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Photochemical behavior of the drug atorvastatin in water

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Abstract—Atorvastatin undergoes a self-sensitized photooxygenation by sunlight in water. The main photoproducts, isolated by chromatographic techniques, have been identified by spectroscopic means. They present a lactam ring arising from an oxidation of pyrrole ring and an alkyl/aryl shift. A mechanism involving singlet oxygen addition and an epoxide intermediate is suggested.

1. Introduction

Atorvastatin calcium is one of the most prescribed drugs in the US and in Europe.[1] It is a synthetic lipid-lowering agent and is widely used in the prevention of cardiovascular events. It is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Moreover, recently it has been observed that atorvastatin, like other statin drugs, can be efficient against Alzheimer's disease.[2] Less than 5% of a dose of atorvastatin is recovered in urine following oral administration. The presence of atorvastatin in sewage effluents and surface waters has been observed in concentration at μg/l levels.[3] The presence of pharmaceuticals in surface and ground waters is an increasingly relevant issue in environmental chemistry.[4] These substances enter into the aquatic environment, and thus they are potential pollutants for the aquatic ecosystem, possibly with adverse effects on aquatic organisms. The occurrence of pharmaceuticals in surface waters has been extensively reviewed, but data on the fate of these xenobiotics in the environment are still limited. These chemicals can be transformed through abiotic processes (hydrolysis, photolysis) into different products, and many searches are now addressed to the identification of these transformation products.[5–8]

In this context, we decided to study the photo-induced transformation processes of atorvastatin in water. Particular attention has been focused on the isolation and characterization of its main photoproducts as well as to the elucidation of the possible mechanistic pathways that lead to the observed products.

2. Results and discussion

Preliminary experiments showed that the drug was recovered unchanged by keeping it in the dark in aqueous solution (at different pHs) even after 30 days.

The photochemical behavior of atorvastatin in water was then studied under different conditions. First of all a solution of atorvastatin (10 μM) was exposed to natural sunlight. The ^{1}H NMR analysis of the irradiation mixture showed the presence of the drug and several products. In order to get amounts of photoproducts suitable for spectroscopic analyses, a series of irradiation experiments were performed on a preparative scale. A dispersion of the drug (80 mg/l) was irradiated by a solar simulator and the irradiation was monitored by RP-TLC analysis. After 14 days, the irradiation mixture was analyzed by NMR spectroscopy revealing that atorvastatin was completely transformed. The same photoproducts as in sunlight irradiation were observed by NMR and RP-TLC analyses. The main photoproducts were then separated by chromatographic techniques employing several stationary and mobile phases. Repeated column/TLC chromatographies and preparative HPLC of the mixture were necessary to isolate compounds **2–5** (Fig. 1).[9] Careful NMR analysis of the fractions containing **5** showed the presence of very close double signals, which were attributed to two diasteromers. The latter could be separated as methyl esters after performing a methylation reaction with CH_2N_2.[10]

The structures for all compounds were elucidated by NMR techniques (COSY, TOCSY, HSQC, HMBC, NOESY) and MALDI-MS experiments.

Keywords: Atorvastatin; Pyrroles; Pyrrol-2(3*H*)-ones; Photooxygenation; 1,2-Migration.
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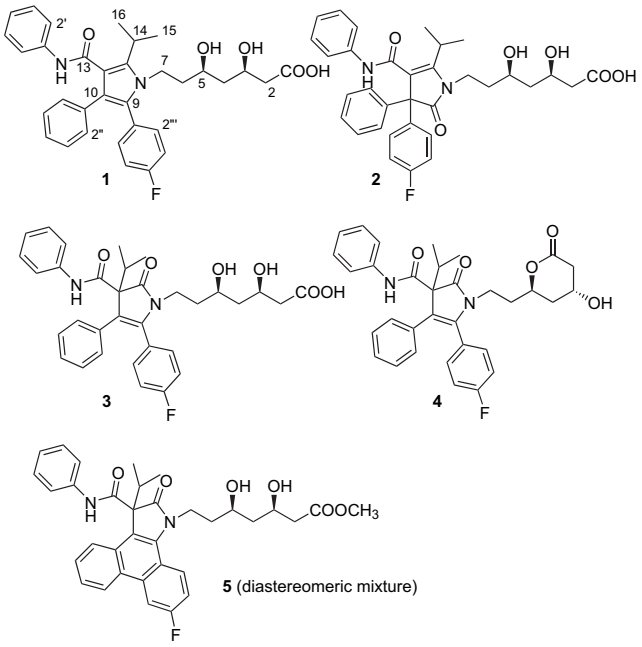


Figure 1. Structure of atorvastatin and photoproducts **2**–**5**.

