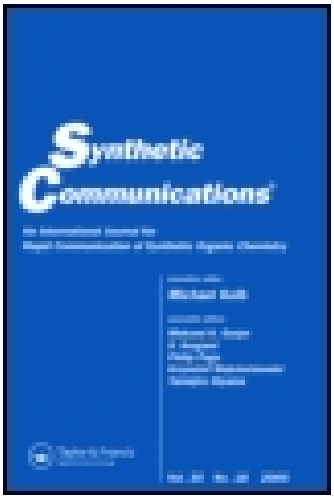

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Preparation and Optical Properties of Novel 3-Alkoxycarbonyl Aza- and Diazacoumarins

Clémentine Féau [a], Emmanuel Klein [a], Paul Kerth [b] & Luc Lebeau [a]

[a] Laboratoire de Chimie Organique Appliquée, CAMB, CNRS-UdS, Faculté de Pharmacie, Illkirch, France

[b] Preventor µTBC GmbH, Pfungstadt, Germany

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PREPARATION AND OPTICAL PROPERTIES OF NOVEL 3-ALKOXYCARBONYL AZA- AND DIAZACOUMARINS

Clémentine Féau,[1] Emmanuel Klein,[1] Paul Kerth,[2] and Luc Lebeau[1]

[1]*Laboratoire de Chimie Organique Appliquée, CAMB, CNRS–UdS, Faculté de Pharmacie, Illkirch, France*
[2]*Preventor μTBC GmbH, Pfungstadt, Germany*

A series of 14 new 3-alkoxycarbonyl 6-aza-, 7-aza-, and 6,8-diaza-coumarins was prepared using various strategies involving either a Knoevenagel or a Pechmann condensation reaction. The coumarin nucleus displays different reactive functional groups allowing straightforward derivatization. The optical properties of the new azacoumarins were measured in methanol.

Keywords: Azacoumarin; chromophore; coumarin; Knoevenagel condensation; Pechmann condensation

Coumarins are structurally simple compounds belonging to the class of benzopyrones.[1,2] Because of their widespread occurrence in nature (more than 1,300 coumarins have been identified from natural source) and their biological and pharmacological activities, they have long been the focus of attention by synthetic chemists. Many natural and synthetic coumarins have shown interesting properties as anticoagulant, antithrombotic, antilipemic, antioxidant, antibiotic, antineoplastic, antiviral, and anti-inflammatory drugs.[3–7] For several decades, the optical properties of coumarins have gained much attention because of applications as optical brighteners, triplet sensitizers, or laser dyes.[8–12] Thus, the synthesis of new members in the coumarin family still is of much interest. With this in mind, we recently focused on the synthesis and spectroscopic study of new 3-alkoxycarbonyl azacoumarins. They are close to the family of coumarin dyes, one of the most famous classes of fluorescent compounds, but 3-alkoxycarbonyl azacoumarins have not attracted much attention until now and no data are available on their coloring and fluorescent properties.

To the best of our knowledge, there are only a few reports in the literature on the synthesis of 3-carboxy azacoumarins and related esters.[13–19] Herein, we describe the preparation and characterization of a series of new 3-alkoxycarbonyl 6-aza-, 7-aza-, and 6,8-diaza-coumarins.

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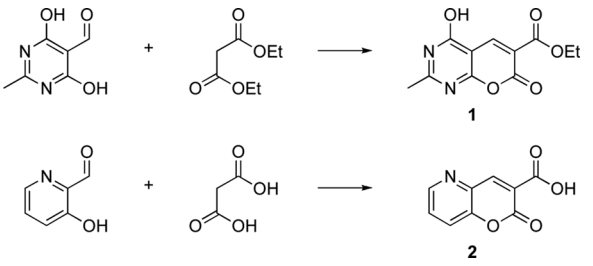
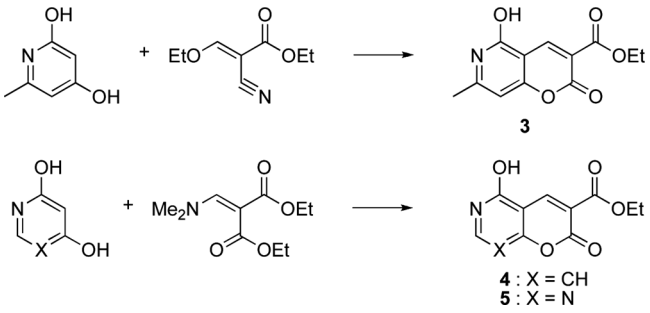
Address correspondence to Luc Lebeau, Laboratoire de Chimie Organique Appliquée, C.A.M.B., UMR 7199 CNRS–UdS, Faculté de Pharmacie, 74 route du Rhin, BP 60024, 67401 Illkirch Cedex, France. E-mail: llebeau@unistra.fr



Scheme 1. Syntheses of 3-carboxy azacoumarins via Knoevenagel condensation reported in the literature.[13,21]

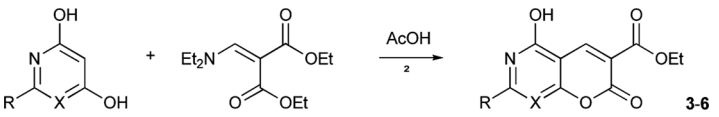
The Knoevenagel and Pechmann reactions are the most common synthetic methods to produce coumarins. The first one involves condensation of salicylic aldehydes with malonic acids or derivatives giving the 3-carboxylic acids (or derivatives) that may successively undergo decarboxylation.[20] The reaction is catalyzed by weak bases. The Knoevenagel condensation was used by Bredereck et al.[13] to prepare 3-ethoxycarbonyl-5-hydroxy-7-methyl-6,8-diazacoumarin **1** and later by Moffett[21] to produce 3-carboxy-5-azacoumarin **2** (Scheme 1). The Pechmann synthesis involves condensation of phenols with β-ketonic esters under acidic conditions.[22] Schmidt and Junek prepared 3-ethoxycarbonyl-5-hydroxy-7-methyl-6-azacoumarin **3** by reacting 2,4-dihydroxy-6-methyl pyridine with ethyl (ethoxymethylene)cyanoacetate (Scheme 2).[17] More recently, Stanovnik et al. reported on the synthesis of 3-ethoxycarbonyl-5-hydroxy-6-azacoumarin **4** and 3-ethoxycarbonyl-5-hydroxy-6,8-diazacoumarin **5** using diethyl *N,N*-dimethylaminomethylene malonate.[19]

