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Research Article

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Synthesis of 6-Phenylethynyl Substituted Coumarins *via* a Sonogashira Coupling

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Abstract In order to develop a chemical approach to analyze opto-electronic and biological properties of the coumarin scaffold, we focused on the synthesis library of new coumarin analogues. Starting from salicylic aldehyde derivatives, the coumarin scaffold was constructed and functionalized via selective iodination, Knoevenagel condensation and Sonogashira coupling. Our library model proposes the functionalization of three positions of the coumarin backbone. An ester or carboxylic acid at **3**-position, various alkynyl moieties at **6**-position and electrodonating groups (EDG) (OH, OCH_3, NEt_2) at **7**-position were introduced. The structures of the synthesized compounds were confirmed by Nuclear Magnetic Resonance (NMR) and High-Resolution Mass Spectrometry (HRMS). Due to the abundance and low cost of terminal acetylenes, these new conjugated enyne coumarins are promising precursors with high synthetic potential, leading to the development of complex systems with a wide range of properties.

Keywords Coumarin, Sonogashira Coupling, alkynyl, electrodonating group

Introduction

Coumarins are a family of very large and extensively studied compounds used in diverse applications. They possess a great significance in organic chemistry and are present in many natural products. Up to now coumarins and its derivatives have been used for their biological activities such as antibacterial [1,2], anti-Alzheimer's disease [3], antifungal [4,5] and antioxidant [6]. In 2012, David E. Jane et al. showed that 6-iodo, 6,8-dibromo and 6,8-diiodo coumarin derivatives are good inhibitors of *N*-methyl-D-aspartate receptors (NMDARs) involved in the control of certain neurological disorders [7]. Since the coumarin core is not a typical synthon or starting material used in organic synthetic chemistry, its direct functionalization is not current otherwise with specific synthetic purpose. In other words, most coumarins are synthesized or designed *de novo* rather than *via* post functionalisation of the coumarin scaffold. The direct electrophilic bromination and Vilsmeier formylation reaction will occur in the site-selectively with some of 7-amino or 7-hydroxyl coumarins [8,9]. However, the direct introduction of alcohols, ketones, and carboxylic acids has historically not been very successful [10]. That's why convergent synthetic ways,

i.e., cross-coupling reaction [11–13], has emerged to allow assembly of diversified coumarin structures. Among them, alkynyl coumarins, are not only found to be useful in pharmaceuticals [14] but also in applications such as functional organic materials [15], for instance organic light-emitting diodes (OLEDs) [16], semiconductors [17] and photovoltaics [18]. For these applications, increasing or maintaining the conjugation *via* certain function is very important and useful. To our and further purpose studies, we attached to the coumarin scaffold, alkynyl at the **6**-position. Also, at **7**-position, electro donor groups (EDG) such as hydroxy (OH), methoxy (OCH_3) and diethylamino (NEt_2) groups were added [19]. Alknyl moiety was introduced to explore the consequences of spatial separation of the ketone and the fluorophore while maintaining the conjugation between these two components. We then synthesized the derivatives compounds *via* a Sonogashira reaction (Pd-catalyzed cross-coupling strategy). The advantage *vs.* Stille reaction is the non-used of toxic and non-environmental organostain compounds. The coupling strategy used here also is better than Suziki-Miyaura reaction, while the boronic acid obtained from this reaction are sometime unstable.

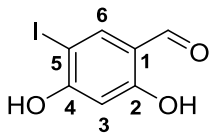
Material and Methods

All air and moisture sensitive manipulations were performed either under nitrogen or *in vacuo* using standard Schlenk techniques. Anhydrous solvents (Et_2O, THF, toluene and cyclohexane) were purchased from Sigma Aldrich. In addition, MeOH was stored over oven dried 4 Å molecular sieves under argon for at least 16 hours prior to use. All chemicals were purchased from Alfa Aesar, Sigma Aldrich and TCI Europe and were used without further purification unless otherwise stated. Analytical thin layer chromatography (TLC) was performed with Merck SIL G/UV_{254} plates. Compounds were visualized by exposure to UV light at 254 nm or by dipping the plates in solutions of phosphomolybdic acid, ninhydrin or potassium permanganate followed by heating. Flash column chromatography was performed in air with silica gel 60 (Fluka). NMR spectra were recorded on an Advance II 400 Bruker or an Advance II 500 Bruker spectrometers in the solvent indicated. ^{1}H-NMR and ^{13}C-NMR chemical shifts (δ) are reported in parts per million (ppm) relative to the TMS scale. Coupling constants *J* are quoted in Hz. The following abbreviations are used for the proton spectra multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, qt: quintuplet, m: multiplet, br: broad, dd: double doublet, dt: double triplet. Coupling constants (*J*) are reported in Hertz (Hz). High-resolution electrospray mass spectra in the positive ion mode were obtained on a Q-TOF Ultima Global hybrid quadrupole/time-of-flight instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source and an additional sprayer (Lock Spray) for the reference compound. The source and desolvation temperatures were kept at 80 and 150 °C, respectively. Nitrogen was used as the drying and nebulizing gas at flow rates of 350 and 50 L/h, respectively. The capillary voltage was 3.5 kV, the cone voltage 100 V and the RF lens1 energy was optimized for each sample (40 V). For collision-induced dissociation (CID) experiments, argon was used as collision gas at an indicated analyser pressure of 5.10^{-5} Torr and the collision energy was optimized for each parent ion (50-110 V). Lock mass correction, using appropriate cluster ions of sodium iodide $(NaI)_nNa^+$, was applied for accurate mass measurements. The mass range was typically 50-2050 Da and spectra were recorded at 2 s/scan in the profile mode at a resolution of 10000 (FWMH).

Starting Iodo-Coumarine

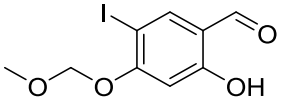
The 6-iodo-7-substituted-2-oxo-2*H*-chromen-3-carboxylic acid were synthesized by a sequence of procedures shown in scheme 1 and 2**.** Compounds 7-(diethylamino)-6-iodo-2-oxo-2*H*-chromene-3-carboxylic acid [19], 2-hydroxy-5-iodobenzaldehyde [20], 2-hydroxy-5-iodo-4-methoxybenzaldehyde [21], 4-(benzyloxy)-2-hydroxybenzaldehyde [22] and 2-hydroxy-4-(methoxy)benzaldehyde [23] were synthesized according to methods reported in literature.

