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Review Article

Overview of Recent Advances in 3-Hydroxycoumarin Chemistry as a Bioactive Heterocyclic Compound

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Abstract: Coumarins or benzo-2-pyrone derivatives are one of the most significant families of natural compounds and are also important in synthetic organic chemistry. They have been widely used as starting materials or precursor molecules in the pharmaceutical, perfumery and agrochemical industries, etc. Hydroxycoumarins are an important class of coumarin compounds that possess several physical, chemical and biological properties. Among the hydroxycoumarins, 3-hydroxycoumarin seems to be the most important because of its numerous chemical, photochemical and biological properties. However, this compound remains less well known compared to others of the same class such as 7-hydroxycoumarin and 4-hydroxycoumarin. This study is therefore devoted to 3-hydroxycoumarin and its applications. The main purpose of this review is to summarize and document the recent advances on 3-hydroxycoumarin, concerning the main routes of its synthesis, its reactivity, its applications in different fields of biology. Several methods for the synthesis of 3-hydroxycoumarin have been described in the literature, most of which use salicylic aldehyde and 1-(2-hydroxyphenyl)ethanone as starting compounds. Other synthesis pathways exist, but they are based on intermediate synthesis compounds. Concerning the reactivity of 3-hydroxycoumarin, many heterocyclic compounds obtained from 3-hydroxycoumarin have been reported in the literature. Among these heterocycles are pyrido[2,3-c]coumarin derivatives, chromeno[4,3-*e*][1,3]oxazine derivatives, dihydropyrano[2,3-*c*] chromenes and 3-coumarinyl carboxylates. Various researches have also concerned the biological properties of this compound. It appears from these numerous studies that 3-hdroxycoumarin is used in fields such as genetics, pharmacology, microbiology, etc.

Keywords: Hydroxycoumarins**,** 3-Hydroxycoumarin, Synthesis Routes, Reactivity, Biological Properties

1. Introduction

Hydroxycoumarins natural or synthetic are of great interest, since many of them show prominent biological activity and photochemical characteristics. Hydroxycoumarins and their derivatives have been extensively examined in various fields like such as biology, medicine, physics and chemistry [1-8]. Specifically, 3-hydroxycoumarin 1 and their derivatives represent less known class of hydroxycoumarin compounds. This compound (Figure 1) which known as 3-hydroxy-2H-chromen-2-one and 3-hydroxy-2H-1-benzopyran-2-one or 3-hydroxychromen-2-one in IUPAC system. Its structure contains two tautomeric keto-enol forms [6].

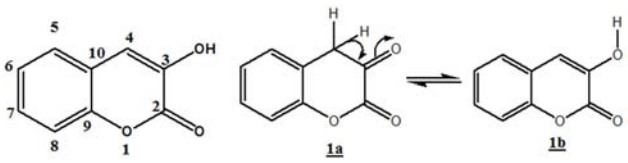

Figure 1. *Numbered structure of compound 1 and totaumeric forms 1a and 1b.*

Also known as 3-hydroxychromenone, this compound represent nowadays, an important precursor in the realm of

organic synthesis. Compounds possessing the 3-hydroxycoumarin nucleus are recently explore for their antioxydant activity [9], fluorescence and photopropecteur properties [6-8]. This review is not exhaustive, the objective is to enhance the title compound, its reactivity and its applications. Thus, we report in present paper, the synthesis and reactivity of 3-hydroxycoumarin. The biological properties of this compound will then be investigated.

2. Synthesis Routes

2.1. 3-Hydroxycoumarin Synthesis Using Salicylic Aldehyde

One of the earliest methods of compound 1 synthesis has been proposed by Trivedi and Sethna [10]. The reaction equations for the method of synthesis are as follows (Figure 2). An equimolecular mixture of salicylic aldehyde 2 and acetylglycine 3 is heated for 1 hour in the presence of 1 equivalent of anhydrous sodium acetate 4 and 2 equivalents of acetic anhydride 5. The intermediate product of the reaction, 3-acetamidocoumarin 6 is then absorbed in a minimal amount of alcohol and heated under reflux with 3N hydrochloric acid for 3 to 4 hours. The 3-hydroxycoumarin 1 is isolated by cooling this reaction mixture.

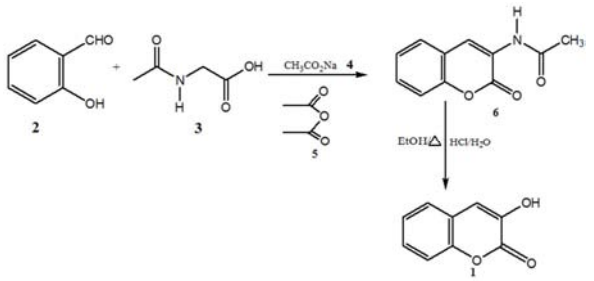

Figure 2. *3-Hydroxycoumarin synthesis using salicylaldehyde 2.*

The reaction certainly takes place by esterification between the phenol function of salicylaldehyde **2** and the acid function of acetylglycine **3** in the presence of sodium acetate **4**. Intramolecular condensation then occurs between the only active methylene of this reaction intermediate and the aldehyde function, under the combined effect of the base and acetic anhydride, a solvent known for its dehydrating character. 3-acetamidocoumarin **6** is then obtained. The last step in the reaction is the substitution of the acetamide function by a hydroxyl in the presence of hydrochloric acid (HCl). The acid then protonates the nitrogen and favours its substitution (Figure 3).

