

Identification of flurbiprofen and its photoproducts in methanol by gas chromatography–mass spectrometry

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ABSTRACT: A sample of 10 mM flurbiprofen in methanol (or ethanol) was photoirradiated with sixteen 8 W low-pressure quartz mercury lamps irradiated at 306 nm in a Panchum PR-2000 photochemical reactor. In total, four major photoproducts derived from each sample were observed from the HPLC chromatogram. The photoproducts were separated and their structures elucidated by various spectroscopic methods. Alternatively, using GC-MS, 11 major photoproducts were observed. A reaction scheme of flurbiprofen in methanol is proposed: the photochemical reaction routes occur mainly via esterification and decarboxylation, followed by oxidation with singlet oxygen to produce a ketone, alcohols and other derivatives. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: Flurbiprofen; HPLC; GC-MS; photoproducts

INTRODUCTION

After the shock withdrawal of two COX-2 inhibitors, Vioxx (rofecoxib) and Bextra (valdecoxib) from the market in late 2004 because of an increased risk of heart attacks and strokes in patients taking the drugs, it has been found that the traditional COX-1 inhibitors are better choices in terms of pharmaceutical efficacy and safety. Flurbiprofen (FB) is a typical 2-arylpropionic (or 2-arylpropanoic) acid endowed with good analgesic, antipyretic and anti-inflammatory properties (Adams *et al.*, 1975). Recently, oral uptakes of NSAIDs (non-steroidal anti-inflammatory drugs) have been reported to be associated with a reduced risk of Alzheimer's disease (AD; Andersen *et al.*, 1995; Gasparini *et al.*, 2005). Although the long-term anti-inflammatory therapy may be beneficial in AD (McGeer and McGeer, 1999), medical treatment with most NSAIDs is limited by their significant gastrointestinal toxicity. Nitric oxide (NO)-releasing NSAIDs have been shown to possess anti-inflammatory activity comparable to the parent drugs with a markedly reduced gastrointestinal

toxicity. These drugs, such as NO-flurbiprofen, NO-naproxen, NO-ketoprofen and NO-aspirin, look promising for their advantages over conventional NO donors (Idris *et al.*, 2004). In a significant number of NSAIDs, especially for 2-arylpropionic acid derivatives, gastrointestinal irritation is the dominant adverse side effect, associated with photosensitivity responses in patients (Boscá *et al.*, 2001). By taking into account of the reported instability factor of aryloethanoic acids to light (Epling and Lopes, 1977), FB has not yet been found to be phototoxic *in vivo*. However, FB is labile to UV light and has been shown to produce phototoxicity when tested *in vitro* (Castell *et al.*, 1992). The analogous alcohol derived from FB at the lower assayed concentration is toxic to fibroblasts. When a flurbiprofen sample was exposed to sunlight, concentrations lower than 1.0×10^{-3} M of the photoproducts produced in the skin were found to exert toxic effects on cell membranes. It has been pointed out that FB causes noxious photoallergic contact dermatitis in the clinical practice (Kawada *et al.*, 2000). Drug-induced photosensitivity or phototoxicity is always related to photoproducts (Moore, 2002). Benoxaprofen, before its withdrawal from the market due to hepatotoxicity, was the most photoactive drug among the various NSAIDs tested. The mechanism of inducing photosensitivity, which in turn is responsible for the high photoactivity of the 2-arylpropionic acids, is expressed by the easy decarboxylation of the carboxylic acid moiety (Navaratnam *et al.*, 1993). In our previous studies concerning NSAIDs of 2-arylpropionic acids, such as

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Abbreviations used: AD, Alzheimer's disease; FB, flurbiprofen; NSAIDs, non-steroidal anti-inflammatory drugs.

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naproxen and carprofen (Hsu *et al.*, 2006; Chen *et al.*, 2003; Sheu *et al.*, 2003), decarboxylation is one of the major photolytic pathways.

