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EXTENSIVE REVIEW OF SUNSCREEN AGENTS BY DOCKING STUDIES

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ABSTRACT

Sunscreens which are widely used by almost every individual on every day basis is a key protector against sun damage and tanning. The damage is not limited to darkening of skin but it leads to carcinoma also. Thus sunscreen plays a major role in prevention of life threatening disease. But surprisingly the one which prevents carcinoma can create carcinoma in turn. Estrogens, progesterone and testosterone play an important role in the development of hormone-sensitive organs including the mammary gland. Exposures to estrogen and androgen receptors showing agonists and antagonists activity affect the growth of the mammary gland, its function and risk of disease during critical window of development. It is found that when the active ingredients bind with some receptors then they act as hormone disruptor. The main focus is onto how sunblockers can impose health hazards by binding with receptors. The binding energy shows how potent disrupting activity these compounds contain. These active ingredients bind effectively more with ERα than with Erβ. These ingredients applied topically not only remains on the skin but also it penetrates the skin and enters the blood stream and is excreted via urine and faeces. Moreover it is found that there is an increase in use of these compounds in various consumer goods as perfumes to enhance the fragrance to candies and other foods as a flavouring agent even at the same time it is used to protect food, beverages and various other consumer goods from degradation on exposure to sunlight. Thus it is found that due to excess exposure to these chemicals accumulation of these ingredients are found much more in blood and hence their effects are also found over period.

KEYWORDS: Sunscreen, UVA & UVB, titanium dioxide, zinc oxide, avobenzone, oxybenzone, octinoxate, octisalate, autodoc vina.

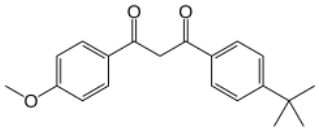
INTRODUCTION

Sunscreens are also known as sunblock, which is a topical photoprotective product applied to protect skin from sunburn and most importantly which can prevent carcinoma. The organic and inorganic active ingredients of Sunscreen work to protect skin from harmful sun's rays. The various formulation of includes sprays, liquids, lotions, powders, and creams. Sunblocks are classified into two main types depending on the type of ingredients used in the formulation: Physical & Chemical sunscreen.[1]

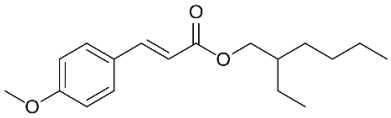
Physical sunscreens: Titanium Dioxide and/or Zinc Oxide, are used in the formulations physical blockers of UVA and UVB rays. These two ingredients are likely to cause adverse skin reactions, thus this can be applied for use on sensitive skin. These sunscreen agents reflect, scatter, absorb, or block sun rays. Titanium Dioxide is a useful addition to cosmetic products, as it doesn't degrade and remains stable even when exposed to UV radiation. Zinc oxide is one of the ingredient that protects the skin from both UVA and UVB rays and is approved by FDA. These are naturally occurring physical sun blockers but can also be synthetically produced. It acts by scattering and reflecting UV rays, thus prevent sun rays from penetrating the skin.[2]

Chemical sunscreens: Various chemical filters used in sunscreens are Avobenzone, Oxybenzone, Octinoxate, Octisalate. Among these the most commonly used chemical filters are Oxybenzone and Avobenzone. This ingredient quickly degrades in sunlight as it is unstable. This chemical filter gets rapidly absorbed into the skin, and is a known endocrine disruptor that can affect thyroid function. It acts as a skin penetration enhancer, hence other hazardous ingredients, they are more likely to pass into the body these chemicals are present in the formula. Chemical sunscreen agents protect you from the sun by absorbing the ultraviolet (UV) and visible sun rays.