2,4-dihydroxy-5-iodobenzaldehyde (1a)



To a solution of 4-(benzyloxy)-2-hydroxy-5-iodobenzaldehyde (2.35 g, 6.63 mmol) in dry DCM (85 mL) was added dropwise a BBr_3 solution (1.0 M in DCM, 20 mL, 20 mmol) at -78 °C under N_2. The reaction mixture was stirred at this temperature for 2 h then allowed to warm up 0 °C for one more hour (1 h). Water was then added and the reaction mixture stirred for another hour. The aqueous layer was extracted with DCM and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was washed with cyclohexane to give the title compound (1.48 g, 86 %) as a solid.^{1}H NMR (500 MHz, DMSO-d_6): δ_H 11.45 (br, 1 H, O<u>H</u>), 10.88 (br, 1 H, O<u>H</u>), 9.91 (s, 1 H, C<u>H</u>O), 7.94 (s, 1 H, H_6), 6.52 (s, 1 H, H_3); ^{13}C NMR (250 MHz, DMSO-d_6) δ_C : 188.7 (-<u>CH</u>O), 163.1, 162.5 (C-5, C-2), 139.9 (C-6), 117.6 (C-1), 102.0 (C-3), 74.0 (C-5); HRMS : calcd. for [$C_7H_5IO_3$]: m/z 263.9283 $[M-H]^-$, found 263.9288 $[M-H]^-$.

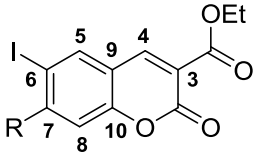
2-hydroxy-5-iodo-4-(methoxymethoxy)benzaldehyde (1b)



To a solution of 2-hydroxy-4-(methoxymethoxy)benzaldehyde (3.0 g, 16.2 mmol), in dry DMF (30 mL) was added N-Iodosuccinimide (4.44 g, 19.77 mmol) at once, the reaction mixture was then stirred at room temperature for 16 h. The reaction mixture was diluted with DCM, and poured into saturated sodium bicarbonate solution. The organic layer was washed with water, dried over $MgSO_4$ and concentrated *in vacuo.* The resulting oil was purified by silica gel column chromatography (cyclohexane/EtOAc (7:3)) to afford the title compound (3.09 g, 50 %) as a solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ_H*:* 11.04 (s, 1 H, O<u>H</u>), 9.98 (s, 1 H, C<u>H</u>O), 7.99 (s, 1 H, H_6), 6.69 (s, 1 H, H_3), 5.31 (s, 2 H, CH_2O), 3.40 (s, 3 H, OCH_3); ^{13}C NMR (250 MHz, DMSO-d_6) δ_C: 189.2 (-CHO), 162.5 (C-4), 160.9 (C-2), 139.5 (C-6), 119.0 (C<u>-</u>1), 102.5 (C-3), 94.6 (O-C-O-), 75.4 (C-5), 56.1 (CH_3-O-); HRMS : calcd. for [$C_9H_9IO_4$]: m/z 307.9546 $[M+H]^+$, found 307.9551 $[M+H]^+$.

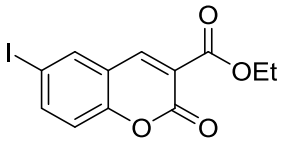
General Procedure 1

Synthesis of Ethyl 6-iodo-7-substituted-2-oxo-2*H*-chromen-3- carboxylate **(2)**



To a solution of the appropriate iodosalicylicaldehyde (1 mmol, 1 equiv.) and diethyl malonate (1.2 equiv.) in absolute ethanol (1.2 mL), a catalytic amount of piperidine (0.1 equiv.) and few drops of glacial acetic acid were added. The reaction mixture was let under reflux for 16 h. A precipitate was formed, filtered off, washed with EtOH, dried and recrystallized from EtOH to lead to desired compounds.

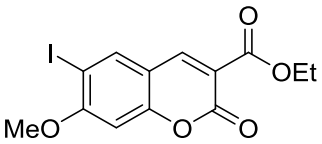
Synthesis of ethyl 6-iodo-2-oxo-2*H*-chromen-3-carboxylate (**2a**)



Desired product was obtained in 13% yield as a solid from 2-hydroxy-5-iodobenzaldehyde (10 g, 40.3 mmol) according to general Procedure **1**.

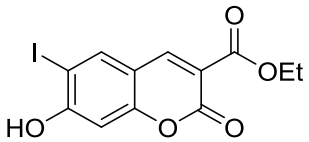
^{1}H NMR (500 MHz, DMSO-d_6) δ_H : 8.16 (s, 1 H, H_4), 8.25 (d, 1 H, J = 2.2 Hz, H_5), 7.94 (dd, 1 H, J = 2.2, 8.7 Hz, H_7), 7.20 (d, 1 H, J = 8.7 Hz, H_8), 4.24 (q, 2 H, J = 7.1 Hz, -C<u>H</u>$_2$CH$_3$), 1.24 (t, 3 H, J = 7.1 Hz, CH_2C<u>H</u>$_3$); ^{13}C NMR (250 MHz, DMSO-d_6) δ_C : 162.3 (-<u>C</u>OOEt), 155.5 (C-2), 154.1 (C-10), 147.2 (C-7), 142.2 (C-5), 138.0 (C-9), 120.0 (C-8), 118.5 (C-4), 118.4, 88.3, 61.3 (-<u>C</u>H$_2$CH$_3$), 14.0 (-CH$_2$<u>C</u>H$_3$); HRMS: calcd. for [$C_{12}H_9IO_4$]: m/z 343.9546 $[M+H]^+$, found 343.9549 $[M+H]^+$.

Ethyl 6-iodo-7-methoxy-2-oxo-2*H*-chromene-3-carboxylate (2b)



Desired product was obtained in quantitative yield as a solid from 2-hydroxy-5- iodobenzaldehyde (9 g, 32 mmol) according to general Procedure **1**.^{1}H NMR (500 MHz, DMSO-d_6) δ_H : 8.68 (s, 1 H, H_4), 8.36 (s, 1 H, H_6), 7.13 (s, 1 H, H_8), 4.28 (q, 2H, J = 7.1 Hz, -C$\underline{H}_2$CH$_3$), 3.96 (s, 3H, -OC$\underline{H}_3$), 1.30 (t, 3H, J = 7.1 Hz, CH$_2$C$\underline{H}_3$);^{13}C NMR (250 MHz, DMSO-d_6) δ_C : 162.6 (-COOEt), 162.4 (C-7), 157.0 (C-10), 155.9 (C-2), 148.0 (C-5), 139.6 (C-4), 114.9 (C-9), 113.4 (C-3), 99.3 (C-8), 81.9 (C-6), 61.0 (-$\underline{C}$H$_2$CH$_3$), 57.6 (-O$\underline{C}$H$_3$), 14.1 (-CH$_2\underline{C}$H$_3$); HRMS : calcd. for [$C_{13}H_{11}IO_5$]: m/z 373.9651 [M+H]$^+$, found 373.9660 [M+H]$^+$.

