Journal of Pharmaceutical and Biomedical Analysis 56 (2011) 678–683

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

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

Determination of photostability and photodegradation products of indomethacin in aqueous media

Fabio Temussi, Flavio Cermola, Marina DellaGreca, M. Rosaria Iesce*, Monica Passananti, Lucio Previtera, Armando Zarrelli

UDR Napoli 4 (Consorzio INCA), IC-REACH Dipartimento di Chimica Organica e Biochimica, Università Federico II, Complesso Universitario Monte S. Angelo, Via Cinthia 4, I-80126 Napoli, Italy

ARTICLE INFO

Article history:
Received 6 April 2011
Received in revised form 4 July 2011
Accepted 5 July 2011
Available online 12 July 2011

Keywords:
Indomethacin
Photodecarboxylation
Photo-oxidation
Arylalkanoic acids
Mesolytic cleavage

ABSTRACT

Photochemical behaviour of indomethacin in aqueous media at 254 nm, 310 nm and sunlight was studied by HPLC. The drug exhibited a similar behaviour in all the irradiation experiments affording eight photoproducts that were separated and identified. The main photochemical routes are suggested to proceed via decarboxylation, followed by oxygenation to give an alcohol and an aldehyde and/or by solvent trapping to produce the alcohol. Photoinduced hydrolysis of CO–N bond and oxidative C2–C3 bond breakage also occur.

1. Introduction

Indomethacin (**1**) is a nonsteroidal anti-inflammatory drug (NSAID) (Fig. 1). Approved by FDA in 1965, it is widely used due to its antipyretic and analgesic properties, more potent than aspirin. Although photostable as crystalline [1], it is photochemically labile in solution, especially in organic solvents [2,3]. The photochemical reaction observed using medium pressure mercury lamp is decarboxylation of the acetic side chain that can be followed by oxidation [2,3]. Daylight irradiation in methanol leads to products that preserve the carboxyl group and have been rationalized as arising via the related acyl radical [4]. Conflicting data have been reported for irradiation in aqueous solution with no photochemical activity in buffered aqueous solution [5] in contrast to the observation of photodegradation to a complex mixture under aerobic and anaerobic conditions [6]. During the last decade, the photochemistry of NSAIDS has received considerable attention mainly to establish the molecular bases of the phototoxic properties sometime exhibited [7–10]. Photosensitivity has been reported with indomethacin [11], and in recent years, the phototoxic effects of the drug have been associated to its ability to generate reactive oxygen species (ROS) [12]. The photobiological risk associated with the use of drugs is of high interest, as shown by the increasing number of related reports, even in environmental field [13]. An adequate approach to analyze the involved mechanisms is represented by photophysical and photochemical studies, including exam of excitation and emission properties, analysis of interaction with biological substrates as well as identification of reaction intermediates and isolation of photoproducts [14].

Here, we have carried out a detailed investigation on the photochemical behaviour of indomethacin in aqueous solution by UV (UVA and UVB) light and by sunlight in an attempt to rationalize the various reported experimental data. Indomethacin exhibits absorption up to 400 nm with the maximum of the lowest energy band at 320 nm so that it is photosensitive in a wide range of light [2]. Particular attention has been focused to the isolation and characterization of photoproducts and elucidation of the involved mechanisms.

2. Materials and methods

2.1. Materials

Indomethacin, analytical standard grade (99%; solubility 50 mg/ml in ethanol), was supplied by Fluka and used without further purification. All other chemicals were purchased from Aldrich and were of reagent or HPLC grade. Aqueous solutions were prepared using Milli-Q water obtained from a Milli-Q gradient system (Millipore).

* Corresponding author. Tel.: +39 081 674334; fax: +39 081 674393.
E-mail address: iesce@unina.it (M.R. Iesce).

0731-7085/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2011.07.005

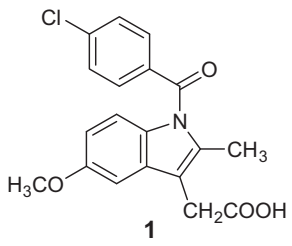

Fig. 1. Indomethacin (**1**, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid).

Indomethacin solution (1×10^{-5} M) was prepared in water:acetonitrile (95:5, v/v) by 1:100 dilution with Milli-Q water of a 10^{-3} M solution of the drug (5 mg in 14 ml of Milli-Q water:acetonitrile, 3/2, v/v).

