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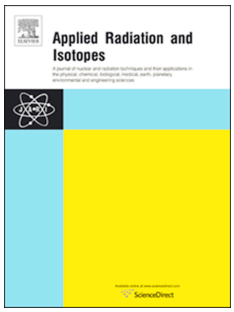

Proposal for an ecofriendly and economic strategy for efficient radioiodination of coumarin derivatives

Nejla Khatir–Hamdi, Malika Makhloufi-Chebli, Artur M.S. Silva, Méziane Brahimi, Hocine Grib

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Graphical Abstract

Proposal for an ecofriendly and economic strategy for efficient radioiodination of coumarin derivatives

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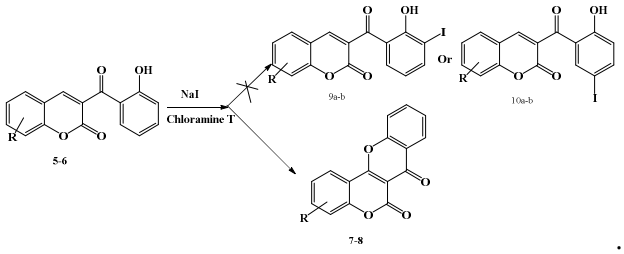

Combination of the calculation of reactivity descriptors and the cold iodine test for some coumarin derivatives in order to optimize the radioiodination reaction. The strongly nucleophilic predicted coumarins were subjected to the action of cold iodine. With two coumarins substituted at 3 by the 2-hydroxybenzoyl group, iodination did not occur but a product of intramolecular heterocyclization was obtained. This strategy is useful for economic and environmentally friendly radioiodination.

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ABSTRACT

Combination of the calculation of reactivity descriptors and the cold iodine test for some coumarin derivatives was used in order to optimize the radioiodination reaction. The strongly nucleophilic predicted coumarins were subjected to the action of cold iodine. With two coumarins substituted at 3 by the 2-hydroxybenzoyl group, iodination did not occur but a product of intramolecular heterocyclization was obtained. This strategy is useful for economic and environmentally friendly radioiodination.

1. Introduction*

The challenge for scientists interested in the iodine 125 labeling reactions for screening of novel potent iodinated radiotracers or radiopharmaceutics is to quickly synthesize, a stable labeled compound, at the lowest cost and in respect of the environment. For these labeling reactions several methods are known (Hanson, 2006; Wager and Jones, 2010; Mushtaq et al., 2016). The molecules submitted to radio iodination are of various types and must give, with a good yield, radioiodinated products which meet the requirements for radiotracer imaging and biodistribution studies. (Wang et al., 2008; Sugiura et al., 2014). The iodination method using chloramine-T (CAT) allows to oxidize the iodide to iodonium cation I^+ and in this case, when the substrate is a nucleophilic molecule, the electrophilic substitution reaction (EAS) is the most appropriate. In addition, electrophilic aromatic substitution is one of the most studied reactions in theoretical chemistry. Indeed, Fukui and other authors (Domingo et al., 2002; Arroyo et al.,2005; Perez et al., 2009; Humberto et al.,2011) have used the frontier of molecular orbital theory (FMO) for the study of these reactions. On the other hand, the iodination test with "cold iodonium " is possible and can be used for the optimization of the radioiodination.

Compounds studied in this work are coumarin derivatives: the coumarin moiety is an important structural motif in natural products and highly bioactive compounds. Coumarin-containing compounds exhibit broad biological activity with, for example, antioxidant, anticoagulant,

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antifungal, anthelmintic, cytotoxic or hypnotic properties (Riveiro et al., 2010; Mahmoud and El –Remaily, 2015). Coumarins are also widely applied as agrochemicals, cosmetics and food. Because of their fluorescent properties, they are also used as colorants, dye laser media, and as nonlinear optical chromospheres.

Two series of coumarin derivatives were subjected to a theoretical study in order to select the compound which is the more suitable to be labeled with iodine 125. Three of them were synthesized and have suffered an iodination reaction. Unexpected results were found for two compounds. The substrates used are called: 2*H*-chromen-2-one **1**, 4-methyl-2*H*-chromen-2-one **2**, 7-hydroxy-2*H*-chromen-2-one **3**, 7-hydroxy-4-methyl-2*H*-chromen-2-one **4**, 3-(2-hydroxybenzoyl)-2*H*-chromen-2-one **5** and 3-(2-hydroxybenzoyl)-2*H*-benzo[h] chromen-2-one **6** (Fig.1).

In this work we demonstrate the contribution of theoretical chemistry and "cold labeling" in the significant reduction of use of chemicals and production of radioactive waste.

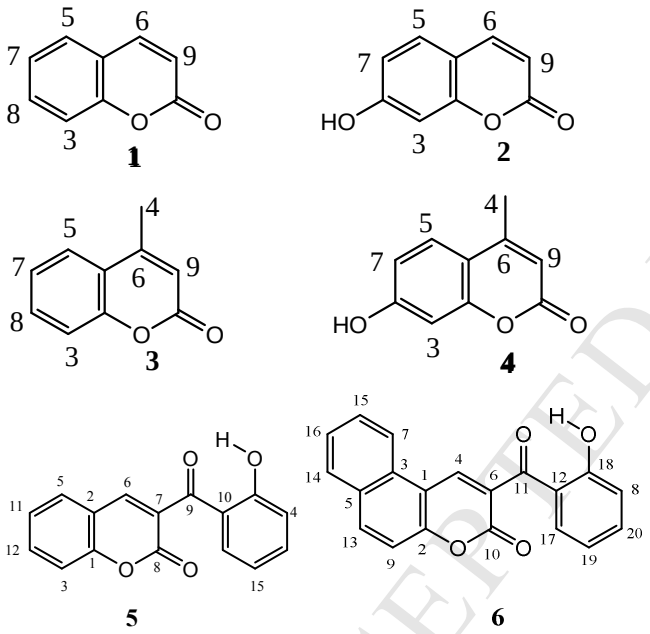


Fig.1. Structure formula of the studied coumarins **1-6** (Gaussian View numbering)

2. Experimental

2.1. Materials and Methods

2.1.1 Apparatus

For synthesis, the multimode microwave reactor (a modified microwave oven candy mga20 m) has a single magnetron (2450 MHz) with a maximum delivered power of 800 W. It was directly graduated in W (from 100 to 800 W). Experiments were carried out in a Pyrex reactor fitted with a condenser. During experiments, time, temperature and power were monitored. Temperature was monitored with the aid of an external infra-red IR thermometer (Flashpoint FZ400).

