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Review on canthin-6-one alkaloids: distribution, chemical aspects and biological activities

Lea Farouil^a, Muriel Sylvestre^a, Alain Fournet^b, Gerardo Cebrián-Torrejón^{a,*}

^a Laboratoire COVACHIM-M2E EA 3592, Université des Antilles, Campus de Fouillole, UFR SEN, Département de Chimie, B.P. 250, 97157 Pointe-à-Pitre Cedex

^b IRD, Laboratoire de Pharmacognosie, Faculté de Pharmacie, Université Paris-Sud, rue J.-B. Clément, 92296 Châtenay-Malabry CEDEX, France.

Corresponding author:

Dr. Cebrián-Torrejón :

Gerardo.cebrian@univ.antilles.fr

Laboratoire COVACHIM-M2E EA 3592, Université des Antilles, 97157 Pointe-à-Pitre Cedex, France.

Tel :

ABSTRACT

Canthin-6-one alkaloids have been a topic of research in many phytochemical and pharmacological laboratories because they are a structurally unique and biologically intriguing family. This review summarizes the diversity, biogenesis, chemistry and bioactivity of canthin-6-ones.

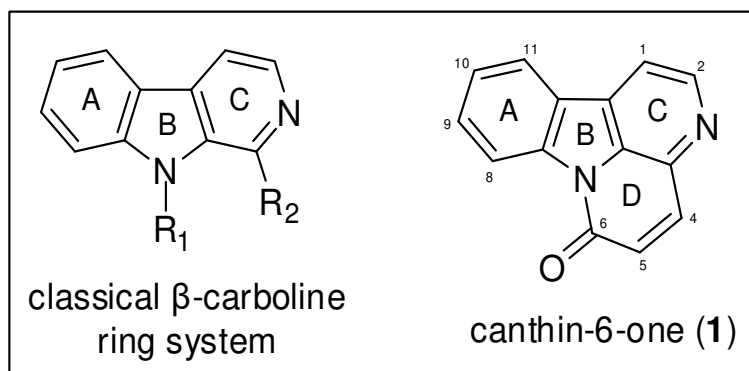
Keywords: canthin-6-one; β -carboline; alkaloids; synthesis; biological activity

1. Introduction

The canthin-6-one (or canthinone) alkaloids are a subclass of β -carboline alkaloids with an additional D-ring (Figure 1). Canthin-6-one (**1**) was first isolated in 1952 by Haynes [1] from the Australian plant species *Pentaceras australis* (F.Muell.) Benth. (Rutaceae). Since then, more than eighty members of this class of alkaloids have been reported from several plants primarily of the Rutaceae and Simaroubaceae families, but also from Malvaceae, Amaranthaceae, Caryophyllaceae,

30 Zygophyllaceae and recently from fungi (*e.g.* *Boletus curtisii* Berk.). Several of these alkaloids have
 31 been bioassayed and show interesting pharmacological activities [2].

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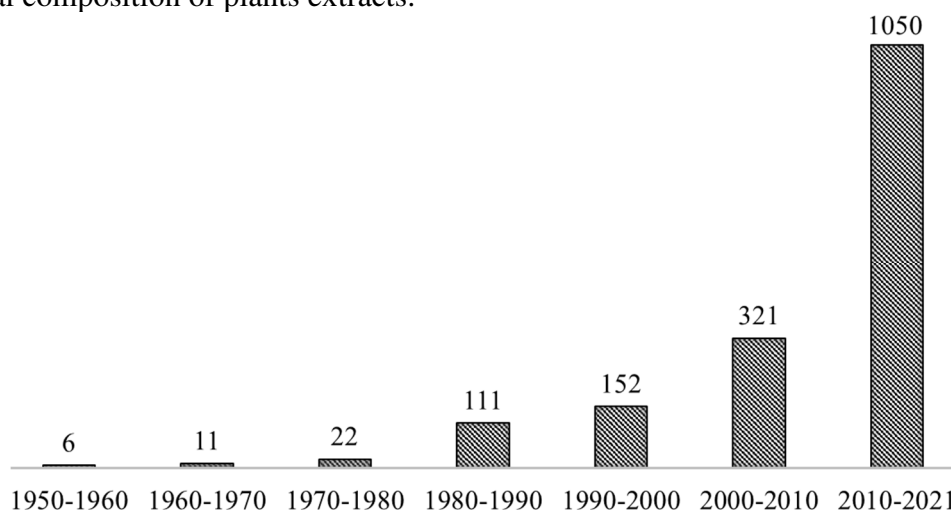


34
 35 **Figure 1.** Canthin-6-one structure.

36

37 The biosynthesis of canthinone-type alkaloids was demonstrated by the Guicciardi [3] group by
 38 feeding experiments with cell cultures of *Ailanthus altissima* (Mill.) Swingle (Simaroubaceae).
 39 Synthetically speaking, there is a paucity of strategies for the synthesis of the basic canthinone
 40 scaffold; some of them present a biomimetic basis, starting from the natural precursors, tryptophan (2)
 41 or tryptamine (3) or derivatives and some others showing a purely synthetic approach.

42 A continuous increase in the number of scientific publications on “canthinones” has appeared over the
 43 course of the last 70 years (Figure 2) showing an undeniable interest of these compounds [4]. Such
 44 reports included numerous biological studies that have confirmed the potential value of these natural
 45 products. The latest review article concerning canthin-6-one alkaloids was published by Dai *et al.*
 46 providing a broad overview of canthin-6-ones. The authors describe the biosynthetic assembly lines,
 47 different synthetic pathway and biological activities of this class of alkaloids that have been published
 48 from 1952 to 2015 [5]. In most publications, canthinones alkaloids have been identified by classical
 49 technics as NMR and Mass spectroscopies. However, over the last few years, other ways of
 50 characterization have been used such as high-performance liquid chromatography (HPLC) with UV
 51 detection [6,7] or innovative application of the voltammetry of microparticles [8] to identify the
 52 phytochemical composition of plants extracts.



53

54

55 **Figure 2.** Occurrence of the number of publications related to “canthin-6-one” from 1952 to 2021

56 (Source: Scholar (28/10/2021)).