Our route to 6-aza- and 6,8-diazacoumarins involved the Pechmann reaction and coumarins **3–6**, which constitute starting material for further modifications. These were prepared according to Kusar et al.[19] However, the reported procedure was slightly modified, and the corresponding dihydroxypyridines or pyrimidines were treated with diethyl *N,N*-diethylaminomethylene malonate (more readily available than diethyl *N,N*-dimethylaminomethylene malonate)[23] in refluxing acetic acid (Table 1). The coumarins were obtained in good yield, except for compound **6**, which was difficult to purify.



Scheme 2. Syntheses of 3-carboxy azacoumarins via Pechmann condensation reported in the literature.[17,19]

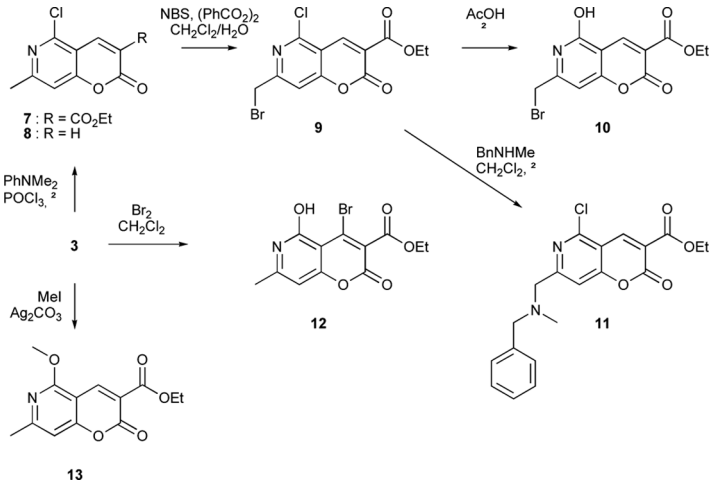
Table 1. 6-Aza- and 6,8-diazacoumarins synthesized via a Pechmann condensation in this work



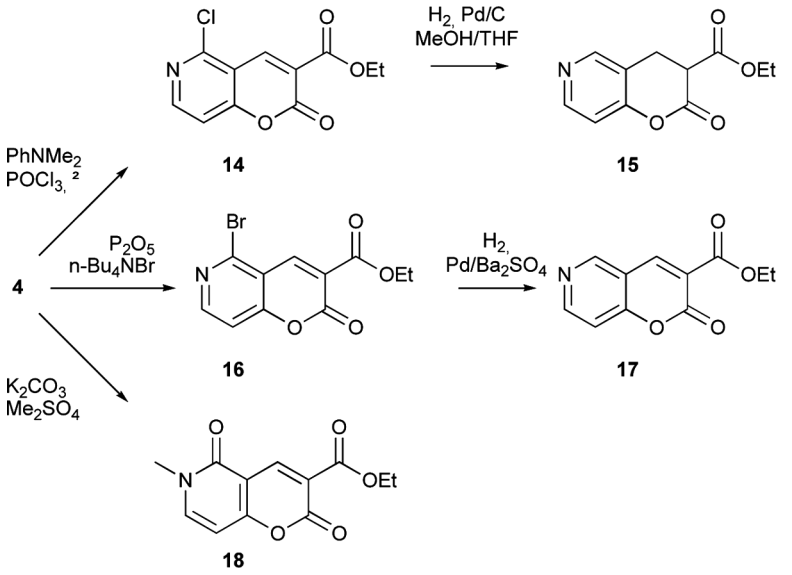
Entry	R	X	Time (h)	Product	Yield (%)
1	CH_3	CH	6	**3**	79
2	H	CH	8	**4**	75
3	H	N	4	**5**	55
4	CH_2OH	N	4	**6**	13

Coumarin **3** was subjected to a series of transformations (Scheme 3). Chlorination at the C^5 position afforded compound **7** together with some decarboxylated coumarin **8**. Coumarin **7** was further brominated at the benzylic position with N-bromosuccinimide (NBS) under radical-promoting conditions. The resulting 7-bromomethyl-5-chlorocoumarin **9** was selectively transformed into 7-bromomethyl-5-hydroxycoumarin **10** by reaction in refluxing acetic acid. On the other side, bromine was easily subjected to nucleophilic displacement by reaction with a secondary amine to yield coumarin **11**. Other reaction sequences were applied to azacoumarin **3**. Treatment of the compound with bromine yielded 4-bromocoumarin **12** in 85% yield, and alkylation at O^5 was achieved by reacting **3** with methyl iodide at room temperature in the presence of silver carbonate to furnish **13** in moderate yield.

Azacoumarin **4** has been as well modified through various functional transformations (Scheme 4). Chlorination with phosphorus oxychloride in the presence of *N,N*-dimethylaniline provided 5-chlorocoumarin **14**, which was quantitatively transformed into substituted pyridine **15** by catalytic hydrogenation. Whatever the catalyst used, reduction of C^4-C^5 double bond could not be avoided. Bromination



Scheme 3. Preparation of 6-azacoumarins substituted at position 7.

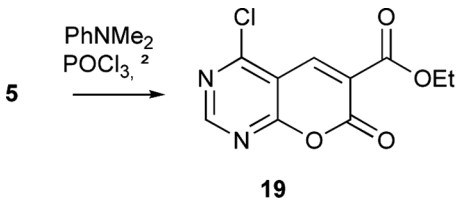


Scheme 4. Preparation of 6-azacoumarins unsubstituted at position 7.

