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# Synthesis of new anticancer and anti-inflammatory isoxazolines and aziridines from the natural (-)-deltoin

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**Keywords**
(-)-deltoin; anti-5-lipoxygenase; anticancer; *Ferula lutea*; heterocycle derivatives

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## Abstract

**Objectives** This work describes the synthesis, the bioactivity and the structure–activity relationship of new derivatives from a natural coumarin.

**Methods** (-)-Deltoin **1** and the corresponding isoxazolines and aziridines were characterized by spectroscopic means. The cytotoxic (HTC-116, IGROV-1 and OVCAR-3 cancer cell lines) and 5-lipoxygenase activity of (-)-deltoin **1** and its structural analogues have been evaluated.

**Key findings** The phytochemical investigation of the ethyl acetate extract of the flowers of *Ferula lutea* (Poir.) Maire has led to the isolation of (-)-deltoin **1**. A series of new isoxazoline ***2a,a′–2f,f′*** and aziridine **3a**,**a′**–**3e**,**e′** derivatives have been prepared by 1,3-dipolar cycloaddition. It has been found that the derivatives **2a** ($IC_{50}$ = 3.3 ± 0.1 μM), **3a**,**a′** ($IC_{50}$ = 5.9 ± 0.1 μM), **3b**,**b′** ($IC_{50}$ = 6.1 ± 0.7 μM) and **3c**,**c′** ($IC_{50}$ = 7.3 ± 0.9 μM) bearing a phenyl isoxazoline, a phenylaziridine, a 4-methlphenylaziridine and a 4-methoxyphenylaziridine, respectively, are more cytotoxic than (-)-deltoin **1** ($IC_{50}$ = 14.3 ± 0.2 μM). The diastereoisomers in mixture (**2f**,**f′**) with a 6-chloropyridin-2-yl system have shown the best anti-5-lipoxygenase activity (% inhibition = 53.1 ± 4.8% at 200 μM).

**Conclusions** Some analogues have been found more bioactive than deltoin **1**. Their activity has been related to the nature of the added heterocycles. It would be interesting to evaluate their *in-vivo* activity.

## Introduction

Very beneficial to the well-being of humans are bioactive compounds containing fruits, vegetables and herbs.[1] Coumarin is a heterocyclic compound, which plays an important role in the domain of natural products and organic synthetic chemistry.[2] The coumarins are classified as simple coumarin, pyranocoumarins, furanocoumarins and coumarins substituted in the pyrone groups.[3] Coumarins that are found in many plants such as *Ferula* species are used in the form of crude drugs in traditional medication.[4] These natural compounds exhibit many biological effects.[5] Coumarins, naturally present in many plants, possess antioxidant, anticoagulant, anti-inflammatory, antimicrobial, anticancer and antiallergic properties.[6,7] The genus *Ferula*, belonging to the Apiaceae family,[8] presents interesting phytochemical features, such as the occurrence of furanocoumarins and coumarins.[9,10] *Ferula lutea* (Poir.) Maire (Apiaceae) is also called as *Ferulago lutea* (Poir.) Grande.[11,12] The roots of *F. lutea* were the subject of previous phytochemical investigation that led to the isolation of new dihydrofuranocoumarins as two inseparable isomers, (-)-5-hydroxyprantschimgin and (-)-5-hydroxydeltoin, together with eight known compounds, (-)-prantschimgin, (-)-deltoin, psoralen, xanthotoxin, umbelliferone, caffeic acid, β-sitosterol and stigmasterol.[13] The same work has indicated the significant cytotoxic activity of (-)-deltoin towards the human colorectal cancer cell lines HCT-116 and HT-29 with $IC_{50}$ values of 0.93 ± 0.11 μM and 7.6 ± 1.05 μM, respectively. The deltoin has been cited to be a hepatoprotective and a TNF-α inhibitor.[14]

Recently, there has been wide interest in compounds bearing isoxazoline moiety because of their unique chemical structure and broad spectrum of biological properties including antibiotic, antithrombolytic, antitumour, anti-HIV and cytotoxic activity.[15] On the other hand, among three-membered heterocycles, aziridines constitute a particular versatile class of molecule, and both physical and chemical properties of aziridines have been studied (theoretical and experimental investigations).[16] The antitumour drug (FR900482) containing aziridine is an example.[17] Many aziridine alkaloids have been proven to be anticancer, antibacterial or antimicrobial. This indicates that the presence of the aziridine ring in natural as well as synthetic compounds is essential for such activity.[18]

For the preparation of isoxazoline and aziridine rings, intermolecular [3 + 2] cycloaddition reaction of arylnitrile oxides and azidobenzenes, respectively, with alkenes represents an efficient and convergent method. It has been the subject of intense research over the last decade, due to its great synthetic value, and has been the most effective process to the synthesis of five-membered heterocycles, which are difficult to be prepared with other means.[16,19]

In view of broad biological activity of furanocoumarins, and as a part of our search for new five-membered heterocyclic compounds, we have suggested to investigate the behaviour of the bioactive (-)-deltoin **1** isolated quantitatively from the flowers of *F. lutea* towards a series of arylnitrile oxides and azidobenzenes as a dipole.[20] The reaction has been regiospecific and has led to a series of new derivatives with a better biological profile. The evaluation of the anti-inflammatory (5-lipoxygenase) and anticancer (HTC-116, IGROV-1 and OVCAR-3 cancer cell lines) activity of all the synthesized heterocycles has been studied and reported here.

## Materials and Methods

### Plant material

*Ferula lutea* flowers were collected from a river valley located at 15 km from the south side of the city of Beja (North West Tunisia), on April 2010, and identified by Professor Féthia Harzallah Skhiri, in the Laboratory of Vegetal Biology and Botanic, High Institute of Biotechnology of Monastir, Tunisia, and a voucher specimen (F.L.F-10) was deposited in the same laboratory.

### General methods

Desorption chemical ionization–high-resolution mass spectrometry (DCI-HRMS) has been run in a GCT 1$^{er}$ Waters, and the ESI$^+$ experiment has been evaluated by Shimadzu QP-1000 EX spectrometer. IR spectra have been recorded on a Perkin–Elmer Fourier transform FT-IR spectrophotometer (4000–400 cm$^{-1}$) using NaCl pellets. $^1$H (300 MHz) and $^{13}$C (75 MHz) NMR spectra have been recorded on a Bruker AM300 spectrometer, using $CDCl_3$ as solvent and none deuterated residual solvent as internal standard. Chemicals shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) in Hertz. Melting points have been determined on a Büchi 510 apparatus using capillary tubes and are uncorrected.

### Chemistry

#### *Extraction and isolation*

The fresh flowers of *F. lutea* (5.8 kg) have been macerated with MeOH/$H_2O$ (7:3, 25 l) at room temperature for 7 days. The corresponding aqueous extract has been obtained after filtration and evaporation of the organic solvent (MeOH) under reduced pressure. The aqueous residue has been extracted successively with ethyl acetate and *n*-butanol to obtain, after evaporation of the solvents, the corresponding extracts (56 and 220 g, respectively). The ethyl acetate extract (50 g) was further subjected to silica gel column chromatography with petroleum ether/ethyl acetate used as an eluent to obtain six fractions. The precipitation of the fraction 3 (13.63 g) in MeOH at −20 °C yielded 3.5 g of compound **1**.

#### *(-)-Deltoin 1*

MP: 104 °C, ([α] = −20.95, cc = 5 mg/ml, $CHCl_3$), $^1$H NMR ($CDCl_3$, 300 MHz): 7.65 (1H, d, *J* = 9.3 Hz, H-4), 7.31 (1H, s, H-5), 6.78 (1H, s, H-8), 6.27 (1H, d, *J* = 9.3 Hz, H-3), 6.06 (1H, qq, $J_1$ = 7.2 Hz; $J_2$ = 1.2 Hz, H-3″), 5.13 (1H, t, *J* = 9.0 Hz, H-2″), 3.33–3.28 (2H, m, H-3′a,b), 1.94 (3H, d, *J* = 7.2 Hz, H-5″), 1.72 (3H, d, *J* = 1.2 Hz, H-4″), 1.67 (3H, s, H-6′), 1.65 (3H, s, H-5′). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 167.2 (C-1″), 163.3 (C-2), 161.3 (C-7), 155.6 (C-8a), 143.6 (C-4), 137.6 (C-3″), 128.5 (C-6), 124.4 (C-5), 123.1 (C-2″), 112.1 (C-4a), 112.5 (C-3), 97.7 (C-8), 89.0 (C-2′), 65.8 (C-4′), 29.5 (C-3′a,b), 22.2 (C-6′), 20.4 (C-5′), 15.7 (C-4″), 15.4 (C-5″). ESI-MS m/z 329 [M+H]$^+$. On the basis of these data and the reported data for deltoin, the compound **1** has been assigned as (-)-Z-deltoin.

