Benzophenone Structure](image)

Benzophenones are used in the grey hair preventions as well as at $10^{-4}$ M in vitro promoted melanin formation in mouse B\textsubscript{16} melanoma cells and 45\% stimulation of tyrsinase activity. Although benzophenones are mildly irritating to the skin, the toxicity and clinical data indicate that they are safe for tropical application to humans in cosmetics at current practices of use and concentration.\textsuperscript{121} Although the photoabsorbing activity of benzophenone-3 occurs on the skin, the compound may also be absorbed through the skin and accumulate in the body. An enzmyo pharmacokinetics study of benzophenone-3 in male Sprague-Dawley rats illustrates that benzophenone-3 absorption from gastrointestinal tract was rapid because it was detected in blood 5 min after administration. Tissue distribution studies indicate that the liver contained the highest concentration of free benzophenone-3 followed by kidney and testis respectively. Urine and faecus analysis indicate that urine was the major route of excretion, followed by faecus.\textsuperscript{122}
Hydroxybenzophenones are used in the pharmaceutical and perfumery industry, in the manufacture of agricultural chemicals,\textsuperscript{123} in metallurgical industry\textsuperscript{124} and in photo cross linking of poly olefins.\textsuperscript{125} Hydroxybenzophenones are also used as photoreceptors in electrophotography and it show low residual potential and high photosensitivity in repeated use.\textsuperscript{126} Tetra-hydroxybenzophenones are used in fluorescent lamp tube coating material to absorb UV radiations.\textsuperscript{127} Benzophenones are ultraviolet light stabilizer therefore they are useful for polymers, lacquers, varnishes and coating materials, in separating films or sheets to protect other articles like dyed fabrics, colored photographs etc., against fading and chemical degradation. Yellowing and discoloring of light colored and white paints, enamels and especially unsaturated polyester resins, laminating and molding compounds can be minimized or substantially eliminated by incorporation of substituted benzophenones.\textsuperscript{128} Benzophenones are used as antirust, rot proofing and antifouling agents.\textsuperscript{129} Benzophenones are used in mite control\textsuperscript{130} and in UV curable acrylate paper coating compounds.\textsuperscript{131} Nitrobenzophenone derivatives are used in the preparation of resin, which show good antihalation property and storage stability they are especially used as positive working resistors for making highly integrated circuits.\textsuperscript{132} Active esters of polymer bound 4-hydroxy-3-nitrobenzophenone is useful as acylating reagents in peptide synthesis.\textsuperscript{133} Benzophenone-3 is used in the preparation of dental resin components.\textsuperscript{134}

In petrochemical refineries and chemical industries, there is a potential for the large scale installation of membrane system because of large volumes liquid and the complex separations. Hence White\textsuperscript{23} has developed a lenzing P84 polyimide SRNF membrane \textit{30} and characterized its properties,

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\begin{array}{c}
\text{30}
\end{array}
\]

This membrane is a favorable polymer for fabrication of asymmetric SRNF membranes with good flux rates and high rejections of solutes.
1.10. BIBLIOGRAPHY


