Exploring Coumarins Reduction: NaBH 4 /MeOH versus Nickel Boride Generated In Situ .

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Exploring Coumarins Reduction: $NaBH_4$/MeOH versus Nickel Boride Generated In Situ.

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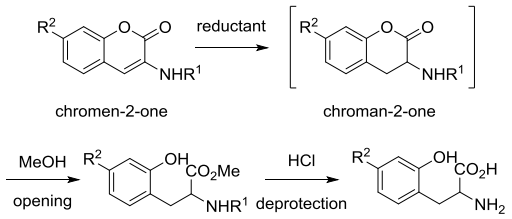
Abstract: The role of reagents $NaBH_4$/MeOH and nickel boride (Ni_2B) generated *in situ* from $NaBH_4$ and $NiCl_2$, are compared in the reduction process of coumarin and a variety of 3,7-substituted coumarins bearing electro-donating (ED-group) or electro-withdrawing groups (EW-group). Coumarins (chromen-2-one) are only reduced with Ni_2B to the cyclic chromanones. This provides a useful and very simple reduction method for electron-rich coumarins, which are resistant to many other reducing methods. DFT calculations underlined the role of substituents electronic effects in the reactivity. Subsequent methanolysis may open the ring to methyl phenylpropanoate esters and alcohols resulting from their reductions can also be produced.

Introduction

Coumarins (chromen-2-ones) are an important and well-known class of biologically active compounds. [1,2] They can be transformed into other compounds having a great variety of functions because they are substitutable by many functional groups (ie cyano, methoxy, hydroxy, amino, carboxyl, nitro groups...). We are interested in the synthesis of unnatural amino-acids bearing a phenol ring like hydroxyphenyl alanine derivatives. Such compounds could be easily obtained from 3,7-substituted coumarins by partial reduction of the chromen-2-one motif as a key step, leading to the desired amino-acids. The chroman-2-one intermediate could be isolated or not before the opening of the cycle and the deprotection step. Indeed, if the unsaturated lactone itself is stable, when hydrogenated, it may be easy opened by alcohol, used as solvent, giving also interesting substituted phenol ester products (scheme 1).



Scheme 1. General scheme for the reduction of coumarins leading to non-natural hydroxyphenyl alanine compounds.

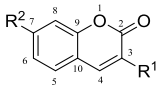
We faced some difficulties in the reduction of electron rich coumarin (*ie.* those bearing an electron donating group conjugated to the C=C bond of the heterocyclic part of the coumarin) to chromanone. In the literature, a wide range of reagents is used to hydrogenate the double bond. [3] It spans from the classic heterogeneous hydrogenation with various catalysts as support (Pd/C, [4,5,6,7] $Pd/CaCO_3$, [8] Pd black, [9] Pt, [10] Ru/Rh , [11] NiRaney) [12] to the use of hydrides such as $NaBH_4$, [13] NH_3BH_3, [14] $NaBH_3CN$ [15] or metals. [16,17] Unfortunately, despite a wide variety of reported coumarins, only a few described the reduction of substituted coumarins bearing ED group. Mills et al. [18] used harsh hydrogenation conditions (103 bar H_2 at 150 °C) to succeed in the reduction process of 8-methoxy-4,7-dimethylcoumarin and 8-methoxy-4,6-dimethylcoumarin. Also, none of the reported coumarins were bearing ED-group at the 3-position. To date, only the group of Semeniuchenko [19] tried to reduce 3-phenyl-7methoxycoumarin and 3-phenylcoumarin under nucleophilic and electrophilic hydrogenation but without success. Similarly, we could not reach good results in the reduction process of coumarins bearing ED-group with commonly used reagents. Particularly, a primary study was undertaken to reduce coumarins bearing benzamido and acetamido groups. A classic hydrogenation with H_2/Pd-C (P_{H_2} = 1 atm) gave no result in methanol and the starting material was recovered after 12 hours at 50°C. Further reagents such as $NaBH_3CN$, $NaBH_4$ and $NaBH_4$ coupled with other reagents ($NaBH_4$ + Pyridine; [20] $NaBH_4$ + Ni Raney [21]) were used. The reaction time and temperature were varied but no reaction could be observed. We were therefore looking for an easy-to-use method (*ie* without using high-pressure hydrogenation or hydrolysable reducing agents…) to allow the effective reduction of the chromen-2-one nucleus that are resistant to reduction (those bearing ED-group). Literature overview shows that nickel boride could be an effective reagent for such conversion.

The reactivity of such nickel boride was already described in the literature by the group of Khurana [22] for the reduction of various substrates. Among them, there are the chalcones, which are structurally very close to coumarins but less conjugated and effectively reduced by Ni_2B. So, we tried to reduce 3,7-substituted coumarins with nickel boride.

However, Ni_2B is always generated in situ from a nickel salt using $NaBH_4$ in methanol. But $NaBH_4$/MeOH is already known as a strong reducing agent itself, and it is possible that it contributes to the reduction process. We therefore undertook to reduce the 3-substituted coumarins with this reagent and to compare the results obtained with Ni_2B.
For this, a variety of coumarins (the unsubstituted coumarin **(1)** and 3- or 3,7-substituted coumarins) was studied to highlight the impact of the electronic effects on the efficiency of the reduction. DFT calculations help us to understand the non-reactivity of $NaBH_4$ as reducing agent for coumarins bearing ED-group. Moreover, different conditions for the reduction were tested to study its selectivity.

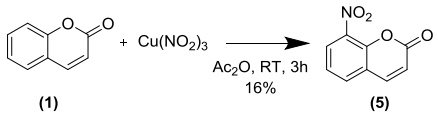
Results and Discussion

We used a representative variety of substituted coumarins (See Scheme 2) and also coumarin **(1)** as the prototypical chromen-2-one. Some of the studied coumarins are commercially available such as coumarin **(1)**, 7-hydroxycoumarin **(2)**, 3-carbethoxycoumarin **(3)**, 3-carbethoxy-7-hydroxycoumarin **(4)**. Other substituted coumarins with EW-groups such as 8-nitro, 3-cyano and with ED-group such as 3-benzamido- and 3-acetamido have been synthetized.



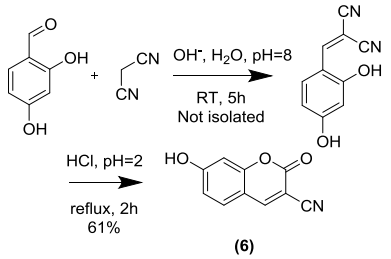
Scheme 2. General structure of a 3,7-substituted coumarin with R^1=H, CO_2Et, NHCOPh, NHCOAc, CN; R^2= OH, H.

Synthesis of coumarins
The 8-nitrocoumarin **(5)** was prepared from the commercially available coumarin **(1)** and copper(II) nitrate salt in acetic anhydride by modifying the method of Kanodia et al. [23] without using montmorillonite as a catalyst (Scheme 3). Despite the low yield obtained, the recovered product is sufficiently pure to be used directly in the following stages.



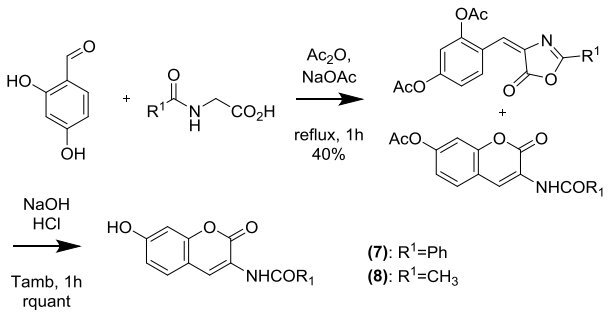
Scheme 3. Synthesis of 8-nitrocoumarin.

