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Oxidative Photodegradation of Prulifloxacin under aerobic condition

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ABSTRACT

*The phototoxic antibacterial drug prulifloxacin (PLF, **1**) is photolabile under aerobic condition in UV-A light. Irradiation of a phosphate buffer solution of **1** under oxygen atmosphere produces one major photoproduct, 6-fluoro-1-methyl-4-oxo-7-[piperazin-1-yl]-1,4-dihydro-[1,3]thiazeto[3,2-a] quinoline-3-carboxylic acid **(2).**The formation of product was explained by oxidative photodegradation of prulifloxacin in an irreversible trapping of the self-photogenerated $^1O_2$ by the type II photodynamic action of the drug. The generation of singlet oxygen during photolysis was confirmed by singlet oxygen scavenger sodium azide (NaN_3).*

Key words: Prulifloxacin, Ulifloxacin, Fluoroquinolone, Photodegradation, Singlet oxygen.

INTRODUCTION

Chemical research on the phototoxicity of drugs has received considerable attention in the past decade, prompted by reports on the photosensitivity side effects caused by many drugs[1].Many photosensitization reactions may be explained on the basis of the mechanism Type I (radical mediated) or Type II (singlet oxygen mediated) [2].There are photosensitizing drugs of varied structural variety and significant variations in the phototoxic mechanisms must be expected depending on the difference in structural features. It is therefore highly significant to study photochemical reaction of each individual photosensitizing drug.

Flouroquinolone antibiotics are a class of compound widely used as broad- spectrum antimicrobial agents in clinical treatment, but these drugs are also well known to exhibit phototoxic, photomutagenic and photocarcinogenic properties [3]. Prulifloxacin (PLF,1), a novel fluroquinolone posses phototosensitizing properties that lead to phototoxic responses in both human and animal subjects [4].It is an antibacterial drug contains a thiazeto-quinolone skeleton with a four-member ring in the 1,2 position. Following oral administration, the drug is

metabolized by esterases to ulifloxacin [5-10]. It is mainly used in the treatment of bronchitis exacerbation and lower urinary tract infection[11]. The most frequent adverse reactions observed in clinical trials were gastric pain, diarrhea, nausea and skin rash[12].

In continuation of our interest in the photochemical reactions involved in the phototoxicity of the photosensitizing drugs and their mechanisms and to delineate the underlying photochemical reaction that may possibly be involved in its phototoxicity, herein we have examined the photo behaviour of the antibacterial drug prulifloxacin (PLF, 1) under aerobic condition, as the photochemical behavior of photosensitizing drugs under aerobic condition is particularly relevant to understand the *in vivo* photobiological effects [13]. Photolysis of PLF, **1** in the presence of oxygen resulted in the formation of one photooxidation product, identified as **2** from its spectral (IR, ^{1}H NMR, ^{13}C NMR, mass spectra) properties (Scheme-1). Formation of the photodegradation product **2** was rationalized as: initial photosensitized generation of singlet oxygen ($^{1}O_2$) by the type II photodynamic action of the drug and; subsequent quenching of the generated singlet oxygen by the drug.

MATERIALS AND METHODS

Apparatus and Chemicals

All chemicals used were of analytical grade. Pure prulifloxacin was obtained from Sigma Aldrich (India), IR spectra were recorded as KBr discs on a Perkin Elmer model spectrum RXI. ^{1}H NM R and ^{13}C NMR Spectra were recorded on a Bruker Avance –DRX -300 Spectrometer using TMS as internal standard and $CDCl_3$ as solvent. High resolution mass spectra were determined with a VG-ZAB-BEQ9 spectrometer at 70 e V ionization voltage. Merck silica gel 60 F_{254} plates were used for analytical TLC; column chromatography was performed on Merck silica gel 60 (60-120mesh).

Irradiation Procedure

A solution of PLF, **1** (150mg, 0.33 mM) in phosphate buffer under aerobic condition was irradiated for 6 hr in a Rayonet photochemical reactor (The Southern New England Ultraviolet Co; Model RPR-208 equipped with four RUL-350 nm fluorescence lamps) for the complete conversion of reactants. Progress of the reaction was monitored by thin layer chromatography (chloroform: methanol; 7:3). At the end of the reaction formation of one major photoproduct was indicated on TLC and photo product was isolated by eluting with dichloromethane - methanol (8:2) on a silica column. The photo product was identified as 6–fluoro –1– methyl -4- oxo-7-[piperazin -1- yl]–1,4-dihydro-[1,3] thiazeto[3,2-a]quinoline-3- carboxylic acid (2) from the following spectral properties.

