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Molecular Mechanisms of Drug Photodegradation and Photosensitization

Mohd Rehan Zaheer[1], Anamika Gupta[2,*], Jawaid Iqbal[2,*], Qamar Zia[3,4,*], Akil Ahmad[1,5], Roohi[6], Mohammad Owais[4], Ali Hashlamon[7], Siti Hamidah Mohd Setapar[5], Ghulam Md Ashraf[8] and Gjumrakch Aliev[9,10,11,*]

Jawaid Iqbal

[1]*Department of Chemistry, Gagan College of Management and Technology, Aligarh-202001, U.P., India;* [2]*Deparment of Chemistry, Aligarh Muslim University Aligarh-202001, U.P., India;* [3]*Department of Biotechnology, Gagan College of Management and Technology, Aligarh, India;* [4]*Interdisciplinary Biotechnology Unit, Aligarh Muslim University, Aligarh 202002 U.P., India;* [5]*Centre of Lipid Engineering and Applied Research, Ibnu Sina Institute for Industrial and Scientific Research, University Technology Malaysia, Johor Bahru-81310, Malaysia;* [6]*Department of Bioengineering, Integral University, Lucknow- U.P., India;* [7]*Department of Chemical Engineering, College of Engineering, King Faisal University, Al-hasa, Saudi Arabia;* [8]*King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia;* [9]*GALLY International Biomedical Research Consulting LLC., 7733 Louis Pasteur Drive, #330, San Antonio, TX, 78229, USA;* [10]*School of Health Science and Healthcare Administration, University of Atlanta, E. Johns Crossing, #175, Johns Creek, GA, 30097 USA;* [11]*Institute of Physiologically Active Compounds, Russian Academy of Sciences, Chernogolovka, 142432, Russia*

Gjumrakch Aliev

Abstract: Drug-induced photosensitivity of the skin is drawing increasing attention. In past few decades, photosensitivity has been reported with an array of drugs, and is now recognized as a noteworthy medical problem by clinicians, regulatory authorities and pharmaceutical industry. The photosensitivity is of two types *i.e.,* phototoxicity and photoallergy. Phototoxic disorders have a high incidence, whereas photoallergic reactions are much less frequent in human population. Several hundred substances, chemicals, or drugs may invoke phototoxic and photoallergic reactions. In order to avoid photosensitive reactions, it is essential to understand the mechanism behind the photosensitizing properties of such substances before these drugs are introduced in clinical settings. Photosensitization is inter-related to photochemical reaction, through the knowledge of which the photosensitivity of a drug can be anticipated. This review highlights the current research status on photosensitizing drugs and its correlation to phototoxicity. Different mechanisms of photodegradation of photolabile drugs have also been discussed.

Keywords: Drug, photoallergy, photodegradation, photosensitization, phototoxicity.

INTRODUCTION

A plethora of substances, chemicals, or drugs are known to induce photosensitive skin reactions. Photosensitivity is an adverse cutaneous reaction that results when a certain chemical or drug is applied topically or taken systemically at the same time when a person is exposed to ultraviolet radiations (UVR) or visible light. Photosensitivity reactions can occur in persons of any age but are more frequent in adults than children, possibly because adults are usually exposed to more medications and topical agents. Moreover, the degree of photosensitivity varies greatly among individuals. Several factors such as quantity and location of the chemical or drug on/in the skin, thickness of the horny layer, degree of melanin pigmentation, immunological status of the affected person, and quantity, spectrum, and penetration of the activating radiation may influence the features of photosensitivity reactions. Photosensitivity reactions may be more specifically categorized as phototoxic or photoallergic in nature [1].

PHOTOTOXIC REACTIONS

In phototoxic reactions, the drug may become activated by exposure to sunlight and cause damage to the skin. The skin's appearance resembles sunburn, and the process is generally acute (has a fast onset). Ultraviolet A (UV-A) radiation (320-400 nm) is most commonly associated with phototoxicity, but ultraviolet B (UV-B) radiation (290-320 nm) and visible light may also contribute to this reaction [2]. A phototoxic reaction typically dissipates once the drug is discontinued or has been cleared from the body. Phototoxicity is a form of photosensitivity that does not depends on an immunological response but is the result of release of energy by photosensitizing agents, causing potentially long term damage to the skin. Phototoxic reactions are dose dependent and will occur in almost any one who takes or applies an adequate amount of the offending agent and is exposed to UVR after topical application. However, the dose necessary to induce such a reaction is different for different individuals. Phototoxic reactions can appear on first exposure to the agent and demonstrate no cross-sensitivity to chemically related agents [3].

PHOTOALLERGIC REACTIONS

Photoallergy is a form of photosensitivity that is immunologically mediated. In photoallergic reactions, the ultraviolet exposure changes the structure of the drug so that it is recognized as an invader by the body's immune system. The immune system initiates an allergic response and causes inflammation of the skin in the sun-exposed areas. These usually resemble eczema and are generally chronic (long lasting). Many drugs in this family are topical agents. This type of photosensitivity may recur after sun exposure even after the drug has cleared from the system. Photoallergic reactions develop only in sensitized persons and are not dose dependent, although a sensitized person is likely to get a stronger reaction at a much higher dose [4].

*Address correspondence to these authors at the "GALLY" International Biomedical Research Consulting LLC, San Antonio, TX 78229, USA;
Tel: +440-263-7461; E-mail: aliev03@gmail.com
Department of Chemistry Aligarh Muslim University Aligarh-202001, UP, India; Tel: +919897878254; E-mail: remiya59@rediffmail.com
Department of Chemistry Aligarh Muslim University Aligarh-202001, UP, India; Tel: +919897828754; E-mail: jiiqbal3@rediffmail.com
Department of Biotechnology, Gagan College of Management and Technology, Aligarh 202001, UP India; Tel: +91-7417775657;
E-mail: qamarbiotech@gmail.com

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In photosensitive patients, it is often difficult to discriminate phototoxicity from photoallergy. However, there are a number of distinguishable features (Table **1**). Photoallergic reactions develop in only a minority of individuals exposed to the chemical and radiation; and are less prevalent than phototoxic skin reactions. The amount of drug required to elicit photoallergic reactions is considerably smaller than that required for phototoxic reactions. Moreover, photoallergic reactions are a form of cell-mediated immunity; their onset is delayed by as long as 24-72 hours after exposure to the drug and light. By contrast, phototoxic responses often occur within minutes or hours of light exposure [3].

A person who is photosensitive may experience some form of dermatitis, a skin rash caused by an allergy to an allergen or physical contact with a particular substance, in this case UVR. The face, outer arms, and upper chest are the most common areas for a rash due to photosensitivity. Photoallergy, like other allergies, tends to occur in previously sensitized individuals; repeat exposure to the same allergen plus UVR exposure can prompt a typical pruritic (itching) and eczematous reaction (red bumps, scaling, and oozing lesions, as in eczema) [5]. Photoallergic reactions resemble allergic contact dermatitis, with a distribution limited to sun-exposed areas of the body. However, when the reactions are severe or prolonged, they may extend into covered areas of skin.

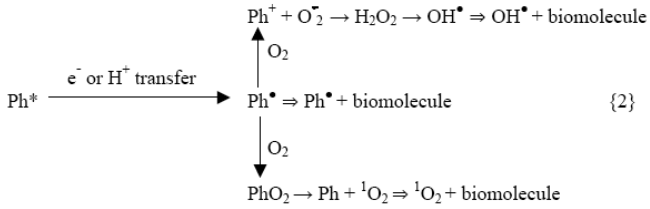
Nowadays, drugs induced photosensitization are receiving considerable amount of attention, since modern life style often associates sunlight exposure with presence of chemical substances in the biological systems [6]. There is a considerable list of drugs belonging to different therapeutic class, such as anti-inflammatory, analgesic, antipyretic, diuretic, and also antibacterial properties that are known to cause photosensitivity (Table **2**). This review highlights some of the photosensitivity reactions induced by these drugs.

MECHANISM OF PHOTOSENSITIZATION OF DRUGS

In general, the generation of an adverse photosensitivity response may involve one or more of the pathways as shown in Fig. (**1**). There are four major pathways through which the excited photosensitizers (Ph*) exerts its phototoxic effects on the biological macromolecules [7]. First of all, an energy transfer {reaction 1} from excited triplet photosensitizer to the oxygen results in the production of excited singlet oxygen which might, in turn, induce membrane lipid/protein oxidation or cause DNA damage.

$$Ph^* + O_2 \rightarrow Ph + {}^1O_2 \Rightarrow {}^1O_2 + \text{biomolecule} \quad \{1\}$$

Second, an electron or hydrogen transfer {reaction 2} to the photosensitizer could form free-radical species, thus exerting a direct attack on the biomolecules. Moreover, the free-radicals can evolve in the presence of oxygen to form secondary free radicals such as peroxyl radicals or the highly reactive hydroxyl radical, a known intermediate in the oxidative damage of DNA and other biomolecules. This latter pathway corresponds to successive reactions which involve the appearance of superoxide anion radical, its dismutation to form hydrogen peroxide followed with the hydrogen peroxide reduction to form hydroxyl radical. Generation of the radical takes place involving either the photosensitizer or the target biomolecule.