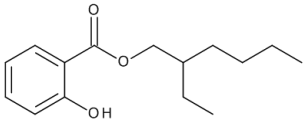
Avobenzone: CAS: 70356-09-1; IUPAC: 3-(4-tert-Butylphenyl)-1-(4-methoxyphenyl)propane-1,3-dione. This is the most commonly used chemical filter used against UVA found in chemical sunscreens. This ingredient quickly degrades in sunlight as it is unstable.[3]



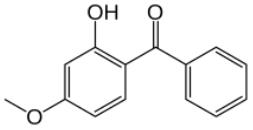
Octinoxate: CAS: 5466-77-3; (RS)-2-Ethylhexyl (2E)-3-(4-methoxyphenyl)prop-2-enoate. This chemical filter gets rapidly absorbed into the skin, and is a known endocrine disruptor that can affect thyroid function. Octyl methoxycinnamate or ethylhexyl methoxycinnamate (INCI) or octinoxate (USAN), trade names Eusolex 2292 and Uvinul MC80, is an organic compound that is an ingredient in some sunscreens and lip balms. It is an ester formed from methoxycinnamic acid and 2-ethylhexanol. It is a liquid that is insoluble in water. It is primarily used in sunscreens and other cosmetics to absorb UV-B rays from the sun, protecting the skin from damage. It is also used to reduce the appearance of scars. Octyl methoxycinnamate is the most common active ingredient in sunscreens for protection against UV-B rays. It may be combined with oxybenzone and titanium oxide. Studies have evaluated the efficacy of octyl methoxycinnamate in preventing postoperative peritoneal adhesions and determined that octyl methoxycinnamate covering peritoneal surfaces decreases adhesion formation. This effect is more notable when octyl methoxycinnamate is applied before the induction of trauma. Chromophore groups, such as C=C, C=O, and O-N=O, have loosely held electrons that are excited by radiation. Hence, octyl methoxycinnamate is able to absorb radiation when the electron energy level is increased to an excited state.[4]



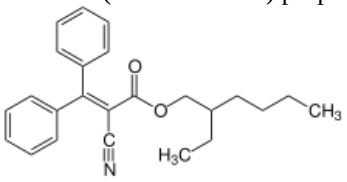
Octisalate: CAS: 118-60-5; IUPAC: 2-ethylhexyl 2-hydroxybenzoate This can absorb UVB rays (but not UVA rays), it acts as askin penetration enhancer, hence other hazardous ingredients, they are more likely to pass into the body when Octisalate is present in the formula. 2-Ethylhexyl salicylate, or octyl salicylate, is an organic compound used as an ingredient in sunscreens and cosmetics to absorb UVB (ultraviolet) rays from the sun. It is an ester formed by the condensation of salicylic acid with 2-ethylhexanol. It is a colorless oily liquid with a slight floral odor. The salicylate portion of the molecule absorbs ultraviolet light, protecting skin from the harmful effects of exposure to sunlight. The ethylhexanol portion is a fatty alcohol, adding emollient and oil-like (water resistant) properties.[5]



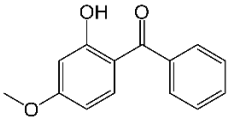
Oxybenzone: CAS: 131-57-7; IUPAC: (2-Hydroxy-4-methoxyphenyl)(phenyl)methanone. It absorbs both UVB and UVA rays, but it is a photosensitizer, as it increases the body's production of free radicals after sun exposure. It's also been implicated as a hormone disruptor, and may affect the production of estrogen in the body.[6]



Octocrylene: CAS: 6197-30-4; 2-Ethylhexyl 2-cyano-3,3-diphenylprop-2-enoate. Absorb both UVB and UVA rays, but like Oxybenzone, it also increases the production of free radicals after being exposed to the sun. This formulated product tends to be thinner, and is easier to spread evenly across the skin leaving less residue. Octocrylene is an organic compound used as an ingredient in sunscreens and cosmetics. It is an ester formed by the condensation of 2-ethylhexyl cyanoacetate with benzophenone. It is a viscous, oily liquid that is clear and colorless. The extended conjugation of the acrylate portion of the molecule absorbs UVB and short-wave UVA (ultraviolet) rays with wavelengths from 280 to 320 nm, protecting the skin from direct DNA damage. The ethylhexanol portion is a fatty alcohol, adding emollient and oil-like (water resistant) properties.[7]