Melting points were determined on a Stuart scientific SPM3 apparatus fitted with a microscope and are uncorrected. IR spectrum was recorded on a BRUKER TENSOR 27 IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d6 solutions on Bruker Avance 300 (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) spectrometers. Chemical shifts are reported in parts per million (δ,ppm) using TMS as internal reference. ^{13}C assignements were made using HSQC, and HMBC (delays for one bond and long-range *J*C/H coupling were optimized for 145 and 7 Hz, respectively). Mass spectra were recorded on a Nermag R10-10C quadrupole mass spectrometer at 70 eV.

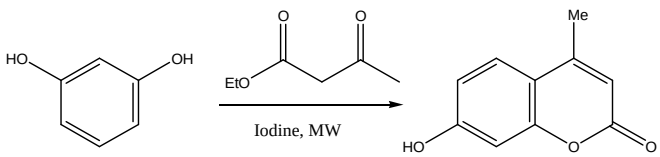
2.1.2 Drugs and Chemicals

Iodine 125 was purchased from Institute of Isotopes, Hungary, Chloramine-T (CAT) was purchased from Sigma Chemical Company, USA, 7-hydroxy-4-methyl-2*H*-chromen-2-one **4**, 3-(2-hydroxybenzoyl)-2*H*-chromen-2-one **5** and 3-(2-hydroxybenzoyl)-2*H*-benzo[h]chromen-2-one **6** have been synthesized in our laboratory. Sodium Thiosulfate, resorcinol, salicylaldehyde, 2-hydroxynaphtaldehyde and iodine were purchased from Sigma -Aldrich-USA. All other chemical reagents were of analytical grade (AR) obtained from reputable manufacturers and used without further purification. The structure of the compounds was characterized by IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis.

2.3. General procedure for the synthesis of 7- hydroxy-4-methyl-2*H*-chromene-2-one (4)

Among the several known methods for the synthesis of coumarins via the Pechmann reaction (Myano and Dorn, 1972; Khan et al., 2003; Manhas et al., 2006) that which was the most known is carried out in the presence of concentrated sulfuric acid catalyst. However the catalyst result in the formation of by-products, presenting a danger of use and corrosion problems, generating low yields and requiring long reaction time. The synthesis was carried out by a fast, inexpensive and environmentally friendly method (Scheme1) described by Prajaparti and Gohain (2007):

A mixture of resorcinol (1.1 g, 10 mmol), ethyl acetoacetate (1.3 g, 10 mmol) and iodine (0.025 g) was placed in a quartz reaction vessel and allowed to react under microwave irradiations at a temperature of 110 °C for 1.5 min. After completion (monitored by TLC), the reaction mixture was cooled to room temperature and added 6% cold sodium thiosulphate solution and stirred for 10–15 min. The precipitated products were then separated, washed with ice-cold water and recrystallized from hot ethanol to afford 7-hydroxy-4-methyl coumarin **4** in 95% yield, mp 184–185 °C .



Scheme 1. Synthesis of 7-hydroxy-4-methyl coumarin **4**

This compound is obtained as pale yellow powder, mp= 184–185 °C, Yield 95%; IR ν (cm^{-1}): 3513 (OH), 3113 (=C–H), 1672 (C=O), 1596 (C=C aromatiques), 1390 (symmetry deformation of CH_3), 1268, 1281 (C-O); ^{1}H NMR

(DMSO-d_6): δ 2.52 (s, 3H, CH_3), 6.13 (s, 1H, H-3), 6.72 (d, $J_{6.8}$ = 2.4.1H, H -8), 6.81 (dd, $J_{6.8}$ = 2.4, $J_{5.6}$ = 8.4.1H, H-6), 7.59 (d, $J_{5.6}$ = 8.4.1H, H-5), 10.53 (s, 1H, OH). Elemental analysis: Calculated for $C_{10}H_8O_3$ C 68.18; H 4.58; Found: C 67.92; H 4.62.

2.4. General procedure for friendly oxidative iodination

Radiolabeled compounds were generally synthesized by direct electrophilic substitution with I* (radioiodine) under oxidative conditions in the presence of chloramine-T (CAT). It is known that the high CAT concentration over iodide concentration is necessary to achieve electrophilic substitution. But, this excess of CAT can also give rise to poly-iodination of activated aromatic systems. For the preliminary cold iodination experiments, we studied only the effects of substrate concentrations, iodide, CAT oxidant, and the effect of reaction time. At first we chose the solvents, compatible with the electrophilic substitution reactions and which completely dissolve the substrate and the reagents used. Indeed, each substrate subjected to iodination must be considered as a special case and not to apply without modification the protocols described in the literature for radio-iodination reactions.