Compound **2** showed a molecular peak at *m/z* 575 $[M+H]^+$ in the MALDI-MS spectrum suggesting, along with the elemental analysis, a molecular formula $C_{33}H_{34}FN_2O_6$. The UV spectrum revealed a band at 203 nm. In the ^1H NMR spectrum, 14 aromatic protons were present in the 7.00–7.40 ppm range; furthermore three methine at δ 4.17, 3.76, and 3.27, eight methylene protons at δ 3.76, 2.40, 1.85, and 1.66, and two methyls at δ 1.45 were in the aliphatic region. The ^{13}C NMR spectrum showed 27 carbon signals. The DEPT spectrum showed two methyls, four methylenes, and eleven methines. A close inspection of the ^1H and ^{13}C NMR spectra of **2** by DEPT and HSQC experiments and comparison with the spectral data for atorvastatin **1** revealed the presence of the following functionalities: three carbonyl groups, one quaternary sp^3-carbon (C-10), three aliphatic methines (C-3, C-5, and C-14), the first two bearing oxygen, four aliphatic methylene carbons (C-2, C-4, C-6, and C-7), two methyls (C-15 and C-16), two quaternary sp^2-carbons (C-11 and C-12), two monosubstituted aromatic rings (C-1′–C-6′, C-1″–C-6″), and one disubstituted aromatic ring (C-1‴–C-6‴). The connection of these functional groups was determined on the basis of ^1H–^1H COSY and HMBC correlations. Long-range correlations from the H-7 protons at δ 3.76 to the carbonyl carbon (δ 181.4) and C-12 (δ 153.4), the H-14 proton at δ 3.27 to the C-11 (δ 119.3) and C-12 quaternary carbons, the latter also correlated with H-14/H-15 methyls in the HMBC spectrum indicating the presence of 1-*H*-pyrrol-2(3*H*)-one. The correlation from H-2″/H-6″ and H-2‴/H-6‴ protons (δ 7.30 and 7.34) to the C-10 (δ 66.6) indicated the linkage of two phenyl groups at the sp^3 quaternary carbon. These correlations were consistent with structure **2**.

Compound **3** showed a molecular peak at *m/z* 575 $[M+H]^+$ in the ESI-MS spectrum suggesting, along with the elemental analysis, a molecular formula $C_{33}H_{34}FN_2O_6$. The UV spectrum revealed a band at 204 nm. The ^{13}C NMR spectrum showed 27 carbon signals. The DEPT spectrum showed two methyls, four methylenes, and eleven methines. A close inspection of the ^1H and ^{13}C NMR spectra of **3** by DEPT and HSQC experiments and comparison with the spectral data for the atorvastatin **1** revealed the presence of the following functionalities: three carbonyl groups, one quaternary sp^3-carbon (C-11), three aliphatic methines (C-3, C-5, and C-14), two of them bearing oxygen, four aliphatic methylene carbons (C-2, C-4, C-6, and C-7), two methyls (C-15 and C-16), two quaternary sp^2-carbons (C-9 and C-10), two monosubstituted aromatic rings (C-1′–C-6′, C-1″–C-6″), and one disubstituted aromatic ring (C-1‴–C-6‴). The connection of these functional groups was determined on the basis of ^1H–^1H COSY and HMBC correlations. Long-range correlations from the H-7 protons at δ 3.79 and 3.56 to the carbonyl carbon (δ 178.2) and C-9 (δ 140.4), the H-14 proton at δ 2.67 to C-10 (120.0), C-11 (δ 69.9), C-12, and C-13; C-11 also correlated with H-14/H-15 methyls in the HMBC spectrum indicating the presence of 1-*H*-pyrrol-2(3*H*)-one. These correlations were consistent with the structure **3** as depicted.