Activity of most frequently used UV filters and its effect



Oxybenzone: Oxybenzone is a derivative of benzophenone an organic compound used in sunscreens. It forms colourless crystals that are readily soluble in most organic solvents. Oxybenzone (benzophenone-3) is an ultraviolet radiation filter commonly used in personal care products including sunscreens. Due to its wide spread use, human exposures to this compound are widespread. Oxybenzone is considered an endocrine disrupting chemical due to its antiestrogenic and antiandrogenic properties. Oxybenzone is a synthetic compound used to protect people and consumer products from solar irradiation. Oxybenzone applied in a sunscreen remains not only on the skin surface, but

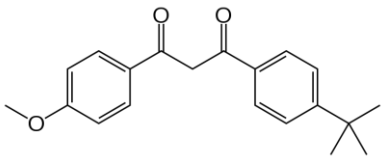
penetrates down the layer on the skin and enters the blood stream, later on it gets excreted via urine and faeces. In addition to dermal exposure, the growing use of oxybenzone has increased its occurence in consumer goods, resulting in exposures via the oral route as well. Oxybenzone-enhanced glass and plastics protect food, beverages, and other consumer goods from degradation caused by sunlight. Moreover, many textiles include oxybenzone for colour stability, and industrial inks contain oxybenzone as a wetting agent and photo-initiator. Finally, oxybenzone is added to perfumes to enhance the fragrance of musk, and to candies and other foods as a flavouring agent. Oxybenzone has recently received significant attention as an environmental pollutant suspected to contribute to coral bleaching across the worlds' oceans as their traces are found in surface water, wastewater and drinking water.

Due to abundant availability of Oxybenzone their presence found to affects hormone signalling in animals, including humans. Several studies have demonstrated that oxybenzone acts as an estrogen receptor (ER) agonist and antagonist in yeast assays, human cell cultures and fish. Thus a single compound having both agonist and antagonist activities for a single receptor seems quite contradictory. Estrogens, progesterone and testosterone which plays an important role in the development of hormone-sensitive organs including the mammary gland. Further, exposures to ER and AR agonists and antagonists during this critical window of development can affect the growth of the mammary gland, its function and risk of disease. Importantly, the mammary gland is a sexually dimorphic structure, therefore male and female glands not only develop differently, and they are affected by endocrine disruptors differently.[8]

At the same time during pregnancy and lactation exposure to oxybenzone, had a long-lasting effects on morphology and expression of hormone receptors in the mouse mammary gland. Estrogen produced by the corpus luteum during early pregnancy induces ductal morphogenesis and is important for the induction of the progesterone receptor (PR) in mammary epithelial cells, which is mediated by estrogen receptor (ER)α. Although ERα is highly expressed in adult mammary epithelial cells, but its expression diminishes in pregnancy and is again highly expressed during lactation.

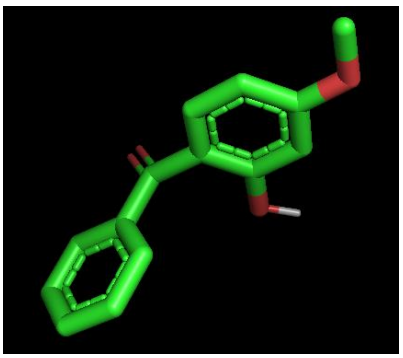
Oxybenzone (benzophenone-3), which is an ERα agonist but it does not appear to be an agonist for ERβ. Oxybenzone is also found to be antiestrogenic and antiandrogenic. Importantly, oxybenzone is found to be present in human urine for around a year even, and its exposure creates adverse health outcomes. As it is an ERα agonist, it is hypothesized that exposure to oxybenzone during pregnancy and lactation would disrupt morphology, cell proliferation, gene expression, and hormone receptor expression in the mammary gland and that these effects would even persist long after exposures ceased.[9]