Traditional chemical methods involving isolation and purification of trace components, such as photoproducts and impurities, are expensive and time-consuming. Most of the high-resolution analytical methods employed for FB, which have been frequently reported in literature, include capillary electrophoresis (Hamoudova and Pospisilova, 2006), HPLC (Teng *et al.*, 2003) and LC-MS (Aldini *et al.*, 2002). Gas chromatography (GC) combined with mass spectrometry (MS) employing capillary columns with incomparably higher resolving power is found to offer a rapid and versatile analytical tool for enantioseparation of FB (Paik *et al.*, 2004). In this study, we attempted to select GC-MS combining high-performance liquid chromatography (HPLC) and the spectroscopic methods for structural determinations of FB photoproducts. We also aimed to unveil the photolytical reaction scheme of this particular drug.

EXPERIMENTAL

General methods and materials

Melting points were determined on a Büchi (Zurich, Switzerland) B-540 apparatus. Flurbiprofen of guaranteed purity (GR grade) was purchased from Tokyo Chemical Industry (Tokyo, Japan). Liquid chromatographic (LC) grade methanol and GR-grade *n*-chloroform were from Merck (Darmstadt, Germany). GR-grade glacial acetic acid and absolute ethanol were the products of Ridel-deHaën (Seelze, Germany). LC-grade acetonitrile was purchased from Labscan Asia (Bangkok, Thailand). The chemicals were used as received. The purities of the chemicals were checked by running HPLC using blank samples.

Photochemical reactor and irradiation conditions

A Panchum PR-2000 photochemical reactor (Taipei, Taiwan), which was equipped with sixteen 8 W low-pressure quartz mercury lamps irradiated at 306 nm (Sankyo Denki G8T5E) as the light source, was used. Irradiation was performed with the samples in stoppered quartz tubes mounted vertically on a merry-go-round rack at a speed of 6 rpm. The light intensity of the monochromatic radiation was measured at 306 nm to be 3.25 mW/cm² using a UVX (UVP, Upland, CA, USA) digital radiometer (serial no. E. 16768).

Sample preparation and photodegradation of flurbiprofen

An amount of 244 mg (10 mm) of flurbiprofen was accurately weighed and placed in a 100 mL volumetric flask. Methanol (or ethanol) was slowly added to make the concentration of the sample exactly 500 µM. The sample was transferred to a quartz tube. The tube was stoppered and irradiated in a

photochemical reactor for 14 (or 10) days. The sample was filtered using a Millipore membrane of 0.45 µm thickness, and the filtrate was then transferred to HPLC for separation. The major photoproducts of the irradiated mixture were collected separately using a preparative HPLC. Four fractions of the major photoproducts, namely **A**, **B**, **C** and **D** (or **E** in ethanol) were collected. The solvent of each fraction was evaporated and then subjected to a series of spectroscopic analyses.

HPLC apparatus and assay conditions

An Alcott 760 HPLC pump system (Norcross, GA, USA) equipped with a Linear UVIS-206 detector (Reno, NV, USA), a DATAAPEX Clarity chromatography station, a CSW 1.7 integrator (Prague, Czech Republic) and a GL Sciences preparative Inertsil 5 ODS-3V column (Tokyo, Japan) of 4.6 i.d. × 250 mm was used with a mobile phase of CH₃OH–CH₃CN–H₂O (deionized water containing 1% acetic acid; 20:40:40, v/v/v). The UV detector was set at 247 nm. A manual Hamilton (Bonaduz, Switzerland) 80565 injector was used with the flow rate controlled to 15 mL/min. The volume of each injection was 200 µL.

GC-MS instrument

Analysis was conducted on a GC (CP-3800, Varian Associates, San Jose, CA, USA) equipped with an ion trap MS detector (Saturn 2000, Varian Associates) and a capillary column (DB-5ms; length, 30 m; film thickness, 0.25 mm; diameter, 0.25 mm; J&W Scientific, USA), in splitless mode (10 psi, split ratio = 20) using helium as the carrier gas. The split vent was opened 1 min after starting the analysis. Injection volume was 1 µL with the injection port and ion trap temperatures set at 280 and 250°C, respectively. Column temperature was initially maintained at 100°C for 2 min and then increased to 250°C at a rate of 10°C/min. When the column temperature had reached at 250°C for 10 min, it was increased again to 280°C at a rate of 10°C/min and maintained at that level for another 5 min. MS analysis was carried out using EI auto mode with an MS scan speed of 1.2 scan/s.

