ELSEVIER

Dyes and Pigments 42 (1999) 45–51

DYES and PIGMENTS

Phenothiazine photosensitizers: part 2. 3,7-Bis(arylamino)phenothiazines☆

Mark Wainwright *, Nicola J. Grice, Lynnette E.C. Pye

Photochemotherapy Group, Department of Applied Biology, University of Central Lancashire, Preston PR1 2HE, UK

Received 20 October 1998; accepted 15 December 1998

Dedicated to Dr. Geoff Hallas in celebration of his 65th birthday.

Abstract

The synthesis and characterisation of a series of phenothiazines for possible use in photochemotherapy is reported. Oxidative amination of 10*H*-phenothiazine using anilines and iodine in tetrahydrofuran led to a series of 3,7-bis(arylamino)phenothiazin-5-ium salts. 4-Substituted primary anilines gave rise to a secondary amino functionality at positions 3- and 7- of the phenothiazine chromophores. The relative ease of deprotonation of these compounds to the corresponding quinoneimines correlated well with the electronic properties of the 4-substituent in the original aniline. In vitro singlet oxygen yields for these derivatives were much lower than for the standard photosensitizer, methylene blue. The use of *N*-methylaniline did not lead to increased photosensitizing efficacy. However, the phenothiazines resulting from the use of benzylamines in place of anilines were more akin to new methylene blue N. All of the derivatives exhibited much greater lipophilicities than methylene blue.

Keywords: Phenothiazines; Photodynamic therapy; Singlet oxygen; Photosensitizers;

1. Introduction

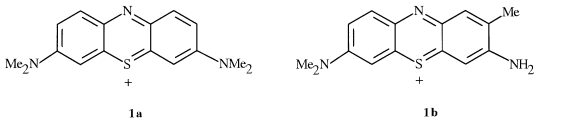
In the area of industrial photosensitization, use is made of the cationic phenothiazinium dye, methylene blue (**1a**) because of its low cost and high singlet oxygen quantum efficiency ($\Phi_\Delta = 0.443$) [2]. In conjunction with this, the widespread use of phenothiazinium dyes such as methylene blue (**1a**), its demethylated analogues, the azures, and toluidine blue O (**1b**) in vital staining led to the investigation of this class of dyes as biological photosensitizers in the developing anti-cancer regimen of photodynamic therapy (PDT). The phenothiazinium dyes exhibit intense absorption maxima in the 600–660 nm region of the spectrum (typically $> 50\,000$ litre mol^{-1} cm^{-1}; log $\varepsilon_{max} > 4.7$) which is also useful in PDT, being in the "therapeutic window" required for efficient tissue penetration by light. Thus the efficacies of **1a** and **1b** against bladder cancer cell lines have been investigated [3], **1a** has been used clinically in the treatment of bladder cancer [4] and recently against inoperable oesophageal tumours [5], skin malignancies and psoriasis [6]. Methylene blue is also employed photodynamically in viral disinfection of whole blood [7] and phenothiazinium derivatives such as

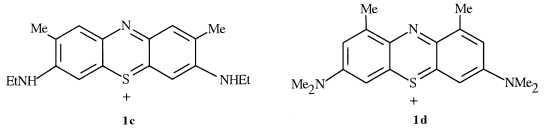
☆ See Ref. [1].

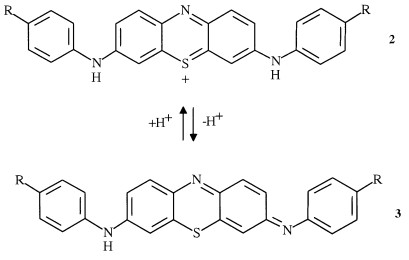
* Corresponding author. Tel.: +44-(0)1772-893534; fax: +44-(0)1772-892929; e-mail: m.wainwright@uclan.ac.uk

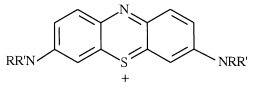
0143-7208/99/$ - see front matter
PII: S0143-7208(99)00008-X

new methylene blue N (**1c**) have been shown to be highly photoactive in vitro against pathogenic bacteria including methicillin-resistant strains of *Staphylococcus aureus* [8]. Notwithstanding this activity, the phenothiaziniums and cationic heterocyclic dyes in general have been largely overlooked as biomedical photosensitizers, the majority of work being carried out on porphyrins and their derivatives [9].