57

58 All related available information on canthin-6-one alkaloids and its distribution, chemical aspects and

59 biological activities was collected via electronic search (using Google Scholar, Pubmed, Scopus and

60 Web of Science) without time limit.

61

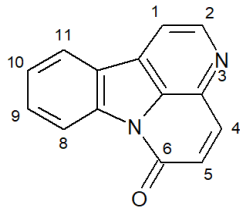
62 **2. Natural occurrence of canthin-6-one alkaloids**

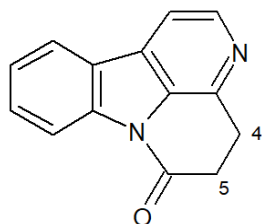
63 The canthinones are a small group of alkaloids; around ninety canthin-6-one alkaloids have

64 been isolated from more than fifty species. Table 1 illustrates the natural distribution and the diversity

65 of natural canthin-6-one alkaloids and classifies the canthin-6-one alkaloids taxonomically.

Table 1. Canthin-6-one alkaloids and their natural occurrence.

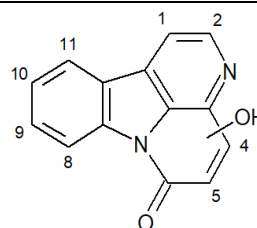
<u>I- Non-substituted canthin-6-ones</u>	
 <p>Canthin-6-one</p>	<ul style="list-style-type: none"> ▪ Rutaceae : <i>Fagara mayu</i>, <i>Fagara viridis</i>, <i>Zanthoxylum belizense</i>, <i>Zanthoxylum coreanum</i>, <i>Zanthoxylum flavum</i>, <i>Zanthoxylum suberosum</i> [9], <i>Fagara zanthoxyloides</i>, <i>Pentaceras australis</i>, <i>Zanthoxylum dipetalum</i>, <i>Zanthoxylum elephantiasis</i> [10,11], <i>Zanthoxylum ovalifolium</i> [9,12], <i>Zanthoxylum rugosum</i> [13], <i>Zanthoxylum chiloperone</i> [14], <i>Zanthoxylum usambarensis</i> [15], <i>Zanthoxylum integrifolium</i> [16], <i>Zanthoxylum budrunga</i> [17], <i>Zanthoxylum dimorphophyllum</i> [18], <i>Phellodendron amurense</i> [19,20], <i>Zanthoxylum paracanthum</i> [21,22]. ▪ Simaroubaceae : <i>Ailanthus altissima</i>, <i>Ailanthus excelsa</i> [23], <i>Picrasma crenata</i>, <i>Picrasma excelsa</i>, <i>Picrasma javanica</i>, <i>Simaba multiflora</i>, <i>Quassia africana</i> [9], <i>Brucea mollis</i> [24], <i>Brucea javanica</i> [25], <i>Pricrolemma granatensis</i> [26], <i>Eurycoma longifolia</i> [27-29], <i>Simarouba glauca</i> [30,31], <i>Eurycoma harmandiana</i> [32], <i>Simaba ferruginea</i> [33], <i>Quassia borneensis</i> [34], <i>Brucea antidysenterica</i> [23,35,36], <i>Soulamea pancheri</i> [23], <i>Picrasma quassioides</i> [37], <i>Hannoa klaineana</i>, <i>Odyendea gabonensis</i> [9] ▪ Malvaceae : <i>Hibiscus syriacus</i> [9] ▪ Amaranthaceae : <i>Aerva lanata</i> [38,39] ▪ Liliaceae : <i>Allium neapolitanum</i> [40] ▪ Boletineae : <i>Boletus curtisii</i> [41]



4,5-dihydrocanthin-6-one

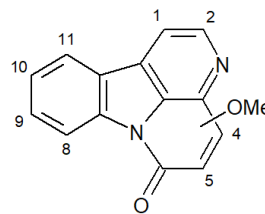
- **Rutaceae** : *Zanthoxylum dimorphophyllum* [18]
- **Simaroubaceae** : *Ailanthus altissima* [3,9]

II- Canthin-6-ones mono-substituted by a heteroatom (O or S)



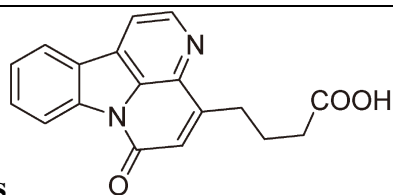
Mono-hydroxylated canthin-6-ones

1-hydroxy-canthin-6-one	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Ailanthus altissima</i>, <i>Ailanthus giraldii</i> [9,42], <i>Eurycoma longifolia</i> [27,29,43]
2-hydroxy-canthin-6-one	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Quassia kerstingii</i> [9], <i>Simarouba glauca</i> [31], <i>Simaba bahiensis</i> [44], <i>Ailanthus altissima</i> [3]
4-hydroxy-canthin-6-one	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Ailanthus altissima</i> [3,9]
5-hydroxy-canthin-6-one	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Simarouba amara</i> [9,45], <i>Brucea mollis</i> [24], <i>Ailanthus altissima</i> [9]
8-hydroxy-canthin-6-one	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Ailanthus excels</i> [23], <i>Odyndea gabonensis</i>, <i>Pierreodendron kerstingii</i>, <i>Simaba multiflora</i> [9], <i>Picrasma quassioides</i> [46,47]
9-hydroxy-canthin-6-one	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Eurycoma longifolia</i> [27,43,48,49], <i>Eurycoma harmandiana</i> [32], <i>Picrolemma granatensis</i> [26], <i>Simarouba berteriana</i> [50]
10-hydroxy-canthin-6-one	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Eurycoma longifolia</i>, <i>Simaba multiflora</i> [9] ▪ Amaranthaceae : <i>Aerva lanata</i> [38,39]
11-hydroxy-canthin-6-one	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Amaroria soulameoides</i> [51], <i>Brucea antydisenterica</i> [23], <i>Quassia kerstingii</i> [9], <i>Brucea mollis</i>, <i>Eurycoma longifolia</i> [28,29,43], <i>Picrasma quassioides</i> [52]