The synthesis of 3-cyano-7-hydroxycoumarin **(6)** was reported in the literature by Fringuelli et al. [24]a (Scheme 4). Under these easy-to-use conditions, a satisfactory yield of the desired coumarin could be obtained.



Scheme 4. Synthesis of 3-cyano-7-hydroxycoumarin

To synthesize the 3-benzamido- **(7)** and 3-acetamido-7-hydroxycoumarine **(8)**, we followed the Erlenmeyer-Plöchl method [25] (Scheme 5). Condensing hippuric acid or acetylglycine with 2,4-dihydroxybenzaldehyde gave a mixture of coumarins and azlactone which can be easily separated by recrystallization or by column chromatography.



Scheme 5. Synthesis of 3-benzamido- and 3-acetamido-7-hydroxycoumarin.

In total, the reduction of eight substituted coumarins were studied using $NaBH_4$/MeOH or $NiCl_2$/$NaBH_4$ as reagents (Figure 1).

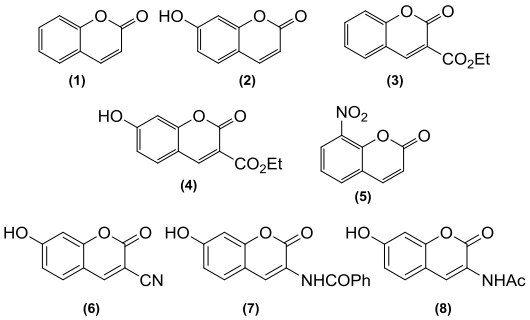
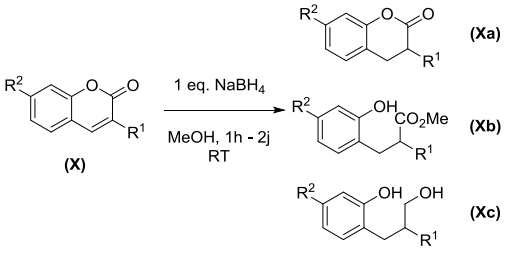


Figure 1. Representations of the 8 studied coumarins studied in this work.

Reduction of coumarins with $NaBH_4$ in methanol (Procedure A)

We expected the formation of the chroman-2-one **(1a)** as the 1,4-hydride addition reduction product but the results obtained on the unsubstituted coumarin **(1)** showed the formation of the methyl ester **(1b)** accompanied by the saturated alcohol **(1c)** (Scheme 6, R^1 = R^2 = H). The formation of the latter alcohol results from the ability of $NaBH_4$/MeOH to reduce ester or lactone to alcohol. [26] For the methyl ester **(1b)**, its formation can be explained by the formation of the chroman-2-one **(1a)** followed by a trans-esterification in methanol to give the methyl ester product **(1b)**.

Even if the reductant $NaBH_4$/MeOH is known to induce both 1,4- and 1,2-hydride addition, [27] we did not observe the formation of an allylic alcohol resulting from an 1,2-hydride addition.



Scheme 6. Possible products expected after reduction of coumarins using $NaBH_4$/MeOH as a reducing agent.

Table 1 summarizes yields obtained for each substituted coumarin.

Table 1. Isolated yields obtained after the reduction using $NaBH_4$/MeOH (1eq $NaBH_4$, 1 eq coumarin; Procedure A). Yields are not optimized.

Coumarins **(X)**	**(Xa)**	**(Xb)**	**(Xc)**
(1)	0 %	16 %	32 %
(2) [a]	0 %	0 %	0 %
(3)	0 %	19 %	61 %
(4)	0 %	10 %	23 %

(5)	0 %	0 %	53 %
(6)	0 %	9.4%	23 %
(7) [a]	0 %	0 %	0 %
(8) [a]	0 %	0 %	0 %

[a] No reaction

The reduction of the C_3-C_4 double bond (1,4-addition) with 1eq. of $NaBH_4$ in methanol is effective with coumarin **(1)**, 3-carbethoxycoumarin **(3)**, 3-carbethoxy-7-hydroxycoumarin **(4)**, 3-cyano-7-hydroxycoumarin **(6)** and 8-nitrocoumarin **(5)**. The total yield of recovered products (ester + alcohol) ranging from 32 to 80%. However, the expected chroman-2-one **(Xa)** was never observed. It is interesting to notice that, in the case of the 3-carbethoxy-7-hydroxycoumarin **(4)**, the reaction is less effective than for its analog **(3)** with a total yield of only 32% compared to 80%.
This lower yield could be explained by the existence of the +M effect of the hydroxyl substituent at the 7-position which enriches the double bond and makes it less electrophilic. For the 8-nitrocoumarin **(5)**, only the alcohol product **(5c)** could be isolated. Indeed, the selectivity trend is in favor to the reduction to the alcohol product **(Xc)** which is always obtained as the main reduction product, however accompanied with the methyl ester **(Xb)** in a lower proportion. No reduction was observed for the 7-hydroxycoumarin **(2)**, 3-benzamido-7-hydroxycoumarin **(7)** or 3-acetamido-7-hydroxycoumarin **(8)**. This lack of reactivity occurred only with the coumarins bearing ED-group. To understand these results, DFT calculations were performed.

DFT Calculations
$NaBH_4$ and, more specifically the formed hydride, is the nucleophile that attacks the double bond. Thus, to evaluate the electrophilic character of coumarins, LUMO calculations were performed. The nucleophilic attack will be easier if the LUMO energy is low. Moreover, with the LUMO and HOMO calculations, the global electrophilicity index (ω) as introduced by Parr et al [28] was computed. This index measures the electrophilic power of a molecule and is defined as the square of its electronegativity (μ) divided by its chemical hardness (η), according to the equation (1).

$$\omega = \frac{\mu^2}{2\eta} \quad (1)$$

The electronegativity and the chemical hardness could be defined through the ionization potential I and the electron affinity A. According to the Koopman's frontier orbitals theorem,[29] values of I and A are respectively equal to the opposite of the HOMO and LUMO energies. Thus, we can write:

$$\mu = -\frac{I+A}{2} \quad \text{and} \quad \eta = \frac{I-A}{2}$$

$$\omega = \frac{(E_{HOMO} + E_{LUMO})^2}{4(E_{HOMO} - E_{LUMO})} \quad (2)$$

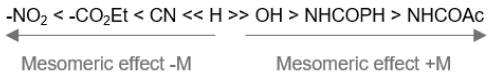
The results are shown in Table 2 and the HOMO energies are given in supporting information (Table S1).

Table 2. Index of electrophilicity (ω) and LUMO Energy (eV) for each studied coumarins.

Coumarins **(X)**	E_{LUMO}	ω
(5)	-0.11574	0.241863
(6)	-0.10396	0.214112
(3)	-0.1013	0.205558
(4)	-0.09612	0.195115

(1)	**-0.0844**	**0.168814**
(7)	-0.08258	0.165912
(2)	-0.07941	0.158825
(8)	-0.07924	0.158667

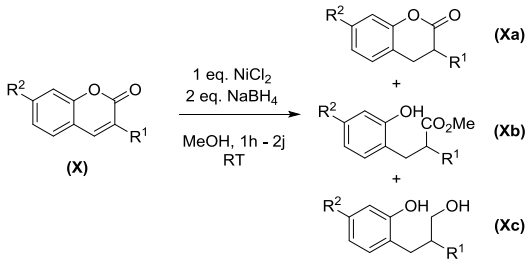
For the LUMO energy, we obtained the following ascending order:
8-nitrocoumarin **(5)** > 3-cyano-7-hydroxycoumarin **(6)** > 3-carbethoxycoumarin **(3)** > 3-carbethoxy-7-hydroxy coumarin **(4)** > coumarin **(1)** > 3-benzamido-7-hydroxycoumarin **(7)** > 7-hydroxycoumarin **(2)** > 3-acetamido-7-hydroxycoumarin **(8)**.
Same order was found for ω and can be correlated with the electronic effect (-M/+M) of each substituent (Scheme 7).