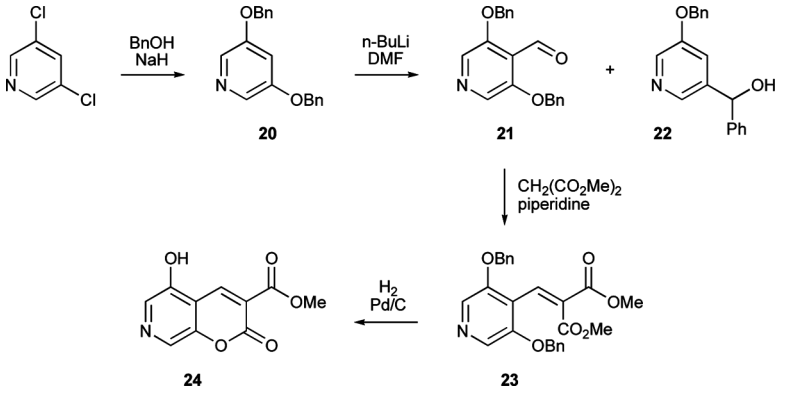
of **4** was realized under the conditions described by Mase et al.,[24] and the resulting bromide **16** offered an access to specifically reduced azacoumarin **17** in 45% yield. Finally, treatment of coumarin **4** with dimethylsulfate resulted in N^6 alkylation, and coumarin **18** was obtained in 89% yield.

The two previous series of transformations were not satisfactorily extended to 6,8-diazacoumarin **5**. As an example, coumarin **5** was converted into the corresponding chloride **19** upon reaction with phosphorus oxychloride (Scheme 5). However, the chlorination compound proved to be unstable and was isolated only in poor yield because of massive back hydrolysis into precursor **5** during purification by silica-gel chromatography.

Until now, no synthesis of 5-hydroxy-7-azacoumarins has been reported in the literature. Indeed, classical routes to coumarins are not effective for that isomer series, and specific access had to be developed. Thus, we propose a synthetic route for the preparation of 3-ethoxycarbonyl-5-hydroxy-7-azacoumarin **24** (Scheme 6). That compound was elaborated starting from 2,5-dichloropyridine, which was converted into dibenzyl ether **20**. Formylation of compound **20** led to 4-pyridinecarboxaldehyde **21** in 61% yield, together with the formation of [5-(benzyloxy)pyridin-3-yl](phenyl)methanol



Scheme 5. Preparation of 5-chloro-6,8-diazacoumarin **19**.



Scheme 6. Preparation of 7-azacoumarin **24**.

22 as a major side product (33%). Knoevenagel condensation of **21** with dimethyl malonate produced compound **23** in good yield, and debenzylation by catalytic hydrogenolysis induced direct cyclization with quantitative formation of 5-hydroxy-7-azacoumarin **24**. Following that strategy, 5-alkoxy derivatives of coumarin **24** may be easily obtained from 3-alkoxy-5-benzyloxypyridine, which is readily available from 3,5-dichloropyridin.

In conclusion, we described the synthesis of a series of original coumarins obtained either by functional transformation of coumarins prepared by known methods (Pechmann or Knoevenagel condensation) or by a new procedure starting from 3,5-dichloropyridine.

EXPERIMENTAL

Silica gel for flash chromatography (silica gel 60, 0.040–0.063 mm, 230–400 mesh ASTM) and thin-layer chromatographic (TLC) plates (0.25-mm silica-gel 60 precoated plates, F_{254}) were from E. Merck. Melting points were determined using a Stuart SMP3 apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker WP-200-Sy, Avance DPX-300, and Avance III-400 instruments, and chemical shifts δ are reported in parts per million (ppm) relative to their standard reference (^{1}H: $CHCl_3$ at 7.27 ppm, HDO at 4.63 ppm, CD_2HOD at 3.31 ppm; ^{13}C: $CDCl_3$ at 77.0 ppm, CD_3OD at 49.0 ppm). Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 Fourier transform (FT)–IR spectrometer in the attenuated total reflection (ATR) mode, and absorptions values ν are in wave numbers (cm^{-1}). Ultraviolet–visible (UV-vis) absorption spectra were recorded in MeOH on a Kontron Uvikon 930 instrument. Absorption maxima λ_{abs} and molar extinction coefficients ε are in $M^{-1}\,cm^{-1}$. Fluorescence spectroscopy was performed with a Jobin Yvon Fluoromax P spectrophotometer equipped with a xenon lamp. Emission maxima λ_{em} are given in nm. Mass spectra (MS) were recorded on a Waters Micromass ZQ instrument, using electrospray ionization (ESI) mode. Mass data are reported in mass units (m/z). High-resolution mass spectra (HRMS) were recorded on a Bruker Daltonics MicrOTOF-Q spectrometer in ESI mode.

Starting Materials

Starting materials were purchased from Sigma-Aldrich (Saint-Quentin Fallavier, France) and Alfa Aesar (Bischeim, France) and used without purification. All reactions were carried out with reagent-grade solvents. When required, solvents were dried according to standard procedures as described elsewhere.[25]

3-Ethoxycarbonyl-5-hydroxy-7-methyl-6-azacoumarin (3)

Diethyl *N,N*-diethylaminomethylene malonate (1.80 g, 7.4 mmol) and 2,4-dihydroxy-6-methylpyridine (0.40 g, 3.2 mmol) were stirred in refluxing AcOH (4 mL) for 6 h. The yellow precipitate was collected by centrifugation and washed with Et_2O to yield analytically pure compound **3** (0.63 g, 79%) as a light orange powder. TLC R_f 0.6 (AcOEt/EtOH 4:1). Mp 291 °C (lit.[17] 295 °C). ^{1}H NMR (DMSO-D_6, 300 MHz) δ 8.51 (s, 1H); 6.27 (s, 1H); 4.25 (q, $J = 7.2$ Hz, 2H); 2.29 (s, 3H); 1.28 (t, $J = 7.2$, 3H). ^{13}C NMR (DMSO-D_6, 50 MHz) δ 166.2; 162.1; 160.0; 155.4; 154.3; 145.6; 111.2; 104.7; 96.6; 60.8; 19.3; 14.0. IR (film) ν 2913; 1615; 1553. UV-vis λ_{abs} 368 (ε 6,500), λ_{em} 442. HRMS (ESI) ($C_{12}H_{11}NO_5$) calcd. 250.0710 $[M + H]^+$; found 250.0706.