According to the δ lactone structure, a molecular ion at *m/z* 579 $[M+Na]^+$ in the ESI-MS was present for compound **4**. The ^1H–^1H COSY experiment showed a correlation series beginning with signal of a methylene at δ 3.79 and 3.56 assigned to H-7 to methylene at δ 1.85, which in turn was coupled with methine at δ 4.52. This latter was correlated to methylene at δ 1.77, which in turn was coupled with methine at δ 4.16 correlated with methylene at δ 2.59 and 2.42. Two doublets were attributed to two methyls at δ 1.16 and 0.95 correlated to methine at δ 2.78. The ^{13}C NMR spectrum of **4** showed 27 carbon signals due to two methyls, four methylenes, eleven methines, and ten quaternary carbons. An HMQC experiment allowed to assign the protons to the corresponding carbons. In the HMBC spectrum, H-7 protons were correlated with C-5, C-9, and C-12, while the H-14 proton was correlated with the C-10, C-11, C-12, C-13, C-15, and C-16. The multiplet at δ 4.52 (H-5) was correlated with C-1 and C-3, while H-3 was correlated with C-1, C-2, and C-5, thus completely dating the structure of **4**.

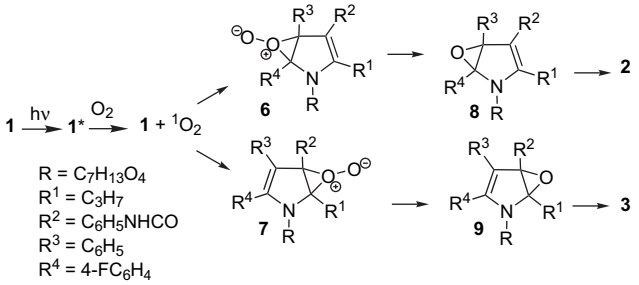
Compound **5** was a ca. 1:1 mixture of diasteromers, which were separated and characterized as methyl esters. One isomer of **5** showed a molecular peak at *m/z* 587 $[M+H]^+$ in the ESI-MS spectrum suggesting, along with the elemental analysis, a molecular formula $C_{34}H_{35}FN_2O_6$. The ^1H NMR spectrum showed the presence of one aromatic ring with three coupled protons, which were also coupled with fluorine atom, and resulted as two double doublet at δ 8.51 (H-6‴), 8.45 (H-3‴) and a double double doublet at δ 7.45. Furthermore, four protons of a 1,2 disubstituted aromatic ring at δ 8.76 (H-6″), 8.60 (H-3″), as doublets and at δ 7.69 (H-5″) and 7.60 (H-4″) as triplets and a phenyl group (H-2′–H-6′) were present in the aromatic region. The aliphatic region of ^1H NMR spectrum presented the usual C7 chain, the isopropyl group, and a methyl. In the ^{13}C NMR spectrum, 30 carbon signals were present, and the DEPT experiment evidenced three methyls, four methylenes, and thirteen methines. The ^1H and ^{13}C resonances were assigned by combination of COSY, DEPT, HMQC, and HMBC experiments. In particular, the HMBC spectrum showed cross-peaks of both the H-7 and H-14 with carbonyl (C-12), the first was correlated with C-5 and C-9, both the H-14 and the

methyls (H-15 and H-16) with the C-11, and the first with C-10 and C-13 carbons. These data indicated the presence of 1-*H*-pyrrol-2(3*H*)-one. In the HMBC spectrum, correlations between H-6‴ and C-9, C4‴, and C3‴ carbons, H-2″ and C-10, C-2″, and C-4″ carbons, and H-3″ and C-2‴ and C-5″ indicate a phenathrene unit.

The other isomer of **5** had the molecular formula $C_{34}H_{35}FN_2O_6$ as deduced from the molecular peak at *m*/*z* 587 $[M+H]^+$ in the ESI-MS spectrum. The general features of the NMR spectra closely resembled those of its isomer, except for the shift of the methyl signals and 6″ methine.