Scheme 7. Mesomeric effect strength.

Table 2 shows that the reduction of coumarins occurs only when the molecules have a LUMO energy E_{LUMO} lower than that of the coumarin **(1)**. On the opposite, the electrophilicity index ω is higher than that of **(1)**. So these values, E_{LUMO} and ω, can be seen as a quantification of the mesomeric effects.

Reduction of coumarin with Nickel Boride (Ni_2B)
To overcome the absence of reduction of the 3,7-substituted coumarins bearing ED-group, the use of nickel boride (Ni_2B) as reducing agent was attempted. Brown [30] first reported its use as a catalyzer for hydrogenation. Later, it was studied by the group of Khurana et al., [22] to reduce a great variety of substrates such as alkenes, alkynes, hetero-arenes (*e.g.* quinolones, quinoxalines), chalcones and α,β-unsaturated five membered lactones the latter two being very close to our coumarin's substrates.
The reduction of coumarins follows a similar procedure as the one described with $NaBH_4$ (see procedure A in experimental part) but this time, $NiCl_2$ is added (Scheme 8). Sodium borohydride reacts with Ni(II) in methanol to give a black precipitate of nickel boride. To avoid the degradation of nickel boride by the formation of nickel oxide, the reaction is conducted under an inert atmosphere.



Scheme 8. General procedure for the reduction of 3,7-substituted coumarin using $NiCl_2$ and $NaBH_4$ as reducing agent.

The reaction mechanism is not fully elucidated as the formed specie can be a mixture of Ni_2B or more probably $(Ni_2B)_2H_3$. Abe et al [31] proposed two mechanisms for the reduction of five membered α,β-unsaturated lactones. First, Ni_2B seems to contribute to an initial activation of the double bond by binding with the carbonyl group. The hydride transfer from BH_4^- can then take place. On the opposite, they proposed a stepwise mechanism involving homogeneous penta-coordinated Ni-complex containing borohydride. The activated hydrogen adsorbed on nickel is then transferred to the C_3-C_4 double bond. To find out which of $NaBH_4$ or Ni_2B (or $(Ni_2B)_2H_3$) is the species that actually transfers hydrides, we used powdered Ni_2B (used as a catalyst) of commercial origin and added $NaBH_4$ on several coumarins. The reduction results are identical to those obtained with $NaBH_4$/MeOH alone (See Figure S1 reported in SI). This result shows that the active species in the nickel boride is very probably the hydride $(Ni_2B)_2H_3$ which, moreover, must be at the origin of the selectivity.

The order of addition of $NaBH_4$ seems to play an important role in the selectivity of the reaction. Two main protocols are generally described in the literature. In the first one, we realized a prior preparation of Ni_2B from $NaBH_4$ and $NiCl_2$ as described by Wölf et al., [32] Brown et al. [30] or Belisle et al. [33] before the addition of substituted coumarins (see Procedure C in the experimental part). In the second one, $NaBH_4$ is added to a mixture of $NiCl_2$ and coumarins as described by Abe et al.,[31] Koroleva et al. [34] or Miyano et al. [35] (see procedure B in the experimental part).

The results and yields obtained according to procedure B for the reduction with nickel boride are shown in Table 3.

Table 3. Isolated yields for the reduction with Nickel Boride (1eq. $NiCl_2$, 2 eq. $NaBH_4$, 1eq coumarin; Procedure B*)

Coumarins **(X)**	**(Xa)**	**(Xb)**	**(Xc)**
(1)	32 %	32 %	32 %
(2)	0 %	32 %	0 %
(3)	12 %	6 %	6 %
(4)	0 %	54 %	5 %
(5)	0%	53 %	0%
(6)	0 %	13 %	3 %
(7)	0 %	53 %	36 %
(8)	0 %	35 %	11 %

*Under these stoichiometric conditions, unreacted coumarin (X) often remains and it decrease the yield (i.e. entry (3)). It is, however, possible to substantially increase the yield of conversion and reduction products formed by adding to the reaction mixture a second portion of preformed Ni_2B. Under these conditions, (3) gives x% of 3a and y% of 3b (see figure S2) It is important to note that the selectivity is not changed.

We first notice that all the coumarins reacted with Ni_2B: the reduction occurred also for **(2)**, **(7)** and **(8)** which contain ED-group while they were inert with $NaBH_4$/MeOH. The conversion yields are quite similar or better compared to the $NaBH_4$/MeOH method (when the reduction occurred).
Then as a second important fact, with Ni_2B, the chroman-2-one **(Xa)** product is this time isolable for **(1)** and **(3)**, whereas it wasn't in the case of $NaBH_4$/MeOH. The general trend of the selectivity seems to favor the formation of the ester **(Xb)** (entries **(2)**, **(4)**, **(5)**, **(6)**, **(7)** and **(8)**) to the detriment of the alcohol **(Xc)** which is exactly the reverse trend with $NaBH_4$/MeOH. The presence of some alcohol may seem surprising with Ni_2B which is not known to reduce esters, [36] so its formation is most certainly attributable to $NaBH_4$ in methanol which is added last in procedure B.
It is interesting to notice that the 8-nitrocoumarin **(5)**, is effectively reduced to **5b** (52%) by Ni_2B but with the concomitant reduction of the nitro group in amine. Indeed the couple $NiCl_2$/$NaBH_4$ is also known to reduce the nitro moiety [37]. For the reduction of compound **(6)**, we should expect also the reduction of the nitrile moiety [38]. However, in our case no reduction product of the cyano group could be isolated.
Moreover, compared to the reduction with $NaBH_4$ alone in methanol, we could notice a slightly different selectivity toward the three possible reduction products. We tried to find conditions allowing greater selectivity, in particular for a better formation of the chroman-2-one **(Xa)** by monitoring the reactions.

Monitoring Studies
Comparison of the $NaBH_4$/MeOH procedure A and Ni_2B procedure B and C was undertaken on coumarin **(1),** because of its high reactivity with both reagent and the easy monitoring of the formed products by ^1H NMR (see SI Tables S2-S3 and Figures S3-S4). The reduction was investigated for various times and various equivalents of $NaBH_4$.

With procedure A ($NaBH_4$/MeOH), a first important fact is again the absence of the chroman-2-one **(1a)** (see SI Table S2 and Figure S3): shorter reaction times still do not allow its identification or isolation. This compound does not therefore appear to be an intermediate for this reaction.
Still with procedure A, the alcohol **(1c)** is always the preponderant product with respect to the ester **(1b)** and its yield therefore increases logically with time and with addition of a supplementary equivalent of $NaBH_4$.
With Ni_2B in procedure B, chroman-2-one **(1a)** is predominant but mixed with ester **(1b)** and alcohol **(1c)** and a small amount of unreduced coumarin (see SI Table S3 and figure S2). Therefore, it appears that Ni_2B is a milder reducing agent than $NaBH_4$/MeOH. When we no longer observe a significant change in the proportions of the reduction products with Ni_2B and in an attempt to reduce the unreacted coumarin, we tried to "restart" the reduction by adding one more equivalent of $NaBH_4$. Results are then very similar to those obtained with $NaBH_4$/MeOH alone (procedure A), if the coumarin **(1)** is effectively consumed, the chroman-2-one **(1a)** has disappeared and the alcohol **(1c)** is predominant relative to the ester **(1b)**. It can be concluded that nickel boride no longer seems to play a role in the reduction when it has been consumed.
One could think that the use of Ni_2B previously formed *before* the addition of coumarin (as in procedure C) could avoid the appearance of alcohol. Indeed with the preformed Ni_2B in procedure C, we do not observe under these conditions the formation of

alcohol or even the formation of the ester **(1b)**: chromane-2-one **(1a)** is the only reduction product formed but accompanied by a substantial amount of unreacted coumarin. Procedure C therefore appears to best represent the intrinsic reactivity of Ni_2B on coumarin. To summarize, in term of selectivity toward the chroman-2-one, it seems that procedure C is the most selective for obtaining the chroman-2-one **(1a)** while procedure A is the most selective for the alcohol product **(1c)**.