6-fluoro-1-methyl-4-oxo-7-[piperazin-1-yl]-1,4-dihydro-[1,3]thiazeto[3,2-a]quinoline-3-carboxylic acid (2)

Yield: 55.5 mg (37%) ; HRMS : calcd for (M^+) C_{16} H_{16} FN_3O_3S, 349.381; found, 349.379; IR (KBr): v = 3400, 1605, 1495 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ13.0 (s,1H,OH) ,7.96 (d,1H, *J*=13 ,5-H), 6.40(d,1H ,*J*=7, 8-H), 6.06 (q,1H, *J*=7, 1-H), 3.58-3.88(m,4H.piperazine), 3.88-4.18 (m,4H,piperazine), 2.20 (d,3H, *J*=7, CH_3) ppm ; ^{13}C NMR (300 MHz, $CDCl_3$):δ 177.5, 171.5, 159.5, 152.6, 143.9, 140.6, 108.5, 52.1, 45.6 ppm; MS, m/z: 349 [M+1]$^+$, 248.20.

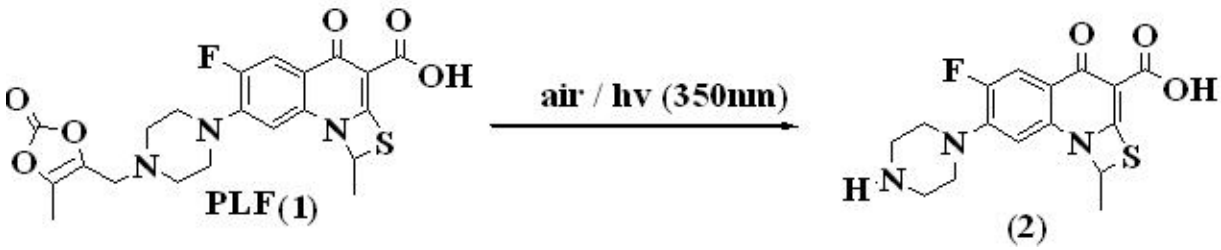
Singlet Oxygen detection

In order to confirm the role of singlet oxygen $^1O_2$ in oxidative photodegradation of PLF **,1** photolysis was performed in the presence of sodium azide (NaN_3) which is normally used as a trap for singlet oxygen ($^1O_2$) [14] .

Similar experiment was carried out by using different sensitizers such as methylene blue, rose Bengal, riboflavin, benzophenone to study the effect of triplet energy of sensitizer on the percentage yields of product (Table-1).

RESULTS AND DISCUSSION

The one major photoproducts, 6-fluoro-1-methyl-4-oxo-7-[piperazin-1-yl] -1,4-dihydro-[1,3] thiazeto [3,2-a] quinoline-3-carboxylic acid **(2)** which was obtained on irradiation of phosphate buffer solution of Prulifloxacin (PLF **,1**) under aerobic condition is depicted in **Scheme-1.**



