Abstract

The thesis entitled “studies on photochemical reactivity of drug molecules and related substances,” describes photochemical studies on drug molecules and related substances and the study of ensuing photochemical processes and mechanisms. Certain drugs are able to produce phototoxicity side effects that are undesired adverse cutaneous reactions that appear as a consequence of the combined action of drugs and sunlight in the treated patients. The variety in molecular structure of phototoxic drugs is immense and almost all classes of drug compounds contain members with adverse photobiological effects. Also, photochemical degradation, by various procedures, including photooxidation, is likely to be an important loss and toxicity mechanism for many drugs and pharmaceuticals in biosystem, and this is of great significance to environmental photochemistry and photobiology. Natural products have served as tools and leads for the development of new drugs and several natural compounds from plants and animal kingdom are now useful drugs. Moreover, plenty of plant materials for their biologically active principal have proved to be of potential medicinal value.

Singlet oxygen, a potential product of photochemical reactions of many compounds is a damaging agent to all living organisms, and also plays a very significant role in plant metabolism. Photosensitizing reactions among secondary plant products is a widespread phenomenon involving ultra-violet as well as visible light. Secondary plant substrates of diverse biogenetic origin are capable of the photogenerating singlet oxygen, and they also act as quenchers of singlet oxygen, suggesting the wide spread
use of these as potent toxic, protective and defensive agents. Thus, photochemical studies on drugs and promising drug molecules is an area of vital importance in current medicinal chemistry, for establishing a relation to its phototoxicity. A satisfactory understanding of this phenomenon requires a detailed knowledge of the photochemistry of such molecules. In principle, photochemical reactivity of drugs can be anticipated on the basis of good knowledge of the possible photochemical mechanisms. To achieve this goal different types of studies have to be undertaken:

(a) Photophysical studies—light absorption and emission (fluorescence, phosphorescence) to determine the nature of involved excited states, as well as their energies. Laser flash photolysis for detection of triplet states of other short-lived transition species that could interact with biomolecules. Singlet oxygen detection (steady state or time resolved near infrared emission).

(b) Photosensitized reactions of biomolecules—photodynamic lipid peroxidation, photomodification of proteins (protein photocrosslinking, drug protein photobinding) drug photosensitizer DNA damage (strand breaks, oxidative damage to bases, pyrimidine dimers).

(c) Photochemical studies—photostability, photodegradation (isolation and identification of drug-derived photoproducts by chromatography and spectroscopy, product-based elucidation of the photochemical mechanisms.

(d) Photooxidation of drug molecules with singlet oxygen.
In the present work we have undertaken basically two of the above aspects ‘c’ and ‘d’ of the drug photochemistry, using some representative examples from established drugs and promising drug (biologically active molecules) class.

Chapter 1 of the thesis includes some basic concepts of photochemistry; some active areas of photobiological research with an outline of their importance; properties, generation and reaction of singlet oxygen; some facts pertinent to human photobiology and a brief survey of the photochemistry and photobiology of drugs and some biologically active natural products.

Second chapter of thesis describes photochemical studies on acyclovir (I) and phenazopyridine hydrochloride. Photodegradation of aqueous solution of acyclovir in phosphate buffer (pH 7) under aerobic condition was studied with light of wavelength >270 nm. Three major products were isolated and identified on the basis of IR, NMR and mass spectral studies. The products were: (2-hydroxyethoxy) methyl spiroiminodihydantoin (2), (2-hydroxyethoxy) methyl (amino)-2-imino-1,2-dihydroimidazole-5-one (3), and 2,2-diamo-no-4-[(2-hydroxyethoxy) methyl] amino)-5-[2H]-oxazolone (4). (Scheme 1) Further the effects of: D$_2$O as reaction medium, added sodium azide and the absence of oxygen on the photodegradation of acyclovir was checked. These observations indicated the involvement of singlet oxygen. The formation of products is explained by the photooxidation of acyclovir.

In an extensive study the antiviral drug acyclovir (1) was treated with triplet excited ketone, generated by thermal decomposition of 3-(hydroxymethyl)-3,4,4-
trimethyl-1,2-dioxetane (HTMD), in the dark. Three major photo-oxidation products were isolated and characterized by spectroscopic studies. The products were (2-hydroxyethoxy) methyl spiroiminodihydantoin (2), (2-hydroxyethoxy) methyl (amino)-2-imino-1,2-dihydroimidazole-5-one (3), and 2,2-diamino-4-[(2-hydroxyethoxy) methyl] amino)-5-[2H]-oxazolone (4). The HTMD-induced reaction was found to occur by two photooxidation mechanisms, at almost equal pace: type I leading to 3 and 4 and type II giving 2. The findings are based upon determination of the exact yields of products in a comparative study with the established photosensitizers, riboflavin (type I) and rose Bengal (type II) (Scheme 2).