To check this behavior with the two types of reducing agent but on another coumarin, we chose carbethoxycoumarin **(3)** (only electron poor coumarin reacts with the two reducing agents). The monitoring studies are depicted Table S4-S5 and Figure S3-S in the SI. When reducing **(3)** by $NaBH_4$/MeOH (procedure A), results very similar to those obtained on coumarin **(1)** are observed: chroman-2-one **(3a)** is not isolated or even identifiable in the reaction mixture, only the alcohol **(3b)** and to a lesser extent the ester **(3c)** are isolated. Even for a longer time (> 1 h) or with additional amounts of $NaBH_4$ (4 eq.), the ester **(3b)** was still present (see SI Table S4 and Figure S3). When using Ni_2B (procedure B) as a reducing agent, the chroman-2-one **(3a)** is the only observable reduction product after 5mn of reaction which is in mixture with unreacted coumarin (31and 69% respectively).
These results confirm that using Ni_2B formed *in situ* from $NiCl_2/NaBH_4$ is a milder reducing agent than $NaBH_4$ in methanol. Its use allows the isolation of the chroman-2-one **(Xa)**, which has never been observed in the case of $NaBH_4$/MeOH.

Conclusion

To conclude, we extended the reducing method implying Ni_2B formed *in situ* from $NaBH_4$ and $NiCl_2$ to electron rich coumarins that did not react with other standard reducing agents. This is especially true for $NaBH_4$/MeOH, which can only reduce the prototypic coumarin **(1)** and electron poor coumarins (*e.g*. 8-nitro, 3-carbethoxy, 3-cyano substituted coumarins). The unreactivity of ED-substituted coumarins (3-benzamido, 3-acetamido, 7-hydroxy) is supported by DFT studies highlighting a low electrophilicity of the double bond and high lying LUMO energy compared to each of EW-substituted coumarins.
Thus, the reduction of both EW- and ED-substituted coumarins was only achievable with Ni_2B formed *in situ* from $NaBH_4$ and $NiCl_2$ with satisfactory to good yields and under very easy-to-use and mild conditions. In addition, Ni_2B makes it possible to obtain chroman-2-one selectively (chroman-2-ones are biologically interesting compounds) [39] and without opening the lactone, especially by preforming Ni_2B before adding the substrate to be reduced.

Experimental Section

Computational Method

All calculations were performed using the Gaussian16 package [40]. Geometries of neutral molecules were optimized using the functional B3LYP in combination with the 6–311+G(d,p) basis set. Vibrational frequency calculations were performed to ensure that each geometry optimization converged to a real minimum and solvent effect were taken into account in the geometry optimizations with the IEFPCM formalism. The solvent used was methanol.

General Information

All starting materials and reagents were obtained from commercial producers and are used without further purification except for synthesized compounds. Solvents were generally used as supplied by the manufacturer. Dry Column Vacuum Chromatography was carried out by using silica gel (Merck Silica Gel 60 – 0,015-0,040 mm) unless otherwise mentioned. Analytical thin layer chromatography (TLC) was run on Merck silica gel 60 F254 precoated plates (250 µm thickness). ^{1}H NMR and ^{13}C NMR were recorded using a Bruker Avance III 400 or 500. The chemical shift δ is given in ppm. High Resolution Mass Spectral data were obtained using a LTQ Orbital XL Thermo Scientific (ESI). HRMS and Spectral Data are given in SI only for the molecules that are not described in the literature. For molecules which are already described in the literature, spectral information are given in the experimental section and compared to the value obtained in the literature. For the monitoring studies, the attribution of the products was carried out from the spectral data obtained in this study and from data already published in the literature.

Preparation of substituted coumarins

8-nitrocoumarin (5). The compound is prepared by reacting 1.00 g of coumarin (6.8 mmol, 1eq.) with 1.65 g of $Cu(NO_3)_2(H_2O)_3$ (6.8 mmol, 1eq.) dissolved in acetic anhydride at room temperature for 2 hours. After completion of the reaction, water (100 ml) is added to the mixture and the desired product is extracted with 3 x 30 mL of diethyl ether, dried over Na_2SO_4 to yield a pure white solid (0.20 g, 16 %). m.p.: 175-178°C; ^{1}H NMR (500 MHz, DMSO-d6): δ=8.75 (d, J=2.6 Hz, 1H), 8.43 (dd, J_1=9.1 Hz, J_2=2.6 Hz, 1H), 8.25 (d, J=9.6 Hz, 1H), 7.63 (d, J=9.1 Hz, 1H), 6.70 ppm (d, J=9.6 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d6): δ=159.4, 157.7, 144.0, 143.8, 127.0, 124.8, 119.6, 118.5, 118.3 ppm; MS (ESI): m/z calcd for $C_9H_5NO_4H^+$: 192.14, found: 192.01 $[M+H]^+$, 213.97 $[M+Na]^+$, 229.96 $[M+K]^+$. GC-EI: m/z calcd for $C_9H_5NO_4$: 191.0; found 191.0 (NIST score 93%).

3-cyano-7-hydroxycoumarine (6).[24]a The compound is prepared by condensation between 1.40 g of 2,4-dihydroxybenzaldehyde (10 mmol, 1 eq.) and 0.80 g of malonitrile (12 mmol, 1.2 eq.) in a 0.2 M NaOH solution under agitation for 5h. The mixture is heated at 90 °C for 2h. A yellow solid is filtered, washed and recrystallized in absolute ethanol to yield a pure yellow solid (1.20 g, 61%). m.p.: 263.7-265.3°C (273-275°C Ref [24]a from acetic acid and water or 262°C Ref [24]b); ^{1}H NMR (500 MHz, DMSO-d_6): δ=8,79 (d, J=2.8 Hz 1H), 7.66 (dd, J_1=2.8 Hz, J_2=8.6 Hz, 1H), 6.93-6.87 (dd, J_1=2.4

Hz, J_2=8.6 Hz, 1H), 6.79 ppm (d, *J*=2.4 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-*d6*): *δ*=165.7, 158.1, 157.2, 153.7, 132.3, 115.8, 115.2, 110.6, 103.0, 96.2 ppm; MS (ESI): *m/z* calcd for $C_{10}H_5NO_3$: 187.03; found: 185.89 $[M-H]^-$, 372.99 $[2M]^+$.

