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Phototransformation of the drug trazodone in aqueous solution

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ABSTRACT

Irradiation of trazodone at 310 nm in water has been investigated. In addition to the OH-substitution in the chlorobenzene ring a peculiar dimerization of the dihydropyridine moiety leading to a cage-like product was involved in the photo-induced modification of the drug. The photoproducts, isolated by chromatographic techniques, have been identified by spectroscopic means. Further support of the structure of the cage-like product was sought by a comparison between the experimental chemical shifts and the values computed at the DFT level.

1. Introduction

The action of light on drugs is continuously examined since many of these molecules absorb in the ultraviolet (UV) spectra range and the consequence may be a significant activity loss or, more seriously, the formation of harmful by-products [1–3]. Photosensitivity can also be associated to light-absorbing drugs [4]. This is the case of trazodone, a largely used antidepressant which has been associated with photosensitivity and skin lesions in patients treated with the drug [5]. Trazodone, 2-(3-(4-(3-chlorophenyl)piperazin-1-yl)propyl)-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one, presents an absorption band at 312 nm ($\log \varepsilon$ 3.53) in UV-B region [in addition to bands at 210 ($\log \varepsilon$ 4.59) and 246 ($\log \varepsilon$ 4.01)]. In our continuing studies on the photochemical behaviour of some of the most used drugs and their environmental fate [6], we have investigated the UV-B photodegradation of trazodone in water with particular attention to the isolation and characterization of the main photoproducts. Irradiation of the drug has also been performed under environmental-like conditions.

2. Experimental

2.1. Chemicals

Trazodone (**1**) hydrochloride, analytical standard grade (99%), KNO_3, humic acid, 2-nitrobenzaldehyde were supplied by Aldrich and used without further purification.

2.2. General procedures

NMR spectra were recorded on a Varian Inova-500 instrument operating at 499.6 and 125.62 MHz for ^1H and ^{13}C, respectively, and referenced with deuterated solvents ($CDCl_3$, CD_3OD). Electronic impact-mass spectra (EI-MS) were obtained with a HP 6890 spectrometer equipped with an MS 5973 N detector. An CH_3CN/H_2O (0.1% HCOOH) solution was used as mobile phase for LC–MS system comprised of an Agilent Technologies 1100 MSD. UV–vis spectra were recorded in methanol on a PerkinElmer Lambda 7 spectrophotometer. IR spectra were recorded on a Jasco FT/IR-430 instrument equipped with single reflection ATR, samples were dissolved in $CHCl_3$ and deposited on the ZnSe crystal.

Irradiations were performed by a photoreactor (Helios Italquartz) equipped with six 15 W lamps with a maximum at

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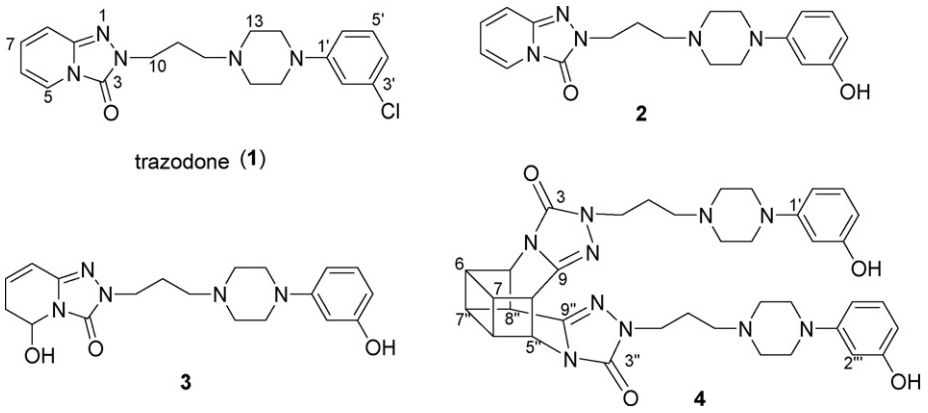


Fig. 1. Trazodone and its photoproducts.