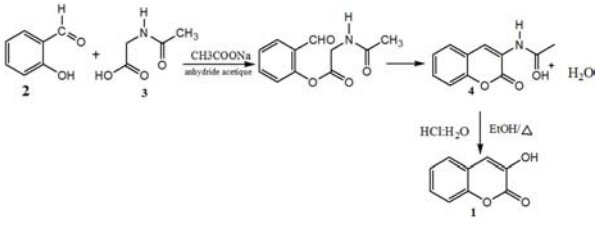

Figure 3. *Formation process of compound 1.*

2.2. 3-Hydroxycoumarin Synthesis Using 2-Methoxycinnamic Acid

Recentely, Dupont and Cotelle [11] obtained the same compound 1 from the derivatives of 3-(o-methoxyphenyl)-2-hydroxypropenoic acid 7 or 2-methoxycinnamic acid using a specific compound which is boron tribromide (BBr3) (Figure 4).

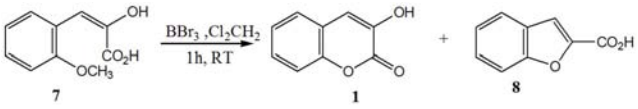

Figure 4. *3-Hydroxycoumarin formation using compound 7.*

The authors indicate that 3-hydroxycoumarin 1 can also be obtained by the reaction of methyl-3-(2-methoxyphenyl)-2,3-epoxypropanoate 9 with boron tribromide. By heating to reflux and prolonging the hydrolysis. After epoxidation of the enol function of 2-methoxycinnamic acid 7, 3-hydroxycoumarin 1 was obtained almost quantitatively (Figure 5).

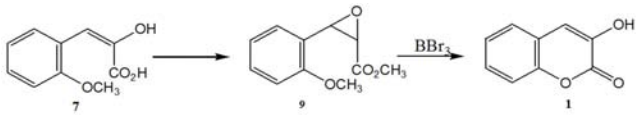

Figure 5. *3-Hydroxycoumarin formation by epoxidation.*

2.3. 3-Hydroxycoumarin Synthesis Using 1-(2-Methoxyphenyl) ethanone

3-Hydroxycoumarin 1 has been obtained in three steps from 1-(2-methoxyphenyl) ethanone 10. As shown in figure 6, the synthesis of 4-benzylidenoxazol-5(4H)-one 12 from compound 10 and N-acetylglycine 11 was used as the first step [12]. The mixture containing compound 7 was treated with boron tribromide to give, as expected, a mixture of benzofuran-2-carboxylic acid 8 and 3-hydroxycoumarin 1 separated by column chromatography.

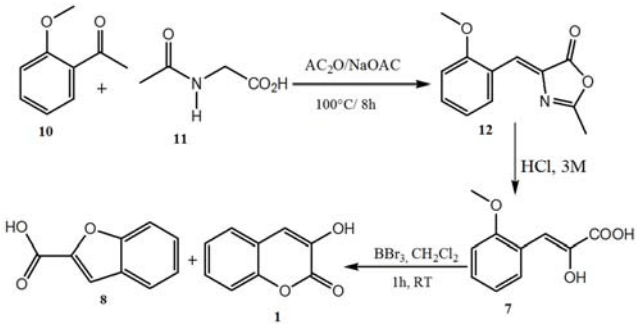

Figure 6. *3-Hydroxycoumarin **1** synthesis using compound 10.*

2.4. 3-Hydroxycoumarin Synthesis Using 1,4-Diacetyl-2,5-piperazinedione as Reagent

According to the method of Gallina and Liberatori [13], 1,4-diacetyl-2,5-piperazinedione 13 was condensed with salicyladehyde 2 in the presence of potassium tert-butoride

(*t*-BuOK) and N,N-dimethylformamide (DMF) to give 3-(z)-salicylidene-2,5-piperazinedione 14 (53%) and another unknow product 15 (43%). Subsequently, the compound 15 was treated with HCl to give 3-hydroxycoumarine (56%), which was completely consistent with the product derived by the reaction of 3-(N-acetyl)-aminocoumarin with HCl [14] (Figure 7).

