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Nonsteroidal Antiinflammatory Drug-Photosensitized Formation of Pyrimidine Dimer in DNA

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ABSTRACT. Phototoxic nonsteroidal antiinflammatory drugs (NSAIDs) may induce DNA damage *in vitro* upon irradiation. In this study, we investigated the ability of ketoprofen (KP), tiaprofenic acid (Tia), naproxen (NP) and indomethacin (IND) to photosensitize the formation of pyrimidine dimers and single strand breaks. Both kinds of damage were sought by analyzing DNA-drug mixtures irradiated at 313 nm by agarose gel electrophoresis. The formation of pyrimidine dimers was evidenced by using endonuclease V from bacteriophage T4 and compared to that induced by acetophenone, a well-known photosensitizer of thymine dimerization. Upon irradiation of DNA alone, pyrimidine dimers were observed while single strand breaks were not detected under our conditions. DNA, in the presence of NSAIDs, undergoes single strand breaks, the quantum yield of the DNA cleavage so induced (ΦC) varying from 5×10^{-4} for KP to 10^{-5} for IND. The formation of dimers was only increased in the presence of KP or Tia. The quantum yields of pyrimidine dimers formed by photosensitization (ΦD) were 2×10^{-4} for KP and 10^{-5} for Tia, respectively. The oxygen and concentration dependence of both processes was analyzed in the case of KP. In aerated solution, KP-photoinduced cleavage of DNA was predominant on the photodimerization process of pyrimidines, whereas in deaerated solution the cleavage was decreased and the dimerization increased. These results reflect competition between a radical process leading to DNA cleavage and a poorly efficient energy transfer between the drug and the pyrimidines at the origin of the dimerization process. BIOCHEM PHARMACOL 55;4: 441–446, 1998. © 1998 Elsevier Science Inc.

KEY WORDS. ketoprofen; naproxen; tiaprofenic acid; indomethacin; photocleavage; photodimerization

Among the various drugs which may induce phototoxic effects, the case of nonsteroidal antiinflammatory drugs (NSAIDs)§ is well known. These drugs, widely used in the treatment of arthritic diseases, may promote enhanced cutaneous photosensitivity. After exposure to the sun, patients may develop reactions characterized mainly by erythema, itching, stinging and burning skin. In order to determine the origin of these phenomena, the photosensitization of biological targets by NSAIDs was investigated. It was shown that many NSAIDs which are derived from propionic acid and are the most phototoxic [1, 4], such as benoxaprofen (BNP), naproxen (NP), ketoprofen (KP), tiaprofenic acid (Tia), suprofen and carprofen, induce membrane damage [5, 11]. Photosensitization of DNA damage by NSAIDs has also been established. In particular, Artuso *et al.* have demonstrated that BNP, KP, Tia, NP and diflunisal photoinduce the formation of single strand breaks (SSB) via mainly radical processes [12, 13]. Singlet oxygen, generated by these compounds under irradiation, did not seem to be significantly involved in the formation of SSB. DNA breakage may be facilitated by a noncovalent drug-DNA interaction as recently suggested for suprofen [14] and naproxen (NP) [15].

Until now, only the formation of single strand breaks has been detected during the photosensitization of DNA by NSAIDs except in the case of BNP, where the formation of pyrimidine dimers was also mentioned [13]. From a general point of view, the photosensitization of pyrimidine dimerization by exogenous agents has been poorly investigated even though pyrimidine dimers, which may be at the origin of skin cancer, can be considered as the major lesion resulting from the irradiation of DNA. This led us to undertake an examination of the occurrence of such damage during the photosensitization of DNA by NSAIDs. It was known as early as 1967 that the main photosensitizers of pyrimidine dimer formation are carbonyl compounds such as acetone, acetophenone or benzophenone [16, 20]; therefore, we first focused our study on ketoprofen (KP) and tiaprofenic acid (Tia), which exhibit structures close to that

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§ *Abbreviations:* AC, acetophenone, methyl phenyl methanone; BNP, benoxaprofen, 2-(4-chlorophenyl)-α-methyl-5-benzoxazole acetic acid; IND, indomethacin, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid; KP, ketoprofen, 2-(3-benzoylphenyl) propionic acid; NP, naproxen, *d*-2-(6-methoxy-2-naphthyl) propionic acid; NSAIDs, nonsteroidal antiinflammatory drug; *r*, drug/DNA base pair molar ratio; S, number of single strand breaks per mole of DNA; SSB, single strand break; Tia, tiaprofenic acid, 2-[4-(2-benzoyl)thiophenyl] propionic acid.