2.2. Apparatus

HPLC system A: Agilent Waters 1525 binary pump HPLC equipped with UV diode-array detector was used for kinetics using a Sinergy Hydro RP18 (4 μm, 250 mm × 4.6 mm) column. Injection 100 μl. The mobile phase was made of eluent A (Milli-Q water) and B (methanol–acetonitrile) (1:1, v/v) (A–B, 1:1 v/v). The flow rate was 0.4 ml min^{-1}.

HPLC system B: Agilent 1100 Series binary pump HPLC equipped with a UV detector set at 254 nm was used for qualitative analysis using a Gemini C18 (5 μm, 250 mm × 4.6 mm) column. Injection 250 μl. The mobile phase was made of eluent A (water with 1% formic acid) and B (acetonitrile) (A–B, 1:1 v/v). The flow rate was 0.8 ml min^{-1}.

Analytical and preparative TLCs were made on Kieselgel 60 F_{254} plates with 0.2 mm and 0.5 or 1 mm layer thickness, respectively (Merck).

Column chromatography was performed using Lichroprep C-18 resin (40–63 μm) (Merck).

NMR spectra were recorded on a Varian Inova-500 instrument operating at 499.709 and 125.62 MHz for ^1H and ^{13}C, respectively, and referenced with deuterated solvents. The carbon multiplicity was evidenced by DEPT experiments. The proton couplings were evidenced by ^1H–^1H COSY experiments. The heteronuclear chemical shift correlations were determined by HMQC and HMBC pulse sequences. ^1H–^1H proximities through space were determined by NOESY.

LC–MS analyses were run on an Agilent1100 MSD instrument using a Gemini C18 (5 μm, 250 mm × 4.6 mm) column. Injection 100 μl. Mobile phase: water with 1% formic acid (A) and acetonitrile (B) whose composition varied according to the following gradient: $t = 0$, A = 50%, $t = 33'$ A = 50%, $t = 35'$ A = 10%. The flow rate was 0.4 ml min^{-1}.

UV/Vis spectra were recorded on a PerkinElmer Lambda 7 spectrophotometer.

IR spectra were run on a Nicolet 5700 FT-IR spectrometer.

2.3. Calibration curve

Calibration curve was obtained by analyzing stock solutions water–acetonitrile (95:5, v/v) of indomethacin (**1**) by HPLC (system A) and plotting the peak areas (detection at 254 nm) versus the theoretical concentrations over a range 1×10^{-4}–1×10^{-6} M. The data were subjected to the least squares regression analysis. Inspection of the plotted calibration curve described by equation: $y = 0.0215x - 0.1655$ and correlation coefficient ($r = 0.999$) confirmed that the calibration curve was linear over the concentration range.

2.4. Photodegradation studies

2.4.1. Photodegradation conditions

Drug solutions were placed in cylindrical quartz tubes (20 cm × 1 cm, 25 ml). UV-B and UV-C irradiations were carried out in a photoreactor (Multirays, Helios Italquartz) equipped with six 15 W lamps with a maximum at 310 nm or with four lamps with a maximum at 254 nm.

Sunlight irradiation was run by exposure of the drug solution to solar light (Naples, October–November 2010). Each experiment was done in triplicate.

2.4.2. Photodegradation experiments

Three samples of drug solution (10^{-5} M, 20 ml) in open quartz tubes were irradiated at 254, 310 and sunlight, respectively, and analyzed time by time by HPLC (system B). The photoproducts were identified by HPLC comparing their t_Rs with those of standard compounds which were isolated and characterized by performing preparative photochemical experiments (see below).

A fourth sample of drug solution (10^{-5} M, 20 ml) in a closed tube saturated with argon was irradiated at 254 nm and analyzed time by time by HPLC (system B).

A further sample (10^{-5} M, 20 ml) was kept in darkness and analyzed by HPLC (system B) at 10, 20 and 30 d.

2.5. Preparative experiments for photoproducts isolation

Indomethacin (50 mg) was dissolved in 140 ml of water–acetonitrile (1:1, v/v, 1×10^{-3} M) and irradiated by four lamps at 254 nm for 4 h. After evaporation of the solvents, the mixture was chromatographed on a RP-18 open column by eluting with (water-1% formic acid)-acetonitrile (3:7, v/v) and gave compounds **8** (5.7 mg), **9** (1.1 mg), **7** (5.8 mg), **6** (3.6 mg), **1** (14.8 mg), **2** (4.3 mg), **3** (10.4 mg), **5** (1.0 mg), successively (Fig. 2).