310 nm (UV-B irradiation). Pyrex or quartz tubes (20 cm × 1 cm, 25 ml) were used. Some solutions were exposed to sunlight.

The course of the reactions was monitored by HPLC using a Synergy Polar-RP 80A column (4 μm, 250 mm × 4.6 mm) or TLC. Analytical and preparative TLC were made on Kieselgel 60 F_{254} plates with 0.2 mm and 0.5 or 1 mm layer thickness, respectively (Merck).

2.3. Experimental procedures

2.3.1. Irradiation of trazodone (*1*) hydrochloride by UV lamps (310 nm) in water

2.3.1.1. Preparative irradiation. Trazodone (**1**) hydrochloride (100 mg) in milliQ water (200 ml; 10^{-3} M) was irradiated as above in four open quartz tubes. After 4 h water was evaporated. The residue (97 mg) was analyzed by ^{1}H NMR and TLC and then, chromatographed on preparative TLC [benzene/acetone/triethylamine (2/2/1)] giving a mixture of trazodone (**1**) (2 mg), fraction A (31 mg), compound **2** (9 mg), fraction B (45 mg) and an intractable polar residue (8 mg). Fraction A was purified on preparative TLC [hexane/$CHCl_3$/CH_3OH (5/4/1)] giving compound **3** (23 mg), while fraction B after purification on TLC [$CHCl_3$/CH_3OH/H_2O (7/3/2), lower layer], afforded compound **4** (12 mg) (Fig. 1).

*2.3.1.2. Spectral data of phototransformation products **2**–**4**.*

*2.3.1.2.1. Compound **2**.* EI-MS: *m/z* 353 $[M]^+$, 338 $[M-OH]^+$, 260 $[M-C_6H_5O]^+$, 191 $[C_{11}H_{15}N_2O]^+$, 162 $[C_8H_8N_3O]^+$, 148 $[C_7H_6N_3O]^+$, 93 $[C_6H_5O]^+$; IR (ZnSe): ν_{max} 3200, 2933, 2830, 1709, 1639, 1602, 1495 cm^{-1}; UV λ_{max} (MeOH) nm: 215 (log ε 4.4), 250 (log ε 3.9), 329 (log ε 3.3); ^{1}H and ^{13}C NMR, see Table 1.

*2.3.1.2.2. Compound **3**.* EI-MS: *m/z* 371 $[M]^+$, 353 $[M-H_2O]^+$, 260 $[M-H_2O-C_6H_5O]^+$, 191 $[C_{11}H_{15}N_2O]^+$, 93 $[C_6H_5O]^+$; IR (ZnSe): ν_{max} 3581, 3310, 2940, 2830, 1705, 1598, 1494, 1179 cm^{-1}; UV λ_{max} (MeOH) nm: 210 (log ε 4.5), 250 (log ε 4.0); ^{1}H and ^{13}C NMR, see Table 1.

*2.3.1.2.3. Compound **4**.* ESI-MS: *m/z* 707 $[M+H]^+$, 354 $[M-C_{19}H_{23}N_5O_2+H]^+$, 192 $[C_{11}H_{15}N_2O+H]^+$; IR (ZnSe): ν_{max} 3337, 2919, 2852, 1685, 1581, 1457, 1196 cm^{-1}; UV λ_{max} (MeOH) nm: 215 (log ε 4.4), 250 (log ε 4.0); ^{1}H and ^{13}C NMR, see Table 2.

2.3.1.3. Quantum mechanical computations. All calculations were performed with the Gaussian 03 suite [7]. A simplified model of dimer **4** was adopted, in which the heptacyclic fused ring system is retained, while the *N*-alkyl substituents are replaced by methyl groups. Geometry optimizations were performed at the density functional theory (DFT) level, using the reliable "hybrid" PBE0 functional [8] and the 6-31+G(d,p) basis set. Minima were checked by frequency calculation. NMR shielding tensors were computed

Table 1
^{13}C and ^{1}H NMR spectral data of trazodone (**1**) and compounds **2**, **3** ($CDCl_3$, 125 MHz for ^{13}C and 500 MHz for ^{1}H NMR, δ in ppm and *J* in Hz)