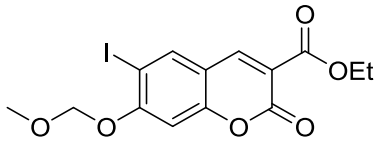
Ethyl 7-hydroxy-6-iodo-2-oxo-2*H*-chromene-3-carboxylate (2c)



Desired product was obtained in 15 % yield as a solid from 2,4-dihydroxy-5- iodobenzaldehyde (1.48 g, 5.6 mmol) according to general Procedure **1**.

^{1}H NMR (500 MHz, DMSO-d_6) δ_H : 11.95 (br, 1 H, O$\underline{H}$), 8.63 (s, 1 H, H_4), 8.31 (s, 1 H, H_5), 6.79 (s, 1 H, H_8), 4.25(q, 2H, J = 7.1 Hz, -C$\underline{H}_2$CH$_3$), 1.27 (t, 3H, J = 7.1 Hz, CH$_2$C$\underline{H}_3$); ^{13}C NMR (250 MHz, DMSO-d_6) δ_C: 163.9 (-COOH); 162.5 (C-7); 158.2 (C-10); 156.4 (C-2); 146.3 (C-5); 140.9 (C-4); 115,1 (C-9); 112.6 (C-3); 98.2 (C-8); 81.5 (C-6); 61.0 (-$\underline{C}$H$_2$CH$_3$), 14.0 (-CH$_2\underline{C}$H$_3$). HRMS: calcd. for [$C_{12}H_9IO_5$]: m/z : 359.9495 [M+H]$^+$, found 359.9500 [M+H]$^+$.

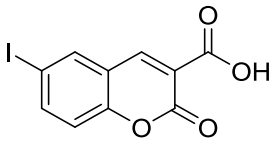
Ethyl 6-iodo-7-(methoxymethoxy)-2-oxo-2*H*-chromene-3-carboxylate (2d)



Desired product was obtained in 80 % yield as a solid from 2-hydroxy-5-iodo-4- (methoxymethoxy)benzaldehyde (2.0 g, 6.49 mmol) according to general Procedure **1**.

^{1}H NMR (500 MHz, DMSO-d_6) δ_H : 8.67 (s, 1 H, H_4), 8.40 (s, 1 H, H_5), 7.14 (s, 1H, H_8), 5.43 (s, 2H, O-CH$_2$-O), 4.28 (q, 2H, J = 7.1 Hz, C$\underline{H}_2$CH$_3$), 3.43 (s, 3H, OC$\underline{H}_3$), 1.30 (t, 3H, J = 7.1 Hz, -CH$_2$C$\underline{H}_3$). ^{13}C NMR (250 MHz, DMSO-d_6) δ_C : 162.5 (-COOEt), 159.5 (C-7), 156.3 (C-10), 155.7 (C-2), 147.7 (C-5), 139.8 (C-4), 114.6 (C-9), 114.1 (C-3), 101.5 (C-8), 94.9 (O-$\underline{C}$H$_2$-O) 82.6 (C-6), 61.0 (-$\underline{C}$H$_2$CH$_3$), 56.3 (-O$\underline{C}$H$_3$), 14.0 (-CH$_2\underline{C}$H$_3$); HRMS : calcd. for [$C_{14}H_{13}IO_6$]: m/z 403.9757 [M+H]$^+$, found 403.9758 [M+H]$^+$.

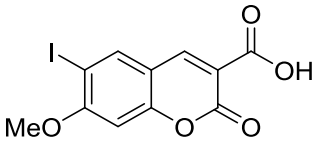
6-iodo-2-oxo-2*H*-chromene-3-carboxylic acid (3a)



A solution of ethyl 6-iodo-2-oxo-2*H*-chromene-3-carboxylate (4.0 g, 11.62 mmol) and NaOH 10 % (18 mL) in ethanol (18 mL) was refluxed during 16 h. After cooling, the reaction mixture was evaporated. The residue was dissolved in water and acidified with diluted HCl to reach pH 1-2. The precipitate was filtered, dried and crystallized from ethanol to give the title compound (3.5 g, 93 %) as a solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ_H : 8.65 (s, 1H,

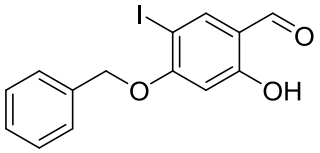
H_4), 8.29 (d, 1H, *J* = 2.2 Hz, H_5), 7.99 (dd, 1H, *J* = 2.2, 8.7 Hz, H_7), 7.25 (d, 1H, *J* = 8.7 Hz, H_8); ^{13}C NMR (250 MHz, DMSO-d_6) δ_C : 163.8 (-COOH), 156.2 (C-2), 154.1 (C-10), 146.9 (C-7), 142.1 (C-5), 138.0 (C-9), 120.3 (C-4), 119.4 (C-8), 118.5 (C-3), 88.4 (C-6); HRMS : calcd. for [$C_{10}H_5IO_4$]: m/z 315.9233 $[M+H]^+$, found 315.9260 $[M+H]^+$.

6-iodo-7-methoxy-2-oxo-2*H*-chromene-3-carboxylic acid (3b)



A solution of ethyl 6-iodo-7-methoxy-2-oxo-2*H*-chromene-3-carboxylate (1.47 g, 3.93 mmol) and NaOH 10 % (6 mL) in ethanol (6 mL) was refluxed during 16 h. After cooling, the reaction mixture was evaporated to dryness; the residue was dissolved in water and acidified with diluted hydrochloric acid (pH 1-2). The precipitate was filtered, dried and crystallized from ethanol to give the title compound (1.30 g, 96 %) as a solid.^{1}H NMR (500 MHz, DMSO-d_6) δ_H : 8.67 (s, 1H, H_4), 8.36 (s, 1H, H_5), 7.12 (s, 1 H, H_8), 3.96 (s, 3H, OC$\underline{H}_3$) ;^{13}C NMR (250 MHz, DMSO-d_6) δ_C : 163.9 (-COOH); 162.2 (C-7), 156.9 (C-10) 156.6 (C-2), 147.7 (C-5), 139.5 (C-4), 114.6(C-3) , 113.5 (C-9), 99. 3 (C-8) , 81.8 (C-6), 57.5 (-O$\underline{C}H_3$); HRMS : calcd. for [$C_{11}H_7IO_5$]: m/z 345.9338 $[M+H]^+$, found 345.9342 $[M+H]^+$.