#### *Preparation of compounds 2a,a′-2f,f′*

The nitrile oxides were prepared according to the general procedure, generated from aldoximes by halogenation followed by an *in-situ* dehydrohalogenation.[20] To compound **1** (0.1 g, 0.32 mmol) in refluxing dichloromethane, the appropriate nitrile oxide (2 equiv.) has been added in the presence of triethylamine (2 equiv.) and the mixture has

been refluxed for 48 h. The resulting mixture has been washed with water to remove salts and then extracted with $CH_2Cl_2$. The organic layer has been dried over anhydrous $Na_2SO_4$. The solvent has been then removed under reduced pressure. The resulting residue has been purified by flash chromatography (cyclohexane/EtOAc (60:40)) to give the corresponding isoxazoline derivatives as separated diastereoisomers **2a**,**a′**–**2e**,**e′** except **2f**,**f′**.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 4,5-dimethyl-3-phenyl-4,5-dihydroisoxazole-4-carboxylate 2a**

Yield 40%; MP: 190 °C; IR band (NaCl) $cm^{-1}$: 1422 (C=N); $^1$H NMR ($CDCl_3$, 300 MHz, δ):7.64 (1H, d, $J$ = 9.6 Hz, H-4), 7.41–7.30 (5H, m, H-8″, H-9″, H-10″, H-11″, H-12″), 7.26 (1H, s, H-5), 6.60 (1H, s, H-8), 6.25 (1H, d, $J$ = 9.6 Hz, H-3), 4.94 (1H, dd, $J_1$ = 7.5 Hz, $J_2$ = 9.3 Hz, H-2′), 3.47 (1H, q, $J$ = 7.2 Hz, H-3″), 3.38–2.95 (2H, m, H-3′a,b), 1.66 (3H, s, H-6′), 1.61 (3H, s, H-5′), 1.52 (3H, s, H-4″), 1.21 (3H, d, $J$ = 7.2 Hz, H-5″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 169.7 (C-1″), 163.3 (C-2), 161.6 (C-7), 159.6 (C-6″), 155.9 (C-8a), 144.0 (C-4), 130.4 (C-7″), 129.0 (C-10″), 128.5 (C-6), 127.1 (C-8″, C-12″), 124.8 (C-9″, C-11″), 123.7 (C-5), 113.1 (C-4a), 112.5 (C-3), 97.9 (C-8), 90.0 (C-2′), 89.4 (C-2″), 84.2 (C-3″), 51.9 (C-4′), 29.8 (C-3′), 23.9, 22.2, 21.7, 14.1 (C-5′,C-6′, C-4″, C-5″); DCI-HRMS $[M+H]^+$ calcd. for $(C_{26}H_{25}NO_6)^+$: 447.1682, found: 447.1686.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 4,5-dimethyl-3-phenyl-4,5-dihydroisoxazole-4-carboxylate 2a′**

Yield 44%; MP: 136 °C; IR band (NaCl) $cm^{-1}$: 1422 (C=N); $^1$H NMR ($CDCl_3$, 300 MHz, δ): 7.62 (1H, d, $J$ = 9.6 Hz, H-4), 7.56–7.38 (5H, m, H-8″, H-9″, H-10″, H-11″, H-12″), 7.26 (1H, s, H-5), 6.75 (1H, s, H-8), 6.25 (1H, d, $J$ = 9.6 Hz, H-3), 5.01 (1H, dd, $J_1$ = 6.9 Hz, $J_2$ = 9.6 Hz, H-2′), 3.48–3.24 (2H, m, H-3′a,b), 3.17 (1H, q, $J$ = 7.5 Hz, H-3″), 1.66 (3H, s, H-6′), 1.62 (3H, s, H-5′), 1.40 (3H, s, H-4″), 1.19 (3H, d, $J$ = 7.5 Hz, H-5″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 168.6 (C-1″), 163.1 (C-2), 161.1 (C-7), 159.9 (C-6″), 155.6 (C-8a), 143.4 (C-4), 130.1 (C-7″), 128.7 (C-10″), 128.1 (C-8″, C-12″), 127.1 (C-6), 126.7 (C-9″, C-11″), 124.1 (C-5), 112.6 (C-4a), 112.3 (C-3), 97.6 (C-8), 89.3 (C-2′), 88.6 (C-2″), 84.1 (C-3″), 50.8 (C-4′), 29.5 (C-3′), 23.5, 21.7, 21.1, 13.7 (C-5′,C-6′, C-4″, C-5″); DCI-HRMS $[M+H]^+$ calcd. for $(C_{26}H_{25}NO_6)^+$: 447.1682, found: 447.1686.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 4,5-dimethyl-3-(p-tolyl)-4,5-dihydroisoxazole-4-carboxylate 2b**

Yield 45%; MP: 196 °C; IR band (NaCl) $cm^{-1}$: 1422 (C=N); $^1$H NMR ($CDCl_3$, 300 MHz, δ): 7.64 (1H, d, $J$ = 9.3 Hz, H-4), 7.28 (2H, d, $J$ = 8.1 Hz, H-8″, H-12″), 7.28 (1H, s, H-5), 7.12 (2H, d, $J$ = 8.1 Hz, H-9″, H-11″), 6.25 (1H, s, H-8), 6.25 (1H, d, $J$ = 9.6 Hz, H-3), 4.93 (1H, dd, $J_1$ = 9.6 Hz, $J_2$ = 7.8 Hz, H-2′), 3.41 (1H, q, $J$ = 7.2 Hz, H-3″), 3.33–3.31 (2H, m, H-3′a,b), 2.34 (3H, s, H-13″), 1.64 (3H, s, H-6′), 1.62 (3H, s, H-5′), 1.51 (3H, s, H-4″), 1.23 (3H, d, $J$ = 7.2 Hz, H-5″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 169.0 (C-1″), 162.6 (C-2), 160.9 (C-7), 158.8 (C-6″), 155.2 (C-8a), 143.3 (C-4), 139.9 (C-10″), 124.0 (C-7″), 128.9 (C-8″, C-12″), 125.5 (C-6), 126.2 (C-9″, C-11″), 122.8 (C-5), 112.3 (C-4a), 111.7 (C-3), 97.2 (C-8), 89.1 (C-2′), 88.7 (C-2″), 83.4 (C-3″), 51.3 (C-4′), 29.2 (C-3′), 29.1, 23.2, 20.9, 21.0, 13.5 (C-5′, C-6′, C-4″, C-5″, C-13″); DCI-HRMS $[M+H]^+$ calcd. for $(C_{27}H_{27}NO_6)^+$: 461.1838, found: 461.1836.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 4,5-dimethyl-3-(p-tolyl)-4,5-dihydroisoxazole-4-carboxylate 2b′**

Yield 39%; MP: 178 °C; IR band (NaCl) $cm^{-1}$: 1422 (C=N); $^1$H NMR ($CDCl_3$, 300 MHz, δ): 7.63 (1H, d, $J$ = 9.3 Hz, H-4), 7.45 (2H, d, $J$ = 8.1 Hz, H-8″, H-12″), 7.24 (2H, d, $J$ = 8.1 Hz, H-9″, H-11″), 7.18 (1H, s, H-5), 6.76 (1H, s, H-8), 6.26 (1H, d, $J$ = 9.6 Hz, H-3), 5.08 (1H, dd, $J_1$ = 9.6 Hz, $J_2$ = 6.6 Hz, H-2′), 3.49–3.24 (2H, m, H-3′a,b), 3.11 (1H, q, $J$ = 7.2 Hz, H-3″), 2.37 (3H, s, H-13″), 1.66 (3H, s, H-6′), 1.62 (3H, s, H-5′), 1.39 (3H, s, H-4″), 1.16 (3H, d, $J$ = 7.2 Hz, H-5″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 169.5 (C-1″), 163.9 (C-2), 160.7 (C-7), 159.2 (C-6″), 156.4 (C-8a), 144.0 (C-4), 141.3 (C-10″), 130.3 (C-8″, C-12″), 127.5 (C-9″, C-11″), 126.1 (C-7″), 125.1 (C-6), 123.8 (C-5), 113.4 (C-4a), 113.1 (C-3), 98.5 (C-8), 89.9 (C-2′), 89.5 (C-2″), 84.9 (C-3″), 51.7 (C-4′), 30.3 (C-3″), 24.3, 22.6, 22.1, 21.9, 14.0 (C-5′, C-6′, C-4″, C-5″, C-13″); DCI-HRMS $[M+H]^+$ calcd. for $(C_{27}H_{27}NO_6)^+$: 461.1838, found: 461.1836.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 3-(4-methoxyphenyl)-4,5-dimethyl-4,5-dihydroisoxazole-4-carboxylate 2c**

Yield 41%; MP: 112 °C; IR band (NaCl) $cm^{-1}$: 1422 (C=N); $^1$H NMR ($CDCl_3$, 300 MHz, δ): 7.64 (1H, d, $J$ = 9.6 Hz, H-4), 7.33 (2H, d, $J$ = 9 Hz, H-8″, H-12″), 7.26 (1H, s, H-5), 6.82 (2H, d, $J$ = 9 Hz, H-9″, H-11″), 6.60 (1H, s, H-8), 6.24 (1H, d, $J$ = 9.6 Hz, H-3), 4.93 (1H, dd, $J_1$ = 9.3 Hz, $J_2$ = 7.5 Hz, H-2′), 4.14 (1H, q, $J$ = 7.2 Hz, H-3″), 3.90–3.76 (2H,m, H-3′a,b), 3.81 (3H, s, H-13″), 1.66 (3H, s, H-6′), 1.6 (3H, s, H-5′), 1.5 (3H, s, H-4″), 1.19 (3H, d, $J$ = 7.2 Hz, H-5″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 168.9 (C-1″), 162.5 (C-2), 160.4 (C-7), 158.4 (C-6″), 143.2 (C-4), 141.6 (C-10″), 127.6 (C-7″), 123.9 (C-8″, C-12″), 122.7 (C-9″, C-11″), 121.6 (C-5), 113.5 (C-4a), 111.6 (C-3), 97.0 (C-8), 88.6 (C-2′), 83.3 (C-3″), 83.2 (C-2″), 54.7 (C-4′), 54.4 (C-13″), 29.1 (C-3′), 23.1, 21.2, 20.8,

13.4 (C-5′, C-6′, C-4″, C-5″); DCI-HRMS $[M+H]^+$ calcd. for $(C_{27}H_{27}NO_7)^+$:477.1788, found: 477.1781.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 3-(4-methoxyphenyl)-4,5-dimethyl-4,5-dihydroisoxazole-4-carboxylate 2c′**

Yield 46%; MP: 102 °C; IR band (NaCl) $cm^{-1}$: 1422 (C=N); $^1H$ NMR ($CDCl_3$, 300 MHz, δ): 7.62 (1H, d, $J$ = 9.6 Hz, H-4), 7.48 (2H, d, $J$ = 8.7 Hz, H-8″, H-12″), 7.23 (1H, s, H-5), 6.9 (2H, d, $J$ = 8.7 Hz, H-9″, H-11″), 6.74 (1H, s, H-8), 6.23 (1H, d, $J$ = 9.6 Hz, H-3), 4.99 (1H, dd, $J_1$ = 9.6 Hz, $J_2$ = 6.6 Hz, H-2′), 4.13 (1H, q, $J$ = 7.2 Hz, H-3″), 3.81 (3H, s, H-13″), 3.38–2.99 (2H, m, H-3′a,b), 1.65 (3H, s, H-6′), 1.60 (3H, s, H-5′), 1.23 (3H, s, H-4″), 1.16 (3H, d, $J$ = 7.2 Hz, H-5″). $^{13}C$-NMR ($CDCl_3$, 75 MHz, δ): 168.6 (C-1″), 163.1 (C-2), 161.1 (C-7), 159.5 (C-6″), 143.5 (C-10″), 128.2 (C-6), 128.1 (C-7″), 126.4 (C-8″, C-12″), 123.0 (C-9″, C-11″), 120.5 (C-5), 114.1 (C-4a), 112.1 (C-3), 97.5 (C-8), 88.7 (C-2″), 84.0 (C-3″), 84.0 (C-2′), 55.2 (C-4′), 55.2 (C-13″), 29.5 (C-3′), 21.7, 21.1, 22.1, 13.7 (C-5′, C-6′, C-4″, C-5″); DCI-HRMS $[M+H]^+$ calcd. for $(C_{27}H_{27}NO_7)^+$:477.1788, found: 477.1781.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 3-(4-butoxyphenyl)-4,5-dimethyl-4,5-dihydroisoxazole-4-carboxylate 2d**