As shown in Figure 1, all photoproducts characterized arise from an oxidation of pyrrole ring and an alkyl/aryl shift with formation of a lactam ring. In addition, compounds **4** and **5** derive from **3** via lactonization and cyclization, respectively. To get information on the possible pathways leading to compounds **2**–**5**, irradiation experiments were run under different conditions, and to shorten the reaction times UV-lamp (Pyrex filter) was used as light source. With this lamp, the drug was converted to compounds **2**–**5** in 8 h (~70%). When the irradiation was carried out under argon atmosphere, the drug was recovered unreacted, confirming that O_2 was directly involved in the phototransformation. Degradation slowed down in the presence of a radical inhibitor as 3-*tert*-butyl-4-anisole (BHA), while it was completely inhibited by sodium azide (NaN_3), a well-known quencher of singlet oxygen. Moreover, when the photooxygenation was carried out in the presence of Rose Bengal, a typical singlet oxygen sensitizer, the reaction was complete already after 8 h. NMR analysis and TLC showed that atorvastatin was transformed in compounds **2**–**5** as main photoproducts.

These data suggest that singlet oxygen may be involved in the photodegradation of the drug and, hence, a Type II (singlet oxygen-mediated) photooxygenation may occur.[11] It is well known that pyrroles are good substrates for singlet oxygen. They often give a mixture of products derived both from 2,5- and 2,3-oxygen addition as well as from hydroperoxides or zwitterionic intermediates, depending on the reaction conditions and on the substituents, and the question of primary adducts is still an open point.[12] Anyhow, hydroxylactams have sometime been found as photooxygenation products from α- or α,α′-unsubstituted pyrroles.[12] So, on the basis of experimental results and literature data a plausible mechanistic interpretation is reported in Scheme 1. The first step should be an energy transfer from the excited drug to oxygen producing singlet oxygen. Then, a 2,3-oxygen addition to the pyrrole moiety probably occurs to give



Scheme 1. Suggested pathways for compounds **2** and **3**.

perepoxides **6** or **7**, which evolve to epoxides **8** or **9**.[13] Migration of the aryl or alkyl moiety gives pyrrolones **2** or **3**, respectively.[14]

Epoxides **8** and **9** were not detected in our experiments, probably due to their easy rearrangement to the corresponding carbonyl compounds.[15] In order to prove the involvement of these intermediates, an oxidation reaction of atorvastatin was carried out by using dimethyldioxirane (DMD). This compound is a well-known epoxidizing agent for diverse unsaturated substrates from alkenes to aromatic compounds, and it reacts with *N*-acylindoles to give the corresponding epoxides that open to form 2-indolinones as rearranged products.[16] The reaction of **1** with DMD was carried out in acetone and after 4 h the reaction mixture showed the presence of compounds **2** and **3**.

Compounds **4** and **5** seem to arise from further modification of compound **3**. Lactonization of a six-membered ring of the dihydroxy heptanoic acid side chain affords compound **4**, while phenantrene **5** is formed through a well-known[17] process in the photochemistry of stilbene-like compounds. In particular, it would be formed by photochemical electrocyclization followed by oxidation, under aerobic conditions, of the dihydrophenantrene intermediate.

3. Conclusions

In conclusion, atorvastatin has been found to be sensitive to sunlight under aerobic conditions and the main photoproducts have been isolated and fully characterized by spectral means (NMR and MS). This behavior agrees with the observation reported in two recent works that atorvastatin is phototransformed with a quantum yield for direct photolysis of 4.5×10^{-3}.[9]

Our data evidenced that in the presence of light and oxygen, the drug is able to act as a self-sensitizer and generate singlet oxygen,[18] and this observation appears of particular interest in the field of photosensitization phenomena by drugs.[19]

4. Experimental

4.1. Chemicals

Atorvastatin calcium was obtained from KEMPROTEC Limited. This and all the other products were used without further treatment: Rose Bengal (RB, Aldrich), NaN_3 (Carlo Erba). Solutions and suspensions of atorvastatin were prepared using Milli Q water. All other solvents were of HPLC grade.