4-(benzyloxy)-2-hydroxy-5-iodobenzaldehyde (3c)



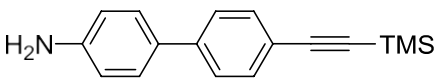
A solution of iodine monochloride (1.7 g, 10.52 mmol) in glacial acetic acid (5.3 mL) was added dropwise to a solution of 4-(benzyloxy)-2-hydroxybenzaldehyde (2.0 g, 8.77 mmol), which was preconsciously dissolved before in glacial acetic acid (13 mL) and then stirred. The mixture was stirred like this at room temperature for 2 h and the resulting suspension was removed by filtration. The residue was dissolved with EtOAc, washed with a saturated sodium thiosulfate solution, dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound (1.31 g, 60 %) as a solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ_H : 11.16 (br, 1H, O$\underline{H}$), 9.97 (s, 1H, H_4), 8.03 (s, 1 H, H_5), 7.50 (d, 2H, *J* = 7.2 Hz, Ar$\underline{H}$), 7.43 (t, 2H, *J* = 7.6 Hz, ArH), 7.36 (t, 2H, *J* = 7.3 Hz, Ar$\underline{H}$), 6.66 (s, 1 H, H_8), 5.25 (s, 2H, -C$\underline{H}_2$O-); ^{13}C NMR (250 MHz, DMSO-d_6) δ_C : 189.4 , 162.8, 162.2, 139.6, 135.7, 128.3 (×2), 127.8, 127.0 (×2), 118.1 (C-9), 101.0 (C-8), 75.0 (C-6), 70.3 (-$\underline{C}H_2$O-); HR-MS (ESI, m/z) : calcd. for [$C_{14}H_{11}IO_3$]: m/z 353.9753. found 353.9757.

Starting 4'-ethynyl-[1,1'-biphenyl]-4-amine

The 4'-ethynyl-[1,1'-biphenyl]-4-amine was synthesized by a sequence of procedures explain in the results and discussions: the compounds 4-iodo-4'-nitro-1,1'-biphenyl [24] and 4'-iodo-[1,1'-biphenyl]-4-amine [23] were synthesized according to literature procedures.

4'-((trimethylsilyl)ethynyl)-[1,1'-biphenyl]-4-amine

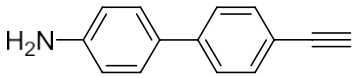


A mixture of 4'-iodo-[1,1'-biphenyl]-4-amine (2.06 g, 6.98 mmol), ethynyltrimethylsilane (1.08 mL, 7.68 mmol), CuI (66 mg, 0.349 mmol) and $PdCl_2(PPh_3)_2$ (147 mg, 0.209 mmol) in dry triethylamine (33 ml) was heated at reflux for 16 h under argon. The reaction mixture was filtered over Celite® and washed with EtOAc. The filtrate was evaporated *in vacuo*, the residue was purified by flash chromatography on silica gel eluting with a mixture of

cyclohexane:EtOAc in different gradient (9:1 to 4:6) to yield a colorless solid (1.63 g, 88 %). Data matches literature values[25].

^{1}H NMR (250 MHz, $CDCl_3$) δ_H : 7.52 (m, 4H, ArH), 7.45 (d, 2H, *J* = 8.3 Hz, ArH), 6.77 (d, 2H, *J* = 8.3 Hz, ArH), 3.76 (br, 2H, NH_2), 0.31 (s, 9H, $SiCH_3$). ^{13}C NMR (250 MHz, $CDCl_3$) δ 151.6, 151.4, 149.4, 148.7, 127.5, 126.4, 125.1 124.6, 103.68, 0.13. HRMS : calcd. for [$C_{15}H_{19}NSi$]: m/z 241.1287

4'-ethynyl-[1,1'-biphenyl]-4-amine



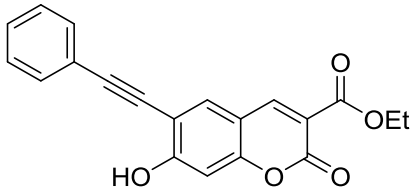
A solution of 4'-((trimethylsilyl)ethynyl)-[1,1'-biphenyl]-4-amine (1.63 g, 6.14 mmol) and NaOH 10 % (14.6 mL) in methanol (61 mL) was refluxed during 16 h. After cooling, the reaction mixture was evaporated and dried. The residue was purified by flash chromatography on silica gel eluting with cyclohexane:EtOAc (9:1 to 1:9) to yield pale orange solid (1.02 g, 86 %). Data matches literature values.[6]

^{1}H NMR (500 MHz, $CDCl_3$) δ_H : 7.58 (m, 4H, ArH), 7.47 (d, 2 H, *J* = 8.7 Hz, ArH), 6.78 (d, 2H, *J* = 8.7 Hz, ArH), 3.60 (br, 2H, NH_2). ^{13}C NMR (250 MHz, $CDCl_3$) δ 151.3, 149.7, 149.2, 132.56, 148.5, 131.8, 127.4, 126.0, 124.7, 124.3, 84.28, 77.67. HRMS: calcd. for [$C_{14}H_{11}N$]: m/z 193.0891

General procedure 2: Synthesis of *phenylethylnyl coumarin* by Sonogashira coupling

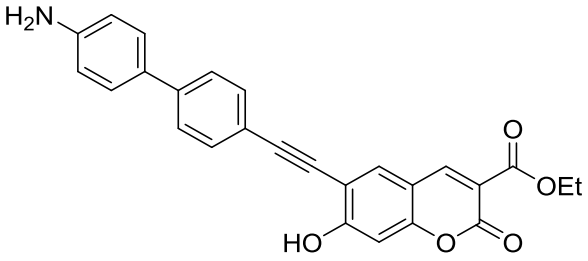
Using a procedure of Rozhkov et al. [19], iodocoumarin derivatives (0.25 mmol, 1 eq), alkyne (0.5 mmol, 2 eq), bis(diphenylphosphino)palladium dichloride (5%, 0.0125 mmol), CuI (10%, 0.025 mmol) and NEt_3 (2 mmol, 8 eq) were dissolved in 2 mL of DMF and stirred at r.t. for 16 h (unless noted otherwise). Progress of the reaction was monitored by TLC using CH_2Cl_2-MeOH 10:1 mixture as eluent. Upon completion of the reaction, solvent was evaporated *in vacuo* and solid residue was purified by flash chromatography using CH_2Cl_2-MeOH 9:1 step gradient solvent system as an eluent (unless noted otherwise). The following new compounds were prepared using this procedure:

Ethyl 7-hydroxy-2-oxo-6-(phenylethynyl)-2*H*-chromen-3-carboxylate (5a)