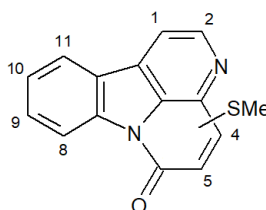
Mono-methoxylated canthin-6-ones

1-methoxycanthin-6-one	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Ailanthus altissima</i>, <i>Ailanthus excelsa</i>, <i>Soulamea pancheri</i> [23], <i>Ailanthus giraldii</i>, <i>Brucea antidysenterica</i>, <i>Hannoa klaineana</i> [9], <i>Brucea antidysenterica</i> [35], <i>Picrasma quassioides</i> [52] ▪ Caryophyllaceae : <i>Drymaria diandra</i> [53] ▪ Leitneriaceae : <i>Leitneria floridana</i> [54]
2-methoxycanthin-6-one	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Simarouba glauca</i> [30,31], <i>Brucea antidysenterica</i> [35], <i>Simaba bahiensis</i> [55], <i>Quassia amara</i> [56]
4-methoxycanthin-6-one	<ul style="list-style-type: none"> ▪ Amaranthaceae : <i>Charpentiana obovata</i> [9] ▪ Simaroubaceae : <i>Simaba ferruginea</i> [33], <i>Eurycoma longifolia</i> [29], <i>Picrasma quassioides</i> [52] ▪ Caryophyllaceae : <i>Drymaria cordata</i> [9], <i>Drymaria diandra</i> [57]
5-methoxycanthin-6-one	<ul style="list-style-type: none"> ▪ Rutaceae : <i>Pentaceras australis</i>, <i>Zanthoxylum elephantiasis</i> [11], <i>Zanthoxylum chiloperone</i> [14,58], <i>Zanthoxylum rugosum</i> [59] ▪ Simaroubaceae : <i>Ailanthus excels</i> [33], <i>Odyndea gabonensis</i>, <i>Picrasma excels</i> [9], <i>Picrasma quassioides</i> [9, 23, 37], <i>Brucea antidysenterica</i> [36], <i>Eurycoma longifolia</i> [27,29], <i>Simarouba amara</i> [45], <i>Leitneria floridana</i> [60] ▪ Leitneriaceae : <i>Leitneria floridana</i> [24,54]
8-methoxycanthin-6-one	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Simaba cuspidata</i> [61]
9-methoxycanthin-6-one	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Simaba cuspidata</i>, <i>Simaba multiflora</i> [9,62], <i>Eurycoma longifolia</i> [27-29,43,48,49], <i>Picrolemma granatensis</i> [26], <i>Eurycoma harmandiana</i> [32], <i>Simarouba glauca</i> [30,31], <i>Simarouba berteroana</i> [50], <i>Simaba polyphylla</i> [63] ▪ Rutaceae : <i>Zanthoxylum paracanthum</i> [22]
10-methoxycanthin-6-one	<ul style="list-style-type: none"> ▪ Simaroubaceae: <i>Simaba multiflora</i> [9], <i>Eurycoma longifolia</i> [27] ▪ Amaranthaceae : <i>Aerva lanata</i> [38,39] ▪ Rutaceae : <i>Zanthoxylum paracanthum</i> [21]
11-methoxycanthin-6-one	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Amaroria soulameoides</i> [51]



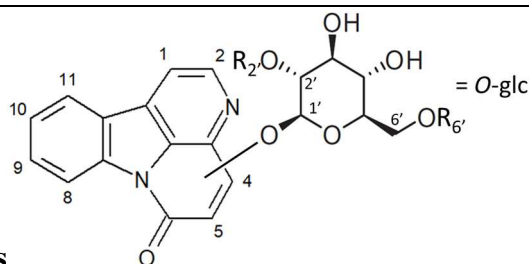
Acid derivatives canthin-6-ones

Canthin-6-one-4-butyrinic acid	▪ Simaroubaceae : <i>Picrasma quasinooides</i> [64]
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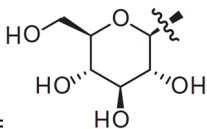
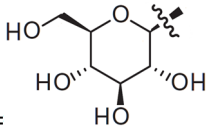


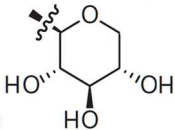
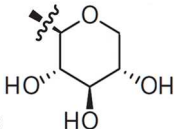
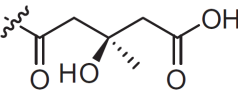
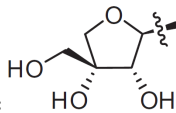
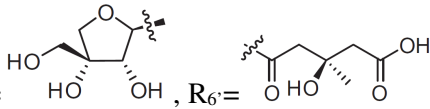
Thiomethylated canthin-6-ones

4-methylthiocanthin-6-one	▪ Boletineae : <i>Boletus curtisii</i> [41] ▪ Rutaceae : <i>Pentaceras australis</i> [9]
5-methylthiocanthin-6-one	▪ Boletineae : <i>Boletus curtisii</i> [41]
9-methylthiocanthin-6-one	▪ Boletineae : <i>Boletus curtisii</i> [41]
11-methylthiocanthin-6-one	▪ Boletineae : <i>Boletus curtisii</i> [41]

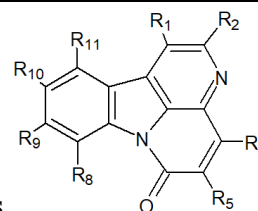


Glucosylated canthin-6-ones

Canthin-6-one-9- <i>O</i> - β -D-glucopyranoside $R_9=O\text{-glc}$ $R_2'=R_6'=H$	▪ Simaroubaceae : <i>Eurycoma harmandiana</i> [32], <i>Eurycoma longifolia</i> [27,29,48]
Canthin-6-one-10- <i>O</i> - β -D-glucopyranoside $R_{10}=O\text{-glc}$ $R_2'=R_6'=H$	▪ Amaranthaceae : <i>Aerva lanata</i> [38,39]
Canthin-6-one-5- <i>O</i> - β -D-glucopyranosyl-(1' \rightarrow 6')- β -D-glucopyranoside $R_5=O\text{-glc}$  $R_2'=H, R_6'=$	▪ Simaroubaceae : <i>Brucea mollis</i> var. <i>tonkinensis</i> [24]
Canthin-6-one-11- <i>O</i> - β -D-glucopyranosyl-(1' \rightarrow 6')- β -D-glucopyranoside $R_{11}=O\text{-glc}$  $R_2'=H, R_6'=$	▪ Simaroubaceae : <i>Brucea mollis</i> var. <i>tonkinensis</i> [24]