This study was conducted by HPLC analyzes; the first tests enabled us to identify the presence of the substrate **4** mono-iodinated and di-iodinated. The optimization of the reaction to obtain a satisfactory yield of mono-iodinated product of **4** was achieved by adopting the protocol described as follows: In a 100 mL flask is introduced 1 mmol of compound **4** at reflux of a solvent mixture (ACN-MeOH v/v) to witch NaI (0.15 g, 1 mmol) is added. The mixture is stirred for five minutes at room temperature until complete dissolution, then 5 ml of CAT (0.227 g, 1mmol) were added dropwise over 20 min. A change of colour from yellow to brown appeared. The mixture is heated at 65°C with magnetic stirring. Progress of the reaction was monitored during two hours by TLC, and stopped with $Na_2S_2O_3$ (10%) in order to reduce the unreacted iodine, stirring is maintaining for 10 min; a change of color from dark brown to light brown is observed. After concentration of the reaction mixture, HCl (10%) is added to an acidic pH (1-2) and a solid is formed, then is filtered and washed several times with cold water, dried and purified with diethyl ether. This compound is obtained as orange powder, ^{1}H NMR (DMSO-d6): δ 2.38 (s, 3H, CH_3), 6.18 (s, 1H, H-3), 6.93 (d, $J_{5.6}$ = 8.6.1H, H-6), 7.72 (d, $J_{6.5}$ = 8.6.1H, H-5), 11.37 (s, 1H, OH).

This procedure was identical for compounds **5** and **6** (Both compounds 5 and 6 were recently synthesized in our laboratory [Khatir-Hamdi et al., 2019]) and resulting in compounds **7** and **8**.

6*H*,7*H*-chromeno[4,3-b]chromene-6,7-dione (7)

White-grey powder, Yield 65%; mp 216°C; I.R ν (cm^{-1}) 1696 (O=C-O), 1500-1600 (C=C aromatic), UV/vis: λ_{abs1}= 292, λ_{abs2} = 318 nm; ^{1}H NMR (DMSO-d6): δ 7.10 (d, 1H, J=8.31Hz, H-12), 7.40 (m, 3H, H-6, H-8, H-15), 7.81 (m, 2H, H-14, H-7), 8.13 (d, 1H, J=8.76Hz, H-5), 8.32 (d, 1H, J=9.33, H-16) ; ^{13}C NMR (DMSO-d6): δ 104.71 (C-3), 117.38 (C-10), 117.61 (C-13), 122.74 (C-8), 123.72 (C-5), 124.38 (C-15), 125.48 (C-12), 126.47 (C-6), 127.12 (C-16), 135.63(C-7), 138.31 (C-14), 153.99 (C-9), 153.60 (C-2), 155.50(C-11), 164.76 (C-4), 172.46 (C-1), MS (ESI^+) m/z (%): 265 (65) $[M+H]^+$, 287 (100) $[M+Na]^+$, 551(26) $[2M+Na]^+$, Elemental analysis: Calculated for $C_{16}H_8O_4$: C 72.73, H 3.05; Found: C 72.77, H 3.02.

8*H*,9*H*-benzo[f]chromeno[3,2-c]chromene-8,9-dione (8)

Light brown powder, Yield 75%; mp 287°C; I.R ν (cm^{-1}) 1737(O=C-O), 1500-1600 (C=C-aromatic); UV/vis: λ_{abs1}= 363, λ_{abs2} = 374 nm ; ^{1}H NMR (DMSO-d6): δ 7.58 (d, 1H, J=8.88Hz, H-8), 7.62 (d, 1H, J=7.65Hz, H-7), 7.65 (t, 1H, H-18), 7.86 (t, 1H, H-12), 7.93 (t, 1H, H-13), 8.11 (m, 3H, H-16, H-17, H-19), 8.38 (d, 1H, J=9.00Hz, H-14), 9.34 (d,1H, J=8.76Hz, H-11); ^{13}C NMR (DMSO-d6): δ 104.29 (C-3), 106.29 (C-8), 116.94 (C-18), 116.57 (C-11), 118.57 (C-20), 123.60 (C-13), 125.28 (C-17), 125.59 (C-10), 126.59 (C-21), 126.66 (C-12), 127.98 (C-14),129.72 (C-6), 130.03 (C-7), 134.99 (C-5), 137.80 (C-19), 153.86 (C-9), 155.24(C-2), 155.78 (C-15), 167.59 (C-4), 172.53 (C-1); MS (ESI^+) m/z (%): 315 (95) $[M+H]^+$, 337 (100) $[M+Na]^+$, 651 (63) $[M+Na]^+$, Elemental analysis: Calculated for: $C_{20}H_{10}O_4$: C 72.26, H 8.49; Found: C 72.32, H 8.45.

2.5. Cold

The latter protocol was reproduced in a low reaction volume (= 1mL so that it is applicable with ^{125}I) and equimolar amounts of **4**, NaI and CAT (2.10^{-6} mol), with initial heating at 100 °C for 3min then 20min at 60 °C, reaction was stopped with $Na_2S_2O_3$ (10%) , HCl (10%) is added to an acidic pH (1-2) and a solid is formed, the sediment is recovered after centrifugation and washed with 100µL of dilute hydrochloric acid solution to remove any traces of unreacted iodine

This synthesis was what we called "*a cold iodination*" or "*a cold labeling* "(with non-radioactive iodine) by adopting the traditional protocol of ^{125}I (Sallam and Mehany, 2009; Lokhande et al., 2011). Analysis of the separated product reveals that iodinated **4** is obtained in a proportion of about 90%. This result is satisfactory, therefore, and has been adopted for the radioactive labeling with ^{125}I.

2.6. Iodine labeling

Direct electrophilic substitution reaction of **4** was done using ^{125}I under oxidative conditions in the presence of chloramine-T (CAT) (El-Momani et al., 2010; Mustapha et al., 2013).