Yield 39%; MP: 143 °C; IR band (NaCl) $cm^{-1}$: 1422 (C=N); $^1H$ NMR ($CDCl_3$, 300 MHz, δ): 7.63 (1H, d, $J$ = 9.6 Hz, H-4), 7.48 (2H, d, $J$ = 9 Hz, H-8″, H-12″), 7.24 (1H, s, H-5), 6.90 (2H, d, $J$ = 9 Hz, H-9″, H-11″), 6.76 (1H, s, H-8), 6.25 (1H, d, $J$ = 9.6 Hz, H-3), 4.97 (1H, dd, $J_1$ = 9.6 Hz, $J_2$ = 7.5 Hz, H-2′), 4.12 (1H, q, $J$ = 6.9 Hz, H-3″), 3.99 (2H, t, $J$ = 6.6 Hz, H-13″), 3.40–3.12 (2H, m, H-3′a,b), 1.79 (2H, q, $J$ = 6.6 Hz, H-14″), 1.66 (3H, s, H-6′), 1.61 (3H, s, H-5′), 1.49 (2H, six, $J$ = 7.5 Hz, H-15″), 1.37 (3H, s, H-4″), 1.17 (3H, d, $J$ = 6.6 Hz, H-5″), 0.99 (3H, t, $J$ = 7.5 Hz, H-16″). $^{13}C$-NMR ($CDCl_3$, 75 MHz, δ): 169.2 (C-1″), 163.6 (C-2), 161.6 (C-7), 161.1 (C-6″), 160.1 (C-10″), 156.1 (C-8a), 144.0 (C-4), 128.7 (C-7″), 124.8 (C-8″, C-12″), 123.5 (C-6), 120.8 (C-9″, C-11″), 115.2 (C-5), 113.1 (C-4a), 112.8 (C-3), 98.1 (C-8), 89.5 (C-2′), 89.2 (C-2″), 84.6 (C-3″), 68.2 (C-13″), 51.4 (C-4′), 31.5 (C-14″), 30.0 (C-3′), 24.0 (C-15″), 22.2, 21.6, 19.5, 14.3, 14.2 (C-5′, C-6′, C-4″, C-5″, C-16″); DCI-HRMS $[M+H]^+$ calcd. for $(C_{30}H_{33}NO_7)^+$: 519.2257, found: 519.2249.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 3-(4-butoxyphenyl)-4,5-dimethyl-4,5-dihydroisoxazole-4-carboxylate 2d′**

Yield 38%; MP: 170 °C; IR band (NaCl) $cm^{-1}$: 1422 (C=N); $^1H$ NMR ($CDCl_3$, 300 MHz, δ): 7.67 (1H, d, $J$ = 9.6 Hz, H-4), 7.37 (2H, d, $J$ = 9 Hz, H-8″, H-12″), 7.29 (1H, s, H-5), 6.86 (2H, d, $J$ = 9 Hz, H-9″, H-11″), 6.65 (1H, s, H-8), 6.27 (1H, d, $J$ = 9.6 Hz, H-3), 4.98 (1H, dd, $J_1$ = 9 Hz, $J_2$ = 7.5 Hz, H-2′), 3.98 (2H, t, $J$ = 6.6 Hz, H-13″), 3.99 (1H, q, $J$ = 7.2 Hz, H-3″), 3.42–3.32 (2H, m, H-3′a,b), 1.82 (2H, q, $J$ = 6.9 Hz, H-14″), 1.64 (3H, s, H-6′), 1.58 (3H, s, H-5′), 1.55 (2H, six, $J$ = 6.6 Hz, H-15″), 1.48 (3H, s, H-4″), 1.31 (3H, d, $J$ = 6.9 Hz, H-5″), 0.98 (3H, t, $J$ = 7.3 Hz, H-16″). $^{13}C$-NMR ($CDCl_3$, 75 MHz, δ): 170.2 (C-1″), 163.7 (C-2), 162.0 (C-7), 161.3 (C-6″), 159.7 (C-10″), 156.3 (C-8a), 144.4 (C-4), 128.9 (C-7″), 125.1 (C-8″, C-12″), 124.0 (C-6), 121.0 (C-9″, C-11″), 115.3 (C-5), 113.4 (C-4a), 112.9 (C-3), 98.3 (C-8), 90.0 (C-2′), 89.8 (C-2″), 84.5 (C-3″), 68.4 (C-13″), 52.4 (C-4′), 31.8 (C-14″), 30.2 (C-3′), 24.3 (C-15″), 22.5, 22.0, 19.8, 14.7, 14.5 (C-5′, C-6′, C-4″, C-5″, C-16″); DCI-HRMS $[M+H]^+$ calcd. for $(C_{30}H_{33}NO_7)^+$: 519.2257, found: 519.2249.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 3-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroisoxazole-4-carboxylate 2e**

Yield 34%; MP: 124 °C; IR band (NaCl) $cm^{-1}$: 1423 (C=N); $^1H$ NMR ($CDCl_3$, 300 MHz, δ): 7.66 (1H, d, $J$ = 9.6 Hz, H-4), 7.55 (2H, d, $J$ = 8.4 Hz, H-8″, H-12″), 7.29 (1H, s, H-5), 7.42 (2H, d, $J$ = 8.4 Hz, H-9″, H-11″), 6.79 (1H, s, H-8), 6.30 (1H, d, $J$ = 9.6 Hz, H-3), 5.05 (1H, t, $J$ = 6.6 Hz, H-2′), 3.69 (1H, q, $J$ = 7.2 Hz, H-3″), 3.36–3.04 (2H, m, H-3′a,b), 1.70 (3H, s,H-6′), 1.65 (3H, s, H-5′), 1.43 (3H, s, H-4″), 1.24 (3H, d, $J$ = 7.2 Hz, H-5″). $^{13}C$-NMR ($CDCl_3$, 75 MHz, δ): 168.8 (C-1″), 163.2 (C-2), 161.2 (C-7), 159.1 (C-6″), 155.8 (C-8a), 143.7 (C-4), 126.3 (C-10″), 129.2 (C-7″), 128.7 (C-8″, C-12″), 128.2 (C-6), 124.3 (C-5), 123.2 (C-9″, C-11″), 112.8 (C-4a), 112.5 (C-3), 97.8 (C-8), 89.7 (C-2′), 88.8 (C-3″), 84.5 (C-2″), 50.9 (C-4′), 29.7 (C-3′), 22.7, 21.9, 21.3, 14.2 (C-5′, C-6′, C-4″, C-5″); DCI-HRMS $[M+H]^+$ calcd. for $(C_{26}H_{24}ClNO_6)^+$: 481.1292, found: 481.129.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 3-(4-chlorophenyl)-4,5-dimethyl-4,5-dihydroisoxazole-4-carboxylate 2e′**

Yield 30%; MP: 116 °C; IR band (NaCl) $cm^{-1}$: 1422 (C=N); $^1H$ NMR ($CDCl_3$, 300 MHz, δ): 7.67 (1H, d, $J$ = 9.6 Hz, H-4), 7.38 (2H, d, $J$ = 7.8 Hz, H-8″, H-12″), 7.37 (1H, s, H-5), 7.31 (2H, d, $J$ = 7.8 Hz, H-9″, H-11″), 6.65 (1H, s, H-8), 6.29 (1H, d, $J$ = 9.6 Hz, H-3), 4.99 (1H, t, $J$ = 9 Hz, H-2′), 3.44 (1H, q, $J$ = 7.2 Hz, H-3″), 3.52–3.32 (2H, m, H-3′a,b), 1.70 (3H, s, H-6′), 1.64 (3H, s, H-5′), 1.59 (3H, s, H-4″), 1.23 (3H, d, $J$ = 7.2 Hz, H-5″). $^{13}C$-NMR ($CDCl_3$, 75 MHz, δ): 169.5 (C-1″), 163.4 (C-2), 161.6 (C-7), 158.9 (C-6″), 156.0 (C-8a), 144.0 (C-4), 126.5 (C-10″), 129.4 (C-7″), 128.3 (C-8″, C-12″), 127.1 (C-6), 124.7 (C-5), 123.7 (C-9″, C-11″), 113.1 (C-4a), 112.7 (C-3), 98.0 (C-8), 90.3 (C-2′), 89.4 (C-3″), 84.5 (C-2″), 51.1 (C-4′), 30.1 (C-3′), 24.0, 22.2, 21.8, 14.3 (C-5′, C-6′, C-4″, C-5″); DCI-HRMS $[M+H]^+$ calcd. for $(C_{26}H_{24}ClNO_6)^+$: 481.1292, found: 481.1298.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 3-(6-chloropyridin-3-yl)-4,5-dimethyl-4,5-dihydroisoxazole-4-carboxylate 2f, f′**