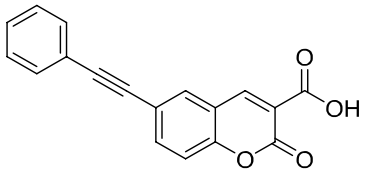
According to General Procedure **2**, ethyl 7-hydroxy-6-iodo-2-oxo-2*H*-chromene-3- carboxylate (0.150 g, 0.41 mmol) in DMF (3.5 mL) was reacted with phenylacetylene (91 µL, 0.83 mmol), bis(diphenylphosphino)palladium dichloride (14 mg, 0.208×10^{-3} mmol), CuI (7.9 mg, 0.416×10^{-3} mmol) and NEt_3 (0.464 mL, 3.33 mmol). The reaction mixture was stirred at room temperature before quenching by water. The aqueous mixture was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated *in vacuo* which, after column chromatography (CH_2Cl_2-MeOH 9:1), gave the phenylethynyl coumarine (0.066 g, 47%) as a solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H : 8.90 (s, 1H, H_4), 8.24 (s, 1H, OH), 7.94 (d, 2H, *J*= 7.0 Hz, ArH), 7.81 (s, 1 H, H_5), 7.63 (s, 1 H, H_8), 7.55 (m, 2H, ArH), 7.46 (m, 1H, ArH), 4.31(q, 2 H, *J* = 7.1 Hz, -CH_2CH_3), 1.32 (t, 3 H, *J* = 7.1 Hz, -CH_2CH_3); ^{13}C NMR (250 MHz, DMSO-d_6) δ_C : 162.5 (-COOEt), 157.2 (C-7), 155.9 (C-10), 152.5 (C-2), 149.3 (C-5), 129.2 - 124.6 (C-4, 6 x ArC), 122.3 (C-3), 115.2 (C-6), 114.5 (C-8), 101.4 (-C≡C-), 98.8 (-C≡C-), 60.9 (-CH_2CH_3), 13.8 (-CH_2CH_3). HR-MS (ESI, m/z) $[M+H]^+$: calcd. for $C_{20}H_{14}O_5$, 334.0841, found 334.0844.

Ethyl-6-((4'-amino-[1,1'-biphenyl]-4-yl)ethynyl)-7-hydroxy-2-oxo-2H-chromene-3- carboxylate (5b)



According to General Procedure **2**, ethyl 7-hydroxy-6-iodo-2-oxo-2*H*-chromene-3- carboxylate (0.150 g, 0.42 mmol) in DMF (3.3 mL) was reacted with 4'-ethynyl-[1,1'- biphenyl]-4-amine (96 mg, 0.51 mmol), bis(diphenylphosphino)palladium dichloride (15 mg, 0.021×10^{-3} mmol), CuI (8 mg, 0.042×10^{-3} mmol) and NEt_3 (0.464 mL, 3.33 mmol). Water was added to the reaction mixture; the residue was filtered. The filtrate was concentrated *in vacuo* then washed with DCM, MeOH and Et_2O to give the title compound (0.112 g, 63 %) as a solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H : 8.88 (s, 1H, H_4), 8.19 (s, 1H, O<u>H</u>), 7.91 (d, 2H, *J*= 8.4 Hz, Ar<u>H</u>), 7.79 (s, 1 H, H_5), 7.70 (d, 2H, *J* = 8.3 Hz, Ar<u>H</u>), 7.56 (s, 1 H, H_8), 7.46 (d, 2H, *J* = 8.2 Hz, Ar<u>H</u>), 6.66 (d, 2H, *J* = 8.4 Hz, Ar<u>H</u>), 5.14 (s, 2H, N<u>H</u>$_2$), 4.30 (q, 2H, *J* =7.1 Hz, C<u>H</u>$_2$CH$_3$), 1.32 (t, 3H, *J* = 7.1 Hz, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (250 MHz, DMSO-d_6) δ_C : 162.8 (-COOEt), 157.7 (C-7), 157.3 (C-10), 156.2 (C-2), 152.7 (C-NH$_2$), 149.7- 125.4 (C-5, C-4, 12 x ArC), 122.2 (C-9), 115.4 (C-3), 114.7 (C-6), 114.3 (C-8), 100.9 (-C≡<u>C</u>-), 99.0 (-<u>C</u>≡C-), 61.2 (-<u>C</u>H$_2$CH$_3$), 14.2 (-CH$_2$<u>C</u>H$_3$). HR-MS (ESI, m/z) $[M+H]^+$: calcd. for $C_{26}H_{19}O_5N$, 425.1263, found 425.1265.

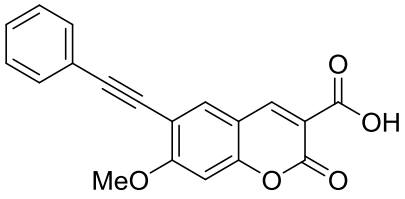
2-oxo-6-(phenylethynyl)-2*H*-chromene-3-carboxylic acid (6a)



According to General Procedure **2**, 6-iodo-2-oxo-2*H*-chromene-3-carboxylic acid (0.1 g, 0.31 mmol) in DMF (2.5 mL) was reacted with phenylacetylene (70 µL, 0.63 mmol), bis(diphenylphosphino)palladium dichloride (11 mg, 0.158×10^{-3} mmol), CuI (6 mg, 0.316×10^{-3} mmol) and NEt_3 (0.35 mL, 2.53 mmol) which, after column chromatography (90 % CH_2Cl_2, 10% MeOH), gave the *phenylethynyl coumarine J* = 9.0 Hz, Ar<u>H</u>), (0.100 g, 77%) as a solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H : 8.90 (s, 1H, H_4), 7.88 (s, 1H, H_5), 7.87 (dd, 1H, *J* = 2.5, 7.5 Hz, H_7), 7.53 (m, 2H, Ar<u>H</u>), 7.46 (d, 1H, H_8) 7.37 (m, 3H, Ar<u>H</u>); ^{13}C NMR (250 MHz, DMSO-d_6) δ_C 163.8 (-COOH), 162.3 (C-7), 154.0 (C-2), 151.0 (C-10), 138.6 (C-5) , 133.1, 131.9 (×2), 129.3, 128.7 (×2), 122.3 (C-4), 118.7 (C-3), 117.7 (C-6, C-9), 115.8 (C-8), 91.2 (-C≡C-), 86.5 (-<u>C</u>≡C-); HR-MS (ESI, m/z) : calcd. for $[C_{18}H_{10}O_4]$: m/z 290.0579 $[M+H]^+$, found 290.0582 $[M+H]^+$.

