Simple Coumarins and Analogues in Medicinal Chemistry: Occurrence, Synthesis and Biological Activity

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Abstract: Coumarins, also known as benzopyrones, are present in remarkable amounts in plants, although their presence has also been detected in microorganisms and animal sources. The structural diversity found in this family of compounds led to the division into different categories, from simple coumarins to many other kinds of policyclic coumarins, such as furocoumarins and pyranocoumarins.

Simple coumarins and analogues are a large class of compounds that have attracted their interest for a long time due to their biological activities: they have shown to be useful as antitumoural, anti-HIV agents and as CNS-active compounds. Furthermore, they have been reported to have multiple biological activities (anticoagulant, anti-inflammatory), although all these properties have not been evaluated systematically. In addition, their enzyme inhibition properties, antimicrobial and antioxidant activities are other foremost topics of this field of research.

The present work is to survey the information published or abstracted from 1990 till 2003, which is mainly related to the occurrence, synthesis and biological importance of simple coumarins and some analogues, such as biscoumarins and triscoumarins. Data are also highlighted, concerning the development of new synthetic strategies that could help in drug design and in the work on SAR or QSAR.

Keywords: Simple coumarins, occurrence, synthesis, biological activity, SAR and QSAR, separation and identification.

INTRODUCTION

The study of coumarins began more than 200 years ago. The name of this chemical family is derived from *Coumarouna odorata Aube (Dipteryx odorata)*, from which was isolated, for the first time, the simplest member of this class, coumarin itself [1]. Coumarin is a widely occurring secondary metabolite that occurs naturally in several plant families and essential oils, and has been used as a fragrance in food and cosmetic products (Fig. **1**). The coumarin nucleus corresponds to benzo-α-pyrone (2*H*-1-benzopiran-2-one) whose systematic nomenclature was established by IUPAC [2][1].

Coumarins have been roughly categorised as follows: a) Simple coumarins, b) Furanocoumarins, c) Pyranocoumarins, d) Biscoumarins and Triscoumarins and e) Coumarinolignans. Although distinctions according to their chemical structure can be made among the several groups of coumarins, the present paper will be largely directed to class a). There will also be a brief reference made to the bis- and triscoumarins isolated during the period of revision.

Over and above the discoveries made by isolation of coumarins from the hundreds of species of plants and other organisms, there are the derivatives of synthetic origin which significantly increases the number of coumarin structures known till today. Considering the technological advance which permitted the facility of determining their chemical structures, one is forced to ask what factor induces the interest in the compounds of this family. From among to several that could be enumerated, we will emphasise on one, which without doubt is of great importance - the diversity of biological activities that these compounds exhibit. Practically from the beginning of the study of coumarins, the attention of the investigation was focussed on the possibility of their therapeutic activity.

In 1936, Von Werder [4] referred the coumarins as therapeutic agents and Bose, in 1958 [5], summarised most of the biological properties of the natural coumarins. In 1964, Soine [6] published a revision on the biological and pharmacological effects of coumarins known up to date,

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[1]The generic name of *coumarin* was applied to all the derivatives having a benzo-α-pirone unit, instead of using the systematic nomenclature. Their names are derived from this common or trivial name or from the name of their natural derivatives (derived from families or species of plants) considered important. To the trivial names are added suffixes or prefixes consonant the type of substituents and their position in the coumarin nucleus [3].

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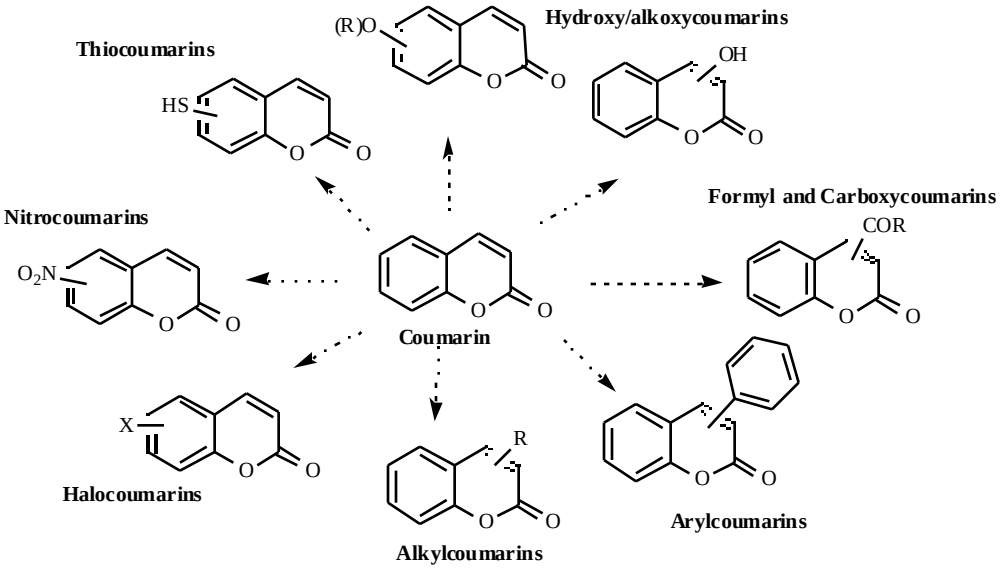


Fig. (1). Coumarin, as a central core for the obtention of simple coumarins.

with particular emphasis on the activity associated with the natural products. More recently, in 1972, Scheel [7] published a review on the biological action of coumarins. Since the 1980´s there have been a number of excellent reviews on coumarins, mainly in respect to the occurrence and biological activities that were published by Murray *et al.* [3, 8, 9], and other authors [10-23].

The present review is to provide an overview of the research related to simple coumarins and analogues, and describe the advances made in this field in recent years, either in isolation or in synthesis, and the most relevant biological properties associated with these systems. Particular emphasis will be given to the more recent methods for the preparation of simple coumarins and analogues, as well as the classic methods that are still commonly used.

The review is arranged according to: A- Natural occurrence of simple coumarins and analogues; B- Methods of syntheses: B1- Synthesis of simple coumarins from classic and non-classic methods, B2- Synthesis of simple coumarins from coumarins and, finally, section (C) is concerned with the most relevant aspects of the biological activity of these compounds.

A- NATURAL OCCURRENCE OF SIMPLE COUMARINS AND ANALOGUES

Coumarins are widely distributed in the plant kingdom and are present in notable amounts in several species, such as Umbelliferae, Rutaceae and Compositae. However, the specific roles of these compounds are not well understood and have been the topic of some debate.

Numerous coumarins have been isolated since the first example was reported in 1812 [1]. Murray *et al.* [3] have written an excellent book that provides a comprehensive overview of naturally occurring coumarins. This information has since then been updated [8-13, 22, 23].

The present work is not intended as an exhaustive review of the field, but is related to only novel simple coumarins that have been isolated in the last decade. Plant coumarins discovered mostly between 1997 and 2003 have been tabulated and the information, so far obtained, on their trivial or systematic names, structure and plant source was included (Tables **1**-**5**). Revised structures of some coumarins were also mentioned. Simple coumarins that are already integrated in some reviews [9, 10, 22, 23] were not included in the tables.

In addition, the literature about natural biscoumarins and triscoumarins, containing simple coumarins as units, will be reviewed.

Biscoumarins

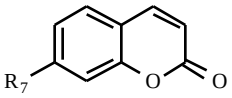
During this period, several biscoumarins were isolated from plants [9, 79-84]. Dimeric coumarin derivatives (phebalin, thamnosin, toddasin) were also identified from Rutaceae and synthesised through expedite methods [85]. The relative stereochemistries of toddalosin from *Toddalia asiatica*, and of edgeworoside C (Fig. **2**) from *Edgeworthia chrysantha*, were established by X-ray crystallography or from the CD spectrum of the aglycone, respectively [9].

Other interesting dimeric compounds were isolated and synthesised, namely those described in the review of Estévez-Braun and González [10].

Triscoumarins

During this period, triscoumarins have been isolated from *Daphne mezereum* and from *Daphne oleoides* [9, 80]. It is important to mention that the stereochemistry of the triscoumarin edgeworoside B (Fig. **2**), isolated from *Edgeworthia chrysantha*, was concluded to be *S* from the CD spectrum of the aglycone [9].

Table 1. Natural Monosubstituted Coumarins



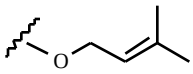
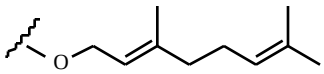
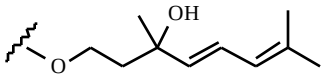
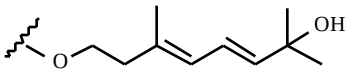
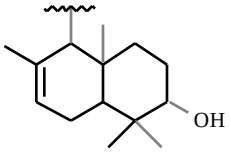
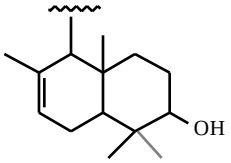
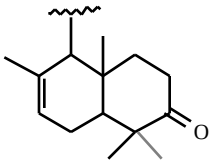
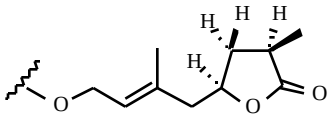
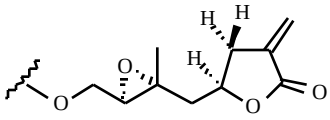
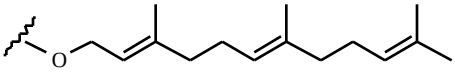
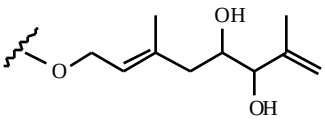
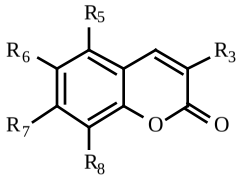
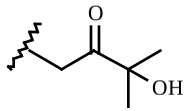
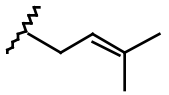
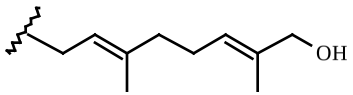
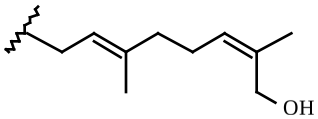
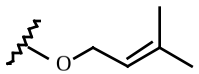
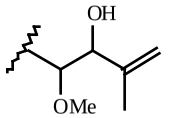
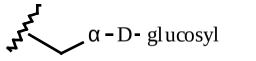
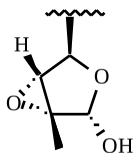
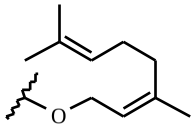
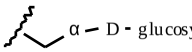
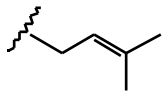
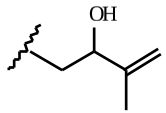
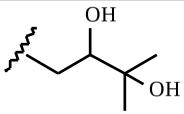
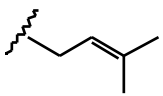
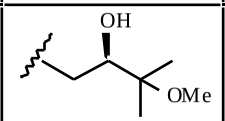
Compound	R_7	Source	Ref.
Herniarine	OMe	*Artemisia dracunculus*	24
Ulopterol		*Baccharis pedunculata*	25
Aurapten (7-Geranyloxycoumarin)		*Citrus hassaku* *Zanthoxylum schinifolium*	26 27
Ferulagol A		*Ferula ferulago*	28
Ferulagol B		*Ferula ferulago*	28
Feselol		*Ferula sumbul*	29
Conferol		*Ferula sumbul*	29
Conferona		*Ferula sumbul*	29
3´´,4´´-Dihydrocapnolactone		*Micromelum minutum*	30
2´,3´-Epoxyisocapnolactone		*Micromelum minutum*	30
Umbelliprenin		*Peucedanum zenkeri*	31
7-(5´,6´-Dihydroxy-3´,7´-dimethylocta-2´,7´-dienyloxy)coumarin		*Zanthoxylum schinifolium*	32

