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Study of the reactivity of 4-hydroxycoumarin towards 3-oxopyrazolidinium ylures and arylidenemalononitriles

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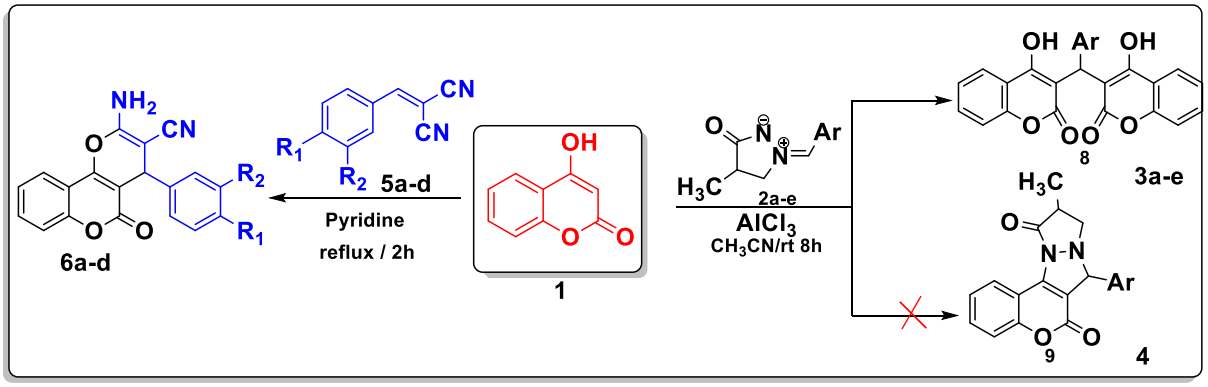
ABSTRACT

In the context of finding new heterocyclic systems pharmacological / biological activities, we were interested in this work in the study of the reactivity of hydroxycoumarin with respect to heterocyclic dipoles of the type: arylmethylidene-3-oxopyrazolidin-1-ium-2-ides 2a–e in acetonitrile in the presence of AlCl3 as catalyst and with arylidenemalononitriles 5a–d in refluxing pyridine. The biscoumarin 3a–e and pyranocomarin 6a–d were obtained with good to excellent yields (74–95%) and characterized by elemental analysis (Scheme 1).



Scheme 1

Keywords: Biscoumarin, 4-hydroxycoumarin, Arylidenemalononitriles, pyranocomarin Cyclization, condensation, 4-methyl-3-oxo-1,2-pyrazolidiniums

INTRODUCTION

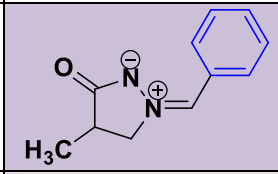
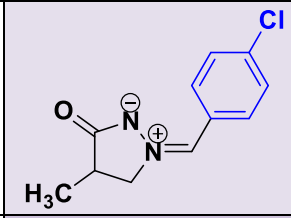
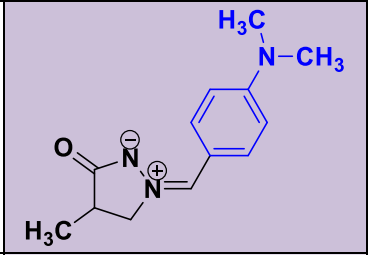
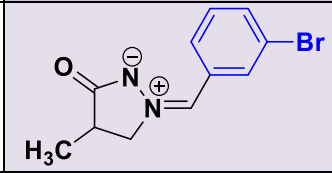
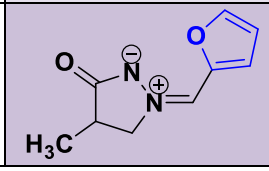
4-Hydroxycoumarin and its derivatives constitute a class of natural [1-6] products representing an interesting substrate in the pharmaceutical drug [7-13]; it has a wide range of biological applications because of their multitude of activities such as anticoagulant [14], Antioxidant [15, 16], anticorrosive [17], anti-inflammatory activities [18, 19], including antimicrobial [20-23], antiviral [24, 25], and anticancer [26-28].
In this regard, coumarin derivatives are important in organic synthesis studies [29-32], on our part due to the development of new therapeutic