Position	**1**		**2**		**3**	
	^{13}C[a]	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
3	150.6 (q)[b]		148.9 (q)		152.7 (q)	
5	124.0 (t)	7.75 (1H, d, 7.0)	123.9 (t)	7.77 (1H, d, 8.0)	70.8 (t)	5.79 (1H, dd, 4.6, 2.8)
6	111.1 (t)	6.53 (1H, td, 7.0, 1.0)	111.0 (t)	6.50 (1H, td, 8.8, 2.0)	31.6 (s)	2.75 (2H, m)
7	130.7 (t)	7.13 (1H, ddd, 8.5, 7.0, 1.0)	130.2 (t)	7.10 (1H, overlapped)	130.4 (t)	6.27 (1H, br dt, 9.5, 4.3)
8	115.6 (t)	6.76 (1H, dd, 8.5, 1.0)	108.6 (t)	6.44 (1H, d, 8.8)	114.7 (t)	6.38 (1H, br d, 9.5)
9	142.2 (q)		141.8 (q)		140.8 (q)	
10	43.5 (s)	4.16 (2H, t, 6.8)	44.8 (s)	4.10 (2H, t, 6.8)	43.7 (s)	3.87 (2H, t, 6.8)
11	23.5 (s)	2.57 m	26.1 (s)	2.06 (2H, quint, 6.8)	25.8 (s)	1.96 (2H, quint, 6.8)
12	55.4 (s)	3.16 m	55.7 (s)	2.49 (2H, t, 6.8)	55.4 (s)	2.47 (2H, t, 7.8)
13	51.9 (s)	3.70 m, 2.95 m	53.2 (s)	2.56 (4H, m)	52.9 (s)	2.55 (4H, m)
14	46.6 (s)	3.62 m	49.1 (s)	3.10 (4H, m)	48.8 (s)	3.12 (4H, m)
1′	150.6 (q)		152.9 (q)		152.7 (q)	
2′	117.6 (t)	6.87, t, 2.0	103.4 (t)	6.35 (1H, br s)	106.8 (t)	6.34 (1H, s)
3′	135.5 (q)		157.4 (q)		156.9 (q)	
4′	115.3 (t)	7.09, br d, 8.0	107.0 (t)	6.33 (1H, br d, 7.8)	103.1 (t)	6.32, br d, 8.5
5′	130.7 (t)	7.19, t, 8.0	130.2 (t)	7.05 (1H, t, 7.8)	130.0 (t)	7.08, t, 8.5
6′	121.8 (t)	6.91, br d, 8.0	115.6 (t)	7.10 (1H, overlapped)	108.5 (t)	6.46, br d, 8.0

[a] Assigned by HSQC and HMBC experiments.
[b] Letters, p, s, t and q, in parentheses indicate, respectively, the primary, secondary, tertiary and quaternary carbons, assigned by DEPT.

Table 2
NMR spectral data of compound **4** in CD_3OD

Position	δ_H[a]	J (Hz)	NOESY	δ_C	HMBC[b]	Computed δ_C
3/3″				154.0 (q)[c]		154.37
5/5″	5.31 dd	9.9, 8.8	8/8″, 6/6″	49.0 (t)	6/6″, 7/7″, 8/8″, 9/9″	50.28
6/6″	3.52 br dd		5/5″, 7/7″	36.9 (t)	8/8″	37.64
7/7″	3.35 obscured			32.7 (t)	5/5″, 6/6″	33.82
8/8″	4.46 dd	9.9, 8.1	5″/5, 7/7″	39.3 (t)	5″/5, 6/6″, 7/7″, 9/9″	41.79
9/9″				143.3 (q)		143.83
10/10″	3.80 m			45.4 (s)	3/3″, 11/11″, 12/12″	
11/11″	1.88 m			26.9 (s)	10/10″, 12/12″	
12/12″	2.34 m 2.22 m			57.1 (s)	11/11″, 13/13″	
13/13″	2.50 m			54.7 (s)		
14/14″	3.07 m		2′/2‴, 6′/6‴	50.6 (s)		
1′/1‴				154.4 (q)		
2′/2	6.38 t	2.3		104.8 (t)	1′/1‴, 3′/3‴, 6′/6‴	
3′/3‴				159.7 (q)		
4′/4‴	6.30 dd	8.2, 2.3		108.3 (t)	2′/2‴, 3′/3‴, 6′/6‴	
5′/5‴	7.03 t	8.2		131.3 (t)	1′/1‴, 3′/3‴	
6′/6‴	6.44 dd	8.2, 2.3		109.3 (t)	2′/2‴, 4′/4‴	

