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Photoinduced Free Radicals from Chlorpromazine and Related Phenothiazines: Relationship to Phenothiazine-Induced Photosensitization

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Chlorpromazine and several other related phenothiazines are known to cause both phototoxic and photoallergic reactions in the skin and eyes of patients receiving these drugs. While the detailed mechanisms of photosensitization are not known, it is obvious that the first step must be the absorption of light by the drug, its metabolites, or photoproducts, or possibly an induced endogenous chemical. In this review, the free-radical photochemistry of phenothiazines is described, and the evidence for the involvement of photoinduced free radicals in photosensitization is examined. Upon irradiation chlorpromazine yields a variety of free radicals including the corresponding cation radical (via photoionization), the neutral promazinyl radical and a chlorine atom ($Cl^{\bullet}$) (via homolytic cleavage), and a sulfur-centered peroxy radical. The chlorpromazine cation radical is probably responsible for some of the observed *in vitro* phototoxic effects of this drug. However, it seems unlikely that the cation radical is involved in phototoxicity *in vivo*, since photoionization only occurs when chlorpromazine is excited into the S_2 level ($\lambda_{ex} < 280$ nm). The promazinyl radical is a more likely candidate for the phototoxic species both *in vivo* and *in vitro*. In addition, this radical can react covalently with proteins and other macromolecules to yield antigens which could be responsible for the photoallergic response to chlorpromazine. Neither oxygen-derived radicals nor singlet oxygen ($^1O_2^*$), appear to be important in chlorpromazine photosensitization. In contrast, it would seem that promazine-induced phototoxicity may result in part from the generation of superoxide ($O_2^{\cdot-}$). The inability of promazine, which lacks a chlorine atom at the 2-position, to undergo homolytic fission to give the promazinyl radical, probably explains why this drug is much less phototoxic than chlorpromazine both *in vivo* and *in vitro*.

Introduction

The interaction of light with chemical agents present in the skin and eyes often results in the photosensitization of both human and animal subjects (*1*). The photosensitizing chemical may be endogenous (protoporphyrin), a drug (declomycin, sulfonamide), a topical agent (4–aminobenzoic acid and its esters in sunscreens) or an environmental agent (anthracene in coal tar) (*2,3*). Photosensitization may take the form of phototoxicity or photoallergy. The phototoxic response is essentially an exaggerated sunburn reaction (*1,2*), while photoallergy is a delayed hypersensitivity reaction (*1,3*). Although the detailed mechanisms of photosensitization are not known, it is obvious that the first step must be the absorption of light by the chemical, its metabolites, photoproducts, or possibly an induced endogenous chemical.

The phenothiazine tranquilizers, e.g., chlorpromazine, have been used to treat many psychotic disorders, particularly those which involve hyperactivity and anxious excitement. However, chlorpromazine and several other related phenothiazines are known to cause both phototoxic and photoallergic reactions in patients receiving low doses of these drugs (*4–6*). High dosage and prolonged treatment can produce severe dermatitis that is frequently accompanied by darkening of the skin due to the deposition of melanin in lower layers of the dermis (*5*). Such patients may also suffer retinal damage, ocular opacity and loss of vision.

In this review, the free-radical photochemistry of phenothiazines will be described, and the evidence for

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the involvement of photoinduced free radicals in phenothiazine photosensitivity will be examined. The structures of the phenothiazine drugs are given in Table 1.

Free-Radical Photoproducts from Phenothiazines

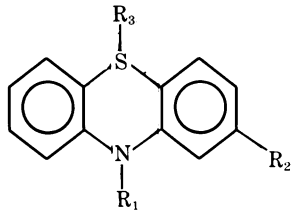
Carbon-Centered Radicals

Grant and Green have reported that, in aqueous solution, chlorpromazine (ClP) is converted into promazine (PH) and 2-hydroxypromazine (POH) upon exposure to sunlight (7). These workers proposed that the chlorpromazine triplet underwent direct homolytic fission to yield a chlorine atom ($Cl^{\cdot}$) and the neutral promazinyl radical ($P^{\cdot}$), which reacted with the solvent to give the observed products

$$ClP \xrightarrow{h\nu} {}^1ClP^* \quad (1)$$

$${}^3ClP^* \rightarrow {}^3ClP^* \quad (2)$$

Table 1. Structures of the phenothiazines.