3-Ethoxycarbonyl-5-hydroxy-6-azacoumarin (4)

Diethyl *N,N*-diethylaminomethylene malonate (4.38 g, 18.0 mmol) and 2,4-dihydroxypyridine (1.00 g, 9.0 mmol) were stirred in refluxing AcOH (8 mL) for 8 h and for 10 h more at rt. The orange precipitate was collected by filtration and washed with Et_2O to yield analytically pure compound **4** (0.84 g, 40%) as a yellow powder. The filtrate was reduced under vacuum, and the residue was purified by silica-gel chromatography to yield another portion of pure compound **4** (0.73 g, 35%). TLC R_f 0.5 (AcOEt/EtOH 4:1). Mp 265 °C (lit.[19] 245–265 °C, dec.). ^{1}H NMR (CD_3OD, 300 MHz) δ 8.78 (s, 1H); 7.71 (d, $J = 7.2$ Hz, 1H); 6.40 (2, $J = 7.2$ Hz, 1H); 4.34 (q, $J = 7.1$ Hz, 2H); 1.37 (t, $J = 7.1$, 3H). ^{13}C NMR (DMSO-D_6, 50 MHz) δ 167.0; 163.2; 160.9; 156.9; 146.6; 142.9; 113.7; 108.1; 98.1; 62.2; 15.1. IR (film) ν 3192; 3094; 1754; 1682. UV-vis λ_{abs} 372 (ε 11,600), λ_{em} 445. HRMS (ESI) ($C_{11}H_9NO_5$) calcd. 236.0553 $[M + H]^+$; found 236.0548.

3-Ethoxycarbonyl-5-hydroxy-6,8-diazacoumarin (5)

Compound **5** (0.15 g, 55%) was obtained as a light yellow powder after silica-gel chromatography, starting from 2,4-dihydroxypyrimidine and following the same procedure as described for **3**. TLC R_f 0.45 (AcOEt/EtOH 4:1). Mp 213 °C (lit.[19] 213–215 °C). ^{1}H NMR ($CDCl_3/CD_3OD$ 1:1, 300 MHz) δ 8.78 (s, 1H); 8.24 (s, 1H); 4.35 (q, $J = 6.9$ Hz, 2H); 1.36 (t, $J = 6.9$, 3H). ^{13}C NMR ($CDCl_3/CD_3OD$ 1:1, 100 MHz) δ 168.3; 160.1; 156.5; 154.3; 152.3; 146.0; 121.2; 115.9; 62.6; 14.4. IR (film) ν 3209; 1766; 1681. UV-vis λ_{abs} 354 (ε 14,200), λ_{em} 417. HRMS (ESI) ($C_{10}H_8N_2O_5$) calcd. 237.0506 $[M + H]^+$; found 237.0497.

3-Ethoxycarbonyl-5-hydroxy-7-hydroxymethyl-6,8-diazacoumarin (6)

Compound **6** (51 mg, 13%) is obtained as colorless glassy solid after silica-gel chromatography, starting from 2,4-dihydroxy-6-hydroxymethylpyrimidine and following the same procedure as described for **3**. TLC R_f 0.3 (CH_2Cl_2/MeOH 1:1). Mp 212–220 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.86 (s, 1H); 4.46 (s, 2H); 4.18 (q, $J = 7.2$ Hz, 2H); 1.29 (t, $J = 7.2$, 3H). IR (film) ν 2924; 1733; 1608. UV-vis λ_{abs} 351 (ε 7,000), λ_{em} 435. HRMS (ESI) ($C_{11}H_{10}N_2O_6$) calcd. 267.0612 $[M + H]^+$; found 267.0606.

3-Ethoxycarbonyl-5-chloro-7-methyl-6-azacoumarin (7)

Coumarin **3** (55 mg, 0.22 mmol) was stirred in refluxing freshly distilled phosphorus oxychloride (2 mL) for 2 h. Toluene (5 mL) was added, and volatile was removed under reduced pressure. The crude residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and purified over silica gel to yield coumarin **7** (50 mg, 85%) as a white powder. TLC R_f 0.3 (Et_2O/*n*-hexane 1:1). Mp 153 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H); 7.03 (s, 1H); 4.40 (q, $J = 7.2$ Hz, 2H); 2.61 (s, 3H); 1.39 (t, $J = 7.2$, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.8; 161.9; 151.8; 154.6; 150.5; 144.4; 119.0; 111.2; 110.1; 62.3; 24.8; 14.1. IR (film) ν 3067; 2985; 1770; 1606. UV-vis λ_{abs} 309 (ε 6,700), λ_{em} 440. HRMS (ESI) ($C_{12}H_{10}ClNO_4$) calcd. 268.0371 $[M + H]^+$; found 268.0360.

5-Chloro-7-methyl-6-azacoumarin (8)

This compound (6 mg, 14%) was obtained as a white powder and was a side product in the preparation of **7**. TLC R_f 0.2 (Et_2O/*n*-hexane 1:1). Mp 136 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98 (d, $J = 9.9$ Hz, 1H); 7.01 (s, 1H); 6.45 (d, $J = 9.9$ Hz, 1H); 2.59 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 161.5; 161.1; 158.4; 149.0; 139.5; 117.5; 111.8; 110.4; 24.5. IR (film) ν 3084; 1752; 1599. UV-vis λ_{abs} 288 (ε 4,400), λ_{em} 438. HRMS (ESI) ($C_9H_6ClNO_2$) calcd. 196.0165 $[M + H]^+$; found 196.0145.