Canthin-6-one-1- <i>O</i> -β-D-xylopyranosyl-(1' → 6')-β-D-glucopyranoside $R_1=O\text{-glc}$  $R_2=H, R_6=$	<ul style="list-style-type: none"> ▪ Simaroubaceae: <i>Ailanthus altissima</i> [65]
Canthin-6-one-5- <i>O</i> -β-D-xylopyranosyl-(1' → 6')-β-D-glucopyranoside $R_5=O\text{-glc}$  $R_2=H, R_6=$	<ul style="list-style-type: none"> ▪ Simaroubaceae: <i>Ailanthus altissima</i> [65]
Canthin-6-one-1- <i>O</i> -[6- <i>O</i> -(3-hydroxy-3-methylglutaryl)]-β-D-glucopyranoside $R_1=O\text{-glc}$  $R_2=H, R_6=$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Ailanthus altissima</i> [66]
canthin-6-one-1- <i>O</i> -β-d-apiofuranosyl-(1'→2')-β-D-glucopyranoside $R_1=O\text{-glc}$  $R_2=$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Ailanthus altissima</i> [66]
Canthin-6-one-1- <i>O</i> -[2-β-D-apiofuranosyl-6- <i>O</i> -(3-hydroxy-3-methylglutaryl)]-β-D-glucopyranoside $R_1=O\text{-glc}$  $R_2=$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Ailanthus altissima</i> [66]

III- Polysubstituted canthin-6-ones



Polyhydroxylated/methoxylated canthin-6-ones

1-hydroxy-2-methoxycanthin-6-one $R_1=OH, R_2=OMe, R_{4\rightarrow 11}=H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Brucea antidysenterica</i> [35]
1,2-dimethoxycanthin-6-one $R_1=R_2=OMe, R_{4\rightarrow 11}=H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Picrolemma huberi</i> [67]
1-hydroxy-11-methoxycanthin-6-one $R_1=OH, R_{11}=OMe, R_{2\rightarrow 10}=H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Brucea antidysenterica</i> [9]
11-hydroxy-1-methoxycanthin-6-one	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Brucea antidysenterica</i> [9],

R ₁ =OMe, R ₁₁ =OH, R _{2→10} = H	<i>Soulamea pancheri</i> [9,23]
1,11-dimethoxycanthin-6-one R ₁ =R ₁₁ =OMe, R _{2→10} = H	▪ Simaroubaceae: <i>Brucea antidyisenterica</i> [9,23,35]
1-hydroxy-2,11-dimethoxycanthin-6-one R ₁ =OH, R ₂ =R ₁₁ =OMe, R _{4→10} = H	▪ Simaroubaceae : <i>Brucea antidysenterica</i> [35]
2-hydroxy-1,11-dimethoxycanthin-6-one R ₁ =R ₁₁ =OMe, R ₂ =OH, R _{4→10} = H	▪ Simaroubaceae : <i>Brucea antidysenterica</i> [35]
10-hydroxy-11-methoxycanthin-6-one R ₁₀ =OH, R ₁₁ =OMe, R _{1→9} = H	▪ Simaroubaceae : <i>Eurycoma longifolia</i> [29,43], <i>Brucea antidysenterica</i> [36]
11-hydroxy-10-methoxycanthin-6-one R ₁₀ =OMe, R ₁₁ =OH, R _{1→9} = H	▪ Simaroubaceae : <i>Eurycoma longifolia</i> [28]
1-hydroxy-9-methoxycanthin-6-one R ₁ =OH, R ₉ =OMe, R _{2→8,10,11} = H	▪ Simaroubaceae: <i>Eurycoma longifolia</i> [27]
4-hydroxy-5-methoxycanthin-6-one R ₄ =OH, R ₅ =OMe, R _{1,2,8→11} = H	▪ Simaroubaceae : <i>Picrasma quassioides</i> [9,47,68], <i>Eurycoma longifolia</i> [27,48]
5-hydroxy-4-methoxycanthin-6-one R ₄ =OMe, R ₅ =OH, R _{1,2,8→11} = H	▪ Simaroubaceae : <i>Picrasma excelsa</i> [9], <i>Picrasma quassioides</i> [9,23,46,47,69,70], <i>Quassia amara</i> [71,72], <i>Eurycoma longifolia</i> [29,43]
4,5-dihydroxycanthin-6-one R ₄ =R ₅ =OH, R _{1,2,8→11} = H	▪ Simaroubaceae : <i>Simarouba glauca</i> [30,31]
4,5-dimethoxycanthin-6-one R ₄ =R ₅ =OMe, R _{1,2,8→11} = H	▪ Simaroubaceae : <i>Odyndea gabonensis</i> , <i>Quassia africana</i> [9], <i>Picrolemma granatensis</i> [26], <i>Simarouba glauca</i> [30,31], <i>Picrasma quassioides</i> [23,46,47,69,72], <i>Eurycoma longifolia</i> [27,43]
11-hydroxy-5-methoxycanthin-6-one R ₅ =OMe, R ₁₁ =OH, R _{1→4,8→10} = H	▪ Simaroubaceae : <i>Picrasma quassioides</i> [73]
1-hydroxy-4,5-dimethoxycanthin-6-one R ₁ =OH, R ₄ =R ₅ =OMe, R _{2,8→11} = H	▪ Simaroubaceae : <i>Picrasma quassioides</i> [47]
10-hydroxy-4,5-dimethoxycanthin-6-one R ₄ =R ₅ =OMe, R ₁₀ =OH, R _{1,2,8,9,11} = H	▪ Simaroubaceae : <i>Picrasma quassioides</i> [46]
4,10-dihydroxy-5-methoxycanthin-6-one R ₄ =R ₁₀ =OH, R ₅ =OMe, R _{1,2,8,9,11} = H	▪ Simaroubaceae : <i>Picrasma quassioides</i> [74]
4,9-dimethoxycanthin-6-one R ₄ =R ₉ =OMe, R _{1,2,5,8,10,11} = H	▪ Simaroubaceae : <i>Eurycoma longifolia</i> [29,43]
9-hydroxy-5-methoxycanthin-6-one R ₅ =OMe, R ₉ =OH, R _{1→4,8,10,11} = H	▪ Simaroubaceae : <i>Odyndea gabonensis</i> [75]
5,9-dimethoxycanthin-6-one R ₅ =R ₉ =OMe, R _{1→4,8,10,11} = H	▪ Simaroubaceae : <i>Eurycoma longifolia</i> [28,29,43]
5-hydroxy-4,9-dimethoxycanthin-6-one R ₄ =R ₉ =OMe, R ₅ =OH, R _{1,2,8,10,11} = H	▪ Simaroubaceae : <i>Eurycoma longifolia</i> [29]
8-hydroxy-9-methoxycanthin-6-one R ₈ =OH, R ₉ =OMe, R _{1→5,10,11} = H	▪ Simaroubaceae : <i>Picrolemma granatensis</i> [26], <i>Eurycoma longifolia</i> [27,29,43]
8,9-dihydroxycanthin-6-one R ₈ =R ₉ =OH, R _{1→5,10,11} = H	▪ Simaroubaceae : <i>Picrasma quassioides</i> [52]

