REVIEW ARTICLE

PHOTOCHEMISTRY OF FLUOROQUINOLONES: A REVIEW

Rahila Bano[1*], Zubair Anwar[2], Nafeesa Mustaan[1], Iqbal Ahmad[2]

[1] Department of Pharmaceutics, Baqai Institute of Pharmaceutical Sciences, Baqai Medical University, Karachi

[2] Department of Pharmaceutical Chemistry, Baqai Institute of Pharmaceutical Sciences, Baqai Medical University, Karachi

Received: February 9, 2017 Accepted: June 14, 2017

ABSTRACT

Fluoroquinolone antibiotics are widely used in the treatment of various infectious diseases in humans and animals. These compounds are sensitive to light and undergo photodegradation in the solid and liquid state to form a number of products which have been identified by chromatographic and spectroscopic methods. The fluoroquinolones in aqueous and organic solvents are degraded on exposure to UV and sunlight by a number of pathways depending on the reaction conditions including medium, wavelength and intensity of light and duration of exposure of the solution. The present review deals with the identification of the photoproducts, photodegradation pathways and mechanism of photodegradation of various fluoroquinolones.

Keywords: Fluoroquinolones, photodegradation, photoproducts.

1. INTRODUCTION

Fluoroquinolones are an important class of antibacterial compounds that are extensively used in the treatment of infectious diseases in both humans and animals[1-4]. They are available in different dosage forms including tablets, capsules, parenterals, eye and ear drops, etc. Fluoroquinolones are sensitive to light[5-9] and undergo photodegradation in the solid and liquid phase. Several studies have been conducted on the photodegradation of fluoroquinolones in aqueous solution including those of ciprofloxacin[6,10-16], clinafloxacin[17], danofloxacin[6,11,14], enrofloxacin[6,7,11,14,18,19], fleroxacin[20-22], levofloxacin[14,23-28], lomefloxacin[12,29,30], marbofloxacin[14], moxifloxacin[13,14,25,31-34], norfloxacin[6,11,18,19,33,35], ofloxacin[12,19,36], rufloxacin[7], sitafloxacin[24], sparfloxacin[37,38], and lomefloxacin[12,29]. A study on the photodegradation of ciprofloxacin, moxifloxacin, norfloxacin and ofloxacin in tablets has also been reported[33].

Fluoroquinolones possess two types of ring structures, a quinolone nucleus with one nitrogen in position 1 (e.g., norfloxacin (NF)), and a naphthyridine nucleus, with nitrogen in positions 1 and 8 (e.g., enoxacin (EN)). Both types of compounds, quinolones and naphthyridines, contain a keto oxygen at C-4 and a carboxylic acid side chain at C-3 position. Moreover, some compounds (e.g., ofloxacin (OF), NF and EN have a piperazinyl moiety at C-7, and others (e.g., moxifloxacin (MF), danofloxacin (DF)) have a diazabicyclononyl moiety at C-7 position. The fluoro group in the molecule may be present at C-6 (e.g., OF, MF, NF) or at C-6 and C-8 positions (e.g., lemofloxacin (LM), fleroxacin (FL), orbifloxacin (OB)). These structural features and conjugated systems impart photosensitivity to fluoroquinones[9,39] as reported by many workers[5-8,40-44] in the field (Fig. 1).

1.1. Photoproducts

The chemical structures of the photoproducts of ciprofloxacin (CF)[14, 33], clinafloxacin (CL)[17], danofloxacin (DF)[14], enrofloxacin (EF)[6,14], fleroxacin (FL)[16], moxifloxacin (MF)[14,33,45], marbofloxacin (MAR)[14], norfloxacin (NF)[33] and orbifloxaxin (OB)[46] have been determined by NMR and MS/MS techniques. However, in some cases only UV, HPLC, FTIR and mass spectral data have been reported[21,23,24,26,47,48]. The various photoproducts of individual fluoroquinolones identified by different workers are reported in Table 1.

* Corresponding Author Email: rahee_qasim@hotmail.com

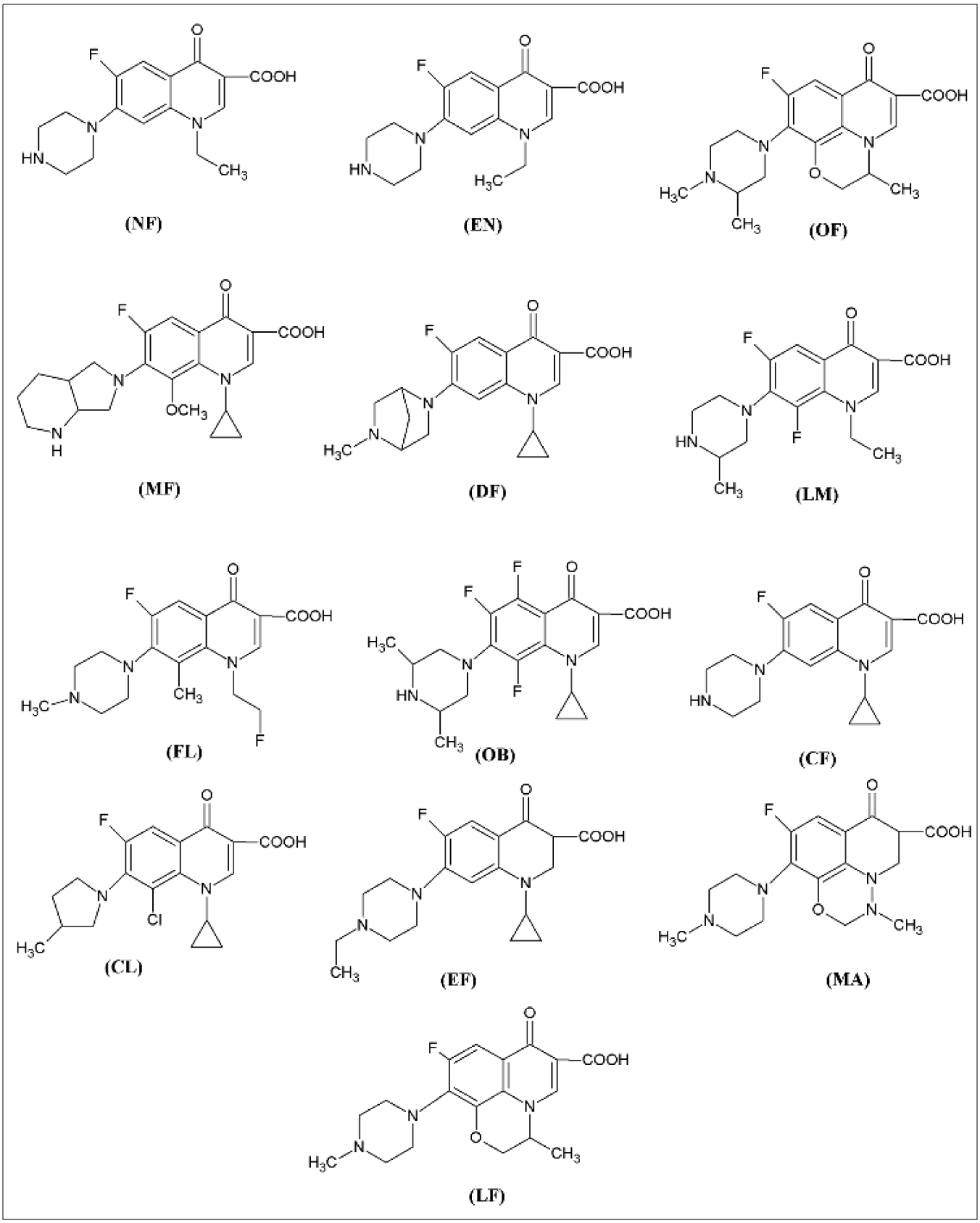


Fig. 1. Chemical structures of fluoroquinolones.