Table 2. Natural Disubstituted Coumarins

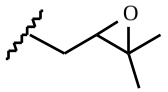
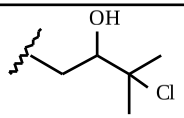
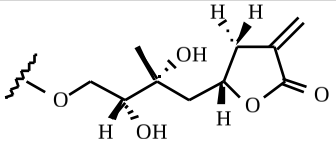
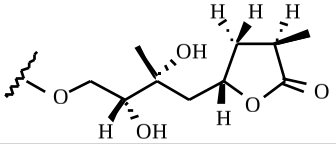
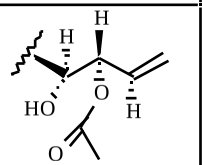
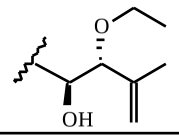
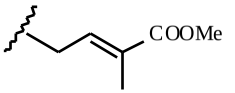
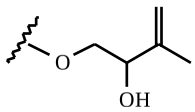
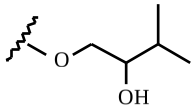
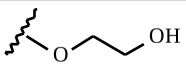


Compound	R_3	R_5	R_6	R_7	R_8	Source	Ref.
Esculetin			OH	OH		*Alchemilla speciosa* *Santolina oblongifolia* *Taraxacum formosanum*	33 34 35
Peucedanone				OH		*Angelica gigas*	36
Osthenol				OH		*Angelica koreana*	37
Artekeiskeanol A			OMe			*Artemisia keiskeana*	38
Artekeiskeanol B			OMe			*Artemisia keiskeana*	38
8-Methoxy-7-prenyloxycoumarin					OMe	*Artemisia carviforia*	39
Scopoletin-β-D-xylopyranosyl(1-6)-β-D-glucopyranoside			OMe	R = β-D-xylopyranosyl(1→6) -β-D-glucopyranosyl		*Atractylodes ovata*	40
Albiflorin-2 Albiflorin-3 (diasteriomers)				OMe		*Boenninghausenia albiflora*	41
Cichoriin-6´-*p*-hydroxyphenyl acetate			OH			*Cichorium intybus*	42

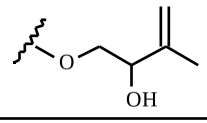
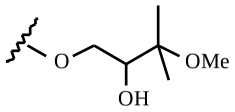
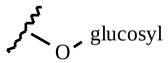
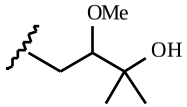
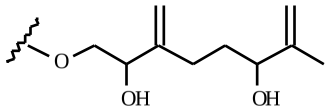
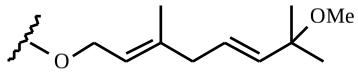
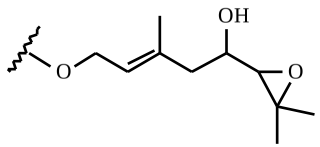
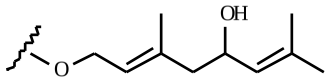
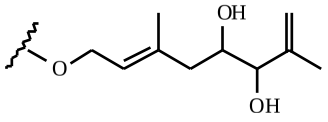
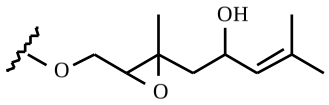
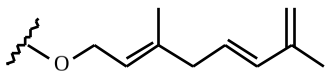
(Table 2). contd.....

Compound	R_3	R_5	R_6	R_7	R_8	Source	Ref.
Marshrin				OMe		*Citrus paradisi*	43
5-Geranyloxy-7-hydroxycoumarin				OH		*Clausena excavata*	44
7-O-(6´-Acetoxy-β-D-glucopyranosyl)-8-hydroxycoumarin 7-O-[6´-O-(3´´,4´´-Dihydroxycinnamoyl)-β-D-glucopyranosyl]-8-hydroxycoumarin				OR R= 6-Ac-β-D-glucosyl R = 6-O-(3,4-dihydroxy-cinnamoyl)-β-D-glucosyl	OH	*Cruciata taurica*	45
7-Hydroxy-8-*O*-(α-D-glucopyranosyl)-2*H*-benzopyran-2-one				OH		*Daphne oleoides*	46
Scopoletin			OMe	OH		*Eurycoma harmandiana* *Guarea rhophalocarpa* *Xeromphis nilotica*	47 48 49
Osthol				OMe		*Ferula sumbul*	29
Auraptenol				OMe		*Ferula sumbul*	29
Meranzin hydrate				OMe		*Ferula sumbul*	29
Suberosin				OMe		*Fortunella margarita*	50
(+)-Trachipleuranin-A				OMe		*Harbouria trachypleura*	51

(Table 2). contd.....

Compound	R_3	R_5	R_6	R_7	R_8	Source	Ref.
Epoxisuberosin				OMe		*Harbouria trachypleura*	51
(±)-Trachipleuranin-B				OMe		*Harbouria trachypleura*	51
8-Hydroxyisocapnolactone-2´,3´-diol					OH	*Micromelum minutum*	30
8-Hydroxy-3´´,4´´-dihydrocapnolactone-2´,3´-diol					OH	*Micromelum minutum*	30
5-Hydroxy-7-methoxycoumarin		OH		OMe		*Morus alba*	52
Omphalocarpinol				OMe		*Murraya omphalocarpa*	53
2´-O-ethylmurrangatin				OMe		*Murraya paniculata*	54
Phebaclavin C				OH		*Phebalium clavatum*	55
Isovirgatenol				OMe		*Pterocaulon polystachyum*	56
3´-Deoxyobtusinin			OMe			*Pterocaulon polystachyum*	56
6-Methoxy-7-(2´-hydroxyethoxy)coumarin			OMe			*Pterocaulon polystachyum*	56

(Table 2). contd.....

Compound	R_3	R_5	R_6	R_7	R_8	Source	Ref.
Virgatenol			OMe			*Pterocaulon virgatum*	57
Virgatol			OMe			*Pterocaulon virgatum*	57
Scopolin			OMe			*Santolina oblongifolia*	34
(+)-7-Methoxy-6-(2´R-methoxy-3´-hydroxy-3´-methylbutyl)coumarin				OMe		*Skimmia laureola*	58
7-(2´,6´-Dihydroxy-7´-methyl-3´-methyleneocta-7´-enyloxy)-8-methoxycoumarin					OMe	*Zanthoxylum schinifolium*	32
Methylschinilenol					OMe	*Zanthoxylum schinifolium*	59
Hydroxyepoxycollinin I					OMe	*Zanthoxylum schinifolium*	59
8-Methoxyanisocoumarin H					OMe	*Zanthoxylum schinifolium*	59
Hydroxyschininallylol					OMe	*Zanthoxylum schinifolium*	59
Hydroxyepoxycollinin II					OMe	*Zanthoxylum schinifolium*	59
Schinitrienin					OMe	*Zanthoxylum schinifolium*	59

(Table 2). contd.....

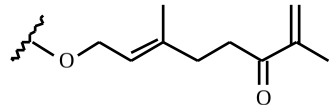
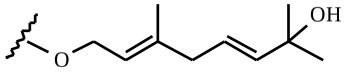
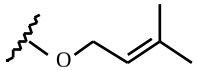
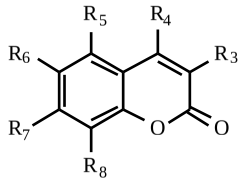
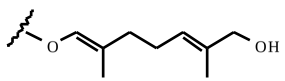
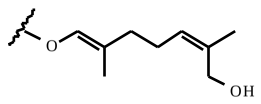
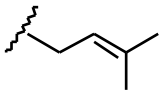
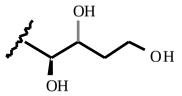
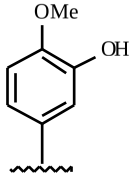
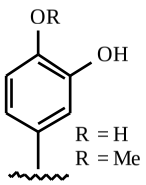
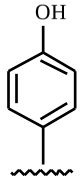
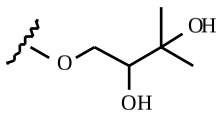
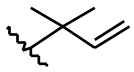
Compound	R_3	R_5	R_6	R_7	R_8	Source	Ref.
Schininallylone					OMe	*Zanthoxylum schinifolium*	59
Isoschinilenol			OMe			*Zanthoxylum schinifolium*	59
Lacinartin					OMe	*Zanthoxylum schinifolium*	60

Table 3. Natural Trisubstituted Coumarins

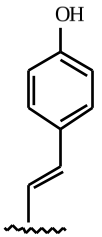
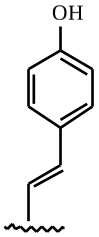
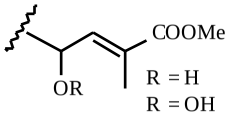
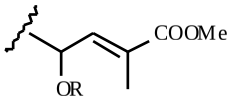
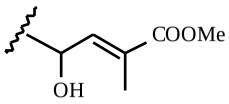
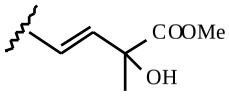


Compound	R_3	R_4	R_5	R_6	R_7	R_8	Source	Ref.
Arteminin			OH	OMe		OMe	*Artemisia apiacea*	61
Artekeiskeanol C				OMe		OMe	*Artemisia keiskeana*	38
Artekeiskeanol D				OMe		OMe	*Artemisia keiskeana*	38
Isocedrelopsin Microfolicoumarin				OR R = H R = Me	OMe		*Cedrelopsis grevei*	62

(Table 3). contd.....

Compound	R_3	R_4	R_5	R_6	R_7	R_8	Source	Ref.
5,7-Dimethoxy-6-(1´,2´,3´-trihidroxypropyl)-2*H*-1-benzopyran-2-one			OMe		OMe		*Daphne oleoides*	46
Seshadrin			OMe		OH		*Exostema mexicanum*	63
3´,4´-Dihydroxy-5,7-dimethoxy-4-phenylcoumarin 3´-Hydroxy-4´,5,7-trimethoxy-4-phenylcoumarin			OMe		OMe		*Exostema mexicanum*	63
4´-Hydroxy-5,7-dimethoxy-4-phenylcoumarin			OMe		OMe		*Exostema mexicanum*	63
6,7-Dimethoxy-8-(2,3-dihydroxy-3-methylbutoxy) coumarin				OMe	OMe		*Gochnatia polymorpha*	64
Rutacultine				OMe	OMe		*Helietta longifoliata*	65

(Table 3). contd.....

