Journal of Pharmaceutical and Biomedical Analysis 50 (2009) 164–170

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Investigation of the photostability properties of memoquin, a quinone derivative for the treatment of Alzheimer's disease

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ARTICLE INFO

Article history:
Received 17 February 2009
Received in revised form 10 April 2009
Accepted 15 April 2009
Available online 23 April 2009

Keywords:
Memoquin
LC–UV/DAD–ESI-MS/MS analysis
Photodegradation kinetics
Photoproducts

ABSTRACT

The photostability properties of memoquin, a multifunctional compound in preclinical development for the treatment of Alzheimer's disease (AD) were investigated in solutions exposed to radiations, using a xenon arc lamp to simulate the natural sunlight. Reversed phase liquid chromatography coupled with diode array detection and electrospray ionization mass spectrometry (LC–UV/DAD–ESI-MS/MS) was applied to follow the photodegradation and disappearance of memoquin after irradiation. Under optimized chromatographic conditions, memoquin was separated with high resolution from the photoproducts formed in the photoexposed solutions. The results showed that memoquin is more stable at physiological and acid pHs, while it has a slow degradation pattern at more drastic conditions such as basic pH ($t_{1/2}$ = 389 min) and in methanolic solutions ($t_{1/2}$ = 465 min). In the irradiated solutions the appearance of photoproducts with lower retention times and molecular weight than memoquin was observed, thus indicating that some fragments were lost from its structure. The photodegradation products were characterized by LC–ESI-MS/MS and LC–UV/DAD analysis. The photoreactive centers were found on the amino groups of the side chains while the 1,4-benzoquinone functionality was maintained. Conversely, memoquin was found to be stable in the dark. These results suggest that, with appropriate handling and storage, memoquin's activity is not impaired.

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1. Introduction

Memoquin (2,5-bis(diamine)-1,4-benzoquinone derivative [1]) is a multifunctional molecule structurally characterized by the presence of a 1,4-benzoquinone functionality in a polyamine skeleton, rationally designed to hit different biological targets involved in Alzheimer's disease (AD) neurodegeneration [2,3]. Memoquin affects several mechanisms relevant to AD: the formation of reactive oxygen species, the processing and aggregation of amyloid β (Aβ) peptides, and acetylcholinesterase activity. In animal models, it causes a remarkable decrease in the formation of AD's neurodegenerative hallmarks and a significant reversal of behavioral deficits. Based on this unique pharmacological profile, memoquin is a promising drug candidate for the treatment of AD. Memoquin is currently in preclinical development at the University of Bologna. At this stage, a more detailed characterization of the photochemical properties of memoquin is required. Information on kinetics, degradation pathways, and the identities of degradation products will be valuable for future formulation and metabolism studies.

In order to achieve a more detailed characterization of the photochemical properties of memoquin, specific photostability studies were performed. Light-induced decomposition can impair drug potency and induce phototoxic effects [4,5]. Quinones are known to be photoreactive compounds, acting as cofactors in photosynthetic reaction centers of photo system II and I or as electron carriers through cell membranes [6,7]. The presence of side chains may change a quinone's photochemistry, as is the case with phylloquinones [8] and other similar quinones [9–11]. In memoquin's structure there are two long and symmetric polyamine side chains that might increase quinone stability and determine a protective effect against photoinduced reactions.

Thus, the aim of the present study was to investigate the photochemical properties of memoquin in solutions exposed to UV radiations, using a xenon arc lamp (solar simulator). We evaluated the effect of the solvent (methanol) and pH (acetate buffer and phosphate buffer in the pH range of 4.0–9.5) on memoquin's photochemical properties and on the degradation kinetics. Memoquin and its photodegradation products were separated by a selective liquid chromatographic (LC) method, suitable for coupling with the mass detection system. The main photoproducts were characterized by LC-DAD and LC–MS/MS analysis, using an electrospray ionization source (ESI) and an ion trap analyzer.

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doi:10.1016/j.jpba.2009.04.017

2. Experimental

2.1. Materials

Memoquin and the photoproduct **PP4** were synthesized as previously reported [12]. Sodium acetate, triethylamine, disodium hydrogen phosphate, phenol and acetic acid were from Sigma–Aldrich (Milan, Italy). Phenomenex Luna phenyl-hexyl stationary phase (150 mm × 3.0 mm I.D.) was from Phenomenex Italia (Bologna, Italy). Acetonitrile and all the other chemicals were of analytical reagent grade (Carlo Erba Reagenti and Sigma–Aldrich, Milan, Italy) and were used without further purification. Water used for the preparation of solutions and mobile phases was purified by a Milli-Rx apparatus (Millipore, Milford, MA, USA).

The buffer solutions were filtered through a 0.45 μm membrane filter and degassed before their use in HPLC.

2.2. Apparatus and experimental conditions

Tests on memoquin's photochemical stability were carried out at room temperature (25 ± 2 °C) using a xenon arc source to simulate natural sunlight exposure. Specifically, a 150 W xenon arc lamp (solar simulator, model 68805, Oriel Corporation, Stratford, CT, USA) was used, with a dichroic mirror (Oriel, model 81405) to block visible and IR radiation in order to minimize sample heating. An air-mass filter 1.5 (Oriel, model 81090) was used to simulate solar conditions and a UV-B-C blocking filter was employed to attenuate the UV-B component. A "beam-turning assembly", containing the dichroic mirror, directed the output beam downward. The UV dose (J cm^{-2}) from the xenon-arc lamp was measured using a Oriel Goldilux model 70127 radiometer fitted with external interchangeable probes for UV-A and UV-B (UV-A dose: 85 μW cm^{-2} and UV-B dose: 15 μW cm^{-2}).