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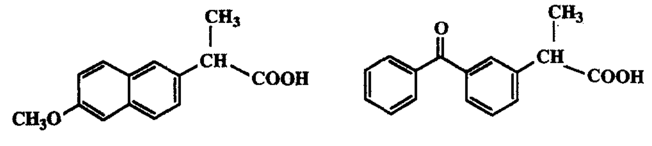
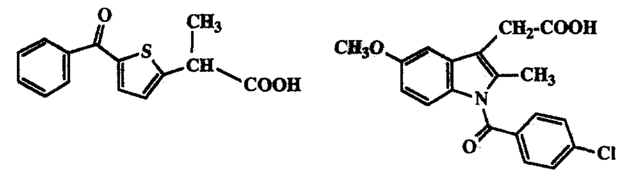


Naproxen (NP) **Ketoprofen (KP)**



Tiaprofenic acid (TIA) **Indomethacin (IND)**

FIG. 1. Structures of the various NSAID compounds tested as DNA photosensitizers.

of benzophenone and are already known to be phototoxic *in vivo* and DNA breaker agents *in vitro*. For comparison, similar studies were also performed on two other NSAIDs: naproxen (NP), a phototoxic propionic acid derivative, and indomethacin (IND), an acetic acid derivative which in contrast reduces UV-induced erythema in normal patients [21, 22] (Fig. 1). Acetophenone (AC), a classical photosensitizer of thymine dimerization, was used as standard. These studies were carried out *in vitro* on $\Phi\chi$-174 DNA which was irradiated at 313 nm in the presence of the drugs. The formation of cyclobutylpyrimidine dimers was detected using phage T4 endonuclease V, a DNA repair enzyme which selectively cuts DNA next to the pyrimidine dimer sites thus leading to single strand breaks by a two-step mechanism [23].

MATERIALS AND METHODS

Chemicals and Biochemicals

KP was purchased from Specia, Tia from Roussel Uclaf, IND from Merck, NP from Syntex, and AC from Aldrich. Supercoiled $\phi\chi$174 DNA (MW 3.6×10^6 Da, 5386 base pairs per molecule) Form I was purchased from Pharmacia. The DNA was used after dilution in 5 mM phosphate buffer (pH 7.4) containing 10 mM NaCl so that the concentration of the solution was 14 nM in DNA molecules or 75.4 μM in bp. The amount of contaminant Form II was checked by agarose gel electrophoresis followed by microdensitometry and was less than 10%. No Form III was detected in the starting material. The electrophoresis-grade agarose was obtained from Touzart and Matignon. DNA concentrations (mg) were determined by UV absorption spectroscopy using a conversion factor of 21 absorbance units/mg of DNA. DNA concentrations in base pairs were determined spectrophotometrically at 260 nm using the extinction coefficient of 13,200 M^{-1} cm^{-1} [24]. Phage T4 endonuclease V was prepared according to the procedure of Lommel *et al.* [23]. Endonuclease activity checked before use was 4.3×10^{12} sites/μL/min. All solutions were prepared in phosphate buffer (5 mM, 10 mM NaCl, pH = 7.4).

Irradiation Procedure

Samples were prepared by mixing 5 μL of 14 nM DNA (75.4 mM bp), 5 μL of drug solution at a fixed concentration in phosphate buffer and 10 μL of phosphate buffer. The sample containing DNA alone was prepared from 5 μL of 14 nM DNA and 15 μL phosphate buffer. The mixture was placed in glass tubes (3 mm diameter) and incubated for 20 min in the dark. For experiments in deaerated conditions, the starting solutions were first bubbled with argon and the tubes containing the mixture then flushed with argon and capped. All the concentrations given in the text are the final concentrations in the tubes. Except for KP experiments using drug concentrations varying from 2.5 to 180 μM, the NSAID concentration was 25 μM. Absorbance at 313 nm in the tube was 8.7×10^{-3} for KP, 9.4×10^{-3} for NP, 50×10^{-3} for IND, 113×10^{-3} for Tia, 0.7×10^{-3} for AC and 1.2×10^{-3} for DNA.