[a] ^{1}H chemical shift values (δ ppm from $SiMe_4$) followed by multiplicity and then the coupling constants (J in Hz).
[b] HMBC correlations from H to C.
[c] Letters, p, s, t and q, in parentheses indicate, respectively, the primary, secondary, tertiary and quaternary carbons, assigned by DEPT.

within the Gauge-including atomic orbitals (GIAO) ansatz [9] at the PBE0/6-311+G(d,p) level. Computed isotropic shieldings were converted into chemical shifts using as reference the values obtained at the same level for tetramethylsilane. In a separate set of calculations, the influence of the CD_3OD solvent used for NMR was explored by adoption of the Polarizable Continuum Model (PCM) [10,11] in combination with the UAHF parametrization for atomic radii [12].

2.3.2. Explorative irradiation

10^{-4} M solution of the drug in milliQ water in a quartz tube was irradiated by six external 15 W lamps emitting at 310 nm and analyzed by HPLC [column: Synergy Polar RP 80A, eluent: H_2O/CH_3OH (75/25)] at 30 min time intervals.

2.3.2.1. Evaluation of quantum yield. The quantum yield of trazodone hydrochloride (1.35×10^{-4} M) was measured in quartz tube (1 cm optical path) by means of the photoreactor (Helios Italquartz) equipped with six 15 W lamps with a maximum at 310 nm. The light flux (1.76×10^{-7} E s^{-1}) was measured by *o*-nitrobenzaldehyde actinometry [13]. The chemical conversion of trazodone hydrochloride was determined by HPLC as above.

2.3.3. Irradiation of trazodone (*1*) hydrochloride by sunlight in water

Trazodone hydrochloride in milliQ water (10^{-3} M) in a quartz tube was exposed to sunlight at r.t. on September 2007 in Naples (latitude 40°N–14°E). The substrate consumption was monitored by HPLC. After 20 h of exposition distributed in 5 days at 4 h a day in the morning (approximate dose of incident irradiation about 1.02 mW/cm^2) analysis of the solution by HPLC [column: Synergy Polar RP 80A, eluent: H_2O/CH_3OH (15/5)] showed the presence of trazodone (55%), compound **2** (12%), compound **3** (4%) and compound **4** (6%).

Kinetic data of trazodone hydrochloride in milliQ water (10^{-4} M) by sunlight exposure as above were also obtained in the presence of humic acid (5 ppm) or nitrate (10 ppm), dissolving trazodone (**1**) hydrochloride (10^{-4} M) in water milliQ at pH 3.5 by adjusting the pH with HCl 2 M. Each solution was analyzed by HPLC [column: Synergy Polar RP 80A, eluent: $H_2O/CH_3OH/CH_3CN$ (8/1/1)] at 1 h time intervals.

3. Results and discussion

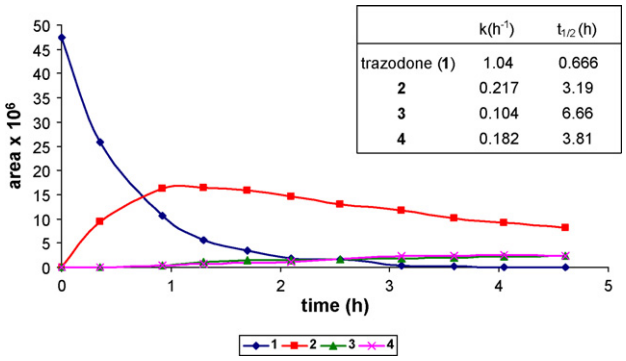
3.1. Product study

Irradiation of trazodone (**1**) hydrochloride at 310 nm in unbuffered conditions gave a mixture of products, which were separated by chromatographic techniques employing diverse stationary and mobile phases and identified as compounds **2**–**4** (Fig. 1). Intractable material was also found. The structures for all compounds were elucidated by NMR techniques (COSY, TOCSY, HSQC, HMBC, and NOESY) and EI-MS, ESI-MS experiments.