The radioactive labeling protocol must be compatible with the constraints imposed by the handling of radioisotopes: the heating time must be reduced to the maximum, the volume of the reaction mixture must be low, the radio iodination will be more efficient, generally we work with a volume less than 100 µL and a maximum of 2 mL (Ardisson et al., 2005).It is therefore a labeling reaction which was carried out on a small scale as follows:

In a tightly stoppered glass tube compound **4** (2.10^{-6}mol) was dissolved in 20µL of a solution of acetonitrile: methanol (v/v) and was added to 6µL of Na ^{125}I(0.5 mCi). A freshly100µL prepared solution of CAT in distilled water (2.10^{-6}mol) was added. After 3 min reaction time at 100 ° C and 20 min at 60 ° C, the reaction was stopped using 0.2N $Na_2S_2O_3$ solutions to ensure that the unreacted iodine was reduced .The reaction mixture was acidified with 4-5 µL of a dilute

hydrochloric acid solution and then centrifuged. The sediment was washed with 100 µl of a dilute hydrochloric acid solution in order to eliminate the unreacted iodine. The sediment was dissolved in 40 µl of a mixture of dichloromethane: methanol (v/v). Aliquot fraction of both dissolved sediment and supernatant were taken for measurement of radioactivity from which the radiochemical yield percent was determinate using an activimeter. The radiochemical purity was determinate by paper chromatography.

3. Theory and computational details

The computational chemistry method offers a unique ability to generate optimal geometry structures, and this through the structural and electronic properties of the reagents and products, it can predict with more or less accuracy which chemical transformations will occur in reaction.

Chemical reactivity studies based on the Hard and Soft Acid-Base (HSAB) principle have played a leading role in explaining the chemical behavior in many molecular systems. HSAB principle becomes relevant, in conjunction with the Density Functional Theory (DFT) framework, to quantitatively describe the global and local parameters directly related the chemical reactivity of molecular species. This theory based local reactivity indicators have become very useful in understanding the details of several classes of chemical reactions (Roy et al., 1998; Chandra and Nguyen, 2002; Faver and Merz, 2010). From the theoretical point view, it was demonstrated that the DFT B3LYP is a reliable method for the calculation of geometries and energies of aromatic heterocycles. The main indexes used in this contribution are given with their definition but without any mathematical proof.

The theoretical investigation presented in this work is based on the calculation of global and local nucleophilicity parameters to facilitate elucidating the mechanism of iodination reaction.

3.1. Global reactivity descriptors:

The electronic chemical potential µ is associated with the feasibility of a system to exchange electron density with the environment (Domingo et al.,2016) at the ground state has also identified with the negative Mulliken electronegativity (*-X)* , it can be expressed as:

$$\mu = -X = E_{Homo} + E_{Lumo}/2 \qquad \text{Eq: 1}$$

The chemical hardness η can be thought as a resistance of a molecule to exchange electron density with the environment.

$$\eta = E_{Lumo} - E_{Homo} \qquad \text{Eq: 2}$$

On the other hand, the chemical softness **S** was introduced as the inverse of the chemical hardness η:

$$S = 1/2\eta \qquad \text{Eq: 3}$$

The electrophilicity ω global index gives of the energy stabilization of a molecule when it acquires an additional amount of electron density from the environment. This index is given by the expression:

$$\omega = \mu^2/2\eta \qquad \text{Eq: 4}$$

The maximum number ΔN_{max} of electrons that an electrophile can acquire is given by the expression:

$$\Delta N_{max} = -\mu/\eta \qquad \text{Eq: 5}$$

3.2. Local reactivity descriptors:

The Fukui function *f*(k) represents the changes in electron density at a point k with respect to the variation of the number of electrons N at a fixed external potential. In the literature most studies have been carried out in the finite difference method, in which the local quantities such as Fukui functions f (k) define the reactivity and selectivity of a specific site in a molecule are as approximated.

$$f_k^- = [q_k(N) - q_k(N-1)] \qquad \text{Eq : 6}$$

$$f_k^+ = [q_k(N+1) - q_k(N)] \qquad \text{Eq : 7}$$

where q_k is the electronic population atom k in a molecule evaluated from Mulliken population analysis(MPA), natural population analysis (NPA) and electrostatic charge(ESP) derived atomic population analysis at the k the atomic site in the neutral (N), anionic (N+1) or cationic(N-1) in a molecule.

$$N = E_{Homo\ (Nucleophilic)} - E_{Homo\ (TCE)} \qquad \text{Eq : 8}$$

The empirical relative nucleophilicity index N is referred to tetracyanoethylene (TCE).This choice allowed convenient handling of a nucleophilicity scale of positive values.

3.3. Local nucleophilicity parameter

The local nucleophilicity parameter based on the nucleophilic Fukui function f_k^- is defined as:

$$N_k = N\, f_k^- \qquad \text{Eq : 9}$$

Where N is the global nucleophilicity index. This parameter defining the local nucleophilicity is used in this contribution for the prediction of the favored site of the coumarins in electrophilic aromatic substitution reactions

3.4. Computational details

The quantum chemistry calculations reported in this contribution have been performed at B3LYP/6-311+g (d,p) level of theory using the Gaussian 09.Revision A 02-SMP (Frish et al., 2016). Stationary points found were characterized as true minima by frequency calculations. The cationic and anionic systems required in the calculations of local indices were kept at the same geometry of the neutral system. The electronic populations were computed using the MPA, MK and NPA.

4. Results and discussion

4.1. *Relative reactivities*

The values of global reactivity descriptors μ,η,ω,S and N were calculated employing equations 1, 2, 3, 4 and 8 respectively (see Table 1). By analyzing the nucleophilicity values N for these compounds, it can be noted:

the nucleophilicity power increases from compound **1** to **4** indicating that coumarin **4** of this series is most nucleophilic molecule N=2.97 eV. The same trends are obtained for **5** and **6** coumarins. Indeed compound **6** is predicted to be more nucleophilic N=2.98 eV than compound **5** N=2.86 eV.

The nucleophilic character of these compounds **1-6** is consistent with calculated electronic potential μ (Table 1) showing that **4** μ=-4.26 eV is characterized by the highest chemical potential followed by **3** μ =-4.36 eV and **2** μ=-2.48 eV respectively. On the other hand, it can be noted the substitution of heteroatomic compound by an electro-donating group (i.e. Me, OH…) yields to an increase of the nucleophilicity as remarked in compounds **1-4**.