Chromatographic analyses were performed at room temperature (25 ± 2 °C). All analyses were performed on a Phenomenex Luna phenyl-hexyl stationary phase (150 mm × 3.0 mm I.D.) under the following chromatographic conditions: mobile phase composed of 20 mM triethanolamine acetate buffer (pH 4.0)/acetonitrile (71/29, v/v), flow rate 0.4 ml/min.

Chromatographic analysis were carried out on an HPLC system consisting of a Jasco PU-1580 (Jasco, Cremella, Italy) solvent delivery system connected to a Jasco auto sampler model AS-2055 and a Jasco DAD-V-530 system.

LC–MS analyses were performed on a Jasco PU-1585 (Jasco, Cremella, Italy) equipped with a Reodyne Model 7125 injection valve (sample loop of 20 μl) connected to a LCQ DUO ion trap mass spectrometer (MS) with electrospray ionization (ESI) ion source, controlled by Xcalibur software 1.3 (Thermo Finnigan, San Jose, CA, USA). Nitrogen was used as sheath gas and helium (0.1 Pa) served as damping and collision gas. Data acquisition and analysis were conducted using Xcalibur software (version 1.0 SR1, Thermoquest, USA). The ESI system employed a 4.5 kV spray voltage (positive polarity), a capillary temperature of 200 °C, and a cone voltage of 14 V. A postcolumn T-splitter (split ratio: 1/3) was used to direct a low amount of the mobile phase into the mass spectrometer via the ESI interface.

The detection was performed with an ion trap mass spectrometer in positive polarity (full scan 100–650 m/z) and in single ion monitoring (SIM) mode on the generated cations at m/z = 633.4 (memoquin), m/z = 485.5 (photoproduct 2, **PP2**), m/z = 513.0 (photoproduct 3, **PP3**), m/z = 577.9 (photoproduct 4, **PP4**), and m/z = 605.0 (photoproduct 5, **PP5**).

MS/MS analyses were performed with an isolation width of 1 Th (m/z); the activation amplitude was around 35% of ejection RF amplitude, which corresponds to 1.85 V.

2.3. Photo stability kinetics studies

To evaluate the effect of different solvent and pH conditions on memoquin's photostability, studies were performed on the compound (0.025 mg ml^{-1}) dissolved in methanol, sodium acetate buffer (0.02 M; pH 4.0–7.0–8.3) and in the mixture composed of phosphate buffer (0.02 M, pH 9.5) and methanol (50/50, v/v). Aliquots (3 ml) of each solution were placed in quartz cells (path length: 1 cm) and closed with screw caps. Quartz cells were placed horizontally and exposed to UV-A radiation (Xe arc lamp) for increasing irradiation times (0–24 h, corresponding to increasing UV doses). Time course experiments were carried out by analyzing the photoexposed solutions by HPLC to follow the disappearance of memoquin. Chromatographic analyses were carried out as described in Section 2.2.

Main compound peak areas were integrated and the percentage of memoquin peak area at the corresponding irradiation time was plotted against time by using a non-linear regression fit (one phase exponential decay equation) and a logarithm linear regression fit. The computer program used to analyze these data was GraphPad Prism 4.0 (GraphPad Software Inc.). These analyses were also carried out on memoquin sample solutions stored in darkness, i.e. an aliquot of 3 ml in a 1 cm quartz cell wrapped in aluminium foil during the simultaneous radiation exposure.

2.4. Photoproducts characterization: LC-DAD and LC–ESI-MS/MS analysis

The photoexposed solutions, treated as described in Section 2.3, were subjected to LC–ESI-MS/MS analysis. The peak apex mass spectra were recorded within 100–650 m/z full scan (positive polarity), providing the total ion current (TIC) chromatograms and the pseudomolecular mass of the analytes. The MS/MS spectra of memoquin (retention time: 14.5 min) and its photoproducts were obtained on the molecular ion with 35 or 40% collision energy. With LC-DAD analyses, memoquin and related photoproducts were also characterized by chromatographic peak apex UV–vis spectra.

2.5. Method validation

Standard stock solutions of memoquin (c = 2.2 mg ml^{-1}) were prepared in methanol and diluted with the mobile phase to the required concentration (range: 2.2–45 μg ml^{-1}). The solutions obtained were analyzed by LC under the chromatographic conditions described in Section 2.2, using DAD detection set at 340 nm. Each solution was injected in duplicate. Calibration graph was then constructed by plotting memoquin peak area versus the corresponding concentration (μg ml^{-1}).

The repeatability of the chromatographic method was evaluated by injecting the same standard solution three times on the same day; the peak areas were integrated and the standard deviations calculated. Method sensitivity was evaluated by progressive dilution of memoquin standard solution by detecting the peak area height at 340 nm.