4a R = Me, R' = Ph
4b R = R' = CH_2Ph
4c R = H, R' = CH_2Ph

Both in cancer PDT and in the emerging antimicrobial regimens, the commercial phenothiazinium dyes have displayed the disadvantages of inherent (dark) toxicity and metabolic deactivation via chromophore reduction to the leuco dye, both of which lower therapeutic efficacy. This suggests a need for the rational design and synthesis of analogues based on e.g. **1a** or **1b** as lead compounds. We have previously shown that alteration of the phenothiazinium chromophore itself can lead to more active photosensitizers such as the 1,9-dimethyl derivative of methylene blue (Taylor's blue, DMMB **1d**) [1] whereas the 4-nitro derivative of **1a**, the commercial dye methylene green, shows no photosensitizing effect [3,10]. Such work apart, there are very few references to chromophoric manipulation. Indeed, analogue synthesis which has appeared in the literature appears to concentrate on varying the amino functionality at positions 3- and 7- to produce analogues of **1a**, with only tertiary amino functionalities [11–13]. It has been demonstrated for a series of benzo[*a*]phenothiazinium photosensitizers that secondary amino functionality at the 5- position (corresponding to 3- or 7- in the phenothiazinium chromophore) allows access in the biological milieu to the neutral quinoneimine form via *N*-deprotonation [2]. Since the commercial phenothiazinium photosensitizers based on methylene blue exhibit much higher singlet oxygen quantum yields than the aforementioned benzologues [1], it is a logical step to examine related phenothiazinium species having secondary amino functionality.

In searching for a preparative route to the secondary aminophenothiazines, the synthesis of ladder oligophenothiazines by Andreani et al. [14] offered a route to the intermediate 7-anilino-3-phenylimino-3*H*-phenothiazine from 10*H*-phenothiazine and aniline with iodine as oxidant [14]. This route offered the advantages of simplicity and wide scope for analogue synthesis. This method was used with a range of anilines differing only in the substituent in the *para*-position to produce a closely related series of phenothiazines. In addition, phenothiazinium salts containing arylamino groups should be somewhat more lipophilic than standard phenothiazinium dyes such as **1a**–**1d** and would thus be of interest from the point of view of cellular uptake and intracellular compartmentalisation.

2. Results and discussion

The method of Andreani et al. [14] proved ideal for the synthesis of the simple bisanilino derivatives required for the current work, yielding a simple, closely-related series of compounds for investigation. Although yields were normally 40–50%, the synthesis was much cleaner than is typical for

phenothiazinium dyes which are normally produced from phenylenediamine thiosulfonic acids and anilines with oxidation by dichromate. The synthesis of phenothiazinium dyes having arylamino groups in positions 3- and 7- using the dichromate method would have been problematic due to the low availability and poor reactivity of the requisite diphenylamine starting materials. In addition, the dichromate method is associated with low yields and protracted purification procedures. In the present work, unreacted 10*H*-phenothiazine was removed simply by radial chromatography on silica.

Proton magnetic spectra of the derivatives were, similar as expected in view of the small variation in structure; the aromatic region was very complex. The broad secondary N–H resonance generally correlated well with the electronic character of the 4-substituent (Table 1).

The derivatives (**2a**–**2g**) differed only in the atom or group in the 4-position of the arylamino moiety, with both electron-withdrawing and electron-releasing substituents being incorporated. This enabled the effects of such substitution on properties relevant to the use of the compounds as photosensitizers in biomedicine to be investigated. Pertinent criteria in this respect obviously include visible absorption properties and singlet oxygen production efficiencies, but acid-base behaviour and lipophilicity (Log*P*) are equally important in predicting pharmacological availability and cellular uptake.