Consequently the first series **1-4** is predicted to be reactive in electrophilic aromatic substitution reactions (EASs). Note that, compound **6** with a benzo fused coumarin skeleton (extended electron cloud) is predicted to be most nucleophilic (μ=-4.6953 eV) than **5** (μ=-4.6230 eV). It is clear that the values of the global reactivity parameters depend on the level of theory used.

Local quantities such as Fukui f_k (Eq: 6-7) defined the reactivity and selectivity of a specific site in a molecule. The local nucleophilicity N_k (Eq: 9) is used for the prediction of the favored site in electrophilic attack.

The analysis of the local nucleophilicity N_k of the first series **1-4** (Table 2) show that N_7 and N_9 would be locations where an electrophilic attack is more probable than a nucleophiliic attack. Indeed, this parameter calculated using MK and NPA for compounds **1-4** has the largest values (in bold in the table 3). In this same series we have indicated that compound **4** is predicted to be more nucleophilic N=2.97eV. This result agrees completely with experience since its mono, di and tri-iodo derivatived have been synthesized (Lele and Sethna, 1956).

For both compounds hybrids **5** and **6**, for the sake of clarity, we compare the sites of the groups of functions of each of the two molecules. Thus for the 2-hydroxybenzoyl function the values of N_k (calculated by NPA) are distributed as follows (in bold in Table 3):

The analysis of nucleophilicity indices given N_k in tableau 3 above show that $N_8(6)<N_{19}(6)$ in position ortho and para /OH , in the same positions $N_4(\mathbf{5})<N_{15}(\mathbf{5})$.It is interesting to note that in 2-hydroxybenzoyl function the OH (electron-releasing ER) is strongly activating but the carbonyl group (electron-withdrawing WG) is moderately deactivating. On the other hand, it is know, when several substituents exist on a cycle: the strongest activating is the one that directs the position of the electrophile on the cycle. Strongly activating groups exert a stronger influence than deactivating or weakly activating groups. Consequently, the N_8, N_{19} of **6** and N_4, N_{15} of **5** values obtained are the highest in Table 3 and predicted to be reactive in EASs

For both functions coumarin of **5** and benzocoumarin of **6** the N_k values calculated by (NPA) are listed in Table 3. The analysis of these values shows that:

The $N_6(5)$ and $N_4(6)$, with the highest value of the local nucleophilicity index would be locations where an electrophilic attack is more probable. The extended electronic cloud in **6** gives the expected result $N_{13}(\mathbf{6})>N_{12}(\mathbf{5})$.On the other hand, Table 3 shows that $N_{15}(\mathbf{6})$ and $N_9(\mathbf{6})$ with the lowest value of the nucleophilicity and it is the same for $N_3(\mathbf{5})$ and $N_5(\mathbf{5})$.

The relative reactivities of compounds 1-6 in EAS reactions have been studied by means of the global nucleophilicity index. It turns out from the present study that the compounds **4**, **5** and **6** are good candidates for electrophilic substitution with iodonium ion.In order to optimize the radio-iodination reaction and to invalidate or confirm the results of the theory we have, therefore, performed the iodination reaction of **4**, 5 and **6** under the conditions involving the "cold iodonium ion".

4.2. HPLC analysis

The chromatogram of compound **4** and iodinated **4** are mentioned in Fig. 2 and .Fig. 3.

Fig. 2 shows the presence of a single peak corresponding to compound **4** with an area of 97.99% and a retention time Rt of 3.71 min. The peak corresponding to the iodinated compound **4** (Fig.3) is eluted after 5.15 min; the area of the peak is estimated at 94.44%.

An increase in the retention time is therefore observed for compound 4 mono-iodinated. The peak corresponding to the unreacted compound **4** is present in low concentration on the chromatogram (5.56%). HPLC analysis has made it possible to demonstrate the lipophilic character of the mono-iodinated compound **4**: indeed, an iodinated compound has its retention time increased. No second peak was observed on the chromatogram of the iodinated compound **4** which can correspond to the diiodinated compound **4**; this analysis therefore confirms the production of the mono-iodinated compound 4 as the majority product according to the adopted protocol.

The HPLC analysis was performed to analyse non-radioactive **4** iodinated by injection of 10 µL of purified solution into the column (RP-18.150x4.6mm) and the UV spectrophotometer detector. The column was eluted with

mobile phase a mixture of acetonitrile: water (70% acetonitrile,
30% water), and the flow rate was adjusted to 1.0 mL/min.

Table 1 *HOMO and LUMO energies ,and global reactivity indices, μ , η , ω , S and N for compounds 1-6 calculated at the B3LYP/6-311+g(d, p).*

Compound	HOMO (eV)	LUMO (eV)	μ (eV)	η (eV)	ω (eV)	S (eV)	N[a] (eV)
1	-6.8895	-2.3073	-4.5984	4.5822	2.3073	0.1091	2.5984
2	-6.7902	-2.1658	-4.4780	4.6244	2.1681	0.1081	2.6978
3	-6.5654	-2.1448	-4.3551	4.4206	2.1453	0.1131	2.9226
4	-6.5137	-2.0167	-4.2652	4.4971	2.0227	0.1111	2.9743
5	-6.6253	-2.6208	-4.6230	4.0045	2.6686	0.1249	2.8627
6	-6.5031	-2.8875	-4.6953	3.6157	3.0486	0.1383	2.9849

[a]The HOMO energy -9.4880 eV of the reference system (TCE) had been calculated at the same computational level

Table 2 *Nucleophilic Fukui functions f_k^- and local nucleophilicity values N_k calculated by using different population analysis.*