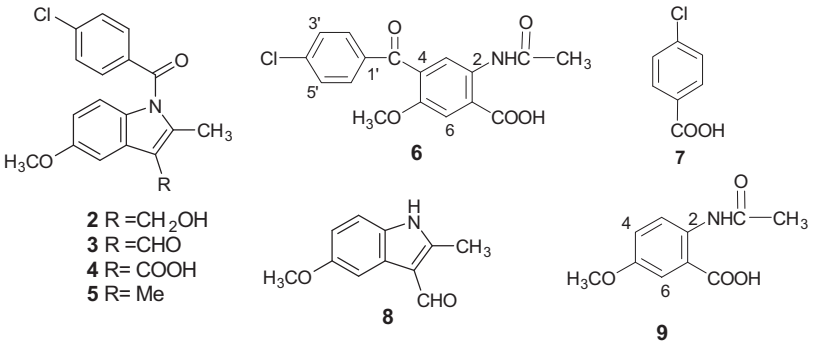

Fig. 2. Photoproducts from indomethacin irradiation in aqueous solution.

In another experiment the drug (36 mg) was dissolved in 20 ml of water–acetonitrile (1:1, v/v, 5×10^{-3} M) and exposed to sunlight (October–November 2010, Naples). After 45 d, evaporation of the solvents gave a residue which was chromatographed as above leading to compounds **8** (3.2 mg), **9** (3.1 mg), **7** (4.8 mg), **6** (1.2 mg), **4** (3.9 mg), **3** (11.3 mg), **5** (1.8 mg), successively (Fig. 2).

Compounds **3** [2], **5** [2] and **8** [15] were identified by comparison of NMR data with those reported. Acid **7** was identified by comparison of NMR with those of an authentic sample. Unknown compounds **2**, **4**, **6** and **9** were characterized by MS, IR and NMR data.

1-(4-Chlorobenzoyl)-3-hydroxymethyl-5-methoxy-2-methyl-1*H*-indole (**2**): LC–MS: *m/z* 352 $[M+Na]^+$; IR ν_{max} ($CHCl_3$) 3453 (OH), 1683 (C=O), 1478 (C–N) cm^{-1}; ^1H NMR (CD_3OD) δ 7.66 (d, *J* = 8.7, 2 H, H-2′ and H-6′), 7.47 (d, *J* = 8.7, 2 H, H-3′ and H-5′), 7.10 (d, *J* = 2.7, 1 H, H-4), 6.83 (d, *J* = 9.0, 1 H, H-7), 6.67 (dd, *J* = 2.7 *J* = 9.0, 1 H, H-6), 4.82 (s, 2 H, CH_2O), 3.84 (s, 3 H, CH_3O), 2.43 (s, 3 H, CH_3); ^{13}C NMR (CD_3OD) δ 168.5 (CON), 156.3 (C-5), 139.7 (C-4′), 129.7 (C-1′), 136.5 (C-2), 131.4 (C-2′ and C-6′), 131.1 (C-9), 130.3 (C-8), 129.4 (C-3′ and C-5′), 118.7 (C-3), 115.2 (C-7), 112.2 (C-6), 101.4 (C-4), 56.0 (CH_3O), 55.8 (CH_2O), 13.3 (CH_3).

1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-carboxylic acid (**4**): LC–MS *m/z* 344 $[M+H]^+$; IR ($CHCl_3$) *ν* 3019 (br band COOH), 1707 (CO), 1672 (CO–N), 1476 (C–N) cm^{-1}; ^1H NMR (CD_3OD) δ 7.71 (s, 1 H, H-4), 7.70 (d, *J* = 8.4, 2H, H-2′ and H-6′), 7.50 (d, *J* = 8.4, 2H, H-3′ and H-5′), 6.88 (d, *J* = 9.0, 1 H, H-7), 6.75 (dd, *J* = 9.0, 2.7, 1 H, H-6), 3.89 (s, 3 H, CH_3O), 2.77 (s, 3 H, CH_3); ^{13}C NMR (CD_3OD) δ 170.3 (COOH), 168.6 (CON), 156.9 (C-5), 147.4 (C-2), 141.1 (C-4′), 132.6 (C-8), 132.0 (C-2′ and C-6′), 130.8 (C-1′), 129.7 (C-3′ and C-5′), 129.2 (C-3), 128.4 (C-9), 114.3 (C-7), 113.4 (C-6), 104.2 (C-4), 56.0 (CH_3O), 15.0 (CH_3).