molecules, we have incorporated 4-hydroxycoumarin respectively with arylidénemalononitriles and 3-oxopyrazolidiniums ylures. This latter is stable as intermediates for the synthesis of various nitrogenous heterocycles, they react as 1,3-dipoles with certain dipolarophils, mainly with alkenes and alkynes and ketones [33]. Among the cyclic dipoles incorporating an N-N bond in a ring the most studied are the N-alkylidene-3-oxopyrazolidinium imides, which are stable and easily accessible. They have been used as 1,3-dipoles in different types of cycloadditions, not only [3 + 2] but also [3 + 3], [4 + 3] and [3 + 2 + 3], giving important products or intermediates for the preparation of many types of pharmaceuticals, agrochemicals and other biologically active compounds [34, 35]. Arylidénemalononitriles and these derivatives exhibit very significant pharmacological activity [36-39].

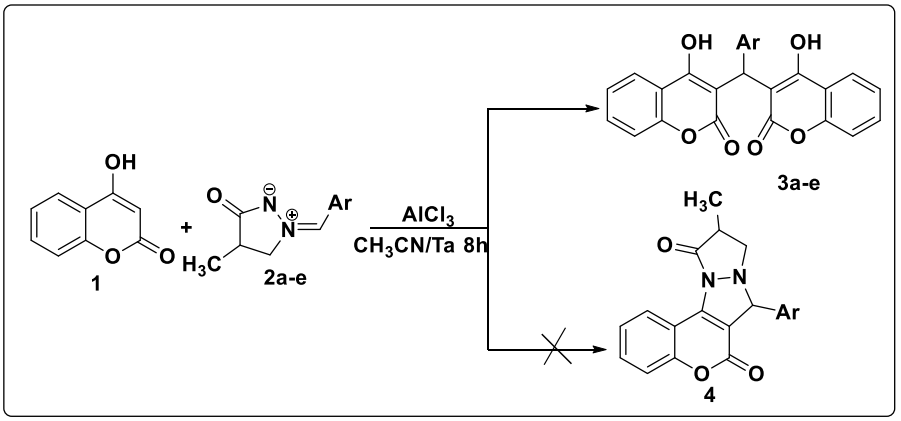
RESULT AND DISCUSSIONS

The treatment of methyl methacrylate with an excess of hydrazine hydrate under ethanol reflux allows to obtained the corresponding pyrazolidinone with a better yield, the condensation of this latter with aromatic aldehydes in ethanol at room temperature in the presence of an acid leads to 4-methyl-3-oxo-1,2-pyrazolidiniums ylures 2a – e with good yields. The compounds are prepared according to the procedure described in the literature [40]. We have succeeded in preparing differently substituted dipoles with good yields (Table 1).

Table 1: Yields for 4-méthyl-3-oxo-1,2-pyrazolidiniums 2a–e

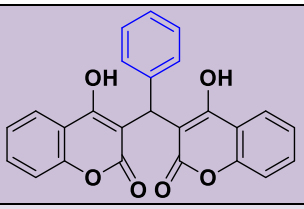
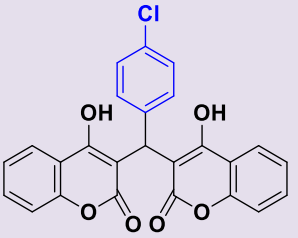
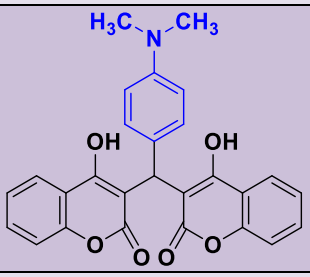
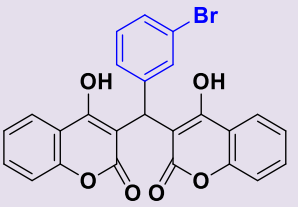
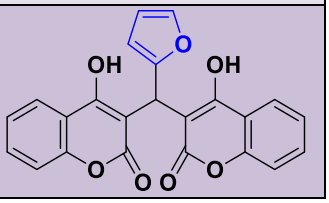
Entry	Ar	Time (h)	mp (°c)	Yield of 2a-e (%)	
2a	C_6H_5	12	123-125	80	
2b	$4\text{-}ClC_6H_5$	16	185-187	86	
2c	$4\text{-}(CH_3)_2NC_6H_4$	12	178-180	82	
2d	$3\text{-}BrC_6H_4$	24	162-164	78	
2e	2-Furyl	20	170-172	86	