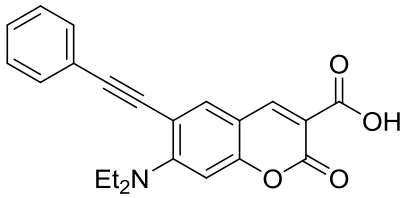
7-methoxy-2-oxo-6-(phenylethynyl)-2*H*-chromene-3-carboxylic acid (6b)



According to General Procedure **2**, 6-iodo-7-methoxy-2-oxo-2*H*-chromene-3-carboxylic acid (0.1 g, 0.28 mmol) in DMF (2.3 mL) was reacted with phenylacetylene (64 µL, 0.58 mmol), bis(diphenylphosphino)palladium dichloride (10 mg, 0.144×10^{-3} mmol), CuI (5.5 mg, 0.289×10^{-3} mmol) and NEt_3 (0.322 mL, 2.31 mmol) which, after column chromatography (CH_2Cl_2-MeOH 9:1), gave the *phenylethynyl coumarine* (0.067 g, 73%) as a solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H : 13.11 (br, 1 H, OH), 8.70 (s, 1 H, H_4), 8.07 (s, 1 H, H_5), 7.53 (dd, 2 H, *J* = 2.0, 7.5 Hz, ArH), 7.43 (m, 3 H, ArH), 7.20 (s, 1 H, H_8), 3.99 (s, 3 H, -OCH_3); ^{13}C NMR (250 MHz, DMSO-d_6) δ_C : 164.1 (-COOH), 163.9 (C-7), 156.7 (C-10), 156.6 (C-2), 148.1 (C-5), 134.2 - 128.7 (6 x ArC), 122.1 (C-4), 114.9 (C-3), 111.4 (C-9), 109.3 (C-6), 99.4 (C-8), 93.3 (-C≡C-), 84.0 (-C≡C-), 57.0 (-OCH_3); HRMS : calcd. for [$C_{19}H_{12}O_5$]: m/z 320.0685 $[M-H]^-$, found 320.0686 $[M-H]^-$.

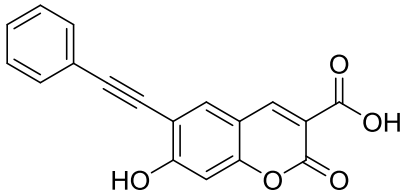
7-(diethylamino)-2-oxo-6-(phenylethynyl)-2*H*-chromene-3-carboxylic acid (6c)



According to General Procedure **2**, Ethyl 7-hydroxy-6-iodo-2-oxo-2*H*-chromene-3- carboxylate (0.1 g, 0.26 mmol) in DMF (2.3 mL) was reacted with phenylacetylene (56 µL, 0.52 mmol), bis(diphenylphosphino)palladium dichloride (9 mg, 0.129×10^{-3} mmol), CuI (4.9 mg, 0.258×10^{-3} mmol) and NEt_3 (0.288 mL, 2.06 mmol) which, after column chromatography (CH_2Cl_2-MeOH 9:1), gave the *phenylethynyl coumarine* (0.031 g, 32 %) as a solid. Data matches literature values.[3]

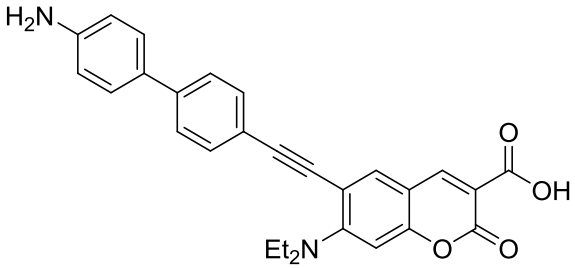
^{1}H NMR (500 MHz, $CDCl_3$) δ_H : 12.79 (br, 1 H, OH), 8.59 (s, 1 H, H_4), 7.97 (s, 1 H, H_5), 7.52 (dd, 2 H, *J* = 2.0, 7.8 Hz, ArH), 7.42 (m, 3 H, ArH), 6.74 (s, 1 H, H_8), 3.67 (q, 4 H, *J* = 7.0 Hz, NCH_2CH$_3$), 1.22 (t, 6 H, *J* = 7.0 Hz, NCH$_2$CH_3); ^{13}C NMR (250 MHz, DMSO-d_6) δ_C : 164.1 (-COOH), 157.7 (C-10), 156.3 (C-2), 154,5 (C-7), 148.1 (C-5), 137.7 - 128.5 (6 x ArC), 122.4 (C-4), 111.3 (C-3), 109.1 (C-9), 106.9 (C-8), 100.8 (C-6), 92.4 (-C≡C-), 88.1 (-C≡C-), 45.3 (2 x NCH$_2$CH$_3$), 12.9 (2 x NCH$_2$CH$_3$); HRMS : calcd. for [$C_{22}H_{19}NO_4$]: m/z 361.1314 $[M+H]^+$, found 361.1315 $[M+H]^+$.

7-hydroxy-2-oxo-6-(phenylethynyl)-2*H*-chromene-3-carboxylic acid (6d)



A solution of ethyl 7-hydroxy-2-oxo-6-(phenylethynyl)-2*H*-chromene-3-carboxylate **(5a)** (60 mg, 0.18 mmol) and NaOH 10% (0.3 mL) in ethanol (1 mL) was refluxed during 16 h. After cooling, the reaction mixture was evaporated to dryness; the residue was dissolved in water and acidified with diluted hydrochloric acid (pH 1-2). The precipitate was filtered, washed with ethanol to give the title compound (40 mg, 74 %) as a solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H : 8.89 (s, 1H, H_4), 8.21 (s, 1H, OH), 7.95 (dd, 2H, *J* = 1.6, 8.3 Hz, ArH), 7.80 (s, 1H H_5), 7.61 (s, 1H, H_8), 7.54 (t, 2H, *J* = 7.8 Hz, ArH), 7.45 (t, 1H, *J* = 7.4 Hz, ArH); ^{13}C NMR (250 MHz, DMSO-d_6) δ_C : 164.0 (-COOH), 157.4 (C-7), 157.1 (C-10), 156.9 (C-2), 149.3 (C-5), 129.4 - 122.4 -(6 x ArC) 116.1 (C-4, C-3, C-9, C-6) 114.9 (C-8), 101.6 (-C≡C-), 99.0 (-C≡C-); HR-MS (ESI, m/z) $[M+H]^+$: calcd. for $C_{18}H_{10}O_5$, 306.0528, found 306.0528.