3. Results and discussion

The aim of the present work was the photostability study of memoquin, a multifunctional drug candidate for the treatment of AD [1–3]. This study was aimed at determining memoquin's photophysical and photochemical properties and structurally characterizing its main photoproducts. In fact, irradiation of benzoquinone [13,14] and other substituted 1,4-benzoquinones [15] in water is known to produce products such as benzene-1,2,4-triol, semiquinone and hydroxylated quinone [16–18]. Since memoquin is characterized by the presence of two symmetric polyamine

chains, we studied the influence of the side chains on 1,4-benzoquinone stability and photoreactivity.

The photostability of memoquin was assessed under different solvent and pH conditions to gain general information on compound handling, storage, and potential phototoxicity. To this end, a xenon arc lamp was used as a solar simulator for photostability studies, according to option 1 of the ICH guidelines [19]. Reference memoquin solutions at the same concentration, kept in the dark, underwent parallel with the irradiation experiments and no degradation was observed in any of the conditions. Moreover, in addition to light-induced degradation conditions, solutions in methanol and buffer (pH 4.0, 7.0 and 8.3) were kept in the dark at three temperatures (37, 50 and 60 °C) for accelerated stability studies. This was to acquire more information on memoquin's stability. Time course memoquin LC-DAD analyses were carried out under the chromatographic conditions reported in Section 2.2. Memoquin solutions were stable when kept for 200 h at 37 and 50 °C, whereas some degradation was observed after 200 h at 60 °C, at pH 7.0 and 8.3 (30% and 70% reduction of memoquin initial concentration, respectively).

Stability studies on memoquin solid state were also carried out by storing fixed amounts of the solid at 60 °C and evaluating its stability after solubilization and injection into the HPLC system. Solid memoquin was stable even after 6 months of storage at 60 °C.

3.1. Method validation

In a previous paper [20], we described a method for selective and sensitive memoquin determination using an LC system coupled with electrochemical detection; this method was useful for determining memoquin in biological samples, but not suitable for coupling with the ESI-MS spectrometer, due to nonvolatile components in the elution buffer. Therefore, a reversed phase LC method was optimized to follow memoquin's disappearance after irradiation; the chromatographic mobile phase was adjusted in order to be suitable for interfacing with the ESI-MS spectrometer. Under the optimized chromatographic conditions, memoquin was retained well enough (retention time: 14.5 min) to allow the analysis and the separation of the products obtained in the photoexposed solutions.

The linearity of the response was studied on five different memoquin standard solutions in the concentration range 2.2–45 μg ml^{-1}. The calibration graph was constructed by plotting the peak areas (Y) (340 nm) against the corresponding memoquin concentrations (X, μg ml^{-1}). The obtained relationship was found to be the following: $y = 137{,}500x(\pm 2221) + 46{,}340$, $r^2 = 0.9992$. The reported statistical data represent the average correlation coefficient, slope, and intercept for calibration curves obtained in two

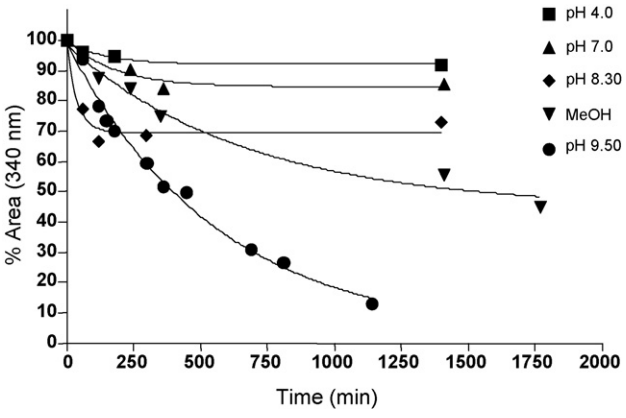

Fig. 1. Photodegradation kinetics of memoquin ($c = 0.025$ mg ml^{-1}) at various pHs and in methanol.