Contrary to was observed in the literature, the reaction of 4-hydroxycoumarin 1 with various ylures of 4-methyl-3-oxo-1,2-pyrazolidiniums 2a-e in acetonitrile and in the presence of AlCl3 as a catalyst at room temperature led to the formation of biscoumarins 3a-e with good yields (80-96%, (scheme 2). No cycloadduct 4 resulting from the addition of the dipole to the C = C double bond was detected under the above conditions.



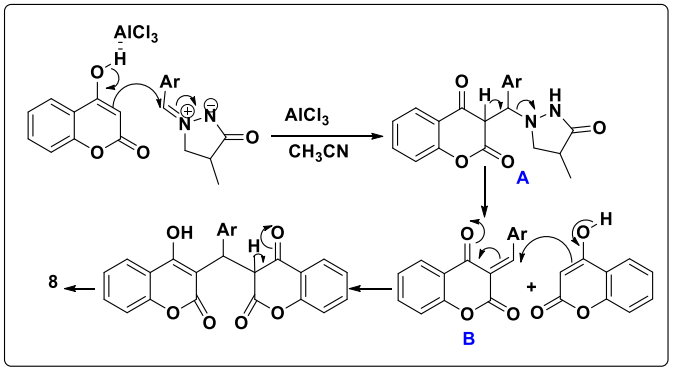
Scheme 2

Table 2: Yields for bis-coumarin derivatives

Entry	Ar	Mp (°C)	Yield (%)	
3a	C_6H_5	225-227	80	
3b	4-ClC_6H_5	250-252	86	
3c	4-$(CH_3)_2NC_6H_4$	270-272	82	
3d	3-BrC_6H_4	258-260	90	
3e	2-furyl	245-248	96	

In the 1H NMR spectrum of compounds 3a-e, more the signals of the aromatic protons, we note a signal in the form of a singlet between 6.20 and 6.30 ppm attributable to the proton of the methylene group CH. The chemical shift of carbon CH appears at around 36 ppm in the 13C NMR spectrum of compounds 3a-e (Table 2).

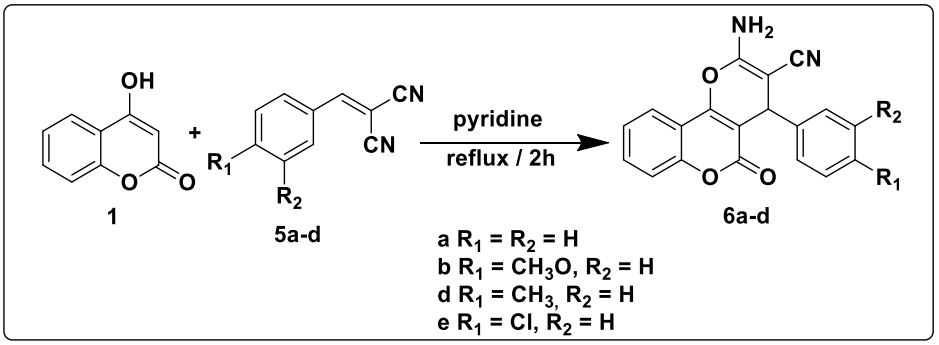
A plausible mechanism to explain the formation of the 3a-e compounds is provided in (Scheme 3). First, 4-hydroxycoumarin reacted with 4-methyl-3-oxo-1, 2-pyrazolidinium 2a-e to give intermediate A. This the latter rearranges via the elimination of pyrazolidinone thus leading to the formation of intermediate B which reacts with a second molecule of 4-hydroxycoumarin to give bis-coumarin 3a-e.