Various spectrometers

For NMR, a Brüker (Ettlingen, Germany) ACE-500 FT-NMR (500 MHz) spectrometer was used. All samples including FB and the photoproducts were prepared by their dissolution in CDCl₃ to concentrations of about 10 mg/mL. Distortionless enhancement by polarization transfer (DEPT) was adopted to distinguish quaternary carbons. Two-dimensional NMR of heteronuclear multiple quantum coherence (HMQC) was used for determining the ¹J (C, H) correlation, and heteronuclear multiple bond connectivity (HMBC) for showing the ²J (C, H) and ³J (C, H) long-range coupling relations. FB and its photoproducts contain ¹⁹F atoms at 3-positions of the biphenyl groups, which showed characteristic ¹H–¹⁹F and ¹³C–¹⁹F coupling constants along with the chemical shifts of all signals (Tables 1 and 2). Chemical shifts, δ, in ppm of ¹H and ¹³C NMR spectra were measured with respect to CHCl₃ (7.26 and 77.00 ppm for ¹H and ¹³C, respectively).

Table 1. ^1H NMR data of FB and its photoproducts^a

Hydrogen at	B (FB)	A	C	D	E
C2	7.15 ^b (1H, d, $J_{\text{HF}} = 12$) ^c	7.20 (1H, d, $J_{\text{HF}} = 11$)	7.75 (1H, d, $J_{\text{HF}} = 12$)	7.15 (1H, d, $J_{\text{HF}} = 12$)	7.14 (1H, d, $J_{\text{HF}} = 13$)
C6	7.18 (1H, d, $J = 8.3$) ^d	7.24 (1H, d, $J = 6.4$)	7.82 (1H, d, $J = 7.8$)	7.17 (1H, d, $J = 8.3$)	7.17 (1H, d, $J = 8.1$)
C5	7.41 (1H, dd, $J = 8.2$, $J_{\text{HF}} = 8.2$)	7.38 (1H, dd, $J = 7.6$, $J_{\text{HF}} = 7.6$)	7.56 (1H, dd, $J = 7.8$, $J_{\text{HF}} = 7.8$)	7.41 (1H, dd, $J = 8.0$, $J_{\text{HF}} = 8.0$)	7.39 (1H, dd, $J = 8.0$, $J_{\text{HF}} = 8.0$)
C2' and C6'	7.53 (2H, d, $J = 7.7$)	7.54 (2H, d, $J = 7.2$)	7.59 ($J=2\text{H}$, d, $J = 7.5$)	7.55 (2H, d, $J = 7.7$)	7.54 (2H, d, $J = 7.8$)
C3' and C5'	7.44 (2H, t, $J = 7.5$)	7.45 (2H, t, $J = 7.2$)	7.49 (2H, t, $J = 7.4$)	7.45 (2H, t, $J = 7.6$)	7.44 (2H, t, $J = 7.6$)
C4'	7.37 (1H, t, $J = 7.3$)	7.36 (1H, t, $J = 6.8$)	7.43 (1H, t, $J = 7.2$)	7.38 (1H, t, $J = 7.4$)	7.36 (1H, t, $J = 7.2$)
C7	3.79 (1H, q, $J = 7.0$)	4.94 (1H, q, $J = 6.4$)	—	3.78 (1H, q, $J = 7.2$)	3.79 (1H, q, $J = 7.2$)
C8	1.57 (3H, d, $J = 7.0$)	1.53 (3H, d, $J = 6.4$)	2.54 (3H, s)	1.56 (3H, d, $J = 7.2$)	1.55 (3H, d, $J = 7.2$)
C9	—	—	—	—	—
C10	—	—	—	3.72 (3H, s)	3.74 (2H, q, $J = 7.2$)
C11	—	—	—	—	1.25 (3H, t, $J = 7.2$)