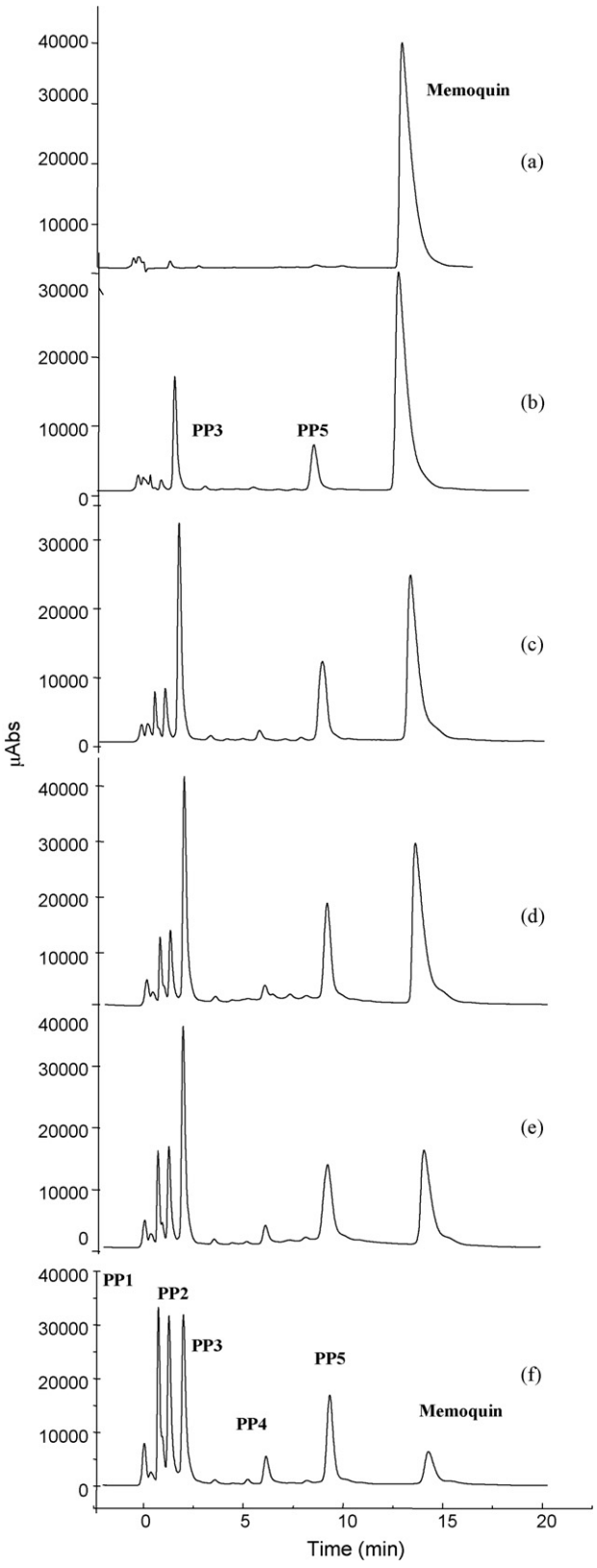

Fig. 2. Memoquin chromatograms obtained at increasing irradiation times (a = 0 h; b = 3 h; c = 7.5 h; d = 9.5 h; e = 11.5 h; f = 19 h). Chromatographic conditions: see Section 2.2.

Table 1
MS/MS data: *m/z* (relative abundance). Collision energy: 35 or 40%.

Memoquin: 633.4 $[M+H]^+$, 588.3 (10) $[M-CH_3$ on the methoxy group; $-CH_2CH_3$ on the amino group$]^+$, 527.3 (20) $[M-CH_3OAr]^+$, 468.2 (30) $[M-CH_3OArCH_2$; $-CH_3$ on the methoxy group; $-CH_2CH_3$ on the amino group$]^+$, 387.2 (12) $[M-CH_3OArCH_2NEt(CH_2)_6]^+$, 371.1 (20) $[M-CH_3OArCH_2NEt(CH_2)_6NH_2]^+$.
PP2: 485.5 $[M+H]^+$, 440.1 (27) $[M-CH_3$ on the methoxy group; $-CH_2CH_3$ on the amino group$]^+$; 377.3 (17) $[M-CH_3OAr]^+$; 343.0 (66) $[M-NHEt(CH_2)_6NH_2]^+$; 326.2 (100) $[M-NHEt(CH_2)_6$; $-OCH_3$ on the benzyl group$]^+$; 251.1 (26) $[M-NHEt(CH_2)_6$; $-CH_3OAr]^+$.
PP3: 513 $[M+H]^+$, 468.2 (27) $[M-CH_3$ on the methoxy group; $-CH_2CH_3$ on the amino group$]^+$; 407.2 (40) $[M-CH_3OAr]^+$; 371.1 (100) $[M-NHEt(CH_2)_6NH_2]^+$; 250.9 (20) $[M-NHEt(CH_2)_6NH_2$; $-CH_3OArCH_2]^+$.
PP4: 577.9 $[M+H]^+$; 471.1 (15) $[M-CH_3OAr]^+$; 455.2 (20) $[M-CH_3OArCH_2]^+$; 359.1 (47) $[M-CH_3OArCH_2NH(CH_2)_6]^+$; 343.0 (18) $[M-CH_3OArCH_2NH(CH_2)_6NH_2]^+$; 324.1 (25) $[M-CH_3OArCH_2NH(CH_2)_6$; $-OCH_3$ on the benzyl group$]^+$.
PP5: 605.3 (5) $[M+H]^+$; 560.2 (10) $[M-CH_3$ on the methoxy group; $-CH_2CH_3$ on the amino group$]^+$, 499.2 (77) $[M-CH_3OAr]^+$; 387.2 (30) $[M-CH_3OArCH_2NH(CH_2)_6]^+$; 371.1 (30) $[M-CH_3OArCH_2NEt(CH_2)_6NH_2]^+$.

different days. Good linearity was therefore obtained even in the absence of internal standards. 95% confidence intervals of the *y*-intercepts were found to be −115,300 to 208,000.

The method's sensitivity was evaluated by injecting into the LC system progressive dilutions of memoquin standard solutions and integrating the resulting peak area. Memoquin solutions ($0.91 \pm 0.19\ \mu g\ ml^{-1}$) provided a signal-to-noise ratio of approximately 3 (limit of detection; LOD). The LOQ (limit of quantitation; S/N = 10) value was $2.22 \pm 0.20\ \mu g\ ml^{-1}$.