Compound	R_1	R_2	R_3	Abbreviation
Phenothiazine	H	H	–	
Promazine	$-(CH_2)_3N(CH_3)_2$	H	–	PH
Chlorpromazine	$-(CH_2)_3N(CH_3)_2$	Cl	–	ClP
Triflupromazine	$-(CH_2)_3N(CH_3)_2$	CF_3	–	
Methoxypromazine	$-(CH_2)_3N(CH_3)_2$	OCH_3	–	$POCH_3$
Acepromazine	$-(CH_2)_3N(CH_3)_2$	$COCH_3$	–	
Compazine	$-(CH_2)_3$-N⟨piperazine⟩N-CH_3	Cl	–	
Perphenazine	$-(CH_2)_3$-N⟨piperazine⟩N-CH_2OH	Cl	–	
Stelazine	$-(CH_2)_3$-N⟨piperazine⟩N-CH_3	CF_3	–	
Fluphenazine	$-(CH_2)_3$-N⟨piperazine⟩N-CH_2OH	CF_3	–	
Promethazine	$-CH_2CHN(CH_3)_2$ CH_3	H	–	
Thioridiazine	$(CH_2)_2$-⟨piperidine⟩ N CH_3	SCH_3	–	
Trifluoperazine	$(CH_2)_3$-N⟨piperazine⟩N-CH_3	CF_3	–	
Chlorpromazine-MNP spin adduct	$-(CH_2)_3N(CH_3)_2$	$-N(\cdot O)-C(CH_3)_3$	–	I
2-Ethoxypromazine	$-(CH_2)_3N(CH_3)_2$	$-OC_2H_5$	–	POC_2H_5
2-Isopropoxypromazine	$-(CH_2)_3N(CH_3)_2$	$-OCH(CH_3)_2$	–	$POCH(CH_3)_2$
2-Dimethylaminopromazine	$-(CH_2)_3N(CH_3)_2$	$-N(CH_3)_2$	–	$PN(CH_3)_2$
2-Hydroxypromazine	$-(CH_2)_3N(CH_3)_2$	OH	–	POH
9-Peroxylchlorpromazine	$-(CH_2)_3N(CH_3)_2$	Cl	$-OO^{\cdot}$	$ClPSOO^{\cdot}$
Chlorpromazine sulfoxide	$-(CH_2)_3N(CH_3)_2$	Cl	=O	ClPSO

$$^3ClP \rightarrow Cl^{\cdot} + P^{\cdot} \quad (3)$$

$$P^{\cdot} + H_2O \rightarrow PH + {}^{\cdot}OH \quad (4)$$

$$P^{\cdot} + {}^{\cdot}OH \rightarrow POH \quad (5)$$

Moore and Tamat have reported that photolysis of chlorpromazine in nitrogen-saturated water results in the production of one mole of Cl^- per mole of drug photolyzed (*8*). The chloride ion may be derived from $Cl^{\cdot}$ by hydrogen abstraction from the solvent or possibly by reaction of electrons, derived from photoionization (*vide infra*), with ground-state chlorpromazine,

$$e^-_{aq} + ClP \rightarrow Cl^- + P^{\cdot} \quad (6)$$

Recent spin-trapping studies have provided additional evidence that anerobic photolysis of chlorpromazine at 330 nm results in the dechlorination to give the neutral radical, $P^{\cdot}$ [Eq. (3)] (*9*). When 2-methyl-2-nitrosopropane (MNP) was used as a trap, one carbon-centered adduct (I) (Table 1) was detected from ClP over the range pH 3.5 to 6.5 (Fig. 1). The hyperfine splitting constants (a^N = 14.1 G; a^H = 0.92 G, and 1.99 G) of the adduct (I) were consistent with a structure containing three aromatic ring hydrogens derived from the reaction of MNP with the neutral promazine radical, $P^{\cdot}$. The detection of this spin adduct implies that $P^{\cdot}$ is sufficiently stable to make the extraction of $H^{\cdot}$ from water [Eq. (4)] and subsequent ${}^{\cdot}OH$ formation very unlikely. $P^{\cdot}$ is, however, able to extract $H^{\cdot}$ from donors such as ethanol or citrate (*9*) to form promazine, PH, and could also react with molecular oxygen, ultimately forming POH (*9*).