Usually, the direct radical mediated-reactions are called type–I reactions whereas singlet oxygen–mediated reactions are considered as type–II reactions. Many photosensitization reactions may be explained on the basis of the type–I or type–II mechanism, but additional pathways also exist. Thus, a covalent photobinding {reaction 3} reaction between photosensitizer and biomolecules could occur, inducing cell damage.

$$Ph^* + \text{Biomolecules} \rightarrow Ph\text{–biomolecules} \quad \{3\}$$

Finally, the photosensitizer could undergo a decomposition {reaction 4} (probably via homolytic process), such that the resulting photoproducts can act either as toxins or as new photosensitizers.

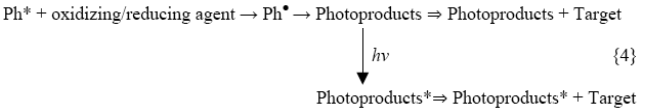


Table 1. Distinguishing Characteristics of Phototoxic and Photoallergic Reactions.

Features	Phototoxicity	Photoallergy
Occurrence	High	Low
Amount of photosensitive agent required/Ultraviolet dose	High	Low
Sharp limits	Yes	No
Onset of reaction	Immediate (Minutes to hours)	Delayed (24-72 hours)
Distribution	Sun exposed areas	Not limited to sun exposed skin, may spread to all parts of body
Incidence after first exposure	Reaction may develop upon first encounter	First encounter symptom-free, a “silent” induction period is required
Clinical symptoms	Excessive sunburn, Rare forms with blisters and skin fragility may resemble porphyria cutanea tarda (pseudoporphyria)	Dermatitis, Erythema and oedema with subsequent development of small vesicles and scaling.
Immune response	No	Yes, Type IV reaction
Cross-reactions	No	May be
Detection	Detected by means of *in vitro* assays.	Assessed only by means of *in vivo* assays.

Table 2. Some of the drugs that cause photosensitivity reactions.

Therapeutic Class	Drugs
Diuretic agents	Hydrochlorothiazide, furosemide, chlorothiazide, bendroflumethiazide, benzthiazide, cyclothiazide, hydroflumethiazide, methyclothiazide, trichlormethiazide, polythiazide, ethacrynic acid, amiloride, triamterene, spironolactone, acetazolamide, metolazone, quinethazone
Antidepressants	Amitriptyline, trimipramine, nortriptyline, protriptyline, desipramine, amoxapine, imipramine, doxepin, clomipramine, maprotiline, citalopram, escitalopram, trazodone, fluoxetine, fluvoxamine, paroxetine, sertraline, bupropion, mirtazapine, nefazodone, venlafaxine
Antimalarials	Chloroquine, quinine, mefloquine, pyrimethamine
Cardiovascular drugs	Amiodarone, nifedipine, quinidine, captopril, enalapril, fosinopril, ramipril, clofibrate, disopyramide, hydralazine, simvastatin
Nonsteroidal anti-inflammatory drugs	Naproxen, ketoprofen, suprofen, tiaprofenic acid, piroxicam, diflunisal, diclofenac, mefenamic acid, nabumetone, sulindac, phenylbutazone indomethacin, ibuprofen, celecoxib, diflunisal, etodolac, meloxicam, naproxen, oxaprozin, piroxicam, rofecoxib, sulindac, valdecoxib
Hypoglycaemics	Glibenclamide, tolbutamide, glipizide tolazamide, chlorpropamide, acetohexamide
Antipsychotic drugs	Chlorpromazine, trifluoperazine, rochlorperazine, thioridazine, chlorprothixene, promethazine, haloperidol, thiothixene, fluphenazine, perphenazine, clozapine, prochlorperazine, ziprasidone, fluphenazine, loxapine, olanzapine, quetiapine, risperidone
Anticonvulsants	Carbamazepine, lamotrigine, phenobarbital (phenobarbitone), phenytoin, perphenazine, fluphenazine, promazine, triflupromazine, trimeprazine, felbamate, gabapentin, lamotrigine, oxcarbazepine, topiramate, valproic acid
Antihistamines	Cyproheptadine, diphenhydramine, brompheniramine, triprolidine, loratadine, cetirizine, cyproheptadine, promethazine
Antimicrobials	Demeclocycline, nalidixic acid, sulfamethoxazole, sulfasalazine, ciprofloxacin, lomefloxacin, sulfamethizole, gentamicin, clofazimine, ofloxacin, norfloxacin oxytetracycline, tetracycline, doxycycline, methacycline, minocycline, trimethoprim, isoniazid, nitrofurantoin
Antiretroviral	Ritonavir, saquinavir, zalcitabine
Antifungals	Flucytosine, griseofulvin, terconazole, voriconazole
Antivirals	Amantadine, acyclovir
Antineoplastics	Fluorouracil, vinblastine dacarbazine, procarbazine, methotrexate, bexarotene, capecitabine, dacarbazine, epirubicin, pentostatin, tretinoin, vinblastine
Antiplatelet	Clopidogrel
Hormones	Corticosteroids, estrogens, progesterones, spironolactone, oral contraceptives
Skin agents	Isotretinoin, methoxsalen, benzocaine, coal tar, hexachlorophene, isotretinoin, minoxidil, tacrolimus, tazarotene, tretinoin, PABA, cinnamates, benzyphenones
Miscellaneous	Gold salts, azathioprine, haematoporphryrin, selegiline, thalidomide

All the photobiological responses to light are the consequences of photochemical changes produced in biological systems. Photobiologists working with ultraviolet radiation are concerned with identifying the photochemical changes that are produced in living tissue by the absorption of ultraviolet light and determining the biochemical and physiological responses of body to this damage [8]. Once the photochemical mechanism is known, it is usually possible to modify the structure of drug, such that the phototoxic reaction never happens. Elucidating the reaction mechanism can also be useful for relating molecular events to the photobiological phenomena [9].

A large number of review are available on drug photochemistry and photosensitization. Nonetheless, the photochemical mechanism of several phototoxic drugs are scattered in different journals and have not yet been covered. This prompted us to re-write a review on the topic for the benefit of researchers working in this field. In this review, we present a collection of examples highlighting the recent researches on photosensitizing drugs along with their mechanism of photodegradation and its correlation to phototoxicity.

Dihydropyredines

Dihydropyridines (DHP) are molecules based upon pyridine, and the parent of a class of molecules that have been semi-saturated with two substituents replacing one double bond. They are particularly well known in pharmacology as L-type calcium channel blockers and are used in the treatment of hypertension.

Amlodipine **(1)** is one of the dihydropyridines that demonstrates phototoxicity [10]. When the aqueous solution of the drug was exposed to sunlight, only one photoproduct **(2)** was formed. Creation of this product can be explained on the basis of a radical cation intermediate formation through photoinduced electron transfer mechanism (Fig. **2**). The intervention of free radical in the reaction mechanism implies that the drug possesses phototoxic

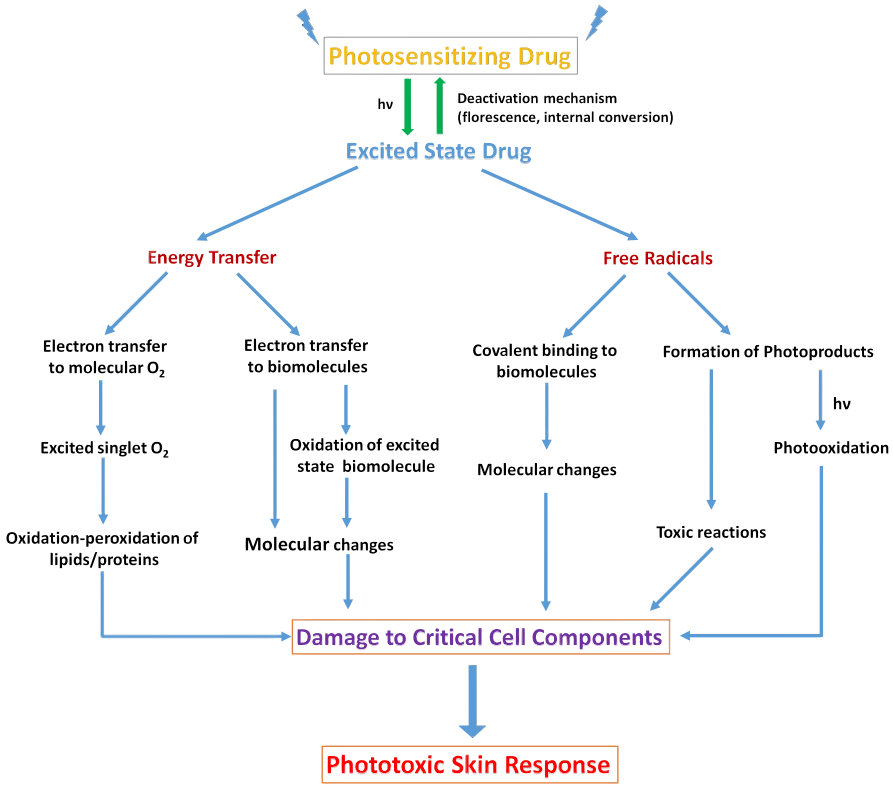


Fig. (1). General scheme of possible reaction processes by which a photosensitizing drug may give rise to adverse photobiological effects (phototoxicity).