Compound	R_3	R_4	R_5	R_6	R_7	R_8	Source	Ref.
5-(4-Hydroxyphenethenyl)-4,7-dimethoxycoumarin		OMe			OMe		*Monotes engleri*	66
5,7,4´-Trihydroxy-4-styrylcoumarin			OH		OH		*Ononis vaginalis*	67
Phebaclavin A Phebaclavin D	 R = H R = OH				OMe	OH	*Phebalium clavatum*	55
Phebaclavin B Phebaclavin E	 R = H R = OH				OH	OMe	*Phebalium clavatum*	55
Phebaclavin F					OH	OH	*Phebalium clavatum*	55
Phebaclavin G					OMe	OH	*Phebalium clavatum*	55

(Table 3). contd.....

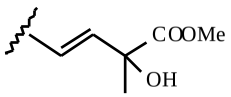
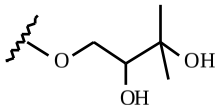
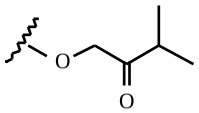
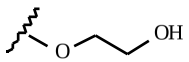
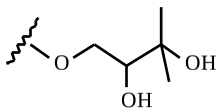
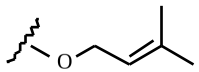
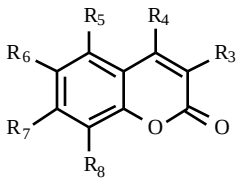
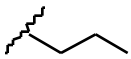
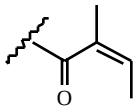
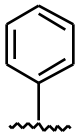
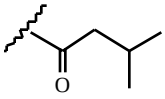
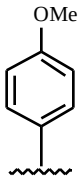
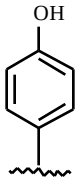
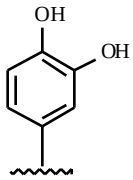
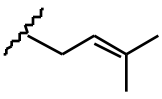
Compound	R_3	R_4	R_5	R_6	R_7	R_8	Source	Ref.
Phebaclavin H					OH	OMe	*Phebalium clavatum*	55
5-(2,3-Dihydroxy-3-methylbutyloxy)-6,7-methylenedioxy coumarin							*Pterocaulon* genus	68
5-(3-Methyl-2-oxobutyloxy)-6,7-methylenedioxy coumarin							*Pterocaulon* genus	68
5-(2´-Hydroxyethoxy)-6,7-methylenedioxy coumarin							*Pterocaulon polystachyum*	56
2´,3´-Dihydroxypuberulin				OMe		OMe	*Pterocaulun redolens*	69
5-(3-Methyl-2-butenyloxy)-6,7-methylenedioxy coumarin							*Pterocaulon virgatum*	70
5-Methoxy-6,7-methylenedioxy coumarin			OMe				*Pterocaulon virgatum*	70
Schinicoumarin	OMe				OMe	OMe	*Zanthoxylum schinifolium*	27

Table 4. Natural Tetrasubstituted Coumarins



Compound	R_3	R_4	R_5	R_6	R_7	R_8	Source	Ref.
(+)-Calanolides E2			OMe		OMe		*Calophyllum genus*	71
Isodispar B			OH		OH		*Calophyllum dispar*	72
O-Methylexostemin			OMe		OMe	OMe	*Exostema mexicanum*	63
Exomexin A			OMe		OMe	OH	*Exostema mexicanum*	63
3´,4´,8´-Trihidroxy-5,7-dimethoxy-4-phenylcoumarin Exomexin B			OMe		OMe	OR R = H R = Me	*Exostema mexicanum*	63
8-Hydroxy-5,6,7-trimethoxycoumarin			OMe	OMe	OMe	OH	*Hibiscus syriacus*	73
Mansonrin B Mansonrin A	Me			OR R = H R = Me		Me	*Mansonia gagei*	74
5-Hydroxy-6,7-methylenedioxy-8-(3,3-dimethylallyl)coumarin			OH				*Pterocaulon polystachyum*	56

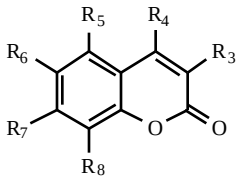
Separation and Identification

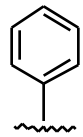
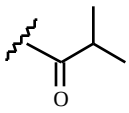
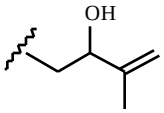
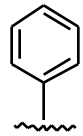
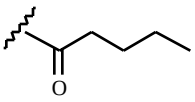
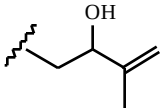
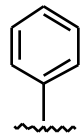
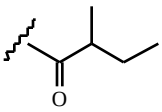
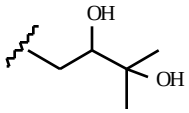
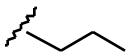
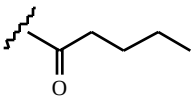
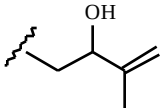
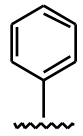
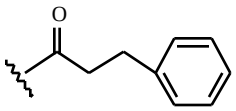
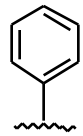
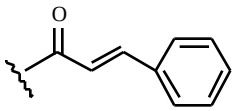
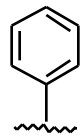
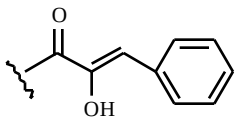
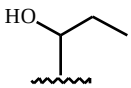
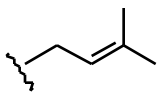
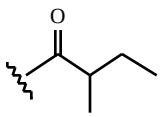
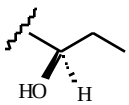
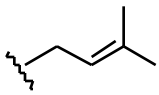
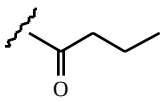
Several techniques of separation and identification have been developed, which were considered of great importance in the isolation of simple coumarins and analogues from plants. Among them HPLC, two dimensional chromatography, NMR, and MS were referred to as the most useful in the field [9, 10, 86-92].

B- METHODS OF SYNTHESIS

The interesting biological properties of coumarins made these compounds very attractive for organic synthesis. The history of coumarin synthesis began in the mid-nineteenth century, with the discovery by Perkin of the famous synthesis of coumarin, a reaction that even nowadays bears his name. From the start, up to recent time, several

Table 5. Natural Pentasubstituted Coumarins



Compound	R_4	R_5	R_6	R_7	R_8	Source	Ref.
Disruptol D		OH		OH		*Calophyllum dispar*	72
Disparinol B		OH		OH		*Calophyllum dispar*	72
Dispardiol B		OH		OH		*Calophyllum dispar*	72
Disparpropylinol B		OH		OH		*Calophyllum dispar*	72
Interruptin A		OH	Me	OH		*Cyclosorus interruptus*	75
Interruptin B		OH	Me	OH		*Cyclosorus interruptus*	75
Interruptin C		OH	Me	OH		*Cyclosorus interruptus*	75
Assamene		OH		OH		*Kayea assamica*	76
Theraphin A		OH		OH		*Kayea assamica*	77

(Table 5). contd.....

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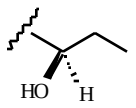
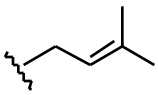
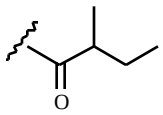
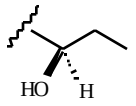
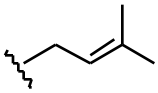
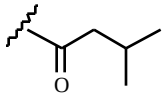
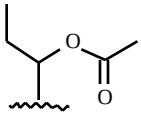
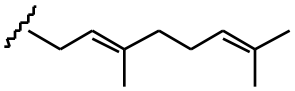
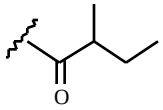
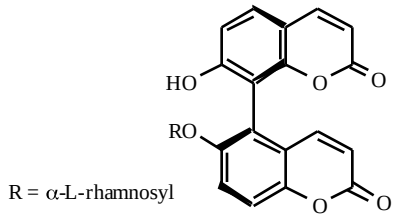
Theraphin B		OH		OH		*Kayea assamica*	77
Theraphin C		OH		OH		*Kayea assamica*	77
Surangin B		OH		OH		*Mammea americana*	78

synthetic strategies for obtaining simple coumarins have been developed.

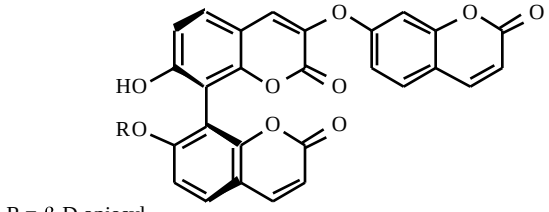
B1- Synthesis of Simple Coumarins from Classic and Non-Classic Methods

Coumarins can be classically synthesised by the Perkin, Pechmann or Knoevenagel reactions. Recently, the Wittig, the Kostanecki–Robinson and Reformatsky reactions were also conveniently applied to the synthesis of this type of heterocycles. However, it is important to note that all the methods reported have some disadvantages, since they lack generality and efficiency, making the development of new reliable high-yielding methods for the synthesis of coumarins an important subject. Below is an overview of the literature published under this topic.

The classical synthesis of coumarin, from salicylaldehyde and acetic anhydride, has been improved by the use of anhydrous sodium fluoride as catalyst or dibenzo-18-crown-6 [9]. The preparation of 3-aryloxycoumarins, with various substitution patterns, was performed *via* the modified Perkin-Oglialoro reaction, by condensation of adequate substituted salicylaldehydes, with the sodium salts of the corresponding aryloxyacetic acids [95].



Edgeworoside C

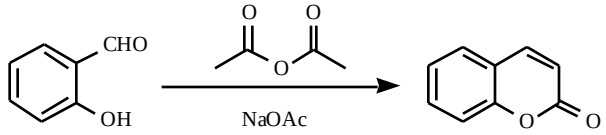


Edgeworoside B

Fig. (2). Structures of dimeric and trimeric simple coumarins.

Perkin Reaction

The Perkin reaction consists in the formation of a coumarin by aldol condensation, of aromatic *ortho*-hydroxybenzaldehyde and acid anhydrides, in the presence of an alkali salt of the acid (Scheme **1**). Several reports on the synthesis of coumarins through this method were published [9, 93, 94].



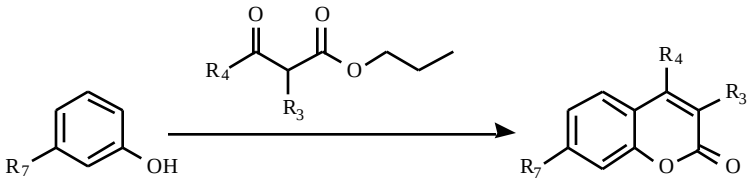
Scheme 1.

Pechmann Reaction

A very valuable method for the synthesis of coumarins is the Pechmann reaction. In general, the coumarins were obtained by condensation of phenols with β-ketoesters, in the presence of acid catalysts (Scheme **2**). The reaction is often referred as Pechmann-Duisberg, when acetoacetic esters and derivatives are used.

This synthetic route has been often used for obtaining natural coumarins and other benzopyrones with biological or industrial interest [9, 96-112]. To mention the interesting synthesis of a 7-*trans*-styrylcoumarin derivative, which was prepared by reacting ethyl 2-methylacetoacetate with 3-*trans*-styrylphenol [113]. Furthermore, fluorescence carriers possessing a coumarin derivative, covalently immobilized on a sensing membrane were also synthesised by this method [114].