Yield 71%; MP: 118 °C; IR band (NaCl) $cm^{-1}$: 1422 (C=N); $^1$H NMR ($CDCl_3$, 300 MHz, δ): **2f**: 8.60 (1H, d, $J$ = 2.4 Hz, H-8″), 7.94 (1H, dd, $J_1$ = 8.4 Hz, $J_2$ = 2.4 Hz, H-12″), 7.76 (1H, d, $J$ = 8.4 Hz, H-11″), 7.66 (1H, d, $J$ = 9.6 Hz, H-4), 7.41 (1H, s, H-5), 6.75 (1H, s, H-8), 6.27 (1H, d, $J$ = 9.6 Hz, H-3), 4.96 (1H, t, $J$ = 8.4 Hz, H-2′), 3.49–3.21 (2H, m, H-3′a,b), 3.43 (1H, q, $J$ = 7.2 Hz, H-3″), 1.66 (3H, s, H-6′), 1.63 (3H, s, H-5′), 1.46 (3H, s, H-4′), 1.24 (3H, d, $J$ = 7.2 Hz, H-5″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): δ:168.5 (C-1″), 163.0 (C-2), 158.1 (C-6″), 157.9 (C-8″), 155.9 (C-8a), 152.6 (C-10″), 147.4 (C-4), 144.9 (C-12″), 136.5 (C-7″), 124.3 (C-6), 123.7 (C-11″), 123.1 (C-5), 112.6 (C-4a), 112.1 (C-3), 97.6 (C-8), 90.2 (C-2′), 89.9 (C-2″), 84.4 (C-3″), 50.7 (C-4′), 31.7 (C-3′), 23.3, 21.6, 21.3, 13.9 (C-5′, C-6′, C-4″, C-5″). $^1$H NMR ($CDCl_3$, 300 MHz, δ): **2f′**:8.58 (1H, d, $J$ = 2.4 Hz, H-8″), 7.94 (1H, dd, $J_1$ = 8.4 Hz, $J_2$ = 2.4 Hz, H-12″), 7.76 (1H, d, $J$ = 8.4 Hz, H-11″), 7.64 (1H, d, $J$ = 9.3 Hz, H-4), 7.38 (1H, s, H-5), 6.61 (1H, s, H-8), 6.26 (1H, d, $J$ = 9.3 Hz, H-3), 4.96 (1H, t, $J$ = 8.4 Hz, H-2′), 3.49–3.21 (2H, m, H-3′a,b), 3.43 (1H, q, $J$ = 7.2 Hz, H-3″), 1.66 (3H, s, H-6′), 1.63 (3H, s, H-5′), 1.46 (3H, s, H-4″), 1.24 (3H, d, $J$ = 7.2 Hz, H-5″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 168.1 (C-1″), 162.8 (C-2), 158.1 (C-6″), 157.9 (C-8″), 155.5 (C-8a), 152.6 (C-10″), 147.4 (C-4), 143.5 (C-12″), 136.2 (C-7″), 124.1 (C-6), 123.3 (C-11″), 123.0 (C-5), 112.6 (C-4a), 112.1 (C-3), 97.6 (C-8), 90.2 (C-2′), 88.9 (C-2″), 84.1 (C-3″), 50.7 (C-4′), 31.7 (C-3′), 22.4, 21.5, 21.0, 13.6 (C-5′, C-6′, C-4″, C-5″); DCI-HRMS $[M+H]^+$ calcd. for $(C_{25}H_{23}ClN_2O_6)^+$: 482.1245, found: 482.1243.

## Synthesis of substituted azidobenzenes

The azidobenzenes have been prepared according to the general procedure.[21] Substituted aniline (0.018 mol) was dissolved in 9.4 ml 1 : 1 ratio of HCl : $H_2O$ and put in a round-bottom flask equipped with a stirrer. The reaction has been agitated at 0–5 °C; sodium nitrite (0.018 mol) was dissolved in 5.13 ml of ice-cold water and added dropwise; sodium azide (0.018 mol) was dissolved in 11.3 ml of water and added dropwise; and then, the reaction has been made to continue for 30 min. The resultant precipitate has been extracted with chloroform and washed successively with water. The organic layer has been dried over anhydrous sodium sulfate, and the solvent stripped out in a rotary evaporator to get azidobenzenes.

## Preparation of compounds 3a,a′-3e,e′

To compound **1** (0.1 g, 0.32 mmol) in refluxing toluene, the appropriate azidobenzene (2 equiv.) has been added and the mixture has been refluxed for 48 h. The resulting residue purified by flash chromatography (cyclohexane/EtOAc (60:40)) has given the corresponding heterocycles **3a,a′-3e,e′**.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 2,3-dimethyl-1-phenylaziridine-2-carboxylate 3a,a′**

Yield 65%; MP: 115 °C; IR band (NaCl) $cm^{-1}$: 1265 (C-N); $^1$H NMR ($CDCl_3$, 300 MHz, δ): **3a**: 7.62 (1H, d, $J$ = 9.6 Hz, H-4), 7.18 (1H, s, H-5), 7.16 (2H, dd, $J_1$ = 8.7 Hz, $J_2$ = 1.2 Hz, H-7″, H-11″), 6.74 (1H, dd, $J_1$ = 8.4 Hz, $J_2$ = 2.7 Hz, H-9″), 6.73 (1H, s, H-8), 6.55 (2H, dd, $J_1$ = 8.1 Hz, $J_2$ = 1.2 Hz, H-8″, H-10″), 6.24 (1H, d, $J$ = 9.6 Hz, H-3), 4.02 (1H, dd, $J_1$ = 9.6 Hz, $J_2$ = 7.2 Hz, H-2′), 3.98 (1H, q, $J$ = 6.9 Hz, H-3″), 3.96 (2H, m, H-3′a, b), 1.62(3H, d, $J$ = 6.9 Hz, H-5″), 1.47 (3H, s, H-6′), 1.41 (3H, s, H-5′), 1.39 (3H, s, H-4″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 173.9 (C-1″), 163.4 (C-2), 161.6 (C-7), 155.9 (C-8a), 146.8 (C-6″), 143.8 (C-4), 129.5 (C-7″, C-11″), 124.6 (C-6), 123.4 (C-5), 123.4 (C-8″, C-10″), 118.6 (C-9″), 112.9 (C-4a), 112.6 (C-3), 98.1 C-8), 88.8 (C-2′), 88.6 (C-2″), 83.4 (C-3″), 52.8 (C-4′), 29.9 (C-3′) 21.6, 21.3, 19.6, 19.0 (C-5′, C-6′, C-4″, C-5″). $^1$H NMR ($CDCl_3$, 300 MHz, δ): **3a′**: 7.61 (1H, d, $J$ = 9.3 Hz, H-4), 7.18 (1H, s, H-5), 7.16 (2H, dd, $J_1$ = 8.7 Hz, $J_2$ = 1.2 Hz, H-7″, H-11″), 6.74 (1H, dd, $J_1$ = 8.4 Hz, $J_2$ = 2.7 Hz, H-9″), 6.71 (1H, s, H-8), 6.55 (2H, dd, $J_1$ = 8.1 Hz, $J_2$ = 1.2 Hz, H-8″, H-10″), 6.25 (1H, d, $J$ = 9.3 Hz, H-3), 4.02 (2H, dd, $J_1$ = 9.6 Hz, $J_2$ = 7.2 Hz, H-2′), 3.98 (1H, q, $J$ = 6.9 Hz, H-3″), 3.96 (4H, m, H-3′a, b), 1.62(6H, d, $J$ = 6.9 Hz, H-5″), 1.47 (3H, s, H-6′), 1.41 (3H, s, H-5′), 1.39 (3H, s, H-4″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 173.8 (C-1″), 163.4 (C-2), 161.6 (C-7), 155.9 (C-8a), 146.8 (C-6″), 143.8 (C-4), 129.5 (C-7″, C-11″), 124.5 (C-6), 123.4 (C-5), 123.4 (C-8″, C-10″), 118.6 (C-9″), 112.9 (C-4a), 112.6 (C-3), 98.0 (C-8), 88.8 (C-2′), 88.6 (C-2″), 83.2 (C-3″), 52.8 (C-4′), 29.7 (C-3′) 21.6, 21.3, 19.6, 19.0 (C-5′, C-6′, C-4″, C-5″); DCI-HRMS $[M+H]^+$ calcd. for $(C_{25}H_{25}NO_5)^+$: 419.1733, found: 419.1738.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 1-(4-chlorophenyl)-2,3-dimethylaziridine-2-carboxylate 3b,b′**

Yield 78%; MP: 95 °C; IR band (NaCl) $cm^{-1}$: 1267 (C-N), 749 (C-Cl); $^1$H NMR ($CDCl_3$, 300 MHz, δ): **3b**: 7.62 (1H, d, $J$ = 9.6 Hz, H-4), 7.25 (1H, s, H-5), 7.11 (2H, d, $J$ = 8.4 Hz, H-7″, H-11″), 6.72 (1H, s, H-8), 6.47 (2H, d, $J$ = 9 Hz, H-8″, H-10″), 6.24 (1H, d, $J$ = 9.6 Hz, H-3), 5.01 (1H, dd, $J_1$ = 9.6 Hz, $J_2$ = 7 Hz, H-2′), 3.96 (1H, q, $J$ = 6.9 Hz, H-3″), 3.10–2.93 (2H, m, H-3′a,b), 1.53 (3H, d, $J$ = 6.9 Hz, H-5″), 1.48 (3H, s, H-6′), 1.41 (3H, s, H-5′), 1.38 (3H, s, H-4″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 173.1 (C-1″), 163.0 (C-2), 161.1 (C-7), 155.5 (C-8a), 146.4 (C-4), 143.4, (C-6″), 129.0 (C-9″), 128.9 (C-7″, C-11″), 123.0 (C-6), 122.7 (C-5), 114.3 (C-8″, C-10″), 112.6 (C-4a), 112.2 (C-3), 97.7 (C-8), 88.4 (C-2′), 88.2 (C-3″), 83.2 (C-2″),