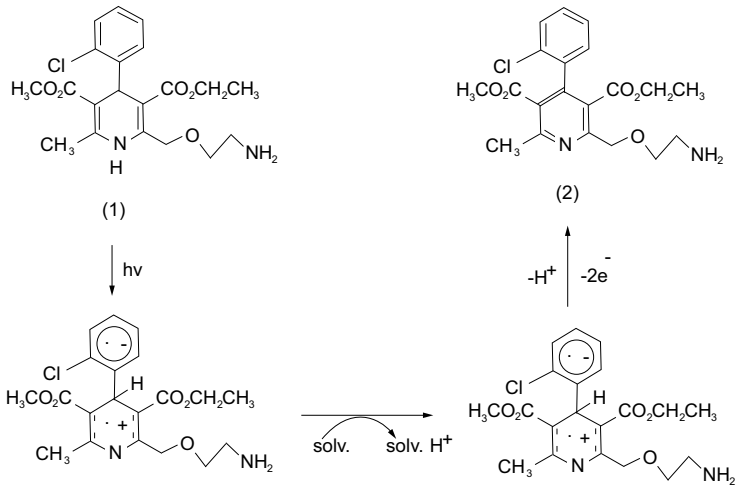


Fig. (2). Reaction scheme for conversion of amlodipine (1) to a photoproduct (2).

effect. Irradiation of 4-oxo-2,2,6,6-tetramethyl piperidinyl-1-oxy radical (TEMPO), a nitroxide, with 4-substituted Hantzsch 1,4-dihydropyridines (**3**) in CH_3CN gives aromatic products (**4**) through a photoinduced electron transfer mechanism (Fig. **3**) [11]. The generation of the free radical in the photodegradation pathway is responsible for the observed phototoxicity of this drug.

Nimodipine and felodipine (**5**), calcium channel blockers of the second- generation DHPs, are widely used as antihypertensive drugs. Its reaction with singlet oxygen ($^1O_2$) results in the formation of dihydropyridine localized triplet or to a pyridine derivative as the main photodegradation product (**6**); being produced by intramolecular electron transfer via a zwitterionic biradical intermediate (Fig. **4A**) [12]. Reaction of singlet oxygen with two other DHP derivatives, nifedipine and nitrendipine, follows similar mode of action as described above (Fig. **4B**) [12]. The phototoxicity of these drugs involved type–II photodynamic action.

Nonsteroidal Anti-Inflammatory Drugs

Carprofen (**7**) is a photosensitizing non-steroidal anti-inflammatory drug (NSAID). It undergoes hasty photodecholorination from its triplet excited state (T_1) to give rise to a photoproduct (**8**). The resulting aryl radical is able to abstract hydrogen atoms from model lipids, mediating their peroxidation by a type–I mechanism. This aryl radical intermediate appears to be responsible for the observed photobiological effects of carprofen (Fig. **5**) [13].

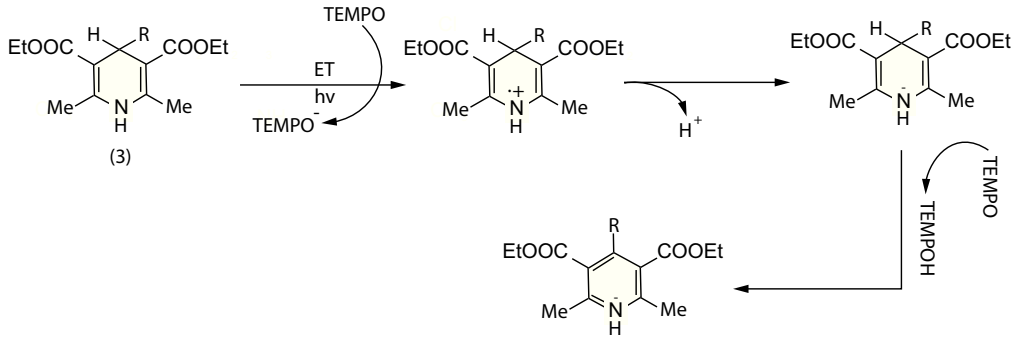
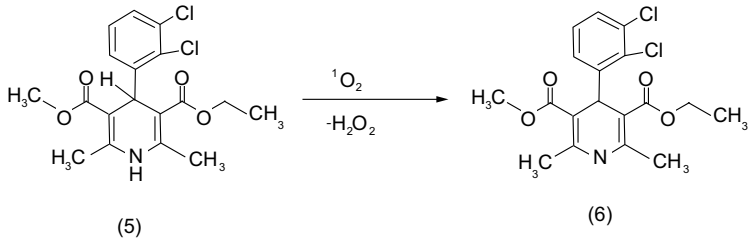
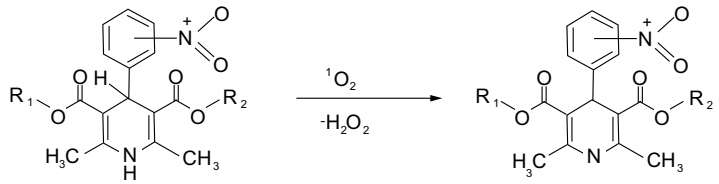


Fig. (3). Reaction scheme for conversion of 4-substituted Hantzsch1, 4-dihydropyridines (DHP) (3) to an aromatic products (4).





Nifedipine $R_1 = R_2 = CH_3$; *o*-NO_2

Nitredipine $R_1 = CH_3$, $R_2 = C_2H_5$; *m*-NO_2

Fig. (4). (**A**) Reaction scheme for conversion of nimodipine and felodipine (5) to dihydropyridine localized triplet or to a pyridine derivative as main photodegradation product (6). (**B**) Reaction scheme for conversion of nifedipine to nitredipine.

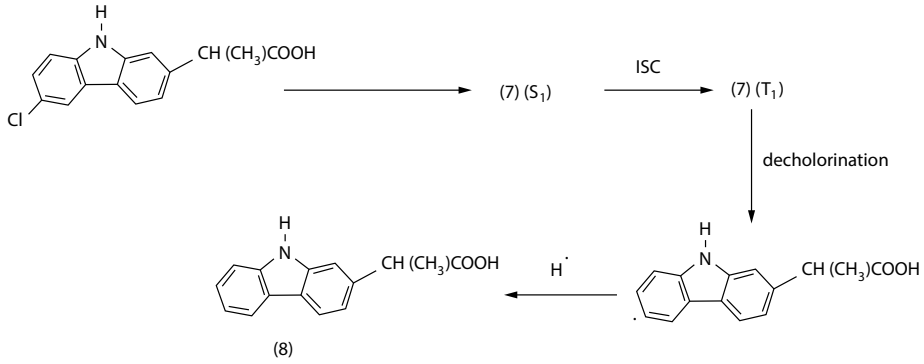


Fig. (5). Reaction scheme for conversion of carprofen (7) to a photoproduct (8).

Indoprofen **(9)** is a NSAID used in the treatment of both osteoarthritis and rheumatoid arthritis and exhibits the same phototoxic effect [14]. Irradiation of Indoprofen in aqueous buffer results in photodecarboxylation and leads mainly to four oxidative photoproducts whose proportions increase with increasing oxygen concentration. The mechanism is outlined in. The phototoxicity of this drug have been proposed to occur through type–I mechanism (Fig. **6**).