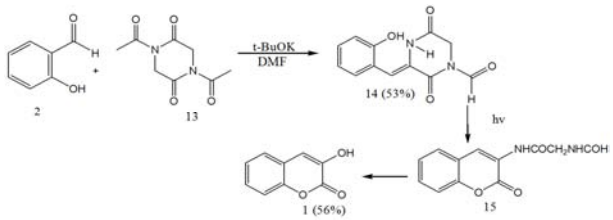

Figure 7. *3-Hydroxycoumarin synthesis using salicylaldehyde 2.*

3. Chemical Properties of 3-Hydroxycoumarin

3.1. Synthesis of Pyrido[2,3-c] Coumarin Derivatives

3-hydroxycoumarin 1 is widely used as a starting material in the synthesis of a number of oxygenated, nitrogenous and other heterocyclic molecules. This is the case of the pyrido[2,3-c] coumarin derivatives. The pyrido [2,3-*c*]coumarin derivatives are structural analogues of santiagonamine 16 (Figure 8), an alkaloid isolated from *Berberis Darwinii* (Berberidacea). This compound has shown interesting properties for wound healing. Pave *et al.* [12] have developed a new method for the preparation of substituted derivatives of pyrido[2,3-*c*]coumarin 17 and its tetrahydro derivatives involving the condensation of 3-hydroxycoumarin 1 with β-aminoketone 18 followed by intramolecular cyclization (Figure 9). These compounds were synthesized to explore the different biological activities that they would contain.

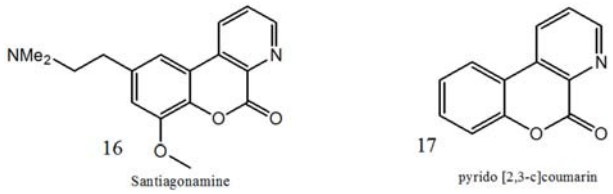

Figure 8. *Structure of santiagonamine and pyrido [2,3-c]coumarin.*

The condensation of 3-hydroxycoumarin 1 and amine 18 in toluene at reflux with a catalytic amount of camphorsulfonic acid (CSA) using a Dean-Stark apparatus yielded aminocoumarin 19. The addition of boron trifluoride diethyl etherate complex to the solution allowed cyclization to the C-4 position of the coumarin. At this stage, a mixture of two products is isolated form intermediate 20 with a yield of 68%, pyrido[2,3-c]coumarin 21 and tetrahydropyrido[2,3-c]coumarin 22 in a ratio of 56/44, respectively.

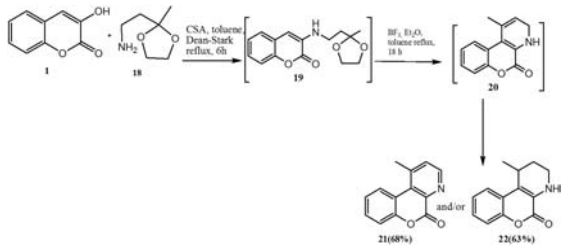

Figure 9. *Synthesis of pyrido[2,3-c] and pyrido[3,2-c]coumarin form compound 1.*

3.2. Synthesis of Chromeno[4,3-e][1,3]oxazine Derivatives

Mondal *et al.* [15] developed a novel methodology for the synthesis of chromeno[4,3-*e*][1,3]oxazine derivatives 25 by the reaction of 3-hydroxycoumarin 1, formaldehyde 24 and amines 23 catalyzed by TiO_2 nanopowder (Figure 10).

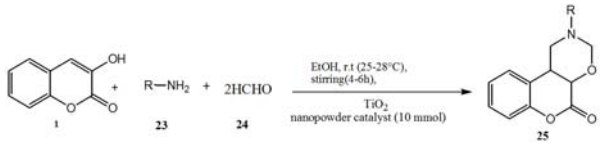

Figure 10. *Synthesis of compounds 25 from 3-hydroxycoumarin.*

This reaction was studied under different catalytic conditions. The optimisation of the reaction took into account some important parameters, including the nature of the catalyst (efficient and environmentally friendly) and the solvent. The various reaction tests were thus carried out in the presence of different catalysts at room temperature (25-28°C) with variable times. Experimental results show that the reaction takes place favourably in acid medium. Among the acids such as acetic acid (AcOH), phosphoric acid (H_3PO_4), ferric chloride ($FeCl_3$) and Titanium dioxide (TiO_2) nanopowder used in the reaction, the authors indicated that in the presence of TiO_2 nanopowder this reaction gives good conversion and yield. Regarding the choice of solvent, analyses showed that among of solvent such as EtOH, MeOH, ACN, DMF, DCM and THF, the best results were obtained at room temperature by stirring the reaction mixture in EtOH with a high yield of the product (88-92%). Following optimization of the reaction condition, the authors also investigated the structural nature of the amine. A variety of amines (R-NH2, variable R) were used under the optimized conditions (Figures 11 and 12). It was found that when aromatic amines with donor groups such as Me, OMe and isopropyl were introduced at different positions of the aromatic ring, they gave good yields of the desired product, whereas groups with an electro-attracting effect such as Cl, Br and NO_2 gave slightly lower yields.

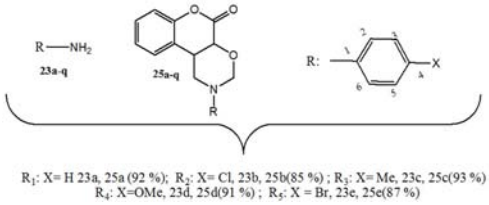

Figure 11. *The nature of the R substituents ($R_{1\text{-}5}$) in the synthesis of the compounds 25.*

The R6-17 are summarized in Figure 12 below. These different substituents give the size of the amine (23f-23q) used for the synthesis of chromeno[4,3-e][1,3]oxazine derivatives, heterocycles 25f-25q.