Although it is a classic synthetic route, several efforts are still being devoted to improve its performance. With this aim in mind, esculetin and 3-hydroxy-6,7-dimethoxycoumarin were (re)synthesised by the Pechmann reaction, in which several parameters were controlled in



Scheme 2.

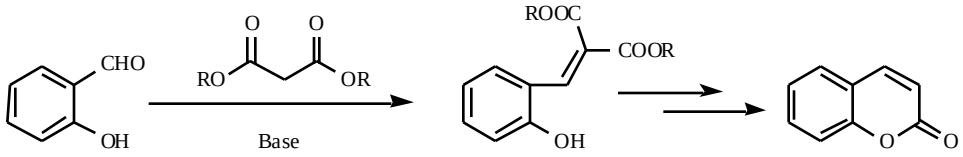
order to improve the yield of the reactions [115]. Montmorillonite clay has been applied, and found to be an effective condensing agent for the synthesis of 7-hydroxy-4-alkylcoumarins [9]. Synthesis of 7-hydroxycoumarins, using Nafion resin/silica nanocomposites and amberlyst 15 as catalysts was also successfully achieved [116]. A variant using microwave irradiation, for the synthesis of 4-substituted 7-aminocoumarins, on a solid support was also published [117].

Knoevenagel Reaction

Condensation of aldehydes with active methylene compounds, in the presence of ammonia or amines, is a reaction known as Knoevenagel. Usually, the reaction is catalysed by weak bases or by suitable combinations of amines and carboxylic or Lewis acids under homogeneous conditions. Moreover, when malonic acid and pyridine, with or without traces of pipiridine, are used the reaction is often named by Doebner modification (Scheme **3**).

A large list of coumarins has been synthesised using this method, for instance, coumarin-3-carboxylic acids, amino- and alkylaminocoumarins, 3-acetylcoumarins, 3-benzoylcoumarins crown ethers and new-bridged heterocycles linked to coumarins [93, 108, 118-129]. The obtention of coumarins by Knoevenagel reaction has also been performed with methylenes activated by heterocycles [130, 131]. Furthermore, C-Glycosyl coumarin derivatives were also synthesised by a one-pot Knoevenagel condensation [132].

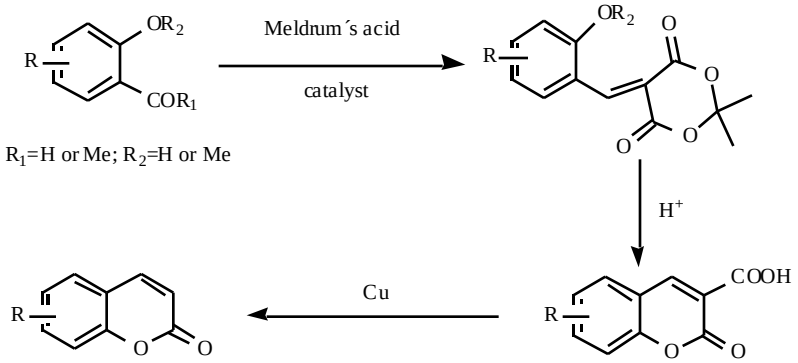
Several modification of the method have been proposed in the literature that were considered of the utmost importance. Isofraxidin (7-hydroxy-6,8-dimethoxycoumarin), a well-known natural coumarin, was obtained through an expedite method using a syringaldehyde derivative and Meldrum´s acid, in the presence of ZnO, that promoted a Knoevenagel type reaction. The 3-carboxylic acid coumarin obtained was further decarboxylated with copper (Scheme **4**) [133]. Another similar process using a solid-phase method also gave substituted 3-carboxycoumarins. These intermediates after thermal decarboxylation led, to the preparation of other coumarins [133, 134]. The obtention of 3-carboxycoumarins was also achieved in a solvent-free one-pot process using Meldrum´s acid and focused microwaves. The synthesis occurs in the presence of environmental catalysts, like kaolinitic clays [135].



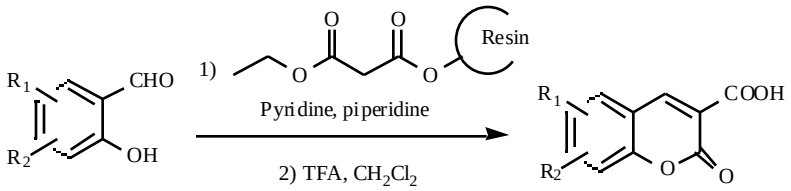
Scheme 3.

The use of heterogeneous catalysts, such as zeolites and clays, for the synthesis of coumarin-3-carboxylic acids is a topic still under investigation [130]. New substituted coumarin-3-carboxylic acids were obtained by a solid phase synthesis, in which ethylmalonate, bound to the Wang resin and *ortho*-hydroxyarylaldehydes were used as starting materials (Scheme **5**) [136].

Moreover, 3,3´-phenylenebiscoumarin derivatives, potential biscoumarin dyes, were obtained by a



Scheme 4.



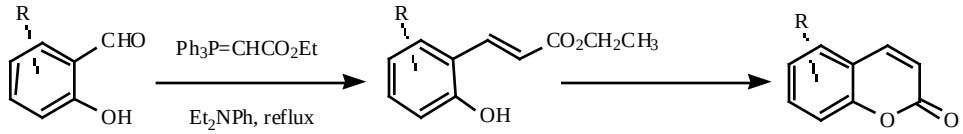
Scheme 5.

Knoevenagel reaction in a biphasic solid/liquid medium, using a strongly basic macroporous resin [137].

Some synthetic procedures were also based on a direct cyclisation of adequate substituted cinnamic acids. These reagents were commercially available, or obtained either by a Knoevenagel condensation or by the cleavage of the pyrone ring of the correspondent coumarin [138]. The synthesis of nitrocoumarins and 3-phenyl- or 6-acylcoumarins has been achieved using this method [139-141]. Moreover, esculetin and its derivatives 5-chloroesculetin and 5-bromoesculetin, were obtained by a biomimetic synthesis from a light-induced cyclisation of *trans*-caffeic acid catalysed by [FeNa(EDTA)] and sulphuric acid [142].

A one-pot three-component tandem Knoevenagel-hetero-Diels-Alder reaction between *in situ*, generated 3-arylidene-2,4-chromanediones and *iso*-propenyl ether, coumarins, like coumurrayin, and other allylcoumarins were synthesised by expedite synthetic strategies in which the Wittig reactions were used [39, 150, 151]. Furthermore, 6-prenylcoumarins and derivatives were obtained starting from 2-prenyloxybenzaldehydes, using a tandem Claisen rearrangement and a Wittig reaction [152]. The same type of reaction was performed by Harayama *et al.* [153], for the synthesis of bromo and methoxycarbonylcoumarins. This type of reaction was conducted in the presence or absence of solvent and was also adequate to obtain methoxy-, hydroxy-, nitro- and 3,4-unsubstituted coumarins [154, 155]. A convenient synthesis of coumarins involving a combination of lithiation and Wittig reaction was also published [156].

Diethyl coumarin-3-phosphonates and diphenyl coumarin-3-phosphinyloxides were obtained in one step, in mild conditions, from acetoxysalicylaldehydes and triethyl



Scheme 6.

derived from (-)-menthol, is described in the literature. From these synthetic approach, new chiral coumarin analogues of the well-known anticoagulants warfarin, coumachlor, and acenocoumaril were obtained [143].

Wittig Reaction

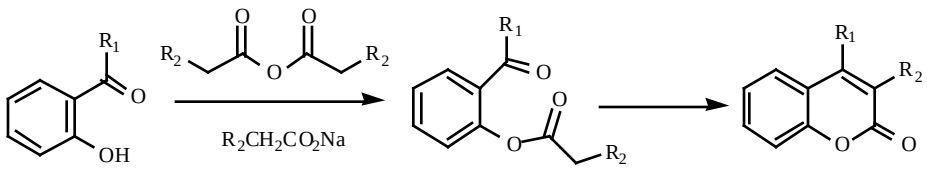
In the Wittig reaction, the alkene formation occurs from carbonyl compounds and phosphonium ylides, proceeding primarily through betaine and/or oxaphosphetane intermediates (Scheme **6**). When the ylide is replaced by a phosphine oxide carbanion or by a phosphonate carbanion, the reaction is referred to Horner or Horner-Emmons-Wadsworth, respectively.

This type of olefination of *ortho*-hydroxycarbonyl aromatic compounds, followed by further lactonisation, is a well-known method for the preparation of coumarin derivatives [9, 108, 122, 144-149]. Natural prenylated phosphonoacetate or diphenyl phosphinyloxide acetate, by the use of a liquid/liquid phase transfer process [157]. The synthesis of (+)-trachylpleuranin-A was performed using Wittig reaction, in which suberosin was obtained from *ortho*-hydroxybenzaldehyde and a phosphorane reagent. A five-step asymmetric synthesis using a sequential [3,3] Claisen-Cope rearrangement, with subsequent Schi asymmetric epoxidation was performed to achieve the goal [51].

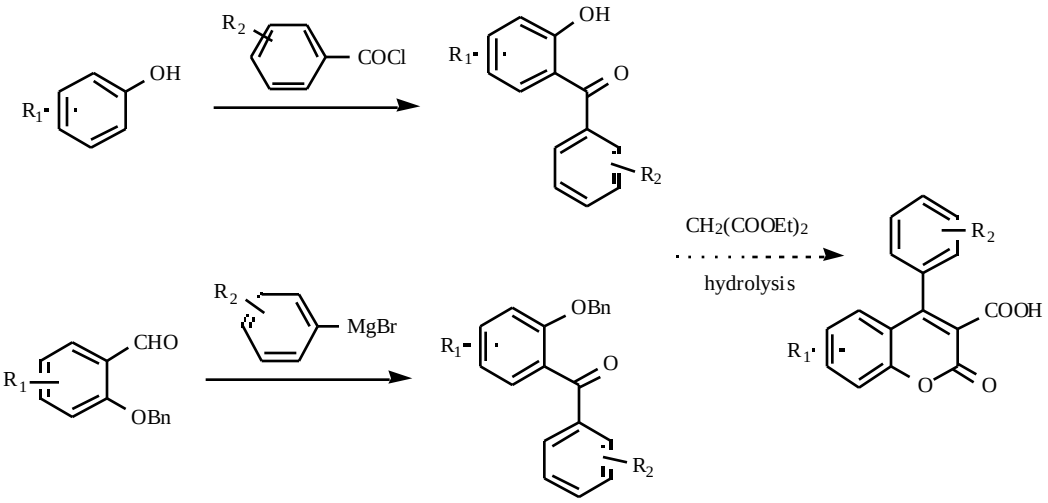
Kostanecki-Robinson Reaction

The formation of coumarins, usually 3- and 4-substituted coumarins, by this reaction occurred by acylation of *ortho*−hydroxyaryl ketones with aliphatic acid anhydrides, followed by cyclisation (Scheme **7**).

By this process, *ortho*-hydroxyketones were converted into phenylcoumarins, 3-cyano-4-methylcoumarins and in



Scheme 7.