3-Ethoxycarbonyl-5-chloro-7-bromomethyl-6-azacoumarin (9)

A mixture of coumarin **8** (1.20 g, 4.5 mmol), NBS (1.00 g, 5.6 mmol), and benzoyl peroxide (0.05 g, 0.2 mmol) in H_2O/CH_2Cl_2 2:1 (30 mL) was stirred under irradiation for 5 h using a 150-W spotlight. Ether was added, and the organic layer was washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$, and the residue was purified by chromatography to yield **9** (0.65 g, 42%) as a yellow solid. A fraction of starting material (0.46 g, 38%) was recovered during purification. TLC R_f 0.35 (CH_2Cl_2). Mp 123 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H); 7.34 (s, 1H); 4.52 (s, 2H); 4.44 (q, $J = 7.2$ Hz, 2H); 1.42 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.1; 161.8; 160.9; 154.1; 151.1; 143.7; 120.4; 112.8; 110.7; 62.6; 31.5; 14.1. IR (film) ν 3075; 1765; 1589. UV-vis λ_{abs} 378 (ε 11,600) [306 (ε 2,600)], λ_{em} 453. HRMS (ESI) ($C_{12}H_9BrClNO_4$) calcd. 345.9476 $[M + H]^+$; found 345.9461.

3-Ethoxycarbonyl-5-hydroxy-7-bromomethyl-6-azacoumarin (10)

Compound **9** (0.31 g, 0.90 mmol) was refluxed for 16 h in acetic acid (5 mL). The yellow precipitate was collected by centrifugation and washed with Et_2O to furnish analytically pure coumarin **10** (0.24 g, 81%) as a yellow powder. TLC R_f 0.4 (AcOEt). Mp 276–279 °C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.49 (s, 1H); 6.61 (s, 1H); 4.48 (s, 2H); 4.26 (q, $J = 7.0$ Hz, 2H); 1.29 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 166.6; 163.0; 160.9; 156.1; 152.1; 146.0; 114.2; 108.0; 99.0; 62.0; 28.4; 15.0. IR (film) ν 3045; 2795; 1770; 1667. UV-vis λ_{abs} 379 (ε 5,200), λ_{em} 457. HRMS (ESI) ($C_{12}H_{10}BrNO_5$) calcd. 327.9815 $[M + H]^+$; found 327.9791.

3-Ethoxycarbonyl-5-hydroxy-7-[(*N*-methyl-*N*-benzyl)aminomethyl]-6-azacoumarin (11)

A mixture of coumarin **10** (36 mg, 0.10 mmol) and methylbenzylamine (26 μL, 0.20 mmol) in CH_2Cl_2 (2 mL) was refluxed for 2 h. Volatile was removed under reduced pressure, and the residue was dissolved in Et_2O and washed with water and brine. The organic layer was dried over $MgSO_4$, evaporated, and purified by chromatography to yield tertiary amine **11** (31 mg, 77%) as a yellow glassy solid. TLC R_f 0.2 (CH_2Cl_2/AcOEt 9:1). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.74 (s, 1H); 7.53 (s, 1H); 7.36–7.17 (m, 5H); 4.44 (q, $J = 7.2$ Hz, 2H); 3.73 (s, 2H); 3.65 (s, 2H); 2.32 (s, 3H); 1.42 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.2; 162.3; 162.1; 154.7; 150.5; 144.4; 138.3; 128.8; 128.4; 127.3; 119.4; 112.0; 109.4; 62.4; 62.3; 62.2; 42.8; 14.1. IR (film) ν. 2924; 1767; 1594. UV-vis λ_{abs} 379 (ε 4,500) [319 (ε 4,200)], λ_{em} 478. HRMS (ESI) ($C_{20}H_{20}ClN_2O_4$) calcd. 387.1106 $[M + H]^+$; found 387.1072.

3-Ethoxycarbonyl-4-bromo-5-hydroxy-7-methyl-6-azacoumarin (12)

Bromine (22 μL, 0.44 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise to coumarin **3** (33 mg, 0.14 mmol) in CH_2Cl_2/H_2O 1:1 (8 mL). The resulting mixture was refluxed for 3 h, cooled down to rt, treated with saturated aqueous $Na_2S_2O_3$ (10 mL), and extracted with AcOEt. The organic layer was dried over $MgSO_4$, reduced under vacuum, and purified by silica-gel chromatography to yield **12** (39 mg, 85%) as a yellow glassy solid. TLC R_f 0.6 (Et_2O/EtOH 9:1). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.28 (s, 1H); 4.39 (q, $J = 7.2$ Hz, 2H); 2.44 (s, 3H); 1.40 (t, $J = 7.2$ Hz, 3H). MS (ESI) 328 $[M + H]^+$, 350 $[M + Na]^+$.

3-Ethoxycarbonyl-5-methoxy-7-methyl-6-azacoumarin (13)

Methyl iodide (0.2 mL, 3.2 mmol) and Ag_2CO_3 (0.32 g, 1.1 mmol) were added to coumarin **3** (0.22 g, 0.9 mmol) in $CHCl_3$ (10 mL). The mixture was stirred at rt for 36 h, and a second portion of methyl iodide (0.2 mL, 3.2 mmol) and Ag_2CO_3 (0.16 g, 0.6 mmol) was added before another 24-h stirring period. Volatile was removed, and the residue was purified by chromatography to yield coumarin **13** (95 mg, 41%) as a white powder. TLC R_f 0.15 (Et_2O/*n*-hexane 3:7). Mp 136 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.74 (s, 1H); 6.68 (s, 1H); 4.39 (q, $J = 7.2$ Hz, 2H); 4.07 (s, 3H); 2.51 (s, 3H); 1.40 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ

163.0; 162.9; 162.8; 161.0; 156.1; 144.3; 115.6; 104.7; 100.9; 61.8; 54.5; 25.2; 14.3. IR (film) ν 2958; 1765; 1703; 1614. UV-vis λ_{abs} 334 (ε 13,200) [354 (ε 7,800)], λ_{em} 424. HRMS (ESI) ($C_{13}H_{13}NO_5$) calcd. 264.0866 $[M+H]^+$; found 264.0842.