Scheme 3

Reactivity of arylidenemalonitriles towards 4-hydroxycoumarin

The first step of this study consists to reacted differently substituted aldehydes with malononitrile in ethanol reflux in the presence of phosphorus pentoxide as a catalyst; it leads to the formation of the corresponding arylidenemalononitriles 4a-d. This latter are then treated, in the second step, with 4-hydroxycoumarin 1 at reflux in pyridine to produce new products of the type: 2-amino-4- (aryl) -4H-benzo[h]chromene-3- carbonitriles 6a-d (Scheme 4).



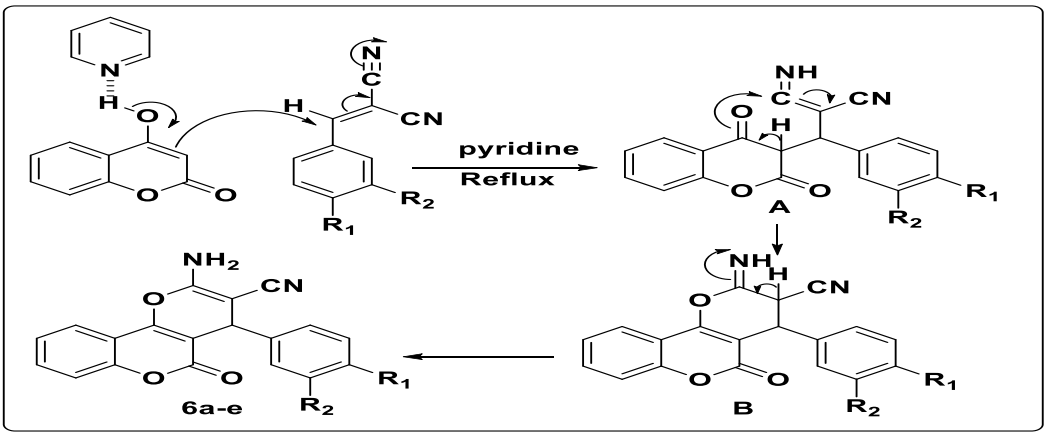
Scheme 4

In the 1H NMR spectrum of compounds 6a-d, we note in particular the presence of a signal at around 4.38 ppm attributable to the proton of the CH group and a signal at 7.38 ppm due to the protons of the NH2 group (Table 3).

Table 3: Yields of new products 6a-e

Entry	R	Yields (%)	Mp (°C)
6a	$R_1 = R_2 = H$	95	258-260
6b	$R_1 = CH_3O$, $R_2 = H$	90	248-250
6d	$R_1 = CH_3$, $R_2 = H$	98	261-263
6e	$R_1 = Cl$, $R_2 = H$	95	256-258

For explain the formation of compounds 6a-e, we have proposed the following mechanism: 4-hydroxycoumarin reacts with arylidenemalononitrile to give intermediate A. This latter rearranges via intramolecular cyclization leading to the formation of intermediate B, which rearranges to give the expected compounds 6a-e (Scheme 5).



Scheme 5

CONCLUSIONS

Our study invented a new practical access to the synthesis of new comarine derivative, by the aldol condensation of 4-hydroxycoumarin with a dipole of the type: 4-methyl-3-oxo-1,2-pyrazolidiniums ylures in the acetonitrile at room temperature and in the presence of AlCl3 as catalyst. We optioned a coumarin dimer bearing an aryl substituent in the central part with an excellent yield. On the other hand, in the presence of arylidènemalononitriles with reflux of pyridine allowing access to various pyranocoumarins, we have developed a rapid and efficient study of the synthesis to access new heterocyclic systems with good yields, which can present promising biological properties.

EXPERIMENTAL SECTION

General procedure for synthesis of compound 2a-e

20 mmol of 4-methyl pyrazolidin-3-one and 20 mmol of the aromatic aldehyde dissolved in 15 ml of ethanol and then we added a few drops of TFA. The mixture stirred at room temperature for various times. After evaporating off the solvent, the crude product obtained recrystallized in ethanol, then washed with ethyl acetate, and filtered under vacuum.

