CHAPTER I
INTRODUCTION

The electromagnetic spectrum emitted by the sun ranges from the very short cosmic rays to the very long radio waves and beyond. The ultraviolet (UV) rays, which comprise the shortest of the nonionizing rays, are responsible for most of the photocutaneous changes. This UV radiation can be divided into three categories; UVC, UVB and UVA[1a] (Fig 1.1). The UVC (200-280 nm) although most energetic and most photoactive among the three, however, does not constitute a risk to general population due to ozone filtration in the earth atmosphere. In contrast, some of the mid UV (UVB, 290-320 nm) can penetrate the ozone layer and, therefore, are responsible for most of the cutaneous photobiological events induced by exposure to the sun. They inhibit DNA, RNA and protein syntheses, induce early and delayed erythema responses causing skin cancer, photoaging and immunosuppression.[2-3] Beneficial effects of UV exposure include new pigment formation, which provides some protection and initiation of the vitamin D cascade. The UVB effects are direct in nature and do not require intermediate photosensitizers.[4] This is because DNA, RNA and protein molecules can directly absorb UVB radiation. These rays do not pass through window glass as a rule. Thus a sturdy piece of window glass can prevent all of these responses.

The long UV or UVA rays (320-400 nm) do pass through window glass and produce a significant number of photobiological effects. In contrast to UVB, UVA causes damages to the cells indirectly, the mechanism usually involves the induction of reactive oxygen species.[4-7] UVA rays induce an immediate erythema which diminishes within 2 hours and a delayed erythema response which reaches a peak at 6 hours. This is in contrast to the UVB delayed erythema which tends to reach a peak in 12 to 24 hours.[1]

Penetration of UV radiation into skin varies with wavelength. As depicted in Fig 1.2, it has been found that the radiation near 300 nm (UVB) can penetrate both the stratum corneum and the epidermis and can cause serve burning (erythema) of the skin.

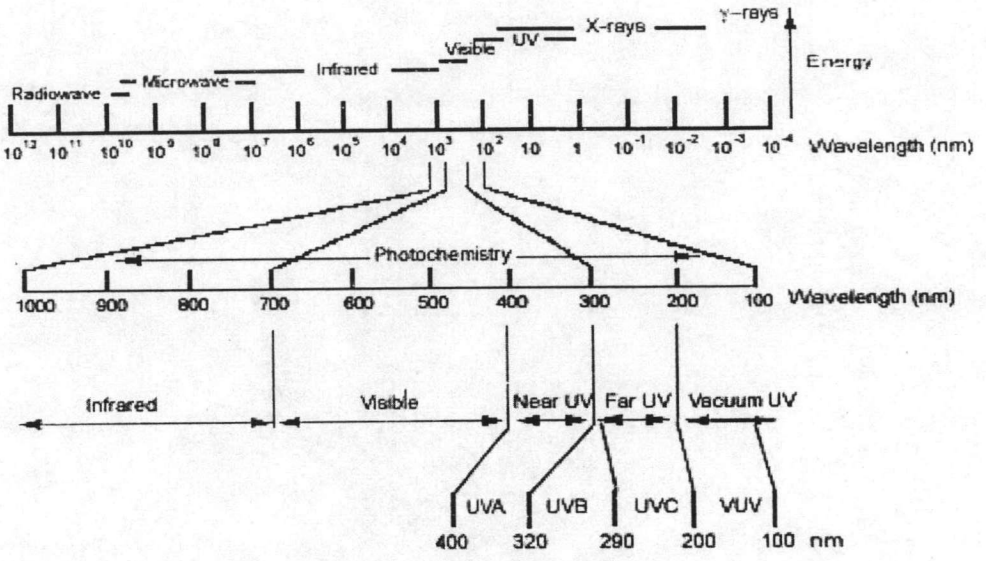


Figure 1.1 Electromagnetic spectrum

Radiation higher than 350 nm starts penetrating the third layer, the dermis, thereby stimulating the formation of melanin, produce tan which protect the skin from an immediate sunburn.[1] Unfortunately, although UVA rays are of lower energy than UVB rays, UVA can penetrate more deeply into the dermis and contributes with UVB to skin cancer and photoaging.