The solutions were irradiated at 313 nm for various periods of time with a Muller reactor device equipped with a 200 W high-pressure mercury lamp (Osram), a water cooling filter and an interference filter (Oriel 313FS 10–50 12% transmission at 313 nm, bandwidth 10 nm). The energy was monitored with an EGG Gamma radiometer-photometer system. The power received by the samples was *ca.* $1.4\ 10^{-3}$ W/cm^2.

Photosensitized Cleavage Experiments

After irradiation, 5 μL of a mixture containing 250 mM HEPES pH 7.45, 75% glycerol and 0.05% bromophenol blue were added to the irradiated solution. The sample was then analyzed by electrophoresis on 0.8% agarose horizontal slab gel in Tris borate buffer, and quantification of the various forms of DNA (I, II, III) was performed as described by Artuso *et al.* [12]. The number of single strand breaks per mole of DNA (S) generated by photosensitization was calculated from the relative percentage of Forms I and II, assuming a Poisson distribution and using the formula $S = \ln C/C_o$, where C_o is the initial concentration of DNA in Form I and C the concentration of Form I after irradiation. A coefficient of 1.66 was used to correct the lower efficiency of ethidium bromide binding to DNA to Form I with respect to Forms II and III [25]. The quantum yield of photosensitized formation of single strand breaks (ΦC) was calculated from the total number of DNA breaks per sec and the number of photons absorbed during the same time by the drug in the sample. The rate of SSB formation was evaluated using only the linear part of the curve $S = f(t)$ to minimize the possible perturbations induced by the photodegradation of the drug and the occurrence of inefficient cleavage or dimerization reactions on Form II.

Photosensitized Dimerization Experiments

At the end of the irradiation, DNA was precipitated by addition of 100 μL of cold ethanol and 2 μL of 3 M sodium acetate buffer (pH = 5.5) to the irradiated mixture. The samples were kept in dry ice for an hour and centrifuged for 45 min (10,000 × *g*). The residue was washed in 70% ethanol, centrifuged and dried under vacuum. Twenty μL of diluted phage T4 endonuclease V in Tris-acetate buffer (pH = 8) were added to the residue, and the solution was incubated for 30 min at 37°. Proteins were removed from the mixture by washing with chloroform-phenol-isoamyl alcohol. The samples were further treated by the same procedure as used for the cleavage experiments. Controls used the same procedure without endonuclease and the residue was dissolved in 20 μM phosphate buffer. It could be considered that the number of dimers due to the direct excitation of DNA in the mixture is very likely similar to that obtained in the absence of drug, since the solution was far too dilute to absorb all the light arriving on the sample, both drug and DNA having very low absorbance. In experiments using KP (25 μM) as photosensitizer, only 2.3% of the incident light was absorbed by the solution: 0.27% by DNA and 2% by KP. Consequently, the quantum yield of photosensitized formation of dimers (ΦD) could be evaluated from the number of single strand breaks detected after treatment by phage T4 endonuclease V, after subtraction of the number of single strand breaks obtained before treatment and of those corresponding to dimers resulting from irradiation of DNA alone. The values of quantum yields of both cleavage and dimerization processes obtained by this method were slightly underestimated since these reactions, occurring on Form II and not leading to Form III, were not taken into account.

RESULTS

Comparative Study of the Photosensitization of DNA Damage by Various NSAIDs

NSAID photosensitization of DNA damage was carried out by irradiating at 313 nm phosphate-buffered solutions of KP, Tia, NP, IND and AC (25 μM) containing supercoiled Φχ 174 DNA (Form I, 18.85 μM in base pairs) over periods of up to 40 sec. The formation of SSB was then analyzed by agarose gel electrophoresis. As seen in Fig. 2, all the NSAIDs photosensitized the formation of SSB. Comparison of these effects for the various compounds at the same concentration corresponding to a drug to base pair molar ratio of 1.4 shows that Tia and KP were significantly more efficient than NP, IND or AC stated as reference. In the case of IND and AC, it should be noted that S did not vary with the irradiation time and remained very low. The qualitative data previously reported [12, 13] can thus be quantified. The quantum yields of SSB (ΦC) induced by NSAIDs under irradiation at 313 nm under our conditions varied from 5×10^{-4} for KP to 10^{-5} for IND, while AC exhibited a higher quantum yield (1.4×10^{-3}) (Table 1).