Chromatographic precision, such as repeatability and reproducibility of the method, was evaluated by analyzing the same standard solution three times on the same day and preparing and analyzing three different standard solutions at the same concentration on 3 different days, under constant conditions of solvent

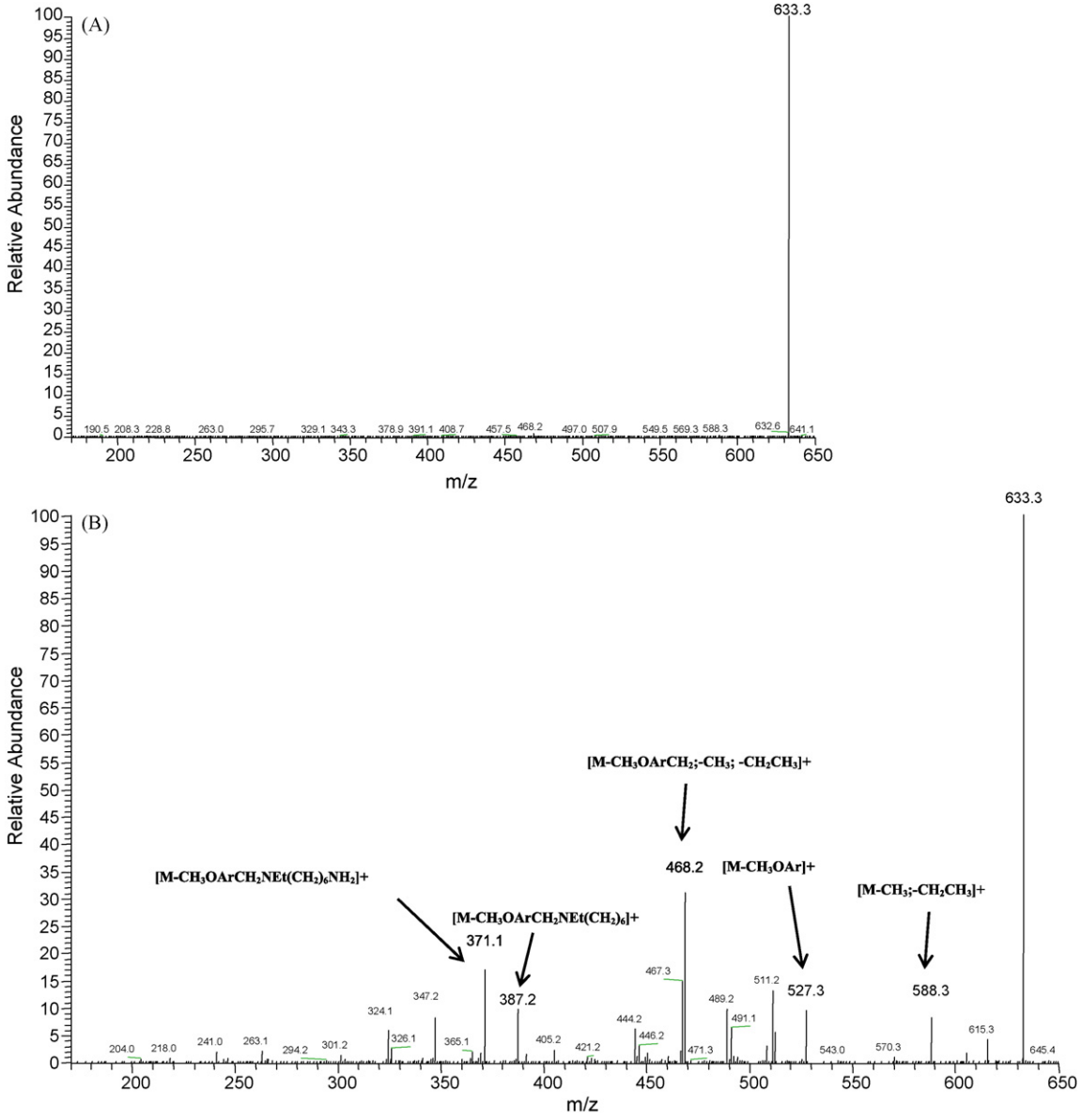

Fig. 3. MS (a) and MS/MS (b) spectra of memoquin (SIM mode at *m/z* = 633.4).

composition, temperature, and flow rate. Precision assays (intraday precision) carried out at 0.025 mg ml^{-1} showed 2.13% as relative standard deviation (%RSD). Interday precision was also satisfactory, with 3.51% as RSD%.

3.2. Memoquin photostability: kinetics of photodegradation

The pH profile of memoquin's photostability was investigated in the pH range of 4.0–9.5. Low concentrations of memoquin (0.025 mg ml^{-1}) were exposed to UV-A radiations and the disappearance of the drug was evaluated by LC–UV-DAD, following the procedure described in Section 2.3. By UV-DAD detection, the peak apex UV spectrum was acquired for unambiguous identification. The characteristic absorption band (λ_{max} at 340 nm) in the UV–vis spectrum can be attributed to the quinone chromophore.

Memoquin was more stable after irradiation in the acidic and neutral solutions, as shown in the photodegradation profile (Fig. 1). It exhibits a low solubility in aqueous solutions at basic pH. Therefore, after preliminary experiments, the photostability was evaluated on drug solutions in methanol and in a mixed methanol/phosphate buffer (pH 8.3 and 9.5) 50:50 (v/v). The kinetics of drug photodegradation was monitored by LC-DAD detection, by plotting the residual percent area over time of irradiation, as shown in Fig. 1.