In oxygen-free isopropanol, chlorpromazine also undergoes homolytic carbon–chlorine bond fission to form the neutral promazine radical ($P^{\cdot}$) which then reacts with the solvent to form promazine, 2-isopropoxypromazine, HCl, and acetone (*10*):

$$Cl^{\cdot} + (CH_3)_2CHOH \rightarrow HCl + (CH_3)_2\dot{C}OH \quad (7)$$

$$P^{\cdot} + (CH_3)_2\dot{C}OH \rightarrow PH + (CH_3)_2CO \quad (8)$$

$$P^{\cdot} + (CH_3)_2\dot{C}OH \rightarrow PHCH(CH_3)_2 \quad (9)$$

A similar mechanism can be proposed to explain the production of promazine and other 2-substituted promazines when chlorpromazine is irradiated in other solvents, e.g., methanol ($POCH_3$), ethanol (POC_2H_5), and aqueous dimethylamine [$PN(CH_3)_2$] (*7*).

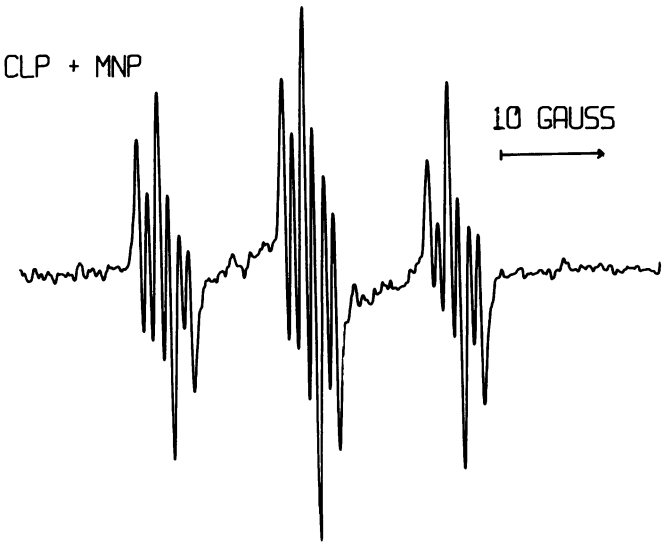


FIGURE 1. Electron spin resonance spectrum of adduct I obtained by irradiation of an aqueous solution (pH 4.0) of chlorpromazine and 2-methyl-2-nitrosopropane (MNP) at 330 nm.

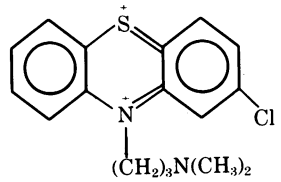
Oxygen-Centered Radicals

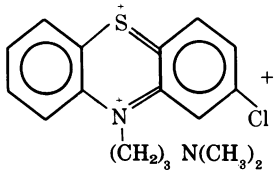
When an aqueous aerated solution of chlorpromazine is irradiated at 330 nm a peroxy radical is trapped by 5,5-dimethyl-1-pyrroline-1-oxide (DMPO) which decays to the hydroxyl radical adduct, DMPO-OH (*9*). Since the yield of the DMPO peroxy radical adduct is not affected by superoxide dismutase, it cannot be derived directly from superoxide. It is suggested instead that a sulfur peroxy radical intermediate may be involved,

$$^3ClP^* \xrightarrow{O_2} ClPSOO^{\cdot} \quad (10)$$

$$ClPSOO^{\cdot} + DMPO \rightarrow DMPO\text{-}OOSPCl \quad (11)$$

$$DMPO\text{—}OOSPCl \rightarrow DMPO\text{—}OOH + \quad (12)$$





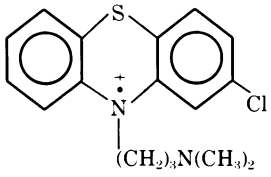
$$+ H_2O \rightarrow ClPSO + 2H^+ \quad (13)$$