Compound **2** showed a molecular ion peak at m/z 353 $[M]^+$ in the EI-MS spectrum suggesting, along with the elemental analysis, a molecular formula $C_{19}H_{23}N_5O_2$. A comparison of mass spectrum and the ^{1}H and ^{13}C NMR spectra of **2** with the spectral data for trazodone (**1**) (Table 1) revealed the presence of the hydroxyl group in the benzene ring instead of chloride in the same position.

Compound **3** showed a molecular ion peak at m/z 371 $[M]^+$ in the EI-MS spectrum suggesting, along with the elemental analysis, a molecular formula $C_{19}H_{25}N_5O_3$. The absence of the pyridine ring by comparison with the spectral data of compound **2** (Table 1) and an additional water molecule in mass spectra suggested hydration of the pyridine ring. In particular, the ^{1}H NMR showed a methine (H-5) signal at δ 5.79, which was correlated in HSQC experiment with the carbon at δ 70.8, and a new methylene signal (H-6) at δ 2.75 correlated with the carbon at δ 31.6. Hypothesis was confirmed by 2D NMR experiments. ^{1}H–^{1}H COSY spectrum showed the correlations of the *m*-disubstituted benzene ring, propyl chain and piperazine ring, indicating that these functionalities were still present. In the same experiment the H-8 methine was correlated to the H-7 methine, which was in turn correlated to the H-6 methylene and this latter was correlated with H-5 methine. The planar structure was completely determined on the basis of an HMBC experiment. The long-range correlations observed from the H-5, H-7 and H-8 protons to C-9 carbon, from the H-5 and H-10 protons to the C-3 carbon, and from the H-6 protons to the C-5, C-7 and C-8 carbons were consistent with structure **3** as depicted.

Compound **4** had molecular formula $C_{38}H_{46}N_{10}O_4$ as established by the elemental analysis and the pseudo molecular ion peak at m/z 707 $[M+H]^+$ in a ESI-MS spectrum. This spectrum presented, further, peaks at m/z 354 and 192 corresponding to $[M-C_{19}H_{23}N_5O_2+H]^+$ and $[C_{11}H_{15}N_2O+H]^+$. A close inspection of the ^{1}H and ^{13}C NMR spectra of **4** (Table 2) by DEPT and HSQC



	k(h⁻¹)	t1/2 (h)
trazodone (**1**)	1.04	0.666
2	0.217	3.19
3	0.104	6.66
4	0.182	3.81

Fig. 2. Kinetics of photodegradation of trazodone (**1**) hydrochloride 10^{-4} M and its photoproducts in water at 310 nm (detection by HPLC using UV detector at 254 nm).

experiments revealed a high symmetric structure and the presence of the following functionalities: a carbonyl group, four tertiary sp^3-carbons C-5, C-6, C-7 and C-8, five aliphatic methylene carbons (C-10, C-11, C-12, C-13, and C-14), one disubstituted aromatic ring (C-1′–C-6′). The connection of these functional groups was determined on the basis of ^{1}H–^{1}H COSY and HMBC correlations (Table 2), and the structure of **4** was elucidated as a dimer of compound **2**. ^{1}H–^{1}H COSY spectrum showed the correlations of the *m*-disubstituted benzene ring, propyl chain and piperazine ring, indicating that these functionalities were still present. In the same experiment the H-8/H-8″ methines were correlated to the H-7/H-7″ methines, which was in turn correlated to the H-6/H-6″ methines and this latter was correlated with H-5/H-5″ methines. In the HMBC spectrum the H-5/H-5″ and H-8/H-8″ protons were heterocorrelated to the C-6/C6″, C-7/C-7″, and C-9/C-9″, the second protons and H-7/H-7″ were heterocorrelated to the C-5/C-5″ carbons. Furthermore, heterocorrelations of H-5/H-5″ and H-6/H-6″ to the C-8/C-8″ were observed. On the basis of the observed correlations the structure of the heptacycle fused ring system was supposed. According to the structure **4** the analysis of NOESY spectrum (Table 2) evidenced NOEs between the H-8/H-8″ methines with both H-5″/H-5 and H-7/H-7″.