Table 1. Photoproducts of fluoroquinolones

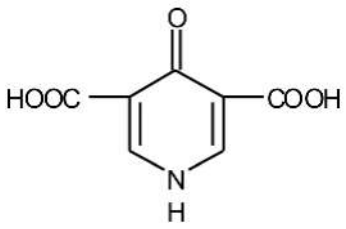
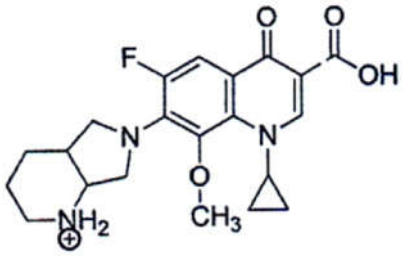
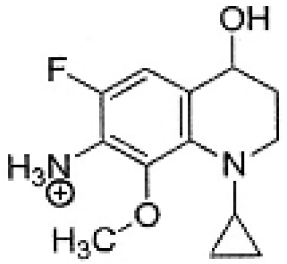
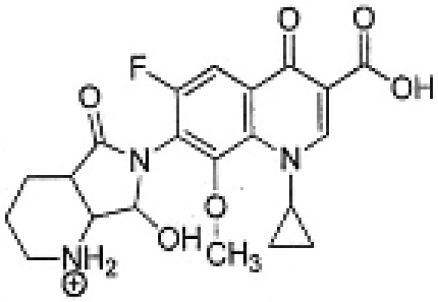
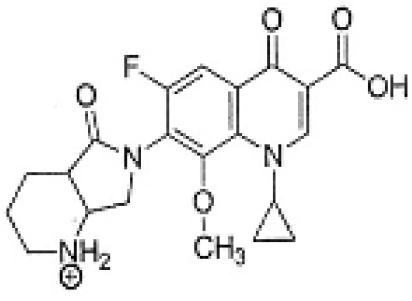
Fluoroquinolone	Products	Structure	Reference
Enrofloxacin	EF-1		6
	EF-2		6
Moxifloxacin	MF-1		33
	MF-2		33
	MF3		33

Table 1 Continued

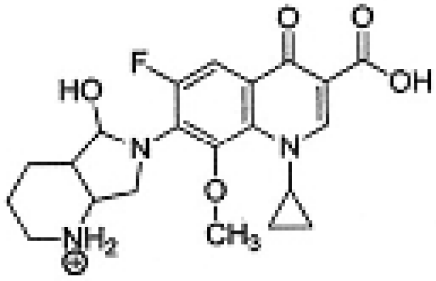
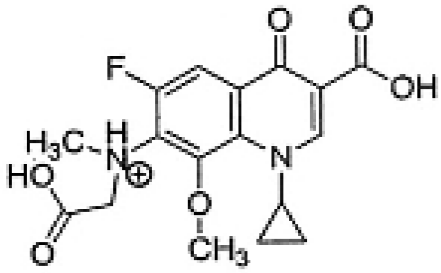
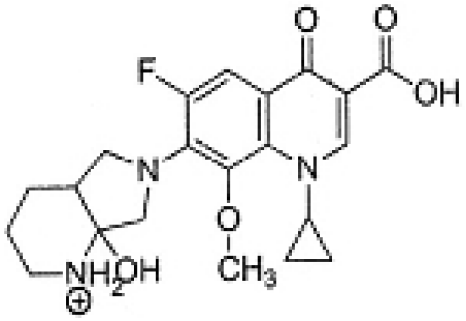
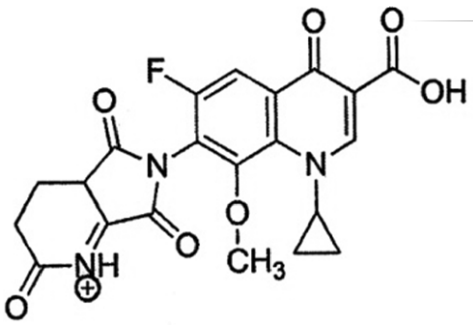
Fluoroquinolone	Products	Structure	Reference
	MF-4		33
	MF-5		33
	MF-6		33
	MF-7		33

Table 1 Continued

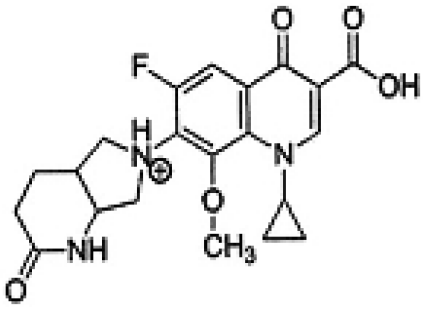
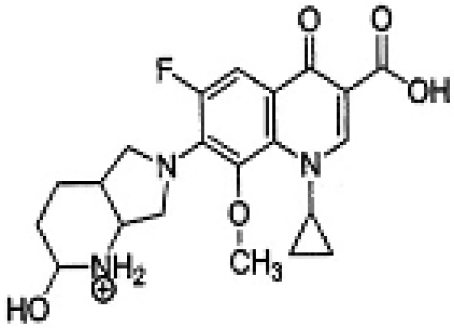
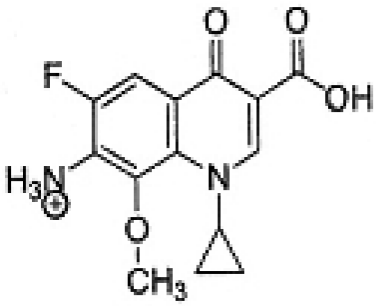
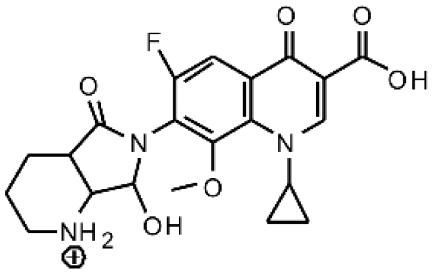
Fluoroquinolone	Products	Structure	Reference
	MF-8		33
	MF-9		33
	MF-10		33
	MF-11		34

Table 1 Continued

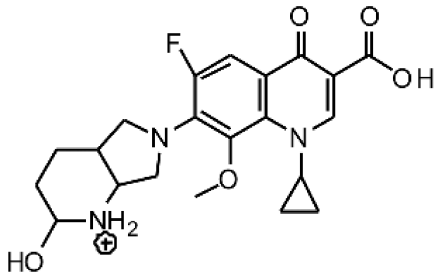
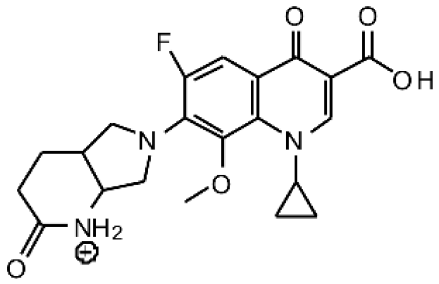
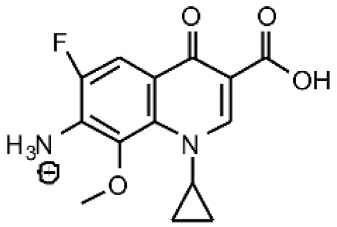
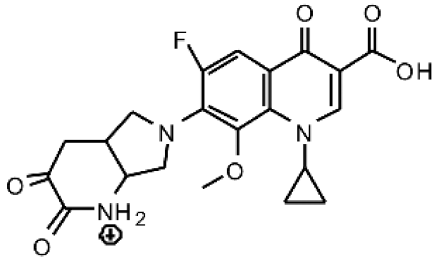
Fluoroquinolone	Products	Structure	Reference
	MF-12		34
	MF-13		34
	MF-14		34
	MF-15		34

Table 1 Continued

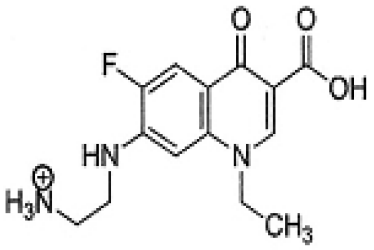
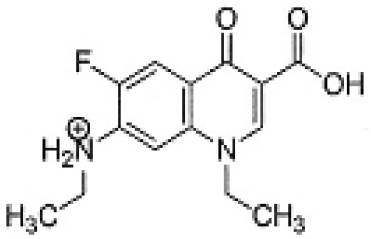
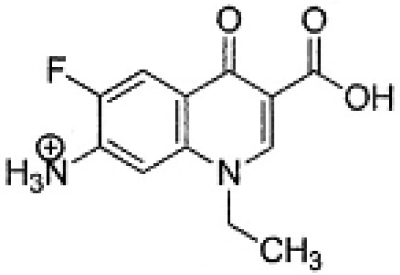
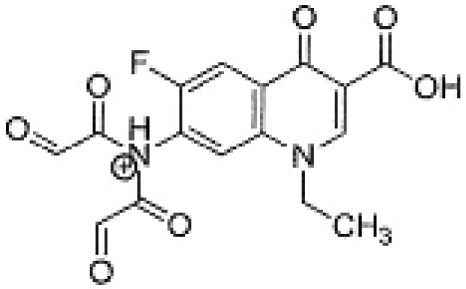
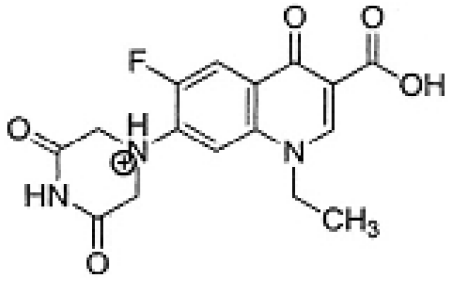
Fluoroquinolone	Products	Structure	Reference
Norfloxacin	NF-1		33, 35
	NF-2		33,35
	NF-3		33,35
	NF-4		33,35
	NF-5		33,35