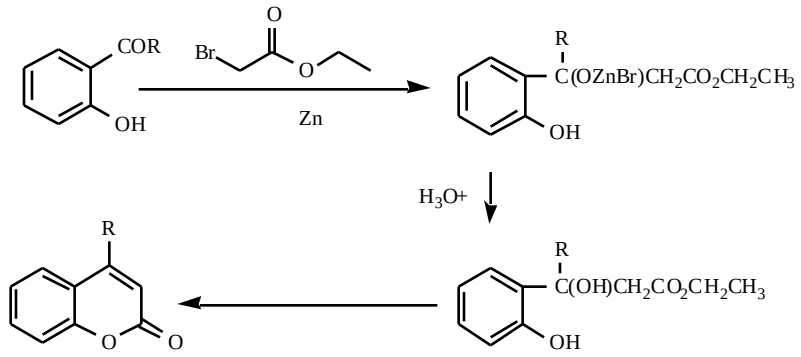


Scheme 8.

other type of coumarin derivatives (Scheme **8**) [96, 158-160]. These coumarins are suitable starting materials for obtaining another type of compounds such as styril and acetyl derivatives, hydrazones, etc.

Reformatsky Reaction

Condensation of aldehydes or ketones with organozinc derivatives of α-halo esters to yield β-hydroxy esters is known as the Reformatsky reaction (Scheme **9**). In appropriate reaction conditions, lactonisation could occur with the formation of coumarins.



Scheme 9.

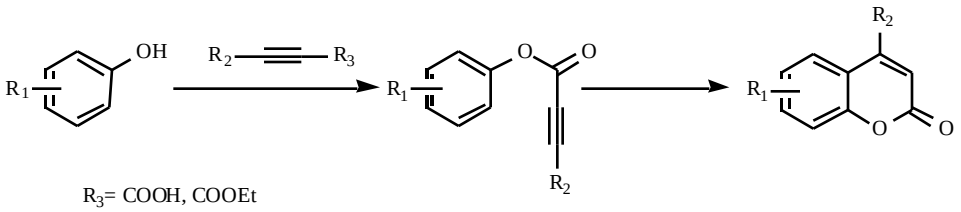
3-Ureido derivatives of 4-phenylcoumarin were synthesised using this method. The synthesis of the 3-coumarincarboxylates intermediates involves the condensation of the adequate 2-hydroxybenzophenones with diethylmalonate, in the presence of base (piperidine or 1,8-diazabicyclo[5.4.0.]undec-7-ene, or KF) [161]. 3-Carboxycoumarins were obtained in excellent yields from the adequate acetophenones, using Meldrum´s acid and natural clays [134, 135].

An original one-pot synthesis of 3-chlorocoumarins and styrenes, by cathodic reduction of trichloroacetyl esters of *ortho*-hydroxyketones and salicylaldehydes in aprotic media is presented by Batanero and Barba [162].

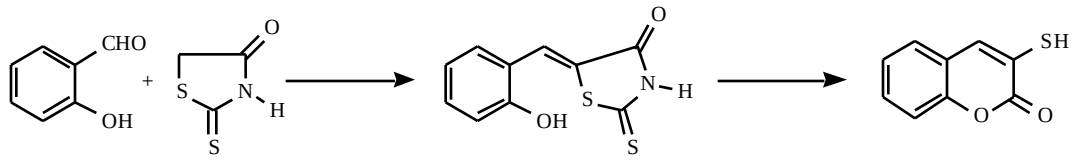
As a case in point, one must refer the synthesis of 4-ciclohexylhydroxycoumarins *via* the Reformatsky reaction [163].

Miscellaneous

Coumarins could also be synthesised by a stereo- and regioselective palladium-catalysed hydroarylation. This reaction occurs between aryl halides and functionalised alkynes, at room temperature, followed by a fast intramolecular reaction (Scheme **10**) [164, 165].



Scheme 10.

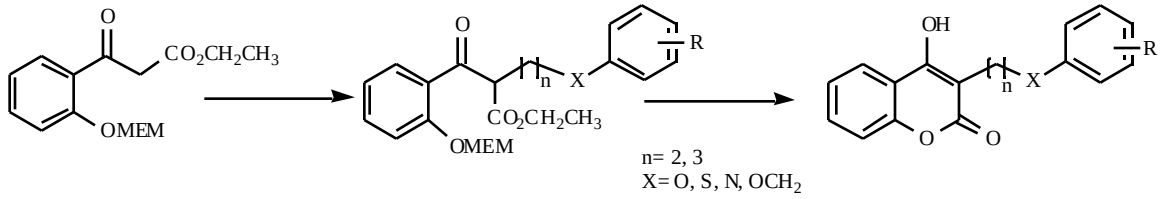


Scheme 11.

7-Hydroxycoumarins have been synthesised either *via* the reaction of 1,3-dihydroxybenzene with ethylacetate (Pechmann reaction) or with propynoic acids, possessing an additional function. These types of acids were able to alkylate the benzene nucleus, under solid acid catalysis [166]. An interesting work appeared in which several important natural 4-substituted coumarins, umckalin methyl ether and ayapin, were synthesised using this route [167].

An interesting palladium-catalysed synthesis of 3- and/or 4-disubstituted coumarins have also been described [168, 169]. In this reaction, phenylacetylene can act as a promotor for the formation of 4-methylcoumarin, or as a reagent for the synthesis of 4-phenylethinyl-3-(1-alkenyl)coumarins [169]. Coumarins could also be generated by a palladium-catalysed carbonylative annulation of terminal alkynes with *ortho*-iodophenols, in the presence of pyridine. The process is effective with terminal alkynes bearing alkyl, aryl, silyl, hydroxyl, ester and cyano substituents [170].

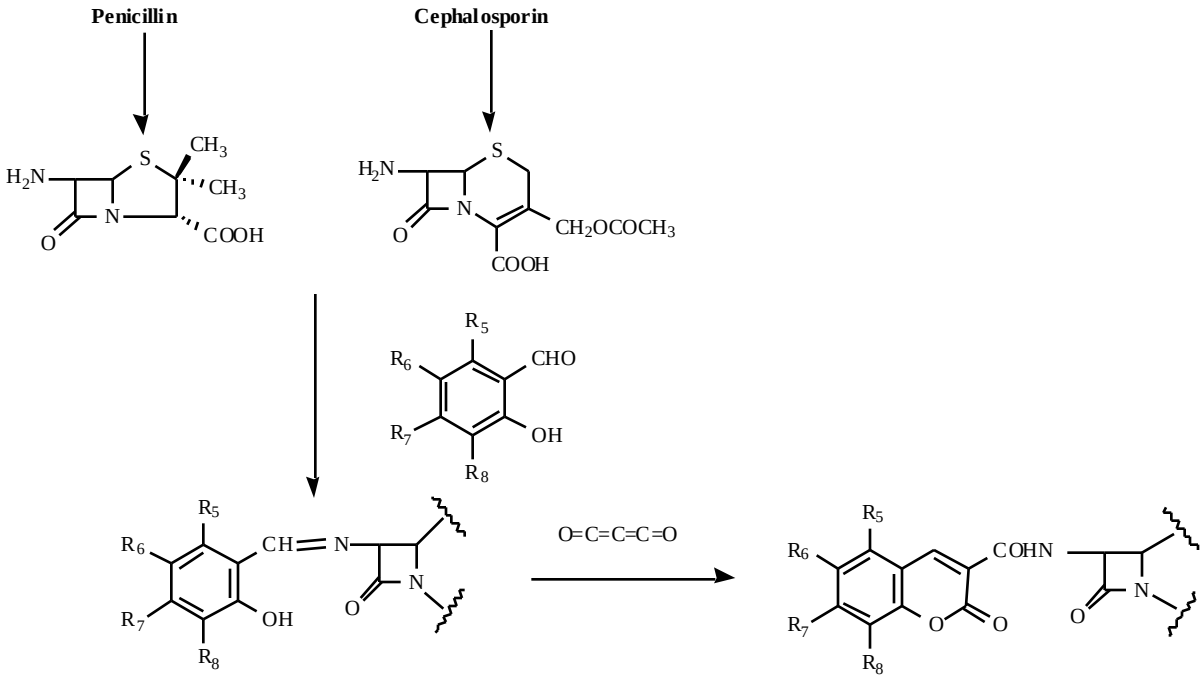
An improved and large-scale synthesis of the natural coumarin scopoletin, considered an important intermediate in the synthesis of other coumarins, was achieved by reacting isovanilin with magnesium monoperoxyphtalate and then with a 3-oxopropionic acid ethylester prepared *in situ*. In contrast to the acidic conditions usually used in the Pechmann reaction, a base is employed as a catalyst of the reaction [171].



Scheme 12.

In addition, an appealing synthetic route for 3-thiocoumarin obtention, by the condensation of salicylaldehyde with rhodamine in a basic medium, was published (Scheme **11**) [172].

In the structure-based design of novel HIV-1 protease inhibitors, several coumarins were synthesised and tested.



Scheme 13.

The general strategy corresponds to the reaction of the suitable nitropropiophenones or propionylbenzonitriles with the anion of dimethyl[(tert-butyloxycarbonyl)methyl]-phosphonate, to obtain the adequated α,β-unsaturated esters, as a mixture of isomers [173]. An analogue methodology was proposed for the synthesis of the same type of coumarins, in which an aromatic hydroxy acid was converted to the imidazolide, after hydroxyl protection that was further elaborated to a ketoester. This pivotal intermediate was deprotonated, and the anion quenched with a variety of substituted alkyl halides, that after deprotection and ring closure gave, in one step, the intended coumarins [174] (Scheme **12**).

3-Substituted-4-hydroxycoumarins, such as isoprenyl-4-hydroxycoumarins, have been obtained by intramolecular Claisen cyclisation [9, 175, 176]. The intramolecular Baylis-Hillman reaction was also found to be a suitable pathway for the synthesis of substituted coumarins [177]. A novel, generally pertinent synthesis of coumarins utilizing ring-closed metathesis is described by Van *et al*. [178]. It involves *O*-allylation of phenols, followed by *ortho*-Claisen rearrangement and subsequent based-induced isomerisation, acylation and finally ring-closing metathesis (RCM) with Grubb´s second generation catalyst. The natural coumarins-ayapin and 5,8-dimethoxycoumarin-were synthesised by this route [178].

A new synthesis of 4-substituted coumarins has been achieved by the Grignard addition of alkyl (or phenyl)magnesium halides to ethyl α-carbethoxycinnamate, in the presence of cuprous bromide. After hydrolysis, decarboxylation and cyclisation 3-substituted-1-indanones were obtained. Baeyer-Villiger oxidation of the later compounds and dehydrogenation of the resulting 3,4-dihydrocoumarins afforded the expected coumarins [179].

Some simple coumarins and semisynthetic penicillins and cephalosporins, substituted with benzo-condensed heterocyclic derivatives appropriately functionalised, were prepared using the reaction of carbon suboxide with Schiff bases (Scheme **13)** [180-182]. Finally, it is important to point out that coumarins could be also obtained from iminocoumarins by an internal rearrangement [183-185].