General procedure for synthesis of compound 3a-e

In a 250 ml round-bottomed flask, the dipole (10 mmol), 4-hydroxycoumarin (10 mmol) and AlCl3 (2 mmol) are suspended with mechanical stirring in 25 ml of absolute acetonitrile at room temperature. After the completion of the reaction monitored by TLC, the solvent is removed under reduced pressure, the crude mixture is separated by chromography on silica gel (hexane-acetate = 4: 6).

General procedure for synthesis of compound 6a-d

4-Hydroxycoumarin (0.01 mol) and substituted arylidenemalononitriles (0.01 mol) added to 15 ml of the pyridine. The reaction mixture brought to reflux for 8 h. The crude product collected by filtration and recrystallized from ethanol, the appropriate product optioned in good yield.

(Z)-Benzylidène-4-méthyl-3-oxopyrazolidin-2-ium-1-ide 2a. White solid; mp 123–125 °C; **^{1}H NMR (DMSO-d$_6$, 300 MHz)** : δ 1.15 (d, 3H, J = 7.2 Hz), 2.68–2.76 (m, 1H), 4.18 (dd, 1H, J = 7.6 Hz, 13.0 Hz), 4.73 (dd, 1H, J = 8.9 Hz, 13.0 Hz), 7.48–7.51 (m, 3H), 7.63 (s, 1H), 8.26–8.30 (m, 2H). **^{13}C NMR (DMSO-d$_6$, 75 MHz)**: δ 15.9 (CH_3), 35.3 (CH), 64.6 (CH_2N), 129.1 (2CH), 130.3 (C), 131.4 (2CH), 131.5 (CH), 132.5 (CH), 187.5 (CO).

(Z)-(4-Diméthylaminobenzylidene)-4-méthyl-5-oxopyrazolidin-2-ium-1-ide 2b. White solid; mp 178-180 °C; **^{1}H NMR (DMSO-d$_6$, 300 MHz):** δ 1.13 (d, 3H, J = 7.2 Hz), 2.60–2.68 (m, 1H), 3.00 (s, 6H, N(CH3)2), 3.98-4.06 (m, 1H), 4.54-4.62 (m, 1H), 6.76 (d, 2H, J = 9.3 Hz), 7.41 (s, 1H), 8.10 (d, 2H, J = 9.3 Hz). **^{13}C NMR (DMSO-d$_6$, 75 MHz):** δ 16.0 (CH3), 35.7 (CH), 40.0 ($2CH_3$), 63.2 (CH2N), 111.6 (2CH), 117.5 (C), 133.5 (2CH), 133.9 (=CH), 152.2 (C), 186.1 (CO).

(Z)-(3-Bromobenzylidene)-4-méthyl-3-oxopyrazolidin-2-ium-1-ide 2c. White solid; mp 162-164°C; **^{1}H NMR (DMSO-d$_6$, 300 MHz):** δ 1.16 (d, 3H, J = 7.2 Hz), 2.70–2.77 (m, 1H), 4.18-4.25 (m, 1H), 4.71-4.78 (m, 1H), 7.47 (t, 1H, J = 8.1 Hz), 7.63 (s, 1H), 7.69 (dd, 1H, J = 8.1 Hz, 0.9 Hz), 8.09 (d, 1H, J = 8.1 Hz), 8.68 (t, 1H, J = 1.5 Hz); **^{13}C NMR (DMSO-d$_6$, 75 MHz):** δ 15.8 (CH_3), 35.1 (CH), 64.8 (CH_2N), 122.3 (C), 130.3 (CH), 130.5 (CH), 131.2 (CH), 132.4 (C), 132.9 (CH), 133.9 (CH), 187.7 (CO).