3-Ethoxycarbonyl-5-chloro-6-azacoumarin (14)

Coumarin **4** (0.10 g, 0.42 mmol) was added to freshly distilled $POCl_3$ (1.3 mL) and *N,N*-dimethylaniline (54 μL, 0.42 mmol), and the resulting mixture was refluxed for 3 h. Volatile was removed under vacuum, and saturated aqueous $NaHCO_3$ was added to the residue to reach pH 7–8. The aqueous solution was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$, reduced under vacuum, and purified by silica-gel chromatography to yield **7** (0.10 g, 93%) as a yellow powder. TLC R_f 0.5 (AcOEt/*n*-hexane 1:1). Mp 99 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.63 (s, 1H); 8.39 (d, $J=5.8$ Hz, 1H); 7.16 (d, $J=5.8$ Hz, 1H); 4.31 (q, $J=7.2$ Hz, 2H); 1.30 (t, $J=7.2$, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.0; 154.6; 152.8; 150.0; 144.9; 144.4; 120.8; 114.0; 111.8; 62.8; 14.5. IR (film) ν 1776; 1695. UV-vis λ_{abs} 295 (ε 8,600) [358 (ε 1,200)], λ_{em} 445. HRMS (ESI) ($C_{11}H_8ClNO_4$) calcd. 254.0220 $[M+H]^+$; found 358.0209.

Ethyl 3,4-Dihydro-2-oxo-2*H*-pyrano[3,2-*c*]pyridine-3-carboxylate (15)

Coumarin **14** (50 mg, 0.23 mmol) and Pd/C 10% (5 mg) in MeOH / tetrahydrofuran (THF) (4:5, 6 mL) were vigorously stirred under a hydrogen atmosphere for 2 h. The catalyst was filtered off and rinsed with MeOH, and the filtrate was evaporated to dryness to yield analytically pure reduced compound **15** (43 mg, 99%) as a colorless glassy solid. TLC R_f 0.3 (AcOEt/EtOH 4:1). ^{1}H NMR (CD_3OD, 300 MHz) δ 8.39 (s, 1H); 8.35 (d, $J=6.6$ Hz, 1H); 7.16 (d, $J=6.6$ Hz, 1H); 4.15 (q, $J=6.9$ Hz, 2H); 3.28 (m, 2H); 1.21 (t, $J=7.2$, 3H). MS (ESI) 222 $[M+H]^+$.

3-Ethoxycarbonyl-5-bromo-6-azacoumarin (16)

Phosphorus pentoxide (0.66 g, 4.7 mmol) was added to coumarin **4** (0.50 g, 2.1 mmol) and *n*-Bu_4NBr (0.83 g, 2.5 mmol) in toluene (6 mL), and the resulting mixture was refluxed for 16 h. Water was added, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and reduced under vacuum, and the residue was purified by silica-gel chromatography to yield coumarin **16** (0.56 g, 88%) as a brown solid. TLC R_f 0.6 (AcOEt/*n*-hexane 1:1). Mp 111 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70 (s, 1H); 8.45 (d, $J=5.6$ Hz, 1H); 7.23 (d, $J=5.6$ Hz, 1H); 4.42 (q, $J=7.2$ Hz, 2H); 1.41 (t, $J=7.2$, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.5; 161.8; 154.6; 153.2; 146.7; 144.8; 121.1; 116.2; 112.2; 63.0; 14.6. IR (film) ν 1768; 1715. UV-vis λ_{abs} 302 (ε 9,600) [360 (ε 2,000)], λ_{em} 444. HRMS (ESI) ($C_{11}H_8BrNO_4$) calcd. 297.9709 $[M+H]^+$; found 297.9690.

3-Ethoxycarbonyl-6-azacoumarin (17)

Coumarin **16** (24 mg, 0.08 mmol) and Pd/$BaSO_4$ 5% (1.2 mg) in CH_2Cl_2 (2.5 mL) were vigorously stirred under a hydrogen atmosphere for 16 h. The catalyst

was filtered off and rinsed with CH_2Cl_2, and the filtrate was evaporated to dryness. The crude residue was purified by silica-gel chromatography to yield compound **17** (8 mg, 45%) as a brown solid. TLC R_f 0.4 (AcOEt). Mp 109 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89 (s, 1H); 8.75 (d, $J = 5.6$ Hz, 1H); 8.57 (s, 1H); 7.28 (d, $J = 5.6$ Hz, 1H); 4.44 (q, $J = 7.2$ Hz, 2H); 1.43 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.2; 160.2; 155.0; 153.9; 151.3; 145.7; 120.1; 114.8; 111.4; 62.4; 14.2. IR (film) ν 1763; 1693. UV-vis λ_{abs} 285 (ε 17,000) [321 (ε 7,700)], λ_{em} 434. HRMS (ESI) ($C_{11}H_9NO_4$) calcd. 220.0604 $[M + H]^+$; found 220.0594.

Ethyl 5,6-Dihydro-6-methyl-2,5-dioxo-2*H*-pyrano[3,2-*c*]-pyridine-3-carboxylate (18)

A mixture of coumarin **4** (140 mg, 0.60 mmol), dimethylsulfate (100 µL, 0.9 mmol), and K_2CO_3 (84 mg, 0.60 mmol) in acetone (15 mL) was refluxed for 1 h. Volatile was removed under reduced pressure, and the residue was purified by chromatography to yield **18** (143 mg, 97%) as a yellow powder. TLC R_f 0.5 (EtOAc/EtOH 4:1). Mp 150 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89 (s, 1H); 7.53 (d, $J = 7.6$ Hz, 1H); 6.27 (d, $J = 7.6$ Hz, 1H); 4.38 (q, $J = 7.2$ Hz, 2H); 3.60 (s, 3H); 1.39 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.1; 162.3; 159.8; 155.6; 146.3; 143.3; 114.7; 107.8; 98.2; 61.8; 37.7; 14.2. IR (film) ν 1760; 1662. UV-vis λ_{abs} 7 (ε 12,700) [264 (ε 4,100)], λ_{em} 447. HRMS (ESI) ($C_{12}H_{11}NO_5$) calcd. 250.0710 $[M + H]^+$; found 250.0693.