52.7 (C-4′), 29.5 (C-3′), 21.8, 21.2, 18.5, 15,0 (C-5′, C-6′, C-4″, C-5″). $^{1}$H NMR ($CDCl_3$, 300 MHz, δ): **3b′**:7.61 (1H, d, *J* = 9.3 Hz, H-4), 7.19 (1H, s, H-5), 7.10 (2H, d, *J* = 8.4 Hz, H-7″, H-11″), 6.70 (1H, s, H-8), 6.44(2H, d, *J* = 9 Hz, H-8″, H-10″), 6.24 (1H, d, *J* = 9.6 Hz, H-3), 4.96 (1H, dd, $J_1$ = 9.6 Hz, $J_2$ = 7.0 Hz, H-2′), 3.96 (1H, q, *J* = 6.9 Hz, H-3″), 3.10–2.93 (2H, m, H-3′a,b), 1.53 (3H, d, *J* = 6.9 Hz, H-5″), 1.48 (3H, s, H-6′), 1.41 (3H, s, H-5′), 1.38 (3H, s, H-4″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 173.1 (C-1″), 162.9 (C-2), 161.1 (C-7), 155.5 (C-8a), 145.0 (C-4), 143.4, (C-6″), 129.0 (C-9″), 128.9 (C-7″, C-11″), 123.0 (C-6), 122.7 (C-5), 114.1 (C-8″, C-10″), 112.6 (C-4a), 112.2 (C-3), 97.6 (C-8), 88.4 (C-2′), 88.2 (C-3″), 83.0 (C-2″), 52.5 (C-4′), 29.5 (C-3′), 21.5, 20.8, 18.4, 15,0 (C-5′, C-6′, C-4″, C-5″) DCI-HRMS $[M+H]^+$ calcd. for $(C_{25}H_{24}ClNO_5)^+$: 453.1343, found: 453.1429.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 2,3-dimethyl-1-(p-tolyl)aziridine-2-carboxylate 3c,c′**

Yield 72%; MP: 110 °C; IR band (NaCl) $cm^{-1}$: 1265 (C-N); $^{1}$H NMR ($CDCl_3$, 300 MHz, δ): **3c**: 7.62 (1H, d, *J* = 9.3 Hz, H-4), 7.18 (1H, s, H-5), 6.97 (2H, d, *J* = 8.1 Hz, H-7″, H-11″), 6.73 (1H, s, H-8), 6.45 (2H, d, *J* = 8.1 Hz, H-8″, H-10″), 6.24 (1H, d, *J* = 9.3 Hz, H-3), 5.03–4.99 (1H, m, H-2′), 3.98 (1H, q, *J* = 6.9 Hz, H-3″), 3.22–2.88 (2H, m, H-3′a,b), 2.88 (3H, s, H-12″), 1.53 (3H, d, *J* = 6.9 Hz, H-5″), 1.47 (3H, s, H-6′), 1.37 (3H, s, H-5′), 1.34 (3H, s, H-4″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 174.1 (C-1″), 163.5 (C-2), 161.6 (C-7), 155.9 (C-8a), 144.5 (C-6″), 143.8 (C-4), 130.0 (C-9″), 129.0 (C-7″, C-11″), 124.6 (C-6), 123.4 (C-5), 113.8 (C-4a), 112.9 (C-8″, C-10″), 112.9 (C-3), 98.1 (C-8), 88.8 (C-2′), 88.6 (C-3″), 83.3 (C-2″), 53.4 (C-4′), 32.1 (C-3′), 29.6, 21.6, 20.6, 19.0, 14.7 (C-5′, C-6′, C-4″, C-5″, C-12″). $^{1}$H NMR ($CDCl_3$, 300 MHz, δ): **3c′**: 7.61 (1H, d, *J* = 9.6 Hz, H-4), 7.16 (1H, s, H-5), 6.97 (2H, d, *J* = 8.1 Hz, H-7″, H-11″), 6.71 (1H, s, H-8), 6.45 (2H, d, *J* = 8.1 Hz, H-8″, H-10″), 6.24 (1H, d, *J* = 9.3 Hz, H-3), 5.03–4.99 (1H, m, H-2′), 3.98 (1H, q, *J* = 6.9 Hz, H-3″), 3.22–2.88 (2H, m, H-3′a,b), 2.88 (3H, s, H-12″), 1.53 (3H, d, *J* = 6.9 Hz, H-5″), 1.47 (3H, s, H-6′), 1.37 (3H, s, H-5′), 1.34 (3H, s, H-4″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 174.0 (C-1″), 163.4 (C-2), 161.6 (C-7), 155.9 (C-8a), 144.4 (C-6″), 143.8 (C-4), 130.0 (C-9″), 129.0 (C-7″, C-11″), 124.5 (C-6), 123.4 (C-5), 113.8 (C-4a), 112.9 (C-8″, C-10″), 112.6 (C-3), 98.0 (C-8), 88.8 (C-2′), 88.6 (C-3″), 83.2 (C-2″), 53.2 (C-4′), 32.1 (C-3′), 29.5, 21.2, 19.0, 19.0, 14.7 (C-5′′, C-6′, C-4″, C-5″, C-12″); DCI-HRMS $[M+H]^+$ calcd. for $(C_{26}H_{27}NO_5)^+$: 433.1889, found: 433.1887.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 2,3-dimethyl-1-(4-(trifluoromethyl)phenyl)aziridine-2-carboxylate 3d,d′**

Yield 79%; MP: 120 °C; IR band (NaCl) $cm^{-1}$: 1265 (C-N); $^{1}$H NMR ($CDCl_3$, 300 MHz, δ): **3d**: 7.61 (1H, d, *J* = 9.6 Hz, H-4), 7.19 (1H, s, H-5), 6.73 (1H, s, H-8), 6.55 (2H, d, *J* = 8.4 Hz, H-7″, H-11″), 6.51 (2H, d, *J* = 8.4 Hz, H-8″, H-10″), 6.25 (1H, d, *J* = 9.6 Hz, H-3), 5.02 (1H, dd, $J_1$ = 9.6 Hz, $J_2$ = 7.2 Hz, H-2′), 4.15 (1H, q, *J* = 7.2 Hz, H-3″), 3.23 (2H, m, H-3′a,b), 1.74 (3H, d, *J* = 7.2 Hz, H-5″), 1.59 (3H, s, H-6′), 1.52 (3H, s, H-5′), 1.42 (3H, s, H-4″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 173.1 (C-1″), 163.3 (C-2), 161.5 (C-7), 156.0 (C-8a), 149.3 (C-6″), 143.8 (C-4), 126.8 (C-6), 124.4 (C-7″, C-11″), 124.3 (C-12″), 123.5 (C-5), 120.2 (C-9″), 112.9 (C-4a), 112.6 (C-8″, C-10″), 112.5 (C-3), 98.1 (C-8), 88.9 (C-2′), 88.8 (C-3″), 83.8 (C-2″), 52.5 (C-4′), 29.9 (C-3′), 22.2, 21.7, 18.8, 14.0 (C-5′, C-6′, C-4″, C-5″). $^{1}$H NMR ($CDCl_3$, 300 MHz, δ): **3d′**: 7.61 (1H, d, *J* = 9.6 Hz, H-4), 7.13 (1H, s, H-5), 6.71 (1H, s, H-8), 6.54 (2H, d, *J* = 8.4 Hz, H-7″, H-11″), 6.51 (2H, d, *J* = 8.4 Hz, H-8″, H-10″), 6.23 (1H, d, *J* = 9.6 Hz, H-3), 4.99 (1H, dd, $J_1$ = 9.6 Hz, $J_2$ = 7.2 Hz, H-2′), 4.15 (1H, q, *J* = 7.2 Hz, H-3″), 3.08 (2H, m, H-3′a,b), 1.54 (3H, d, *J* = 7.0 Hz, H-5″), 1.59 (3H, s, H-6′), 1.52 (3H, s, H-5′), 1.42 (3H, s, H-4″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 173.1 (C-1″), 163.3 (C-2), 161.5 (C-7), 156.0 (C-8a), 149.2 (C-6″), 143.8 (C-4), 126.8 (C-6), 124.4 (C-7″, C-11″), 124.3 (C-12″), 123.5 (C-5), 120.2 (C-9″), 112.7 (C-4a), 112.6 (C-8″, C-10″), 112.5 (C-3), 98.0 (C-8), 88.9 (C-2′), 88.6 (C-3″), 83.7 (C-2″), 52.2 (C-4′), 29.9 (C-3′), 21.9, 21.4, 18.7, 14.0 (C-5′, C-6′, C-4″, C-5″); DCI-HRMS $[M+H]^+$ calcd. for $(C_{26}H_{24}F_3NO_5)^+$: 487.1607, found: 487.1604.

**7-oxo-3,7-dihydro-2H-furo[3,2-g]chromen-2-yl)propan-2-yl 1-(3,5-dichlorophenyl)-2,3-dimethylaziridine-2-carboxylate 3e,e′**

Yield 82%; MP: 100 °C; IR band (NaCl) $cm^{-1}$: 1266 (C-N); $^{1}$H NMR ($CDCl_3$, 300 MHz, δ): **3e**:7.64 (1H, d, *J* = 9.6 Hz, H-4), 7.22 (1H, s, H-5), 6.74 (1H, s, H-8), 6.71 (1H, dd, $J_1$ = 1.5 Hz, $J_2$ = 3.3 Hz, H-9″), 6.39 (1H, d, *J* = 1.5 Hz, H-7″), 6.32 (1H, d, *J* = 1.5 Hz, H-11″), 6.25 (1H, d, *J* = 9.3 Hz, H-3), 5.06 (1H, dd, $J_1$ = 9.6 Hz, $J_2$ = 7.5 Hz, H-2′), 4.15 (1H, q, *J* = 6.9 Hz, H-3″), 3.35 (2H, m, H-3′a,b), 1.57 (3H, d, *J* = 6.9 Hz, H-5″), 1.52 (3H, s, H-6′), 1.40 (3H, s, H-5′), 1.25 (3H, s, H-4″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 172.8 (C-1″), 163.2 (C-2), 161.1 (C-7), 155.8 (C-8a), 148.3 (C-8″), 148.2 (C-6″), 143.7 (C-4), 135.6 (C-10″), 124.2 (C-6), 123.8 (C-9″), 123.4 (C-5), 112.5 (C-7″), 111.3 (C-4a), 111.5 (C-3), 98.0 (C-8), 88.7 (C-2′), 88.4 (C-3″), 83.7 (C-2″), 52.2 (C-4′), 29.8 (C-3′), 22.4, 18.6, 14.3, 14.2 (C-5′, C-6′, C-4″, C-5″). $^{1}$H NMR ($CDCl_3$, 300 MHz, δ): **3e′**:7.62 (1H, d, *J* = 9.3 Hz, H-4), 7.17 (1H, s, H-5), 6.72 (1H, s, H-8), 6.71 (1H, dd, $J_1$ = 1.5 Hz, $J_2$ = 3.3 Hz, H-9″), 6.39 (1H, d, *J* = 1.5 Hz, H-7″), 6.32 (1H, d, *J* = 1.5 Hz, H-11″), 6.24 (1H, d, *J* = 9.6 Hz, H-3), 4.96 (1H, dd, $J_1$ = 9.6 Hz, $J_2$ = 7.5 Hz, H-2′), 4.15 (1H, q, *J* = 6.9 Hz, H-3″), 3.14 (2H, m, H-3′a,b), 1.57 (3H, d, *J* = 6.9 Hz, H-5″), 1.52 (3H, s, H-6′), 1.40 (3H, s, H-5′), 1.25 (3H, s, H-4″). $^{13}$C-NMR ($CDCl_3$, 75 MHz, δ): 172.8