10-hydroxy-9-methoxycanthin-6-one R ₉ =OMe, R ₁₀ =OH, R _{1→8,11} = H	▪ Simaroubaceae : <i>Eurycoma longifolia</i> [27,28,43]
9,10-dimethoxycanthin-6-one R ₉ =R ₁₀ =OMe, R _{1→8,11} = H	▪ Simaroubaceae : <i>Eurycoma harmandiana</i> [32], <i>Eurycoma longifolia</i> [27-29,43,48]

Polymethoxylated/glucosylated canthin-6-ones

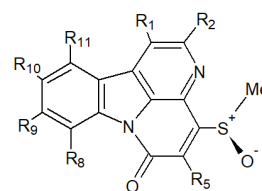
Canthin-6-one-9-methoxy-5- <i>O</i> -β-D-glucopyranoside R ₅ = <i>O</i> -glc, R ₉ =OMe, R _{1→4,8,10,11} = H	▪ Simaroubaceae : <i>Simarouba berteriana</i> [50], <i>Eurycoma longifolia</i> [29]
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Alkylated canthin-6-ones

5-methyl-9-methoxy-canthin-6-one R ₅ =Me, R ₉ =OMe, R _{1→4,8,10,11} = H	▪ Zygophyllaceae : <i>Peganum nigellastrum</i> [76]
5-ethyl-9-methoxy-canthin-6-one R ₅ =Et, R ₉ =OMe, R _{1→4,8,10,11} = H	▪ Zygophyllaceae : <i>Peganum nigellastrum</i> [76]

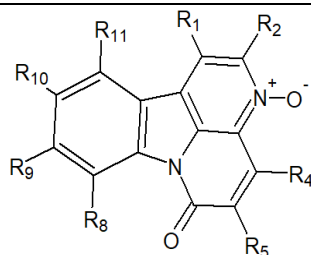
Alkoxyated canthin-6-ones

5-hydroxymethylcanthin-6-one R ₅ = CH ₂ OH, R _{1→4,8→11} = H	▪ Simaroubaceae : <i>Ailanthus altissima</i> [9,77], <i>Eurycoma longifolia</i> [27]
(<i>R/S</i>)5-(1'-hydroxyethyl)canthin-6-one R ₅ = CH(OH)CH ₃ , R _{1→4,8→11} = H	▪ Simaroubaceae : <i>Eurycoma longifolia</i> [29], <i>Ailanthus altissima</i> [78]
5-hydroxymethyl-9-methoxy-canthin-6-one R ₅ = CH ₂ OH, R ₉ =OMe, R _{1→4,8,10,11} = H	▪ Simaroubaceae : <i>Eurycoma longifolia</i> [27]
8-hydroxymethyl-1-methoxy-canthin-6-one R ₈ = CH ₂ OH, R ₁ =OMe, R _{2→5,9→11} = H	▪ Euphorbiaceae : <i>Euphorbia bivonae</i> [79]
5,8-dihydroxymethylcanthin-6-one R ₅ =R ₈ = CH ₂ OH, R _{1→4,9→11} = H	▪ Euphorbiaceae : <i>Euphorbia bivonae</i> [79]
(<i>R/S</i>)5-(1'-hydroxyethyl)-9-methoxycanthin-6-one R ₅ = CH(OH)CH ₃ , R ₉ =OMe, R _{1→4,8, 10, 11} = H	▪ Simaroubaceae : <i>Eurycoma longifolia</i> [79]



Polyhydroxylated/methylsulfoxide canthin-6-ones

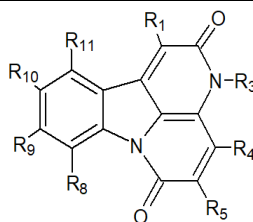
1-hydroxy-4-methylsulfoxidecanthin-6-one R ₁ =OH, R _{2→11} = H	▪ Boletineae : <i>Boletus curtisii</i> [41]
1,9-dihydroxy-4-methylsulfoxidecanthin-6-one R ₁ = R ₉ =OH, R _{2,5,8,10,11} = H	▪ Boletineae : <i>Boletus curtisii</i> [41] ▪ Rutaceae : <i>Pentaceras australis</i> [9]



Substituted N-oxides

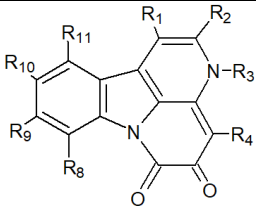
Canthin-6-one-3- <i>N</i> -oxide $R_{1 \rightarrow 11} = H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Ailanthus altissima</i> [9], <i>Brucea mollis</i> [24], <i>Eurycoma harmandiana</i> [32], <i>Simarouba berteriana</i> [50], <i>Eurycoma longifolia</i> [27,28], <i>Simaba bahiensis</i> [44-45], ▪ Rutaceae : <i>Zanthoxylum chiloperone</i> [80], <i>Zanthoxylum paracanthum</i> [22]
1-methoxycanthin-6-one-3- <i>N</i> -oxide $R_1 = OMe, R_{2 \rightarrow 11} = H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Ailanthus altissima</i> [81]
2-methoxycanthin-6-one-3- <i>N</i> -oxide $R_2 = OMe, R_{1,4 \rightarrow 11} = H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Simaba bahiensis</i> [55]
9-hydroxycanthin-6-one-3- <i>N</i> -oxide $R_9 = OH, R_{1 \rightarrow 8,10,11} = H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Eurycoma longifolia</i> [28,49], <i>Simarouba berteriana</i> [50], <i>Eurycoma longifolia</i> [27]
9-methoxycanthin-6-one-3- <i>N</i> -oxide $R_9 = OMe, R_{1 \rightarrow 8,10,11} = H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Eurycoma longifolia</i> [43,49], <i>Picrolemma granatensis</i> [26]
11-hydroxycanthin-6-one-3- <i>N</i> -oxide $R_{11} = OH, R_{1 \rightarrow 10} = H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Brucea mollis</i> [24], <i>Simarouba berteriana</i> [50]