Compound		Mulliken population (MPA)		Electrostatic population (MK)		Natural population (NPA)	
		f_k^-	N_k	f_k^-	N_k	f_k^-	N_k
	C3	0.017	0.044	0.028	0.073	0.008	0.021
	C5	0.070	0.182	-0.037	- 0.096	-0.018	-0.047
1	C6	0.040	0.104	0.005	0.013	0.001	0.003
	C7	0.068	0.177	0.187	**0.486**	0.149	**0.387**
	C8	0.059	0.153	0.034	0.088	0.077	0.200
	C9	0.094	0.244	0.130	**0.338**	0.120	**0.312**
	C3	0.001	0.003	0.026	0.070	0.006	0.016
	C5	0.093	0.251	-0.036	-0.097	-0.015	-0.040
2	C7	0.084	0.227	0.188	**0.507**	0.137	**0.369**
	C8	0.071	0.192	0.00	0.024	0.080	0.216
	C9	0.099	0.267	0.174	**0.469**	0.130	**0.353**
	C3	0.047	0.137	0.004	0.012	0.019	0.055
	C5	0.022	0.064	-0.079	-0.231	-0.006	-0.017
3	C6	0.023	0.067	0.004	0.012	-0.009	-0.026
	C7	0.076	0.222	0.150	0.438	0.109	**0.319**
	C9	0.120	0.351	0.194	**0.567**	0.165	**0.482**
	C3	0.018	0.054	0.044	0.131	0.019	0.057
	C5	0.012	0.036	-0.021	-0.062	0.004	0.012
4	C7	0.087	0.259	0.147	**0.437**	0.103	**0.306**
	C9	0.081	0.241	0.229	**0.681**	0.168	**0.500**

Table 3. *Nucleophilic Fukui functions f_k^- and local nucleophilicity values N_k at the different sites of two systems **5** and **6** calculated using different population analyses. The values of local nucleophilicity indexes of benzoyl group are given in bold*

Compound		Mulliken population (MPA)		Electrostatic population (MK)		Natural population (NPA)	
		f_k^-	N_k	f_k^-	N_k	f_k^-	N_k
	C3	0.018	0.052	-0.009	-0.026	0.003	0.009
	C4	0.047	**0.135**	0.097	**0.278**	0.030	**0.086**
	C5	0.031	0.089	-0.005	-0.014	0.013	0.037
	C6	0.033	0.094	0.041	0.117	0.276	0.790
5	C11	0.048	0.137	0.078	0.223	0.026	0.079
	C12	0.036	0.103	0.054	0.155	0.047	0.135
	C13	0.027	**0.077**	0.010	**0.046**	-0.064	**-0.183**
	C15	0.068	**0.195**	0.162	**0.464**	0.173	**0.495**
	C16	0.020	**0.057**	-0.051	**-0.146**	0.046	**0.132**
	C4	0.014	0.042	-0.009	-0.027	0.155	**0.463**
	C7	0.036	0.107	0.054	0.161	0.063	0.188
	C8	0.013	**0.039**	0.061	**0.182**	0.047	**0.140**
	C9	0.004	0.012	0.025	0.075	0.020	0.060
	C13	0.04	0.120	0.088	0.263	0.061	0.182
6	C14	0.055	0.164	0.087	0.260	0.058	0.173
	C15	0.01	0.042	0.035	0.104	0.024	0.071
	C16	0.028	0.084	0.030	0.089	0.045	0.134
	C17	-0.004	**-0.012**	-0.043	**-0.128**	-0.002	**-0.006**

C19	0.069	**0.206**	0.128	**0.382**	0.092	**0.275**
C20	0.005	**0.015**	-0.007	**-0.021**	0.010	**0.030**

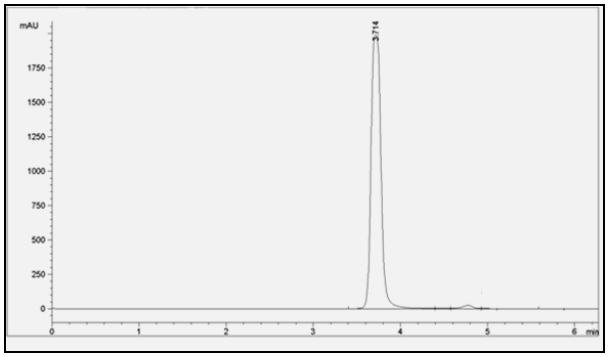


Fig.2. HPLC analysis of compound 4

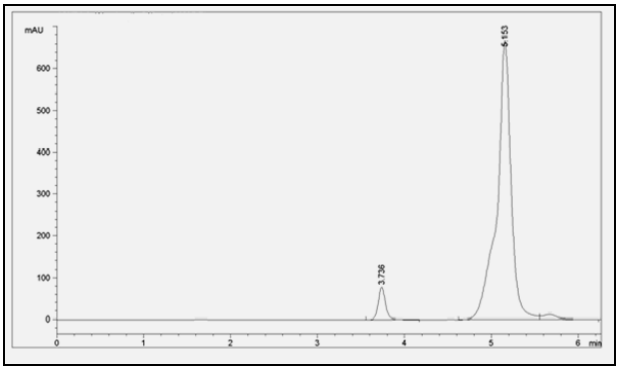


Fig.3. HPLC analysis of iodinated compound **4**

The ^{1}H NMR spectrum of the iodinated compound **4** confirms mono-iodination at position 3, in fact the peak at 6.72 ppm observed in the spectrum of compound **4** is absent in this spectrum. The protocol adopted made it possible to obtain **4** mono-iodine as the majority product and the di-iodinated in a very small proportion.

4.3. Radiolabeling of compound 4

4.3.1. Radiochemical purity:

Fig. 4 shows that the radiochemical purity percent of the radioiodinated **4** was 99.98%.

For the paper chromatography, the free radioiodide (I^-) remained near the origin, while the radioiodinated **4** moved with the solvent front.