4.2. General procedures

HPLC experiments were carried out on an Agilent 1100 HPLC system equipped with an UV detector, the column used was a RP-18 column (Luna Prep C-18, 10 μm, 250×10 mm). Nuclear magnetic resonance (NMR) spectra were recorded at 500 MHz for [^{1}H] and 125 MHz for [^{13}C] on a Fourier Transform NMR Varian 500 Unity Inova spectrometer and at 400 MHz for [^{1}H] and 100 MHz for [^{13}C] on

a Bruker AC 400 spectrometer. The carbon multiplicity was evidenced by DEPT experiments. The proton couplings were evidenced by ^{1}H–^{1}H COSY experiments. The heteronuclear chemical shift correlations were determined by HMQC and HMBC pulse sequences. ^{1}H–^{1}H proximities through space within a molecule were determined by NOESY. Matrix assisted laser desorption ionization (MALDI) mass spectra were recorded using a Voyager-DE MALDI-TOF mass spectrometer. Electrospray mass spectra were recorded using a WATERS Z-Q mass spectrometer equipped with an electrospray ionization (ESI) probe operating in positive or negative ion mode. The scan range was 80–2000 *m/z*. UV–vis spectra were recorded in MeOH on a Perkin–Elmer Lambda 7 spectrophotometer. IR spectra were recorded in CH_2Cl_2 on a Nicolet 5700 FT-IR spectrometer. Reverse phase liquid chromatography was performed over Lichroprep RP-18 resin (Merck). Analytical TLC was performed on precoated Merck aluminum sheet (DC-Alufolien Kielselgel 60 F_{254}, 0.2 mm) or RP-18 F_{254} plates with 0.2 mm film thickness. The spots were visualized by UV light or by spraying with H_2SO_4/AcOH/H_2O (1:20:4). The plates were then heated for 5 min at 110 °C. Prep. TLC was performed on a Merck Kiesegel 60 F_{254} plates, with 0.5 or 1 mm film thickness.

4.3. Irradiation conditions

Irradiation experiments were performed with a 150 W solar simulator Oriel equipped with a Xenon lamp (spectral output 200–2400 nm) on a suspension of atorvastatin calcium (40 mg) in Milli Q water (500 ml), or solution 10 μM, in a Pyrex beaker for 14 days at room temperature.

An analogous preparation of atorvastatin calcium was exposed to sunlight for 14 days (on September in Naples) in an open Pyrex flask.

In an attempt to gain some mechanistic information, other irradiation experiments were performed using a photoreactor equipped with a 500 W high-pressure mercury lamp (through a Pyrex filter).

In a typical procedure, a suspension of atorvastatin calcium (10 mg in 20 ml of water) in the presence of a sensitizer (molar ratio atorvastatin:sens = 10:1 or as otherwise indicated) in an open Pyrex tube was irradiated at room temperature under stirring at a distance of 15 cm from the lamp.

NaN_3 and the pharmaceutical was used in a 1:3 molar ratio. In the experiment carried out under argon atmosphere, the suspension was saturated with the gas for 30 min before irradiation and then kept closed.

4.4. Photoproduct isolation

The suspension after 14 days irradiation by solar simulator was dried under vacuum, and the acetone-soluble reaction mixture (40 mg) was separated by silica-gel TLC eluting with the organic phase of the mixture AcOEt/EtOH/H_2O (3:1:5) to give five fractions.

Fractions 2 and 4 were pure photoproduct **2** (11 mg) and **3** (4 mg), while fractions 1, 3, and 5 were mixtures of several products.

Fraction 3 (8 mg) was chromatographed on silica-gel TLC eluting with CH_2Cl_2/MeOH (95:5) to afford photoproduct **4** (4 mg) and the diastereomeric mixture of **5** in small quantities.

In order to obtain greater quantities of these products, a suspension of atorvastatin was kept at sunlight exposure (40 mg) for 14 days. The irradiation mixture was dried under vacuum and chromatographed on a RP-18 resin open column eluting with CH_3CN/H_2O (1:1) to afford four fractions (A, B, C, and D). Fraction D was a crude mixture of photoproducts **5** (8 mg). To achieve the separation of the diasteroisomeric compounds, the mixture was subjected to methylation with excess of diazomethane in ether solution. Methylation was quantitative and the resulting mixture was separated on a RP-18 HPLC column eluting with CH_3CN/H_2O (1:1).