(C-1″), 163.2 (C-2), 161.1 (C-7), 155.5 (C-8a), 148.3 (C-8″), 148.2 (C-6″), 143.7 (C-4), 135.6 (C-10″), 124.2 (C-6), 123.8 (C-9″), 123.3 (C-5), 112.5 (C-7″), 111.3 (C-4a), 111.5 (C-3), 97.9 (C-8), 88.7 (C-2′), 88.4 (C-3″), 83.5 (C-2″), 52.2 (C-4′), 29.7 (C-3′), 21.5, 18.6, 14.3, 14.2 (C-5′, C-6′, C-4″, C-5″); DCI-HRMS $[M+H]^+$ calcd. for $(C_{25}H_{23}Cl_2NO_5)^+$: 487.0953, found: 487.0960.

## Biological evaluation

### *5-lipoxygenase inhibitory*

The 5-lipoxygenase enzyme has long been known to be an important modulator of inflammation in other disease states. The anti-5-lipoxygenase activity of deltoin **1** and its derivatives (**2a**,**a′**–**2f**,**f′**, **3a**,**a′**–**3e**,**e′**) has been determined on soya bean lipoxygenase with modifications.[22] One concentration (20 µl) of each compound has been mixed individually with 150 µl sodium phosphate buffer (pH 7.4) containing (20 µl) of 5-lipoxygenase and 60 µl of linoleic acid (3.5 mM), yielding a final volume of 250 µl. However, the blank does not contain the substrate, but will be added 30 µl of buffer solution. All compounds are resuspended in the DMSO followed by dilution in the buffer so that the DMSO does not exceed 1%. The mixture has been incubated at 25 °C for 10 min, and the absorbance has been determined at 234 nm. The absorption change with the conversion of linoleic acid to 13-hydroperoxyoctadeca-9,11-dienoate (characterized by the appearance of the conjugated diene at 234 nm) has been flowed for 10 min at 25 °C. Nordihydroguaiaretic acid (NDGA), a phenolic anti-5-lipoxygenase, was used as a positive control.[22] The percentages of enzyme activity were obtained at 200 µM. All measurements were performed in triplicate.

### *Cytotoxic activity*

The human cancer cell lines (HCT-116, IGROV-1 and OVCAR-3) have been used for cytotoxic assay.[23] The cells were grown in RPMI-1640 medium supplemented with 10% fetal calf serum (Gibco, Gaithersburg Maryland, USA), air and 5% $CO_2$. The isolate was added to a medium containing $1 \times 10^6$ cells/ml, L-glutamine (2 mM) and gentamicin (50 µg/ml), and kept at 37 °C in a fully humidified atmosphere. After 18 h of incubation at 37 °C in 5% $CO_2$ incubator, the tubes have been centrifuged at 8000*g* for 10 min. The supernatant has been decanted, and the pellets have been washed with 20 mM of phosphate-buffered saline solution. Each pellet has been dissolved in 100 µl (2 mg/ml) MTT solution in a tube, incubated at 22 °C for 4 h and centrifuged at 8000*g* for 10 min. All the pellets have been dissolved in 500 µl DMSO and read spectrophotometrically at 500 nm. Doxorubicin and tamoxifen, drugs in cancer chemotherapy, have been used as positive control against HCT-116, and IGROV-1 and OVCAR-3, respectively.[23] Cytotoxic activity has been expressed as $IC_{50}$, and defined as the concentration of the sample required to cause a 50% decrease signal. The calculation of the $IC_{50}$ was performed by logarithmic regression.

## Statistical analysis

Data from the experiments were subjected to analysis of variance (ANOVA) using SPSS 16.0 for Windows (SPSS Inc. Chicago, IL, USA). The inhibition data relative to 5-lipoxygenase inhibition and cytotoxic activity have been transformed using arcsin-square root (arcsin $\sqrt{x}$) transformation before ANOVA. Means were separated at the 5% significance level by a least significant difference test (Student's *t*-test).

# Results and Discussion

## Chemistry

(-)-Deltoin **1** was isolated from the ethyl acetate extract of the flowers of *F. lutea*, showing on TLC a spot featuring a characteristic blue fluorescence under UV light. ES-MS of compound **1** gave a pseudomolecular ion peak $[M+H]^+$ at m/z 329, which is consistent with the molecular formula $C_{19}H_{20}O_5$. Its structure was elucidated on the basis of the $^1H$ and $^{13}C$ NMR spectral data and by comparison with literature.[10] The $^1H$ NMR spectrum has shown two signals at $\delta_H$ 6.27 (1H, d, $J$ = 9.3 Hz) and $\delta_H$ 7.65 (1H, d, $J$ = 9.3 Hz) as AB-type signals, attributable to H-3 and H-4. The same $^1H$ NMR spectrum displayed an ABX system at $\delta_H$ 5.13 (1H, t, $J$ = 9.0 Hz, H-2′), $\delta_H$ 3.33–3.28 (2H, m, H-3′a,b). These data suggested the presence of the dihydrofuranocoumarin skeleton in **1**. The presence of two closed singlets at $\delta_H$ 6.78 and 7.31 is attributable to the aromatic protons H-8 and H-5, respectively. The other signals on the same spectrum coincide with the spectral data of an angeloyl moiety in **1**.[13,24]

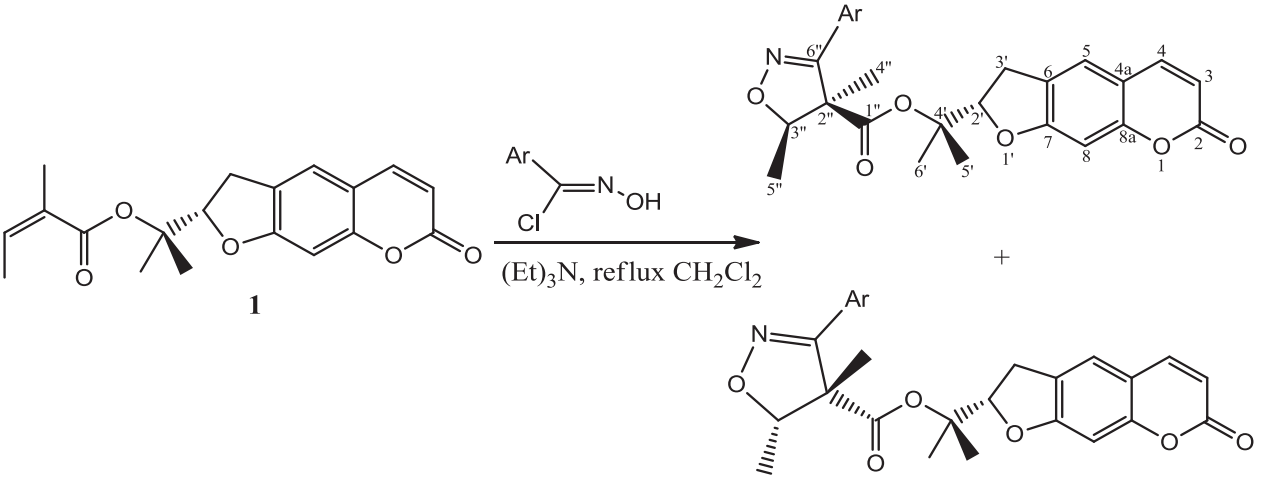
The $^{13}C$ NMR spectrum of compound **1** reinforces the above spectral data by showing 19 signals including 11 attributed to the dihydrofuranocoumarin system. The angeloyl fragment was also identified by the observation of the corresponding carbon atoms at $\delta_C$ 167.2, 123.1, 137.6, 15.7 and 15.4 ppm attributable to C-1″, C-2″, C-3″, C-4″ and C-5″, respectively.[13] Compound **1** has been identified as (-)-deltoin by its optical rotation power ($[\alpha]_D = -20.95$, $c$ = 0.5 mg/ml, $CHCl_3$).

(-)-Deltoin **1** used as a dipolarophile has been treated with various arylnitrile oxides generated *in situ* from aromatic oxime precursors, in refluxing dichloromethane for 48 h, to give the desired new isoxazolines **2a**,**a′**–**2f**,**f′** in 30–71% yield. The undertaken reaction proceeded with

complete regiospecificity to provide two separable diastereoisomers except **2f**,**f′** (Scheme 1).

The ratio of diastereoisomers in mixture (**2f**,**f′**) has been determined from quantitative $^1$H NMR spectrum, by the integration of the peaks. Indeed, it has been found that the diastereoisomers of the above case were formed in 50 : 50 ratio.