Red blood cell lysis via photosensitization by various phototoxic drug such as naproxen and suprofen has been investigated in detail [15, 16]. The deaerated solutions of naproxen **(10)**, when irradiated underwent a decarboxylation process via intermediate radicals; while under aerobic conditions photo-oxidation leading to the formation of the photoproduct 6-methoxy-2-acetonaphthone **(11)**. A molecular mechanism involving free radicals and singlet oxygen as important intermediates has been proposed (Fig. **7**). In

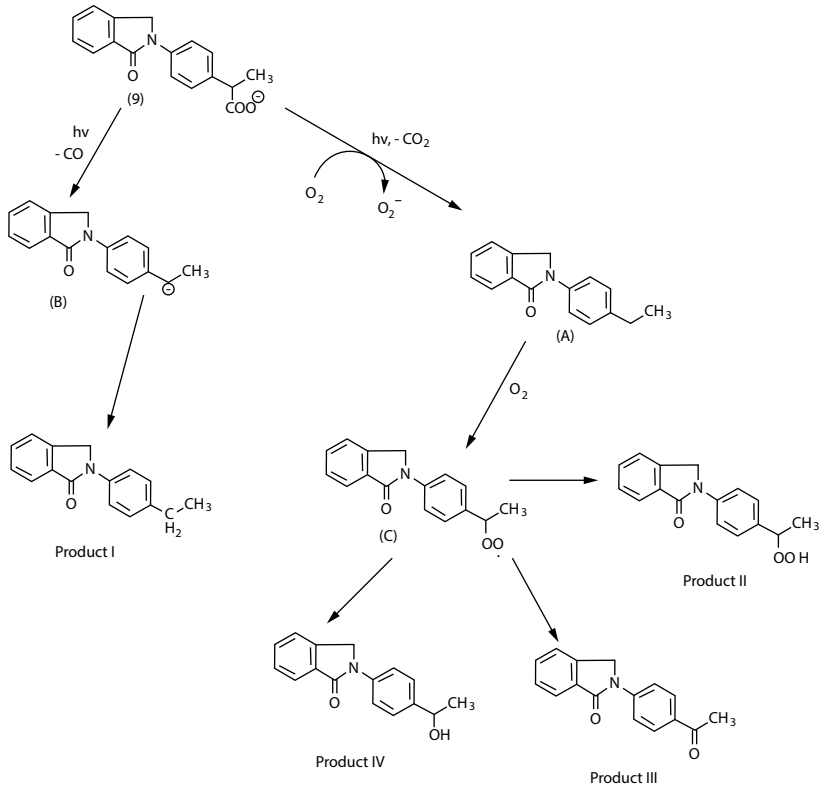


Fig. (6). Reaction scheme for conversion of indoprofen (9) to four oxidative photoproducts.

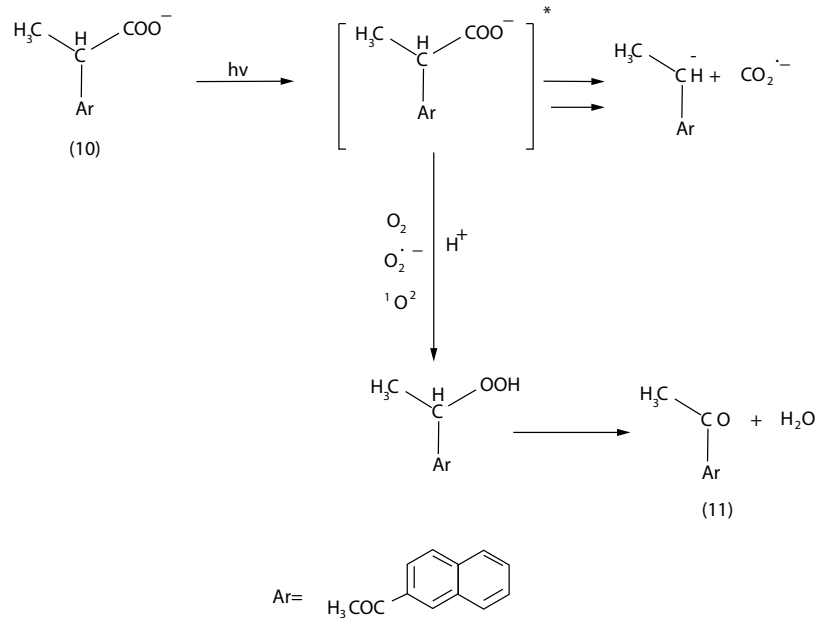


Fig. (7). Reaction scheme for conversion of naproxen (10) via intermediate radicals to the photoproduct 6-methoxy- 2-acetonaphthone (11).

case of suprofen (**12**), when the drug is irradiated at 310-390 nm in deaerated buffered solutions (pH 7.4), it leads to a decarboxylation process with the formation of p-ethyl phenyl 2-thienyl ketone (**13**); whereas in aerated solutions, the formation of photoproduct I and the photoproducts p-acetyl phenyl 2-thienyl ketone (**14**) and p-(1-hydroxyethyl) phenyl-2-thienyl ketone (**15**) occurs. The overall results of suprofen photodegradation and a hemolysis demonstrated that cell damage is provoked principally by the direct attack of drug radicals and secondarily by singlet oxygen and hydroxyl radicals (Fig. **8**).

The irradiation of aerated solution of the novel anti-inflammatory drug, benzydamine, results in its photosensitization through several competing pathways, namely, singlet oxygen mediated oxidation, and electron-transfer mechanisms [17]. The ability of benzydamine to participate as sensitizer in several types of photochemical reaction is relevant to the observed clinical photosensitivity of the drug.

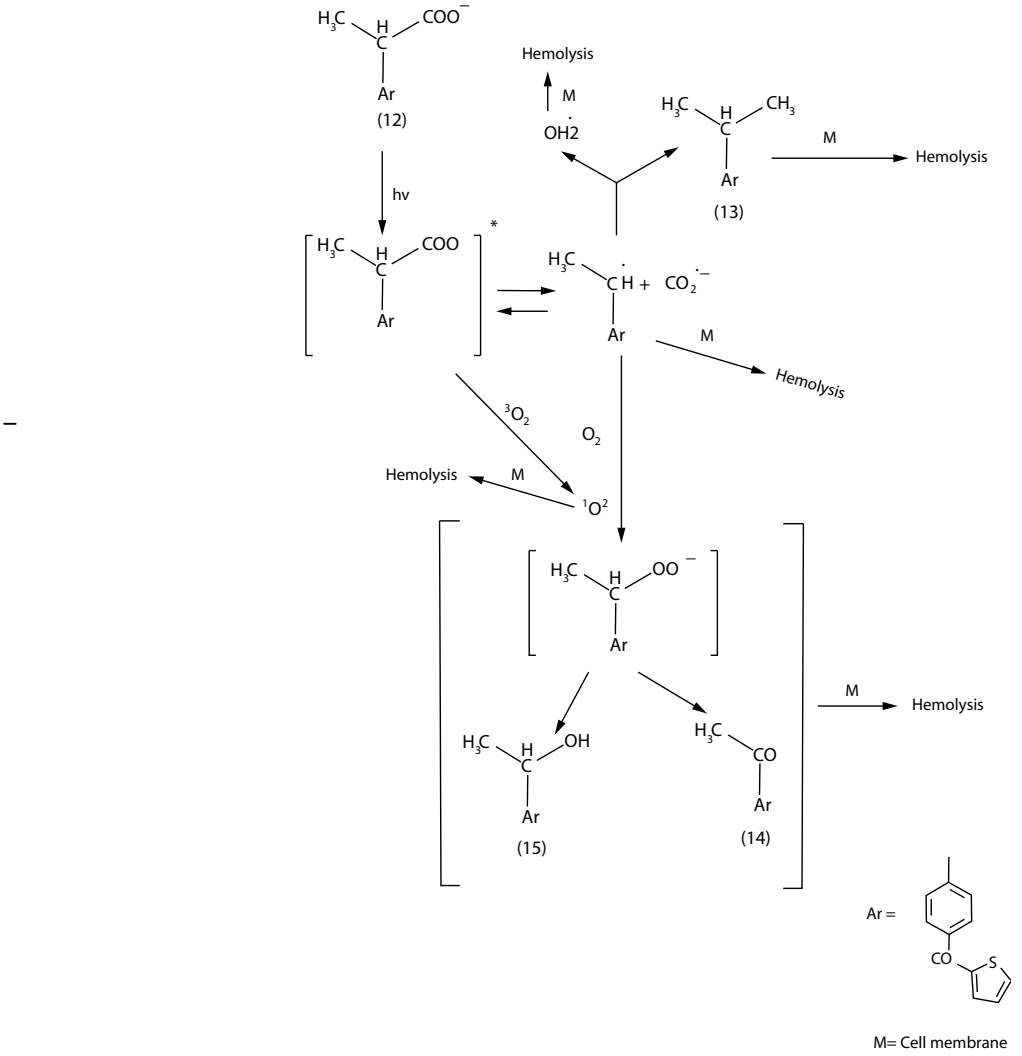


Fig. (8). Reaction scheme for conversion of suprofen (12) to p-ethylphenyl2-thienylketone (13) and photoproducts p-acetylphenyl 2-thienyl ketone (14) and p-(1-hydroxyethyl)phenyl-2-thienylketone (15).