2-Acetamido-4-(4-chlorobenzoyl)-5-methoxybenzoic acid (**6**): LC–MS: *m/z* 348 $[M+H]^+$; IR ν_{max} ($CHCl_3$) 3419 (NH), 3002 (br band, COOH), 1673 (CO + COAr), 1588 (N–C=O), 1461 (C–N) cm^{-1}; ^1H NMR (CD_3OD) δ 8.51 (s, 1 H, H-3), 7.81 (s, 1 H, H-6), 7.75 (d, *J* = 9.0, 2 H, H-2′ and H-6′), 7.48 (d, *J* = 9.0, 1 H, H-3′ and H-5′), 3.72 (s, 3 H, CH_3O), 2.15 (s, 3 H, CH_3); ^{13}C NMR (CD_3OD) δ 199.0 (CO), 175.1 (COOH), 175.0 (CON), 156.2 (C-5), 141.2 (C-4′), 138.3 (C-2), 134.0 (C-4), 132.8 (C-2′and C-6′), 131.1 (C-1′), 130.9 (C-1), 130.3 (C-3′ and C-5′), 120.2 (C-3), 114.2 (C-6), 56.3 (CH_3O), 12.6 (CH_3).

2-Acetamido-5-methoxybenzoic acid (**9**): LC–MS: *m/z* 232 $[M+Na]^+$; IR ν_{max} ($CHCl_3$) 3423 (NH), 2995 (br band, COOH), 1670 (CO), 1611 (N–C=O), 1466 (C–N) cm^{-1}; ^1H NMR (CD_3OD) δ 8.37 (d, *J* = 9.2 Hz, 1 H, H-3), 7.62 (d, *J* = 2.8 Hz, 1 H, H-6), 6.96 (dd, *J* = 9.2, 2.8 Hz, 1 H, H-4), 3.79 (s, 3 H, CH_3O), 2.15 (s, 3 H, CH_3); ^{13}C NMR (CD_3OD) δ 174.0 (COOH), 170.1 (CONH), 155.2 (C-5), 134.2 (C-2), 125.0 (C-1), 122.5 (C-3), 118.8 (C-4), 117.1 (C-6), 56.4 (CH_3O), 25.4 (CH_3).

2.6. Photodegradation of photoproducts *2*, *3*, *5*, *8*

10^{-4} M solutions of products **2**, **3**, **5** and **8** in water/acetonitrile (95:5, v/v, 20 ml) were prepared by 1:10 dilution with water of each 10^{-3} M solution.

Each solution in open quartz tube was irradiated at 254 nm and analyzed time by time by HPLC (system B). The photoproducts were identified by HPLC as above.

A further solution of each sample was kept in darkness and analyzed by HPLC (system B) at 1, 5 and 10 d.

2.7. Phototransformation kinetics

Indomethacin solutions (10^{-5} M) were prepared in water/acetonitrile (95:5, v/v) as above. Kinetics were determined using stock solutions, in quartz tubes (25 ml) which were irradiated at 254 nm, 310 nm and by sunlight. At suitable time intervals samples were withdrawn and analyzed by HPLC (system A).

Table 1
Kinetics of photodegradation of indomethacin (10^{-5} M).

light	254 nm	310 nm	sunlight
k (min^{-1})	0.055	0.0156	9.3×10^{-4}
$t_{1/2}$ (min)	12.6	44	744

2.8. Evaluation of quantum yield at 310 nm

The quantum yield of indomethacin (**1**) was measured at 310 nm using 10^{-5} M solutions in quartz tubes (1 cm optical path). The light flux (1.90×10^{-7} Es^{-1}) was measured by *o*-nitrobenzaldehyde [16]. The chemical conversion of compound **1** was determined by HPLC (system A).

3. Results and discussion

Indomethacin is scarcely soluble in water so that acetonitrile was used as cosolvent to prepare clear solutions. A 10^{-5} M solution (water/acetonitrile 95:5, v/v) was generally used. Under these conditions a quantum yield of 1.5×10^{-4} was found by irradiation of the drug at 310 nm according to the low value measured in other polar solvents [2]. The drug was exposed to UV lamps centered at 254 and 310 nm as well as to sunlight. The changes of the drug under the light sources were monitored by HPLC. Table 1 reports the corresponding kinetics.

Chromatographic analysis evidenced that the drug was photochemically degraded affording eight photoproducts (Fig. 2).

Fig. 3 reports the HPLC (system B, see Section 2.2) profiles of each solution at selected times. Identification of photoproducts was made by comparison of retention times with those of authentic samples obtained by preparative experiments.