Scheme 1
Photochemistry of phenazopyridine hydrochloride (5) was studied in different reaction media including the drug adsorbed on silica gel. This resulted in photochemical cyclodehydrogenation, reductive photodegradation and rearrangement of the drug molecule. Four major products were isolated and identified on the basis of IR, NMR and mass spectral studies. The products were: pyrido[3,4-c]cinnoline-2,4-diamine (6), N,N'-phenylpyridine-2,3,4,6-tetraamine (7), pyridine-2,3,6-triamine (8), 2,6-diamino-1-(4-aminophenyl)pyridin-4(1H)-one (9) (Scheme 3).
Chapter 3 of the thesis records the photochemistry of two anti-inflammatory drugs desonide (10) and clobetasol propionate (14) was studied in aerobic as well as in anaerobic conditions with different irradiation wavelengths (254 nm and 310 nm) in acetonitrile and 2-propanol. The photoproducts were characterized on the basis of their IR, $^1$H-NMR, $^{13}$C-NMR, mass spectral and elemental analysis studies. The products from the photolysis of desonide were: $^{11}\beta$, 21-dihydroxy-16α, 17α-(1-methylethylidenedioxy)-1,5-cyclopregn-3-ene-2,20-dione 11, $^{11}\beta$-hydroxy-16α, 17α-(1-methylethylidenedioxy) androsta-1,4-diene-3-one 12, 17β-hydroperoxy-11β-hydroxy-16α, 17α-(1-methylethylidenedioxy) androsta-1,4-diene-3-one 13 (Scheme 4). From the photolysis of clobetasol (14) products were: 21-chloro-9-fluoro-11-hydroxy-16-methyl-17(1-oxopropoxy)-1,5-cyclopregn-3-ene-2,20-dione 15 (254 nm),
21-chloro-9-fluoro-11-hydroxy-16-methyl-17(1-oxopropoxy)-18,20-cyclopregn-1,4-diene-3-one 16. 9-fluoro-17-hydroperoxy-16-methyl-17(1-oxopropoxy) androsta-1,4-diene-3-one 17 (Scheme 5).
The chapter 4 records our investigation on the photoreactivity of anti-cancer drug flutamide (18, FM) adsorbed on silica on the silica gel TLC plates. The results were consistent with the formation of nitroso derivative 19 as the sole stable photoproduct, formation of which was realized by the structural changes of flutamide occurring upon its compartmentalization in the silica gel intermolecular cavities (Scheme 6).
The photostability of three flutamide oral dosage formulations (tablets available in India) were studied using indirect sunlight (daylight) and continuous artificial light. The extent of photodecomposition of FM was determined using a specific reversed phase high performance liquid chromatography (HPLC) method. The effectiveness of artificial and natural sunlight on FM photodegradation was also determined using both pure FM powder as well as a methanolic FM solution for comparison to tablet form. All the tested FM formulations were likely to be photostable up to at least 12 weeks of continuous artificial and natural day light exposure, compared with pure FM powder and methanolic solution. Photodegradation of FM powder and methanolic solution exposed to indirect sunlight was faster than the artificial light.

Chapter 5 of the thesis describes photooxygeination reaction of two plant-derived terpenoids tinosponone (20) and furanoeremophilane (24). The reaction of tinosponone with singlet oxygen was studied by using different combinations of photosensitizers (i.e. rose bengal, methylene blue, riboflavin and benzophenone), solvents (i.e. benzene, chloroform, acetone, acetonitrile and methanol) and singlet oxygen scavengers (i.e. DABCO and sodium azide). Two major products: (3S,4aS,4bS,8R,8aR,10aR)-8-hydroxy-3-(5'-hydroxy-2'-oxo-2',5'-dihydrofuran-3'-yl)-4a,8a-dimethyl-3,4,8,8a,9,10-hexahydro-10aH-benzo[f]isochromene-1,5 (4aH,4bH)-dione (21) and (3S,4aS,4bS,8R,8aR,10aR)-8-hydroxy-4a,8a-dimethyl-3-((1'R)-3'-oxo-4',6'-dioxa-bicyclo[3.1.0]hexan-1'-yl)-3,4,8,8a,9,10-hexahydro-10aH-benzo[f] isochromene-1,5(4aH,4bH)-dione (22) were isolated in all the solvents except methanol. In methanol a single product (3S,4aS,4bS,8R,8aR,10aR)-8-hydroxy-3-
(5'-hydroperoxy-2'-methoxy-2',5'-dihydrofuran-3'-yl)-4a,8a-dimethyl-3,4,8a,9,10-hexahydro-10aH-benzo[f] isochromene-1,5(4aH,4bH)-dione (23) was obtained (Scheme 7). All products were characterized on the basis of IR, $^1$H-NMR, $^{13}$C-NMR, mass spectral and elemental analysis studies. The formation of products was explained by photooxidation of tinosponone. Effect of different solvents with the variation of added singlet oxygen sensitizers and singlet oxygen scavengers was observed on the yields of photooxidation products and was correlated to the rate of singlet oxygen formation.

The photochemical oxygenation reaction of 2β-angeloyloxy-10β-H-furoeremophilane (24), a sesquiterpene, was studied in benzene and methanol. Three photoproducts were isolated and characterized by IR, $^1$H-NMR, $^{13}$C-NMR and mass spectral studies. Sesquiterpene itself was found to be singlet oxygen ($^1$O$_2$) sensitizer. Addition of rose bengal increased the rate of photooxidation whereas as DABCO was found to decrease the rate of photolysis proving the involvement of $^1$O$_2$ in these photoreactions. 2β-angeloyloxy-8-hydroxy-10β-H-eremophilanolide (25) and 2β-angeloyloxy-7,8-epoxy-10β-H-eremophilanolide (26) were obtained as products in benzene. Photolysis in methanol gave a single product 2β-angeloyloxy-10β-H-8-methoxy-12-hydroxy-7,11-dihydro-eremophilanolide (27). Reaction was also carried out by adsorbing compound (24) on silica gel bound rose bengal which yielded the products 25 and 26 with an increase in the rate of reaction (Scheme 8).
Scheme 7

Scheme 8