IV- Canthinediones

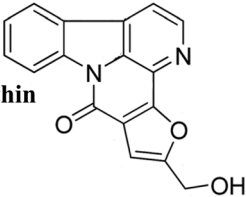
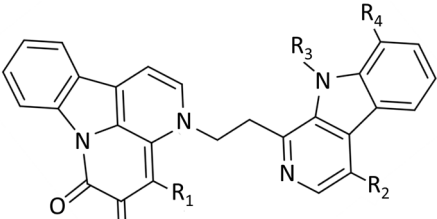
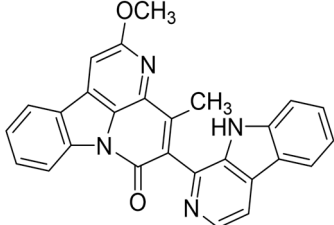
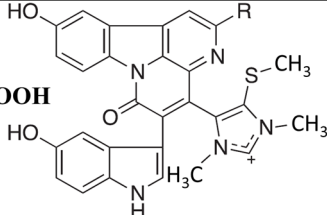


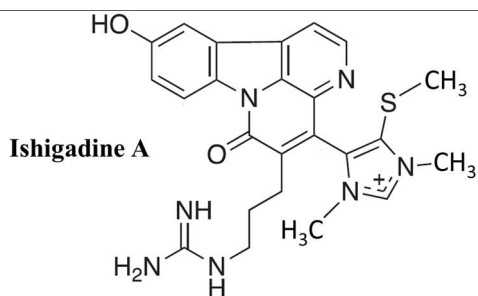
2,6-diones

Canthin-2,6-dione $R_{1 \rightarrow 11} = H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Eurycoma harmandiana</i> [9], <i>Simaba multiflora</i> [82]
5-methoxy-canthin-2,6-dione $R_5 = OMe, R_{1 \rightarrow 4,8 \rightarrow 11} = H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Samadera indica</i> [9]
3-methylcanthin-2,6-dione $R_3 = Me, R_{1,4 \rightarrow 11} = H$	<ul style="list-style-type: none"> ▪ Simaroubaceae: <i>Picrasma quassioides</i> [83]
3-methoxycanthin-2,6-dione $R_3 = OMe, R_{1,4 \rightarrow 11} = H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Simaba multiflora</i> [9,82], <i>Simaba cuspidata</i> [61], <i>Simaba bahiensis</i> [44]
10-hydroxy-3-methoxycanthin-2,6-dione $R_3 = OMe, R_{10} = OH, R_{1,4 \rightarrow 9,11} = H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Simaba multiflora</i> [9,82]

5,6-diones	
	
3-methylcanthin-5,6-dione $R_3=Me, R_{1,2,4 \rightarrow 11}=H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Picrasma quassioides</i> [9,46,47,72,84,85], <i>Eurycoma longifolia</i> [28]
4-hydroxy-3-methylcanthin-5,6-dione $R_3=Me, R_4=OH, R_{1,2,8 \rightarrow 11}=H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Picrasma quassioides</i> [9,84]
4-methoxy-3-methylcanthin-5,6-dione $R_3=Me, R_4=OMe, R_{1,2,8 \rightarrow 11}=H$	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Picrasma quassioides</i> [9,68,84]
9-methoxy-3-methylcanthin-5,6-dione $R_3=Me, R_9=OH, R_{1,2,4 \rightarrow 8,10,11}=H$	<ul style="list-style-type: none"> ▪ Simaroubaceae: <i>Eurycoma longifolia</i> [28]

V- Other derivatives

 <p>Furancanthin</p>	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Picrasma quassioides</i> [73]
 <p>Amarastelline A $R_1=R_2=R_4=H, R_3=OCH_3$</p> <p>Picrasidine N $R_1=R_4=H, R_2=R_3=OCH_3$</p> <p>Picrasidine M $R_1=R_3=H, R_2=R_4=OCH_3$</p> <p>Picrasidine U $R_1=R_2=R_4=OCH_3, R_3=H$</p>	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Picrasma quasinooides</i> [68,85,86], <i>Quassia amara</i> [87]
 <p>Quassidine E</p>	<ul style="list-style-type: none"> ▪ Simaroubaceae : <i>Picrasma quasinooides</i> [47]
<p>Hyrtimomine D $R=H$</p> <p>Hyrtimomine E $R=COOH$</p> 	<ul style="list-style-type: none"> ▪ Sponges: <i>Hyrtios</i> sp. [88]



- Sponges: *Hyrtios* sp. [89]

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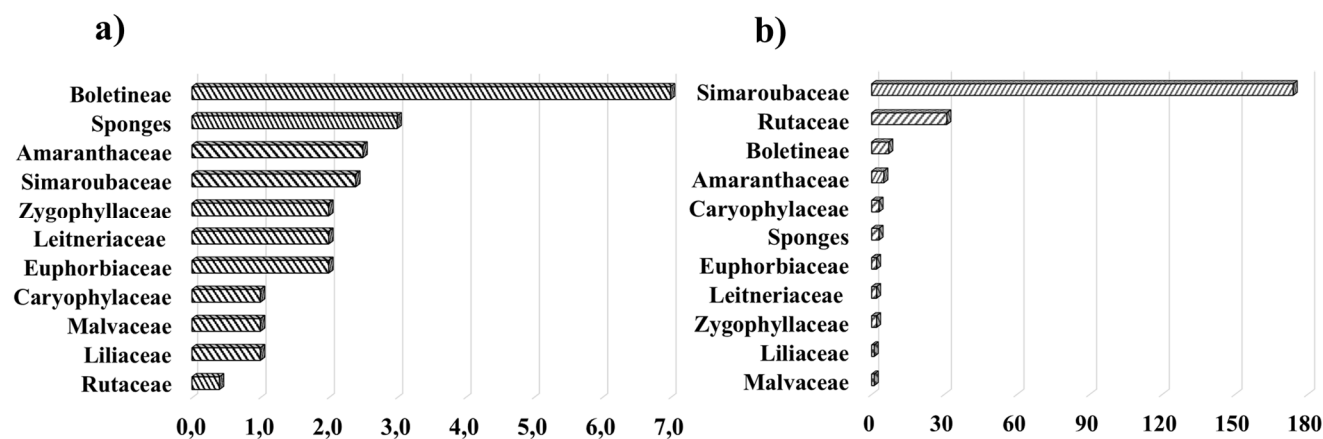
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Large amounts of these alkaloids occur in the root bark and leaves of Rutaceae and Simaroubaceae and lesser amounts are found in their heartwood. Other genus belonging to Malvaceae, Amaranthaceae, Zygophyllaceae, Caryophyllaceae and Leitneriaceae contain canthin-6-one alkaloids. More recently, several *S*-containing derivatives have been identified from Boletineae [41]. The natural occurrence of canthin-6-one alkaloids is illustrated in Figure 3.