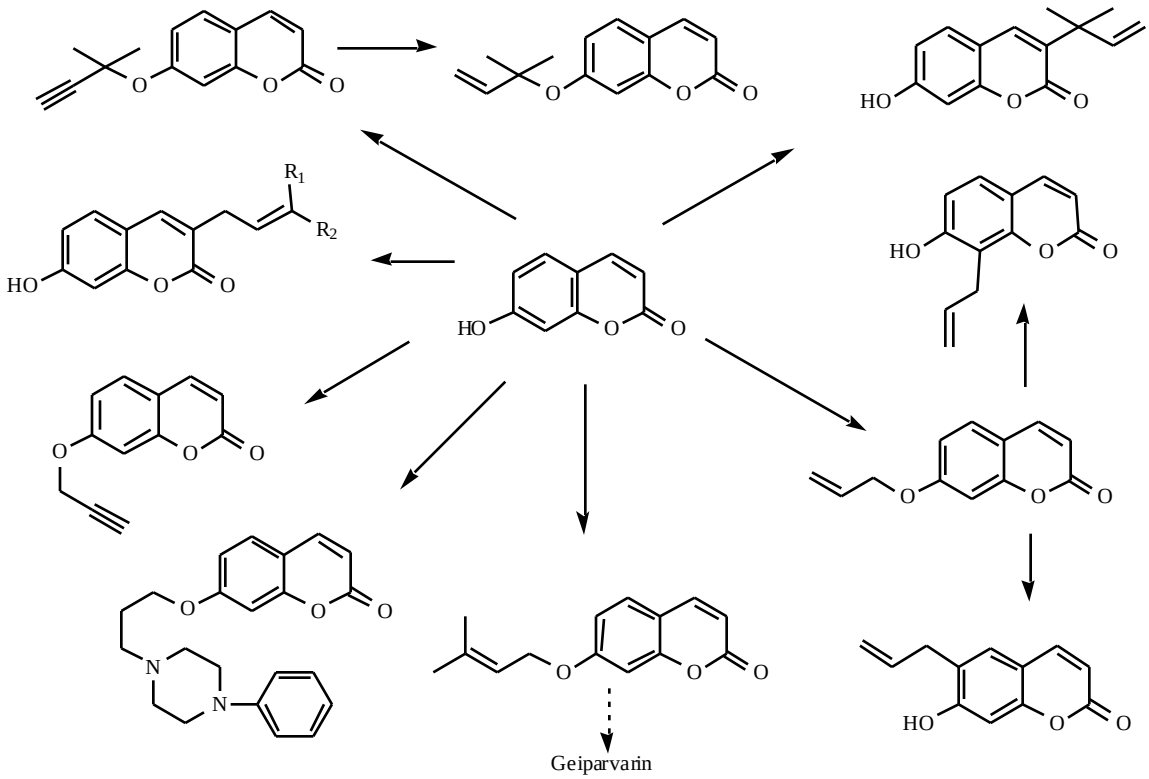
B2 - Synthesis of Simple Coumarins from Coumarins

In recent years, a modification of the general strategy of synthesis of simple coumarins has been observed. This is related, perhaps, to the necessity of rapidly obtaining these type of coumarins, for their immediate application in the area of medicinal chemistry, in structure-activity-relationships studies, or in analytical chemistry. In consequence, in the last years, several compounds of this chemical family were commercially available.

So, it was found important to emphasize in this review on the work done in the synthesis of simple coumarins, which used simple coumarins as starting materials. The new synthetic strategies and the results of a (re) evaluation of other synthetic methods will be mentioned.

From Coumarin

3-Hydroxyscopoletin and 3-hydroxyisoscopoletin were obtained by a direct 3-hydroxylation of a coumarin ring *via*



Scheme 14.

a purely chemical method conducted by a Cu^{2+} - ascorbic acid – O_2 system [186]. Halocoumarin derivatives were also synthesised from coumarin being the starting material, halogenated selectively at C-3 position with a new reagent (copper (II) halide adsorbed on alumin) [187]. Coumarin 3,4-epoxi, an important metabolic marker, was successfully synthesised via the addition of dimethyldioxirane to coumarin [188]. Fluorescent polymerizable metal-chelating lipids and DNA-intercalating coumarin carriers have also been obtained using coumarin as a building block [189, 190].

From Hydroxy/Alkoxycoumarins and Thiocoumarins

Several simple coumarin derivatives were synthesised from 7-hydroxycoumarin, and derivatives, using a plethora of interesting synthetic strategies [89, 113, 191-203]. *N*-acetylglucosamides with coumarin aglycones have also been synthesised from 7-hydroxycoumarins [204]. Isoprenylcoumarins, like 3-(1,1-dimethylallyl)coumarins, could be obtained from coumarin or from 7-hydroxycoumarin, by a sigmatropic rearrangement of allylethers or through a different strategy which involves an Ireland-Claisen rearrangement [205].

As an example, the synthesis of several derivatives of umbelliferone was outlined in Scheme **14**, from which one can examine the diversity of chemical structures that can be prepared from a simple and economic starting material [194, 205-207].

Synthesis of dimeric simple coumarins, prepared from 7-hydroxycoumarin, *via* homonuclear Diels-Alder dimerisation of hydroxybutenyl and pentadienyl coumarins have been performed, with the view to the synthesis of the natural coumarins-phelabin and toddasin [85]. The total synthesis of the natural coumarins: suberosin, demethylsuberosin, ostruthin, balsamiferone and gravelliferone was performed through tandem thermal Claisen-Cope rearrangements of the adequate coumarates, prepared from the correspondent umbelliferone derivatives [208].

It is also important to note that 7-hydroxycoumarin have also been used as a starting material for the synthesis of different coumarin-heptanucleotides, that were important tools in "antisense", "antigene" or "anticode" strategies [209]. In addition, it is imperative to point out an elegant synthetic strategy presented by Olson and Slossberg [210], for the synthesis of coumermycin A1, using a commercial 7,4-dihydroxycoumarin derivative.

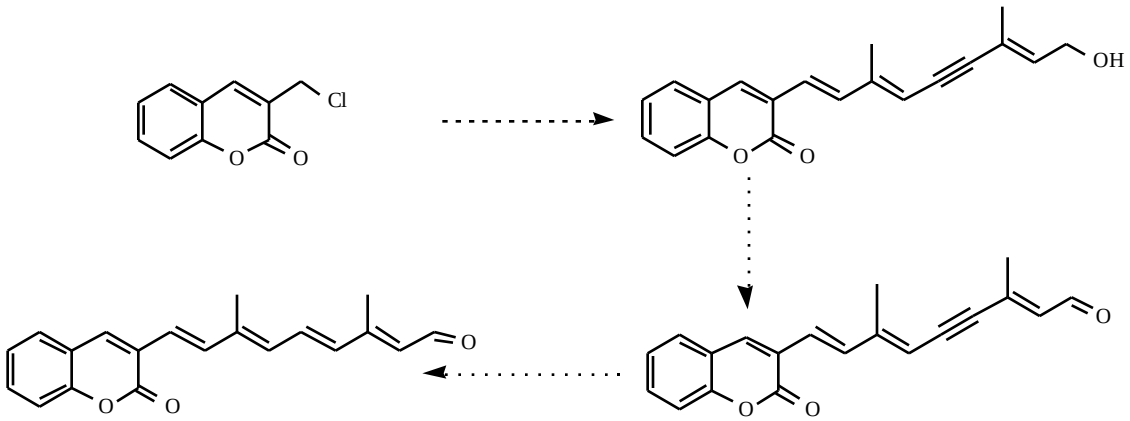
4-Hydroxy- and 6-hydroxycoumarins, have also been important starting materials for the preparation of several simple coumarins derivatives, which are known to possess important biological and pharmacological properties [196, 211-213]. A convenient route for the preparation of 3-formyl-4-hydroxycoumarin, and other type of dissubstituted coumarins, was reported using these types of coumarins as starting materials [214-216]. The reaction of 4-hydroxycoumarin with activated carboxylic acid derivatives or triflic anhydride gave a variety of functionalised coumarin derivatives [9, 217, 218]. To note that the condensation of 4-hydroxycoumarin with several amines afford several important 4-aminocoumarins, *e.g*. ureidomethylenecoumarins, *N*-coumarinylcarbamates and *N*-coumarinylaminoacids [219].

Bis(coumarin) and other adducts have been synthesised from the reaction of 4-hydroxycoumarin with several aliphatic aldehydes [220-224]. Synthesis of some coumarins derivatives with a α−methylidene-γ-butyrolactone moiety from 4-hydroxy- or 7-hydroxycoumarin, via alkylation and Reformatsky-type condensation, has also been published [225-227]. New analogues of the antibiotic novobiocin were synthesised by Schio *et al*. [228], in which arylsubstituents were incorporated into a 4-hydroxycoumarin. The carbon-carbon bond formation occurs *via* a palladium catalysed reaction between p-toluenesulfonate derivatives and aryltrialkylstannanes.

The synthesis of a urinary coumarin metabolite *N*-acetyl-*S*-(3-coumarinyl)-D,L-cysteine methyl ester was elegantly done by Eisenbrand *et al*. [172]. The new synthetic route comprises the reaction of 3-thiocoumarin with *N*-acetyl-3-chloro-D,L-alanine methyl ester.

From Arylcoumarins

3-Phenylcoumarin was used, among other purposes, as a synthon for the synthesis of several 3-heteroarylcoumarins [229].



Scheme 15.

From Halocoumarins and Analogues

Halocoumarins and related compounds have been used for the synthesis of formyl and aryl derivatives of coumarins, among others [187, 230]. The natural coumarins gleinene and gleinadiene have been synthesized using 5,7-dimethoxy-8-iodocoumarin as building block [9]. A number of fluorescent 3-arylcoumarins have been synthesised by the photo-coupling of 3-bromocoumarin with aromatic and heteroaromatic compounds [231]. The synthesis of a coumarin, analogue of retinal, that was used for study of the bacteriorhodopsin chromophore binding site, was done *via* a Wittig olefination of a 3-chloromethylcoumarin (Scheme**15**) [232].

The synthesis of several heteroaromatic coumarinyl derivatives from haloacetyl- and halocoumarins is reported in the literature [233-236]. In order to look for new phosphorous-containing coumarin derivatives, with potential biological activities, the synthesis of new coumarin phosphonates and phosphates was developed. In this context, new phosphonocoumarins were obtained by reacting the appropriate coumarin derivatives, 3-bromobenzyl and 3-bromoacetylcoumarins, with phosphites [237]. Hydroxylated 3-benzylcoumarins have also been obtained by sigmatropic rearrangement of 3-(aryloxymethyl)coumarins, previously prepared from 3-chloromethylcoumarins [238].

From Formylcoumarins

A series of novel coumarin-4-carboxamidoximes, 3-(coumarin-4-yl)-1,2,4-oxadiazole, 3-(coumarin-4-yl)tetrahydroisoxazole, 4-(isoxazolinyl or 1,2,4-oxadiazolyl)coumarins and 3-(coumarin-4-yl)dihydropyrazole derivatives were synthesised from 4-formylcoumarin [103, 239, 240]. The synthesis of novel coumarin derivatives of aminomethanephosphonic acid was performed in a one-step process, by treatment of various substituted 4-formylcoumarins with tris(trimethylsilyl)phosphite, and subsequent solvolysis of the silylated product [241].

From Nitro- and Azidocoumarins

Nitrocoumarins, which have been synthesised using cerium (IV) ammonium nitrate in good yields, are often employed as precursors of aminocoumarins, which in turn are important building blocks for the synthesis of flurophores [141, 242]. Several aminocoumarins were obtained by photoreactions of 4- and 3-azidocoumarins, in the presence of different types of nucleophiles [243].