(Z)-(4-Chlorobenzylidene)-4-méthyl-3-oxopyrazolidin-2-ium-1-ide 2d. White solid; mp 185-187 °C; **^{1}H NMR (DMSO-d$_6$, 300 MHz):**δ 1.15 (d, 3H, J = 7.2 Hz), 2.68–2.77 (m, 1H), 4.16-4.23 (m, 1H), 4.69-4.77 (m, 1H), 7.58 (d, 2H, J = 8.7 Hz), 7.64 (s, 1H), 8.29 (d, 2H, J = 8.7 Hz); **^{13}C NMR (DMSO-d$_6$, 75 MHz)**: δ 15.8 (CH_3), 35.2 (CH), 64.6 (CH_2N), 129.2 (C), 129.3 (2CH), 131.1 (=CH), 132.9 (2CH), 135.9 (C), 187.5 (CO).

(Z)-4-Méthyl-2-(furylidene)-3-oxopyrazolidin-2-ium-1-ide 2e. White solid; mp 170-172 °C; **^{1}H NMR (DMSO-d$_6$, 300 MHz):** δ 1.14 (d, 3H, J = 7.2 Hz), 2.67–2.80 (m, 1H), 4.06-4.13 (m, 1H), 4.62-4.70 (m, 1H), 6.77 (dd, 1H, J = 4.0 Hz, 3.4 Hz), 7.58 (d, 1H, J = 4.1 Hz), 7.75 (s, 1H), 7.95 (d, 1H, J = 3.0 Hz). **^{13}C NMR (DMSO-d$_6$, 75 MHz)**: δ 15.8 (CH_3), 36.0 (CH), 63.0 (CH_2N), 113.8 (CH), 119.5 (CH), 121.4 (CH), 146.6 (C), 147.1 (CH), 187.1 (CO).

2-(Benzylidene)malononitrile 5a. White solid; mp 88-90°C; **^{1}H NMR (DMSO-d$_6$)**: δ 7.57–7.68 (m, 3H, H-Ar), 7.91–7.95 (m, 2H, H-Ar), 8.52 (s, 1H, H-vinyl). **^{13}C NMR (DMSO-d$_6$):** δ 82.1 (C), 113.7 (CN), 114.6 (CN), 129.9 (2CH), 131.0 (2CH), 131.8 (C), 134.8 (CH), 162.0 (CHvinyl).

2-(4-Methoxybenzylidene)malononitrile 5b. yellow solid; mp 110–112°C; **^{1}H NMR (DMSO-d$_6$)**: *δ* 3.86 (s, 3H, CH_3O), 7.14 (d, 2H, *J* = 9.0 Hz),

7.93 (d, 2H, *J* = 9.0 Hz), 8.34 (s, 1H, H-vinyl).**^{13}C NMR (DMSO-d_6):** δ 56.4 (CH_3O), 77.3 (C), 114.3 (CN), 115.2 (CN), 115.6 (2CH), 124.6 (C), 133.8 (2CH), 160.9 (CHvinyl), 164.8(=CO).

2-(4-Methylbenzylidene)malononitrile 5c. White solid; mp 130–132°C; **^{1}H NMR (DMSO-d_6)**: δ 2.39 (s, 3H, CH_3), 7.41 (d, 2H, *J* = 8.1 Hz), 7.84 (d, 2H, *J* = 8.1 Hz), 8.45 (s, 1H, H-vinyl). **^{13}C NMR (DMSO-d_6):** δ 21.9 (CH_3), 80.4 (C), 113.9 (CN), 114.8 (CN), 129.2 (C), 130.6 (2CH), 131.1 (2CH), 146.1 (C), 161.8(CHvinyl).

2-(4-Chlorobenzylidene)malononitrile 5d. White solid; mp 148–150°C; **^{1}H NMR (DMSO-d_6)**: δ 7.67 (d, 2H, *J* = 8.4 Hz), 7.92 (d, 2H, *J* = 8.4 Hz), 8.51 (s, 1H, H-vinyl). **^{13}C NMR (DMSO-*d_6*):** δ 82.7 (C), 113.5 (CN), 114.5 (CN), 130.2 (2CH), 130.6 (C), 132.6 (2CH), 139.5 (C), 160.6 (CHvinyl).