Table 1 Continued

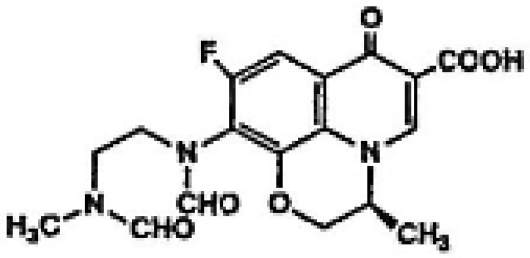
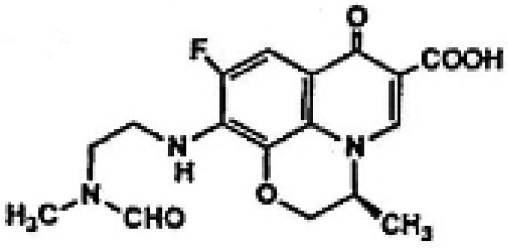
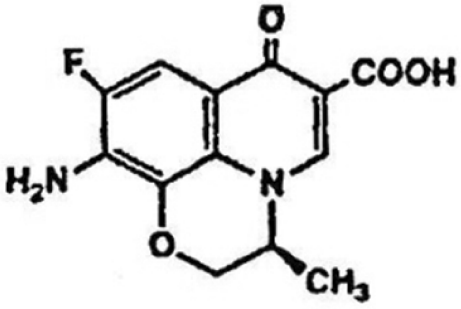
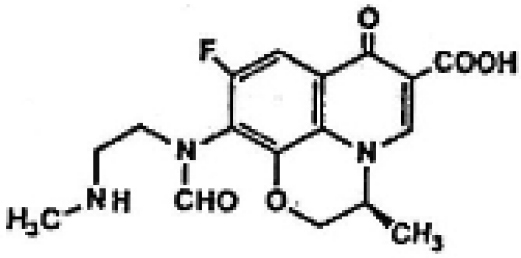
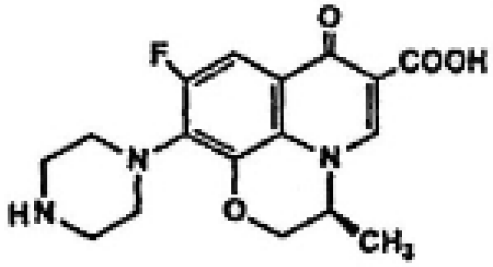
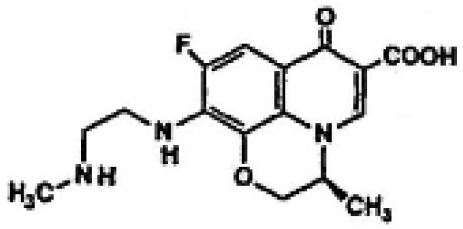
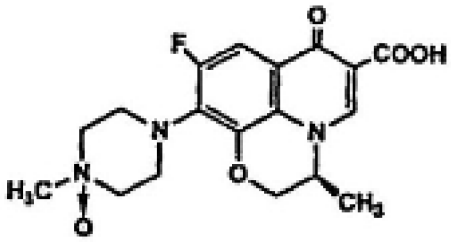
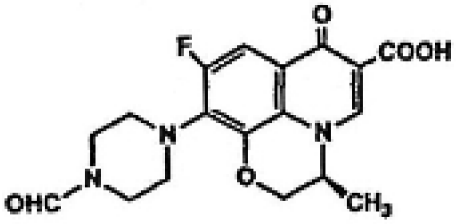
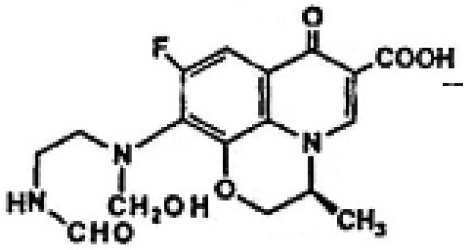
Fluoroquinolone	Products	Structure	Reference
Levofloxacin	LF-1		23
	LF-2		23
	LF-3		23
	LF-4		23
	LF-5		23

Table 1 Continued

Fluoroquinolone	Products	Structure	Reference
	LF-6		23
	LF-7		23
	LF-8		23
	LF-9		23

1.2. Photodegradation Pathways

Several workers have studied the mode of photodegradation of fluoroquinolones in aqueous solution on the basis of the identified or partially identified products. Pathways have been proposed for the photodegradation of individual fluoroquinolones and for the formation of various products by different modes. However, the nature of the photoproducts formed would depend on the reaction conditions including the medium, wavelength and intensity of irradiation source and the duration of exposure of the drug solution. The details of these studies are presented as follows.

1.2.1. Studies conducted by Burhenne and coworkers

Burhenne et al.[6,11,18] were among the early workers who studied the photodegradation of fluoroquinolone carboxylic acids in aqueous solution. An irradiation intensity of 200 w/m^2 generated by a xenon lamp lead to the degradation of these compounds with half-lives ranging from 20.6 to 105.9 min. The kinetic data on various fluoroquinolones carboxylic acids are reported in Table 2. These authors proposed a scheme for the photodegradation pathways of EF, CF, DF and NF on the basis of the photoproducts of these compounds identified by MS, GC-MS and ^{1}H NMR spectrometry (Fig. 2). The photodegradation pathways of individual fluoroquinolones suggested by Burhenne et al.[11,18] are described in the following sections.

1.2.1.1. Enrofloxacin (EF)

In the photodegradation of EF (compound 1), the ethyl group of the molecule is primarily abstracted which leads to the formation of CF (compound 2). This is followed by the oxidation of the piperazine ring to give compound 6 (Fig. 2). A direct oxidation of the ethylpiperazine moiety and abstraction of the ethyl group results in the formation of the compound 5. The compounds 5 and 6 react subsequently to form the compound 7 which is then converted to the compound 8 (Fig. 2).

1.2.1.2. Ciprofloxacin (CF)

CF (compound 2) is photodegraded to compound 6 which is then transformed to the compound 7 by cleavage of the piperazine ring. This is followed by removal of the ethyleneamino group in the side chain to form the compound 8 (Fig. 2).

1.2.1.3. Danofloxacin (DF)

The photodegradation of DF (compound 3) has been shown to result in the formation of one major compound which has been identified as the compound 8. This compound is also formed by the irradiation of EF and CF through the compound 7 by the removal of the side chain (Fig. 2).

Table 2. Half-lives and photolytic constants of the active ingredients and some main photoproducts

Substance	EF	CF	DF	NF	Compound 5	Compound 7	Compound 8
Order of kinetics	1$^{st\ a}$	2$^{nd\ b}$	1$^{st\ a}$	1$^{st\ a}$	1$^{st\ a}$	1$^{st\ a}$	2$^{nd\ b}$
Photolysis constant	k_1 = 0.0191	$k_2.C_0$ = 0.0111	k_1 = 0.0336	k_1 = 0.00655	k_1 = 0.0233	k_1 = 0.0193	$k_2.C_0$ = 0.0031
$t_{1/2}$ (min)	36.2	90.2	20.6	105.9	29.7	35.9	329.5
Correlation coefficient of linear regression	0.9939	0.9921	0.9983	0.9949	0.9997	0.9994	0.9957