From Alkylcoumarins

A convenient synthesis of 6-acylcoumarins from 6-alkylcoumarins, was reported [99]. 7-Phenoxymethyl and 7-anilinomethyl coumarins were prepared by bromination of the methyl group of 7-methylcoumarin with *N*-bromosuccinimide [113]. 4-Methylcoumarins were used for the synthesis of coumarin-caged compounds, for instance, as phototriggers of 8-bromo-substituted cyclic nucleotides [244]. Sulfonation of a series of 7-hydroxy-4-methylcoumarins was performed, in order to develop nonsteroidal coumarin sulfamates [104, 245].

From Coumarincarboxylic Acids and Analogues

Carboethoxycoumarins have been used as starting materials to obtain several substituted coumarin derivatives [164, 246-248]. The reaction of 3-acyl and 3-ethoxycarbonylcoumarins with the hydrazide of *p*-nitrophenylacetic acids afforded 3-arylcoumarins [249]. Phosphino- and phosphono substituted-coumarins, besides new 4-coumarin-3-ylcoumarins, were prepared in high yields from 3-acetylcoumarins [246, 250]. Synthetic approaches were also described, based on the coupling of coumarincarboxylic chlorides to the N-1 of iminoalditol, a process that corresponds to the obtention of novel lipophilic derivatives used as β-glucosidase inhibitors [251]. Polyfunctionally substituted heterocoumarins with biological interest were prepared using 3-acetylcoumarins as reagent [252-254]. The obtention of coumarin-substituted penicillins was performed by a semisynthetic process between 7-aminocephalosporanic acid and activated coumarin-3-acyl derivatives [180].

C- BIOLOGICAL ACTIVITY OF SIMPLE COUMARINS AND ANALOGUES

Numerous biological activities have been attributed to simple coumarins and analogues. Among them, antimicrobial, antiviral, anticancer, enzyme inhibition, anti-inflammatory, antioxidant, anticoagulant and central nervous system activities will be discussed in particular.

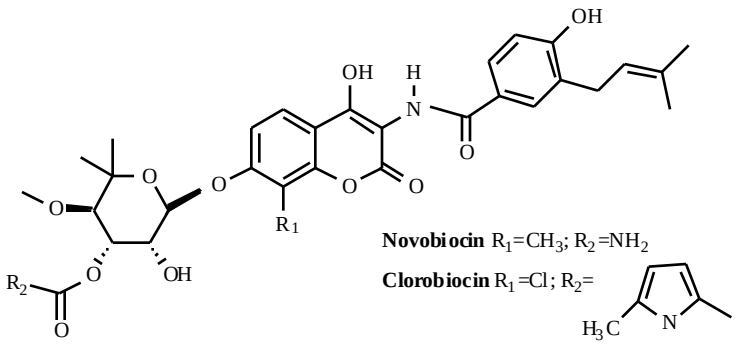


Fig. (3). Structures of natural coumarin antibiotics.

Because of its importance antiviral activity will be discussed separately. Further, the prodrug strategy using coumarins and other applications of simple coumarins will be highlighted.

Antimicrobial and Molluscicidal

Novobiocin and clorobiocin (Fig. **3**) are coumarin antibiotics of natural origin, which are inhibitors of DNA girase, and have a broad spectrum towards *Gram*-positive bacteria, including methicilin resistant strains of *staphylococci* species [228, 255].

Due to some limitations of these compounds, particularly with regard to solubility, toxicity and development of resistance, a novel series of coumarin analogues has been synthesised. Over the past years, several efforts were directed towards the design of effective, orally bioavailable coumarin antibiotic inhibitors of bacterial DNA gyrase [256]. From these studies, a series of coumarin congeners has appeared that bear the coumarin part of the molecule and isosteres, like carboxyl or basic amino groups, in order to improve the antibacterial activity [93, 108, 217, 256]. Molecular modelling has been used in conjunction with crystallographic and biological data, in an attempt to design compounds that mimic the structure and activity of the coumarin antibiotic novobiocin, possessing however, a better profile [257]. It is also important to mention other excellent works published in the area that is an intrinsic part of this network [258, 259]. From this research it was found, for instance, that novobiocin analogues, bearing different amino groups, displayed excellent inhibitory activity against DNA gyrase supercoiling [260]; the introduction of dialkyl substituents at the 5,5´-position of novobiose leads to coumarin analogues with improved *in vitro* and *in vivo* antibacterial activity [261]; incorporation of alkyl, alkylamino and aryl substituents afford new analogues of coumarin-containing antibiotics with interesting activities [109, 228]. A series of novobiocin-like coumarincarboxylic acids has also been synthesised bearing L-rhamnosyl moiety, instead of L-novobiose, as the sugar portion of the molecule. It was found that when alkyl side-chains at C-5 of coumarin were introduced, an enhancement of the *in vitro* antibacterial properties was observed [108].

Some coumarins of natural and synthetic origin were screened for their antimicrobial activity [25, 69, 85, 124, 180, 181, 192, 236, 247, 262-266]. Several coumarin derivatives were also tested for their antifungal activity [195, 253]. A free 6-OH on the coumarin nucleus was found to be important for its antifungal activity and, curiously, a free 7-OH on the same nucleus, was important for antibacterial activity [195].

A preliminary exploration of coumarin analogues as novel antimicrobial agents, was carried out in order to determine the basic features of the structure, which are responsible for the biological activity. The substitutent ester or carboxylic acid on the coumarin ring was found to be important for inhibitory activity against *Gram*-positive and *Gram*-negative bacteria. The presence of phenolic hydroxyl groups and/or carboxylic acid was found necessary for enhanced activity against *Helicobacter pylori* [267].

The coumarins escopoletin, osthol and phebalosin, isolated from Rutales species were assayed for the inhibition of the glycolytic enzyme *T. cruzi* GAPDH [268]. Recently, a 3D QSAR study was also performed which gave important information on the subject [269]. From the stem bark of *Exostema mexicanum* (Rubiaceae), which is used in folk medicine as a quinine substitute for malaria treatment, two phenylcoumarins and other natural coumarins were isolated, and their antiplasmodial activity evaluated [63, 270]. Recently, a novel antifilarial lead compound (7-*O*-[4-methylpiperazine-1-(2-acetyl)]coumarin was proposed by Tripathi *et al*. [271].

References for the molluscicidal activity of some 4-phenylcoumarin derivatives have already been described [63, 272]. This activity was also found to be ascribed to coumarins from *Ethulia conyzoides* and to dicoumarol [273].

Acaricidal activity of plant extracts and coumarins was also investigated, from SAR studies of bioactive compounds being performed for the purpose [274].

Antiviral

The antiviral activity of simple coumarins focuses essentially on the inhibition of HIV-1 protease (HIV-PR) and HIV-1 integrase. The recent advances in the development of coumarin derivatives as potent anti-HIV agents, concerning the discovery, structural modification and structure-activity relationships studies, have been a topic of different reviews or updated articles [275-278]. With this goal, the inhibitory activity of various coumarins towards HIV-1 protease has been investigated, and classified as a class of drugs of interest as antiviral agents [173, 174, 279]. From this, phenprocoumon, warfarin and substituted 4-hydroxy-2-pyrone derivatives are, actually, referred to as first generation of HIV-PR inhibitors [280]. It was also found that certain coumarin dimers, particularly those containing hydrophobic moieties on the linker, display potent inhibitory activity against HIV-1 integrase [222, 224, 281]. The identification of the HIV-1 integrase pharmacophore has been done by molecular modelling studies, and validated using a 3D database [159].

Plant-derived leading compounds for chemotherapy of human immunodeficiency virus (HIV) infection have also been described [29, 71, 282].

In addition, some coumarin derivatives were tested for their activity against Herpes simplex virus (HSV). From these studies, 5,7,4´-trihydroxy-4-styrylcoumarin was found to exhibit a significant antiviral activity [67, 283]. It is worthwhile to note that the natural collinin, greveal, has significant anti-HBV DNA replication activity [32].

Anticancer

Among the coumarins screened for anticancer activity, geiparvarin (Fig. **4**) was found to be the most representative. Geiparvarin is a natural coumarin based structure, isolated from the leaves of *Geijera parviflora* Lindl, which is known for its significant *in vitro* cytostatic activity [284].

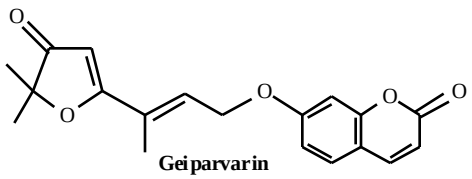


Fig. (4). Structure of the natural coumarin geiparvarin.

The compound is constituted of three units: a furan-3(*2H*), an unsaturated alkenyloxysubstituent and a coumarin moiety. The first mentioned unit is essential for the activity as it could work as an alkylating agent of bionucleophiles, through a Michael-type reaction. In that way, geiparvarin became a challenging lead compound, for the synthesis of analogues that could also be promising candidates for anticancer activity. Thus, geiparvarin analogues were synthesised, in order to determine the structural features (SAR) that account for its *in vitro* cytostatic activity [196, 285, 286]. Among these, 7-[(2,3,4,5-tetrahydro-4-methylidene-5-oxo-2-phenylfuran-2-yl)methoxy]-2*H*-1-benzopyran-2-one was the most potent, exhibiting a good selective and inhibitory activity [196].

Moreover, the inhibitory effects of several simple coumarins, synthesized or isolated from plants, on cytotoxic activity have also been reported [26, 72, 74, 102, 287-300].

The *in vitro* effects of 4-hydroxycoumarin were studied, employing melanoma and the non-malignant fibroblastic cell lines. It was proposed that the compound might be a useful adjuvant for melanoma therapy [301]. Hydroxycoumarins with a nitro group in the aromatic ring have been shown to be selective anti-proliferative agents that mediate apoptosis in renal carcinoma cells, through modulation of mitogen-activated protein kinases [290, 302]. It is important to note that the chemopreventive effects of several natural coumarins have been evaluated [102, 303].

The mutagenicity of simple coumarins has also been studied [33, 304]. It was found that the antimutagenicity of this class of compounds was linked to the presence of polar functions at carbons 3-, 4-, and 7-.

Finally, extensive programs of chemical modifications, aimed at establishing structure-activity relationships and identifying new candidates for pre-clinical and clinical evaluations have been carried out along the years [196, 260]. Moreover, it is important to stress that other promising anticancer agents, structurally based on coumarin, have already been proposed. This type of compounds being cytochrome P450 1B inhibitors could act, for instance, by enzyme inhibition [305].

Synthetic routes to develop nonsteroidal sulfamate-based active site-directed inhibitors of the enzyme steroid sulfatase, a topical target in the treatment of postmenopausal women with hormone-dependent breast cancer, have been described [104, 245]. In a structure-activity relationship (SAR) study, 4-methylcoumarin 7-*O*-sulfamate (COUMATE) and its derivatives were synthesised. From this study, it was found that 3,4-dimethylcoumarin 3-*O*-sulfamate was more potent than COUMATE as an estrone sulfate (E1-STS) inhibitor, in intact MCF-7 cells. A pharmacophore for active site-directed sulfatase inhibition was also proposed in the literature [104]. Further, SAR studies have been carried out to acquire information regarding the active site of ES (Estrone Sulfatase) [95, 306, 307]. Furthermore, an excellent review of steroid sulphatase inhibitors for breast cancer therapy has been published recently [308].