$$DMPO\text{—}OOH \rightarrow DMPO\text{—}OH \quad (14)$$

The yield of DMPO-OH follows the absorption curve of chlorpromazine fairly closely over the range 250 nm to 350 nm suggesting that the peroxy radical is formed from the triplet state of chlorpromazine via excitation into either the S_1 or S_2 energy levels (*9*). When promazine was irradiated under the same conditions DMPO trapped a peroxy adduct at pH 4 and the DMPO-OH decay product at pH 6.5 (*9*). Since the signal intensity of the DMPO-OH adduct did decrease in the presence of superoxide dismutase, superoxide must be generated during the irradiation of promazine. Similar findings have been reported by Decuyper et al. (*11*).

Phenothiazine Cation Radicals

The free radical cations of phenothiazines may be generated by a variety of methods, including air oxidation in strong acid solutions, oxidation by horseradish peroxidase/H_2O_2 and electrolytic oxidation (*12–14*). Felmeister and Discher (*15*) have also detected the chlorpromazine cation radical (II) in aqueous acidic solutions of the drug irradiated with a mercury arc lamp.

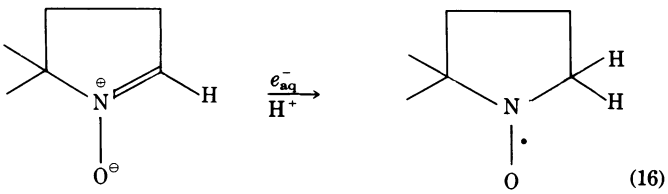


II

Flash photolysis studies of either anerobic or aerobic aqueous solutions of chlorpromazine at 347 nm (*16*) and 254 nm (*17*) have provided additional evidence for photoionization of the drug to yield the chlorpromazine cation radical ($ClP^{+\cdot}$) and the aqueous electron (e_{aq}^-)

$$ClP \xrightarrow{h\nu} ClP^{+\cdot} + e_{aq}^- \qquad (15)$$

More recently Motten et al. (*9*) have shown in a spin trapping study that when chlorpromazine is photolyzed at 270 nm (i.e., into the S_2 absorption band) a strong signal characteristic of the DMPO-H adduct is observed in addition to carbon- and oxygen-centered adducts. Since the DMPO-H signal was suppressed in the presence of N_2O, it was concluded that the spin trap had reacted with an electron [Eq. (16)].



(16)

However, in contrast to the flash photolysis study of Navaratnam and co-workers (*16*), no DMPO-H was observed when chlorpromazine was excited at 330 nm. The flash photolysis experiment used a 25 nsec flash, which is long compared to the chlorpromazine singlet state lifetime of only 1.3 nsec (R. D. Hall, unpublished data). Thus it is possible that a substantial steady state triplet population could have been produced during the flash photolysis experiment. Triplet-triplet absorption and subsequent electron ejection could under these conditions be pseudo first-order with respect to light intensity as was observed by Navaratnam et al. (*16*).

The cation radicals of chlorpromazine and other phenothiazines have been characterized by their absorption spectra (*18–20*) and electrochemical properties (*21,22*). The electron spin resonance (ESR) spectra of the phenothiazine cation radical in aqueous (*23*) and acetonitrile (*24*) solutions have been analyzed. However, it is only recently that the aqueous solution spectra of cation radicals derived from chlorpromazine and the other phenothiazine tranquilizers have been successfully analyzed and simulated (*12*).

The ESR spectrum of the chlorpromazine cation radical generated by air oxidation in acid solution is shown in Figure 2. In addition, the aqueous ESR spectra of promazine, 2-chlorophenothiazine, promethazine, and trimeprazine have been recorded and analyzed (*12*).

Other Chlorpromazine Radicals

Forrest and co-workers (*25*) have reported the formation of a colorless free radical when dilute aqueous solutions of chlorpromazine were exposed to a sunlamp for 3 hr. The free radical character of the photoproduct was inferred from ESR spectra of a solid sample of the corresponding 2,4-dinitrophenylhydrazine derivative. However, Borg and Cotzias (*13*) failed to observe any free radicals in aqueous solutions of chlorpromazine irradiated with ultraviolet radiation. It was suggested that the ESR spectrum of the solid derivatives isolated by Forrest et al. was due to the formation of the cation radical during derivatization. Later, Piette and Forrest (*26*) reported the generation of a purple/blue substance by photooxidation of chlorpromazine. The ESR spectrum of this photoproduct indicated that it was not identical to the red chlorpromazine cation radical (II) formed under acidic conditions.