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Figure 3. Distribution of canthin-6-one alkaloids cited in table 1 in the nature. a) Recurrence and b) diversity of canthin-6-one alkaloids for each family.

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3. Biosynthesis of canthin-6-ones

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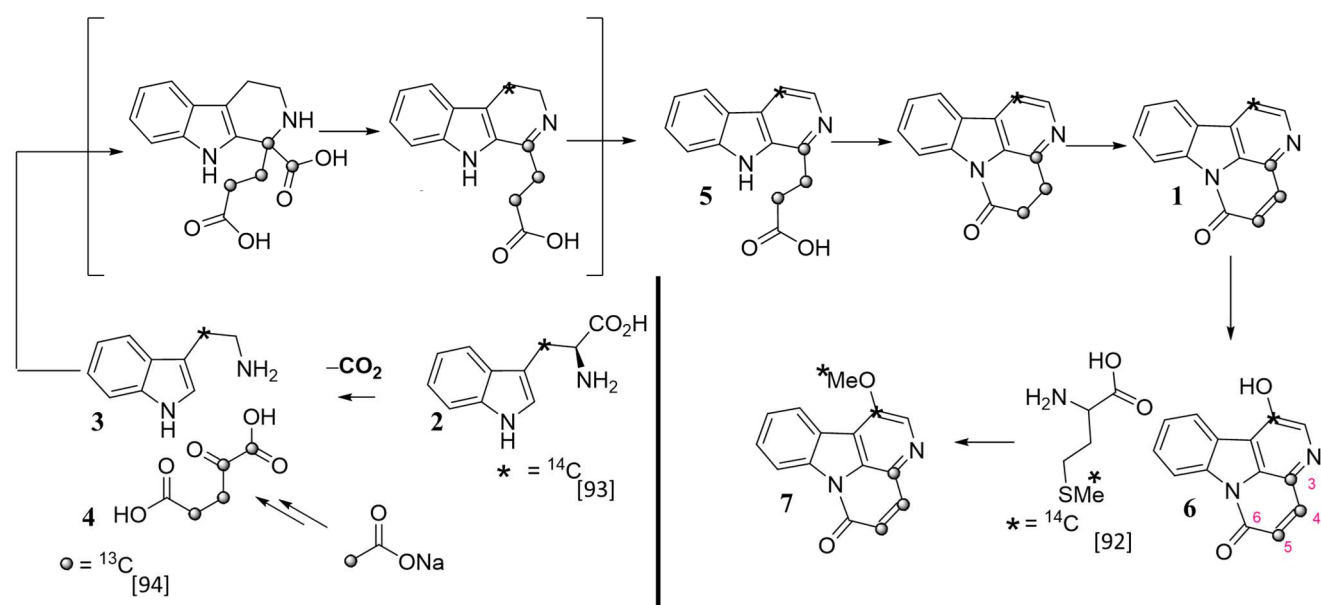
Despite the utility of this family of compounds, in the eighties, canthin-6-one (**1**) and its derivatives had no real commercial interest. However they had been studied as a model system for the production of alkaloids by plant cell cultures, due to the success of high yields of canthinones from cell suspensions of *Ailanthus altissima* Swingle (Simaroubaceae) [90].

The reported biosynthetic hypotheses for formation of canthin-6-one (**1**) building blocks, originated from the proteinogenic amino acid tryptophan (**2**) was first predicted by Anderson *et al.* [91]. They investigated the uptake of L-[methylene ^{14}C] tryptophan (**2**) by *Ailanthus altissima* cells and demonstrated the incorporation of the radio-label into canthin-6-one (**1**), 1-hydroxycanthin-6-one (**6**) and 1-methoxycanthin-6-one (**7**) (Schema 1). Similar studies with tryptamine (**3**) have also shown incorporation of the radio-label into canthinone alkaloids [92]. The postulated key steps rely on several presumed precursors isolated from cell cultures of *Ailanthus altissima* by Crespi-Perellino and coworkers in 1986 [3,93]. In these experiments cells were fed radio-labeled tryptophan (**2**) and various alkaloids products were extracted and isolated according to their radiochromatographic peak. This allowed the synthesis of labeled canthin-6-one by the addition of each labeled intermediate to the cellular culture. As result of these experiments they proposed the synthesis of canthin-6-one scaffold by condensation of tryptophan and suggested an origin from tricarboxylic acid cycle (TCA) for the carbon atoms C-3, C-4, C-5 and C-6, resulting in a series of β -carboline intermediates in various states of oxidation (Schema 1).

Several publications support the Crespi-Perellino *et al.* [3] hypothesis. For example the biogenic studies performed by the Phillipson group, where they had shown the origin from methionine of the methyl group of 1-methoxycanthin-6-one (**7**) [92] (Schema 1).

Following the first experimental biosynthetic study of canthinones performed by Crespi-Perellino *et al.*, [3]. Aragozzini and coworkers proposed ketoglutarate as an early precursor for the carbon atoms C-3, C-4, C-5 and C-6 of canthin-6-one (Schema 1) by feeding (^{13}C) sodium acetate to cell cultures of *Ailanthus altissima* and evaluating the labeled sites by ^{13}C NMR spectrometry [94] (Schema 1).

Schema 1. Biosynthetic building blocks, including the tryptophan (**2**), the ketoglutarate (**4**) and the methylmethionine (**5**) with the respective labels employed by Crespi-Perellino (^{14}C), Aragozzini (^{13}C) and Anderson (^{14}C).



A study of Movassaghi's alternative conditions for the Bischler–Napieralski reaction allowed to formulate a general strategy for the synthesis of all intermediates in the canthin-6-one biosynthetic pathway and their chemical interconversions [95]. The results with a nanoparticulate mimic system of the relevant biosynthetic assembly lines have been disclosed and merit further developments. Finally, biological evaluations using *C. elegans* revealed new findings that may contribute to a better understanding of the role of canthin-6-one alkaloids in chemical ecology.