Avobenzone



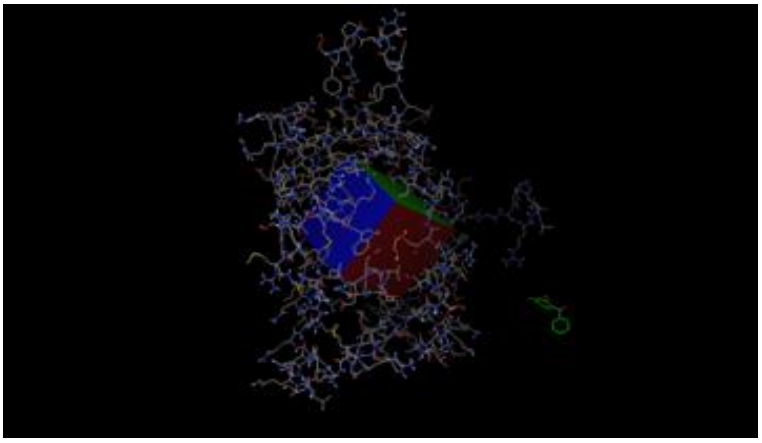
Avobenzone (butyl methoxydibenzoylmethane) is also an endocrine disruptor that directly binds to estrogen receptor β and α and acts as an estrogen agonist. It is also found that 71% of personal care products contain avobenzone, which is the highest proportion among the various compositions. The amount of avobenzone in personal care products is limited to 3% by The Food and Drug Administration (FDA) and 5% by Cosmetics Directive of the European Union, and it is toxic if products have avobenzone concentrations greater than 5%. Avobenzone acts as an agonist or antagonist by reacting with estrogen receptors. Additionally, avobenzone is also found in underwater environments such as seawater swimming pools, making this potential toxin easily accessible to the human body. Hence a docking study is being done to analyse the binding energy which in turn helps to identify the level of adverse effect that these drug can impose on human health after it binds with ERα.[10]

Oxybenzone



Ligand

Protein



Grid box

The binding energy is calculated using Auto-Dock-Vina, pymol visualization tool is used to generate the ligand structure in pdbqt format for undergoing docking study.To perform docking generation of "grid-box" is required to identify the location of docking. Here ligands are obtained from PubChem in sdf format but the structures of Ligands, Oxybenzone and Avobenzone are drawn in Mervin sketch. The protein structure of ERα is downloaded from PDB Data bank .Structures were prepared for docking simulations by adding polar hydrogens and formatting them as PDBQT files using AutoDockTools 1.5.7. Docking was performed using AutoDock Vina 1.1.2. The binding box used was sized and centered on the active site of each receptor based on predictions. Exhaustiveness and energy range were set to 8 and 4, respectively. The center x,y,z and size x,y,z denotes the details about the grid box created to undergo docking.In each docking round, we generated 9 binding modes, from which the one with the lowest binding energy (in Kcal/mol) was selected. Visualization of the protein-ligand complexes was done with PyMOL visualization tool.[11]