Further support of the proposed structure **4** was sought by a comparison between the experimental chemical shifts and the values computed at the DFT level, an approach that is gaining wide acceptance. The comparison concentrates on the core heptacyclic system, whose bulky and flexible *N*-alkyl substituents were therefore replaced by methyl groups. Validated protocols based on DFT were adopted to calculate geometries and ^{13}C NMR chemical shifts [14]; these latter are reported in Table 2 alongside their experimental counterparts. A linear correlation between the two sets gives a correlation coefficient of 0.99994, with a maximum deviation from the linear correlation of 1.1 ppm in essence, this results confirms the excellent compatibility of the proposed structure with the measured carbon spectrum. To explore the influence of the CD_3OD solvent used for NMR on solute geometry and spectroscopic parameters, geometry optimization and chemical shift computation were repeated with adoption of the PCM [10,11]. In the PCM approach, the solvent is represented by an infinite dielectric medium characterized by the relative dielectric constant of the bulk, and a set of optimized radii (in the present instance, the UAHF radii [12]) are used to build an effective cavity occupied by the solute within the solvent. However, the correlation coefficient between computed and experimental carbon chemical shifts was almost unchanged (0.99976).

3.2. Mechanistic interpretation

Trazodone had a quantum yield Φ 3.8×10^{-3} and $t_{1/2}$ 0.666 h when irradiated in water at λ 310 nm. As shown in Fig. 1, all photoproducts isolated arise from a substitution of chlorine in the aryl ring with a hydroxyl group. The HPLC analysis at different times evidenced that the firstly formed derivative was compound **2**, while formation of the other two products **3** and **4** was slower (Fig. 2). On the basis of these data, it is presumable that photoionization of the benzene ring is the primary photochemical process, followed by the nucleophilic attack of the solvent to the radical cation **5** and loss of HCl (Fig. 3). Photochemical aromatic substitution ($S_{RN}1Ar^*$) is a well-known process [15], and in particular, photohydrolysis of halobenzenes occurs with a highly favorable quantum yield [16].