Singlet Oxygen

While singlet oxygen ($^1O_2$*) is not a radical species it has been implicated in the phototoxicity of many chemicals (*4*). However, the generation of singlet oxygen during photoirradiation of the phenothiazines is still somewhat controversial. Davies and co-workers (*10*) have shown that, under aerobic conditions, there is no photodegradation of chlorpromazine dissolved in isopropanol. They have suggested that this is due to energy transfer from the triplet state of the drug to molecular oxygen to yield singlet oxygen:

$$^3ClP^* + {}^3O_2 \rightarrow ClP + {}^1O_2^*$$

Moore and Tamat (*8*) have found that the photode-

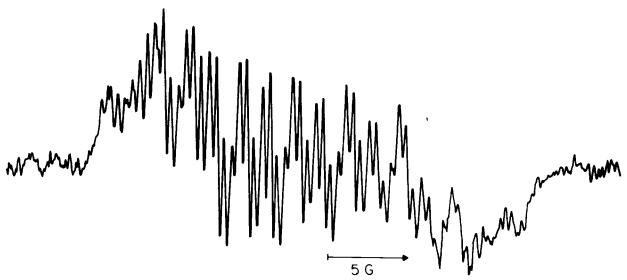


FIGURE 2. Electron spin resonance spectrum of the chlorpromazine cation radical in 20% DCl.

chlorination of chlorpromazine and prochlorperazine in methanol is also inhibited in the presence of oxygen.

Davies and co-workers have also reported (*10*) that, when chlorpromazine is irradiated in isopropanol in the presence of the singlet oxygen scavenger 2,5-dimethylfuran, there is rapid oxygen uptake which is inhibited by 1,4-diazabicyclo[2.2.2]octane (DABCO). Moore (*27*) has studied a series of phenothiazine tranquilizers in methanol solution and shown that 2,5-dimethylfuran stimulates oxygen uptake in the presence of promethazine, promazine, chlorpromazine, prochlorperazine, trifluperazine and thioridiazine. In contrast, Decuyper and co-workers (*28*) failed to detect singlet oxygen during the irradiation of ethanol solutions of promazine, triflupromazine, methoxypromazine, and acepromazine using the method of Lion et al. (*29*). Similar results were obtained by the same workers in aqueous solution using cholesterol attached to polystyrene latex beads as the singlet oxygen monitor. More recently Hall and Chignell (unpublished results) have also failed to detect the 1270 nm emission from singlet oxygen during the photolysis of deuterium oxide solutions of chlorpromazine. However, a very weak emission was observed from chlorpromazine dissolved in oxygenated *n*-hexane. Thus it is not clear at the present time whether singlet oxygen does play a role in chlorpromazine phototoxicity.

Free Radical Mechanisms of Phenothiazine Photosensitivity

Phototoxicity

Upon irradiation the phenothiazines are known to elicit a wide variety of phototoxic responses (Table 2). While it seems likely that free radicals do play a significant role in phenothiazine phototoxicity, there is often only indirect evidence that these highly reactive chemical species are involved. For example, Decuyper and co-workers have shown that strand breakage in ϕX174 DNA, caused by photoirradiation of promazine, methoxypromazine, or triflupromazine, can be mimicked by the corresponding cation radicals generated either chemically or enzymatically (peroxidase/H_2O_2) (*11*). Merville and co-workers (*41*) have found the cation radicals of chlorpromazine, methoxypromazine, promethazine, triflupromazine and acepromazine all cause a crosslinking of erythrocyte ghost membrane proteins which is similar to that observed when the membranes are photoirradiated in the presence of these same drugs. Other studies have shown that phenothiazine cation radicals are probably involved in the photoinduced inhibition of (Na^+ + K^+)-adenosinetriphosphatase by chlorpromazine, thioridiazine, triflupromazine, and trifluoperazine (*46–48*). It is of interest to note that the enzyme inhibition caused by irradiation in the presence of chlorpromazine could be reversed by cysteine or dithiothreitol (*47*). This suggests that the loss of enzyme activity may be the result of oxidation of essential sulfhydryl groups by the cation radical. The cation radicals of phenothiazines are also known to react with ascorbic acid, NADH, various sulfhydryl compounds, α-tocopherol, adrenalin, and dihydroxyphenylalanine (*49,51–53*). However, the observation that photoionization of chlorpromazine occurs only upon excitation into the S_2 level (λ_{ex} <280 nm) (*9*) makes it unlikely that direct photoformation of phenothiazine cation radicals by sunlight (λ >300 nm) is important in cutaneous and ocular photosensitivity *in vivo*.