3, 3'-[(Phényl) méthylene]bis(4-hydroxy-2*H*-chromen-2-one) 3a. White solid; mp 225-227°C; **^{1}H NMR (DMSO-d_6)**: 6.28 (s, 1H; CH), 7.07-7.28 (m, 9H, H-Ar), 7.48-7.51 (m, 2H, H-Ar), 7.80-7.83 (m, 2H, H-Ar), 11.58 (s, 2H, OH). **^{13}C NMR (DMSO-d_6):** 36.6 (CH), 103.9 (2C), 115.9 (2CH), 120.4 (2C), 123.3 (2CH), 124.6 (2CH), 125.3 (CH), 127.1 (2CH), 128.2 (2CH), 131.4 (2CH), 142.8 (C), 153.0 (2C), 165.1 (2C), 168.2 (2CO).

3, 3'-[(4-Chlorophényl)méthylene]bis(4-hydroxy-2*H*-chromen-2-one) 3b. White solid; mp 190-192°C; **^{1}H NMR (DMSO-d_6)**: 6.24 (s, 1H; CH), 7.09-7.28 (m, 8H, H-Ar), 7.48-7.54 (m, 2H, H-Ar), 7.80-7.83 (m, 2H, H-Ar), 11.64 (s, 2H, OH). **^{13}C NMR (DMSO-d_6):** 36.2 (CH), 103.6 (2C), 115.9 (2CH), 120.3 (2C), 123.4 (2CH), 124.6 (2CH), 128.1 (2CH), 129.0 (2CH), 129.8 (C), 131.5 (2CH), 141.9 (C), 153.0 (2C), 164.9 (2C), 168.2 (2CO).

3, 3'-[(4-(Diméthylaminophenyl) méthylene]bis(4-hydroxy-2*H*-chromen-2-one) 3c. White solid; mp 270-272°C; **^{1}H NMR (DMSO-d_6)**: 2.89 (s, 6H, $N(CH_3)_2$), 6.20 (s, 1H; CH), 6.77-6.81 (m, 2H, H-Ar), 6.99 (d, 2H, H-Ar), 7.20-7.30 (m, 4H, H-Ar), 7.47-7.53 (m, 2H, H-Ar), 7.81 (dd, 2H, H-Ar), 11.45 (s, 2H, OH). **^{13}C NMR (DMSO-d_6):** 35.8 (CH), 42.3 (NCH_3), 104.1 (2C), 115.9 (2CH), 120.4 (2C), 123.3 (2CH), 124.5 (2CH), 127.9 (2CH), 131.3 (2CH), 141.9 (C), 152.9 (2C), 165.0 (2C), 168.1 (2CO).

3, 3'-[(3-Bromophényl)méthylene]bis(4-hydroxy-2*H*-chromen-2-one) 3d. White solid; mp 258-260°C; **^{1}H NMR (DMSO-d_6)**: 6.27 (s, 1H; CH), 7.13-7.30 (m, 8H, H-Ar), 7.49-7.55 (m, 2H, H-Ar), 7.83 (dd, 2H, H-Ar), 11.58 (s, 2H, OH). **^{13}C NMR (DMSO-d_6):** 36.5 (CH), 103.3 (2C), 116.0 (C), 120.3 (2C), 121.8 (2CH), 123.5 (2CH), 126.4 (CH), 129.6 (CH), 130.5 (CH), 131.6 (2CH), 146.9 (C), 152.9 (2C), 164.9 (2C), 168.3 (2CO).

3, 3'-[(Furyl)méthylene]bis(4-hydroxy-2*H*-chromen-2-one) 3e. White solid; mp 245-248°C; **^{1}H NMR (DMSO-d_6)**: 6.24 (s, 1H; CH), 7.14-7.34 (m, 7H, H-Ar), 7.32-7.43 (m, 2H, H-Ar), 7.68-7.82 (m, 2H, H-Ar), 11.76 (s, 2H, OH). **^{13}C NMR (DMSO-d_6):** 32.1 (CH), 102.0 (2C), 102.3 (CH), 105.6 (CH), 115.9 (2CH), 116.2 (2C), 123.2 (2CH), 124.6 (2CH), 130.0 (2CH), 140.1 (CH), 152.9 (2C), 164.4 (2C), 168.3 (2CO).