The drug thiocolchicoside (2-dimethoxy-2-glucosidoxythio colchicine), is photolabile under irradiation with UV-A light in both aerobic as well as anaerobic conditions [18]. Irradiation of a methanol solution of thiocolchicoside produces two photoproducts without a glucoside group. One of the compound loses the methylthio-group, while the other is oxidized (only under aerobic conditions) to sulfoxide. Thiocolchicoside has been screened *in vitro* in different concentrations for UV-Vis (Ultraviole-Visible)-induced phototoxic effects in a photohemolysis test, in the presence and absence of different radical scavengers, singlet oxygen and superoxide anion radical ($O^{\bullet}_2$) quenchers. Studies on peripheral blood mononuclear cells (lymphocytes) demonstrated that the drug exerts phototoxic effects [18]. Protection by GSH (glutathione), DABCO (1, 4-Diazabicyclo [2.2.2] octane), sodium azide and SOD (Superoxide dismutase) are indicative of both type–I and type–II photosensitization pathways mediated by free radicals and singlet molecular oxygen.

Antineoplastic Drugs

Tirapazamine (**16**), a potential antitumor phototoxic agent, which has been found to be capable of acting selectively under hypoxic environment; a condition commonly found in rapidly growing tumors. One of the proposed mechanisms of action of this compound is the enzymatic electron transfer and subsequent proton transfer to generate free radical, which undergoes β-fission to generate 3-aminobenzo-1, 2, 4-triazine- *N*- oxide (**17**) and hydroxyl radical, which is well established as a promoter of nucleic acid cleavage (phototoxicity) (Fig. **9**) [19].

The anti-cancer drug flutamide (**18**) is photolabile under UV-B light in either aerobic or anaerobic conditions [20]. Irradiation of a methanol solution of this drug produces several photoproducts **(19) (20) (21) (22)** and **(23)**; one by photoreduction of the nitro group, another by rupture of the aromatic-NO bond of the parent compound, two as a result of the rupture of the CO–NH bond and one derived from the photoreduction product by scission of the aromatic-NH_2 bond. The phototoxicity of flutamide was shown to occur through radical mediated (type–I) process (Fig. **10**).

Decarbazine is clinically effective in the treatment of several malignant disorders, including metastatic malignant melanoma, Hodgkin's disease and soft tissue sarcomas, in combination with other anticancer drugs. The drug induces photosensitizing effect in patients undergoing cancer chemotherapy. On UVA-irradiation, photoactivated decarbazine generates the carbene and aryl radicals, which may induce both DNA adducts and 8-oxo-dG formation, resulting in photogeno-toxicity [21].

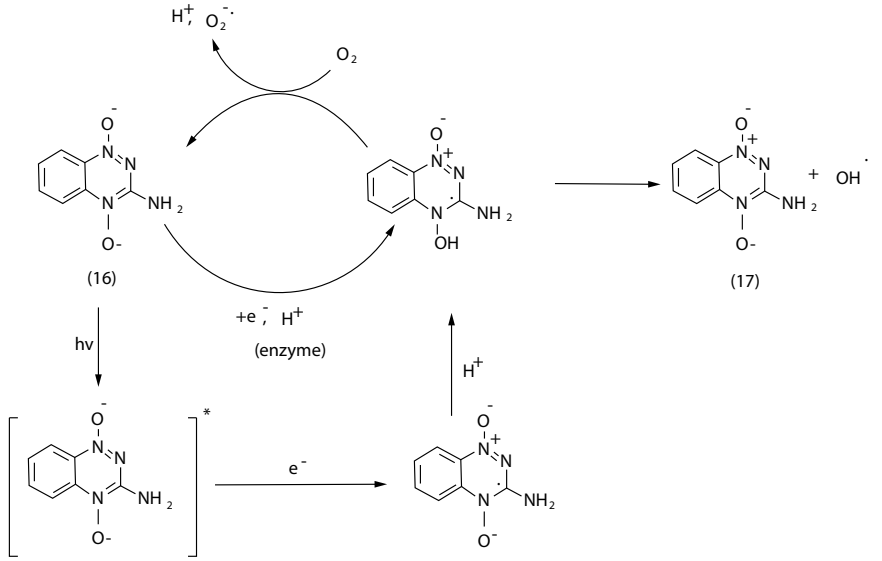


Fig. (9). Reaction scheme for conversion of Tirapazamine (16) to generate 3-aminobenzo-1,2, 4-triazine-N- oxide(17).

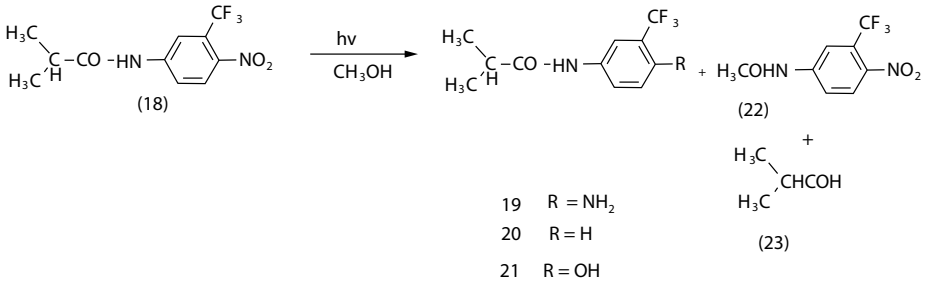


Fig. (10). Reaction scheme for conversion of flutamide (18) to five products under different conditions (19, 20, 21, 22, 23).

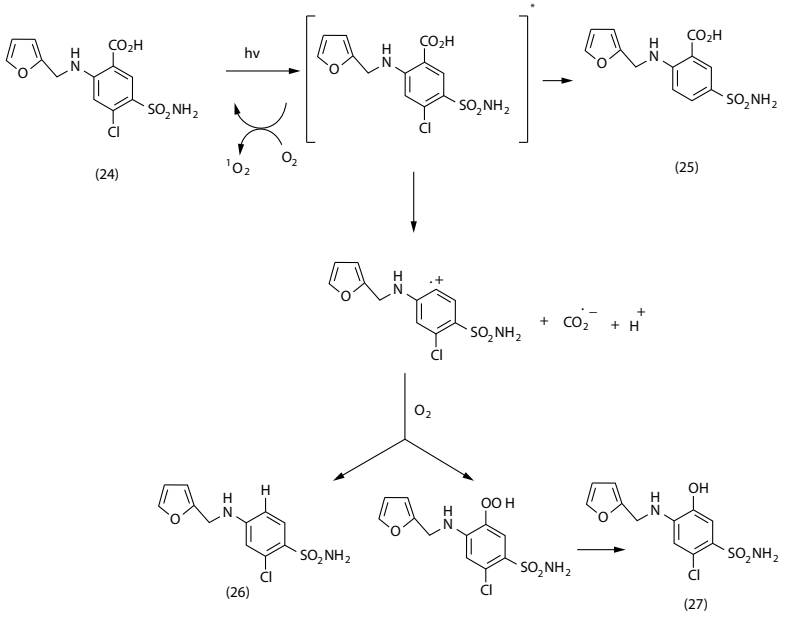


Fig. (11). Reaction scheme for conversion of furosemide (24) to photoproducts (25, 26, 27).

A spectroscopic study of irradiated photosensitizing drug, camptothecin, in the presence and absence of copper has been performed to explore and identify the radical species generated in these processes [22]. The report indicated that camptothecin is a promising photosensitizer. It also stated that the radicals and singlet oxygen generated upon illumination, play a central role in DNA cleavage and the induction of apoptosis in cancer cells [22].

Diuretic and Anti Diabetes Drugs

The diuretic drug, furosemide **(24)**, is known to be photolabile under both aerobic and anaerobic conditions [23]. Irradiation of a methanol solution of **(24)** under oxygen produces several photoproducts (**25**), (**26**), (**27**) and singlet oxygen, while under argon the photoproducts (**25**) and (**27**) have been isolated. The findings indicated that phototoxicity mechanism for this drug most probably involves reactions of singlet oxygen and superoxide oxygen with cellular components than reactions of a free radical intermediate or stable photoproducts (Fig. **11**).

The diuretic drug acetazolamide (**28**) was found to be photolabile under irradiation with UV-B (at 300 nm) light under aerobic conditions. Moreover, photodegradation of the drug with UV-A light (at 337 nm, N_2 laser) as well as its photosensitizing degradation by rose bengal has also been observed [24]. Two photoproducts (**29**) and (**30**) were isolated and identified, that were found to be identical in both conditions. Sensitization reaction involving singlet oxygen leads to the decomposition of acetazolamide. Acetazolamide has been shown to photosensitize the reduction of nitro blue tetrazolium in PBS. The reaction is more efficient in deoxygenated condition and is quenched in the presence of SOD. These results indicate that direct electron transfer from the excited state of acetazolamide to the substrate occurs; speculating that the superoxide molecule could be involved as an intermediate when the oxygen is present (Fig. **12**).