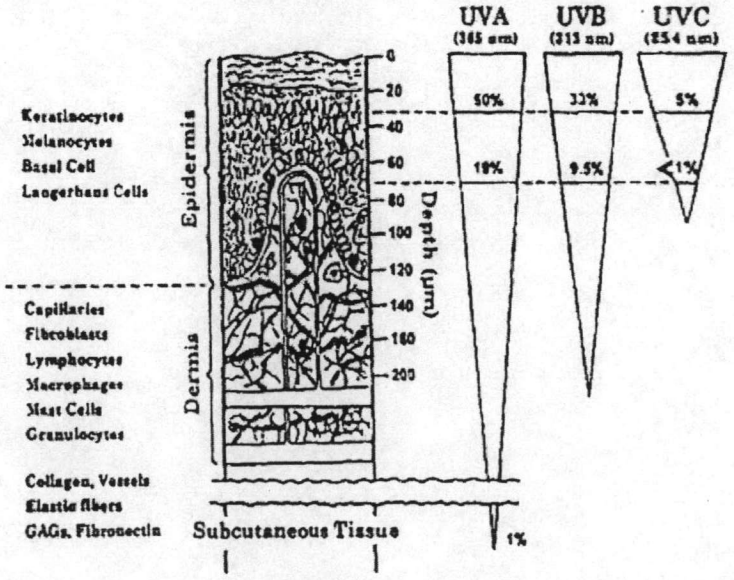


Figure 1.2 Light penetration into the skin

1.1 Classification of Sunscreen Chemicals[1]

Sunscreen chemicals may be classified according to the type of protection they offer as either physical blockers or chemical absorbers.

1.1.1 Physical Blockers

These are chemicals that reflect or scatter the ultraviolet radiation. Its physical appearance is non-soluble and therefore, can reflect part of the UV radiation. Examples of physical blockers include zinc oxide, titanium dioxide, and red petrolatum. Most physical blockers are currently being used in conjugation with chemical absorbers to achieve high sun protection factors.

The optical in the UV region of the physical blockers is also partly achieved because these substances exhibit semiconductor properties. Therefore, photons of energy around that of the band gap between the valence band and the conduction band can be absorbed producing characteristic absorption band for the substances. The characteristic wavelengths of titanium dioxide and zinc oxide are 387-405 and 384 nm respectively. Thus UV radiation is effectively scattered and absorbed by the particles, thereby making these substances suitable UV blockers. However, because of the semiconductor properties of these oxides, they have been increasingly used as photocatalysts for the degradation of organic pollutants in wastewaters.[8] Since, by their nature, sunscreen preparations are exposed to sunlight, the photocatalytic behavior of these blockers needs to be considered. There are many reports which affirm that photoexcited titanium dioxide can cause cell death both *in vitro* and *in vivo*.[9]

1.1.2 Chemical Absorbers

These chemicals absorb the harmful ultraviolet radiation. They are soluble organic molecules whose absorption bands are in UV region. The choices of the correct filter compounds usually follow the following criteria:[10]

Absorption Range. Depending upon the desired UV absorption, a choice is made between one or more UVB filters, a certain bandwidth filter, or a filter corresponding to a combination of UVA and UVB filters.

UVA absorbers are chemicals having absorption band in the 320-360 nm region of the ultraviolet spectrum. Examples of UVA absorbers include benzophenone, anthranilates and dibenzoyl methanes.

UVB absorbers are chemicals that absorb radiation in the 290-320 nm region of the ultraviolet spectrum. Examples of UVB absorbers include *p*-aminobenzoate (PABA) derivatives, salicylates, cinnamates and camphor derivatives.

Solubility Whether a sunscreen is based on oil or aqueous gel, the chosen filter compound must be compatible with its base. In the case of emulsions, either water- or oil-soluble filter compounds may be used. Often a combination is desirable due to cost or effectiveness considerations.