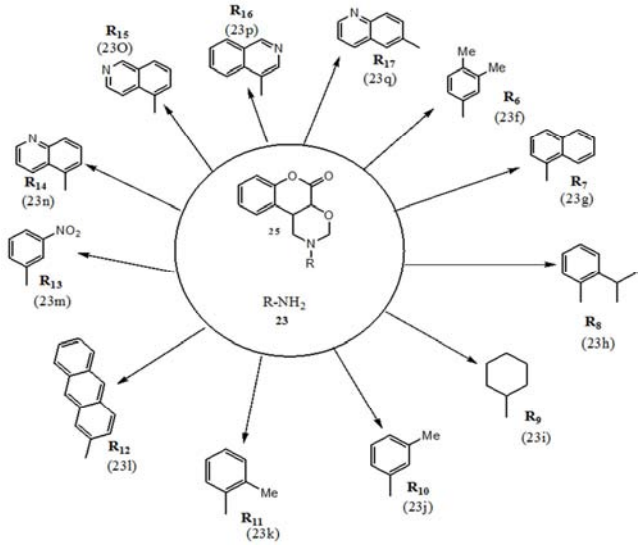

Figure 12. *Nature of subtituents R6-17 in the compounds 25 synthesis.*

R_6: 25f (94%); R_7: 25g (92%); R_8: 25h (79%); R9: 25i (82%); R_{10}: 25j (90%); R_{11}: 25k (88%); R_{12}: 25l (76%); R_{13}: 25m (80%); R_{14}: 25n (90%); R_{15}: 25O (85%); R_{16}: 25p (88%); R_{17}: 25q (87%).

3.3. Synthesis of Dihydropyrano [2,3-c]chromenes

Pyrano[3,2-*c*]chromene derivatives have attracted the attention of the scientific community because of their wide range of biological and pharmaceutical activities. These derivatives show antihyperglycemic and antidyslipidemic properties [16], cytotoxic [17], anti-inflammatory properties [18]. These compounds are components of many natural products such as calanolides, calanone, calophyllolides, etc. Sanjay *et al.* [19] have developed an efficient and environmentally friendly protocol for the synthesis of dihydropyrano[2,3-c]chromenes 28 by a single-point three-component coupling reaction of aromatic aldehyde 26, malononitrile 27 and 3-hydroxycoumarin 1 using nano-structured ZnO as a catalyst (Figure 13).

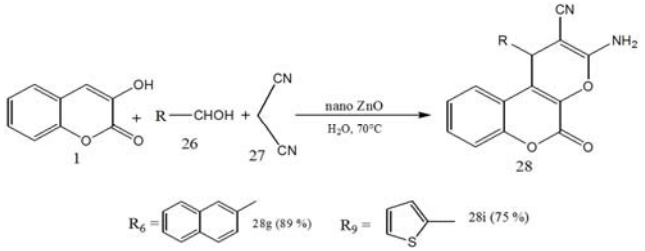

Figure 13. *Synthesis of dihydropyrano[2,3-c]chromene derivatives over nano ZnO.*

R_1=C_6H_4, 28a (87%); R_2=*p*-$NO_2C_6H_4$, 28b (91%) R_3=*p*-$MeOC_6H_4$, 28c (78%); R_4=*p*-BrC_6H4, 28d (89%); R_5=*p*-MeC_6H_4, 28e (83%); R_7=*p*-FC_6H_4, 28f (90%); R8=*p*-CNC_6H_4, 28h (90%), R_9=*p*-(CHO)-C_6H_4, 28j (65%).

The authors investigated beforehand the optimal conditions for this synthesis. The choice of the catalyst, the temperature, the kinetics of the reaction. Several catalysts were experimented in order to improve the yield of the specific synthesis. The results showed that when the reaction uses nano ZnO; it allowed to obtain the desired product with a yield of 91% in 2.5 h. When optimizing the reaction conditions, the effect of temperature was also monitored. The results showed that at 70°C, the product yield is maximum.

3.4. Synthesis of 3-Coumarinyl Carboxylates

Hydroxycoumarins react remarkably quickly with several acyl chlorides to give acyl derivatives of coumarin [20-32]. Previous work has shown that phenols, particularly hydroxycoumarins and some similar compounds such as homophthalic anhydrides, are suitable for acylation reactions with different results. Indeed, in the case of homophthalic anhydride, there is only *C*-acylation, where as in the case of hydroxycoumarin derivatives, acylation could be either *O*-acylation or *C*-acylation [6-7, 32]. Several acylation processes for compound 1 have been described. According to the mechanism of this acylation in a basic medium, an alcoholate anion 1i is formed at the hydroxyl function. This anion could be in equilibrium with mesomeric carbanion 1ii as follows (figure 14). In general, triethylamine (Et_3N), pyridine (Py), piperidine and potassium cyanide (KCN) are used as appropriate bases.