N-(7-acetoxy-2-oxo-2H-chromen-3-yl) benzamide. [41] The compound is prepared by condensation 2.00 g of 2,4-dihydroxybenzaldehyde (14 mmol, 1eq.) with 2.20 g of hippuric acid (12.6 mmol, 0.9 eq.) in presence of 0.70 g of sodium acetate (8.4 mmol, 0.6 eq.) dissolved in acetic anhydride. The mixture is heated under reflux under agitation for 1 hour. After cooling, an orange solid is filtered, washed with water and ethanol. Purification by column chromatography (gradient DCM:Acetone, Rf=0,56) gives a pure yellow solid (0,80 g, 20%). m.p.: 185.0-188.2°C (190-191 Ref [41]); ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.01 (d, *J*=8.8 Hz, 1H), 8.20 (d, *J*=7.1 Hz, 1H), 7.70–7.56 (m, 2H), 7.60–7.45 (m, 2H), 7.35 (s, 1H), 7.20 (dd, J_1=9.0 Hz, J_2=2.3 Hz, 1H), 7.10 (d, *J*=2.3 Hz, 1H), 2.44 (s, 3H), 2.36 ppm (s, 3H).

N-(7-hydroxy-2-oxo-2H-chromen-3-yl) benzamide (7).[42] The compound is prepared by saponification of compound N-(7-acetoxy-2-oxo-2H-chromen-3-yl) benzamide with NaOH in H_2O:MeOH. After agitation during 1 hour at room temperature, 12N HCl is added dropwise to the mixture until the pH is acid. A white solid is filtered and washed to give the pure product (0,76g, rquant). m.p.: 279.4-279.5°C (285-287°C Ref [42] from acetic acid); ^{1}H NMR (400 MHz, DMSO-d*6*): *δ*=9.59 (s, 1H), 8.45 (s, 1H), 7.96 (dd, J_1=7.1 Hz, J_2=1.8 Hz, 2H), 7.67–7.51 (m, 4H), 6.84 (dd, J_1=8.5 Hz, J_2=2.3 Hz, 1H), 6.79 ppm (d, *J*=2.3 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6): *δ*=169.3, 166.3, 158.1, 151.9, 151.0, 133.9, 132.7, 129.3, 129.1, 128.0, 124.1, 119.6, 117.6, 110.3 ppm; MS (ESI): *m/z* calcd for $C_{16}H_{11}NO_4H^-$: 280.06; found: 279. 89 $[M-H]^-$.

3-acetamido-7-acetoxycoumarine. [43] Similar procedure as for compound N-(7-acetoxy-2-oxo-2H-chromen-3-yl) benzamide is followed but condensation is made with acetylglycine instead of hippuric acid. Compound is obtained after filtration without any further purification as a yellow solid (0.80g, 54%). m.p. : 234.5-235.1 °C (233-234 °C Ref [43]); 8.60 (s, 1H), 7.96 (s, 1H), 7.44 (d, *J*=8.5 Hz, 1H), 7.06 (d, *J*=2.2 Hz, 1H), 7.00 (dd, J_1=8.5 Hz, J_2=2.2 Hz, 1H), 2.27 (s, 3H), 2.18 ppm (s, 3H).

3-acetamido-7-hydroxycoumarine (8).[43] Similar procedure as for compound **(7)** is followed. Compound is obtained after filtration without any further purification as a light pink solid (0.76 g, rquant). m.p.: 304.0-304.1 °C (303-304°C Ref [44]); ^{1}H NMR (400 MHz, DMSO-d*6*): *δ*=9.54 (s, 1H), 8.49 (s, 1H), 7.50 (d, *J*=8.4 Hz, 1H), 6.79 (dd, J_1=8.4, J_2=2.3 Hz, 1H), 6.73 (d, *J*=2.3 Hz, 1H) 2.13 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*=175.4, 174.9, 164.7, 163.0, 156.7, 134.1, 133.7, 131.0, 126.2, 118.8, 116.6, 107.1, 29.0 ppm; MS (ESI): *m/z* calcd for $C_{11}H_9NO_4H^+$: 220.05; found: 219.95 $[M+H]^+$.

Procedure A. General Procedure for the reduction of substituted coumarin with sodium borohydride

Coumarin ranging from 0.3 to 6.2 mmol (1eq), dissolved in 10 mL of dry methanol, is introduced in a round bottom flask under agitation and inert atmosphere (N_2). $NaBH_4$ (1 eq.) is added to the mixture at 0°C. The mixture is left at room temperature up to total consumption of starting material (followed by TLC). 1 or 2 eq. of $NaBH_4$ may be added for reaction's completion. The mixture is hydrolyzed with 30 mL water and extracted with 3 x 20 mL diethyl ether. The organic layers are recovered, dried over $MgSO_4$ and dry-evaporated under vacuum. Pure products are obtained after Dry Column Vacuum Chromatography (DCVC) purification.

Procedure B. General Procedure for the reduction of coumarin with Nickel Boride:

Coumarin ranging from 0.3 to 6.2 mmol (1eq) and $NiCl_2$ (1eq), dissolved in 5 mL dry methanol, are introduced in a round bottom flask under agitation and inert atmosphere (N_2). $NaBH_4$ (2 eq.) are added to the mixture at 0°C. The mixture is left at room temperature up to total consumption of starting material (followed by TLC). 1 eq. of $NiCl_2$ and 2 or 4 eq. of $NaBH_4$ may be added for reaction's completion. The mixture is neutralized with 1N HCl and filtered over celite. The filtrate is recovered with 30 mL water and extracted with 3 x 20 mL of diethyl ether. The organic layers are recovered, dried over $MgSO_4$ and dry-evaporated. Pure products are obtained after Dry Column Vacuum Chromatography (DCVC) purification.

Procedure C. Alternative Procedure for the reduction of coumarin with Nickel Boride:

Same protocol as procedure B but Ni_2B is pre-formed with 1eq. of $NiCl_2$ and 2eq. of $NaBH_4$ in dry methanol under inert atmosphere. The coumarin is added afterwards to the mixture.

Chroman-2-one (1a).[8] Starting from coumarin **(1),** the compound is obtained according to procedure B or procedure C with 0.80 g of $NiCl_2$ (3.4 mmol, 1eq) and 0.20 g of $NaBH_4$ (6.8 mmol, 2eq.). After 5 minutes the reaction is completed and the desired product is obtained either in mixture with the starting material or other product of the reaction. For procedure B the compound is obtained in mixture with compound **(1b)**. For procedure C, the compound is obtained in mixture with the un-reacted reagent **(1)**. (0.2 g, 41% Procedure C, 0.15 g, 32% Procedure B). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*=7.17-7.11 (m, 2H), 7.05–6.97 (m, 2H), 2.94 (dd, J_1=8.3 Hz, J_2=6.2 Hz 2H), 2.72 ppm (dd, J_1=8.3 Hz, J_2=6.2 Hz 2H). ^{13}C NMR (126 MHz, $CDCl_3$): *δ*= 173.4, 155.6, 130.1, 127.6, 126.9, 115.3, 51.6, 33.7, 25.9 ppm. GC-MS (EI): m/z calcd for $C_9H_8O_2$: 148.0; found: 148.0 [M] (98.6% NIST score).

Methyl 3-(2-hydroxyphenyl)propanoate (1b).[44] The compounds is obtained according to procedure A or B starting from 0.50 g of 2H-chromen-2-one (3.4 mmol, 1 eq.) with 0.13 g of $NaBH_4$ (3.4 mmol, 1 eq.) or 0.8 g of $NiCl_2$ (3.4 mmol, 1eq.) and 0.26 g of $NaBH_4$ (6.8 mmol, 2eq.). Compound **(1b)** was obtained as a pure product for procedure A but for procedure B it was obtained in mixture with compound **(1a).** The two compounds couldn't be separated by column chromatography in the case of procedure B. The compound or mixture was obtained as a clear oil (0.09 g, 16% Procedure A, 0.2 g, 32% Procedure B). ^{1}H NMR (500 MHz, DMSO-d*6*): *δ*= 9.37 (s, 1H), 7.08–6.97 (m, 2H), 6.78 (d, *J*=7.4 Hz, 1H), 6.70 (t, J_1=7.4 Hz, 1H), 3.58 (s, 3H), 2.78 (t, *J*=8.7 Hz, 2H), 2.56 ppm (t, *J*=8.7 Hz, 2H).^{13}C NMR (126 MHz, DMSO-d*6*): *δ*=173.43, 155.58, 130.13, 127.7, 126.9, 119.3, 115.3, 51.6, 33.7, 25.9 ppm; GC-MS (EI): m/z calcd for $C_9H_{12}O_3$: 180.0; found: 180.0 [M] (NIST score 85.95%).