[a] min^{-1}

[b] M^{-1}, min^{-1}

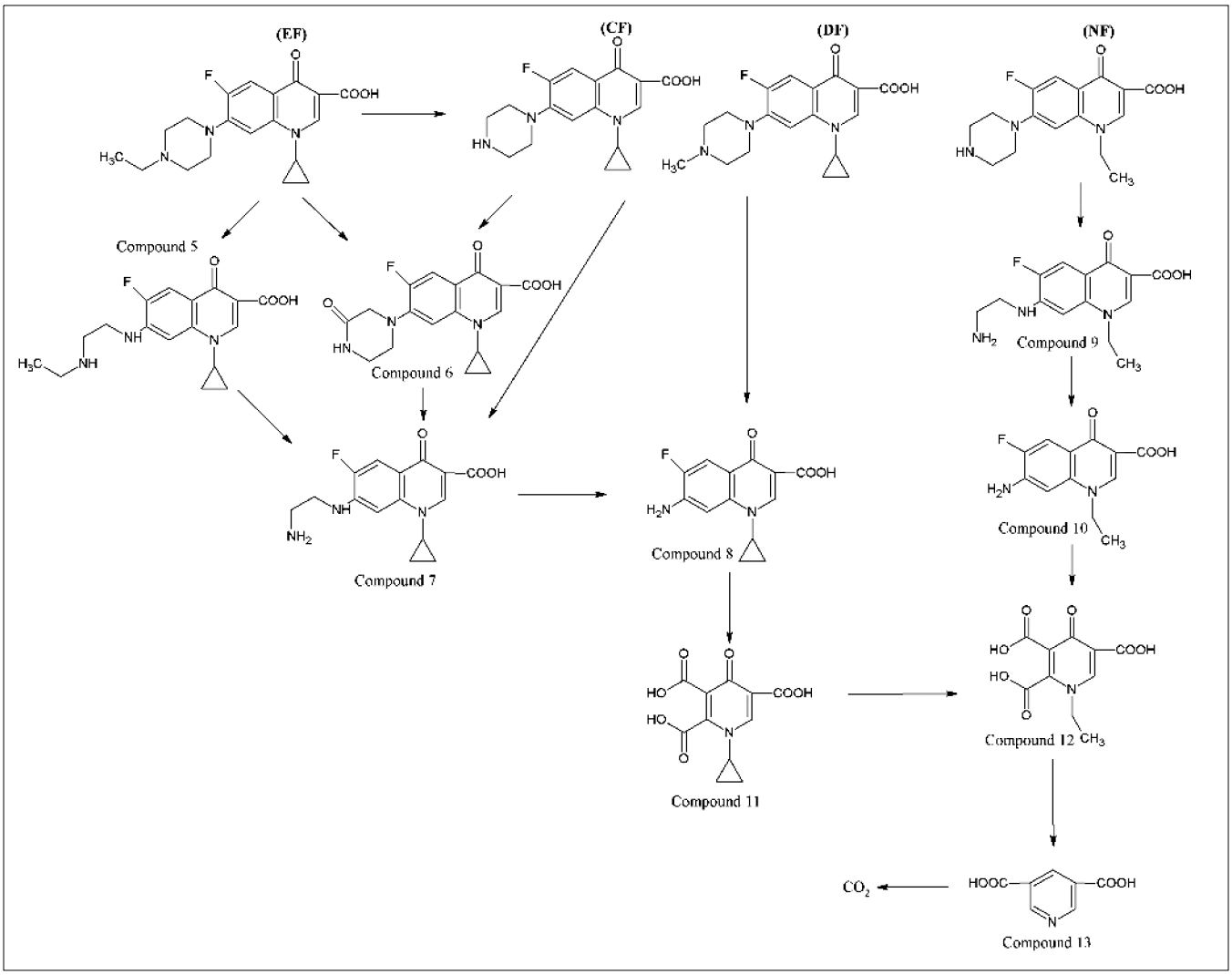


Fig. 2. Photodegradation pathways of EF, CF, DF and NF[18].

1.2.1.4. Norfloxacin (NF)

The UV irradiation of NF (compound 4) results in the formation of the compound 9 which on oxidation of the ethyleneamine side chain gives compound 10. These compounds are analogues of compounds 7 and 8 which have been derived from the photodegradation of EN, CF and DF and differ only in the ethyl instead of cyclopropyl substitution in position 1 of the quinolone ring (Fig. 2). The studies of Burhenne et al.[11,18] on the photodegradation of EF, CF, DF and NF shows that there is a correlation between the photodegradation products of EF and CF. The final photodegradation product of these compounds is 8 which is also derived as the major product of DF. This product is structurally similar to the final photoproduct of NF. The photodegradation reactions of all these compounds involve cleavage of the piperazine/ diazabicyclononane ring followed by the oxidation of ethylamino side chain to give the final products (Fig. 2).

Burhenne et al.[6] carried out a photodegradation study of ^{14}C- labeled EN under drastic conditions for 700 hours using a xenon lamp with an irradiation intensity of 800w/m^2. They concluded that under these conditions the photodegradation of fluoroquinolones in aqueous solution proceeds in two main steps involving (i) the degradation of the piperazine ring forming 7-amino compounds and (ii) the photodegradation of these compounds to CO_2 formed intermediate polar photoproducts. These products are formed by the breakdown of

the quinolone nucleus and include pyridine tri- and dicarboxylic acids.

1.2.2. Studies conducted by Sturini and coworkers

Sturini et al.[14] conducted a detailed study of the photodegradation of fluoroquinolones in water by sunlight and determined the structures of the photoproducts on the basis of HPLC-ESI-MS/MS techniques. The photodegradation pathways of the individual fluoroquinolones suggested by the authors are presented in the following sections:

1.2.2.1. Ciprofloxacin (CF)

The irradiation of CF results in the formation of a main photoproduct from substitution of the fluoro group in position 6 by a hydroxyl group ($C1_{WT}$). Three minor photoproducts are also formed, including $C3_W$ and $C2_W$, which arise from the reductive dehalogenation and, in the latter case, by subsequent oxidative degradation of the piperazine ring. The last product, $C4_W$, is formed by conversion of the amine function of the piperazine ring to an amide function (Fig. 3).

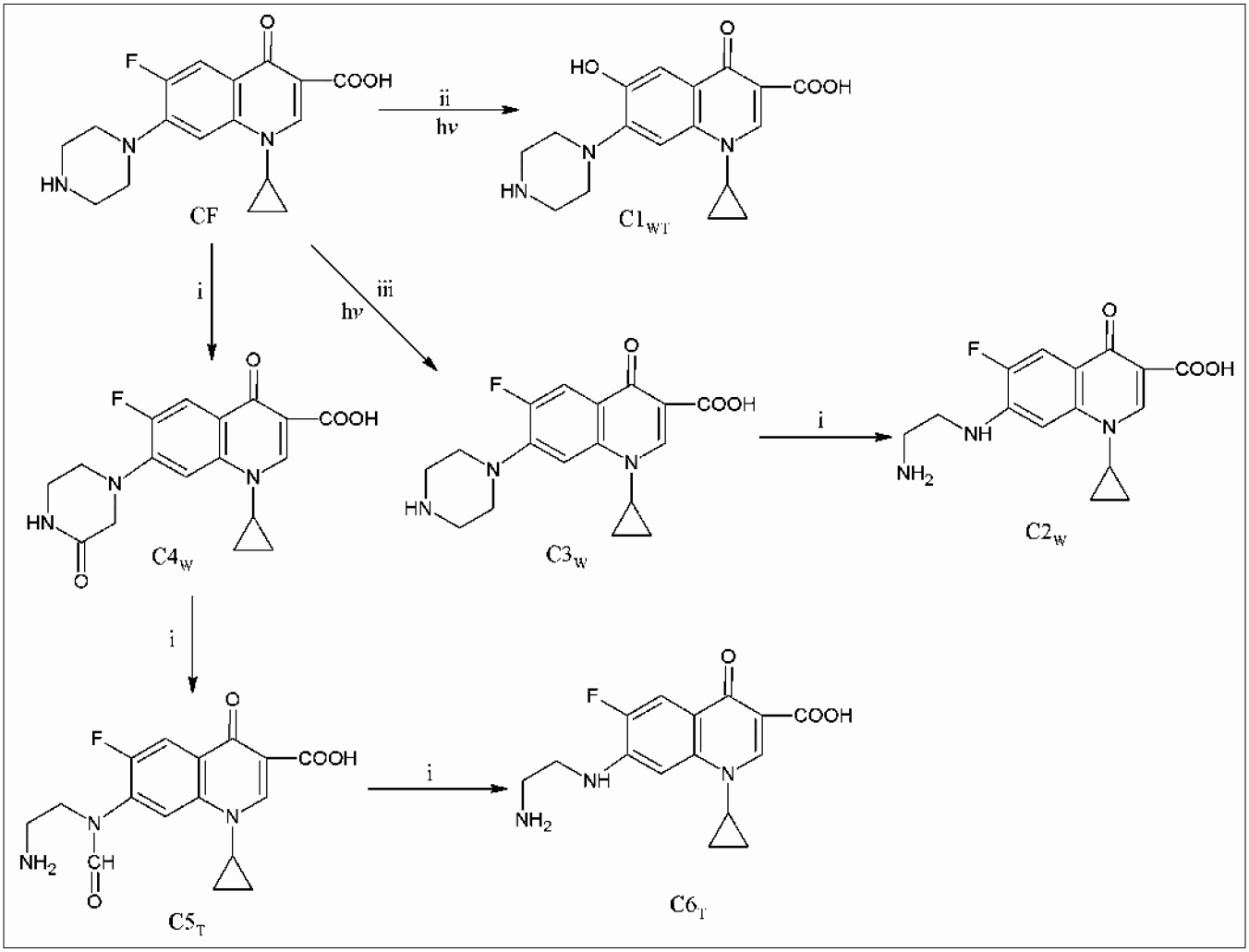


Fig. 3. Degradation paths and byproducts in the photolysis (W) and photocatalysis (T) of CF[14].