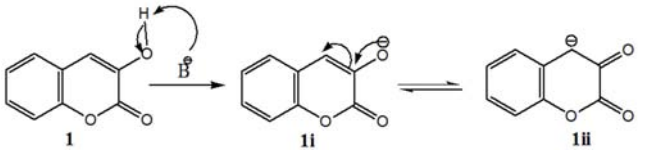

Figure 14. *Mesomeric equilibrium between alcoholate anion and carbanion from 3-hydroxycoumarin.*

Saba *et al.* [33-34] have adapted a method described by J. Schnekenburger [35] for the acylation of homophthalic anhydride. This method will also be used for the acylation of compound 1. Thus, 3-hydroxycoumarin reacts in the presence of pyridine or triethylamine with an acid anhydride or acid chloride to yield the *O*-acylation compound exclusively and quantitatively [36-39] (Figure 15; Table 1).

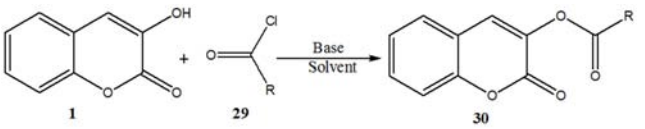

Figure 15. *Acylation of 3-hydroxycoumarin.*

30a: CH_3 30b=C_2H_5, 30c: R=C_6H_5; 30d: R=*p*-ClC_6H_4; 30e: R=*p*-FC_6H_4; 30f: R=*p*-$NO_2C_6H_4$: 30g: R=*p*-$tBuC_6H_4$; 30h: R=*p*-MeC_6H_4; 30i: R=*p*-$CH_3OC_6H_4$; 30j: R: p-CNC_6H_4; 30k: R=*p*-$(CH_3)_2NC_6H_4$; 30l: 3,5-$(NO_2)_2C_6H_3$.

Table 1. *Preparation of 3-coumarinyl carboxylates.*

Entry	R	Yield (%)	MP (°C)	Aspect
30a	CH_3	89	183-184	Colourless crystals

Entry	R	Yield (%)	MP (°C)	Aspect
30b	C_2H_5	76	120	Colourless crystals
30c	C_6H_5	74	108-110	Colourless crystals
30d	*p*-ClC_6H_4	70	148-149	Colourless crystals
30e	*p*-FC_6H_4	80	178-179	White powder
30f	*p*-$MeOC_6H_4$	91	178-179	Colourless crystals
30g	*p*-*t*BuC_6H_4	84	140-143	Colourless crystals
30h	*p*-MeC_6H_4	80	179-181	Colourless crystals
30i	*p*-$NO_2C_6H_4$	83	262,5	Colourless crystals
30j	*p*-CNC_6H_4	67	234-236	Colourless crystals
30k	*p*-$(CH_3)_2NC_6H_4$	79	234-236	Colourless crystals
30l	3,5-$(NO_2)_2C_6H_3$	68	236-238	Colourless crystals

These types of compounds are usually in the form of crystals. This is the case for carboxylates of 4-hydroxycoumarin [40-42] and 7-hydroxycoumarin [43-46]. In the case of 3-hydroxycoumarin, the crystalline structure has been established for compounds 30b, 30c, 30d, 30e, 30g, 30j, 30h [6-7, 47-51]. The crystallographic data are here reported for compound 30b, 30e, 30g, 30h.

Crystallographic data of compound 30b

Chemical formula: $C_{12}H_{10}O_4$; Formula weight: 218.20; Crystal description: prism, colourless; Melting point (K): 351; Crystal system: Monoclinic; space group: *P*21/*c*; Temperature (K): 293; Wavelength (A): 1.54184; Unitcell dimensions: a=12.1179 (4) A, b=5.7243 (2) A, c=15.3275 (5) A, β=94.881; (3)°; Volume (A 3): 1059.36 (6); Z=4; Radiation type: Cu *K*α; Absorption coefficient (mm-1): 0.87; Density (Mgm−3): 1.368; F (000): 456; Crystal size (mm): 0.46 × 0.16 × 0.08; 6028 measured reflections; 1930 independent reflections; *R*int=0.020; *R* [*F*2 > 2σ (*F*2)]=0.038; *wR* (*F*2)=0.117; *S*=1.06; 1930 reflections; 145 parameters.

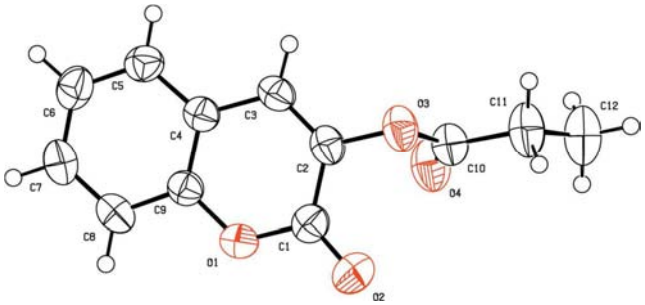

Figure 16. *Ortep structure of compound 30b.*

Crystallographic data of compound 30e

Chemical formula: $C_{16}H_9FO_4$; Formula weight: 284.23; Crystal description: prism, colourless; Melting point (K): 452-454; Crystal system: Triclinic; space group: P1; Temperature (K): 293; Wavelength (Å): λ=1.54184; Unit cell dimensions: *a*=6.8116 (2) Å, *b*=7.2402 (2) Å, *c*=13.4826 (3) Å, α=96.943 (2); β=90.862 (2); γ=106.139 (2); Volume (Å^3): 633.21 (3); Z=2; Radiation type: Cu*K*α; Absorption coefficient (mm^{-1}): 1.00; Density (Mg m^{-3}): 1.491; F (000): 292; Crystal size (mm): 0.36 × 0.26 × 0.16; 12676 measured reflections; 2358 independent reflections; *R*int=0.017; *R* [*F*2 > 2σ (*F*2)]=0.036; *wR* (*F*2)=0.100; *S*=1.09; 2358 reflections; 191 parameters.