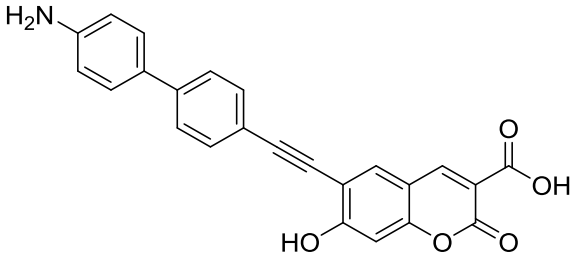
6-((4'-amino-[1,1'-biphenyl]-4-yl)ethynyl)-7-(diethylamino)-2-oxo-2H-chromene-3- carboxylic acid (6e)



According to General Procedure 2, ethyl 7-hydroxy-6-iodo-2-oxo-2*H*-chromene-3- carboxylate (0.2 g, 0.56 mmol) in DMF (4.1 mL) was reacted with 4'-ethynyl-[1,1'-biphenyl]- 4-amine (120 mg, 0.62 mmol), bis(diphenylphosphino) palladium dichloride (18 mg, 0.03×10^{-3} mmol), CuI (10 mg, 0.056×10^{-3} mmol) and NEt_3 (0.576 mL, 4.13 mmol). Water was added to the reaction mixture; the residue was filtered and washed with DCM, MeOH and Et_2O to give the title compound (0.220 g, 95%) as a solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ_H : 8.62 (br, 1H, H_4), 7.96 (s, 1H, H_5), 7.60 (d, 2H, *J* = 8.4 Hz, Ar<u>H</u>), 7.49 (d, 2H, *J* = 7.7 Hz, Ar<u>H</u>), 7.41 (d, 2H, *J* = 8.6 Hz, Ar<u>H</u>), 6.74 (s, 1H, H_8), 7.41 (d, 2H, *J* = 8.3 Hz, Ar<u>H</u>), 3.70 (q, 4H, *J* = 6.9 Hz, $NC\underline{H}_2CH_3$), 1.25 (t, 6H, *J* = 6.9 Hz, $NCH_2C\underline{H}_3$).

^{13}C NMR (250 MHz, DMSO-d_6) δ_C : 162.0 (-<u>C</u>OOH), 157.5 (C-10), 156.8 (C-2), 154,9 (C-7), 152.6 (Cq-NH_2), 148.6 (ArC), 147.2 (ArC), 140.1 (C-5), 137.2 -126.3 (8 x ArC), 124.3 (C-4), 116.9 (C-3), 115.8 (C-9), 114.2(C-8, C-6), 101.0 (-C≡C-), 99.0 (-C≡C-),45.3 (2 x $N\underline{C}H_2CH_3$), 12.9 (2 x $NCH_2\underline{C}H_3$). HR-MS (ESI, m/z) $[M+H]^+$: calcd. for $[C_{28}H_{24}N_2O_4]$: m/z 452.1736 $[M+H]^+$, found 452.1741 $[M+H]^+$.

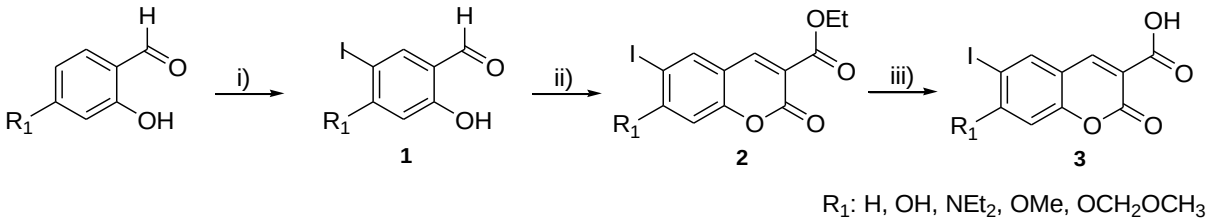
6-((4'-amino-[1,1'-biphenyl]-4-yl)ethynyl)-7-hydroxy-2-oxo-2H-chromene-3-carboxylic acid (6f)



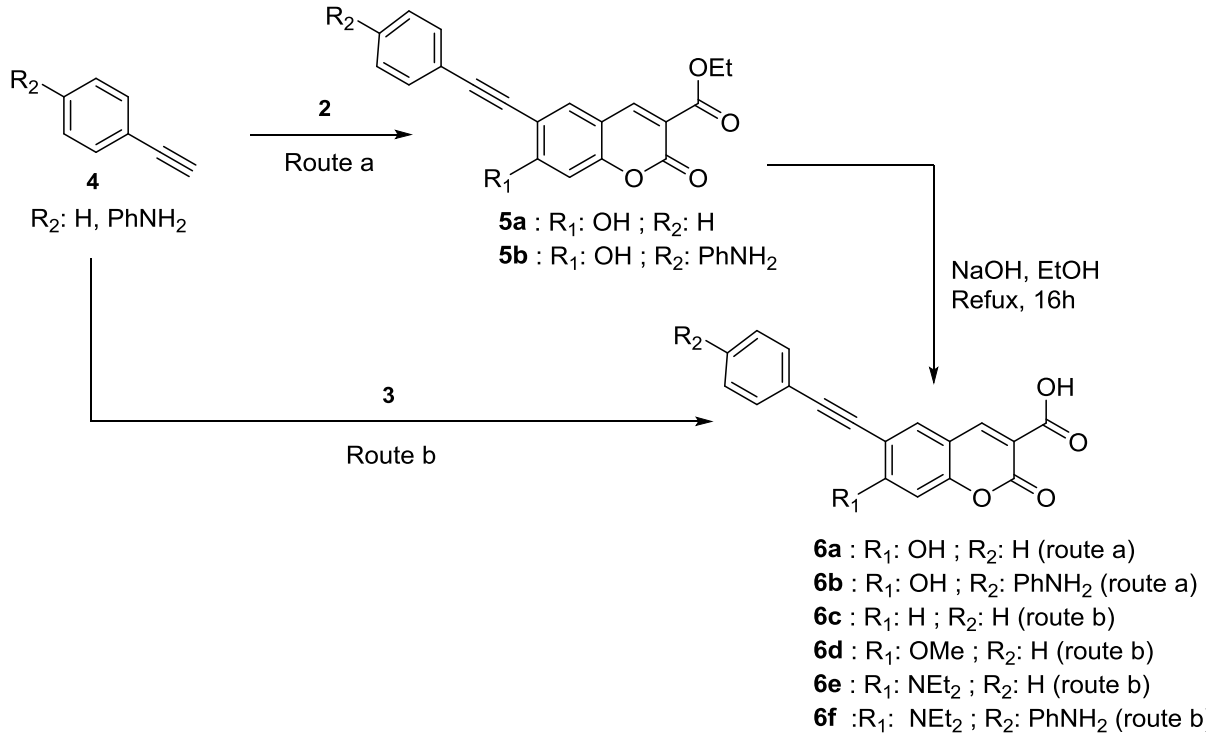
A solution of ethyl-6-((4'-amino-[1,1'-biphenyl]-4-yl)ethynyl)-7-hydroxy-2-oxo-2*H*- chromene-3-carboxylate (60 mg, 0.18 mmol) and NaOH 10% (0.3 mL) in ethanol (1 mL) was refluxed during 16 h. After cooling, the reaction mixture was evaporated to dryness; the residue was dissolved in water and acidified with diluted hydrochloric acid (pH 1-2). The precipitate was filtered, washed with ethanol to give the title compound (0.11 mg, 74%, contaminated with NH_4Cl) as a solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H*:* 8.90 (s, 1H, H_4), 8.20 (s, 1H, O<u>H</u>), 7.92 (d, 2H, *J*= 8.6 Hz, Ar<u>H</u>), 7.79 (s, 1H, H_5), 7.71 (d, 2H, *J* = 8.4 Hz, Ar<u>H</u>), 7.57 (s, 1H, H_8), 7.47 (d, 2H, *J* = 8.7 Hz, Ar<u>H</u>), 6.67 (d, 2H, *J* = 8.3 Hz, Ar<u>H</u>); ^{13}C NMR (250 MHz, DMSO-d_6) δ_C*:* 162.0 (-<u>C</u>OOH), 157.6 (C-7), 157.1 (C-10), 157.0 (C-2), 152.6 (Cq-NH_2), 149.4 (ArC), 148.8 (ArC), 141.5 (C-5), 127.2 -125.3 (8 x ArC), 122.1 (C-4), 115.9 (C-3), 114.8 (C-9), 114.2(C-8, C-6), 100.8 (-C≡C-), 98.9 (-C≡C-). HR-MS (ESI, m/z) $[M+H]^+$: calcd. for $C_{24}H_{15}O_5N$, 397.0950, found 397.0954.