The photolabililty of the antidiabetes drug, gliclazide (**31**), under aerobic conditions and UV-B light has been studied [25]. Irradiation of a phosphate buffered solution of gliclazide under oxygen atmosphere produces two photo products as (**32**) and (**33**). The photochemistry of (**31**) involves cleavage of the S-N and C (O)-N bonds (Fig. **13**). The reported results indicated that gliclazide exhibits radical mediated (type–I) phototoxicity.

Antibiotics

The *in vitro* photochemical reactions of antibacterial drugs, sulfamethoxazole alone and in combination with trimethoprim, have been studied to obtain information on its photosensitization mechanism [26]. Sulfamethoxazole in aqueous solution, on exposure to UVB radiation, generates free radicals and singlet oxygen, with the neutral molecule being at least twice as active as the sulfamethoxazole anion. Photoexcited sulfamethoxazole can participate in electron transfer to cytochrome-c and nitro blue tetrazolium, and sensitizes the peroxidation of linoleic acid and the hemolysis of human erythrocytes, predominantly by a free radical mechanism. Trimethoprim is relatively inactive in the same photochemical system [26].

Amodiaquine **(34)**, an antimalarial drug, possess undesirable photosensitizing properties, generating phototoxic side effects in both the skin and the eye [27]. UV irradiation of amodiaquine leads to the formation of a photoproduct produced through concerted cycloaddition of singlet oxygen to the aminophenolic ring

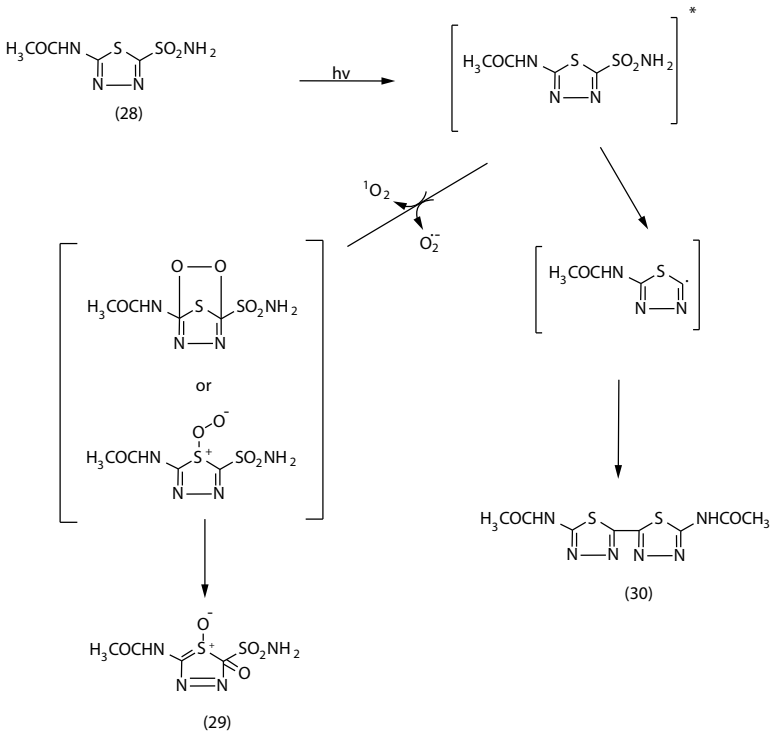


Fig. (12). Reaction scheme for conversion of acetazolamide (28) to photoproducts (29, 30).

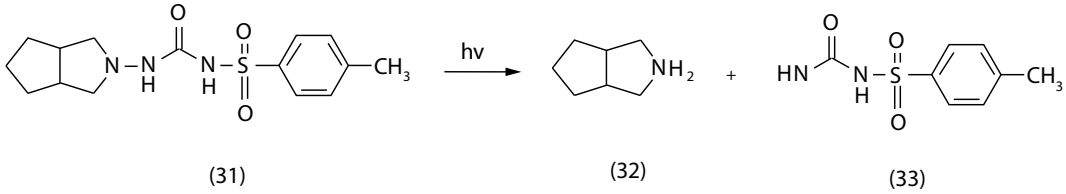


Fig. (13). Reaction scheme for conversion of gliclazide (31) to photoproducts (32, 33).

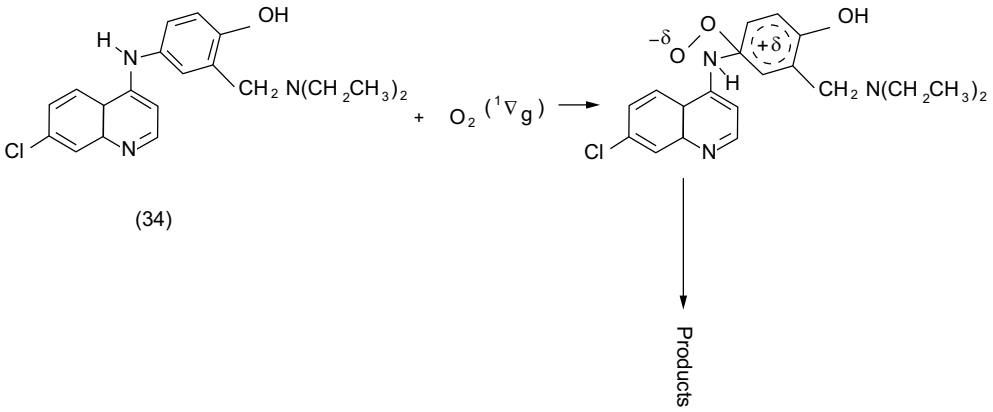


Fig. (14). Reaction scheme for conversion of amodiaquine (34) to photoproducts.

of this drug (Fig. **14**). The study indicated that singlet oxygen formation account for the observed phototoxic effect of this drug [27].

Vasoregulator Drugs

The potential phototoxic activity of naphazoline (NP), 2-(1-naphthylmethyl) imidazolone (**35**), belonging to the vasoregulator class of drugs, was investigated by studying its photoreactivity towards DNA [28]. Photocleavage studies combined with laser flash photolysis experiments provide clear evidences that the transient species produced under NP photolysis reacts with the DNA, thereby promoting its breakage under both aerobic and anaerobic conditions (Fig. **15**).

Beta-Blocker Drug

The photochemistry of phototoxic drug propranolol (PR), 1-isopropylamino-2-(1- naphthyloxy) propan-2-ol (**36**) has been studied to decipher its phototoxicity mechanism [29]. PR photodecomposition takes place in an aerated aqueous medium, leading to the formation of 6-hydroxy-1,4-naphthoquinone (**37**) as the sole stable photoproduct, Creation of this photoproduct demonstrated that photodegradation occurs via a type–II mechanism involving irreversible trapping of self-photogenerated singlet molecular oxygen (Fig. **16**) [29].

Lipid-Lowering and Anesthetic Agents

Atorvastatin **(38),** is one of the most frequently prescribed drug worldwide [9], as an agent for lowering blood cholesterol. However, clinical cases of cutaneous adverse reactions have been reported and being associated with the photosensitivity disorders. On the basis of its photophysical and photochemical reactions, the phototoxicity of atorvastatin can be attributed to the singlet oxygen formation, with the phenanthrene-like photoproduct as a photosensitizer (Fig. **17**).

The HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibitor, fluvastatin (**39**), undergoes a rapid photodegradation upon UV-A irradiation in buffered aqueous solution to give rise to a benzocarbazole-like photoproduct (**40**) [30]. This benzocarbazole-like photoproduct acts as a strong photosensitizer and may be responsible for the phototoxicity of the drug (Fig. **18**).

The anti-hyperlipoproteinemic drug, fenofibrate, was found to be photolabile under both aerobic and anaerobic conditions [31]. Irradiation of a methanol solution of this drug under argon

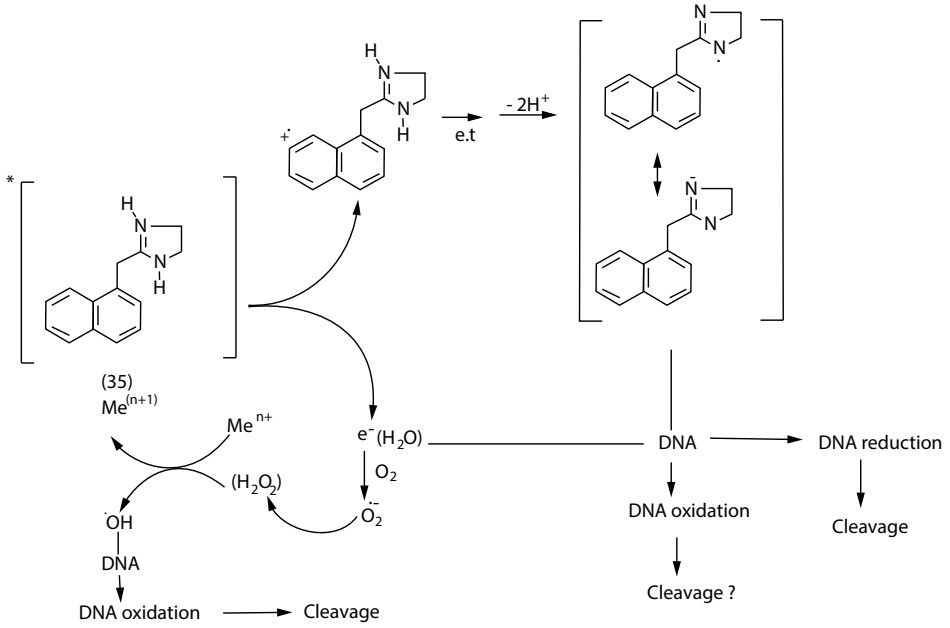


Fig. (15). Reaction scheme for conversion of naphazoline (NP), 2-(1-naphthylmethyl) imidazolone (35) to photoproducts.