As evidenced in Fig. 3 chromatograms are similar with similar peaks, although with different intensities, likely due to the different light power and irradiation times. In order to get major amounts of photoproducts 10^{-3} M solutions (water–acetonitrile 1:1, v/v) were used and irradiated at 254 nm and sunlight (4 h and 45 d, respectively). Chromatographic separation of the products was obtained by repeated TLCs of irradiation mixtures. All photoproducts isolated (Fig. 2) were characterized by NMR techniques (COSY, HSQC, HMBC, NOESY) and LC–MS experiments. Aldehyde **3** and 3-methylindole **5** were previously isolated by irradiation of the drug in methanol [2]. The peak of compound **5** is not present in above chromatograms (Fig. 3) since it can be detected by HPLC using different chromatographic conditions. Careful HPLC analysis showed that it is also present in small amount under dilute conditions. NH-indole **8** was previously prepared and described as an intermediate for a synthetic scope [15]. *p*-Chlorobenzoic acid **7** was identified by comparison of its data with those of a commercially available sample. Alcohol **2**, acid **4**, anthranilic acids **6** and **9** are new.

Irradiation mixtures were in-time changing suggesting the formation of light-sensitive products. Due to the presence of the same chromophore (N-chlorobenzoylindole) alcohol **2**, aldehyde **3** and 3-methylindole **5** exhibit similar absorption bands as the drug and, hence, similar photosensibility. This was confirmed by irradiating these compounds at 254 nm in 10^{-4} M solution (H_2O/MeCN 95:5, v/v). In Table 2 we report the percentage of conversion and the related photoproducts after 20 min of UVC irradiation. NH-indole **8** was irradiated under the same conditions. Its HPLC peak decreased in time and only compound **9** was identified in very low amount.