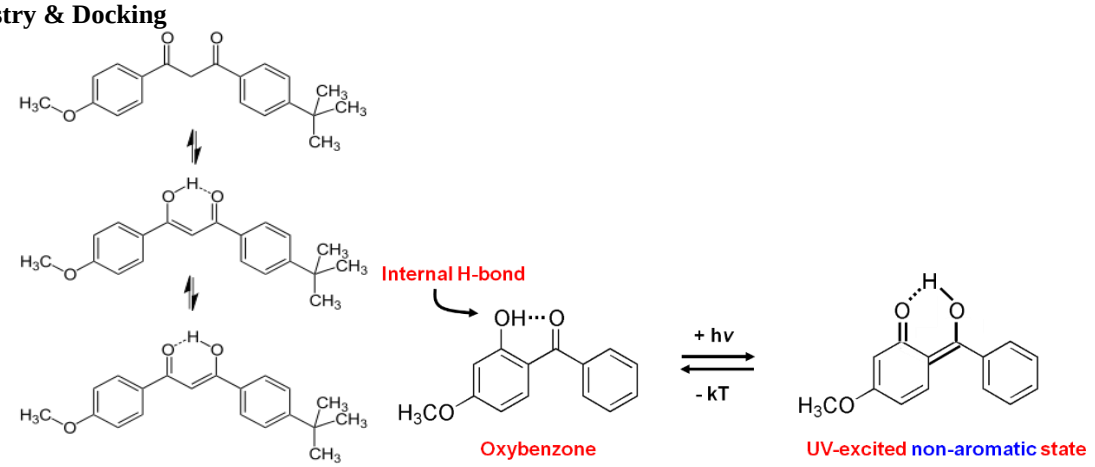
1. receptor = protein.pdbqt
ligand = ligand.pdbqt
center_x = 12.320
center_y = 20.323
center_z = 13.198
size_x = 40
size_y = 40
size_z = 40
energy_range = 4
exhaustiveness = 8

2. mode | affinity | dist from best mode
| (kcal/mol) | rmsd l.b.| rmsd u.b.

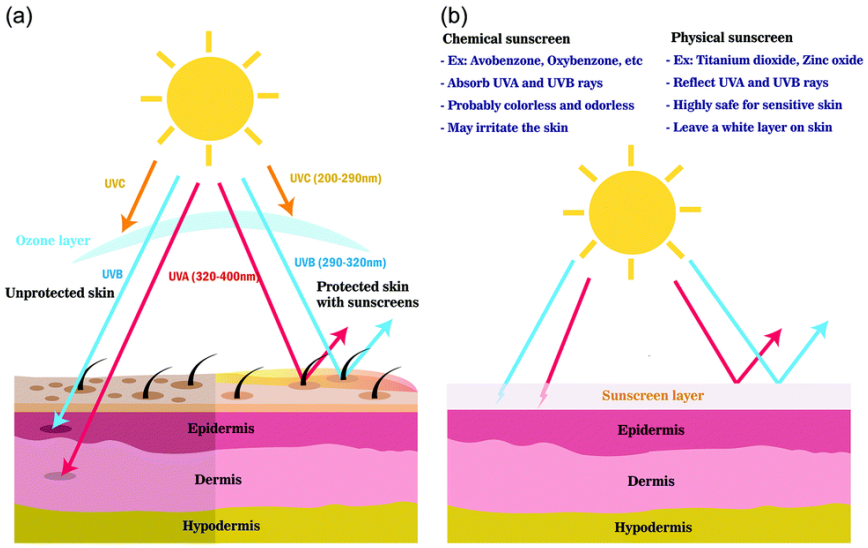
1	-4.8	0.000	0.000
2	-4.8	1.541	2.117
3	-4.7	2.376	4.050
4	-4.7	2.829	3.797
5	-4.6	1.750	2.493
6	-4.6	10.640	12.026
7	-4.5	3.752	4.741
8	-4.5	4.004	5.195
9	-4.5	11.231	12.203

3. Avobenzone [it forms cyclic structure by intramolecular rearrangement to form a cyclic structure which prevents to pass UV light. Avobenzone (trade names Parsol 1789, Milestab 1789, Eusolex 9020, Escalol 517, Neo Heliopan 357 and others, INCI Butyl Methoxydibenzoylmethane) is an oil-soluble ingredient used in sunscreen products to absorb the full spectrum of UVA rays.[12]