1.2.2.2. Danofloxacin (DF)

The photodegradation of DF has been found to give two main products ($D3_{WT}$, $D4_{WT}$). $D3_{WT}$ arises by OH substitution in place of fluoro group at C-6 and $D4_W$ from reductive dehalogenation of DF. Four minor photoproducts ($D1_W$, $D2_W$, $D5_W$, $D6_{WT}$) have also been identified. $D6_{WT}$ arises from oxidative demethylation of the aliphatic amine moiety and the other three ($D1_W$, $D2_W$, $D5_W$) by subsequent oxidation of the above primary photoproducts. Thus the photodegradation of DF involves a series of redox reactions to form various products (Fig. 4).

1.2.2.3. Enrofloxacin (EF)

The reaction scheme for the photodegradation pathways of EF proposed by Sturini et al.[14] is quite complex and is based on a series of reactions leading to the formation of the primary and secondary products (Fig. 5). The irradiation of an aqueous EF solution by sunlight gives nine products (E_{WT}, B_{WT}, D_{WT}, A_W, C_W, $E1_W$, $E2_W$, $E3_W$, $E4_W$). Five products (E_{WT}, B_{WT}, D_{WT}, A_W C_W), have previously been identified by Sturini et al.[14,49]. E_{WT} results from the oxidation of piperazine ring, D_{WT} by substitution of OH group in place of F at position 6 and A_W by reductive defluorination. In all cases further degradation takes place involving the oxidation of the side chain of piperazine ring to give the products B_{WT} and C_W. The efficient photodegradation of DF observed in these studies may be due to the overwhelming side chain degradation initiated by H abstraction.

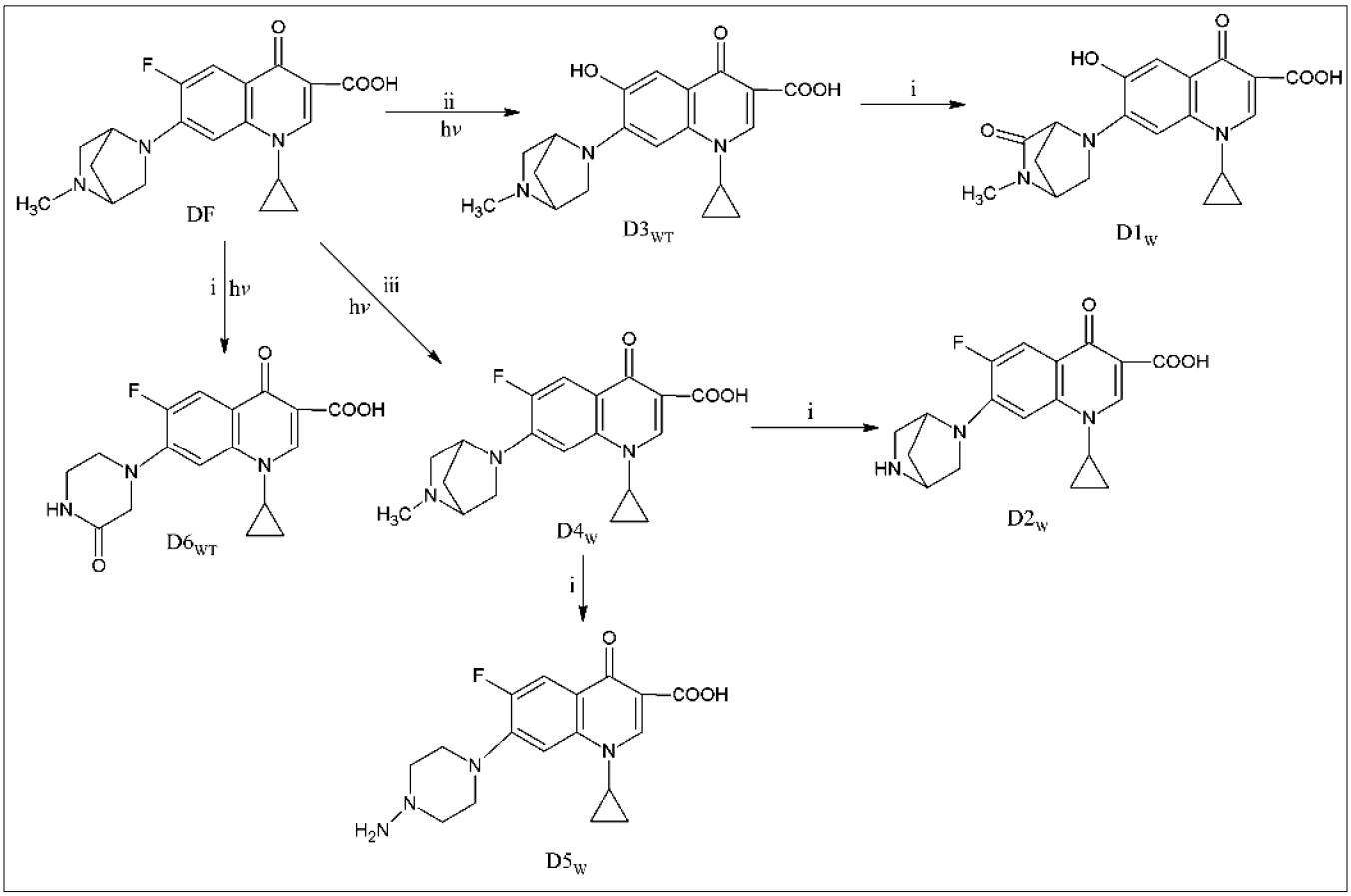


Fig. 4. Degradation paths and byproducts in the photolysis (W) and photocatalysis (T) of DF[14].

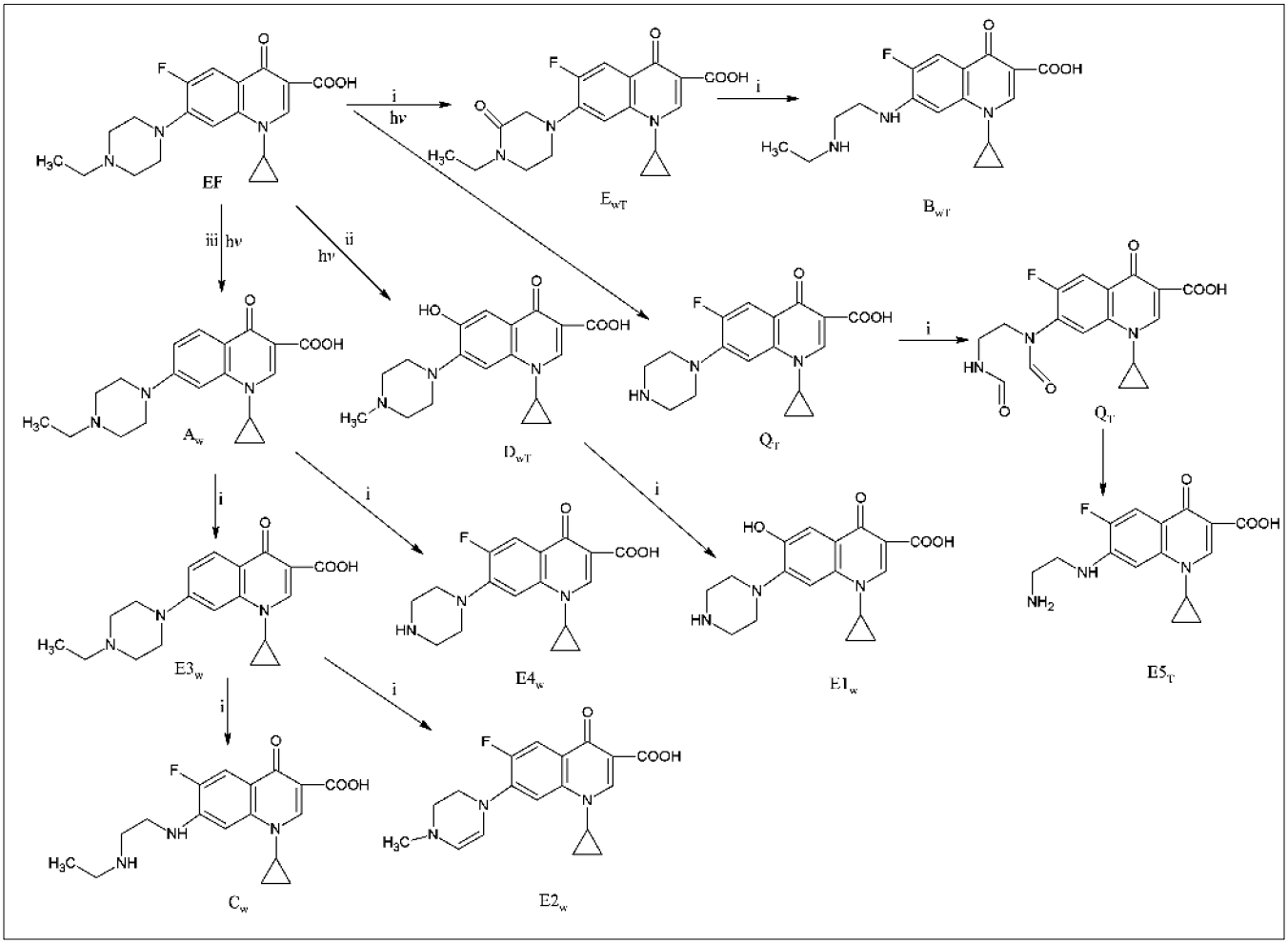


Fig. 5. Degradation paths and byproducts in the photolysis (W) and photocatalysis (T) of EF [14].