^a In CDCl_3 at 298 K; ^b Chemical shift (δ) in ppm; ^c $J(^1\text{H}, ^{19}\text{F})$ and ^d $J(^1\text{H}, ^1\text{H})$ in Hz.**Table 2.** ^{13}C NMR data of FB and its photoproducts^a

Carbon	B (FB)	A	C	D	E
1	141.0 ^b (7 ^c)	147.4 (7)	138.7 (7)	141.8 (7)	142.0 (8)
2	115.4 (24)	113.1 (23)	116.7 (37)	115.2 (23)	115.2 (24)
3	159.7 (249)	159.8 (248)	160.5 (250)	159.6 (249)	159.7 (248)
4	128.1 (14)	128.0 (14)	134.7 (14)	127.8 (14)	127.7 (14)
5	130.9 (4)	130.8 (4)	131.8 (3)	130.9 (4)	130.7 (3)
6	123.6 (3)	121.2 (3)	125.2 (3)	123.5 (3)	127.0 (3)
1'	135.4	135.6	135.5	135.4	135.4
2' and 6'	128.9 (3)	128.9 (3)	129.8 (3)	128.9 (3)	128.9 (2)
3' and 5'	128.4	129.1	129.5	128.4	128.4
4'	127.7	127.6	129.3	127.6	127.6
7	44.7	69.6	197.3	44.9	45.1
8	18.0	25.2	27.5	18.4	18.4
9	179.0	—	—	174.4	174.0
10	—	—	—	52.2	61.0
11	—	—	—	—	14.1

^a In CDCl_3 at 298 K; ^b Chemical shift (δ) in ppm; ^c $J(^{13}\text{C}, ^{19}\text{F})$ in Hz.

For IR, a Bio-Rad Digilab (Cambridge, MA, USA) FTS-40 FT-IR was used. Each sample was mixed with KBr in a 1:100 (w/w) ratio to make the disc for taking the IR spectrum.

For UV, a Helions Alpha (Unicam Instrument, Cambridge, UK) was used. Each sample of approximately 100 μm in methanol was prepared and placed in a quartz cell for measurement of the UV spectrum.

Characterization of flurbiprofen and its photoproducts by spectroscopic methods

A, 1-(3-fluorobiphenyl)ethanol. Pale yellow liquid. IR (KBr) in cm^{-1} : $\nu = 3390$ (O—H stretching), 2971 (weak, C—H

stretching), 1268 (medium, C—F stretching), 1075 (C—O stretching), 875, 698. UV, λ_{max} in nm (absorbance): 207 (1.798), 245 (1.084). EI-MS (70 eV), m/z (relative intensity, %): 216 (86), 201 (78), 199 (10), 173 (43), 153 (100), 77 (18), 51 (17).

B(FB), 2-(3-fluorobiphenyl)propanoic acid. M.P. 113–114°C. IR (KBr) in cm^{-1} : $\nu = 2935$ (weak, C—H stretching), 1701 (strong, C=O stretching), 1419 (medium, C—O—H bending), 1216 (medium, C—F stretching), 875, 698 (medium). UV, λ_{max} in nm (absorbance): 205 (0.874), 247 (0.458). EI-MS (70 eV), m/z (relative intensity, %): 244 (49), 199 (100), 183 (22), 178 (30), 170 (25), 152 (21), 133 (11), 77 (20), 51 (14).

C, (3-fluoro-4-phenyl)acetophenone. M.P. 116–118°C. IR (KBr) in cm^{-1} : ν = 2952 (weak, C—H stretching), 1738 (strong, C=O stretching), 1278 (medium, C—F stretching), 887, 699. EI-MS (70 eV), m/z (relative intensity, %): 214 (65), 100 (100), 170 (54), 151 (10). UV, λ_{max} in nm (absorbance): 206 (1.697), 251 (0.793).

D, methyl, 2-(3-fluorobiphenyl)propanoate. Yellow liquid. IR (KBr) in cm^{-1} : ν = 2954 (weak, C—H stretching), 1736 (strong, C=O stretching), 1222 (medium, C—F stretching), 1063 (C—O—C stretching), 850, 765, 585. UV, λ_{max} in nm (absorbance): 207 (1.928), 225 (0.880), 247 (1.348). EI-MS (70 eV), m/z (relative intensity, %): 258 (59), 199 (100), 178 (23), 170 (11), 77 (7).