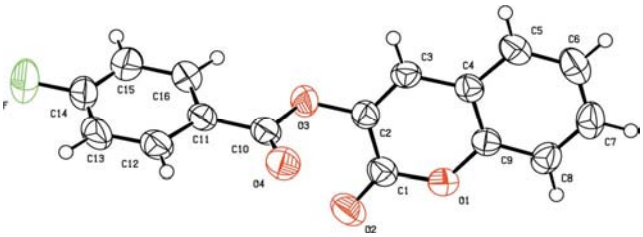

Figure 17. *Ortep structure of compound 30e.*

Crystallographic data of compound 30g

Chemical formula: $C_{20}H_{18}O_4$; Formula weight: 322.34; Crystal description: Prism, colorless; Melting point (K): 410-413 K; Crystal system: Monoclinic; space group: *C*2/*c*; Temperature (K): 298; Wavelength (Å): λ=0.71073; Unit cell dimensions: *a*=22.8977 (5) Å, *b*=5.9947 (1) Å, *c*=24.0352 (7) Å; β=93.297 (2)°; Volume (Å^3): 3293.73 (13); Z=8; Radiation type: Mo*K*α; Absorption coefficient (mm^{-1}): 0.09; Density (Mg m^{-3}): 1.300; F (000): 1360; Crystal size (mm): 0.34 x 0.12 x 0.06; 19994 measured reflections; 3005 independent reflections; *R*int=0.031; *R* [*F*2 > 2σ (*F*2)]=0.048; *wR* (*F*2)=0.127; *S*=1.12; 3005 reflections; 290 parameters.

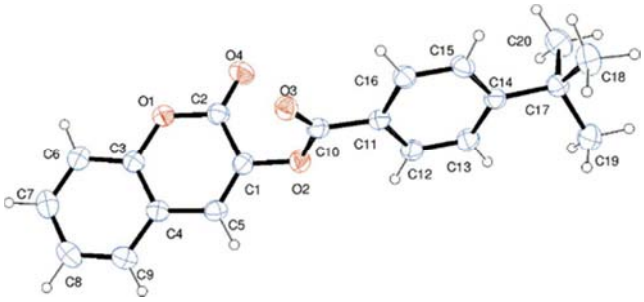

Figure 18. *Ortep structure of compound 30g.*

Crystallographic data of compound 30h

Chemical formula: $C_{17}H_{12}O_4$; Formula weight: 280.27; Crystal description: prism, colourless; Melting point (K): 443-445; Crystal system: Triclinic; space group: P-1; Temperature (K): 293 (2); Wavelength (Å): 0.71073; Unit cell dimensions: a=6.8221 (2) Å, b=7.1714 (3) Å, c=14.1270 (6) Å, α=93.239 (4), β=92.492 (3)°, γ=101.299 (3)°; Volume (Å^3): 675.62 (5); Z=2; Radiation type: MoKα; Absorption coefficient (mm^{-1}): 0.10; Density (Mg m^{-3}): 1.378; F (000): 292; Crystal size (mm): 0.44 x 0.28 x 0.28; 9533 measured reflections; 2866 independent reflections; *R*int=0.017; *R* [*F*2 > 2σ (*F*2)]=0.047; *wR* (*F*2)=0.133; *S*=1.07; 2866 reflections; 190 parameters.

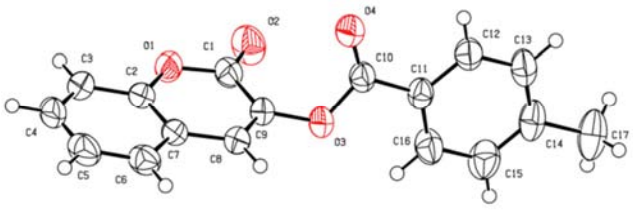

Figure 19. *Ortep structure of compound 30h.*

4. Biological Properties

4.1. Antioxidant Properties

Bailly *et al.* [9] synthesized a series of hydroxylated 3-hydroxycoumarins 33 by the reaction of 3-aryl-2-hydroxypropenoic derivatives 32 with boron tribromide (BBr_3) (figure 21). They were evaluated for their ability to bind the 2,2-diphenyl-1-picrylhydrazyl radical 31 (Figure 20), superoxide anion radical ($O_2^{\cdot}$), hydroxyl radical (HO•) and peroxynitrite anion (HNO_3^{-}) and to inhibit copper-induced peroxidation of human LDL.