To obtain information on the kinetics of the process at basic pH and methanol, linear relationships were observed according to the equation: $\ln A = \ln A_0 - kt$, where A is the remaining memoquin peak area, A_0, the initial percentage of the drug (100%), k, the slope (rate constant) and t is time (min). Memoquin's photodegradation occurred by following apparent first-order kinetics. The following data were obtained: methanol: $\ln A = 4.958 - 0.00101t$ ($r^2 = 0.9862$), half life $t_{1/2} = 465$ min; pH 9.5: $\ln A = 4.602 - 0.00183t$ ($r^2 = 0.9836$), half life $t_{1/2} = 389$ min. Memoquin's photodegradation pattern was characterized by half lives between 6.5 and 8 h. Photodegradation rate was faster at pH 9.5 than in methanol. It is worth noting that, at acidic and neutral pHs, memoquin, after an initial degradation, was stable even after 1 day of continuous photoexposure.

Thus, by observing the kinetics obtained by one phase exponential decay analysis, it is possible to appreciate an enhanced photoreactivity trend with pH increase. In fact at pH 4.0 and pH 7.0, a very small (9% and 15%, respectively) loss of peak area is observed even after long radiation exposure up to 24 h. With an increase in pH, a marked reduction of peak area was observed, followed by the almost complete disappearance of memoquin at pH 9.5. In methanol, the trend was similar, but the photodegradation occurred at a slightly lower rate. At pH 8.3 the photodegradation was fast but it reached a constant plateau value when 30% of memoquin broke down.

Therefore memoquin solutions at basic pHs and in methanol showed lower stability; at pH 9.5 in the photoexposed solutions (Fig. 2), the appearance of more hydrophilic photoproducts (**PP1**-**PP5**) at lower retention times were observed, namely **PP1** (retention time: 2.54 min), **PP2** (retention time: 2.96 min), **PP3** (retention time: 3.61 min), **PP4** (retention time: 7.32 min), and **PP5** (retention time: 10.16 min).

In Fig. 2 overlaid chromatograms at increasing irradiation times (range: 0–19 h) show that **PP3** and **PP5** were the first ones to appear, reaching a maximum and then slowly decreasing, whereas **PP1**, **PP2** and **PP4** had a delayed formation and appeared later in the chromatograms of the photoexposed solutions. These last photo-