3-Ethoxycarbonyl-5-chloro-6,8-diazacoumarin (19)

Compound **19** (22 mg, 9%) was obtained as a brown glassy solid from coumarin **5**, following the same procedure as described for **7** unless *N,N*-dimethylaniline (1 eq.) was introduced in the reaction mixture before refluxing. R_f 0.5 (CH_2Cl_2/EtOH 95:5). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.93 (s, 1H); 8.70 (s, 1H); 4.46 (t, $J = 6.9$ Hz, 2H); 1.43 (t, $J = 6.9$, 3H). MS (ESI) 255 $[M + H]^+$.

3,5-Bis(benzyloxy)pyridine (20)

Benzyl alcohol (12.9 mL, 125.0 mmol) was slowly added to a mixture of 3,5-dichloropyridine (7.38 g, 49.8 mmol) and NaH (60% in oil; 5.00 g, 125.0 mmol) in anhydrous DMF (40 mL) at 0 °C. When hydrogen evolution had ceased, the suspension was heated at 80 °C and stirred for 20 h. Then it was cooled down to rt, water was added, and the dark reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with water and brine and then dried over $MgSO_4$. Solvent was removed under vacuum, and the residue was recrystallized from Et_2O to yield compound **20** (6.52 g, 45%) as a white powder. R_f 0.2 (Et_2O/*cyclo*-hexane 1:1). Mp 111–112 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.07 (d, $J = 2.2$ Hz, 2H); 7.44–7.33 (m, 10H); 6.90 (t, $J = 2.2$ Hz, 1H); 5.09 (s, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.5; 136.0; 130.5; 128.6; 128.2; 127.4; 108.5; 70.4. IR (film) ν 1576. HRMS (ESI) ($C_{19}H_{17}NO_2$) calcd. 292.3512 $[M + H]^+$; found 292.3505.

3,5-Bis(benzyloxy)pyridine-4-carbaldehyde (21)

Pyridine **20** (4.0 g, 13.7 mmol) in anhydrous THF (65 mL) was treated dropwise with 1.6 M *n*-BuLi (9.4 mL, 15.0 mmol) at −78 °C. At the end of the addition, anhydrous DMF (2.1 mL, 27.4 mmol) was introduced in the flask, and the reaction mixture was stirred for 35 min before H_2O (40 mL) was added. Then the mixture was allowed to warm at rt and was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and reduced under vacuum. The residue was purified by silica-gel chromatography to yield compound **21** (2.68 g, 61%) as a white solid. R_f 0.4 (Et_2O). Mp 103 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.61 (s, 1H); 8.21 (s, 2H); 7.45–7.37 (m, 10H); 5.29 (s, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.4; 154.0; 135.5; 129.6; 128.3; 127.7; 127.1; 118.5; 71.4. IR (film) ν 1692; 1559. HRMS (ESI) ($C_{20}H_{17}NO_3$) calcd. 320.1281 $[M+H]^+$; found 320.1266.

[5-(Benzyloxy)pyridin-3-yl](phenyl)methanol (22)

Compound **22** (1.31 g, 33%) is a side product in the preparation of **21** and was obtained as an orange powder. R_f 0.2 (Et_2O). Mp 71 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.24–8.20 (m, 2H); 7.41–7.33 (m, 11H); 5.86 (s, 1H); 5.07 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.9; 140.0; 143.3; 141.1; 136.0; 135.7; 128.5; 128.1; 127.6; 127.4; 126.4; 120.0; 73.1; 70.1. IR (film) ν 3030; 1582. MS (ESI) 292 $[M+H]^+$; 314 $[M+Na]^+$. HRMS (ESI) ($C_{19}H_{17}NO_2$) calcd. 292.1332 $[M+H]^+$; found 292.1322.

Dimethyl 2-{[3,5-bis(Benzyloxy)pyridin-4-yl]methylene}malonate (23)

Dimethyl malonate (0.42 mL, 3.7 mmol) and piperidine (0.32 mL, 3.3 mmol) were added to pyridine carbaldehyde **21** (1.05 g, 3.3 mmol) in anhydrous THF (20 mL). The reaction mixture was refluxed for 8 h. Volatile was removed under reduced pressure, and the residue was dissolved in AcOEt and washed with saturated aqueous NH_4Cl. The organic layer was dried and purified by chromatography to yield **23** (1.32 g, 92%) as a white solid. R_f 0.4 (Et_2O). Mp 74 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.05 (s, 2H); 7.84 (s, 1H); 7.40–7.36 (m, 10H); 5.19 (s, 4H); 3.86 (s, 3H); 3.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.0; 164.7; 152.0; 135.6; 135.1; 130.4; 130.3; 128.5; 128.1; 127.1; 119.8; 71.5; 52.6; 51.8. IR (film) ν 1730; 1713; 1454; 1433. HRMS (ESI) ($C_{25}H_{23}NO_6$) calcd. 434.1598 $[M+H]^+$; found 434.1591.

3-Methoxycarbonyl-5-hydroxy-7-azacoumarin (24)

Compound **23** (91 mg, 0.21 mmol) and Pd/C 10% (6 mg) in THF (5 mL) were vigorously stirred under a hydrogen atmosphere for 4 h. Catalyst was removed by filtration over a celite pad and rinsed with MeOH. The filtrate was reduced under vacuum to yield analytically pure coumarin **24** (48 mg, 99%) as an orange powder. R_f 0.05 (Et_2O). Mp 198 °C. ^{1}H NMR ($CDCl_3/CD_3OD$ 1:1, 300 MHz) δ 8.83 (s, 1H); 8.12 (s, 1H); 8.05 (s, 1H); 3.91 (s, 3H). ^{13}C NMR ($CDCl_3/CD_3OD$ 1:1, 50 MHz) δ 162.6; 155.6; 151.3; 150.0; 142.5; 131.8; 128.0; 119.5; 112.5; 52.4. IR (film) ν 3258; 1732; 1585. MS (ESI) 244 $[M+Na]^+$, 465 $[2M+Na]^+$. UV-vis λ_{abs} 340 (ε 8,500), λ_{em} 555. HRMS (ESI) ($C_{10}H_7NO_5$) calcd. 222.0397 $[M+H]^+$; found 222.0377.