The highly reactive neutral radicals formed by the homolytic fission of the carbon–chlorine bond in chlorpromazine ($Cl^\cdot$, $P^\cdot$) [Eq. (3)] and related phenothiazines may also play a role in phototoxicity. Decuyper and coworkers have shown that ϕX174 DNA strand scission by photoirradiated chlorpromazine increases under anerobic conditions (*11*). The denaturation of salmon sperm DNA by chlorpromazine and light is also enhanced in the absence of oxygen (*44*). Since oxygen would react rapidly with $Cl^\cdot$ and $P^\cdot$ it seems reasonable to assume that these radicals are involved. In this regard it is of interest to note that of the eight phenothiazines tested by Jose for photomutagenesis in *S. typhimurium*, only those that contained a chlorine atom (chlorpromazine, compazine, perphenazine) were active (*31*).

It is not clear at the present time what role active oxygen species ($^1O_2$, $^\cdot OH$, $O_2^{\cdot-}$) play in phenothiazine phototoxicity. Kochevar and Lamola have found that oxygen caused only a small increase in chlorpromazine-induced photohemolysis of human erythrocytes (*37*). Similar results have been reported by Johnson (*39*). However, Copeland et al. (*42*) have observed that oxygen is necessary for the disruption of liposomes by light in the presence of chlorpromazine. In addition, the presence of oxygen enhances both the inactivation of ϕX174 bacteriophage (*32*) and the strand breaking of ϕX174 DNA (*11*).

The apparent inability of chlorpromazine to generate singlet oxygen upon irradiation (*28*) makes it unlikely that this active oxygen species is involved in the phototoxicity of this drug. Additional evidence for the lack of involvement of singlet oxygen has been provided by Nilson and co-workers, who have found that neither histidine nor β-carotene (quenchers of singlet oxygen) protects against chlorpromazine-induced photohemolysis of human erythrocytes (*40*). These workers also failed to demonstrate an effect of deuterium oxide (which increases the lifetime of $^1O_2$*) in the same system.

Decuyper and co-workers have suggested that superoxide may play a role in the strand breakage of ϕX174 DNA observed during irradiation under aerobic conditions in the presence of promazine, triflupromazine, and methoxypromazine (*11*). Recent spin-trapping studies by Motten et al. (*9*) have confirmed that superoxide is indeed generated during the irradiation of aqueous solutions of promazine. While the DMPO-hy-

droxyl radical adduct has been observed during the photoirradiation of chlorpromazine, promazine, triflupromazine, and methoxypromazine (*9,11*) it seems unlikely that the hydroxyl radical is a primary photoproduct and therefore this reactive species cannot be involved in the phototoxicity of these drugs.

Kochevar and Lamola (*37*) have found that red cells are lysed in the dark by incubation with chlorpromazine solutions that had been previously irradiated in the absence of oxygen. This suggests that chlorpromazine photoproducts may be responsible for some of the phototoxic effects of this phenothiazine. Dimeric and higher polymeric photoproducts from chlorpromazine have been shown to cause red blood cell lysis in the absence of light (*38*).

Photoallergy

The photoallergic effect of chlorpromazine must be due to the covalent modification of proteins or other molecules to produce an antigen. The mechanism of the subsequent immunological response is presumably sim-

Table 2. Phototoxicity of phenothiazines.