Results and Discussion

Coumarin derivatives were synthesized starting from substituted salicylicaldehydes according to the pathway reported in Scheme 1.



Scheme 1 : Synthesis of 6-iodo-7-substituted-2-oxo-2H-chromen-3-carboxylic acid i) ICl, CH_3COOH; ii) Diethyl malonate, EtOH, piperidine, reflux 16h; iii) NaOH 10%, EtOH



Scheme 2 : Synthesis of ethyl 6-iodo-7-substituted-2-oxo-2H-chromen-3-carboxylic acid. Route a) Compound 2, step 1. CuI, $PdCl_2(PPh_3)_2$, NEt_3, DMF; step 2 NaOH, EtOH, reflux 16h. Route b) Compound 3, CuI, $PdCl_2(PPh_3)_2$, NEt_3

The ethyl 6-iodo-7-substituted-2-oxo-2*H*-chromen-3-carboxylate **2** were obtained by a two steps reaction reported in literature. Indeed, first able selective mono-iodination of commercially available and appropriate salicylicaldehyde was done with an excess of iodine monochloride in acetic acid leads to corresponding 5-iodosalicylicaldehydes (**1**) in good yields. Presence of the heavy iodine atom quenched the fluorescence. In a second step, without Wang resin, Knoevenagel condensation happens between the various 5-iodosalicylicaldedydes (**1**) and diethyl malonate in the presence of piperidine in ethanol under reflux condition, which afforded in good yields also of ethyl 6-iodo-7-substituted-2-oxo-2*H*-chromen-3-carboxylate **(2).** From **(2)**, alkaline hydrolysis of the carboxylate group (ester function) with 10 % NaOH was done to obtain the 6-iodo-7-substituted-2-oxo-2*H*-chromene-3-carboxylic acid **(3)**. To obtain our new conjugated enyne coumarins, we substituted the 6-position of the corresponding derivatives with the 4'-ethynyl-[1,1'-biphenyl]-4-amine (**4**). The choice of this moiety was due to the presence of a perfect conjugation between the triple bond and the phenyl group. Thus, compound **4** was synthesized in four reaction steps starting from biphenyl. Based on the work described by L.S. Reddy et al [24] and Y.N zhang et al, [23] we obtained 4-iodo-4'-nitro-1,1'-biphenyl and 4'-iodo-[1,1'-biphenyl]-4-amine respectively. In the following work, 4'-((trimethylsilyl)ethynyl)-[1,1'-biphenyl]-4-amine is obtained in 88% yield by a nucleophilic substitution reaction between 4'-iodo-[1,1'-biphenyl]-4-amine and ethynyltrimethylsilane. Thus, we reacted 4'-iodo-[1,1'-biphenyl]-4-

amine with ethynyltrimethylsilane under reflux of triethylamine anhydride for 16 hours. This reaction was carried out in the presence of copper iodide and bis(diphenylphosphino) palladium dichloride. Based on the work carried out by M.J. Matos et al, [6] we synthesized 4'-ethynyl-[1,1'-biphenyl]-4-amine in 86% yield. For our part, we reacted 4'-((trimethylsilyl)ethynyl)-[1,1'-biphenyl]-4-amine with 10% sodium hydroxide solution at reflux for 16 hours. Therefore, addition of an EDG in position **7** happens and substitution of iodine for the alkylnyl group in position **6**, using Sonogashira result in a dramatic fluorescence enhancement.

While it's well known by density functional theory (DFT) calculations of the energy gap between HOMO (the highest occupied molecular orbitals) and LUMO (the lowest unoccupied molecular orbitals) that the **7**-substituted coumarins showed more bathochromic shifted spectrum (red-shifted about 100 nm) compared to the **6**-substituted ones for their more efficient conjugated structure. Compounds **2** and **3** were then subjected to Sonogashira cross-coupling reaction conditions. The optimal protocol was found to involve the use of 5% catalyst bis(diphenylphosphino) palladium dichloride ($PdCl_2(PPh_3)_2$) and 10 % copper iodide (CuI) in the presence of triethylamine (Et_3N) as base in DMF at room temperature overnight (16h). These reaction conditions allowed facile introduction of various alkynyl modules at the 6-position of the coumarin scaffold with good yields. This general procedure allowed us to obtain the desired compounds in high yields and simplify reaction work up, limiting the presence of by-products. For those unsuccessful synthesis, it's either due to the insolubility of the afforded compounds or to the impossibility to introduce the phenylethynyl at the position -6 because of the steric clutter. For this reason, when it was possible, we just synthetized the corresponding ethyl 6-iodo-7-substituted-2-oxo-2*H*-chromene-3-carboxylate **(5)** by the reduction of the ester group in NaOH, and then obtained the corresponding carboxylic acid form **(6).**

Conclusion

In this article, we have synthesized by using readily available reagents, and fully characterized a new series of 3,6,7-substituted coumarins, which could reveal their potentials as versatile biodynamic agents. In addition, introduction of EDG and alkynyl in position 6 and 7 could influence not only the physical and chemical properties, but also their biological activity. We will investigate the effect of the length and nature of the π-conjugation system on emission properties. By the way in perspective studies, the enzyme activity (inhibition) and selectivity (accessibility of the carbonyl group to the enzyme active site) could also be interesting. The introduction of groups such as azide in the coumarin scaffold, permit to further get *via* click chemistry with copper salt, a triazole function. They are under study adding on to the coumarin scaffold obtained with Sonogashira reaction.

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Conflict of interest

The authors declare no conflicts of interest regarding the publication of this paper.

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