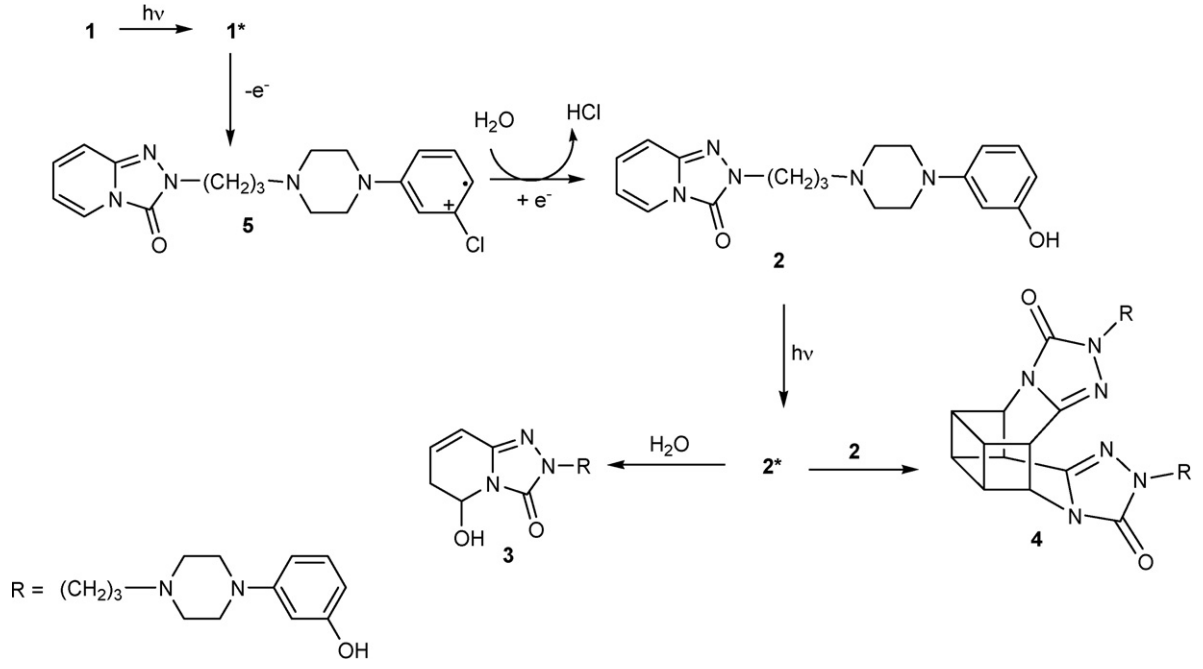


Fig. 3. Suggested pathways for photoproducts **2**–**4**.

Table 3
Kinetics of trazodone (**1**) hydrochloride by sunlight irradiation

Condition[a]	$k\,(h^{-1}) \times 10^2$	$t_{1/2}$ (h)
milliQ water	3.01	23.0
pH 3.5	6.33	10.9
Humic acid[b]	3.15	22.0
Nitrate[c]	2.48	27.8

[a] Solution of drug (10^{-4} M) in milliQ water in quartz tube.
[b] 5 mg/l.
[c] 10 mg/l.

The phototransformation of chloroanilines (absorption bands in the λ range 270–290 nm with tails at λ > 300 nm) in aminophenols is very specific [17,18] and in some cases it has also been observed by sunlight irradiation in long time [18].

In a second stage formation of compounds **3** and **4** occurred via the excited **2**, and both pathways involved diene system of triazolopyridinone moiety (absorption bands in the λ range 300–315 nm) [19]. The experiments showed that water-adduct **3** was found neither under buffered neutral or basic conditions nor in the dark under acid conditions. It could form from **2** through a light- and HCl-induced nucleophilic attack of water to the electron-poor diene system conjugated with the electron-withdrawing imine group [20].

Peculiar is the formation of the cage-like structure **4**. It should result by two [2+2] cycloadditions of the 5,6 double bond of a molecule of **2** with the 7,8 double bond of another molecule. Photodimerization of triazolopyridines has been reported to lead to cisoid-fused cyclobutane derivatives by interaction of the 5,6- and 7,8-double bonds [21]. Cage-like photodimers as **4** have been found only by irradiation of suitably substituted derivatives, namely with an alkyl chain (>2C) connecting the two chromophores, at 254 nm [22]. We were not able to recognize isomers in the intractable polar material. It is noteworthy that compound **4** is also formed in more dilute solution (from 10^{-3} to 10^{-4} M).

3.3. Phototransformation under environmental simulated conditions

Our interest to environmental fate of drugs [6] induced to test the photochemical behaviour of trazodone under environmentally relevant conditions. We found that the drug by exposition to solar light (September 2007, Naples, latitude 40°N–14°E) converted more slowly. The first photoproduct observed after 4 h was compound **2** but the mixture became complicated in time. After 20 h the drug was transformed about 45% giving photoproducts **2**–**4** among other unidentified compounds. The kinetics under different conditions (milliQ water, pH 3.5, humic acid, nitrate) were also investigated according to standard procedures [6]. As shown in Table 3, the phototransformation rate was slightly accelerated by acid medium, while in the presence of humic acid or nitrate comparable behavior was observed. HPLC analysis confirmed that in all the four experiments the same products **2**–**4** were formed in similar amounts.

4. Conclusions

Trazodone has been found to be light-sensitive, and this can be accounted for the phototoxicity demonstrated with the drug [4,5]. It is interesting to note that the same photoproducts are found under mild environmental simulated conditions.

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