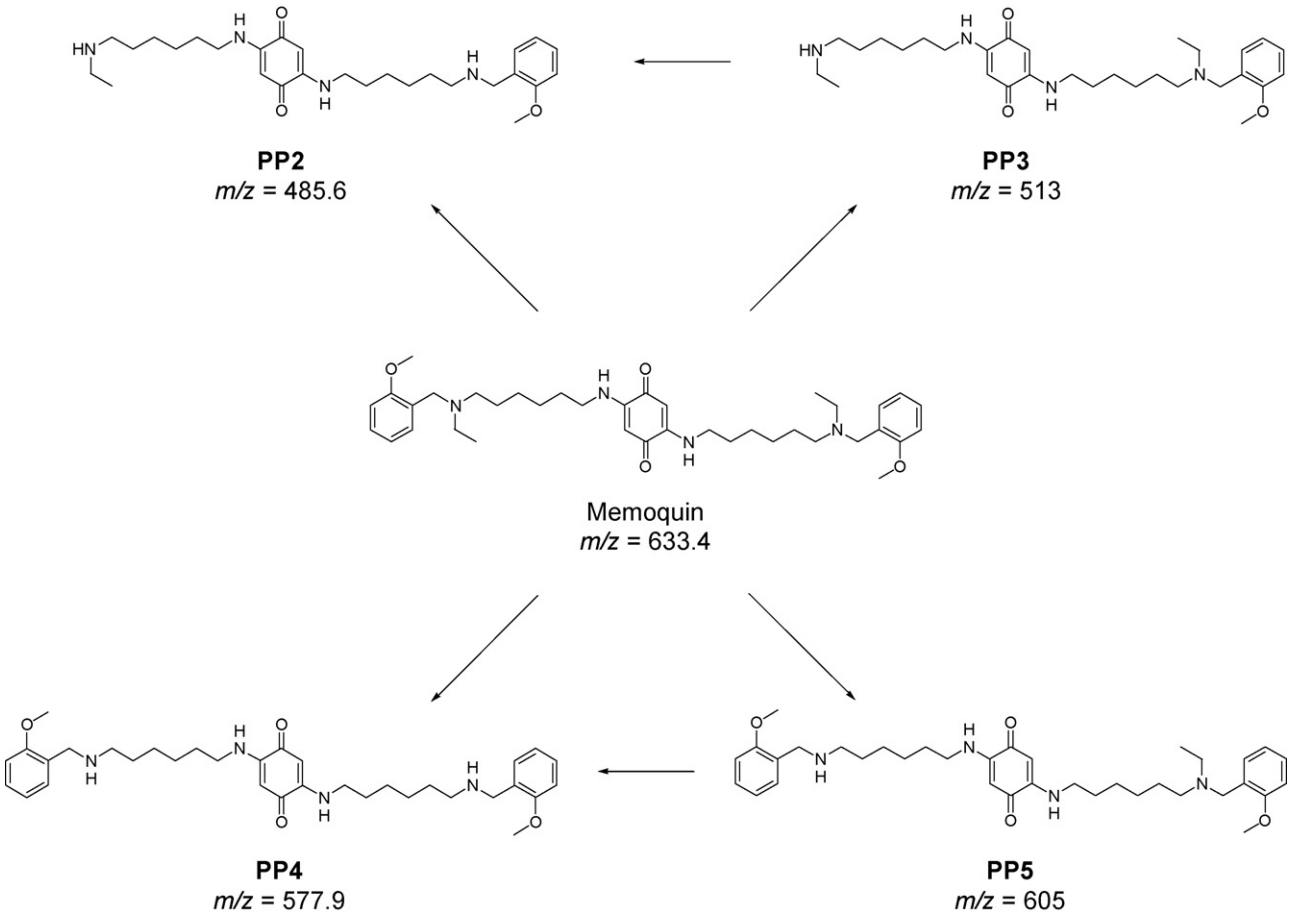

Fig. 4. Memoquin photoproducts characterized after UV photoexposure in basic solutions.

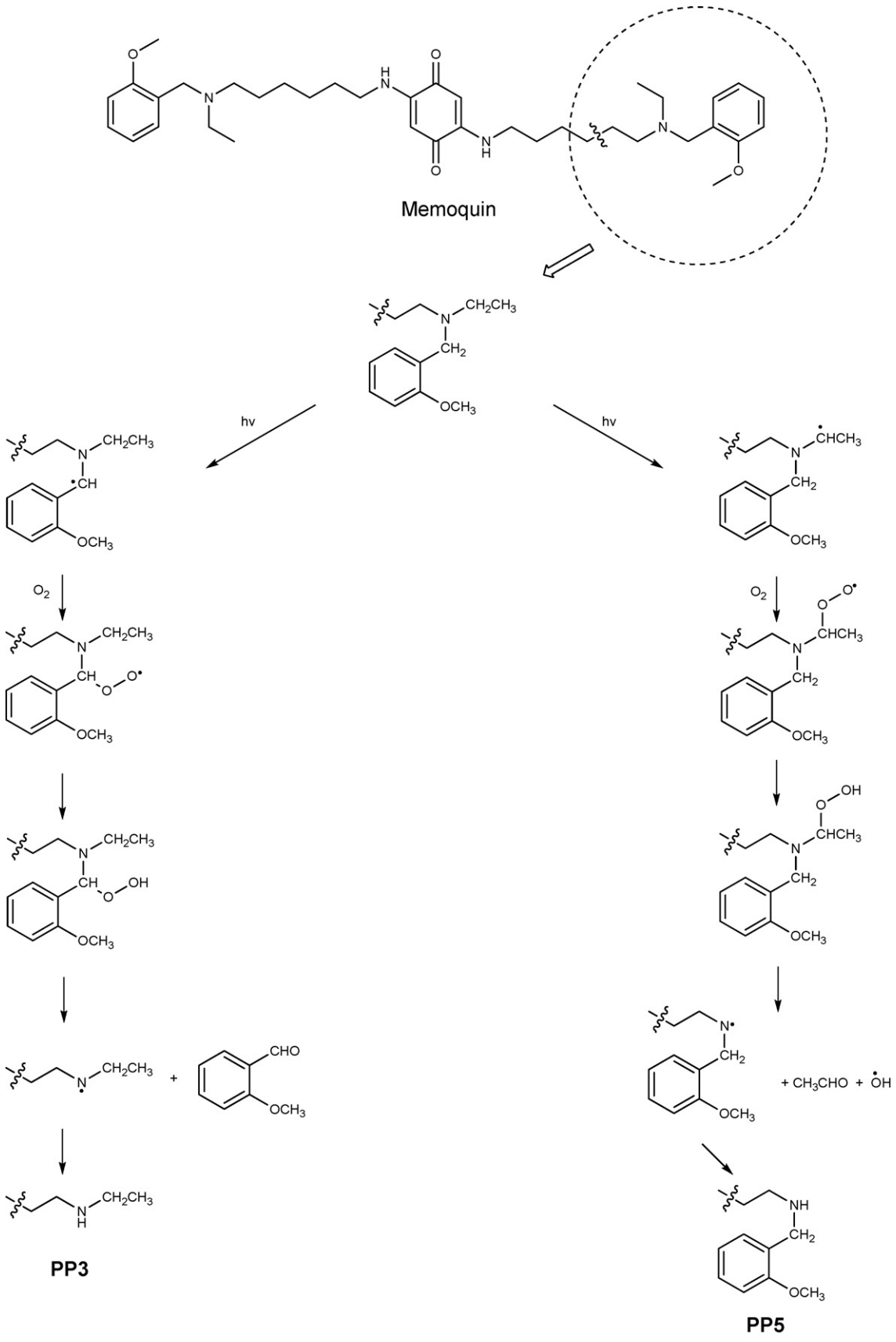

Fig. 5. Photodecomposition pattern for memoquin.

products might derive from **PP3** and **PP5** degradation. In the pH range 4.0–7.0, the radiation exposure caused only one main photoproduct formation (**PP3**) and a small amount of **PP5**.