2-(3-hydroxypropyl)phenol (1c).[45] Similar procedure as for compound **(1b).** It was purified by column chromatography eluted with a gradient of cyclohexane: EtOAc to yield a pure yellow oil (0,16 g, 32% Procedure A and B). ^{1}H NMR (500 MHz, DMSO-*d6*): *δ*=9.17 (s, 1H), 7.04 (dd, J_1=7.4 Hz, J_2=1.1 Hz, 1H), 6.98 (td, J_1=8.0 Hz, J_2=1.1 Hz, 2H), 6.77 (dd, J_1=8.0 Hz, J_2=1.8 Hz, 1H), 6.70 (td, J_1=7.4 Hz, J_2=1.8 Hz, 1H), 4.42 (t, *J*=4.6 Hz, 1H),

3.41 (td, J_1=6.8 Hz, J_2=4.6 Hz, 2H), 2.54 (t, J_1=9.5 Hz, 2H); 1.67 ppm (tt, J_1=9.5 Hz, J_2=6.8 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-*d6*): δ=155.5, 130.1, 128.6, 127.0, 119.2, 115.2, 61.0, 33.1, 26.6 ppm; GC-MS (EI): *m/z* calcd for $C_9H_{12}O_2H^+$: 152.08; found: 152.0 [M] (NIST score 80.6%).

Methyl 3-(2,4-dihydroxyphenyl)propanoate (2b). The compound is prepared according to the procedure B starting from 1.00 g 7-hydroxycoumarin **(2)** (6.2 mmol, 1eq.) with 1.40 g of $NiCl_2$ (6.2 mmol, 1 eq.) and 0.46 g of $NaBH_4$ (12.4 mmol, 2 eq.) and was purified by recrystallization in chloroform and washed with diethyl ether to yield a pure oil (0.40 g, 32%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.83 (d, J=8.1 Hz, 1H), 6.33 (d, J=2.6 Hz, 1H), 6.29 (dd, J_1=8.1 Hz, J_2=2.6 Hz, 1H), 3.61 (s, 3H), 3.42 (q, J=7.0 Hz, 1H), 2.75 (dd, J_1=7.2 Hz, J_2=5.2 Hz, 2H), 2.75 (t, J=7.0 Hz, 2H), 2.60 ppm (t, J=7.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ= 176.4, 155.5, 155.0, 131.2, 119.4, 108.1, 104.3, 52.3, 35.9, 24.1 ppm; MS (ESI): *m/z* calcd for $C_{10}H_{12}O_4H^+$: 197.07; found: 197.05 $[M+H]^+$, 219.04 $[M+Na]^+$, 194.93 $[M-H]^-$. HRMS (ESI): *m/z* calcd for $C_{10}H_{12}O_4H^+$: 197.08084; found: 197.08079 $[M+H]^+$.

Ethyl 2-oxochroman-3-carboxylate (3a).[46] The compound was obtained according to procedure B starting from 0.20 g of ethyl 2-oxo-2H-chromene-3-carboxylate **(3)** (0.9 mmol, 1 eq.) with 0.20 g of $NiCl_2$ (0.9 mmol, 1 eq.) and 0.08 g of $NaBH_4$, (1.8 mmol, 2eq.) and was purified by column chromatography (gradient cyclohexane:EtOAc) to yield a pure yellow oil (0,011 g, 6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.27–7.20 (m, 1H), 7.15 (d, J=7.4 Hz, 1H), 7.09–6.97 (m, 2H), 4.22–4.05 (m, 2H), 3.69 (dd, J_1=8.5 Hz, J_2=6.0 Hz, 1H), 3.35 (dd, J_1=15.8 Hz, J_2=8.5 Hz, 1H), 3.11 (dd, J_1= 15.8 Hz, 6.0 Hz, 1H), 1.14 ppm (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ=168.2, 165.2, 151.4, 129.0, 128.8, 125.0, 121.9, 116.6, 61.8, 46.0, 26.8, 14.3 ppm; MS (ESI): *m/z* calcd for $C_{12}H_{12}O_4H^+$: 220.07; found: 221.03 $[M+H]^+$, 243.01 $[M+Na]^+$.

1-Ethyl 3-methyl 2-(2-hydroxybenzyl)malonate (3b). Same as for **(3a).** The compound is obtained as a pure yellow oil (0.04 g, 19% Procedure A or 0.03 g, 12% Procedure B). ^{1}H NMR (500 MHz, DMSO-*d6*,): δ=9.52 (s,1H), 7.04 (td, J_1=7.9 Hz, J_2=1.8 Hz, 1H), 6.99 (dd, J_1=7.7 Hz, J_2=1.8 Hz, 1H), 6.79 (d, J=7.9 Hz, 1H), 6,69 (t, J=7.7 Hz, 1H), 4.06 (q, J=6.9 Hz, 2H), 3.82 (t, J=7.8 Hz, 1H), 3.03 (m, 2H), 1.10 ppm(t, J=7.8 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-*d6*): δ=169.0, 155.8, 130.9, 128.3, 123.9, 119.2, 115.3, 61.3, 52.7, 51.1, 30.1, 14.3; MS (ESI): *m/z* calcd for $C_{13}H_{16}O_5$: 252.10; found: 275.07 $[M+Na]^+$, 291.06 $[M+K]^+$; HRMS (ESI): *m/z* calcd for $C_{13}H_{16}O_5H^+$: 253.10705; found: 253.10700 $[M+H]^+$; elemental analysis calcd (%) for $C_{12}H_{12}O_4$: C 61.88, H 6.40; found: C 61.79, H 6.57.

Ethyl 3-hydroxy-2-(2-hydroxybenzyl)propanoate (3c). Same as for **(3a).** The compound is obtained as a pure yellow oil (0.12 g, 61% Procedure A or 0.02 g, 8% Procedure B). ^{1}H NMR (400 MHz, DMSO-*d6*): δ=9.34 (s, 1H), 7.06 (td, J_1=7.6 Hz, J_2=1.7 Hz, 1H), 7.03 (dd, J_1=7.6 Hz, J_2=1.7 Hz, 1H), 6.83 (dd, J_1=8.0 Hz, J_2=1.2 Hz, 1H), 6.73 (td, J_1=8.2 Hz, J_2=1.2 Hz, 1H), 4.82 (s, 1H), 4.03 (qq, J_1=7.1 Hz, J_2=4.8 Hz, 2H), 2.86 (tdd, J_1=8.2 Hz, J_2=6.4 Hz, J_3=4.8 Hz, 1H), 2.77 (dd, J_1=13.3 Hz, J_2=6.4 Hz, 1H), 2.69 (td, J_1=13.3 Hz, J_2=8.2 Hz, 1H), 1.12 ppm (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d6*): δ=174.4, 155.7, 130.9, 127.7, 125.5, 119.1, 115.3, 62.6, 59.9, 48.5, 29.6, 14.5 ppm; MS (ESI): *m/z* calcd for $C_{12}H_{14}O_5$: 224.26; found: 247.06 $[M+Na]^+$, 263.05 $[M+K]^+$; elemental analysis calcd (%) for $C_{12}H_{14}O_5$: C 64.25, H 7.2; found: C 61.96, H 7.31.