Sun Protection Factor (SPF) The ability of sunscreen to protect the skin from UVB is defined as the Sun Protection Factor (SPF). SPF is the ratio of the amount of UVB radiation required to produce minimal pinkness (erythema) in skin covered by a sunscreen to the amount of UVB radiation required to produce a similar level of pinkness in unprotected skin.

Other important criteria in achieving the desired level of protection include the interaction of the filter compound with the sunscreen base, as well as its interaction with the skin itself.

The chemical absorbers currently used in the sunscreen industry can be classified into seven broad categories. Their structures are shown in Fig 1.3

I Cinnamate derivatives (**I**)

II *p*-Aminobenzoate derivatives (**II**)

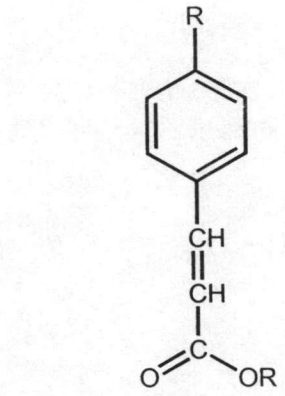
III Salicylates (**III**)

IV Benzophenone (**IV**)

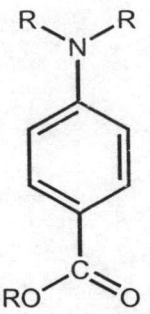
V Camphor Derivatives (**V**)

VI Dibenzoylmethanes (**VI**)

VII Antranilates (**VII**)



I



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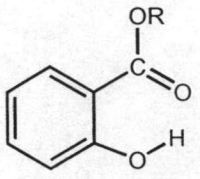

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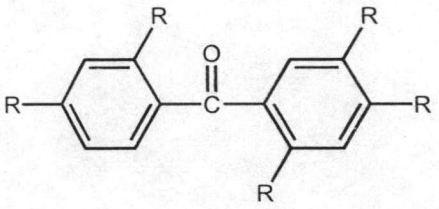
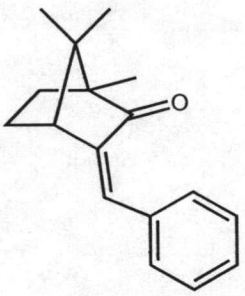
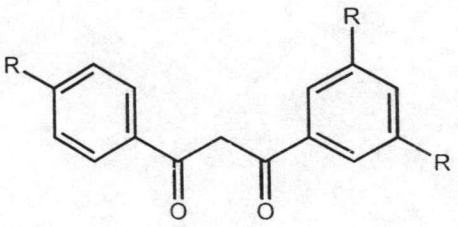


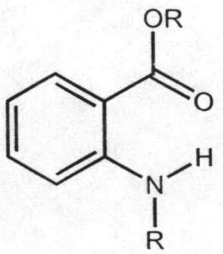
IV



V



VI



VII

Figure 1.3 The seven major groups of chemical sunscreen filters currently used in the suncare industry

1.2 Mechanism of Sunscreen Action

In general chemical absorbers usually contain an aromatic ring conjugated with a carbonyl group. Often an electron-releasing group such as amine or methoxy group, is substituted in the ortho- or para- position of the aromatic ring. In other words, these molecules contain conjugated systems that allow electron delocalization upon absorption of a photon. They absorb the harmful short-wave (high-energy) UV rays (250-340 nm) and convert the remaining energy into innocuous longer wave (lower-energy) radiation (usually above 700 nm). Mechanism of absorber molecule is depicted in Fig 1.4.