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REFERENCES

1. Murray, R. D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins: Occurrence, Chemistry, and Biochemistry*; John Wiley & Sons: New York, 1982; p. 227.
2. O'Kennedy, R.; Thornes, R. D. *Coumarins: Biology, Applications, and Mode of Action*; John Wiley & Sons: Chichester, 1997; p. 358.
3. Egan, D.; O'Kennedy, R.; Moran, E.; Cox, C.; Prosser, E.; Thornes, R. D. The pharmacology, metabolism, analysis, and applications of coumarin and coumarin-related compounds. *Drug Metab. Rev.* **1990**, *22*, 503–529.
4. Hoult, J. R. S.; Paya, M. Pharmacological and biochemical actions of simple coumarins: Natural products with therapeutic potential. *Gen. Pharmacol.* **1996**, *27*, 713–722.
5. Lacy, A.; O'Kennedy, R. Studies on coumarins and coumarin-related compounds to determine their therapeutic role in the treatment of cancer. *Curr. Pharm. Design* **2004**, *10*, 3797–3811.
6. Kostova, I. Coumarins as-inhibitors of HIV reverse transcriptase. *Curr. HIV Res.* **2006**, *4*, 347–363.
7. Hadjipavlou-Litina, D.; Kontogiorgis, C.; Pontiki, E.; Dakanali, M.; Akoumianaki, A.; Katerinopoulos, H. E. Anti-inflammatory and antioxidant activity of coumarins designed as potential fluorescent zinc sensors. *J. Enzyme Inhib. Med. Chem.* **2007**, *22*, 287–292.
8. Bissell, E. R.; Larson, D. K.; Croudace, M. C. Some 7-substituted-4-(trifluoromethyl)coumarin. *J. Chem. Eng. Data* **1981**, *26*, 348–350.
9. Specht, D. P.; Martic, P. A.; Farid, S. Ketocoumarins: A new class of triplet sensitizers. *Tetrahedron* **1982**, *38*, 1203–1211.
10. Zahradnik, M. *The Production and Application of Fluorescent Brightening Agents*; John Wiley & Sons: New York, 1992.
11. Samsonova, L. G.; Gadirov, R. M.; Ishchenko, V. V.; Khilya, O. V. Photophysical properties of coumarins in relation to the nature of their third and seventh substituents. *Opt. Spectrosc.* **2007**, *102*, 878–884.
12. Christie, R. M.; Morgan, K. M.; Islam, M. S. Molecular design and synthesis of *N*-arylsulfonated coumarin fluorescent dyes and their application to textiles. *Dyes Pigments* **2008**, *76*, 741–747.
13. Bredereck, H.; Simchen, G.; Santos, A. A. Synthesis in the heterocyclic series, IX: Syntheses and reactions of 4,6-disubstituted pyrimidine-5-aldehydes. *Chem. Ber.* **1967**, *100*, 1344–1352.
14. Moffet, R. B. Azacoumarins. *J. Org. Chem.* **1970**, *35*, 3596–3600.
15. Dejardin, J. V.; Lapiere, C. L. Synthèse dans le domaine des azacoumarines, I: Aza-7-coumarine et acide aza-7-coumarine carboxylique-3. *Bull. Soc. Chim. Fr.* **1978**, 72–74.
16. Dejardin, J. V.; Lapiere, C. L. Synthèse dans le domaine des azacoumarines, II: L'acide aza-5-coumarine carboxylique-3 et ses dérivés. *Bull. Soc. Chim. Fr.* **1978**, 75–82.
17. Schmidt, H. W.; Junek, H. Synthesis with nitriles, 50: Cyclization reactions to pyrano[3,2-c]pyridines and pyrano[3,2-c]quinolines with ethoxymethylenemalodinitrile and ethyl cyanoacetate. *Monatsh. Chem.* **1978**, *109*, 1075–1080.
18. Dejardin, J. V.; Lapiere, C. L. Synthèse dans le domaine des azacoumarines, III: Hydroxy-4-aza-5-coumarine et hydroxy-4-aza-7-coumarine. *Bull. Soc. Chim. Fr.* **1979**, 289–298.

19. Kusar, M.; Svete, J.; Stanovnik, B. Diethyl *N,N*-dimethylaminomethylenemalonate in the synthesis of fused heterocyclic systems. *J. Heterocycl. Chem.* **1996**, *33*, 1041–1046.
20. Jones, G. The Knoevenagel condensations. In *Organic Reactions*; Wiley-Interscience: New York, 1967; vol. 15, pp. 204–599.
21. Moffet, R. B. Azacoumarins. *J. Org. Chem.* **1970**, *35*, 3596–3600.
22. Sethna, S.; Phadke, R. The Pechmann reaction. *Org. React.* **1953**, *7*, 1–58.
23. Hurd, C. D.; Sherwood, L. T. J. The 1-amino-2-nitroethenes. *J. Org. Chem.* **1948**, *13*, 471–476.
24. Kato, Y.; Okada, S.; Tomimoto, K.; Mase, T. A facile bromination of hydroxyheteroarenes. *Tetrahedron Lett.* **2001**, *42*, 4849–4851.
25. Lebeau, L.; Olland, S.; Oudet, P.; Mioskowski, C. Rational design and synthesis of phospholipids for the two-dimensional crystallization of DNA gyrase, a key element in chromosome organization. *Chem. Phys. Lipids* **1992**, *62*, 93–103.