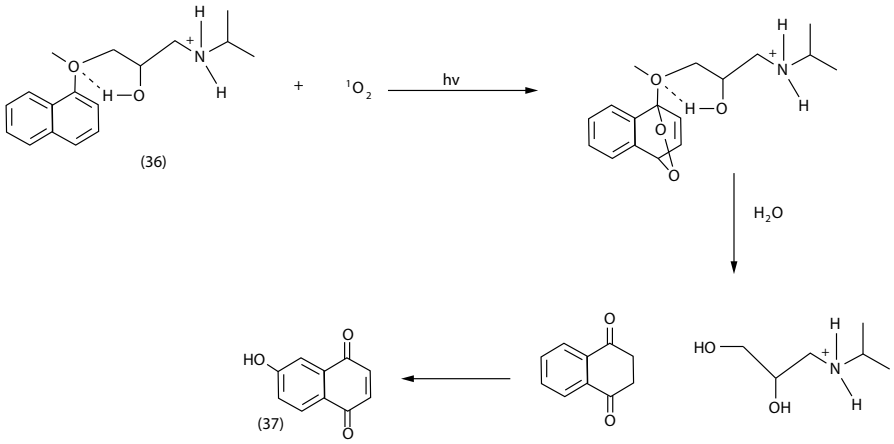


Fig. (16). Reaction scheme for conversion of propranolol (PR), 1-isopropylamino-2-(1- naphthyloxy)propan-2-ol (36) to 6-hydroxy-1,4-naphthoquinone (37).

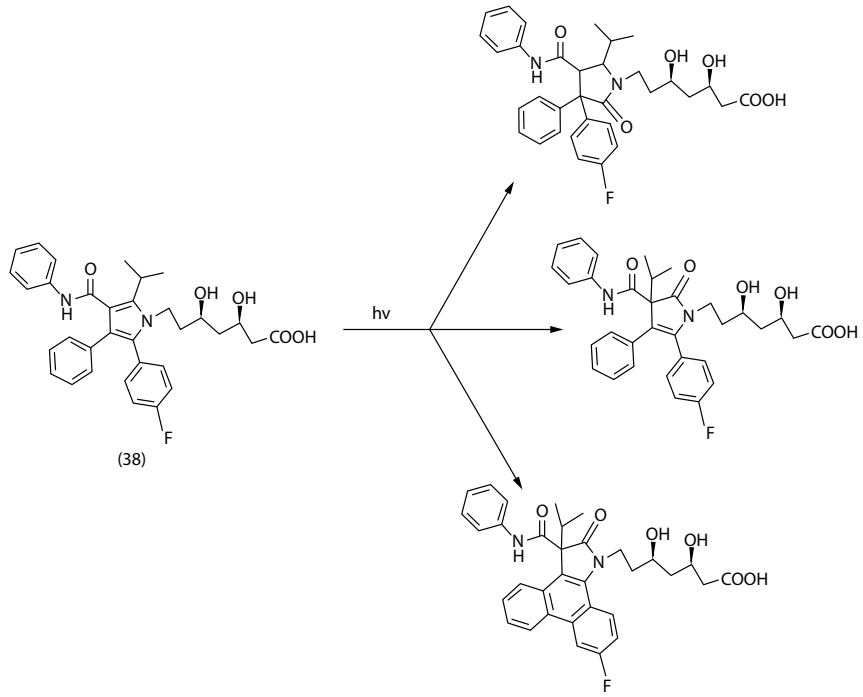


Fig. (17). Reaction scheme for conversion of atorvastatin calcium (38) to phenanthrene-like photoproducts.

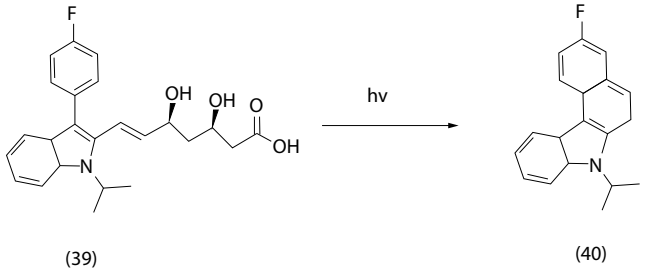


Fig. (18). Reaction scheme for conversion of fluvastatin (39) to benzocarbazole-like photoproduct (40).

produced numerous photoproducts, namely, isopropyl 4-(1-[4-chlorophenyl]-1,2-dihydroxy) ethylphenoxyisobutyrate, 1,2-*bis* (4-chlorophenyl)-1,2-*bis* (4-[isopro-poxycarbonylisopropoxy] phenyl) ethane-1,2-diol and 4-(4-chlorobenzoyl) phenol; while under oxygen, the photoproducts 4-chloroperbenzoic acid, methyl 4-chlorobenzoate, 4-chlorobenzoic acid and singlet oxygen were formed. This behavior can be explained through the involvement of free radicals, singlet oxygen and stable photoproducts.

The reaction between the anaesthetic agent, 2, 6-diisopropylphenol (propofol, PPF, **41**), and singlet oxygen has been investigated in aqueous solutions [32]. The reaction of the propofol with singlet oxygen (produced by light irradiation of rose bengal), leads to the formation of two reaction products, 2,6-diisopropyl-*p*-benzoquinone (**42**) and 3,5,3',5'-tetraisopropyl-(4,4')-diphenoquinone (**43**) (Fig. **19**).

Antidepressant and Antiplatelet Drugs

Lamotrigine, an anticonvulsant and antidepressant drug, produces phototoxic responses in some patients [33]. Lamotrigine absorbs UV light, generating singlet oxygen. Moreover, when the reaction was carried out in acetonitrile, a small amount of superoxide anion radical was also detected. Thus, lamotrigine acts as a

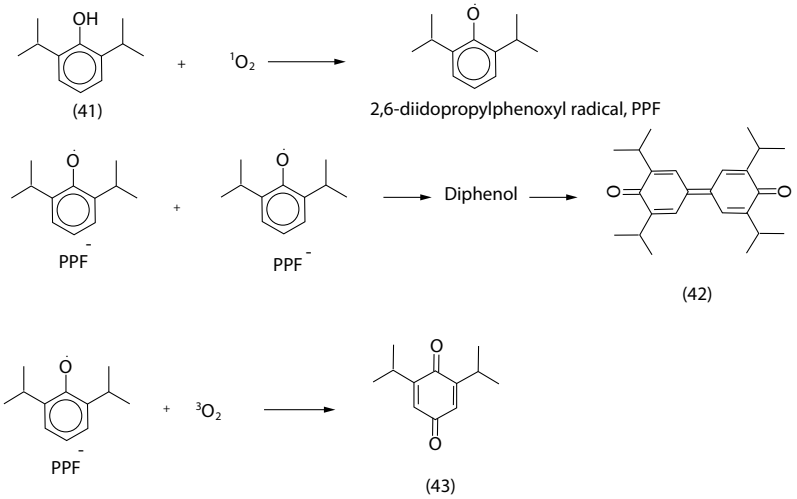


Fig. (19). Reaction scheme for conversion of 2,6-diisopropylphenol (propofol, PPF, 41) to two reaction products, 2,6-diisopropyl-p-benzoquinone (42) and 3,5,3',5'-tetraisopropyl-(4,4')-diphenoquinone (43).