The presence of the arylamino groups in the 3- and 7-positions of the phenothiazinium chromophore allowed the formation of neutral quinoneimine species **3**, the pK_a values of these being determined by the functionality in the anilino ring. In all cases except **3g**, the neutral species exhibited λ_{max} values at approximately 100 nm lower than the corresponding cations (Table 2). The λ_{max} values of the quinoneimines **3** in ethanol correlated well with the electronic character of the substituent in the arylamino group. Thus the quinoneimines having electron-withdrawing substituents absorbed at shorter wavelengths than the parent bisanilino compound **3a** in the decreasing order: H > I > Cl > NO_2 (Table 2). Similarly, the electron-donating substituents caused bathochromic shifts relative to **3a** (EtO, MeO > Me > H, Table 2). In our hands the quinoneimine form of the 4-nitroanilino derivative (**3g**) did not give the expected bathochromic shift in solutions of low pH, Indeed, only the addition of concentrated hydrochloric acid to an alcoholic solution of **2g** caused any change in the broad absorption centred at 513 nm, giving a yellow-brown solution with a large absorption at around 400 nm. This is suggestive of protonation at *N*-10 of the phenothiazine residue rather than of the imino nitrogen.

In terms of their potential application in photodynamic therapy, it is likely that the cations **2**

Table 1
Chemical shifts in $CDCl_3$ for NH in 7-arylimino-3-arylaminophenothiazines **3**

R	EtO	MeO	Me	H	I	Cl	NO_2
δ_{NH} (ppm)	6.66	6.65	6.72	6.81	6.80	6.96	7.01

Table 2
Spectrophotometric data, relative singlet oxygen yields, lipophilicities and pK_a values for the photosensitizers

	R in 2/3	λ_{max} (nm)[a]	Log ε_{max}[a]	Relative $^1O_2$ yield (%)[a]	Log *P*	pK_a
1a	–	653	4.98	100.0	−0.10	–
1b	–	628	4.89	86.0	−0.21	7.5
1c	–	630	4.85	135.0	+1.20	11.0
1d	–	648	4.91	122.0	+1.01	–
2a	H	660	4.57	1.6	–	5.3
2b	Me	662	4.73	2.4	–	6.4
2c	OMe	668	4.68	0.3	–	7.6
2d	OEt	668	4.68	0.8	–	7.4
2e	Cl	656	4.85	2.0	–	6.5
2f	I	664	4.79	1.8	–	6.3
2g	NO_2	400	4.26	1.4	–	–
3a	H	562	4.30	1.7	> +3.5	–
3b	Me	569	4.53	1.6	> +3.5	–
3c	OMe	577	4.48	1.2	> +3.5	–
3d	OEt	577	4.51	0.5	> +3.5	–
3e	Cl	560	4.57	1.2	> +3.5	–
3f	I	564	4.57	2.2	> +3.5	–
3g	NO_2	513	4.26	–	–	–
4a	–	654	5.00	2.9	+2.55	–
4b	–	656	4.26	109.0	+3.01	–
4c	–	600	4.54	68.5	+2.42	–

[a]Measured in methanol.

would be of more interest because of their higher λ_{max} values (Table 2). With the exception of the nitro compound **2g**, the cations exhibited equal or greater λ_{max} values than methylene blue (**1a**) and approximate red shifts of 30 nm compared to the directly analogous new methylene blue N (**1c**). This is a consequence of the latter having alkylamino auxochromes rather than arylamino.

It has been suggested that the formation of neutral quinoneimine species is of importance in the photosensitizing action of benzo[*a*]phenothiazine analogues of Nile blue in tumours, intracellular uptake of the neutral species into lysosomes being followed by intralysosomal protonation, thus inhibiting removal of the (photoactive) cation [15]. The influence of distant groups on ionisation, as in the current work, may thus be of use in the fine control of organelle selectivity and uptake. The large bathochromic shift from the neutral quinoneimine **3** to the corresponding cation **2** may also be of use in controlling the selectivity of photosensitization, since monochromatic laser or narrow-waveband illumination would allow selective excitation of the photoactive cation only, without effect on the quinoneimine elsewhere in the cell.