1-Ethyl 3-methyl 2-[(2,4-dihydroxybenzyl)malonate (4b). The compound is prepared according to procedure A or B from 0.20 g of 3-carbethoxy-7-hydroxycoumarin **(4)** (0.8 mmol, 1 eq.) with 0.03 g of $NaBH_4$ (0.8 mmol, 1 eq.) or 0.20 g of $NiCl_2$ (0.8 mmol, 1eq.) and 0.06 g of $NaBH_4$ (1.6 mmol, 2eq.). It was purified by DCVC (gradient cyclohexane:ether) to yield a yellow oil (0.02 g, 10% Procedure A, 0.12 g, 54% Procedure B). ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.94 (d, J=8.2 Hz, 1H), 6.41-6.30 (m, 2H), 4.20 (qd, J_1=7.3 Hz, J_2=4.4 Hz, 2H), 3.80 (t, J=7.2 Hz, 1H), 3.74 (s, 3H), 3.13 (d, J=7.3 Hz, 2H), 1.26 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 170.5, 155.9, 155.3, 131.8, 116.3, 108.1, 104.3, 62.1, 53.2, 53.0, 28.5, 13.9 ppm; GC-EI *m/z* calcd for $C_{13}H_{16}O_6$: 268.0; found: 268.1.

Ethyl 2-(2,4-dihydroxybenzyl)-3-hydroxypropanoate (4c). See **(4b).** Purification by DCVC with a gradient cyclohexane: diethyl ether to yield a yellow oil (0.05 g, 23% in case of procedure A and 0, 01 g, 5% in case of procedure B). ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.92–6.84 (m, 1H), 6.34 (d, J=2.5 Hz, 1H), 6.32–6.29 (m, 1H), 4.20–4.08 (m, 2H), 3.86 (dd, J_1=11.6 Hz, J_2=3.2 Hz, 1H), 3.51 (dd, J_1=11.6 Hz, J_2=4.0 Hz, 1H), 2.94–2.81 (m, 2H), 2.63 (ddt, J_1=9.6 Hz, J_2=7.0 Hz, J_3=3.6 Hz, 1H), 1.23 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.1, 156.0, 155.2, 131.7, 116.1, 108.0, 104.1, 77.3, 77.0, 76.7, 62.3, 53.1, 28.7, 26.9, 13.9 ppm; HRMS (ESI): *m/z* calcd for $C_{12}H_{16}O_6H^+$: 241.10705; found: 241.10726 $[M+H]^+$.

Ethyl 3-(3-amino-2-hydroxyphenyl)propanoate (5b). The compound was obtained according to procedure A or B starting from 0.20 g of 8-nitrocoumarine **(5)** (1 mmol, 1eq.) with 0.25 g of $NiCl_2$ (1 mmol, 1eq.) and 0.04 g of $NaBH_4$ (2 mmol, 2eq.). The compound is obtained without further purification as brown oil (0.10 g, 53%). Warning the nitro moiety is reduced to an amine moiety. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.30 (s, 1H), 6.48 (d, J=8.3 Hz, 1H), 6.32 (d, J=2.7 Hz, 1H), 6.26 (dd, J_1=8.3 Hz, J_2=2.7 Hz, 1H), 4.37 (s, 3H), 3.58 (s, 3H), 2.65 (t, J=7.8 Hz, 2H), 2.51 ppm (t, J=7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=178.2, 151.1, 145.9, 131.9, 120.7, 118.2, 56.4, 38.8, 30.9 ppm; MS (ESI): *m/z* calcd for $C_{10}H_{13}O_3H^+$: 195.09; found: 196.08 $[M+H]^+$, 234.04 $[M+K]^+$. HRMS (ESI): *m/z* calcd for $C_{10}H_{13}O_3H^+$: 196.09682; found: 196.09686.

2-Nitro-6-(3-hydroxypropyl)phenol (5c). The compound was obtained according to procedure A starting from 0.15 g of 8-nitrocoumarine **(5)** (0.8 mmol, 1 eq.) with 0.03 g of $NaBH_4$ (0.8 mmol, 1eq.), and was purified by DCVC (gradient cyclohexane:ether) to yield a pure yellow oil (0.08 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.99-7.95 (m, 2H), 6.86 (d, J=8.1Hz, 1H), 3.64 (t, J=5.8 Hz, 2H), 2.78 (t, J=7.6 Hz, 2H), 1.88 ppm(dq, J_1=7.6 Hz, J_2=5.8 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=161.2, 127.7, 126.7, 124.2, 116.9, 60.4, 31.3, 25.1 ppm; MS (ESI): *m/z* calcd for $C_9H_{11}NO_4H^+$: 198.19; found: 198.04 $[M+H]^+$, 220.02 $[M+Na]^+$; HRMS (ESI) *m/z* calcd for $C_9H_{11}NO_4$-H^+: 196.06153; found: 196.06176.

Methyl 2-cyano-3-(2,4-dihydroxyphenyl)propanoate (6b). The compound is prepared according to the procedure A or B starting from 0.60 g of compound **(6)** (3.5 mmol, 1eq.) with 0.13 g of $NaBH_4$ (3.5 mmol, 1eq.) or 0.46 g of $NiCl_2$ (3.5 mmol, 1eq) and 0.26 g of $NaBH_4$ (7 mmol, 2eq.) and was purified by DCVC (gradient cyclohexane:ether) to yield a green fluorescent oil (0.01 g, 13%). ^{1}H NMR (400 MHz, DMSO-*d6*): δ=9.50 (s, 1H), 9.19 (s, 1H), 6.89 (d, J=8.2 Hz, 1H), 6.30 (d, J=2.4 Hz, 1H), 6.17 (dd, J_1=8.2 Hz, J_2=2.4 Hz, 1H), 4.24 (dd, J_1=9.0 Hz, J_2=5.9 Hz, 1H), 3.72 (s, 3H), 3.09 (dd, J_1=13.7 Hz, J_2=5.9 Hz, 1H), 2.90 ppm (dd, J_1=9.0 Hz, J_2=13.7 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-*d6*): δ=167.3, 158.2, 156.7, 131.6, 117.6, 113.0, 106.6, 102.7, 53.5, 31.1, 30.2 ppm; MS (ESI): *m/z* calcd for $C_{11}H_{11}NO_4H^+$: 222.21; found: 222.04 $[M+H]^+$, 244.00 $[M+Na]^+$, 259.99 $[M+K]^+$. HRMS (ESI): *m/z* calcd for $C_{11}H_{11}NO_4H^+$: 222.07608; found: 222.07568.

2-(2,4-dihydroxybenzyl)-3-hydroxypropanenitrile (6c). Same procedure as **(6b).** The compound is obtained as a green fluorescent oil (0.05 g, 4%). ^{1}H NMR (500 MHz, DMSO-*d6*): δ=9.40 (s, 1H), 6.92 (d, J=8.2 Hz, 1H), 6.35 (d, J=2.4 Hz, 1H), 6.21 (dd, J_1=8.2 Hz, J_2=2.4 Hz, 1H), 3.61–3.45 (m, 2H), 3.06 (dtd, J_1=8.8 Hz, J_2=6.7 Hz, J_3=4.8 Hz, 1H), 2.76 (dd, J_1=13.6 Hz, J_2=6.7 Hz, 1H), 2.68 ppm (dd, J_1=13.5 Hz, J_2=8.8 Hz, 1H); ^{13}C NMR (126 MHz,

DMSO-*d6*): *δ*=157.7, 156.5, 131.5, 122.1, 114.5, 106.5, 102.8, 61.4, 35.4, 29.1 ppm; MS (ESI): *m/z* calcd for $C_{10}H_{11}NO_4$: 193.07; found: 216.02 $[M+Na]^+$, 231.97 $[M+K]^+$; HRMS (ESI): *m/z* calcd for $C_{10}H_{11}NO_4H^+$: 194.08117; found: 194.08070 $[M+H]^+$; elemental analysis calcd (%) for $C_{10}H_{11}NO_4$: C 59.71, H 5.02, N 6.33; found: C 60.11, H 6.33, N 6.15.