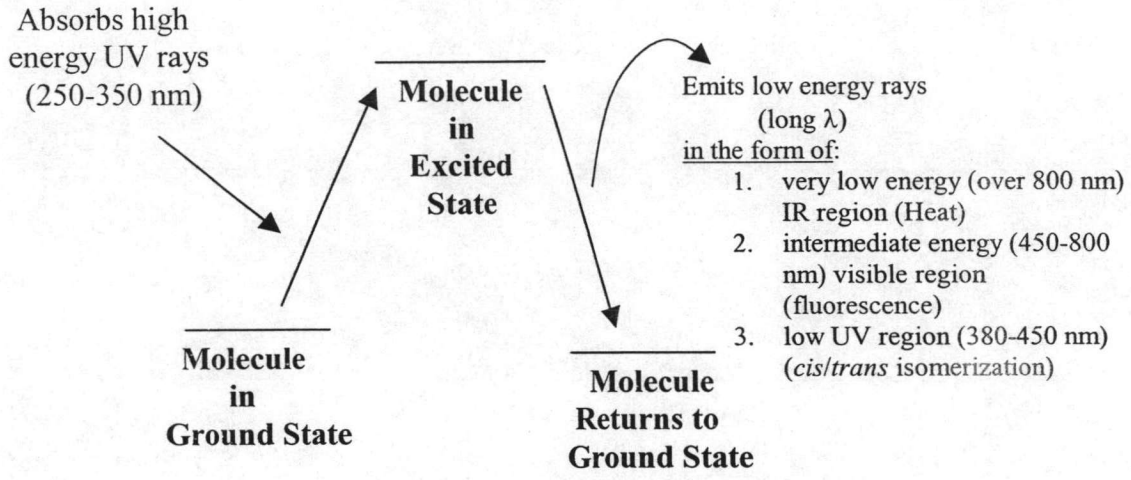


Figure 1.4 Schematic representation of the process in which a sunscreen chemical absorbs the harmful high-energy rays and renders them relatively harmless low energy rays.

1.3 Effect of Vehicle on the Ultraviolet Absorbance of Sunscreen

1.3.1 Effect of pH[1b]

The UV absorption spectra of acidic and basic compounds can be affected by pH. In acidic compounds, for example phenol, the use of alkaline conditions (pH over 9) will assist in the formation of anions. This tends to increase delocalization of electrons causing decrease of the energy required for the electronic transition in the UV spectrum, hence, a bathochromic shift is observed (longer wavelength or λ_{max}). In the opposite manner, acidic conditions of aniline (pH below 4) will assist the formation of cations

with aromatic amines. The protonation of the unbound lone pair of electrons prevents resonance delocalization of the electrons and as a result, a hypsochromic shift toward lower wavelength occurs.

1.3.2 Effect of Solvent

The use of different solvents in cosmetic formulations may profoundly influence the effectiveness of a sunscreen chemical.[11] There are two groups of sunscreen: one that is more polar (e.g. PABA (**II**), benzophenones (**IV**)) and the other that is considered to be less polar (e.g. cinnamates (**I**), dibenzoylmethane (**VI**)). The main ingredient in the cosmetic preparation that usually causes the wavelength of maximum absorbance (λ_{max}) to shift is the solvent or vehicle. If the solvent is very volatile and evaporates when the sunscreen formulation is placed upon the skin, then other less volatile ingredients in high concentration will affect the UV characteristics of the sunscreen chemical.

If the sunscreen is polar, then interactions with polar solvents will be quite extensive. This extensive solvent stabilizes the ground state, thereby inhibiting electron delocalization. The net result would be a hypsochromic shift to lower wavelength. On the other hand, if the sunscreen is less polar, then interactions with polar solvents are different because the excited state is more polar than the ground state. This then lowers the energy requirements for the electronic transition; hence, a higher λ_{max} would be expected, and bathochromic shift occurs.

1.3.3 Effect on the Extinction Coefficient[11]

The value of the extinction coefficient (ε) is the basis on which the effectiveness of a sunscreen chemical is assessed. Therefore, chemicals with a high extinction coefficient are more efficient in absorbing the energy of the harmful UV radiation than chemicals with a lower extinction coefficient.