In view of the longer wavelengths encountered for the cations **2** compared to **1c**, which would allow greater penetration of light through tissue, the singlet oxygen yields in vitro were lower than expected, being only approximately 1–2% that of the standard **1a**. It is noticeable that the quinoneimines **3** were also photosensitizers of a similar magnitude to the cations **3**. This is of interest, since photosensitization using green light (ca. 550 nm) has recently been shown to be as effective as red light in the treatment of topical malignancy [16]. The singlet oxygen yields reported for both species **2** and **3** are very similar to those reported by Cincotta et al. [15] in their work on benzo[*a*]-phenothiazine derivatives. Here also, bathochromic shifts of approximately 20 nm were observed on going from the phenothiazinium species to the benzo[*a*]-fused analogues with a concomitant decrease in the singlet oxygen yield, the benzologues having typical absolute quantum yields of around 0.025 compared with approximately 0.50 for the parent phenothiazinium (equivalent to 5%) [2,15]. The anilino derivatives produced in the present work may thus be considered as having closer aromatic character to the benzophenothiazinium salts than to the alkylaminophenothiazine analogues.

The synthesis of the *N,N′*-dimethyl analogue of **2a** was carried out in order to provide a tertiary amino analogue much closer in structure to methylene blue (**1a**). The resulting compound (**4a**) showed only a slight improvement on the secondary arylamino compounds, thus underlining the considerable involvement and negative effect of the *N*-aryl groups on the photosensitizing efficacy of the phenothiazinium chromophore. Conversely, the bis-dibenzylamino analogue **4b** showed a significantly greater singlet oxygen yield than **1a** whilst the di(benzylamino) compound **4c** was approximately half as efficient in this respect as the diethylamino compound **1c** which has additional chromophore methylation. The improved results for **4b** and **4c** were expected as a consequence of the separation of the phenyl substituents from the chromophore by methylene spacers.

It is worthy of note at this point that in earlier work the singlet oxygen yields exhibited by acridine orange and proflavine, using the photooxidation of DPIBF method, were lower than those recorded for the cations **2** and yet both acridines exhibited excellent photosensitizing activity against a range of bacteria in vitro [17].

As expected from the extra aromatic character of the derivatives, their aqueous solubilities were extremely low—much lower than any of the commercially available derivatives **1**. Indeed, this "hyperlipophilicity" precluded the exact measurement of log *P* values using the conventional spectrophotometric method. It could only be stated with certainty that the log *P* values of the derivatives **2** were $> +3.5$ (Table 2). The photosensitizers **4** were all more hydrophilic than **2** and in fact gave appreciably coloured aqueous solutions, although the direct methylene blue derivatives **4a** and **4b** exhibited far greater lipophilicity than methylene blue. Although aqueous solubility is desirable in clinically-used photosensitizers, it is not essential, even for intravenous delivery where co-solvents such as dimethyl sulfoxide may be employed.

As a result of the very low aqueous solubilities of the derivatives, pK_a measurement using the

spectrophotometric method of absorption at varying pH values was problematical. The method was eventually carried out using aqueous ethanol (60:40 v/v) as solvent, the differences between the values derived in such a solvent mixture and in water being acknowledged [18]. However, this did give a measure of the order of basicity of the quinoneimines, which exhibited an approximate correlation with the electronic character of the 4-substituent in the aryl moiety, the order being MeO > EtO > Me > Cl > I > H > > NO_2 (Table 2).