Methyl 2-benzamido-3-(2,4-dihydroxyphenyl)propanoate (7b).The compounds was prepared according to procedure B starting from 0.10 g of N-(7-hydroxy-2-oxo-2H-chromen-3-yl)benzamide **(7)** (0.3 mmol, 1 eq.) with 0.07 g of $NiCl_2$ (0.3 mmol, 1 eq.) and 0.02 g of $NaBH_4$ (0.6 mmol, 2eq.), and was purified by DCVC (gradient of DCM: MeOH) to yield a pure white solid (0.09 g, 53%). m.p./b.p.: 70.9 °C; ^{1}H NMR (400 MHz, DMSO-d*6*): *δ*=9.46 (s, 1H), 9.04 (s, 1H), 8.64 (d, *J*=7.4 Hz, 1H), 7.80 (d, *J*=7.0 Hz, 2H), 7.58–7.51 (m, 1H), 7.50–7.40 (m, 3H), 6.89 (d, *J*=8.2 Hz, 1H), 6.29 (d, *J*=2.4 Hz, 1H), 6.11 (dd, J_1=8.2 Hz, J_2=2.4 Hz, 1H), 4.65-4.69 (m, 1H), 3.61 (s, 3H), 3.06 (dd, J_1=13.6 Hz, J_2=5.3 Hz, 1H), 2.84 ppm (dd, J_1=13.6 Hz, J_2=9.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): *δ*=173.0, 166.7, 157.5, 156.4, 134.2, 131.9, 131.7, 128.7, 128.6, 127.7, 127.6, 114.4, 106.4, 102.8, 60.2, 53.6, 52.1, 31.5 ppm; HRMS (ESI): *m/z* calcd for $C_{17}H_{17}NO_5H^+$: 316.11797; found: 316.11795 $[M+H]^+$, 329 $[M+Na]^+$, 338 $[M+K]^+$, 314 $[M-H]^-$;elemental analysis calcd (%) for $C_{17}H_{17}NO_5$: C 64.74, H 5.44, N 4.44; found: C 64.79, H 5.85, N 4.43.

***N*-(1-(2,4-dihydroxyphenyl)-3-hydroxypropan -2-yl)benzamide (7c).** Same as for **(7b)**. Obtention of a pure clear oil (0.08 g, 36%). ^{1}H NMR (500 MHz, DMSO-*d6*): *δ*=9.22 (s, 1H), 8.94 (s, 1H), 8.00 (d, *J*=8.1 Hz, 1H), 7.80 (d, *J*=7.6 Hz, 2H), 7.54–7.48 (m, 1H), 7.48-7.41 (m, 2H), 6.89 (d, *J*=8.3 Hz, 1H), 6.26 (d, *J*=2.7 Hz, 1H), 6.10 (d, *J*=8.2 Hz, 1H), 4.69 (s, 1H), 4.12-4.08 (m, 1H), 3.52–3.39 (m, 2H), 2.78 (dd, J_1=13.6 Hz, J_2=5.6 Hz, 1H), 2.61 ppm (dd, J_1=13.6 Hz, J_2=8.6 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-*d6*): *δ*=166.4, 156.9, 156.4, 135.3, 131.5, 131.4, 128.6, 128.6, 127.6, 116.1, 106.4, 102.7, 63.3, 53.0, 49.0, 40.5, 40.4, 40.4, 40.3, 40.15, 39.9, 39.8, 39.6, 39.4, 30.9 ppm; HRMS (ESI): *m/z* calcd for $C_{16}H_{17}NO_4H^+$: 288.12303; found: 288.12313; elemental analysis calcd (%) for $C_{16}H_{17}NO_4$: C 66.87, H 5.97, N 4.87; found: C 64.89, H 6.05, N 4.87.

Methyl 2-acetamido-3-(2,4-dihydroxyphenyl)propanoate (8b). The compounds was prepared according to procedure B starting from 0.20 g of 3-acetamido-7-hydroxycoumarine **(8)** (0.8 mmol, 1 eq.) with 0.20 g of $NiCl_2$ (0.8 mmol, 1 eq.) and 0.06 g of $NaBH_4$ (1.6 mmol, 2eq.). It was purified by DCVC (gradient of EtOAc: Acetone) to yield a pure yellow oil (0.07 g, 35%). ^{1}H NMR (400 MHz, DMSO-*d*6): *δ*=9.29 (s, 1H), 9.03 (s, 1H), 8.13 (d, *J*=7.5 Hz, 1H), 6.77 (d, *J*=8.2 Hz, 1H), 6.25 (d, *J*=2.4 Hz, 1H), 6.09 (dd, J_1=8.1 Hz, J_2=2.4 Hz, 1H), 4.38 (td, J_1=8.8 Hz, J_2=6.3 Hz, 1H), 3.53 (s, 3H), 2.85 (dd, J_1=13.5 Hz, J_2=6.3 Hz, 1H), 2.61 (dd, J_1=13.5 Hz, J_2=8.8 Hz, 1H), 1.77 ppm (s, 3H) ; ^{13}C NMR (100 MHz, DMSO-*d*6): δ=1737.9, 174.5, 162.3, 161.3, 136.3, 118.9, 111.0, 107.5, 57.6, 56.7, 36.7, 27.5 ppm; MS (ESI): *m/z* calcd for $C_{12}H_{15}NO_5$: 253, found: 253 $[M+H]^+$, 252 $[M-H]^-$. HRMS (ESI): *m/z* calcd for $C_{12}H_{15}NO_5H^+$: 254.10230; found: 254.10251.

***N*-(1-(2,4-dihydroxyphenyl)-3-hydroxypropan-2-yl)acetamide (8c).** Same as for **(8b)**. Obtention of a pure clear oil (0.01 g, 11%). ^{1}H NMR (400 MHz, DMSO-*d*6): *δ*= 9.15 (s, 1H), 8.97 (s, 1H), 7.61 (d, *J*=8.0 Hz, 1H), 6.81 (d, *J*=8.1 Hz, 1H), 6.24 (d, *J*=2.4 Hz, 1H), 6.12 (dd, J_1=8.1 Hz, J_2=2.4 Hz, 1H), 4.62 (t, *J*=5.5 Hz, 1H), 3.86-3.75 (m, 1H), 3.31 (t, *J*=5.4 Hz, 1H), 2.63 (dd, J_1=13.8 Hz, J_2=6.5 Hz, 1H), 2.41 (dd, J_1=13.8 Hz, J_2=7.5 Hz, 1H), 1.77 (s, 3H), ^{13}C NMR (100 MHz, DMSO-*d*6): *δ*= 169.54, 156.96, 156.48, 131.35, 116.05, 106.36, 102.82, 63.07, 52.05, 31.11, 23.23; MS (ESI): *m/z* calcd for $C_{11}H_{15}NO_4$: 225.10; found: 223.95 $[M-H]^-$.

Supporting Information Summary

Supporting information contains the details of the experimental and computational methods used with references, NMR and MS graphs and interpretations,optimised geometry and TD-DFT data

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