1.2.2.4. Levofloxacin (LF)

The photodegradation of LF leads to the formation of seven products including $L1_W$, $L2_W$, $L3_W$, $L4_W$, $L5_W$, $L6_W$, and $L7_W$ (Fig. 6). The most abundant of these products result from the reduction and cleavage of the piperazine ring to give $L7_W$ and $L6_W$, respectively. The minor products of LF are formed by the solvolysis of the fluoro group to form $L5_{WT}$ and by reductive defluorination to form $L4_{WT}$. This is followed in both cases by oxidative degradation of the amine side chain to give $L2_W$ and, respectively, the products, $L1_W$, $L3_W$ and $L4_W$. The products obtained on the photocatalysis of LF result from oxidative degradation of the amine side chain to form $L7_{WT}$ and a further product $L9_T$ via $L6_{WT}$. The product $L8_T$ is also directly formed from LF by a different path through the oxidative degradation.

1.2.2.5. Marbofloxacin (MAR)

The irradiation of MAR leads to the cleavage of dihydrooxadiazine ring to give two main products, F_{WT} and D_W. The photocatalysis reaction of MAR, on the other hand, gives the product F_{WT}, by competitive direct excitation along with two other products, $Ma1_T$ and $Ma2_T$. These products arise from the stepwise oxidative degradation of MAR involving the piperazine side chain. These reactions are shown in Fig. 7.

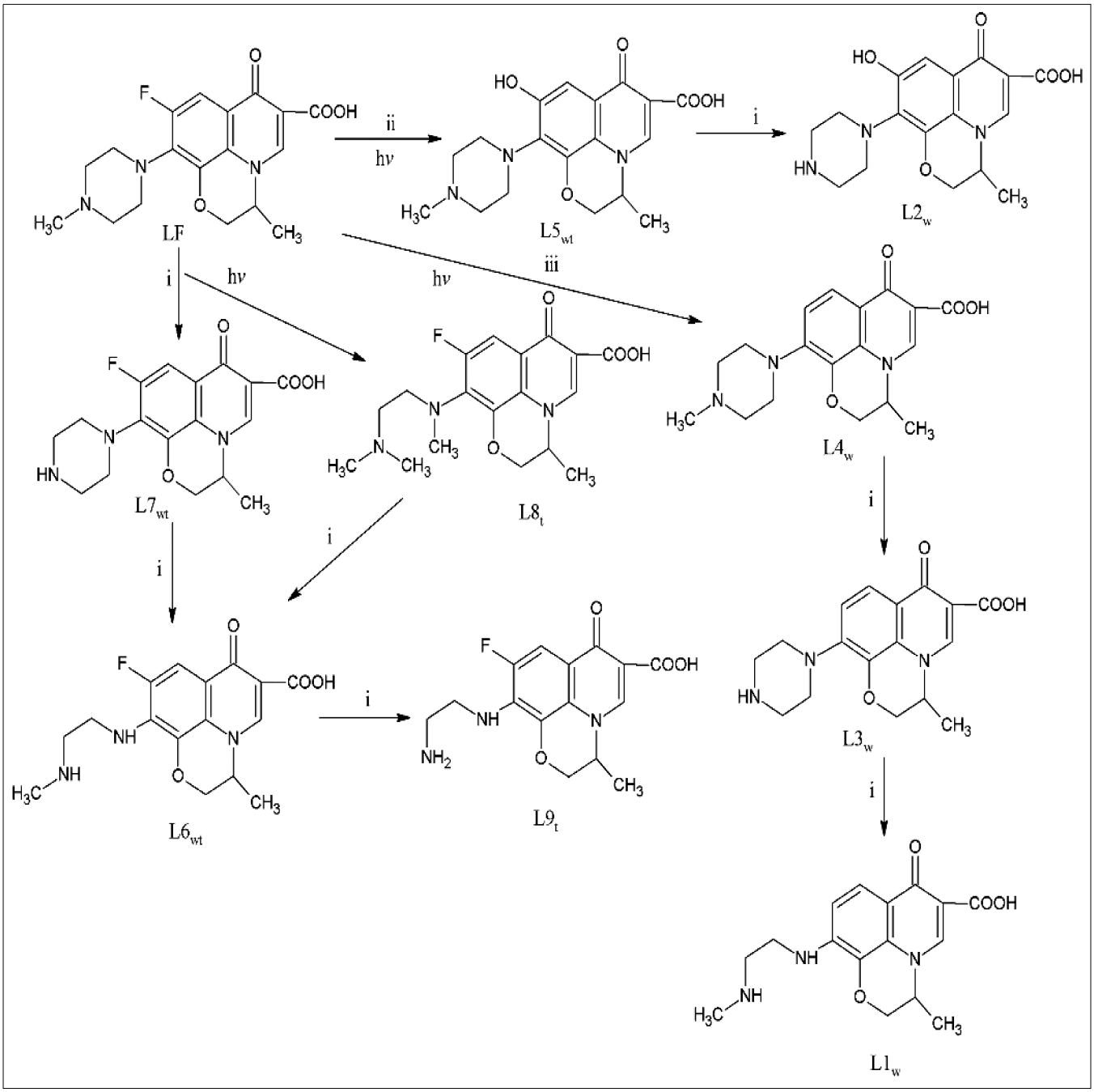


Fig. 6. Degradation paths and byproducts in the photolysis (W) and photocatalysis (T) of LF [14].

1.2.2.6. Moxifloxacin (MF)

Sturirni et al.[14] have presented a detailed scheme for the pathways involved in the photodegradation and photocatalysis of MF (Fig. 8). The photodegradation of MF in aqueous solution gives six products that are formed from OH/F substitution at position 6 ($M3_{WT}$ and $M1_{WT}$, $M2_{WT}$ and further oxidation), reductive dehalogenation combined with side chain oxidation ($M6_W$ and $M5_W$) and direct side chain oxidation ($M4_{WT}$), in roughly equivalent amounts. On the other hand, photocatalysis gives small amounts of $M3_{WT}$ and its degradation products, $M10_T$, $M1_{WT}$ and $M2_{WT}$. The main photoproducts resulting from the primary oxidative degradation of the amine side chain are $M4_{WT}$ along with $M9_T$, $M8_T$, $M7_T$, and $M11_T$. The formation of these