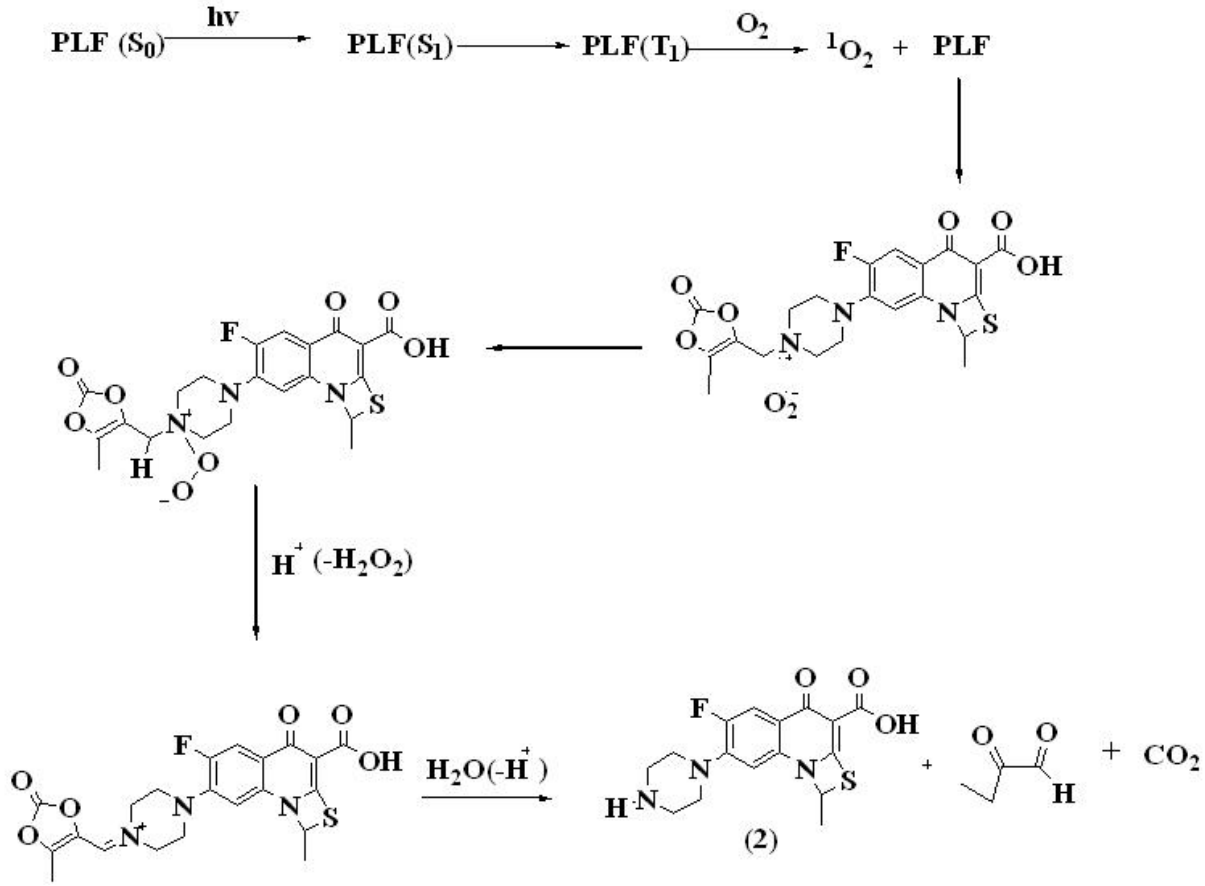
Scheme-1: Oxidative photodegradation product of prulifloxacin.

The result indicates that these photoproduct is formed by irreversible trapping of self-photogenerated singlet molecular oxygen. The formation of photoproduct through oxygenation is relevant to understand the mechanism of photo biological effect of PLF, **1**. The oxidative photodegradation pathways of PLF is shown in Scheme 2

Irradiation of PLF gave triplet excited state of drug (^{3}PLF) which generates singlet oxygen ($^1O_2$) through energy transfer to molecular oxygen. Reaction of this active species with PLF ground state produced $PLF^{\bullet+}$ and $O_2^{\bullet-}$.There are sufficient examples in the literature on the reaction of singlet oxygen ($^1O_2$) with aliphatic amines [15, 16] (as the piperazinyl ring of PLF); the reported result is the generation of an amine radical cation and superoxide anion ($O_2^{\bullet-}$) The subsequent step is the reaction of these intermediates to form an iminium cation [17]., which may be hydrolyzed to give photoproduct **(2),** 2-oxopropanal and carbon dioxide. Oxidative photodegradation of PLF, **1** to give **2** is in agreement with this mechanism.

When PLF was irradiated with singlet oxygen scavenger sodium azide (NaN_3) it compete with drug for singlet oxygen ($^1O_2$), and with the decreased availability of singlet oxygen ($^1O_2$) therefore slowed down the rate of photodegradation.

In order to further ascertain the oxidative photodegradation of PLF, **1** by its quenching of the self-generated singlet oxygen, the drug was photolysed under the same experimental condition, in the presence of well known photosensitized singlet oxygen generator, where same photoproduct was obtained in different yields**.**



Scheme-2: Mechanistic pathway of oxidative photodegradation of prulifloxacin.

Rose bengal and methylene blue was much more efficient than riboflavin and benzophenone in the photosensitized decomposition of PLF, **1** (Table 1). This may be due to the fact that rose Bengal and methylene blue, with lower triplet energies, produce singlet oxygen in large amount [18, 19] by type II mechanism [20]. On other hand riboflavin and benzophenone (higher triplet energies) act mainly by type I photosensitized photooxidation, do not produce significant amount of $^1O_2$ [21].

Table1. Effect of Triplet energies of different sensitizers on the yields of product

Sensitizer	Triplet energy (kcal /mole)	Yields of product (%)
Methylene Blue	33.5 – 34.0	36.4
Rose Bengal	39.2 -42.2	35.0
Riboflavin	57.8	34.9
Benzophenone	68.6 -69.1	33.6

The oxidative photodegradation of PLF, **1** to produced (**2**) is relevant to understand the mechanism of oxygen-dependent photo biological effect of drugs and also give knowledge that one can alter the rate and direction of biochemical reactions of drug by using both singlet oxygen ($^1O_2$) generators and singlet oxygen ($^1O_2$) quenchers.

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