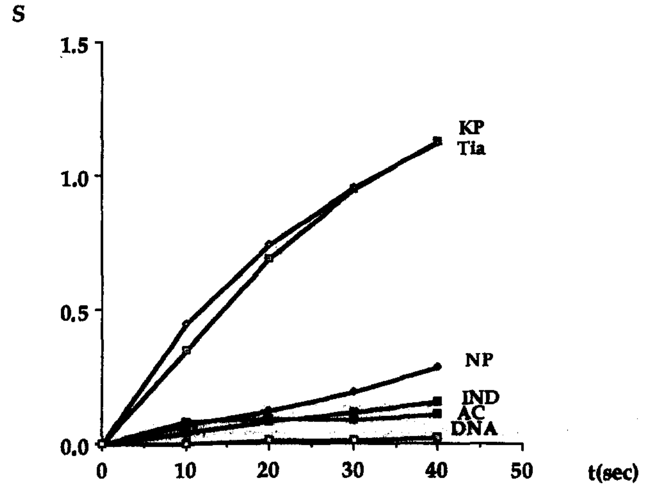


FIG. 2. Influence of irradiation time on the mean number of SSB per DNA molecule (S) photoinduced in the presence of KP, Tia, NP, IND and AC at a same concentration (25 μM) or in the absence of photosensitizer.

Irradiation of DNA alone, under the same conditions, did not induce the formation of SSB, but the action of phage T4 endonuclease V on the solution of irradiated DNA promoted SSB corresponding to the formation of dimers. When DNA was irradiated in the presence of KP or Tia or AC, the number of dimers thus formed was increased. This number was not significantly modified by NP and was slightly reduced by IND. Among the whole set compounds studied, AC was by far the most efficient photosensitizer of pyrimidine dimerization. Regarding only NSAIDs, it appears that only KP and Tia photosensitized the formation of pyrimidine dimers in DNA. The number of dimers due to the photosensitization was plotted versus the irradiation time. Figure 3 shows that the dimers induced by NSAIDs increased slightly with the irradiation time except for NP. In this case, a clear enhancement of the rate of formation of the dimers was observed after a short period of irradiation. This modification of the behavior of NP with the irradiation time may be due to the formation of photodegradation products more efficient than NP itself. The quantum yields of dimerization induced on DNA by NSAID photosensitization ΦD at 313 nm were found to be 2×10^{-4} for KP, 10^{-5} for Tia and 6×10^{-3} for AC for a drug/DNA base pair molar ratio of 1.4. As can be seen in Table 1, NSAIDs mainly photosensitize DNA cleavage. They are less efficient on pyrimidine dimerization.

TABLE 1. Quantum yields of SSB (ΦC) and dimers (ΦD) due to the photosensitization by NSAIDs and AC (25 μM, r = 1.4) at 313 nm

	KP	Tia	NP	IND	AC
$\Phi C \times 10^3$	0.5	0.05	0.1	0.01	1.4
$\Phi D \times 10^3$	0.2	0.01			6

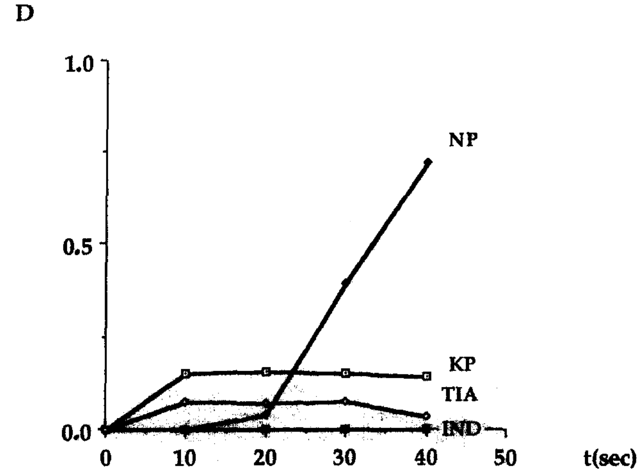


FIG. 3. Influence of irradiation time on the mean number of dimers per DNA molecule (D) photosensitized by KP, Tia, NP and IND.