3. Experimental

10*H*-Phenothiazine and the following compounds were purchased from Aldrich (Gillingham, UK) and were used without further purification: aniline; *p*-toluidine; *p*-anisidine; *p*-phenetidine; 4-chloro- and 4-iodoanilines; *N*-methylaniline, benzylamine, dibenzylamine, resublimed iodine, methylene blue, 1,3-diphenylisobenzofuran (DPIBF), methanol (spectrophotometric grade) and 1-octanol. Tetrahydrofuran (Aldrich) was dried over sodium wire before use.

^{1}H NMR spectra were measured in $CDCl_3$ using a Bruker WM250 instrument. All spectrophotometric measurements were carried out on a Hewlett Packard 8452A diode array spectrophotometer.

3.1. General procedure, 7-Arylamino-3-arylamino-3H-phenothiazines

The aniline derivative (0.2 mol) in tetrahydrofuran (30 cm^3) was added dropwise to a cooled mixture of 10*H*-phenothiazine (4 g, 0.02 mol) and iodine (15.2 g, 0.12 mol) in tetrahydrofuran (40 cm^3). The temperature during addition was kept $\leqslant 20°C$ with external cooling as required and the reaction mixture was then stirred overnight at room temperature. The slurry was poured into benzene (200 cm^3), filtered, washed with benzene and dried in vacuo.

A sample of the crude solid (1 g) was dissolved in 100 cm^3 dichloromethane and shaken with a mixture of 10% (w/v) sodium thiosulfate solution (5 cm^3) and concentrated ammonium hydroxide (10 cm^3). The organic solution was then washed with water, dried and evaporated to approximately 10 cm^3 and was then chromatographed using radial chromatography ("Chromatotron") on silica (60 PF_{254}, Merck) with 5% triethylamine in dichloromethane as eluent. The resulting deep maroon fraction in dichloromethane was washed with water to neutral pH, dried and the solvent removed in vacuo. Spectrophotometric and physicochemical data for the compounds are given in Tables 1 and 2.

3.1.1. 7-Phenylamino-3-phenylimino-3H-phenothiazine **3a**

(45%) From 10*H*-phenothiazine and aniline as a plum-coloured microcrystalline solid, m.p. 215–6°C (Lit [15] gives 216–18°C) Found C 75.90; H 4.55; N 10.89; S 8.38%. $C_{24}H_{17}N_3S$ requires C 75.96; H 4.51; N 11.07; S 8.45%.

3.1.2. 7-(4-Methylphenylamino)-3-(4-methylphenylimino)-3H-phenothiazine **3b**

(48%) From 10*H*-phenothiazine and 4-methylaniline as a purple powder, m.p. 205–6°C. Found C 76.47; H 5.21; N 10.36; S 7.77%. $C_{26}H_{21}N_3S$ requires C 76.62; H 5.19; N 10.31; S 7.87%.

3.1.3. 7-(4-Methoxyphenylamino)-3-(4-methoxyphenylimino)-3H-phenothiazine **3c**

(47%) From 10*H*-phenothiazine and 4-methoxyaniline as a red-purple powder, m.p. 216–7°C. Found C 71.29; H 5.07; N 9.60; S 7.10%. $C_{26}H_{21}N_3O_2S$ requires C 71.05; H 4.82; N 9.56; S 7.29%.

3.1.4. 7-(4-Ethoxyphenylamino)-3-(4-ethoxyphenylimino)-3H-phenothiazine **3d**

(51%) From 10*H*-phenothiazine and 4-ethoxyaniline as a red-purple powder, m.p. 206°C (dec.) Found C 70.61; H 5.51; N 8.82; S 6.70%. $C_{28}H_{25}N_3O_2S$ requires C 71.92; H 5.39; N 8.99; S 6.86%.

3.1.5. 7-(4-Chlorophenylamino)-3-(4-chlorophenylimino)-3H-phenothiazine **3e**

(38%) From 10*H*-phenothiazine and 4-chloroaniline as purple needles, m.p. 210–11°C. Found C 64.64; H 3.45; Cl 16.00; N 9.22; S 7.01%. $C_{24}H_{15}Cl_2N_3S$ requires C 64.29; H 3.37;Cl 15.81; N 9.37; S 7.15%.