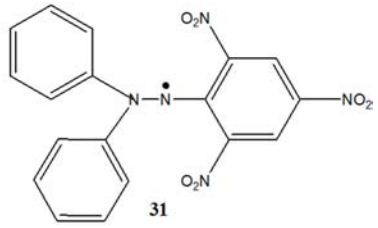

Figure 20. *Structure of 2,2-diphenyl-1-picrylhydrazyl radical.*

All of the compounds tested exhibited a variety of antioxidant activities (Table 2). The results of the study established that the hydroxylated compounds on the C-6 and C-7 positions are the most active of the series with antioxidant powers comparable to those of quercetin and vitamin C. In addition, the introduction of a hydroxyl group at the C-3 position is sufficient to improve the extinguishing properties since coumarin did not react in all four tests. Substitution of the phenyl ring with another hydroxyl group resulted in a significant increase in antioxidant properties. A precise analysis of the results showed that the most effective compounds in the series were 33c and 33e. The authors also analyzed the behavior of these compounds in the radical scavenging mechanism. It appears from this investigation that these compounds form *o*-and *p*-quinonoid derivatives on radical scavenging. This suggests that they may serve as new lead compounds for pharmacological research.

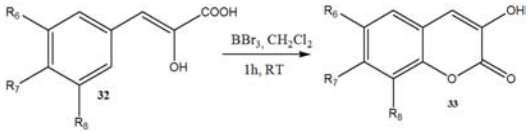

Figure 21. *Synthesis of compound 33.*

32a: R6=R7=R8=H; 32b: R6=R7=H, R8=OH; 32c: R6=R8=H, R7=OH; 32d: R7=R8=H, R6=OH.
32e: R6=R7=OH, R8=H. 33a: R1=OCH3, R2=R3=R4=H; 33b: R1=R2=OCH3, R3=R4=H; 33c: R1=R3=OCH3, R2=R4=H; 33d: R1=R4=OCH3, R2=R3=H; 33e: R1=R3=R4=OCH3, R2=H.

Table 2. *Antioxidant activities of 3-hydroxycoumarin derivatives and test compounds.*

Entry	DPPH log Z	Scavenging ECR_{50}	% Superoxide radical scavenging	% Hydroxyl radical scavenging	LDL oxidation ED_{50} (µM)	Peroxynitrite scavenging IC_{50} (µM)
33a	1.34±0.08	>19.00	Inactive	Inactive	27.2±1.7	>50.0
33b	1.59±0.07	2.85±0.10	7.0±0.3	46.6±3.1	10.0±0.6	3.44±0.14
33c	2.55±0.13	0.24±0.01	40.7±3.0	82.4±4.4	4.53±0.09	1.24±0.04
33d	1.60±0.08	7.61±0.39	4.2±0.2	51.0±2.4	36.3±2.5	5.49±0.32
33e	2.18±0.10	0.55±0.03	57.2±3.5	81.6±4.3	8.92 + 0.30	1.94±0.05
Quercetin	2.43±0.12	0.25±0.01	65.2±2.6	78.0±3.9	3.50±0.07	1.10±0.04
Trolox	-	-	27.5±1.4	48.8±2.2	10.0±0.7	1.02±0.03
Vitamin C	-	-	30.4±1.6	11.0±0.8	2.50±0.05	1.17±0.03
Coumarin	inactive	inactive	inactive	Inactive	Inactive	Inactive

4.2. 3-Hydroxycoumarin Action on Tyrosinase

Human tyrosinase: tyrosinase is one of the key enzymes for the biosynthesis of melanin in mammals. Its decreased activity has been targeted for the prevention of skin hyperpigmentation disorders such as melasma and age spots. Work on the formulation of 3-hydroxycoumarin 1 loaded vesicles for topical applications by Schlicha *et al.* [52], showed that 3-hydroxycoumarin 1 has a strong ability to inhibit recombinant human tyrosinase. In vitro skin penetration and permeation studies have shown that these formulations effectively cross the barrier represented by the stratum corneum, delivering 3-hydroxycoumarin to the deep layers of the skin. The effect of applying the liquid and gel formulation at different times was also evaluated.

Mushroom tyrosinase: the structure-activity relationships and interactions of four hydroxycoumarins, including 3,4, 6,7-hydroxycoumarin (Figure 22) with tyrosinase in the mushroom were also studied [53]. These different compounds showed different behaviours during the action of the enzyme. 3-Hydroxycoumarin was found to be a potent inhibitor of the enzyme compared to other hydroxylated coumarins. These results were compared with those obtained by in silico predictions to obtain potentially useful information for the synthesis of new coumarin inhibitors that resemble the structure of 3-hydroxycoumarin.