The structures of these compounds have been confirmed according to their spectral data. Compound **2b′**, as an example, was obtained as a white solid. Its DCI-HRMS gave pseudomolecular ion peak $[M+H]^+$ at m/z 462.1836, which is consistent with the molecular formula $C_{27}H_{27}NO_6$. Furthermore, the $^1$H NMR spectrum of this compound was compatible with the proposed structure. In addition to the signals corresponding to the protons introduced by the dihydofuranocoumarin moiety of (-)-deltoin **1**, we have observed the presence of new signals consequent to a characteristic AA′BB′ pattern for aromatic hydrogens. Examination at 300 M*Hz* offered excellent resolution with two doublets at $\delta_H$ 7.45 (2H, d, $J$ = 8.1 Hz, H-8″, H-12″) and at $\delta_H$ 7.24 (2H, d, $J$ = 8.1 Hz, H-9″, H-11″). The same $^1$H-NMR spectrum revealed the presence of characteristic




**2a,a'** Ar = phenyl

**2b,b'** Ar = 10"-methylphenyl

**2c,c'** Ar = 10"-methoxyphenyl

**2d,d'** Ar =10"-butoxyphenyl

**2e,e'** Ar = 10"-chlorophenyl

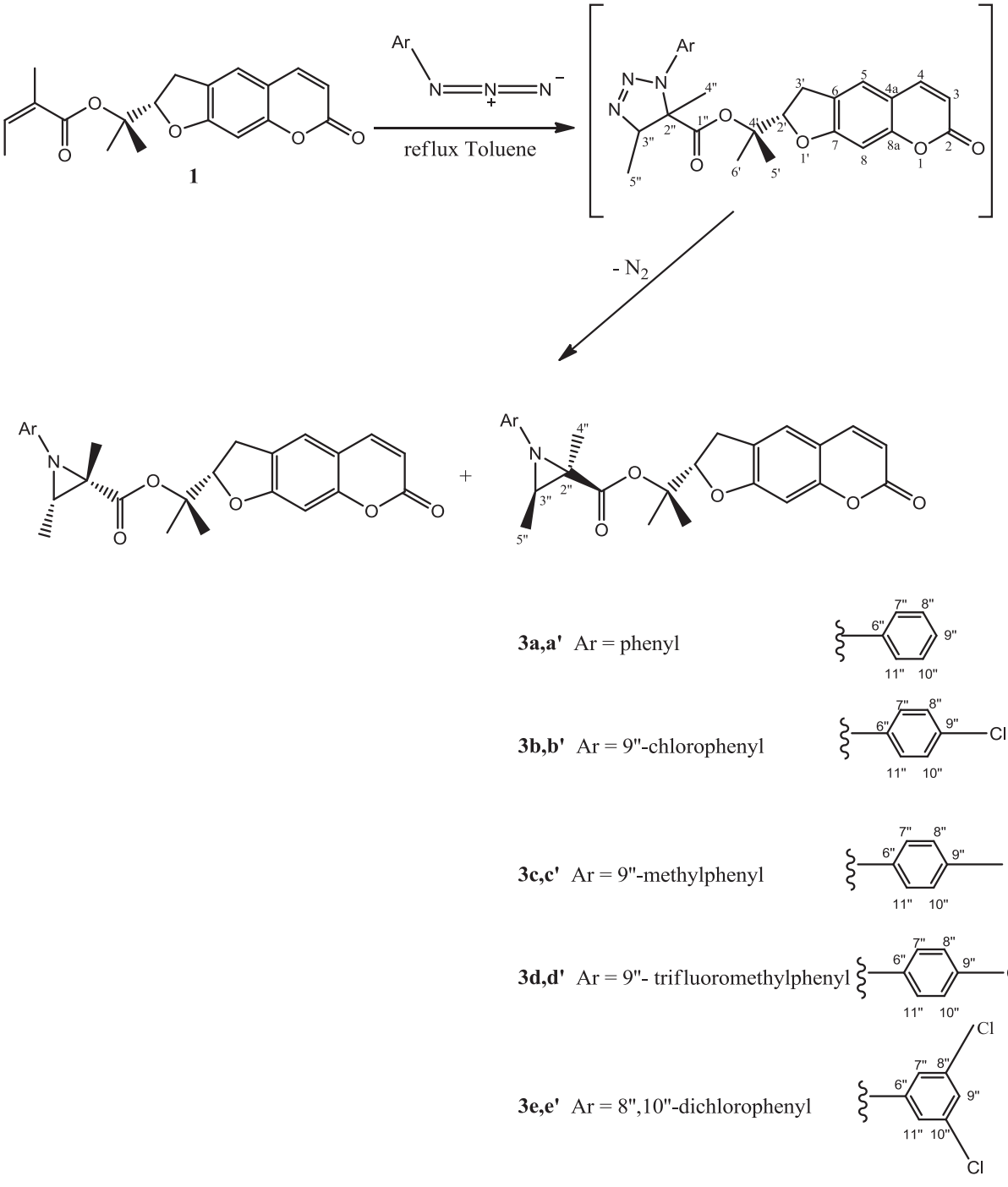
**2f,f'** Ar = 10"-chloropyridin-2-yl

**Scheme 1** Synthesis of (-)-deltoin derivatives **2a**,**a′**–**f**,**f′**.

signals at $\delta_H$ 3.11 (1H, q, $J$ = 7.2 Hz, H-3″), 1.39 (3H, s, H-4″) and 1.16 (3H, d, $J$ = 7.2 Hz, H-5″) attributable to H-3″, $(CH_3)$-4″ and $(CH_3)$-5″ of the isoxazoline ring, respectively. The $^{13}$C-NMR spectrum confirmed the above spectral data by the observation of signals at $\delta_C$ 130.3 (C-8″, C-12″), 127.5 (C-9″, C-11″), 126.1 (C-7″) and 141.3 (C-10″) relative to carbons of the tolyl ring. The same spectrum showed a signal at $\delta_C$ 159.2 attributable to the quaternary carbon of the iminic function C-6″.

Following the same way, (-)-deltoin **1** has been treated according to the *1,3*-dipolar cycloaddition with various azidobenzenes as a dipole in refluxing anhydrous toluene for




**Scheme 2** Synthesis of (-)-deltoin derivatives **3a**,**a′**–**e**,**e′**.

**Table 1** 5-lipoxygenase inhibition capacity (per cent inhibition (%)) and cytotoxicity (HCT-116, IGROV-1 and OVCAR-3 cells lines) ($IC_{50}$ (μM)) of (-)-deltoin **1** and its derivatives **2a**,**a′**–**f**,**f′** and **3a**,**a′**–**e**,**e′**

| Compound | 5-lipoxygenase inhibition (%) at 200 μM | Cytotoxic activity† ($IC_{50}$ μM) | | |
|---|---|---|---|---|
| | | HCT-116 | IGROV-1 | OVCAR-3 |
| 1 | 12.2 ± 1.2[f] | 14.3 ± 0.2[c] | 49.0 ± 2.1[f] | 49.0 ± 1.8[e] |
| 2a | 27.6 ± 6.1[d] | **3.3 ± 0.1**[b*] | >100[i] | 63.0 ± 5.3[f] |
| 2a′ | 23.8 ± 5.3[e] | >100 [g] | 98.0 ± 3.5 [h] | 89.0 ± 3.7 [h] |
| 2b | – | 21.6 ± 1.1[d] | 50.0 ± 5.0[f] | 56.0 ± 3.2[f] |
| 2b′ | – | >100 [g] | >100[i] | 71.0 ± 4.3 [g] |
| 2c | 13.5 ± 6.1[f] | 69.1 ± 1.7[f] | 63.0 ± 3.0[f] | 65.0 ± 5.1[f] |
| 2c′ | – | 62.8 ± 1.9[f] | >100[i] | 63.0 ± 1.6[f] |
| 2d | 23.1 ± 4.6[e] | 17.3 ± 0.8[c] | >100[i] | 31.6 ± 1.7[c] |
| 2d′ | 26.0 ± 4.1[d] | >100 [g] | >100[i] | >100[k] |
| 2e | 23.8 ± 5.3[e] | 14.3 ± 0.3[c] | 42.7 ± 4.2[d] | 57.0 ± 2.1[f] |
| 2e′ | 3.3 ± 1.2 [h] | 37.3 ± 0.9[e] | >100[i] | 98.0 ± 6.2[j] |
| 2f+2f′ | **53.1 ± 4.8**[b] | **4.3 ± 0.1**[b] | >100[i] | >100[k] |
| 3a+3a′ | 8.3 ± 0.4 [g] | **5.9 ± 0.1**[b] | 39.8 ± 3.0[d] | 71.0 ± 2.6[i] |
| 3b+3b′ | 7.0 ± 0.3 [g] | **6.1 ± 0.7**[b] | 31.6 ± 2.1[c] | 56.0 ± 2.9[f] |
| 3c+3c′ | – | **7.3 ± 0.9**[b] | **6.3 ± 0.5**[b] | 18.0 ± 0.7[b] |
| 3d+3d′ | 8.9 ± 0.4 [g] | 16.2 ± 0.5[c] | 31 ± 2.0[c] | 40.0 ± 1.9[d] |
| 3e+3e′ | 36.2 ± 1.8[c] | 13.3 ± 0.0[c] | 62 ± 5.1[e] | 56.0 ± 2.4[f] |
| Doxorubicin | | 0.2 ± 0.0[a] | | |
| Tamoxifen | | | 2.0 ± 0.1[a] | 1.3 ± 0.1[a] |
| NDGA | 98.0 ± 0.1[a] | | | |

–, not active. Different letters in columns indicate significant differences among fractions at $P < 0.05$ (LSD test). †Cytotoxicity as $IC_{50}$ for each cell line is the concentration of the compound that inhibits 50% of the cell multiplication after 48 h of treatment. *Bold type indicates relatively significant activity.

48 h, provided with complete regiospecificity the expected 1,2,3-triazoles, which lose a molecule of nitrogen to yield the corresponding aziridines **3a**,**a′**–**e**,**e′** (Scheme 2).

The ratio (50 : 50) of diastereoisomers in mixture has been determined from quantitative $^1$H-NMR spectra, by integration of the peaks.

The structures of these compounds were confirmed according to their spectral data. Compounds **3b** + **3b′** (also noted **3b**,**b′**), as an example, were obtained as a yellow oil as a mixture of diastereoisomers. Their common DCI-HRMS gave pseudomolecular peak $[M+H]^+$ at m/z 454.1429, which is consistent with the molecular formula $C_{25}H_{24}NO_5Cl$. The $^1$H-NMR spectrum showed the appearance of a new signal at $\delta_H$ 3.96 attributable to H-3″ of the aziridine ring in addition to the characteristic signals of the protons introduced by the dihydrofuranocoumarin system. The disappearance of the ethylenic proton signal at $\delta_H$ 6.06 (1H, qq, $J_1$ = 7.2 Hz; $J_2$ = 1.2 Hz) of the angeloyl fragment in (-)-deltoin **1** was in agreement with the undertaken cycloaddition reaction. The same spectrum also has shown four doublets at $\delta_H$ 6.47 (2H, d, $J$ = 9 Hz, H-8″, H-10″), 6.44 (2H, d, $J$ = 9 Hz, H-8″, H-10″) and at $\delta_H$ 7.11 (2H, d, $J$ = 8.4 Hz, H-7″, H-11″), 7.10 (2H, d, $J$ = 8.4 Hz, H-7″, H-11″) as AA′BB′-type signals characteristic of the aromatic hydrogens introduced by the azido-*p*-chlorobenzene. The $^{13}$C-NMR spectrum confirmed the above spectral data by the observation of new signals at $\delta_C$ 143.4 (C-6″), 128.9 (C-7″, C-11″), 114.3, 114.1 (C-8″, C-10″) and 129.0 (C-9″) relative to carbons of the introduced aromatic system. The disappearance of C-2″ and C-3″ signals ($\delta_C$ 123.1 and 137.6, respectively) in the angeloyl system of (-)-deltoin **1** was in accordance with the obtained structures.