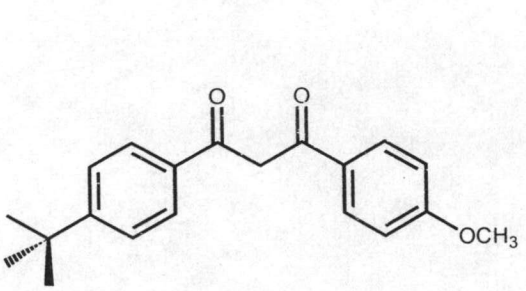
All the electronic transitions for any compounds may be characterized as *symmetry allowed* or *symmetry forbidden*. Symmetry-allowed transitions generally have high extinction coefficient, and symmetry-forbidden transitions have lower extinction coefficients. The degree of resonance delocalization in a molecule can predict the relative λ_{max} and a similar qualitative prediction for its extinction coefficient is possible.

1.4 Literature Reviews

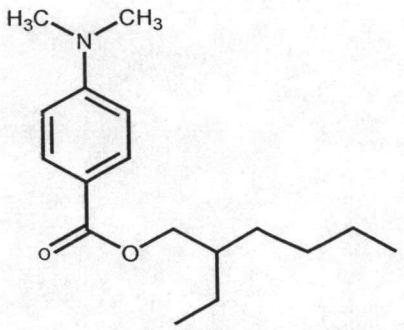
The American Cancer Society estimates that more than half a million new cases of skin cancer are diagnosed every year and that about 90% are caused by exposure to the sun.[12] As a consequence, several measures, such as sun avoidance, clothes, sunglasses, and sunscreen are available for attenuating the sun's harmful effects. As evidenced by several studies, sunscreens can prevent sunburn[1] and UV-induced DNA damage[13,14] that cause the skin cancer. For instance, in 2000, V. Bissonauth and others[14] have shown that the sunscreen can prevent simulated sunlight-induced epidermal disorganization. The frequencies of cyclobutane pyrimidine dimers, the photooxidative products, were significantly reduced by the sunscreen.

Nevertheless, many reports have shown that several UV absorbers lost the absorption ability after UV exposure. For example, in 1990 N. A. Shaath and others[15] studied the stability of various UV filters when subjected to UV light. It was shown that butylmethoxy dibenzoylmethane (**VIII**) and octyl dimethyl PABA (**IX**) significantly degraded in the non-polar solvents such as mineral oil but no degradation was detected in the polar solvents such as 20.6 and 31.2 percent ethanol/water mixture. In isopropylmyristate (IPM), octyl dimethyl PABA exhibited 52.8 percentage of photochemical degradation. Also, 2-ethylhexyl-*p*-methoxycinnamate (OMC) (**X**) showed moderate degradation in mineral oil, IPM and ethanol/water mixture.

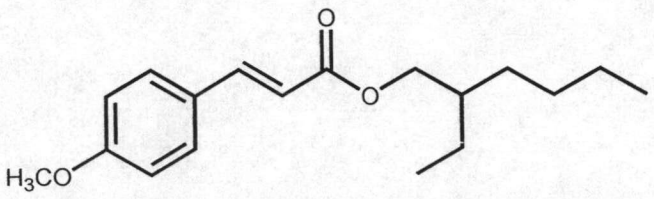
In 1995 J. Meijer and M. Loden[16] studied the stability of OMC in an ordinary sun lotion using HPLC. Analysis of light exposed OMC at room temperature by reverse phase HPLC revealed a new peak with slightly lower retention time. This new peak was dramatically increased while the OMC peak was significantly decreased after more light exposure. The authors suggested a *cis-trans* isomerization of OMC based on the report of cis to trans photoisomerization of cinnamic acid.[17] Similary, in 1999 N. Tarras-Wahlberg and others also reported that octyl dimethyl PABA (**IX**) and OMC (**X**) were not stable against UV irradiation.[18] Their UV absorbance decreased rapidly upon additional exposure to UV light. They have also shown that butylmethoxy dibenzoylmethane (**VIII**), a UV-A filter, lost much of its UV protection capacity after UV irradiation. In 2001, S. Pattanaargson and P. Limpong[19] affirmed that a trans to cis-