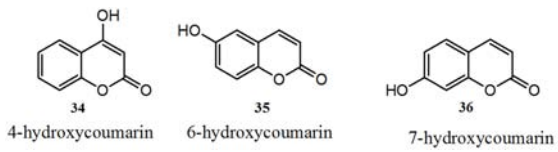

Figure 22. *Structure of hydroxylated coumarins.*

4.3. 3-Hydroxycoumarin as Inhibitors of Moniliophthora Perniciosa Fungus

3-hydroxycoumarin is an in vitro, in vivo and in silico inhibitor of the fungus *Moniliophthora perniciosa* compared to the standard defense activator acibenzolar-S-methyl 37 and

systemic fungicidal tebuconazole 38 [54]. Initially, in vitro tests for inhibition of basidiospore germination were performed using four different concentrations of 3-hydroxycoumarin, resulting in 100% inhibition at the concentration of 1000 ppm. Subsequently, this substance was used in vivo in four different treatments of cocoa plants of the SIC-23 genotype, with regard to the order of application. Data analysis showed greater inhibition when 3-hydroxycoumarin was applied after inoculation. In silico tests show that 3-hydroxycoumarin inhibits the production of chitin synthase by the fungus. Chitin synthase is a key enzyme in the chitin biosynthesis pathway. Therefore, the present study identifies a potential inhibitor of *Moniliophthora perniciosa* which is 3-hydroxycoumarin and suggests the best application methodology.

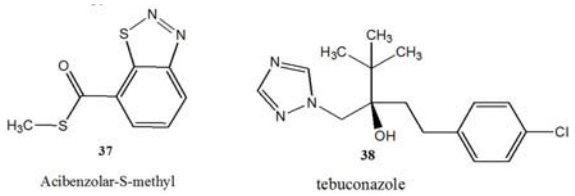

Figure 23. *Structure of two reference fungicides.*

4.4. 3-Hydroxycoumarin as New Matrix for DNA Analysis

The structure of 3-hydroxycoumarin contains a conjugated system consisting of a phenyl ring and a ketone group, which should have sufficient absorption for 337 nm. In addition, the hydroxyl group and the two carbonyl groups are considered important for a good matrix for time-of-flight mass spectrometry by laser desorption/ionization (MALDI-TOF MS) in DNA analysis [55-56]. Compared to conventional matrices of 3-hydroxypicolinic acid and 6-aza-2-thiothymine (ATT), 3-hydroxycoumarin has a significant improvement in resolution, S/N ratio, spot-to-spot-, and sample-to-sample reproducibility for the DNA segments analyzed. At present, despite extensive research, the matrices used in practice for DNA detection have been limited to 3-hydroxypicolinic acid 39 [57], picolinic acid 40 [58], 6-aza-2-thiothymine 41 [59], and 2,4,6-trihydroxyacetophenone 42 [60]. The introduction of 3-hydroxycoumarin as a template, initially used to analyze 67 m DNA, has greatly increased MALDI MS ability to analyze DNA.

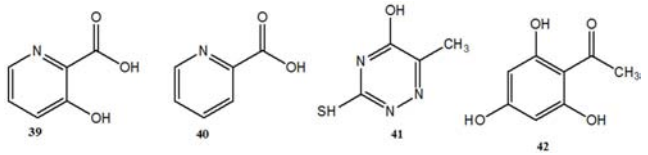

Figure 24. *The matrices used in practice for DNA detection.*

4.5. Photoprotective Properties of 3-Hydroxycoumarin Against UVB Deleterious Effects

Many studies have shown the photoprotective properties of 3-hydroxycoumarin against the deleterious effects of UVB, as shown in the study by Goodwin and Pollock [61]. They reported on the UV-absorbing properties of 29 coumarin derivatives, including 3-hydroxycoumarin. Other recent work has also shown the properties of nucleus-bound coumarins. According to the various studies, the photoprotective effect of these compounds is linked to their ability to absorb UV radiation. These results are corroborated by experimental results on the photoprotective capacity of 3-hydroxycoumarin against UVB from sea urchin gametes and embryonic cells [14].

4.6. Human 15-LOX-1 inhibitors Based on 3-Hydroxycoumarin

Lipo-oxygenase enzymes are one of the causes of several diseases such as inflammation, cancer, asthma, allergies, strokes, etc. [62]. Because of their importance as therapeutic targets, work has been devoted to the discovery of pathways for the synthesis of new and potent inhibitors of this lipo-oxygenase. Several natural and synthetic derivatives of hydroxycoumarins have been reported as lipo-oxygenase inhibitors [63-67]. Most of them inhibit lipo-oxygenase pathways using the redox mechanism with their hydroxyl groups. Alavi *et al.* [66] analysed the lipo-oxygenase inhibitory power of monohydroxycoumarins against human 15-LOX-1 enzymes and their radical scavenging activity was comparatively observed. Among the coumarins mentioned, the 3-hydroxy derivative was the potent lipo-oxygenase inhibitor with an IC50 value of 9.5 µm. The authors showed that the replacement of 3-hydroxy with a 3-amino group led to the elimination of lipo-oxygenase inhibitory activity.

5. Conclusion

In this review, we discussed the synthesis, reactivity and biological properties of 3-hydroxycoumarin. About the synthesis of this compound, it is interesting to note that salicylaldehyde and 1-(2-Methoxyphenyl)ethanone are the oldest and most widely used starting compounds to our knowledge. Regarding reactivity, we have noticed that 3-hydroxycoumarin is already involved in the synthesis of some heterocycles sought for their multiple biological properties. We hope to have made the readers of this journal aware of the current interest of the scientific community in 3-hydroxycoumarin. It seems likely that 3-hydroxycoumarin will be a popular building block for the synthesis of heterocycles, and that other elegant and innovative developments and applications for this compound will emerge in the future.

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