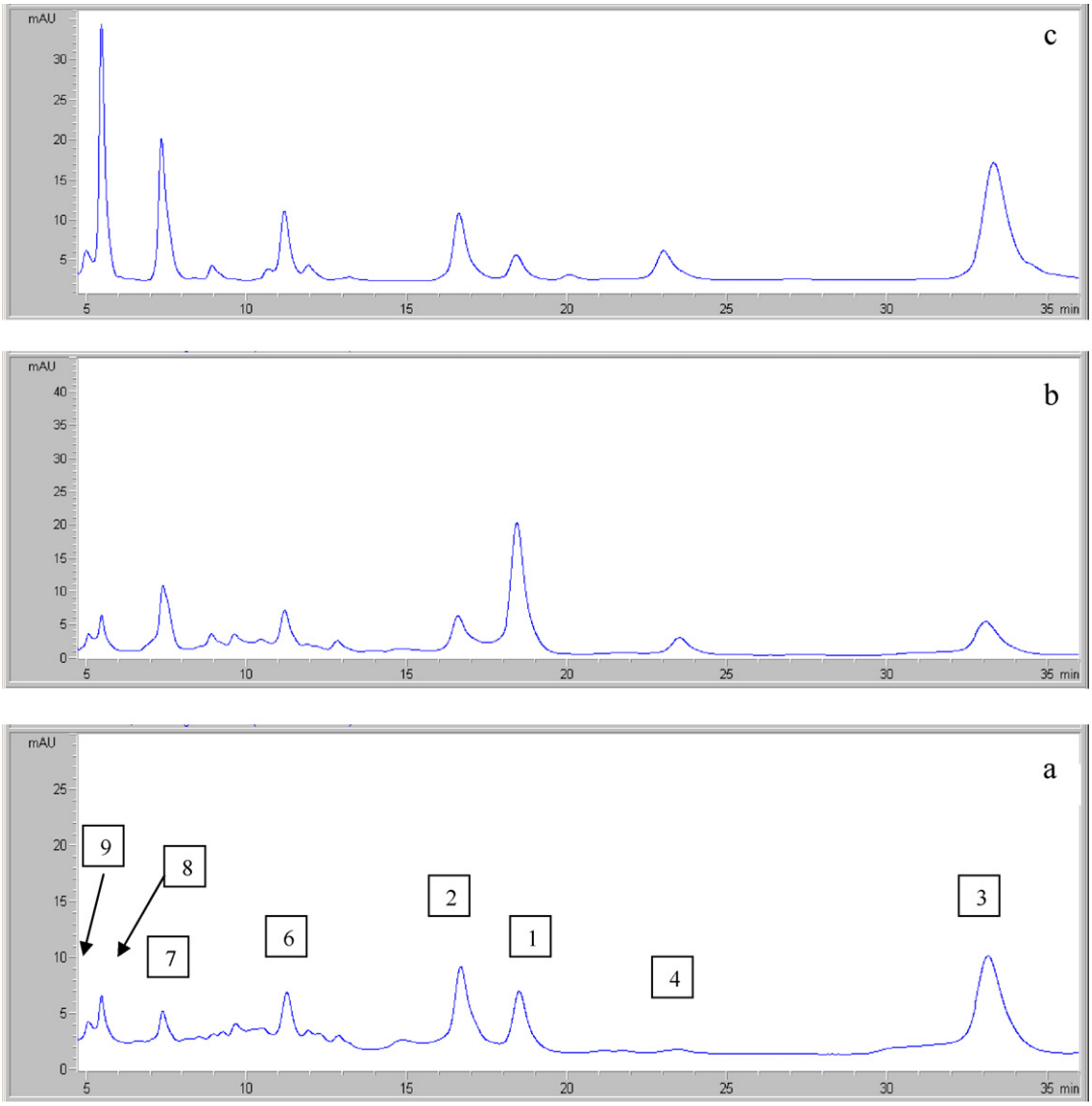

Fig. 3. Representative HPLC profiles of irradiation mixtures of indomethacin in H_2O/MeCN (95:5 v/v, 10^{-5} M): (a) after 30 min of UVC (254 nm) irradiation, (b) after 90 min of UVB (310 nm) irradiation and (c) after 19 d of sunlight exposure.

3.1. Mechanistic interpretation

As shown in Fig. 3, the main degradation products are alcohol **2** and aldehyde **3** found in all the mixtures (even in deaerated solutions) together with minor compounds **6** and **7**. Methylindole **5** is detected in low amount. Acid **4** forms in prolonged experiments (by UVB and sunlight) and in oxygenated media. Anthranilic acids **6** and **9** are not found in deaerated media. Analysis of products structures indicates that degradation of indomethacin involves (a) decarboxylation of the acetic chain, (b) fragmentation of the amide bond and (c) oxidative cleavage of C2–C3 bond of indole ring. The proposed pathways for the photoinduced degradation of the drug are shown in Fig. 4. On the basis of the well-known photochemistry of structurally related arylkanoic acids [10,17,18] and the photochemical behaviour of indoles in water [19,20] we suggest that an initial photoionization occurs leading to the radical ion **10**. Decarboxylation then occurs via a mesolytic cleavage [17] giving the methyl radical **11**. This species adds oxygen affording the corresponding alcohol **2** and/or aldehyde **3** likely via a peroxide radical **12** or, to a lesser extent, undergoes a hydrogen shift giving 3-methylindole **5**. It is also possible that fragmentation of the radical ion **10** produces the cation **13** that can be trapped by the nucleophilic solvent (water) to give alcohol **2**. This route should account for the finding of alcohol **2** even in degassed solution. The mesolytic cleavage has been previously suggested for naproxen photodegradation [18]. The presence in indomethacin of the electron-rich alkoxyarylindole system should promote this route as suggested for the role of alkoxynaphtalenic system in naproxen photodegradation [17,18].

Formation of *N*-acyl anthranilic acid **6** can be explained by the photochemical oxidative cleavage of C2–C3 bond, as reported for 2-, 3- and 2,3-dimethylindoles, through the intermediacy of peroxidic species (dioxetane or hydoperoxide) [21]. It is noteworthy that

Table 2
UVC irradiation of alcohol **2**, aldehyde **3**, methylindole **5** and NH-indole **8**.

Compound[a]	**2**	**3**	**5**	**8**
Conversion (%)[b]	40	75	>90	30
Photoproducts	**3**, **6**, **7**	**4**, **7**, **8** (trace), **9** (trace)	**2** (trace), **6**, **7**	**9** (trace)

[a] 10^{-4} M, H_2O/MeCN 95:5, v/v.
[b] After 20 min.