4.5. Reaction with dimethyldioxirane

A solution of DMD (~0.5–0.12 M) in acetone was obtained according to literature procedure.[20] To a solution of atorvastatin calcium (5 mg) in acetone (10 ml), 5 ml of the DMD solution (~0.5–0.12 M) in acetone were added under stirring. The reaction mixture was dried under vacuum and analyzed by ^{1}H NMR spectroscopy. NMR analysis evidenced the formation of photoproducts **3** and **4**.

4.6. Spectral data

4.6.1. Atorvastatin (1). UV λ_{max} (CH_3OH) nm: 206 (log ε 7.0); ν_{max} ($CHCl_3$) 2964, 1723, 1658, 1607 cm^{-1}; ESI-MS *m/z* (%): 597 (12), 581 (25), 559 (85), 415 (100); δ_H (500 MHz, CD_3OD) 7.55–6.98 (14H), 4.18 (2H, m, H-7a and H-3), 3.93 (1H, m, H-7b), 3.67 (1H, m, H-5), 3.40 (1H, m, H-14), 2.36 (1H, dd, *J* 10.2, 4.8 Hz, H-2a), 2.26 (1H, dd, *J* 10.2, 2.4 Hz, H-2), 1.70 (2H, m, H-6), 1.60 (1H, m, H-4), 1.50 (6H, d, *J* 7.2 Hz, H-15, H-16), 1.41 (1H, m, H-4); δ_C (125 MHz, CD_3OD) 181.5, 170.0, 164.5, 140.5, 139.8, 137.5, 135.5, 131.5, 130.6, 130.1, 129.4, 128.3, 126.6, 124.0, 122.0, 119.8, 117.2, 117.0, 69.6, 45.5, 44.7, 42.5, 42.0, 28.1, 23.3.

4.6.2. Compound 2. Colorless oil; UV λ_{max} (CH_3OH) nm: 203 (log ε 11.9); ν_{max} ($CHCl_3$) 3040, 2920, 2854, 1712, 1602, 1097 cm^{-1}; ESI-MS *m/z* (%): 613 (15), 597 (20), 575 (100). Anal. calcd for $C_{33}H_{35}FN_2O_6$: C, 68.97, H, 6.14, F, 3.31, N, 4.87. Found: C, 76.09, H, 6.05, F, 3.28, N, 4.84; δ_H (500 MHz, CD_3OD) 7.40–7.00 (14H), 4.17 (1H, m, H-3), 3.76 (3H, m, H-5, H-7), 3.27 (1H, m, H-14), 2.40 (2H, m, H-2), 1.85 (2H, m, H-6), 1.66 (2H, m, H-4), 1.45 (6H, d, *J* 6.5 Hz, H-15, H-16); δ_C (125 MHz, CD_3OD) 181.4 (C-9), 176.8 (C-1), 166.2 (C-13), 164.0 (C-4‴), 153.4 (C-12), 141.3 (C-1‴), 139.3 (C-1′), 132.4 (C-1″), 130.7, 130.2, 129.5, 126.2, 122.1, 119.3 (C-11), 116.7, 116.6, 68.7 (C-5), 68.3 (C-3), 66.6 (C-10), 45.0 (C-4), 43.9 (C-2), 39.6 (C-7), 37.7 (C-6), 28.5 (C-14), 21.4, 21.2 (C-15, C-16).

4.6.3. Compound 3. Amorphous white powder; UV λ_{max} (CH_3OH) nm: 204 (log ε 12.5); ν_{max} ($CHCl_3$) 2957, 2924, 2855, 1714, 1712, 1600, 1364, 1088 cm^{-1}; ESI-MS *m/z* (%): 613 (10), 597 (25), 575 (100). Anal. calcd for $C_{33}H_{35}FN_2O_6$: C, 68.97, H, 6.14, F, 3.31, N, 4.87. Found:

C, 76.10, H, 6.00, F, 3.29, N, 4.89; δ_H (500 MHz, CD_3OD) 7.53 (2H, d, *J* 8.0 Hz), 7.36 (4H, m), 7.12 (8H, m), 4.02 (1H, m, H-3), 3.79 (1H, m, H-7a), 3.72 (1H, m, H-5), 3.56 (1H, m, H-7b), 2.67 (1H, m, H-14), 2.38 (2H, m, H-2), 1.48–1.68 (4H, m, H-4, H-6), 1.18 (3H, d, *J* 6.8 Hz, H-15), 0.92 (3H, d, *J* 6.8 Hz, H-16); δ_C (125 MHz, CD_3OD) 178.2 (C-12), 175.8 (C-1), 168.6 (C-13), 164.0 (C-4‴), 140.4 (C-9), 135.3, 134.0, 132.0, 131.9, 130.3, 129.6, 128.8, 128.2, 126.4, 123.4, 120.0, 117.4, 117.2, 69.9 (C-11),69.6 (C-5), 68.6 (C-3), 45.0 (C-4), 44.1 (C-2), 39.9 (C-7), 36.2 (C-6), 33.5 (C-14), 18.8 (C-15), 17.9 (C-16).

4.6.4. Compound 4. Amorphous white powder; UV λ_{max} (CH_3OH) nm: 202 (log ε 0.42). ν_{max} ($CHCl_3$) 2925, 2854, 1730, 1700, 1605, 1428, 1236, 1157, 1074 cm^{-1}; MALDI-MS *m/z* (%): 579 (30), 556 (100). Anal. calcd for $C_{33}H_{35}FN_2O_6$: C, 71.21, H, 5.98, F, 3.41, N, 5.03. Found: C, 71.18, H, 6.00, F, 3.39, N, 5.00; δ_H (500 MHz, CD_3OD) 7.50–7.24 (6H, m), 7.16 (8H, m), 4.52 (1H, m, H-5), 4.16 (1H, m, H-3), 3.79 (1H, m, H-7a), 3.56 (1H, m, H-7b), 2.78 (1H, m, H-14), 2.59 (1H, dd, *J* 3.9, 17.6 Hz, H-2a), 2.42 (1H, dd, *J* 17.6 Hz, H-2a), 1.85 (2H, m, H-6), 1.77 (2H, m, H-4), 1.16 (3H, d, *J* 7.0 Hz, H-15), 0.95 (3H, d, *J* 7.0 Hz, H-16); δ_C (125 MHz, CD_3OD) 178.2 (C-12, C-13), 172.5 (C-1), 162.5 (C-4‴), 143.7 (C-9), 138.0, 135.1, 134.5, 134.1, 132.2, 130.3, 130.1, 129.6, 128.8, 126.6, 123.8, 122.2 (C-10), 117.4, 117.2, 76.1 (C-5), 63.6 (C-3), 39.4 (C-2, C-7), 35.6 (C-6), 33.1 (C-14), 18.8 (C-15), 17.6 (C-16).