2-Amino-4, 5-dihydro-5-oxo-4-phénylpyrano [3,2-c]chromene-3-carbonitrile 6a. White solid; mp 242-244°C; **^{1}H NMR (DMSO-d_6)**: 4.45 (s, 1H, CH), 7.27-7.35 (m, 5H, H-Ar), 7.40 (s, 2H, NH_2), 7.45-7.52 (m, 2H, H-Ar), 7.7 (td, 1H, H-Ar), 7.91 (dd, 1H, H-Ar). **^{13}C NMR (DMSO-d_6):** 37.4 (CH), 58.5 (=C), 104.5 (C), 113.4 (C), 117.0 (CH), 119.7 (CN), 122.9 (CH), 125.1 (CH), 127.6 (CH), 128.1 (2CH), 128.9 (2CH), 133.4 (CH), 143.7 (C), 152.6 (C), 153.9 (C), 158.5 (C), 160.0 (C=O).

2-Amino-4, 5-dihydro-4-(4-methoxyphenyl)-5-oxopyrano [3,2-c]chromene-3-carbonitrile 6b. White solid; mp 248-250°C; **^{1}H NMR (DMSO-d_6):** 3.72 (s, 3H, OCH3), 4.40 (s, 1H, H-4), 6.87 (d, 2H, J = 8.1 Hz, H-Ar), 7.18 (d, 2H, J = 8.1 Hz, H-Ar), 7.37 (s, 2H, NH2), 7.45 (d, 1H, J = 8.3 Hz, H-Ar), 7.49 (t, 1H, J = 7.8 Hz, H-Ar), 7.70 (t, 1H, J = 7.7 Hz, H-Ar), 7.89 (d, 1H, J = 7.7 Hz, H-Ar). **^{13}C NMR (DMSO-d_6):** 55.9, 59.1, 105.1, 113.8, 114.7, 117.4, 120.2, 123.3, 125.5, 129.6, 133.7, 136.3, 152.9, 153.9, 158.8, 159.2, 160.4.

2-Amino-4, 5-dihydro-5-oxo-4-p-tolylpyrano[3,2-c]chromene-3-carbonitrile 6c. White solid; mp 235-237°C; **^{1}H NMR (DMSO-d_6)**: 2.27 (s, 3H, CH_3), 4.41 (s, 1H, H-4), 7.10-7.16 (m, 4H, H-Ar), 7.38 (s, 2H, NH_2), 7.44-7.52 (m, 2H, H-Ar), 7.7 (td, 1H, H-Ar), 7.90 (dd, 1H, H-Ar). **^{13}C NMR (DMSO-d_6):** 21.1 (CH_3), 37.0 (CH), 58.6 (=C), 104.6 (C), 113,5 (C), 117.0 (CH), 119.7 (CN), 122.9 (CH), 125.1 (CH), 128.0 (2CH), 129.5 (2CH), 133.4 (CH), 136.7 (C), 140.8 (C), 152.6 (C), 153.7 (C), 158.4 (C), 160.0 (C=O).

2-Amino-4-(4-chlorophényl)-4,5-dihydro-5-oxopyrano[3,2-c]chromene-3-carbonitrile 6d. White solid; mp 256-258°C; **^{1}H NMR (DMSO-d_6)**: 4.50 (s,1H, H-4), 7.31 (d, 2H, J = 8.2 Hz, H-Ar), 7.36 (s, 2H, NH_2), 7.38 (s, 2H, H-Ar), 7.44 (d, 1H, J = 8.2 Hz, H-Ar), 7.49 (t, 1H, J = 7.6 Hz, H-Ar), 7.71 (t, 1H, J = 7.8 Hz, H-Ar), 7.92 (d,1H, J = 7.8 Hz, H-Ar). **^{13}C NMR (DMSO-d_6) :** 58.6, 104.4, 113.8, 117.3, 119.8, 123.4, 125.4, 129.3, 130.4, 132.6, 133.7, 143.1, 153.0, 154.4, 158.9, 160.3.

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