*3.1.6. 7-(4-Iodophenylamino)-3-(4-iodophenylimino)-3*H*-phenothiazine* **3f**

(38%) From 10*H*-phenothiazine and 4-iodoaniline as a deep red powder, m.p. 230–1°C. Found C 45.86; H 2.54; I 39.90; N 6.47; S 5.30%. $C_{24}H_{15}I_2N_3S$ requires C 45.66; H 2.3; I 40.21; N 6.66; S 5.08%.

*3.1.7. 7-(4-Nitrophenylamino)-3-(4-nitrophenylimino)-3*H *phenothiazine* **3f**

(20%) From 10*H*-phenothiazine and 4-nitroaniline as a purple-red solid, m.p. 188°C (dec.) Found C 60.82; H 3.20; N 14.81; S 6.60%. $C_{24}H_{15}N_5O_4S$ requires C 61.4; H 3.22; N 14.92; S 6.83%

*3.1.8. 3,7-Bis(*N*-methyl-*N*-phenylamino)phenothiazin-5-ium iodide* **4a**

(51%) From 10*H*-phenothiazine and *N*-methylaniline as a blue-black solid, mp. 168–70°C Found C 58.22; H 4.20; I 22,.60; N 7.66; S 6.01%. $C_{26}H_{22}IN_3S$ requires C 58.32; H 4.14; I 23.7; N 7.85; S 5.99%.

3.1.9. 3,7-Bis(dibenzylamino)phenothiazin-5-ium iodide **4b**

(50%) From 10*H*-phenothiazine and dibenzylamine as a blue-black solid, m.p. 184–7°C Found C 66.95; H 4.76; I 17.54; N 5.70; S 4.35%. $C_{40}H_{34}IN_3S$ requires C 67.13; H 4.78; I 17.73; N 5.87; S 4.48%.

3.1.10. 3,7-Dibenzylaminophenothiazin-5-ium iodide **4c**

(32%) From 10*H*-phenothiazine and benzylamine as a blue-black solid, m.p. 195–6°C Found C 76.43; H 5.22; N 10.25; S 7.68%. $C_{26}H_{21}N_3S$ requires C 76.63; H 5.19; N 10.31; S 7.87%.

3.2. Singlet oxygen production

Singlet oxygen production by the photosensitizers was assayed using the decolourisation of 1,3-diphenylisobenzofuran (DPIBF) in methanol. Thus the decrease in absorption at 410 nm was monitored spectrophotometrically with time. By assuming that the decrease in absorption of DPIBF at 410 nm is directly proportional to its reaction with singlet oxygen, the percentage decrease in absorption caused by each of the photosensitizers under identical conditions thus gave a measure of its photosensitizing efficiency. Thus, the decrease in DPIBF absorption after 10 min due to MB photosensitization was taken as unity and the efficiencies of the other photosensitizers calculated as fractions thereof.

3.3. Log P

The lipophilicities of the photosensitizers were calculated in terms of log *P*, the logarithm of their partition coefficients between phosphate-buffered saline and 1-octanol. The data were calculated using the standard spectrophotometric method [19] based on the relationship:

$$\mathrm{Log}P = \mathrm{Log}\left\{\frac{(A - A^1)}{A^1} \bullet \frac{V_W}{V_O}\right\}$$

where A and A^1 are the absorption intensities before and after partitioning, respectively, and V_W and V_O are the respective volumes of the aqueous and 1-octanol phases. The extremely low aqueous solubilities of **2a–2g** meant that the volumes of 1-octanol required for the extraction of approximately half of the photosensitizer from 0.10 l of aqueous solution were very low (μl), leading to difficulty in the calculation of log *P*. The figures given for **2a–2g** in Table 3 are thus approximate.