VIII



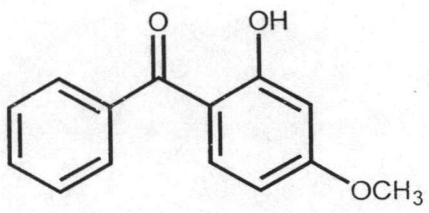
IX



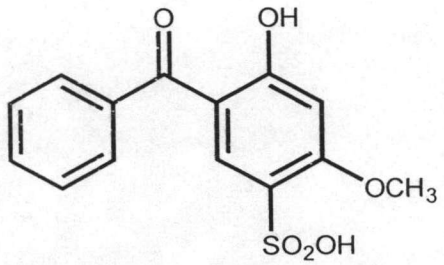
X

configurational change of OMC does occur upon light exposure and its photo-degradation product, *cis*-OMC, was isolated using HPLC. Confirmation of *cis*-OMC was done by NMR and MS. The photoisomerization of OMC has been studied using steady state and laser flash photolysis[20], photoisomerization quantum yield was found to be fairly high (~0.5-1).

In 1997 G. Marti-Mestres and others[21] reported the photostability of six UV-filters in different vehicles. Oxybenzone **(XI)**, sulisobenzone **(XII)**, octyl dimethyl PABA (Padimate O; **IX)**, OMC and butylmethoxy dibenzoylmethane (Avobenzone; **VIII)** were studied in paraffin oil, propylene glycol (PG), IPM, coconut oil, oil in water (O/W) and water in oil (W/O) emulsion. It was found that more polar UV-filters such as oxybenzone and sulisobenzone had high stability in more polar solvents, PG and W/O emulsion. Moderate degradation of the two UV-filters was found in less polar solvents i.e., paraffin oil, coconut oil and O/W emulsion. On the other hand, less polar UV-filters such as Padimate-O, OMC and Avobenzone were photostable in less polar solvents but extreme degradation was found in more polar vehicles.



XI



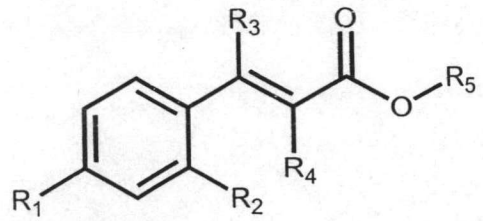
XII

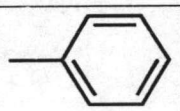
In 2000 they reported effects of added oxybenzone and/or OMC on particle size of submicron emulsion.[22] It was found that the addition of OMC did not significantly modify the mean droplet diameters of the emulsions, while effects of the oxybenzone on droplet diameter were demonstrated.

Decrease of protection efficiency upon sun exposure is, however, not the only defect current sunscreen industry is facing, other non-ideal characteristics need to be improved include reduction of photoreaction of sunscreen with skin or other compounds, improving spanning of absorption band to absorb all harmful UV rays and minimizing absorption of sunscreen through skin cells. For instance, in 1996, K. U. Schallreuter and others[23] showed an evidence for the rapid photo-oxidation of oxybenzone, a popular UV A filter, to its semiquinone followed by Michael addition to active thiolate groups of thioredoxin reductase, an anti-oxidant enzyme, in the epidermis. Although oxybenzone is an excellent broad spectrum UV A filter, its rapid oxidation followed by the inactivation of important anti-oxidant system indicated that this substance may be rather harmful to the epidermis.

At the moment, although many sunscreens have been on market, literatures, however, indicate that cinnamate derivatives are the most popular UVB filters. This is because cinnamates have an extra conjugated unsaturation making the compound quite effective in UV absorption. Cinnamates are also insoluble in water making them suitable for most waterproof sunscreen formulations. As a result, there are many approved cinnamate derivatives used in the United States, Europe and Asia.[24] Table 1.1 shows the four cinnamate derivatives already approved by FDA. Nonetheless, all of the cinnamate derivatives present on the market can protect only the UVB region of the UV spectrum.