Influence of the Presence of Oxygen and of Drug Concentration on the Photosensitization of DNA Damage by KP

The influence of various parameters was studied in the particular case of KP. When the same experiments as above were performed under a nitrogen atmosphere, the KP-photosensitized formation of SSB was twofold lower than in the presence of air. In contrast, the number of dimers photosensitized by the drug was increased by a factor of 1.6 (Fig. 4). The presence of oxygen quenched the photosensitized formation of dimers and simultaneously enhanced the formation of SSB.

The influence of the drug concentration on the efficiency of both reactions was studied for a change in KP concentration from 2.5 μM to 185 μM, r varying from 0.14 to 10.3. The number of SSB observed for a constant time (10 sec) of irradiation of DNA (18.85 μM) increased slightly from 0.23 to 0.35 as r was varied from 0.14 to 1.4 and then remained at the same level when r was increased up to 10.3. The photosensitization of pyrimidine dimers by KP only occurred when the concentration was sufficiently high. The number of dimers per mole of DNA, induced by the drug for the same time of irradiation, became significant (0.16) only for $r = 1.4$. Then, it increased to 0.28 when r increased up to 10.3. The quantum yields of both cleavage and dimerization processes decreased as r increased (Fig. 5).

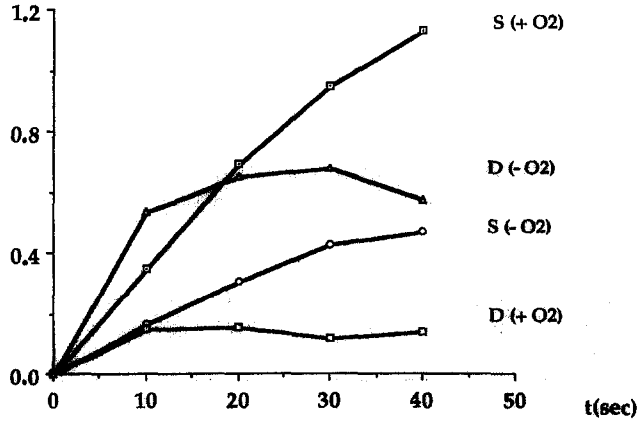


FIG. 4. Influence of irradiation time on the mean number of SSB or dimers per DNA molecule photosensitized by KP in aerated or deaerated solutions.

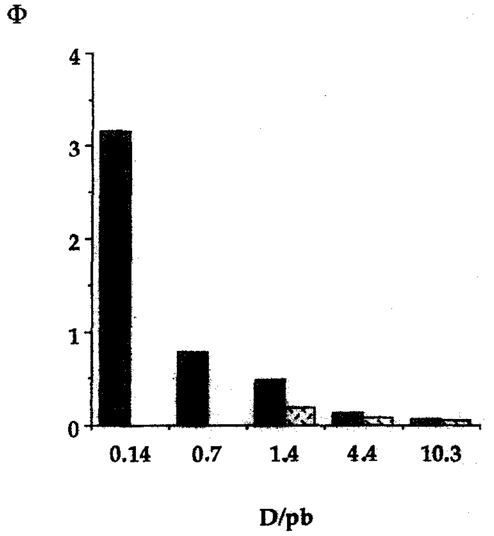


FIG. 5. Influence of the drug to base pair ratio on the quantum yields of formation of SSB (■) or dimers (▨) photosensitized by KP.

DISCUSSION

Our findings demonstrate that NSAIDs photosensitize DNA damage with different efficiencies depending on the structure of the drug and the type of damage. As previously reported, all the compounds investigated induce DNA cleavage upon irradiation at 313 nm [12–13, 15]. The quantum yields of SSB formation, ΦC, vary from 5×10^{-4} for KP to 10^{-5} for IND at 313 nm for a drug to DNA base pair ratio $r = 1.4$. They are of the same order of magnitude as the value recently given by Condorelli *et al.* for Suprofen, $\Phi C = 10^{-4}$ for $r = 1.8$ [14]. The quantum yield determined by De Guidi *et al.* for Naproxen for $r < 0.5$ was slightly higher, 4.3×10^{-3} [22] than that given here for $r = 1.4$, which is consistent with the fact that the quantum yield decreases as r increases.