Paper chromatography were used to determine the radiochemical purity obtained : strips of precoated (0.75 mm) silica gel 60 F_{254} plates were used, 1-2µL of the reaction mixture (sediment dissolved in dichloromethane/MeOH) was placed 2 cm above the lower edge of a paper strip (1cm width and 13 cm length), and allowed to evaporate spontaneously. Fresh mixture of Dichloromethane/MeOH (5:1) was used as a mobile phase. After complete development, the paper strips were removed, dried, and coated with cello-bands and were cut into 0.5 cm sections, they were counted by an NaI(TI) γ-ray scintillation counter. ITLC chromatogram was obtained from these counts. The radiochemical yield percent of labeling of compound **4** was calculated from counts of the fractions of supernatant and the fractions of sediment which gives 64.5% (table 4). Iodination and radiolabeling of **4** were easy and expected results were observed.

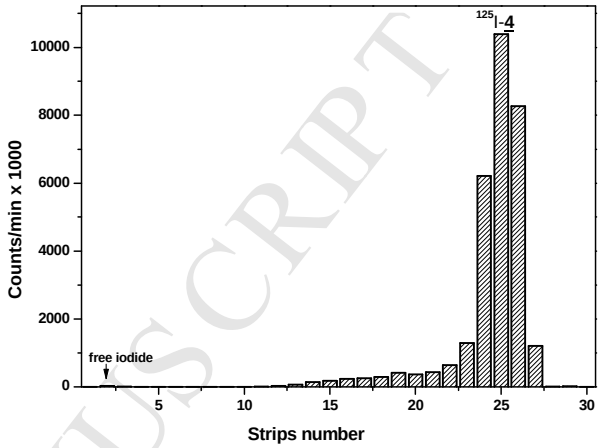


Fig. 4. Radiochemical purity of radioiodinated **4** tracer using paper chromatography

Table 4. *Radiochemical yield percent of the obtained^{125} I-4*

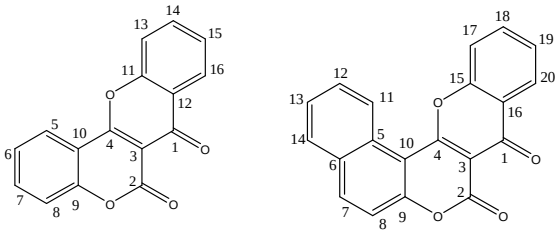
Total activity (µCi)	Counts of supernatant fractions (µCi)	Counts of precipitating fractions (µCi)	Radiochemical yield%
517.8	133.47	333.88	64.5

4.4. *Iodination of compounds 5 and 6*

We have shown following the results of the theoretical study that compounds **5** and **6** are, like compound **4**, predicted to be reactive in the electrophilic substitution reaction. We then tried, at first, the iodination reaction of "cold" iodine according to the same protocol described for **4**. The result of the reaction would therefore be an iodinated product. The structure of obtained compound **7** was confirmed by masse spectra and ^{1}H and ^{13}C NMR data. To our surprise the compound **7** obtained is not iodinated.

The mass spectrometry confirms that **7** is obtained from **5** by loss of a dihydrogen molecule. Indeed, the presence of the peaks at m/z 265 (65%), 287 (100%) and 551 (26%) correspond to ions $(M+H)^+$, $(M+Na)^+$ and $(2M+Na)^+$. The new product **7** ($C_{16}H_8O_4$, M=264) is obtained with yield of 65%. The iodination reaction did not take place and the loss of a dihydrogen molecule suggests the cyclization of **5** (Scheme 3) to give a new product 6*H*,7*H*-chromeno[4,3-b]chromene-6,7-dione **7** (Fig.5).

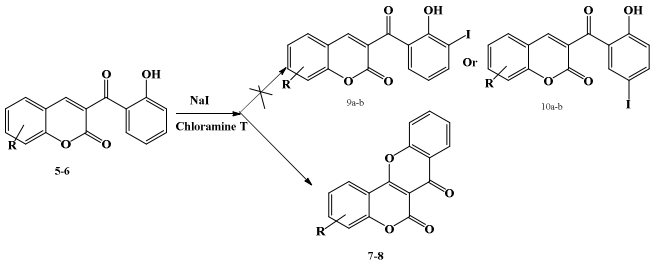
The ^{1}H NMR spectrum of this compound indicates that the resonance of –OH group and H-4 was not observed and confirms the disappearance of the proton signal.



6*H*,7*H*-chromeno[4,3-*b*]chromene-6,7-dione (7) 8*H*,9*H*-benzo[*f*]chromeno[3,2-*c*]chromene-8,9-dione (8)

Fig. 5. Chemical structure of compounds 7 and 8

The same phenomenon was observed on compound **6**, the structure of obtained compound **8** was confirmed by masse spectra, ^{1}H and ^{13}C NMR data. The compound **8** obtained is not iodinated and its mass shows a loss of a dihydrogen molecule relative to the mass of the product **6**. The new product ($C_{20}H_{10}O_4$, M=314) was obtained with good yield 75%, it is not iodinated and suggests the cyclization of **6** (Scheme 2) afforded 8*H*,9*H*-benzo[f]chromeno[3,2-c]chromene-8,9-dione **8** (Fig.5).



Scheme. 2. Synthesis of compounds **7 and 8** catalysed by NaI in the presence of chloramine T

4.5. Mechanism reaction

The mechanism of the reaction can be explained by the approach of the ions I^+ formed by oxidation of anions I^- ions by chloramine T to the carbonyl electron-withdrawing pole of coumarin followed by an intramolecular cyclization to form the compounds **7** and **8** (Scheme 2). In order to confirm this mechanism, the reaction was repeated with compound **5** in the presence of I_2 and concentrated H_2SO_4 in DMSO with reflux heating. The isolated product of this reaction is identical to compound **7**.