E, ethyl, 2-(3-fluorobiphenyl)propanoate. Pale yellow liquid. IR (KBr) in cm^{-1} : ν = 2957 (weak, C—H stretching), 1737 (strong, C=O stretching), 1226 (medium, C—F stretching), 1064 (C—O—C stretching), 767, 585. UV, λ_{max} in nm (absorbance): 206 (1.445), 247 (0.974). EI-MS (70 eV), m/z (relative intensity, %): 272 (43), 199 (100), 179 (17), 77 (5).

RESULTS AND DISCUSSION

HPLC chromatogram of flurbiprofen after photoirradiation

In this study, 10 mM of FB in methanol (or ethanol) was placed in a photochemical reactor and subjected to irradiation under a normal atmosphere for 14 (or 10) days. After the HPLC analyses, four major photoproducts were observed from the chromatogram. Their retention times in methanol are arranged in increasing order of **A**, 13.3; **B (FB)**, 17.1; **C**, 21.8 and **D**, 39.0 min [shown in Fig. 1(a)]; in ethanol, **A**, 13.3; **B (FB)**, 17.4; **C**, 21.6 and **E**, 66.8 min [Fig. 1(b)]. Using the prepara-

tive column, each fraction was collected with the solvent evaporated and carried out by various spectroscopic analyses. In addition to the chemical shifts, ^1H and ^{13}C NMR exhibit the coupling constants of H&bond;F, C&bond;F of all components (Tables 1 and 2), thus facilitate the identification of C3 and its vicinal C and H signals clear and unambiguous. The structures of **A**, **B** and **C** were 1-(3-fluorobiphenyl)ethanol, 2-(3-fluorobiphenyl)propanoic acid (**FB**) and (3-fluoro-4-phenyl)acetophenone, respectively. **D** and **E** were identified as the methyl and ethyl esters of FB, which were resulted from the esterification process.

GC-MS features of flurbiprofen and photoproducts

In methanol, the GC total ion chromatogram showed 11 signals (excluding some minor components) between retention times (RTs) of 15 and 24 min, which were numbered in sequence from compound **1** to **11** (Fig. 2). The tailing of compound **11 (FB)** was obviously caused by its successive intermolecular hydrogen bonding of the carboxyl groups.

Developments over the last few decades have made GC linking to quadrupole ion trap mass spectrometer an excellent tool for biomolecular analysis. Stafford *et al.* (1984) made two major advances. First, they developed the mass-selective instability mode operation that all ions created over a given time period were trapped and then sequentially ejected from the ion trap into a conventional electron multiplier detector. Thus, all ions were stored while mass analysis was performed, unlike the mass-selective stability mode of operation where only one value of m/z at a time was stored. Second, a helium gas of about 1 mtorr within