Phenothiazine	Biological systems	Phototoxic effect	Effect of oxygen[a]	Inhibitors	Reactive species identified	Reference
Chlorpromazine	*S. typhimurium*	Mutagenesis	ND[b]	ND	ND	(*30*)
Chlorpromazine	Chinese hamster cells	Cell death	ND	ND	ND	(*30*)
Chlorpromazine, compazine, perphenazine	*S. typhimurium*	Mutagenesis	ND	ND	ND	(*31*)
Chlorpromazine, triflupromazine, methoxypromazine	ϕX174 bacteriophage	Inactivation	+	ND	Not $^1O_2$*	(*32*)
Chlorpromazine	*E. coli*, DNA, BSA[c]	Covalent binding	ND	ND	ND	(*33*)
Chlorpromazine	Human fibroblasts	Growth inhibition, DNA binding	ND	ND	ND	(*34*)
Chlorpromazine	Adenovirus 5	DNA damage (single strand breaks)	ND	ND	ND	)*35*)
Chlorpromazine	*E. coli*	Cell death	ND	ND	ND	(*36*)
Chlorpromazine	Human erythrocytes	Hemolysis	+	ND	ND	(*37*)
Chlorpromazine	Human erythrocytes	Hemolysis	−	ND	ND	(*38*)
Chlorpromazine	Human erythrocytes	Hemolysis	−	ND	ND	(*39*)
Chlorpromazine	Human erythrocytes	Hemolysis	+	ND	ND	(*40*)
Methoxypromazine, promethazine, triflupromazine, aceprom-azine	Human erythrocyte membranes	Crosslinking	−	NaN_3	Cation radical $OH^•$ (methoxy-promazine)	(*41*)
Chlorpromazine	Human erythrocyte membranes	Crosslinking	−	ND	$P^•$	(*41*)
Chlorpromazine	Liposomes	Lysis	+	Cysteamine, tocopherol	ND	(*42*)
Chlorpromazine	RNA, DNA, Purines, pyrimidines	Covalent binding	ND	ND	ND	(*43*)
Chlorpromazine	ϕX174 DNA	Strand breakage	+ −	ND	$P^•$	(*11*)
Promazine, triflupromazine methoxypromazine	ϕX174 DNA	Strand breakage	+ +	*tert*-BuOH, benzoate, formate	Cation radical $OH^•$, $O_2^{•-}$	(*11*)
Chlorpromazine	DNA (Salmon sperm)	Denaturation	−	ND	ND	(*44*)
Chlorpromazine	DNA	Intercalation	ND	ND	Cation radical	(*45*)
Chlorpromazine	$(Na^+ + K^+)$-ATPase	Inhibition	ND	ND	Cation radical	(*46,47*)
Thioridazine triflupromazine, trifluperazine	$(Na^+ + K^+)$-ATPase	Inhibition	ND	ND	Cation radical	(*48*)
Chlorpromazine	Ascorbate	Oxidation	ND	ND	Cation radical	(*49*)
Chlorpromazine	GSH, BSA	Oxidation of SH groups	+	ND	Cation radical	(*50*)

[a] Effects: − = inhibition of phototoxicity + = enhancement of phototoxicity.
[b] ND = not determined.
[c] BSA = bovine serum albumin.

ilar to other types of delayed hypersensitivity (*54*). Covalent binding of chloropromazine to a variety of macromolecules (RNA, DNA, serum albumin, purines, pyrimidines) under the influence of light has been demonstrated (*33,43*). Davies and co-workers (*10*) have suggested that for chlorpromazine the promazinyl radical ($P^{\cdot}$) may be the reactive species that generates the antigen *in vivo*. However, the possibility that chlorpromazine photoproducts chemically modify biological macromolecules without covalently binding must also be considered.

Conclusion

Even though phenothiazines have been studied for decades, the detailed photochemistry of these substances is as yet incompletely known. Future research on this class of drugs should determine the role of active oxygen species $^1O_2$*, $O_2^{\cdot-}$, and $^{\cdot}OH$ in photosensitization; the detailed mechanism of the reaction of phenothiazines with oxygen; the chemistry of the promazinyl radical, $P^{\cdot}$; the structure, characteristics, and possible role *in vivo* of the Forrest chloropromazine radical (*25*); and the roles of stable photoproducts such as dimers and multimers, and sulfoxides in phototoxicity.

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