The diastereoselectivity of the reaction was ascertained by the duplication of the most of the signals indicated above.

## Biological activity

### *5-lipoxygenase inhibitory*

All compounds have been evaluated for their 5-lipoxygenase inhibition effect (Table 1). There is no report in literature indicating that (-)-deltoin **1** and its derivatives were tested against this enzyme. The results have shown that (-)-deltoin **1** did not exhibit any considerable inhibition (% inhibition = 12.2 ± 1.2%) of 5-lipoxygenase at the used concentration (200 μM). The prepared derivatives have been shown to be inactive to moderately active and the noted per cent inhibitions of most of them ranged from 3.3 ± 1.2% (compound **2e′**) to 53.1 ± 4.8% (mixture **2f+f′**) at 200 μM. These results were in agreement with one of our earlier works that described the anti-5-lipoxygenase activity of certain isoxazolines prepared from harmine.[25] The results of the above work have shown that cycloadducts with isoxazolines bearing a phenyl, a 4-methylphenyl, a 4-methoxyphenyl and

a 4-chlorophenyl have been found to be inactive.[23] For aziridines, our findings have shown that the mixture of diastereoisomers **3e**,**e′** displayed the best activity against 5-lipoxygenase with a per cent inhibition value of 36.2 ± 1.8% at 200 μM. No previous work dealt with the description of the anti-5-lipoxygenase of aziridine derivatives.

### *Cytotoxic activity*

Cytotoxic activity of the various products (**1**, **2a**,**a′**–**2f**,**f′** and **3a**,**a′**–**e**,**e′**) tested against the human cell lines HCT-116, IGROV-1 and OVCAR-3 (Table 1) has been assessed using MTT assay, which is reliable to detect the proliferation of the cells. The results showed that (-)-deltoin **1** exhibited a good cytotoxic activity against the colon cell line HCT-116 ($IC_{50}$ = 14.3 ± 0.2 μM) and a moderate cytotoxic activity against the ovary cell lines IGROV-1 and OVCAR-3 with $IC_{50}$ values of 49.0 ± 2.1 and 49.0 ± 1.8 μM, respectively.

It has been found that one of the two diastereoisomers named **2a** was found to be the most active against the human colon cell line HCT-116 ($IC_{50}$ = 3.3 ± 0.1 μM), and it was four and thirty-seven times more active than (-)-deltoin **1** ($IC_{50}$ = 14.3 ± 0.2 μM) and its stereoisomer **2a′** ($IC_{50}$ = 122.9 ± 2.5 μM), respectively. This finding showed the importance of the stereochemistry of the stereogenic centres (C-2″ and C-3″) when the isoxazoline system bears an unsubstituted phenyl. The determination of the stereochemistry of the formed diastereoisomers was not possible by the NOESY experiment, which led to the same conclusion (a *nOe* between H-3″ and H-4″ in both structures). Moreover, after several attempts of recrystallization of all compounds prepared, it was difficult to determine the stereochemistry of each diastereoisomer using the X-ray diffraction.

The relatively high activity of the derivative **2a** compared to those of (-)-deltoin **1** and to the rest of derivatives **2** showed the contribution of the isoxazoline moiety to this activity. This result was supported by some anterior studies showing the cytotoxic activity, towards various cancer cell lines, of several isoxazoline derivatives. However, the manner of attachment of this ring in the molecule certainly affects the cytotoxic activity.[26–28]

The absence of any significant improvement in activity of (-)-deltoin **1** by incorporating an isoxazoline system bearing an aromatic ring at C-6″ with a chlorine, a methyl, a methoxy and a butoxy all in *para*-position has shown the importance of the nature of the aromatic moiety used,[25] in addition to the stereochemistry of the asymmetric centres introduced.

The mixture of diastereoisomers **2f**,**f′** was more active against HCT-116 cell line than (-)-deltoin **1** with an $IC_{50}$ value of 4.3 ± 0.1 μM. This result has shown clearly the contribution of the 2-chloropyridin group attached to the isoxazoline at C-6″ by comparison with the other aromatic systems used to improve the cytotoxic activity of (-)-deltoin **1**. On the other hand, taking into account the importance of stereochemistry in the case of the activity of the stereoisomer **2a** compared to **2b** against the same cancer cell line, it is very likely that the stereochemistry of one of the stereoisomers in mixture (**2f**,**f′**) also has an effect on this activity, as it can be from a synergistic effect. In addition, except of the couple of the diastereoisomers **2c** and **2c′**, the cytotoxic activity is reversed with the inversion of the absolute configuration of the introduced asymmetric centres (case of the couples **2a**, **2a′**, **2b**, **2b′**, **2d**, **2d′** and **2e**, **2e′**).

The introduction of the isoxazoline system with a variety of aromatic rings does not seem to improve the activity of (-)-deltoin **1** against the ovary cell line IGROV-1 and OVCAR-3 except in limited cases (**2d** ($IC_{50}$ = 31.6 ± 1.7 μM) and **2e** ($IC_{50}$ = 42.7 ± 4.2 μM) against OVCAR-3 and IGROV-1, respectively). This result is certainly due to the selectivity of the products tested towards these cancer cell lines.[29]

The results have shown that the mixture of diastereoisomers **3a**,**a′**, **3b**,**b′** was more than twice of the cytotoxic than (-)-deltoin **1** ($IC_{50}$ = 14.3 ± 0.2 μM) against HCT-116, and they exhibited $IC_{50}$ values of 5.9 ± 0.1 and 6.1 ± 0.7 μM, respectively. Our findings were supported by results from the literature describing the cytotoxic potential of some aziridine derivatives against Hep2, CT-5′ and BC-M1 cells, with LD50 values ranging from 4 to 12 μM.[30]

The increase in the activity of compounds **3a**,**a′** compared to that of (-)-deltoin **1** was due to the simple phenyl aziridine moiety introduced by the cycloaddition reaction. The mono-chlorination in *para*-position of the aromatic ring as compared to the compounds **3e**,**e′** ($IC_{50}$ = 13.3 ± 0.0 μM) supported the activity of the mixture **3b**,**b′** against HCT-116. It has been found that the substitution of the 4-position in the phenyl group attached to the nitrogen of the aziridine ring in compounds **3a**,**a′** by a methyl group (**3c**,**c′**) or a chlorine atom (**3b**,**b′**) did not influence considerably this activity, whereas the trifluoromethyl group in **3d**,**d′** ($IC_{50}$ = 16.2 ± 0.5 μM) and the two chlorine atoms in 3,5-positions in **3e**,**e′** ($IC_{50}$ = 13.3 ± 0.9 μM) can be the origin of the loss in activity by comparison with that of the compounds **3a**,**a′**. It has been shown that independently of the stereochemistry of the two asymmetric centres introduced by the aziridine system, the nature of the substitute in the aromatic ring seemed to influence the activity against HCT-116. The three cancer cell lines used (HCT-116, IGROV-1 and OVCAR-3) showed a particular sensitivity to the mixture **3c**,**c′** ($IC_{50}$ = 7.3 ± 0.9, 6.3 ± 0.5 and 18.0 ± 0.7 μM, respectively) compared to the remaining of the synthesized derivatives. This finding can be explained by the nature of the aromatic ring (*para*-methylphenyl), in addition to the stereochemistry of the introduced stereogenic centres (C-2″ and C-3″), as it can be interpreted by a possible synergistic effect still retaining the first two cited factors.[31]

The aziridine derivatives, except **3c**,**c′**, have shown a moderate cytotoxic activity against the ovary cell lines IGROV-1 and OVCAR-3 with $IC_{50}$ values ranging from 31.0 ± 2.0 to 71.0 ± 2.6 μM. This difference is due to the selectivity of the products tested against these cancer cell lines.[29]

A review of the literature showed that the furanocoumarin moiety exists in a cytotoxic natural extract. Prantschimgin, an analogous of deltoin, isolated from the same plant (*F. lutea*), is an example that it has showed cytotoxic activity against HT-29 and HCT-116 with $IC_{50}$ values of 5.20 ± 1.02 and 14.95 ± 4.9 μM, respectively. Furthermore, imperatorin, a natural furanocoumarin isolated from *Angelica dahurica,* was also found to be able to function as a cancer suppressor by inducing apoptosis in HepG2 cells through both death receptor- and mitochondria-mediated pathways.[32] These findings do not exclude the involvement of the furanocoumarin moiety in the cytotoxic activity of all compounds tested.[13]

All synthesis compounds are new and have not been investigated for cytotoxic activity.

## Conclusion

The natural hepatoprotective, TNF-α inhibitor and cytotoxic (-)-deltoin **1** isolated quantitatively from the flowers of *F. lutea*, has been subjected to a [3 + 2] cycloaddition reaction towards a series of arylnitrile oxides and azidobenzenes as a dipole. The reactions were regiospecific and led to a series of new isoxazoline and aziridine derivatives. Cytotoxic activity evaluated against three cancer cell lines (HCT-116, IGROV-1 and OVCAR-3) has shown that compound **2a** from the series of the isoxazoline derivatives and **3a**,**a′**, **3b**,**b′** and **3c**,**c′** from that of the aziridine derivatives have been the best cytotoxic effect. The isoxazoline derivative (mixture **2f+f′**) has shown the best result against 5-lipoxygenase compared to NDGA.

## Declaration

### Conflict of interest

The authors declare that there are no conflict of interests regarding the publication of this article.

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