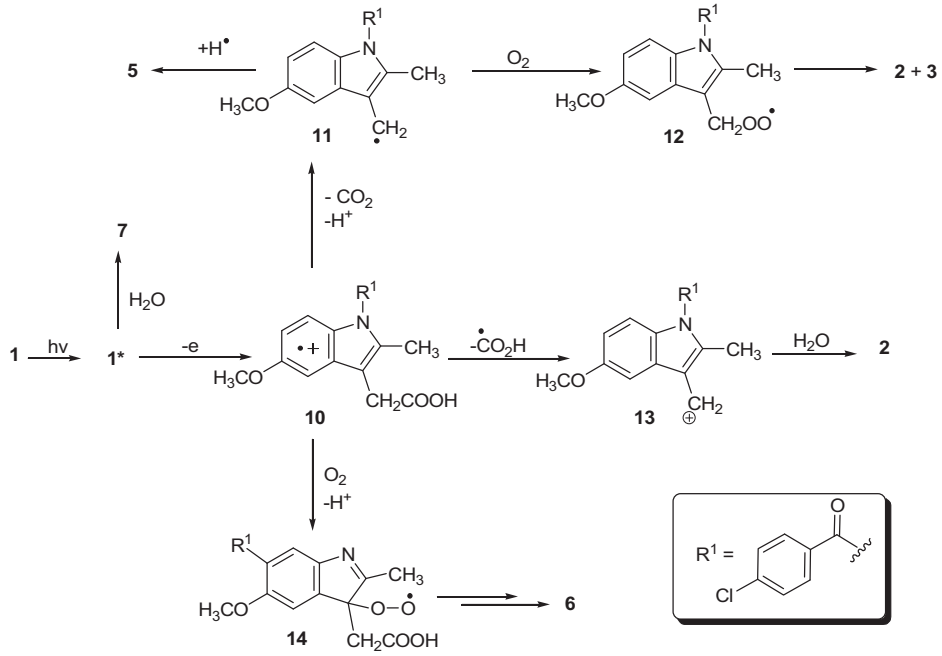

Fig. 4. Suggested mechanisms for the main degradation photoproducts of indomethacin in aqueous solution.

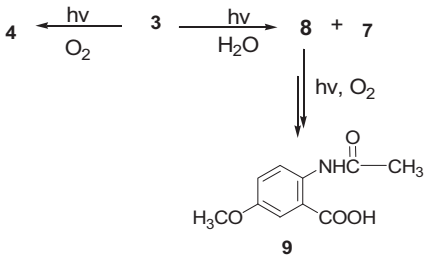

Fig. 5. Secondary photodegradation routes.

in anthranilic acid **6** the *p*-clorobenzoyl group is at C-6. This substitution should be due to an electrophilic or radical reaction dictated by OMe group, e.g. starting from radical ion **10** (Fig. 4), rather than a photo-Fries rearrangement, as observed in other *N*-acylindoles, that involves C-7 or C-4 position [22]. On the other hand, previous studies on indomethacin did not report the presence of these rearranged products in organic, even polar, solvents [2,3].

Photoinduced hydrolysis of the *N*-benzoyl function could be responsible for the finding of chlorobenzoic acid **7** that can be formed by the drug **1** as well as by all the other *N*-acylated indoles **2–5**. Control experiments showed that these compounds were recovered unchanged by keeping them in water solution in darkness, even after 10 d.

Compounds **4**, **8** and **9** are minor products and could originate as reported in Fig. 5.

4. Conclusion

Eight photoproducts have been isolated by UV or solar irradiation indomethacin in aqueous solution confirming the earliest observation of the drug photodegradation in water (under anaerobic and aerobic conditions) as a complex reaction [6]. In addition to radical species, investigation highlights the possible involvement of cationic species promoted by the ionization of the aryl portion prior to decarboxylation. These results give a further support to the general photodecarboxylation mechanism of arylalkanoic acids and to the classification into two different groups depending on the ability of the aryl ring to act as an electron-acceptor moiety (ketoprofen, suprofen, tolmetin) or as an electron-donor moiety (naproxen, carprofen, indomethacin) [9,17].

The involvement of radical and electrophilic species could account for the phototoxic effects, sometime observed, in therapeutic uses of the drug. The first one might be linked to the lipid peroxidation, and hence, to the damage produced in the cell membrane [12], while the other one suggests a possible role in the alkylation of nucleophilic groups present in the protein or other biomolecules.

It is noteworthy that the photochemical behaviour of indomethacin in water is quite different from that observed in organic solvents, even in methanol [2,3], and could be due to the peculiar role of water to favor photoionization reaction, to stabilize ionic intermediates and trap electrophilic species.