The mechanism proposed for these chain breaks is a Type I mechanism [12–15] involving hydroxyl radicals. It is well known that hydroxyl radicals detected by scavengers are very efficient in chain break production [26]. Such a mechanism has been given by Charlier *et al.* for benzophenone [16, 27], hydroxyl radicals resulting from hydrogen abstraction by the excited triplet state of benzophenone to a molecule of water. Since then, characterization of the final products of purine and pyrimidine photosensitization by benzophenone has confirmed the involvement of a Type I mechanism, but indicates that the initial step is more likely an electron transfer from the bases to the triplet-excited benzophenone rather than hydrogen abstraction

[28–30]. Recently, flash-photolysis experiments on benzophenone-adenine mixtures which indicate the formation of the benzophenone radical anion, have supported this hypothesis [31]. Such a mechanism, leading to the formation of a nucleotide radical cation which is rapidly deprotonated to give the neutral radical, could also explain the DNA cleavage observed. The behavior of KP under irradiation, which may be compared to that of benzophenone [32], leads us to propose, as for KP-mediated DNA cleavage, the participation of a charge transfer process. The influence of the presence of oxygen, which increased the yield of chain break production mediated by benzophenone [27], was correlated to a decrease in the rate of benzophenone photolysis in the presence of oxygen. The same effect on ΦC is observed here with KP. Found also by Artuso *et al.* for short irradiation times, it was reversed for longer periods of time.

When DNA is irradiated in the presence of NSAIDs, pyrimidine dimers are formed simultaneously with SSB. However, it appears that only KP and Tia promote the formation of more dimers than those observed by irradiating DNA alone. The quantum yields of dimers arising from photosensitization were *ca.* 2×10^{-4} for KP, 10^{-5} for Tia and 6×10^{-3} for AC. This latter value may be favorably compared to the quantum yield of thymine dimerization photosensitized by acetophenone, 1.6×10^{-3} [33]. In contrast with KP and Tia, NP and IND do not enhance the formation of dimers in DNA upon irradiation, IND leading to a number of dimers lower than that formed in the absence of drug. Thus, it appears that only NSAIDs with a carbonyl function photosensitize the formation of pyrimidine dimers. It is well known that many excited ketones can react with DNA by triplet energy transfer [34, 35]. This requires the triplet state of the photosensitizer to be higher than that of thymine (73 kcal mol^{-1}), which is the mononucleotide lowest in energy [31]. Benzophenone, with a triplet energy of approximately 69 kcal mol^{-1}, is not a good candidate for such a transfer. This explains how benzophenone, as well as benzophenone-like compounds such as KP or Tia, promotes pyrimidine dimers only in a low yield [36]. The competition between electron and energy transfer may also reduce the formation of dimers, since in this case the triplet state is quenched by the electron donor [37]. NP, which may have a triplet state close in energy to that of naphthalene derivatives (59–61 kcal mol^{-1}) [38], cannot sensitize the formation of pyrimidine dimers, as observed. The value of the triplet state energy of IND was not known, but the quenching observed with IND suggests that it would be lower than that of thymine, the energy gap thus allowing energy transfer from an excited state of DNA to the ground state of IND to occur.

The influence of oxygen on the efficiency of photodimerization by KP is in agreement with the involvement of an energy transfer. The decrease in the number of pyrimidine dimers observed in the presence of oxygen may be attributed to quenching of the triplet state of the drug by molecular oxygen. The same effect was observed with dimer photosensitization by benzophenone, acetophenone and acetone [39]. The variation of the drug/DNA base pair molar ratio induces an increase in the number of SSBs or dimers induced after 10 sec of irradiation. In the case of the cleavage reaction, this number reached a constant value for $r > 1.4$ which cannot be attributed to self-quenching, since the concentration of the drug was very low ($\sim 10^{-5}$ M). Another hypothesis may be proposed to explain the presence of this plateau. Recently, De Guidi *et al.* [15] observed a similar pattern of variations for NP-induced DNA cleavage. They assumed that a drug-DNA complex is formed and that only DNA-bound NP molecules are responsible for the cleavage. A similar association may explain the saturation observed in our case.

In conclusion, this paper presents one of the first examples of phototoxic drugs photosensitizing the formation of cyclobutylpyrimidine dimers in DNA *in vitro*. KP and, with a lower efficiency, Tia, simultaneously induce chain breaks and dimers. Their behavior may be considered as resulting from their benzophenone-like structure, which is able to induce both electron and energy transfer to DNA [32, 37]. Their ability to form thymine dimers, which are one of the major lesions of DNA following UV irradiation, make such photosensitizers particularly dangerous.

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