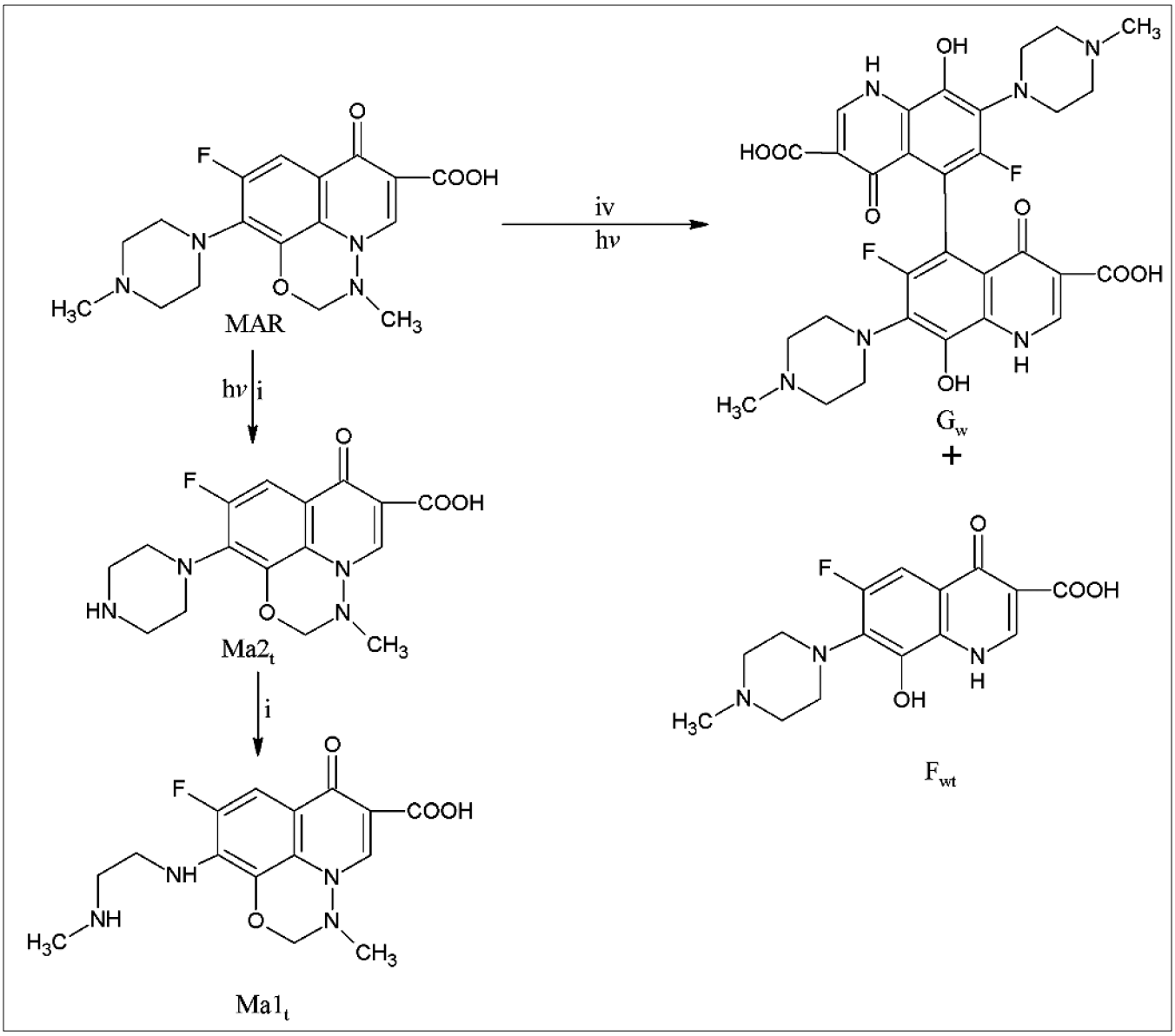


Fig. 7. Degradation paths and byproducts in the photolysis (W) and photocatalysis (T) of MAR[14].

products depends on the experimental conditions and the radiation source employed.

All the photodegradation reactions carried out on different fluoroquinolones in aqueous solution[11] involved irradiation by sunlight which has a variable spectrum of emission wavelengths and intensity[50] and, therefore, the formation of a variety of photoproducts (primary and secondary) under different exposure conditions. In photochemical studies it would be necessary to irradiate a drug solution under controlled conditions of light wavelengths / intensity, temperature, dissolved oxygen, pH and exposure time, to obtained reliable results in terms of product formation and the rates of the reaction. The irradiation conditions must be constant to achieve reproducible data for interpretation and meaningful conclusion.

1.2.3. Mechanism of photodegradation

Sturini et al.[14] as a result of the study of photochemistry of a number of fluoroquinolone

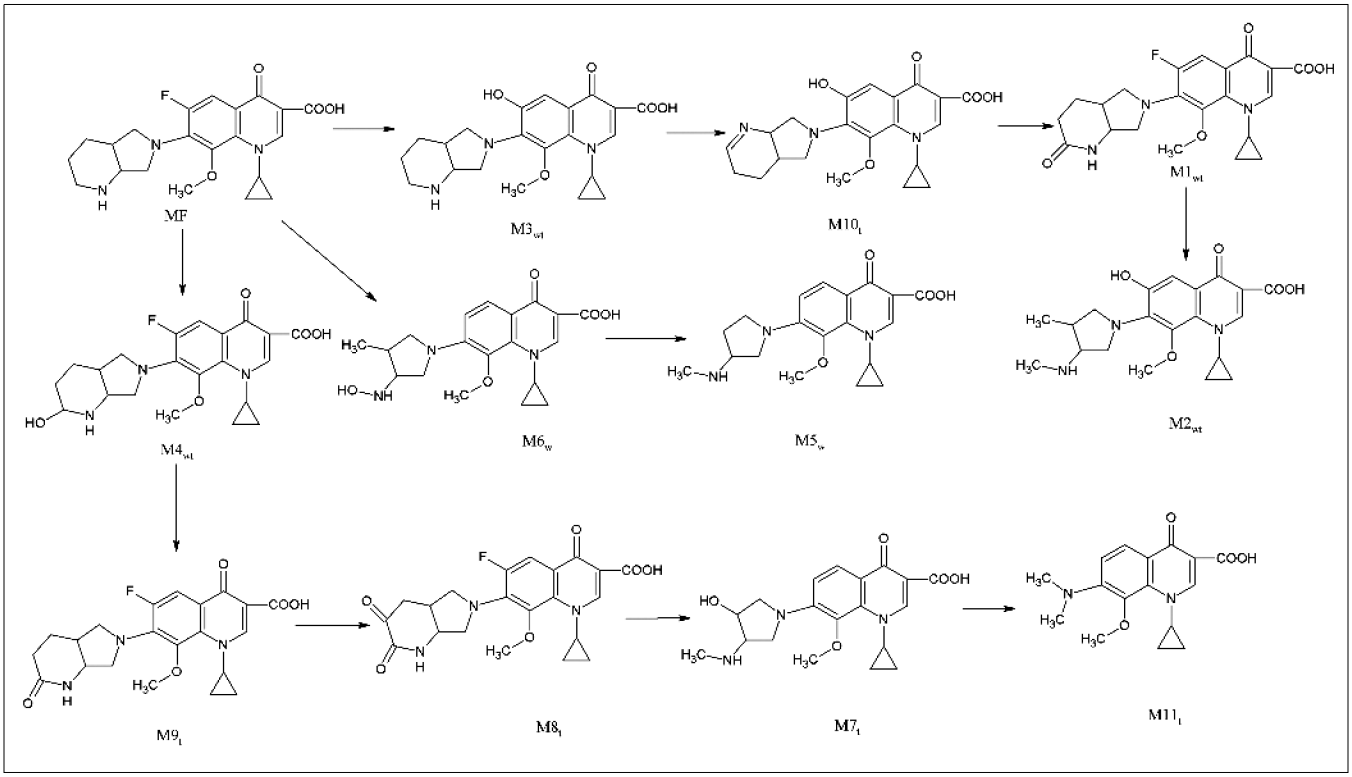


Fig. 8. Degradation paths and byproducts in the photolysis (W) and photocatalysis (T) of MF[14].

compounds in water, suggested the involvement of two types of reactions in the photodegradation process. The first type includes unimolecular photoreactions that proceeds via the excited triplet state and involve either (i) photosubstitution of fluorine on carbon-6 of the aromatic ring by OH group or (ii) reductive dehalogenation. The efficiency of these two processes would differ with the structure of fluoroquinolone and has been found to be lowered by electron donating groups as indicated by the effect of an OMe group in LF.

The second type of photodegradation process includes the bimolecular reactions in which the excited triplet state of the molecule attacks the ground state molecule causing electron or hydrogen transfer from the electron rich moiety present in the molecule, e.g. amino side chain (Fig. 9). This has been found to be a general process (except for MAR which has a competitive outcome, N-N bond cleavage), the efficiency of which would depend on the structure of the amine side chain. This process could be considered more important with tertiary than the secondary amines and with five rather than six member rings. Thus the fastest photodegrading fluoroquinolones are DF and MF, which have a 2,5-diazabicyclo[2.2.1]hexane and a 2,8-diazabicyclo[4.1.0]nonane side chain, respectively.

1.2.4. Kinetics of photodegradation

The study of the kinetics of photodegradation reactions of fluoroquinolones by Sturini et al.[14] indicates that at low concentration (20–50 μg L^{-1}) degradation obeys to a first-order kinetics because light absorption is proportional to the concentration of the compound. The fitting of the kinetic data by a biexponential law in some cases (MAR) may be due to the formation of a second ionic component.