References

[1] N. Ekiz-Gücer, J. Reisch, Photochemical studies, 58. Photostability of indomethacin in the crystalline state , Pharm. Acta Helv. 66 (1991) 66–67.
[2] A.C. Weedon, D.F. Wong, The photochemistry of indomethacin , J. Photochem. Photobiol. A 61 (1991) 27–33.
[3] R. Dabestani, R.H. Sik, D.G. Davis, G. Dubay, C.F. Chignell, Spectroscopic studies of cutaneous photosensitizing agents. XVIII. Indomethacin , Photochem. Photobiol. 58 (1993) 367–373.
[4] A.-B. Wu, H.-W. Cheng, C.-M. Hu, F.-A. Chen, T.-C. Chou, C.-Y. Chen, Photolysis of Indomethacin in Methanol , Tetrahedron Lett. 38 (1997) 621–622.
[5] D.E. Moore, P.P. Chappuis, A comparative study of the photochemistry of the non-steroidal anti-inflammatory drugs, naproxen, benoxaprofen and indomethacin , Photochem. Photobiol. 47 (1988) 173–180.
[6] E. Pawelczyk, B. Knitter, K. Knitter, Kinetics of drug decomposition. Part 50: Graphic method for calculation of zero-order rate constants of sequential reaction of indomethacine photodegradation , Pharmazie 32 (1977) 483–485.
[7] K.A.K. Musa, L.A. Eriksson, Theoretical investigation of NSAID photodegradation mechanisms , Quantum Biochem. 2 (2010) 805–834.
[8] P. Nayak, Commonly used photosensitizing medications: their adverse effects and precautions to be considered , Int. J. Pharm. Sci. 4 (2010) 135–140.
[9] G. De Guidi, S. Ragusa, M.T. Cambria, A. Belvedere, A. Catalfo, A. Cambria, Photosensitizing effect of some nonsteroidal antiinflammatory drugs on natural and artificial membranes: dependence on phospholipid composition , Chem. Res. Toxicol. 18 (2005) 204–212.
[10] For a review F. Bosca, M.L. Marin, M.A. Miranda, Photodecarboxylation of acids and lactones: antiinflammatory drugs , in: W. Horspool, F. Lenci (Eds.), CRC Handbook of Photochemistry and Photobiology, 2nd ed., CRC Press, Boca Raton, 2004, pp. 64-1–64-10.

[11] R.S. Stern, M. Bigby, An expanded profile of cutaneous reactions to nonsteroidal anti-inflammatory drugs. Reports to a specialty-based system for spontaneous reporting of adverse reactions to drugs , J. Am. Med. Assoc. (JAMA) 252 (1984) 1433–1437.
[12] S. Onoue, Y. Tsuda, Analytical studies on the prediction of photosensitive/phototoxic potential of pharmaceutical substances , Pharm. Res. 23 (2006) 156–164.
[13] F. Comeau, C. Surette, G.L. Brun, R. Losier, The occurrence of acidic drugs and caffeine in sewage effluents and receiving waters from three coastal watersheds in Atlantic Canada , Sci. Total Environ. 396 (2008) 132–146.
[14] B. Quintero, M.A. Miranda, Mechanisms of photosensitization induced by drugs: a general survey , Ars Pharmaceutica 41 (2000) 27–46.
[15] K. Torisu, K. Kobayashi, M. Iwahashi, H. Egashira, Y. Nakai, Y. Okada, F. Nanbu, S. Ohuchida, H. Nakai, M. Toda, Development of a prostaglandin D_2 receptor antagonist: discovery of a new chemical lead , Eur. J. Med. Chem. 40 (2005) 505–519.
[16] D. Dulin, T. Mill, Development and evaluation of sunlight actinometers , Environ. Sci. Technol. 16 (1982) 815–820.
[17] K. Pitchumani, D. Madhavan, Induced diastereoselectivity in photodecarboxylation reactions , in: W. Horspool, F. Lenci (Eds.), CRC Handbook of Photochemistry and Photobiology, 2nd ed., CRC Press, Boca Raton, 2004, pp. 65-1–65-14.
[18] F. Bosca, M.A. Miranda, L. Vano, F. Vargas, New photodegradation pathways for Naproxen, a phototoxic non-steroidal anti-inflammatory drug , J. Photochem. Photobiol. A 54 (1990) 131–134.
[19] A.L. Sobolewski, W. Domcke, Photoinduced charge separation in indole-water clusters , Chem. Phys. Lett. 329 (2000) 130–137.
[20] W.G. McGimpsey, H. Goerner, Photoionization of indole, *N*-methylindole and tryptophan in aqueous solution upon excitation at 193 nm , Photochem. Photobiol. 64 (1996) 501–509.
[21] C.A. Mudry, A.R. Frasca, Photo-oxidation of indole derivatives , Tetrahedron 29 (1973) 603–613.
[22] D.L. Oldroyd, A.C. Weedon, Solvent- and wavelength-dependent photochemistry of *N*-benzoylindole and *N*-ethoxycarbonylindole , J. Photochem. Photobiol. A. 57 (1991) 207–216.