References

[1] Wainwright M, Phoenix DA, Rice L, Burrow SM, Waring JJ. Increased cytotoxicity and phototoxicity in the methylene blue series via chromophore methylation. J Photochem Photobiol B: Biol 1997;40:233–9.
[2] Cincotta AH, Cincotta L, Foley JW. Novel benzophenothiazinium photosensitizers: preliminary in-vivo results. SPIE Proc 1990;1203:202–10.
[3] Fowler GJS, Rees RC, Devonshire R. The photokilling of bladder-carcinoma cells in vitro by phenothiazine dyes. Photochem Photobiol 1990;52:489–94.
[4] Williams JL, Stamp J, Devonshire R, Fowler GJS. Methylene blue and the photodynamic therapy of superficial bladder cancer. J Photochem Photobiol B Biol 1989;4:229–34.

[5] Orth K, Ruck A, Stanescu A, Beger HG. Intraluminal treatment of inoperable oesophageal tumours by intralesional photodynamic therapy. Lancet 1995;345:519–20.
[6] Schick E, Ruck A, Boehncke WH, Kaufmann R. Topical photodynamic therapy using methylene blue and 5-aminolaevulinic acid in psoriasis. J Dermatol Treat 1997;8:17–19.
[7] Lambrecht B, Norley SG, Kurth R, Mohr H. Rapid inactivation of HIV-1 in single donor preparations of human fresh frozen plasma by methylene blue/light treatment. Biologicals 1994;22:227–31.
[8] Wainwright M, Phoenix DA, Laycock SL, Wareing DRA, Wright PA. Photobactericidal activity of phenothiazinium dyes against methicillin-resistant strains of *Staphylococcus aureus*. FEMS Microbiol Lett 1998;160:177–81.
[9] Bonnett R. Photosensitizers of the porphyrin and phthalocyanine series for photodynamic therapy. Chem Soc Rev 1995;19–33.
[10] Wainwright M, Phoenix DA, Marland L, Wareing DRA, Bolton FJ. A study of the photobactericidal properties of the phenothiazinium series. FEMS Immunol Med Microbiol 1997;19:75–80.
[11] Motsenbocker M, Masuya H, Shimazu H, Miyawaki T, Ichimori Y, Sugawara T. Photoactive methylene-blue dye derivatives suitable for coupling to protein. Photochem Photobiol 1993;58:648–52.
[12] Strekowski L, Hou D-F, Wydra RL, Schinazi RF. A synthetic route to 3-(dialkylamino)phenothiazin-5-ium salts and 3,7-disubstituted derivatives containing two different amino groups. J Heterocyclic Chem 1993;30:1693–5.
[13] Leventis N, Chen M, Sotiriou-Leventis C. Synthesis of substituted phenothiazines analogous to methylene blue by electrophilic and nucleophilic aromatic substitutions in tandem. A mechanistic perspective. Tetrahedron 1997;53:10083–92.
[14] Andreani E, Costa Bizzarri P, Della Casa C, Fiorini M, Salatelli E. Ladder oligophenothiazines by direct thionation of *N*-arylanilino derivatives. J Heterocyclic Chem 1991;28:295–9.
[15] Cincotta L, Foley JW, Cincotta AH. Phototoxicity, redox behavior, and pharmacokinetics of benzophenoxazine analogues in EMT-6 murine sarcoma cells. Cancer Res 1993;53:2571–80.
[16] Fritsch C, Stege H, Saalman G, Goerz G, Ruzicka T, Krutmann J. Green light is effective and less painful than red light in photodynamic therapy of facial solar keratoses. Photodermatol Photoimmunol Photomed 1997;13:181–5.
[17] Wainwright M, Phoenix DA, Marland J, Wareing DRA, Bolton FJ. In vitro photobactericidal activity of aminoacridines. J Antimicrob Chemother 1997;40:587–9.
[18] Albert A, Serjeant EP. In: The determination of ionization constants. London: Chapman and Hall, 1971. p. 39.
[19] Pooler J, Valenzeno DP. Physicochemical determinants of the sensitizing effectiveness for photooxidation of nerve membranes by fluorescein derivatives. Photochem Photobiol 1979;30:491–8.