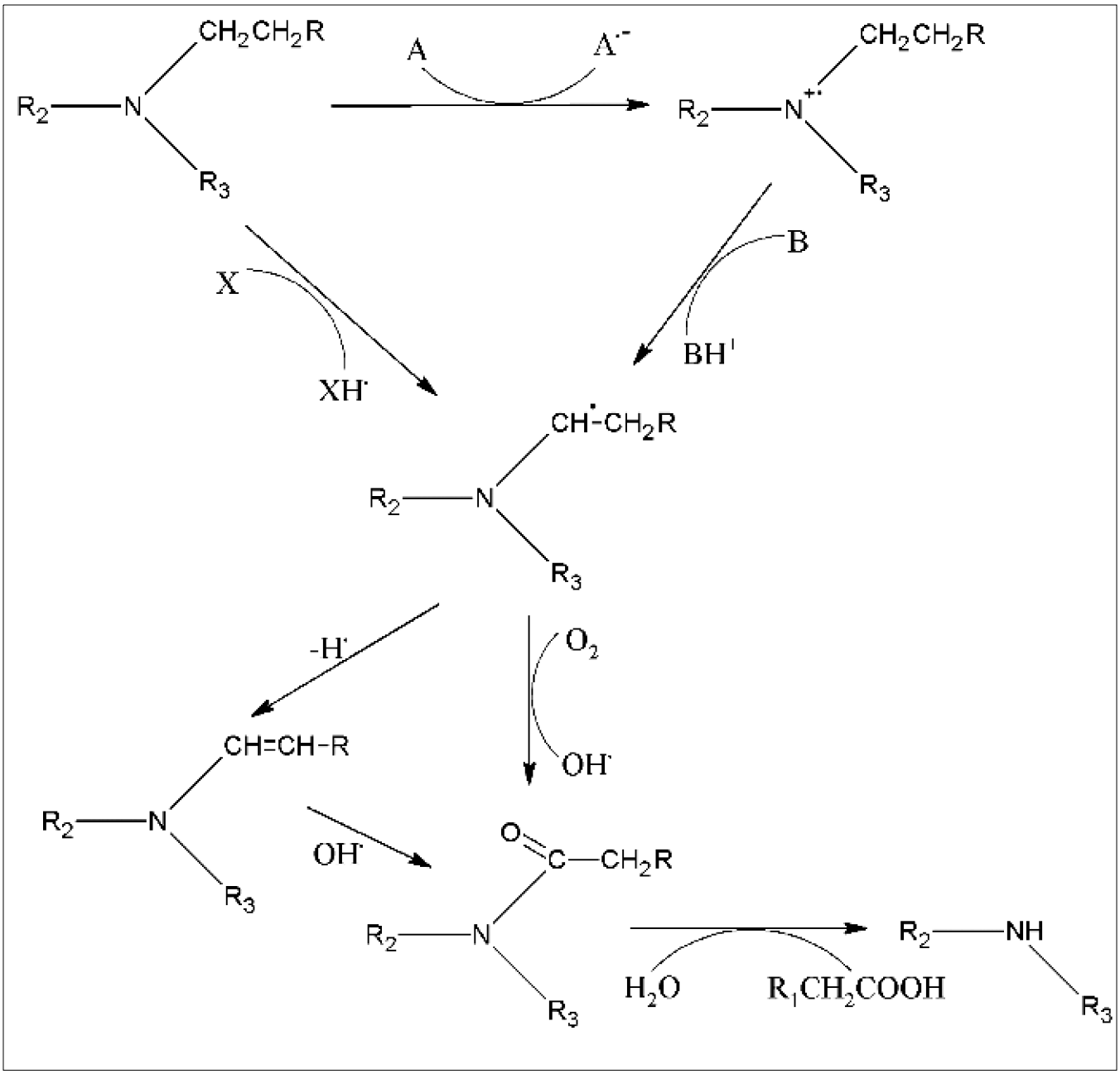


Fig. 9. Biomolecular photoreaction paths for selected fluoroquinolones[14].

This behavior represents the role of two ionic species in the rate of the photodegradation of fluoroquinolones.

1.2.5. Studies conducted by Araki and coworkers

Araki et al.[24] studied the photochemical behavior of sitafloxacin [(-)-7-[(7*S*)-7-amino-5-azaspiro[2,4]heptan-5-yl]-8-chloro-6-fouro-1-[(1*R,*2*S*)-2-flouro-1-cyclopropyl]-1,4-dihydro-4-oxo-3-quinocarboxylic acid] (STFX) in aqueous solution using fluorescent lamp for 350000 lux. They identified two major photoproducts using HPLC, ^{1}HNMR and MS spectrometry. The two products, (P–1) was identified as 7-[7-amino-5-azaspiro [2.4 heptan-5-yl]-6-floro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid and (P–2) as the structure of STFX oxidized at the 7-position and with chlorine eliminated at the 8-position. Both products contained a dissociated C–Cl bond at the 8-position.

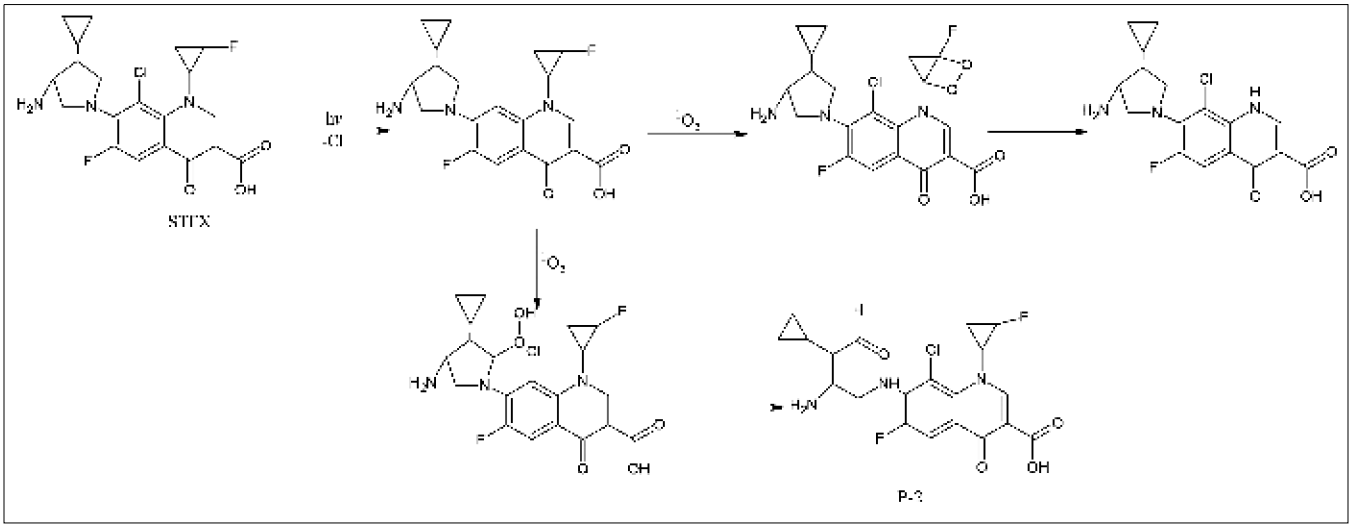


Fig. 10. Photodegradation of STFX according to type II mechanism[24].

The photodegradation of compounds may occur either by Type I mechanism (a free radical chain process termed as auto-oxidation) or Type II mechanism (involving the excited singlet oxygen, $^1O_2$, termed as oxygenation). The heterocyclic compounds such as pyrrole and furan undergo photooxidation by Type II mechanism. Since a pyrrole ring is present in STFX, it is degraded by Type II mechanism. On photoirradiation STFX generates $^1O_2$, and then reacts with $^1O_2$ to form a dioxeton intermediate. Further reactions lead to its hydrolysis and the formation of photoproducts (P–1) and (P–2). The photodegradation pathway of STFX is presented in Fig. 10. However, according to the authors the details of the mechanism of its photochemical reactions are not clear. The reaction follows first-order kinetics in acid, neutral and alkaline media according to Type II mechanism.

1.2.6. Studies Conducted by Ahmad and Coworkers

Ahmad et al. conducted photodegradation studies on levofloxacin[27], moxifloxacin[34] and norfloxacin[35] in aqueous solution by UV irradiation. They isolated and identified a number of photoproducts of these compounds by LC/MS/MS technique (Table 1) and proposed the mechanism of their formation in acid, neutral and alkaline solutions. The various photoproducts of these fluoroquinolones are formed by oxidative and hydrolytic degradation involving several steps.

2. CONCLUSION

Fluoroquinolones are important antibacterial agents that undergo degradation in aqueous solution on exposure to sunlight and UV light, giving rise to a number of inactive or toxic products by different mechanisms. The extent of degradation depends on the chemical structures, photosensitivity and irradiation conditions of fluoroquinolones. The photodegradation of fluoroquinolones results in a loss of potency, changes in efficacy and possible toxicity of these compounds. It is, therefore, necessary to take necessary precautions to avoid exposure of fluoroquinolones to light during manufacturing, storage and use. The addition of photostabilizers to the formulations may help to reduce the likelihood of degradation during manufacturing processes and administration.

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