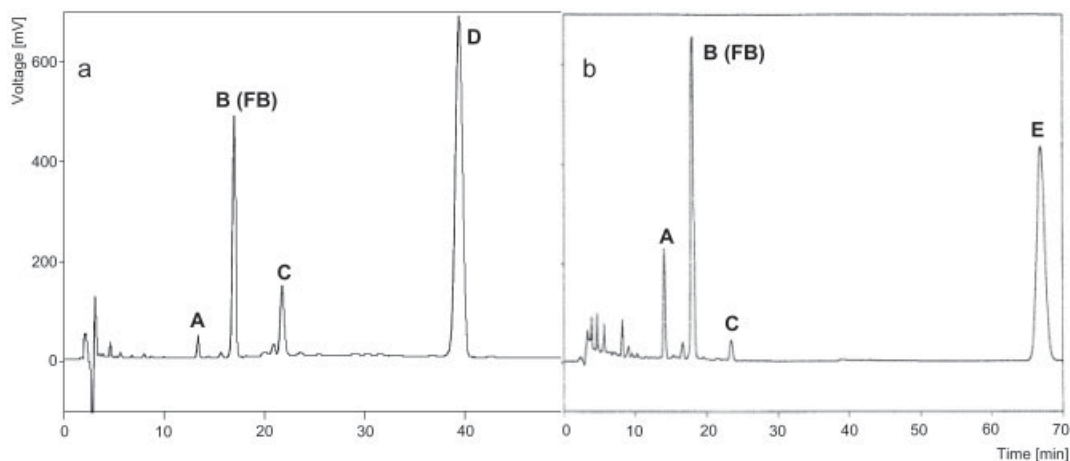


Figure 1. (a) HPLC chromatogram of flurbiprofen after photoirradiation for 14 days in methanol; (b) HPLC chromatogram of flurbiprofen after photoirradiation for 10 days in ethanol. Column, Inertsil 5 ODS-3V (4.6 i.d. $\times$ 250 mm); mobile phase, $\text{CH}_3\text{OH}:\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (1% AcOH added) = 20:40:40 (v/v/v).

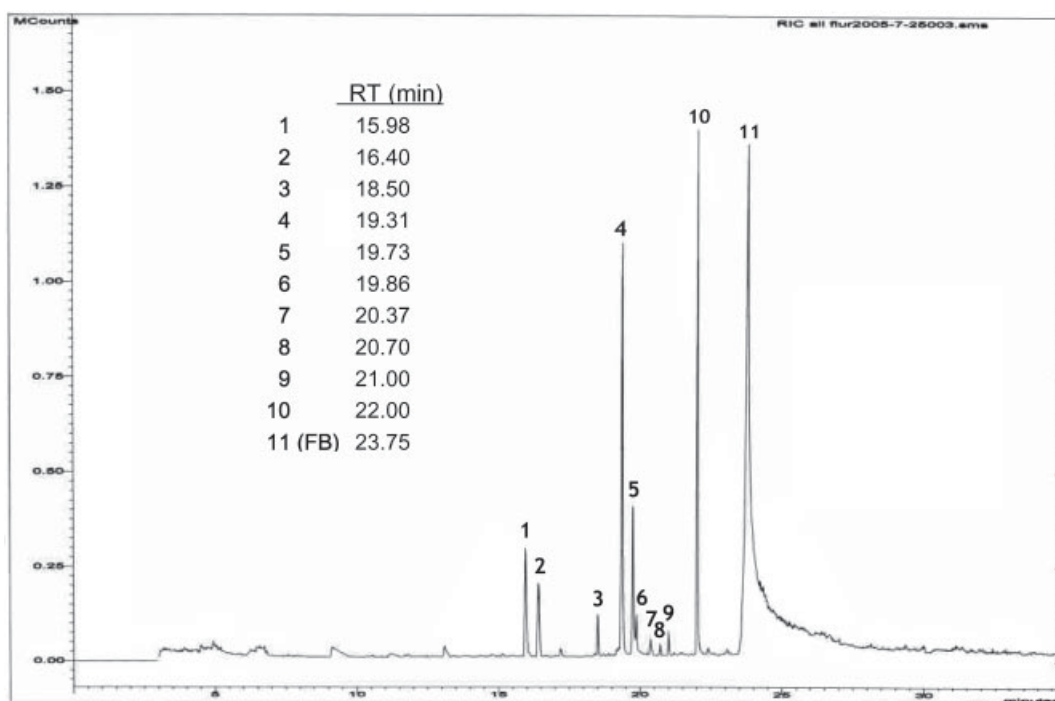


Figure 2. GC total ion chromatogram of flurbiprofen and photoproducts.

the trapping volume greatly improved the mass resolution of the instrument. In this study, four components were resolved from HPLC vs 11 from GC-MS in the separation processes with sharp signals and peak symmetry indicating the latter method is the more sensitive one.