4.6.5. Compound 5. Colorless oil (one diastereomer); UV λ_{max} (CH_3OH) nm: 204, 238, 332; ν_{max} ($CHCl_3$) 3481, 3334, 3010, 2932, 1717, 1697, 1601, 1450, 1314, 1163 cm^{-1}; ESI-MS *m/z* (%): 609 (44), 587 (100). Anal. calcd for $C_{33}H_{35}FN_2O_6$: C, 69.61, H, 6.01, F, 3.24, N, 4.78. Found: C, 69.58, H, 5.98, F, 3.25, N, 4.75; δ_H (500 MHz, CD_3OD) 8.76 (1H, d, *J* 9.0 Hz, H-6″), 8.60 (1H, d, *J* 9.0 Hz, H-3″), 8.51 (1H, dd, *J* 5.5, 9.5 Hz, H-6‴), 8.45 (1H, dd, *J* 2.0, 11.5 Hz, H-3‴), 7.69 (1H, t, *J* 7.0 Hz, H-5″), 7.60 (1H, t, *J* 7.0 Hz, H-4″), 7.49 (2H, d, *J* 8.0 Hz, H-2′, H-6′), 7.45 (1H, ddd, *J* 2.0, 9.5, 11.0 Hz, H-5‴), 7.29 (2H, t, *J* 8.0 Hz, H-3′, H-5′), 7.09 (1H, t, *J* 8.0 Hz, H-4′), 4.67 (1H, m, H-7a), 4.45 (1H, m, H-7b), 4.20 (1H, m, H-3), 4.02 (1H, m, H-5), 3.42 (1H, m, H-14), 2.44 (2H, m, H-2), 2.15 (1H, m, H-6a), 2.05 (1H, m, H-6b), 1.74 (2H, m, H-4), 1.35 (3H, d, *J* 6.5 Hz, H-15), 0.66 (3H, d, *J* 6.5 Hz, H-16); δ_C (125 MHz, CD_3OD) 179.2 (C-12), 173.0 (C-1), 165.5 (C-13), 162.0 (C-4‴), 137.6 (C-1′), 137.0 (C-9), 134.7 (C-2‴, C-1″), 129.1 (C-3′, C-5′), 129.0 (C-3″), 128.0 (C-2′, C-6′), 128.6 (C-5″), 127.1 (C-6″), 125.5 (C-6‴), 125.2 (C-4″), 124.9 (C-4′), 123.4 (C-3″), 120.7 (C-2′, C-6′), 120.0 (C-10), 118.2 (C-1‴), 116.1 (C-5‴), 109.5 (C-3‴), 69.3 (C-5), 69.0 (C-3), 66.4 (C-11), 42.0 (C-4), 41.4 (C-2), 40.0 (C-7), 37.2 (C-6), 35.6 (C-14), 18.2 (C-16), 17.7 (C-15). The other diastereomer. Colorless oil; UV λ_{max} (CH_3OH) nm: 204, 238, 332; ν_{max} ($CHCl_3$) 3481, 3334, 3010, 2932, 1717, 1697, 1601, 1450, 1314, 1163 cm^{-1}; ESI-MS *m/z* (%): 609 (44), 587 (100). Anal. calcd for $C_{33}H_{35}FN_2O_6$: C, 69.61, H, 6.01, F, 3.24, N, 4.78. Found: C, 69.58, H, 5.98, F, 3.25, N, 4.75; δ_H (500 MHz, CD_3OD) 8.68 (1H, d, *J* 8.0 Hz, H-6″), 8.58 (1H, d, *J* 8.0 Hz, H-3″), 8.49 (1H, dd, *J* 5.5, 9.5 Hz, H-6‴), 8.46 (1H, dd, *J* 2.0, 11.0 Hz, H-3‴), 7.67 (1H, t, *J* 7.5 Hz, H-5″), 7.59 (1H, t, *J* 7.5 Hz, H-4″), 7.45 (2H, d, *J* 8.5 Hz, H-2′, H-6′), 7.45 (1H, obscured, H-5‴), 7.25 (2H, t, *J* 8.5 Hz, H-3′, H-5′), 7.07 (1H, t, *J* 8.0 Hz, H-4′), 4.65 (1H, m, H-7a), 4.44 (1H, m, H-7b), 4.32 (1H, m, H-3), 4.18 (1H, m, H-5), 3.42 (1H, m, H-14), 2.48 (2H, m, H-2), 2.08 (2H, m, H-6), 1.68 (2H, m, H-4), 1.38 (3H, d, *J* 7.0 Hz, H-15), 0.63 (3H, d, *J* 7.0 Hz, H-16); δ_C (125 MHz, CD_3OD) 177.8 (C-12), 173.6 (C-1), 166.2 (C-13), 162.3 (C-4‴), 137.6 (C-1′), 137.0 (C-9), 134.5 (C-2‴, C-1″), 129.0 (C-3′, C-5′), 128.8 (C-3″), 128.1 (C-2′, C-6′, C-5″), 126.5(C-6″, C-6‴), 125.4 (C-4′, C-4″), 124.8 (C-3″), 123.4 (C-2′, C-6′), 119.3 (C-10), 118.2 (C-1‴), 116.1 (C-5‴), 109.5 (C-3‴), 70.5 (C-5), 69.1 (C-3), 52.1 (C-11), 42.4 (C-4), 41.5 (C-2), 40.9 (C-7), 37.6 (C-6), 35.0 (C-14), 18.4 (C-16), 17.5 (C-15).

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