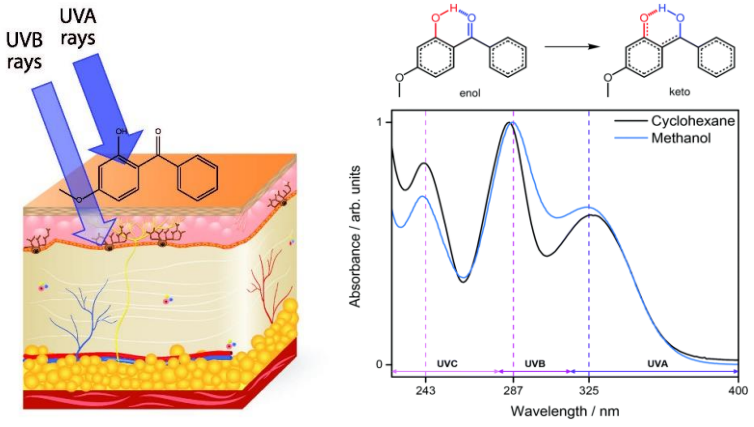
Chemistry & Docking



Due to steric hindrance –OH and >C=O react with each other to form hydrogen bind and prevents to cross UV light across he dermis. This form Vander Waal's bonding with receptor because the receptor is a macromolecular bed having huge chain of lipoprotein [lipid: ester -COO- and protein: -NHCO-]; -CO- is common in lipid & protein and oxybenzone, so the synergistic approach of oxybenzone and stratum corneum of skin/dermis helps to bind the drug with skin layer to prevent UV light incorporation. There are two kinds of sunscreen agents: chemical and physical. Chemical sunscreen agents protect you from the sun by absorbing the ultraviolet (UV) and visible sun rays, while physical sunscreen agents reflect, scatter, absorb, or block these rays. Oxybenzone is an organic compound used in sunscreens. It is a derivative of benzophenone. It forms colorless crystals that are readily soluble in most organic solvents. It is used as an ingredient in sunscreen and other cosmetics because it absorbs UV-A ultraviolet rays. Oxybenzone, or benzonephenone-3, is one of the most common chemical filters found in commercial chemical sunscreens. It forms colorless crystals that are readily soluble, and provides UV coverage. Oxybenzone is one of the common active ingredients in sunscreens that are sold in the US. The FDA says it is safe. Oxybenzone absorbs UVB and UVA II rays, resulting in a photochemical excitation and absorption of energy. Upon return to ground state, the absorbed energy results in emission of longer wavelength radiation and decreased skin penetration of radiation which reduces the risk of DNA damage. Composition and mechanism of action of sunscreening agents vary from exerting their action through blocking, reflecting, and scattering sunlight. Chemical sunscreens absorb high-energy UV rays, and physical blockers reflect or scatter light. Oxybenzone — also called benzophenone-3 and sometimes Milestab 9, Eusolex 4360, Escalol 567, or KAHSCREEN BZ-3 — is a chemical compound that is the active ingredient in most over-the-counter sunscreens and other personal care and skincare products. The key difference between oxybenzone and avobenzone is that oxybenzone is safe to be used in sunscreen that is applied on human skin whereas avobenzone is not safe to be used in sunscreen because it can degrade in the sun and produce harmful radicals.[13]



Oxybenzone is a chief ingredient in sunscreens and skin-care products. The primary function of oxybenzone is to block harmful ultraviolet (UV) rays and prevent UV rays from reaching the skin. UV rays are known to cause skin cancer. Oxybenzone prevents the direct interaction of skin with these harmful rays.[14]



λmax in UV shows 287nm in UVB, 243nm in UVC & 325nm in UVA from polar solvent methanol and cyclohexane as nonpolar solvent for both keto & enol form of oxybenzene.