Structural characterization of photoproducts of FB by GC-MS

Photodechlorination was reported for the carprofen series (Chen *et al.*, 2003; Sheu *et al.*, 2003). However, photodefluorination of FB and its photoproducts were not observed in this case under comparative conditions implying stronger bond enthalpy of C-F than C-Cl (484 vs 338 kJ/mol). Sixteen 8 W low-pressure quartz mercury lamps were irradiated at 306 nm, which was equivalent to an irradiation energy of 392 kJ/mol (Turro, 1991); the energy supplied was not strong enough to break a C—F bond. Using GC-MS (EI-MS) and the fragmentation patterns provided all the necessary information in elucidation of the chemical structures of 11 photoproducts in methanol with their IUPAC names listed in Table 3. Starting from **11**, the major photolytic route proceeds by the typical decarboxylation to generate **1**; the following oxidation produced **4** and **5** (a ketone and an alcohol); esterification to form **10** is a common occurrence. Solvent (CH₃OH) participation in the addition to C=C of photoproduct

2 becoming **3** (route a) and **6** (route b) and addition to C=O bond of forming hemiacetal **7** from photoproduct **4** (route c) were observed. Protonation of photoproduct **11** becoming **9** and dehydrogenation (immediate after oxidation, dehydration) of **1** (or **5**) becoming **2**; **3** becoming **8** prevailed. The formation of all photoproducts after irradiation occurred at the propionic acid side chain of FB with the biphenyl ring intact (Scheme 1).

Pharmacological effect of NSAIDs and photoproducts

If phototoxicity is related to NSAIDs and photoproducts, some pharmacological effects must be tested. Recently in our laboratory, the methyl ester of indomethacin has been demonstrated to inhibit prostaglandin E₂ (PGE₂), NO production, inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX 2) protein expression. The ester also exhibited strong cytotoxicity in promyelocytic leukemia HL-60 cells (Chao *et al.*, 2005). The pharmacological effects of FB and photoproducts are currently under investigation.

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Table 3. Structure elucidation of photoproducts by GC-MS after photolysis of flurbiprofen

Compound	Retention time (min)	MW (g/mol)	EI-MS: <i>m/z</i> (relative abundance)	Fragmentation sites	Chemical structure ^a
1	15.98	200	133 (4), 152 (3), 165 (10), 170 (6), 178 (2), 183 (12), 185 (100), 200 (76)		
2	16.40	198	50 (7), 85 (4), 133 (3), 151 (2), 165 (4), 170 (7), 177 (8), 180 (10), 198 (100)		
3	18.50	230	150 (4), 170 (8), 199 (25), 215 (100), 230 (21)		
4 (C)^b	19.31	214	150 (3), 170 (25), 199 (100), 214 (53)		
5 (A)	19.73	216	153 (68), 173 (60), 199 (53), 201 (73), 216 (100)		
6	19.86	230	85 (8), 125 (3), 153 (5), 170 (23), 199 (100), 216 (10), 230 (78)		
7	20.37	245	170 (10), 199 (28), 215 (100), 245 (3)		
8	20.70	228	151 (40), 170 (12), 183 (20), 198 (23), 213 (8), 209 (13), 228 (100)		
9	21.00	245	151 (21), 199 (30), 228 (61), 229 (100), 245 (15)		
10 (D)	22.00	258	152 (3), 178 (10), 183 (7), 199 (100), 258 (78)		
11 (B)	23.75	244	152 (3), 170 (3), 179 (15), 183 (10), 199 (100), 244 (88)		

^a IUPAC names: **1**, 2-fluoro-4-ethylbiphenyl; **2**, 2-fluoro-4-vinylbiphenyl; **3**, methyl 1-(3-fluorobiphenyl)ethyl ether; **4**, (3-fluoro-4-phenyl)acetophenone; **5**, 1-(3-fluorobiphenyl)ethanol; **6**, 2-(3-fluorobiphenyl)propan-1-ol; **7**, 1-methoxy-1-(3-fluorobiphenyl)ethanol (hemiacetal of **4**); **8**, methyl 1-(3-fluorobiphenyl)vinyl ether; **9**, protonation of **11**; **10**, methyl 2-(3-fluorobiphenyl)propanoate; **11**, 2-(3-fluorobiphenyl)propanoic acid (FB).

^b Photoproducts isolated by HPLC.