3.3. Structural characterization of the photoproducts

In order to characterize the structure of the photoproducts by LC-DAD analysis, UV spectra acquired on each peak apex showed no significant changes of the UV spectral absorption, all photoproducts maintaining the same memoquin UV absorption profile with the characteristic band with maximum wavelength at 340 nm, which suggests the stability of the quinone moiety. Photoexposed solutions were analysed by LC–ESI-MS/MS for structural elucidation of the degradation products. The analyses by HPLC coupled with mass spectrometry with electrospray ionization interface, a soft ionization technique, provided information on the molecular weight of the photoproducts. Then, tandem mass analyses (MS/MS) of the selected molecular ions furnished structural information on the memoquin photoproducts. Memoquin's MS spectrum and MS/MS spectrum are shown in Fig. 3a and b, respectively. A scheme of fragmentation, representative of the fragmentation pattern of all the main photoproducts is reported in Fig. 4.

The m/z value of 605 found for **PP5** may correspond to two hypothetic compounds, that is the structure of memoquin after the loss of either one ethyl group (−28) from the benzyl nitrogen or two methyl groups from the methoxy substituents of the aromatic rings, leading to the phenolic derivative. The main fragments containing the methoxybenzyl group in **PP5** MS/MS spectrum (Table 1) allowed us to exclude the generation of the phenolic photoproducts, thus confirming in **PP5** structure the loss of the ethyl substituent from the benzylamino group of the side chain. In the presence of oxygen, in fact, N-dealkylation is a common photodecomposition pattern (Fig. 5). A tertiary amine may undergo homolysis of the α-C–H bond to give a radical, which is attacked by ground state oxygen, leading to a peroxide which decomposes to give a secondary amine [21]. In this regard, in the case of memoquin, besides the ethyl group (**PP5**), the loss of the benzylamine substituent was also observed. In fact, **PP3** (513 m/z), a photoproduct also formed at acidic pH, could result from the loss of the methoxybenzyl group (−121.15) by following a similar mechanism as shown in Fig. 5. **PP2** (485.6 m/z) structure was thought to derive from **PP3** by the loss of the ethyl group on the second tertiary nitrogen. **PP4** was the only photoproduct identified by direct comparison of its retention time and UV spectrum with the memoquin analogue, previously synthesized, with both the secondary benzylic nitrogens [12]. **PP4** identification was confirmed by LC–ESI-MS/MS analyses and UV spectra obtained on the peak apex by LC-DAD. Therefore, the photoreactive centers, on which all the modifications took place, were found to be of the benzylamino group.

Further structural confirmation was established by inducing the fragmentation of the photoproducts' molecular ions and analyzing the ion fragments by LC–ESI-MS/MS. As reported in Table 1, MS/MS data of memoquin and its photoproducts revealed the presence of common fragments, thus confirming the identification of the photoreactive centers in memoquin's structure. In particular, by comparing the MS/MS spectra data of memoquin and its photoproducts (Table 1), the most common fragments transpired to be those deriving either from the loss of the methyl from the methoxy group or the ethyl substituent on the benzylic nitrogen of the side chains (−45 mass units); or from the partial (−106 mass units) or complete loss of one side chain (m/z values of 387 and 371) (Fig. 4b).

Despite efforts to characterize it, **PP1** was the only (minor) photoproduct not identified, owing to its elution with the solvent, hindering the on-line mass spectrum evaluation. **PP1**'s retention was not modified even in a mobile phase composed of 100% buffer. **PP1**, showing the UV absorption band maximum at 340 nm, was collected by multiple injections, concentrated, and analyzed by direct infusion with the ESI-MS system by using both positive and negative polarity and by using APCI source. Unfortunately, no detectable mass was observed in the mass range 100–650 m/z.

Finally, we were unable to reveal the formation of other photoproducts in the low UV range, using the UV-DAD system.

4. Conclusions

Memoquin, a new molecule in preclinical development for the treatment of AD, was exposed to UV-A radiation by employing a solar simulator, according to the ICH guidelines. The photochemical studies on memoquin solutions showed the influence of the different solvents and pHs on the photodegradation process and reaction rates. In particular, memoquin was found to be more stable at acidic and neutral pHs, whereas at basic pH and in methanol, it was photodegraded at a faster rate. The obtained photoproducts were identified and characterized by LC–UV/DAD–ESI-MS/MS analyses. The results of this study show that memoquin is subjected to photodegradation reactions involving the tertiary benzylamino groups of the side chains, while the antioxidant centre (1,4-diamino benzoquinone) is not affected.

In the course of accelerated thermal stability studies, memoquin was stable in methanol and buffer solution (pH 4.0–8.3) when kept in the dark at 25, 37 and 50 °C. Memoquin's solid form was also found to be stable after 6 months of storage at 60 °C in the dark. Taken together, these results suggest that memoquin can be stored in the dark without impairing its stability.

Acknowledgements

Thanks are due to Michele Troilo for his valuable technical assistance. This work was supported by grants from MIUR (Rome, Italy) (PRIN 2007 and FIRB RBNE03FH5Y) and the University of Bologna.

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