Table 1.1 Names and Chemical Structures of Cinnamate Derivatives



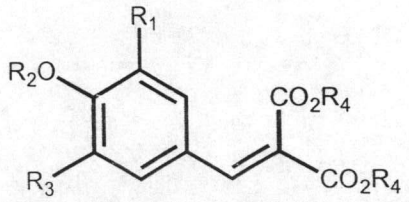
No.	Name	R_1	R_2	R_3	R_4	R_5
X	2-ethylhexyl-*p*-methoxycinnamate	OCH_3	H	H	H	C_8H_{17}(iso)
XIII	diethanolamine-*p*-methoxycinnamate	OCH_3	H	H	H	diethanolamine salt
XIV	2-ethoxyethyl-*p*-methoxycinnamate	OCH_3	H	H	H	$CH_2CH_2OC_2H_5$
XV	ethylhexyl-α-cyano-β-phenylcinnamate	H	H		CN	C_8H_{17}(iso)

In 1997 A. Deflandre[25] proposed the use of novel substituted dialkylbenzalmalonates (Table 1.2) as photostable solar filters. The patent suggests combining other UVA filters with these dialkylbenzalmalonate derivatives to create sunscreens those can absorb all both UVA and UVB radiation.

It is very clear that at the moment there is no UV-filter that can absorb both UVA and UVB. The broad band UVA and UVB fitering properties of any sunscreens, nowadays, is achieved by combining more than one filters in the formulation. This combining practice yields sunscreen formulation with satisfying filtering range and without exuding the concentration limits recommended by FDA. Such practice has, however, put consumer on exposure to more chemical and hence, more risk developing irritation. Moreover, interactions of chemicals within the formulation can occur.[21] This research is, therefore, focused on developing compound(s) that can absorb all ranges of

harmful UV rays (UVA and UVB) by itself. The approach to get to the goal is by the modification of cinnamates structures. The studies on structural modification of *trans*-cinnamate and benzalmalomate derivatives as broad band UV-A and UV-B filter have never been reported in chemical literature.

Table 1.2 Names and Chemical Structures of Dialkylbenzalmalonate Derivatives



No.	Name	R_1	R_2	R_3	R_4
XVI	diethyl-4-methoxybenzalmalonate	H	OCH_3	H	C_2H_5
XVII	diethyl-4-*tert*-butoxybenzalmalonate	H	$OC(CH_3)_3$	H	C_2H_5
XVIII	diisopropyl-4-methoxybenzalmalonate	H	OCH_3	H	C_3H_7 (iso)
XIX	di-(2-ethylhexyl)-4-methoxybenzalmalonate	H	OCH_3	H	C_8H_{17}(iso)
XX	diethyl-4-*n*-butoxy-3-methoxybenzalmalonate	OCH_3	OC_4H_7	H	C_2H_5
XXI	diisopropyl-4-*n*-butoxy-3-methoxybenzalmalonate	OCH_3	OC_4H_7	H	C_3H_7 (iso)
XXII	di-(2-ethylhaexyl)-3,4-dimethoxybenzalmalonate	OCH_3	OCH_3	H	C_8H_{17}(iso)
XXIII	diisopropyl-3,4,5-trimethoxybenzalmalonate	OCH_3	OCH_3	OCH_3	C_3H_7 (iso)
XXIV	diisoamyl-4-methoxybenzalmalonate	H	OCH_3	H	C_5H_{11}(iso)
XXV	diethyl-4-*n*-hexyloxybenzalmalonate	H	OC_6H_{14}	H	C_2H_5

1.5 Research Goal

The goal of this research is to improve the UV protection capacity of cinnamate and benzalmalonate derivatives. More specifically, the research is concentrated on developing cinnamate and benzalmalonate derivatives which can absorb both UV A and UV B portion of the electromagnetic spectrum. The approach is based upon the assumption that the position and the number of electron donation groups on the aromatic ring will affect both the absorption wavelength and molar absorptivity of the compounds. Therefore, objectives of this research can be summarized as follows:

1. To synthesize various cinnamate and benzalmalonate derivatives.
2. To determine absorption wavelength, molar absorptivity, photostability and skin irritation of the synthesized compounds.