Receptor = protein.pdbqt
Ligand = ligand.pdbqt

center_x = 22.356
center_y = 5.690
center_z = 21.769

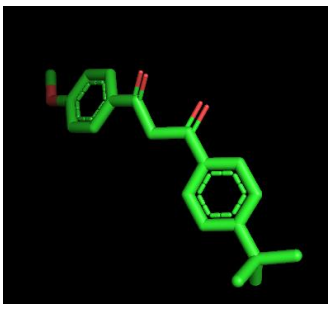
size_x = 40
size_y = 40
size_z = 40

energy_range = 4
exhaustiveness = 8

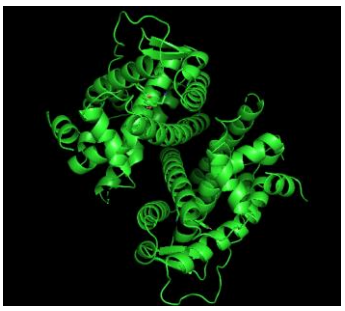
mode	affinity (kcal/mol)	dist from best mode rmsdl.b.	rmsdu.b.
1	-5.9	0.000	0.000
2	-5.7	2.482	3.742
3	-5.5	15.715	19.183
4	-5.5	28.210	30.189
5	-5.5	2.785	3.962
6	-5.4	14.791	16.467
7	-5.4	25.541	27.771
8	-5.2	25.668	28.199
9	-5.2	28.268	29.586

Thus the above details study of binding energy shows that on an average the energy for active site binding is quite reasonably good and effective in terms of showing estrogenic agonist and antagonist activity.[15]

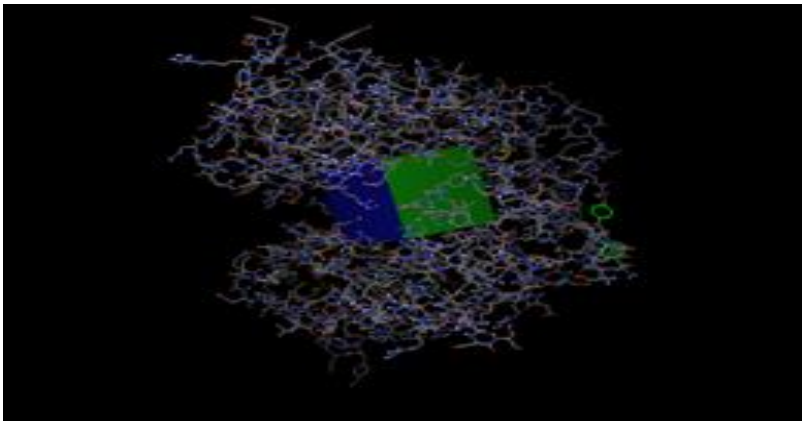
Avobenzone



Ligand



Protein



Grid box

receptor = protein.pdbqt
ligand = ligand.pdbqt

center_x = 12.320
center_y = 20.323
center_z = 13.198

size_x = 40
size_y = 40
size_z = 40

Energy range = 4
Exhaustiveness = 8

mode	affinity (kcal/mol)	dist from best mode rmsdl.b.	rmsdu.b.
1	-8.1	0.000	0.000
2	-7.8	3.007	7.234
3	-7.5	2.657	4.956
4	-7.3	3.136	7.412
5	-7.1	2.776	5.470
6	-7.1	32.296	33.905
7	-7.1	3.528	7.189
8	-7.0	2.822	3.688
9	-7.0	3.512	4.843

Hence the above details study of binding energy shows quite good reasonable binding character of the drug Avobenzone with the protein ERα as a result estrogenic agonist and antagonist activity is found.[16-20]

CONCLUSION

In general, it is found that the commercially available sunscreen raises several biosecurity health hazards and environmental pollution concerns. As UV filters, can never get completely replaced by natural extract but substantially there is decrease in the overall reliance on physical or chemical UV filters. This study provides a strong foundation on the status of harmful effects that UV Filters impose on human health as well on environment.

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