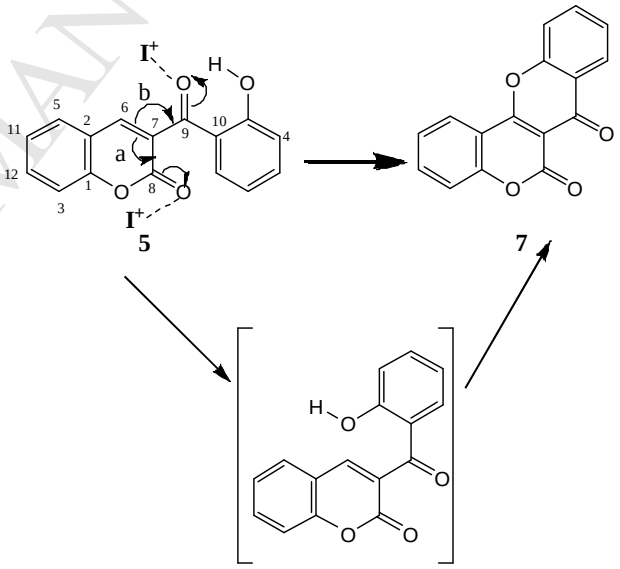
The theoretical calculations (Khatir-Hamdi et al., 2018) have shown that the optimized structure of **5** shows that the coumarin ring and the benzoyl group are not in the same plane. Indeed, the dihedral angle $C_8C_7C_9C_{10}$ is 51.88°. The cyclization imposes a molecular rearrangement which involves a rotation around the bond C_7-C_9 to give a rotamer **5a** (Scheme 3). The latter would not be obtained by the pathway b which involves the formation of the double bond $C_7 = C_9$.

The pathway b does not allow this rearrangement, all the more as the high electron density is concentrated between the two oxygen atoms of the coumarin cycle. The local nucleophilicity calculations for **5** gave N_6 (5) = 0.790 and for 6 N_4 (6) = 0.463 these sites are, therefore, predicted to be favorable for electrophilic attack, but the experience shows that it is the cyclization that takes place and the iodination reaction did not happen.

4.5.1. Main HMBC and NOESY correlations of 8H,9H-benzo[f]chromeno[3,2-c]chromene-8,9-dione (8)

The structures and purities of the products obtained were deduced from their NMR spectra (extended 2D NMR analyses: HSQC, HMBC and NOESY), and mass spectrometry data. As a representative example, the ^{1}H NMR spectrum of **8** exhibited the absence of singlet at 8-9 ppm and broad peak at 11-12 ppm corresponding to H-4 of coumarin and phenolic OH respectively. The aromatic and benzopyran-2-one protons are conserved and appear with a slight shift towards the weak fields at 7.58-9.34 ppm. The NOESY spectrum of **8** did not allow us to conclude that the compound obtained underwent intramolecular cyclization, since NOE effects were observed between (H-17, H-11) and (H-18, H-11) (Fig.6).

The HMBC connectivities of **8** were the key to proof the structure of the compound obtained; namely that between H-8 and C-4 carbon, which is also correlated with H-11 (Fig.6). These correlations are compatible with structure **8**. The HMBC connectivities of **8** have unequivocally assigned all of their carbon resonances (Fig.6). All the data described for compound **8** are similar to the other of compound **7** which allowed us to conclude that we obtained only the cyclized compounds and not the iodine compounds. All these data supports the structure of 8*H*,9*H*-benzo[f]chromeno[3,2-c]chromene-8,9-dione **(8)**



Scheme. 3. Mechanism proposal for the formation 6H,7H-chromeno[4,3-b]chromene-6,7-dione **7 .**

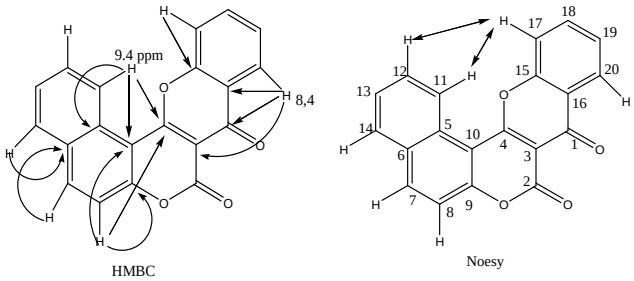


Fig. 6. Main HMBC and NOESY correlations of **8**

5. Conclusion

The results obtained permit the following conclusions:

The use of a theoretical study of the electrophilic aromatic substitution reaction allows classifying the target molecules according to their nucleophilicity and gives the most reactive sites with iodonium I+ cation. However, it must be admitted that the presence of iodine in a reaction medium can induce unpredictable reactions. For this last reason the non-radioactive iodine labeling reaction is recommended.

Compound **4**, which have been predicted to be the most nucleophilic and its predicted sites most likely to bind the iodonium ion, have been suitably labeled with cold and radioactive iodine. The tests were conducted under the conditions of volume, temperature and time most favorable to radiolabeling. The theoretical study of the two hybrid compounds **5** and **6** predicted the target sites of iodination but the cold iodine labeling experiment revealed their particular behavior and two new non-iodized products were characterized.

The combination of theoretical study and cold iodine labeling technique can be usefully applied in radiolabeling reactions. The nucleophilic character and target sites of iodonium are predicted by a calculation that is often fast and inexpensive. Non-radioactive iodine tests can confirm or rule out the iodination reaction. Thus, this proposed method predicts the behavior of molecules in electrophilic aromatic substitution (EAS) reactions and at the same time it allows the economical and environmentally friendly use of radioactive iodine.

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Highlights

The calculation of global and local nucleophilicity parameters for coumarin derivatives.

Iodination tests with cold iodine and analysis of the compounds obtained.

The iodonium cation causes intramolecular heterocyclization without iodination.

the combination of theoretical calculations - cold iodine is a useful strategy.