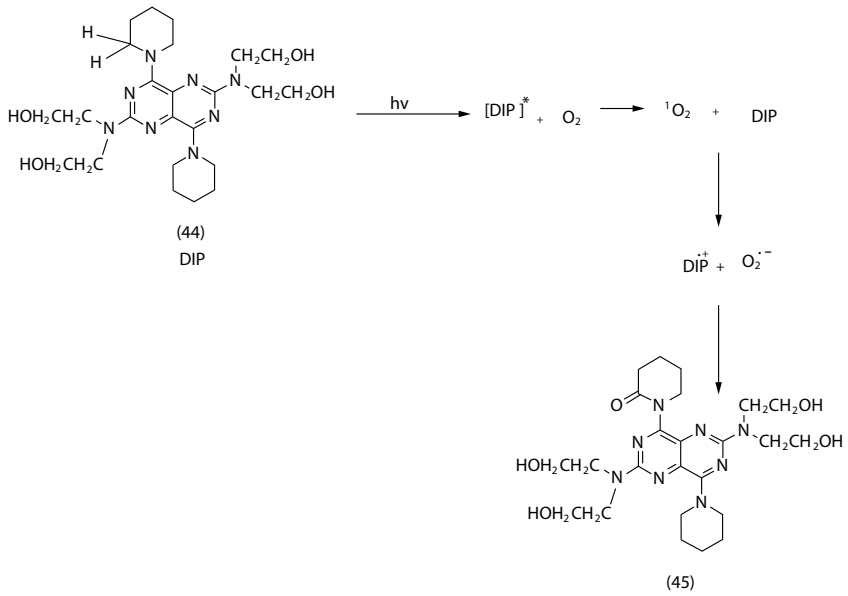


Fig. (20). Reaction scheme for conversion of dipyridamole (44) to a photoproduct (45).

moderate photosensitizer producing mild phototoxicity, resulting in the oxidation of the linoleic acid, mainly by the contribution of singlet oxygen.

The photochemical reactions of dipyridamole (**44**), a healing agent, under UV-A and aerobic conditions resulted in the formation of the photoproduct (**45**). The photodegradation of dipyridamole occurs probably via a type–II mechanism involving irreversible trapping of self-photogenerated reactive oxygen species (ROS). The formation of singlet oxygen and superoxide anion radical during the dipyridamole photodegradation makes one suspicious of a possibility that dipyridamole could be involved in the oxidative stress in biological systems (Fig. **20**) [34].

Triflusal (**46**) is a platelet antiaggregant drug with photoallergic side effects [35]. However, it is considered a prodrug, since it is metabolized to 2-hydroxy-4-trifluoro methylbenzoic acid (**47**), the pharmacologically active form. The active drug (**47**) was found to be photolabile under various conditions. Its major photodegradation pathway appears to be the nucleophilic attack at the trifluoromethyl moiety leading to the formation of a photoproduct (**48**). The photobinding of (**48**) to proteins such as bovine serum albumin (BSA) has been demonstrated using ultraviolet–visible (UV–Vis) and fluorescence spectroscopy. Nucleophilic groups present in the protein appear to be responsible for the formation of covalent drug photoadducts, which is the first step involved in the photoallergy shown by triflusal (Fig. **21**).

Amitriptyline (**49**) is a tricyclic antidepressant drug, used to treat a number of mental disorders. This drug induces photosensitizing reactions in humans, as an adverse effect [36]. Upon UV-A irradiation, it photochemically transforms into photoproducts (**50**) and (**51**). The phototoxicity of amitriptyline can be attributed to radical formation via type–I mechanism (Fig. **22**).

CONCLUSION

The photochemistry of pharmaceuticals is an area of growing concern as the number of drugs found to be photosensitive/phototoxic is increasing. Since all the adverse photobiological effects produced by photosensitizing/phototoxic drugs are the consequences of photochemical reactions, it is important to

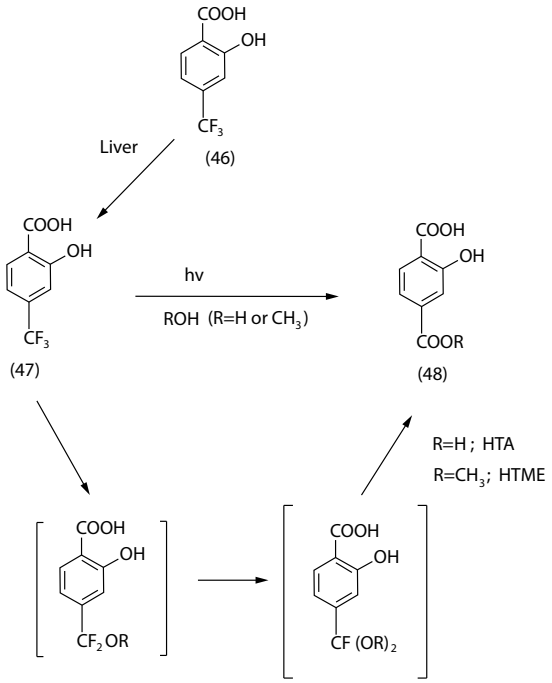


Fig. (21). Reaction scheme for conversion of trifluoromethylbenzoic acid (46) to a photoproduct (47, 48).

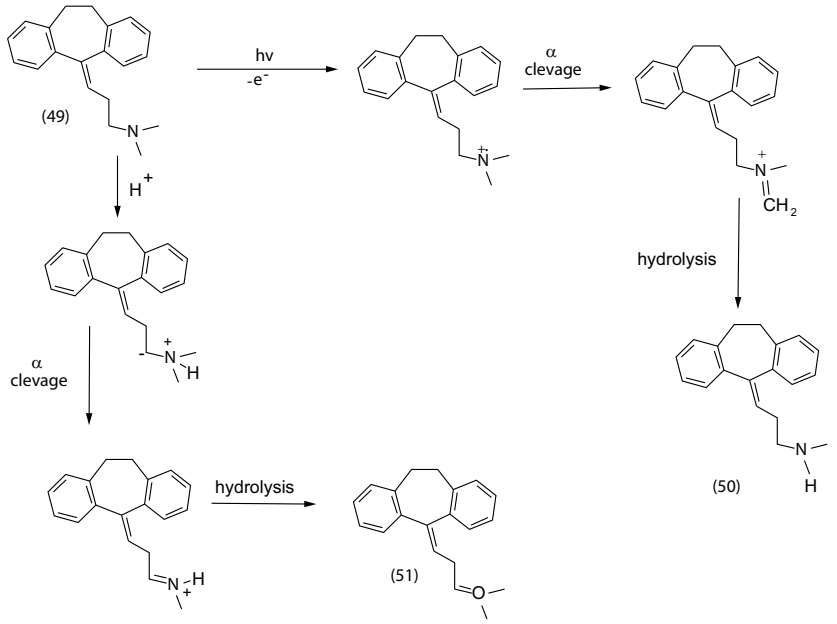


Fig. (22). Reaction scheme for conversion of Amitriptyline (49) into photoproducts (50, 51).

stimulate more chemists to work on the molecular basis of photobiological problems. The dated interest of photochemists in the properties of the electronically excited states of compounds of pharmaceutical use has been rapidly increasing during the last decade. This is not only connected to the increasing number of cases of drug-photoinduced disorders, but it has also attracted considerable attention from a more fundamental photochemical standpoint. Thus, it is worthy to stress that studies performed on drugs bearing either simple or complex chromophoric structures have provided remarkable contributions to the broad area of the molecular mechanisms of photo-initiated reactions.

Drug photosensitization is a major problem since the abnormal reactions seriously limit or exclude the usage of drugs. Every now and then, new photosensitizers come into the market whereas others are abandoned. This problem of photosensitization can only be prevented by the complete knowledge of mechanism involved, which helps in providing information about the part of molecule responsible for such adverse effects. Furthermore, the mainstays of management of drug-induced photosensitivity include avoidance of the causative agent, by seeking shade and staying out of direct sunlight between 10 AM and 4 PM (generally the sun's most intense hours), employing high-SPF (sun protection factor) broad spectrum sunscreen protection for symptomatic relief from it. Therefore, some combination of sun avoidance and sun protection is the preferred strategy to prevent the unwanted effects of photosensitivity.

The prevalence of photosensitivity in the general population is uncertain. There is a need for randomized, controlled trials of strategies for prevention, control, and treatment of photosensitivity disorders. Moreover, additional data are needed for a better assessment of the risk of photosensitivity that is associated with many drugs. Patients need to be counselled regarding the possible photosensitizing properties of both prescription and non-prescription medications. For a possible clinical follow-up testing on potential risks, controlled clinical studies e.g. determination of the minimal erythema dose (MED) in volunteers are encouraged. In case of potential risks identified either *in vitro* or in phototoxicity testing in human, an appropriate clinical safety survey should be performed both before and after marketing authorization. With these strategies, risks associated with photosensitivity can be avoided.

AUTHORS' CONTRIBUTIONS

MRZ, AG and JI conceived the idea and wrote the manuscript with portions contributed by AA, QZ and R. QZ, MO and AH critically reviewed the manuscript. QZ and GMA formatted the whole manuscript according to journal requirements, prepared the images in TIFF format and inserted citations using endnote program. SHMS and GA critically reviewed the whole manuscript and suggested significant modifications.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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