The inhibition of carbonic anhydrase II by steroidal and non-steroidal sulphamates was described, from docking studies being performed with selected compounds [309].

Enzyme Inhibition

Some natural and synthetic coumarins have been found to be cholinesterase inhibitors, which are considered to be a promising approach for the treatment of Alzheimer´s disease, and for possible therapeutic applications in the treatment of Parkinsons´s disease [36, 54, 310].

A series of synthetic coumarin derivatives was evaluated as inhibitors of monoaminooxigenase (MAO). Ether derivatives demonstrate MAO-B selectivity, and sulfonic ester derivatives demonstrate MAO-A selectivity [113, 311]. A QSAR study of coumarin derivatives acting on MAO B was done, revealing the importance of lipophilic interactions in modulating the inhibition and excluding any dependence on electronic properties [113]. In addition, a number of natural coumarins possessing MAO inhibitory activities have also been described [60, 73, 312].

Steroid 5α-reductase type I inhibitory activities of a series of umbelliferone derivatives were evaluated in cell culture systems [207]. A SAR study was performed in order to elucidate the essential structural requirements for the activity. A natural prenylated coumarin, osthenol was also revealed to be a new potential inhibitor of 5α-reductase type I in LNCaP cells [37].

Studies on the mechanism of biochemical action of substituted benzopyran-2-ones have been done. Coumarins bearing one acetoxy group, at the C-3 or C-4 position and 4-methylcoumarins bearing a single acetoxy group, at the C-5, C-6 or C-7 were synthesised, and the effects on rat liver microsomal protein transacetylase were examined [313]. In another study, 7-acetoxy-4-methylcoumarin proved to be a superior substrate in comparison to the 5-acetoxy-4-methylcoumarin. The best activity was exhibited by 7,8-diacetoxy-4-methylcoumarin [314].

A series of esters and amides of coumarin derivatives were synthesised and evaluated for their inhibitory activity towards bovine α-chymotrypsin, as potential inhibitors of serine proteases [121, 125]. A pharmacophore, associated to the inhibition of α-chymotrypsin has been built, based on the structural and electronic characterization of a series of coumarin derivatives [315]. An interesting investigation of the inhibition mechanism of coumarins on chymotrypsin by mass spectrometry was also reported [316].

Moreover, other enzyme targets were chosen for testing coumarins, such as cyclic AMP phosphodiesterases, β-glucosidase and β-glucuronidase, 5-lipoxygenase and protein kinases [183, 251, 317-320].

Several coumarins were tested for their xanthine oxidase inhibitory activity. It was found by a SAR study that the

unsubstituted coumarin was not active and that at least one hydroxyl group was required for the activity [321].

Antioxidant

Sixteen plant-derived and various synthetic simple coumarins with various hydroxyl groups and other substituents were tested for their antioxidant activity namely, in relation to the ability to inhibit lipid peroxidation and to scavenge reactive species, for instance, hydroxyl and superoxide radicals, and hypochlorous acid [52, 240, 322-324]. Several coumarins have shown beneficial biochemical profiles in relation to pathophysiological processes dependent upon reactive oxygen species [107, 323-327]. Classic and three-dimensional (3-D)QSAR analyses of radical scavengers, structurally based on coumarin, have also been performed [200].

The photodynamic damage prevention done by some hydroxycoumarins was evaluated, and compared with that of *p*-aminobenzoic acid (PABA) as a model sun screen. The activity could be related to their antioxidant action which could minimize skin photoaging [328].

Anti-Inflammatory

It has been found that several coumarins isolated from plants or of synthetic origin possess significant anti-inflammatory and/or analgesic activities [34, 239, 240, 329-335]. In a QSAR study for lead optimisation in the design of coumarins as potent non-steroidal anti-inflammatory agents, it was found that substituents in the coumarin positions C4- and C7- contributed to the high activity [336]. New diaminoether coumarinic derivatives with anti-inflammatory and antioxidant activity were also synthesised. Lipophilicity and ionisation were found to be important physicochemical parameters which correlated with the biological activity [336].

Anticoagulant and Cardiovascular

Warfarin (Fig. **5**) is considered, even today, the dominant coumarin anticoagulant, owing to its excellent potency and good pharmacokinetic profile. While its market form is the racemic sodium salt, the anticoagulant activity of the (*S*)-(-) enantiomer is known to be six times higher than that of the (+) enantiomer [143]. Nevertheless, 4-hydroxycoumarin derivatives have been proved to possess higher anticoagulant effect than warfarin [221]. In order to check if coumarin anticoagulants are reversibly bound to human serum albumin, a study on the structure-affinity was prepared [337]. A 3-D QSAR model was also developed to explain the interactions modulating this activity [338].

In the search for platelet aggregation inhibitors, several coumarins, either of natural or synthetic origin have been tested [27, 53, 59, 225-227, 318, 339, 340].

A number of coumarin compounds possessing anticoagulant activity, like their prototype dicoumarol (Fig. **5**), have been synthesised as potential drugs for the management of myocardial infarction [143].

It is well-known that several coumarin derivatives have been shown to possess cardiovascular properties. Carbochromem (3-diethyl-aminoethoxycarbonylmethoxy-4-methylcoumarin), is a specific potent coronary vasodilator, which has been used for many years in the treatment of *angina pectoris*. Although the mechanism of action still remains unknown it has been reported that carbochromen coronary effects could be mediated by an increased release of prostaglandins. Thus, it was found useful to perform the synthesis of several coumarin analogues, structurally related to carbochromen, suitable for SAR studies on the above mentioned activity [112].

Structure-antiangiogenic activity relationships based on the inhibitor 4-senecioyloxymethyl-6,7-dimethoxycoumarin, isolated from *Crinum latifolium*, have been done [111]. It was found that a 6,7-dimethoxy moiety is an important chemical feature for the mentioned bioactivity.

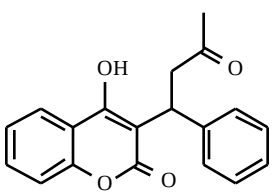
Novel 3-ureido derivatives of 4-phenylcoumarin were synthesised and evaluated for acyl-CoA (cholesterol acyltransferase) inhibitory activity. Some of these compounds were found to be useful as hypocholesterolemic and antiatherosclerotic agents [161]. Coumarin derivatives of heterocyclic compounds were designed and synthesised, and their preliminary screening as lipid-lowering agents was performed as a promising approach in the treatment of cardiovascular diseases [129].

To mention that the methoxy derivative osthole, isolated from *Cnidium monnieri*, was reported to possess vasorelaxing effect on rabbit corpus cavernosum [341].

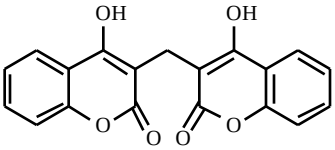
Cloricromene conjugates with short-chain alkylaminoacids were synthesised as lipophilic amide conjugates, in order to improve the activity of the lead compound and obtain more stable compounds in the blood stream [342].

Central Nervous System (CNS)

Phenylpiperazine coumarin derivatives were synthesised, and the affinities of these compounds for



Warfarin



Dicoumarol

Fig. (5). Structures of the lead compounds warfarin and dicoumarol.

dopaminergic (D_{2A}, D_3) and serotonergic ($5HT_{1A}$) receptors were evaluated. The results obtained confirm the importance of the *N*-arylpiperazine fragment in the modulation of this type of activity [194]. SAR studies on antipsychotic compounds were also performed, in which several 4-ciclohexylhydroxycoumarins were engaged [343, 344].

The potential neuroprotective effects of the natural coumarin-fraxetin on the signalling pathways, using a neuronal cell model of Parkinson´s disease were also studied [345].

Miscellaneous

Hepatoprotective activity of coumarins from *Morus alba* L. (Moraceae) have been studied. Further, the mechanism of coumarin-induced hepatotoxicity was investigated, using different coumarin substrates [346]. Osthol, a natural coumarin isolated from dried fruits of *Cnidium monnieri* (Umbelliferae), reveals to possess anti-allergic activity [347]. Some simple coumarins show the capacity to modulate agonist-evoked calcium responses in thyroid FRTL-5 cells, a non-excitable cell line, and to stimulate endogenous amino acid, released from synaptosomes [78, 348].

The role of some simple coumarins, particularly butenyl and butadienyl ethers of umbelliferone, in the defence response of plant cells has also been reported [9, 349].

Prodrug Strategy

Prodrug strategy represents a promising approach for modification of the undesirable physico-chemical properties of some drugs, allowing for their delivery to the desired site of action [350, 351]. Simple coumarins have also been applied in this field. As examples, one can refer to the coumarin-based prodrug systems that have been developed for the preparation of esterase-sensitive drugs containing amines, peptides, and peptidomimetics [352-358]. As expected, the drug release rates from these prodrug systems were found to be dependent on the structural features of the drug.

Other Applications

The fluorescence derivatisation is one of the most sensitive detection techniques for the trace analysis of environmental and biologically relevant molecules. The fluorescent properties, which are intrinsic to some coumarins, make them useful compounds for this type of application. It is not surprising that a lot of work has been reported on this topic, in which different coumarins, such as amino or hydroxycoumarins have been used as fluorescent derivatising reagents [120, 122, 359-364]. The synthesis of fluoroionophores, consisting of coumarins fused to crown ethers was performed, allowing for the development of a new class of photoactive macrocycles. This type of compounds could be used as cation dependent fluorescent signalling systems or triplet sensitisers [119]. Fluorescent spectroscopic studies of novel coumarins have been done, in order to develop new fluorescent probes, applied either in water or in micelles [137, 282, 365-372]. Nifedipine analogues with a coumarin fluorophore linked at different positions of the dihydropyridine ring were also synthesised as potential fluorophore-linked calcium channel antagonists [123]. Also, a calcium indicator structurally based on a coumarin structure was synthesised, which may be useful for the measurement of calcium concentrations in the endoplasmic reticulum of living cells [373]. Some detectors having coumarin as fluorophore have also been described [374-375]. In addition, 7-alkoxycoumarins are widely used as specific indicators of activity of cytochrome P450 isozymes. These compounds are required for use in characterizing the activity of mutant enzymes [376]. Liposomes incorporating fluorescent metal-chelating lipids, which were prepared with a coumarin moiety, find applications as membrane probes in molecular recognition of peptides, 2D protein, recrystallisation, protein targeting and biological sensing [189].

CONCLUDING REMARKS

Coumarins are a group of heterocyclic compounds currently being of great interest. For this reason, the isolation and the structural characterisation of novel derivatives, together with the development of new synthetic methods and biological properties, are topics of growing interest for a great number of research groups. It is therefore, of utmost importance that the study of this topic, and the development of new synthetic strategies, is one of the areas of most up-to-date research and primordial. It is even more important to stress that the metabolic studies related to the biotransformation of coumarin and derivatives, that have already been initiated, are actually an emergent area of research [172, 377-379].

Efforts were made to review the state of the art in the area of simple coumarins and analogues, mainly as regards to what has been done during the last twelve years. Not surprisingly, many questions arise from the literature that remain to be answered. Efforts were also made to search the literature published during the intended period, although there were several difficulties in finding some references or to place the subject owing to the lack of clarity of the topics. Apologises to the authors, who were not for one reason or another, mentioned in this work.

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