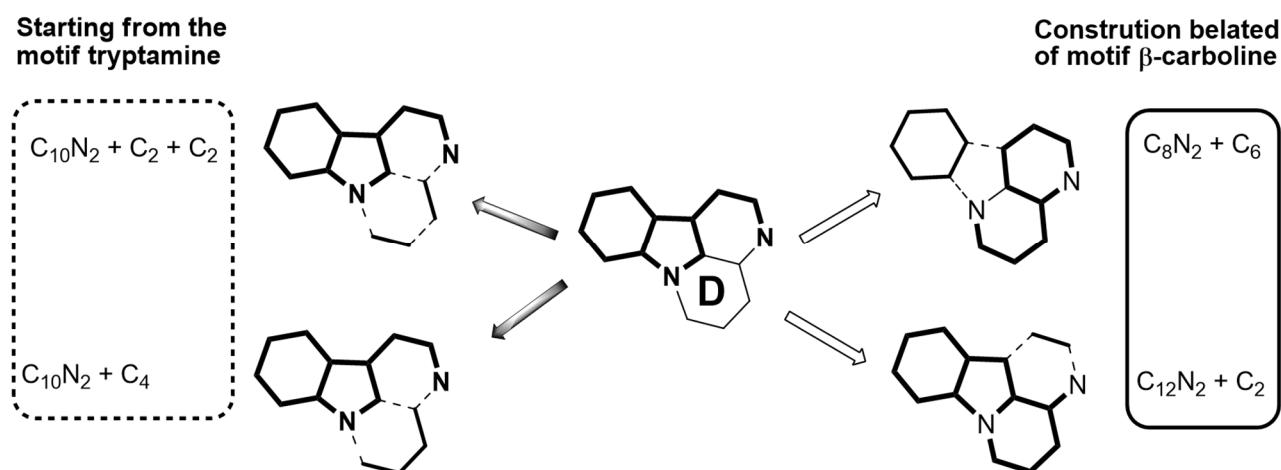
A filamentous fungus, *Cunninghamella blakesleeana* CGMCC 3.970, was used as a microbial system to mimic mammalian metabolism of 4,5-dimethoxy-canthin-6-one, a canthin-6-one type alkaloids, which is a major bioactive constituent of a traditional Chinese medicine (the stems of *Picrasma quassioides*). The metabolic pathways of 4,5-dimethoxy-canthin-6-one were proposed, and the metabolic processes involved phase I (*O*-demethylation, dehydroxylation, demethoxylation, *N*-oxidation, hydroxylation, and oxidative ring cleavage) and phase II (glycosylation) reactions [96].

4. Synthesis of canthin-6-ones

The various strategies utilized for synthesis of canthinone alkaloids employ two well known reactions: the Pictet–Spengler and Bischler–Napieralski cyclizations. In the case of canthinones, the starting reagent utilized is tryptamine (**3**). There are also a few original synthetic schemes in that are not derived from tryptamine (**3**) or indole-precursors.

For clarity, we have divided the different approaches into several groups depending on the number of carbons presented by each reactive. The strategies used in most of the work are based on the cyclization of Bischler–Napieralski as well as the Pictet–Spengler to obtain a compound derived from combinations of intermediates $C_8N_2 + C_6$, $C_{12}N_2 + C_2$, $C_{10}N_2 + C_2 + C_2$ or $C_{10}N_2 + C_4$. Sometimes these intermediates may be involved in a cyclization inter- or intramolecular to form the canthinone skeleton. Most of these syntheses are facing final steps of oxidation, which in general are the cause of low to very low yields [97–101]. In schema 2, we show the four different approaches that will be developed for the synthesis of the basic structure of canthinones [80,97–123].

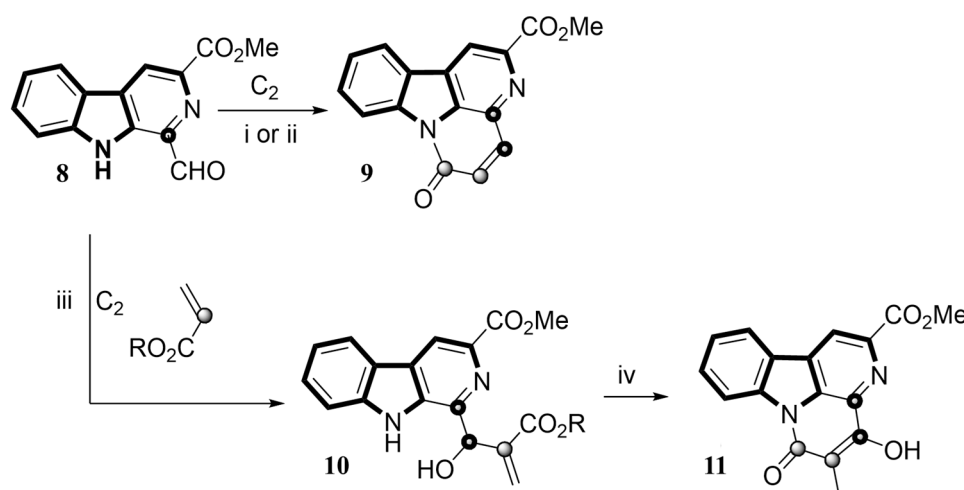
Schema 2. Different synthetic strategies to reach the canthin-6-one scaffold.



4.1. Synthesis based on the strategy $C_{10}N_2 + C_2 + C_2$

There are many examples of $C_{10}N_2 + C_2 + C_2$ synthesis strategy starting from the methyl ester of tryptophan (**2**) including the work of Settimj and colleagues [106]. They reported that the Perkin reaction of β -carboline 3-carbomethoxy derivatives (**8**) with acetic anhydride under basic conditions gave methyl canthin-6-one-2-carboxylate (**9**) (Schema 3, i). A similar approach was followed by the group of Murakami [121,122], employing stronger basic conditions (*t*-BuOK in DMSO). The work developed by Condie and coworkers [103-104] demonstrate another strategy to reach the synthesis of the canthin-6-one core. In this case, they propose the conversion of the 1-fomyl- β -carboline (**8**) to tetracyclic compounds possessing the canthin-parent structure by treatment of the aldehyde (**8**) with phosphorane (Schema 3, ii). Another synthesis with similar features was published by the Singh group [119], this time additional carbons were introduced from acrylates (**10**) *via* Baylis-Hilman reaction followed by intramolecular cyclization resulting in the canthinone scaffold as shown in molecule (**11**) (Schema 3, iii et iv).

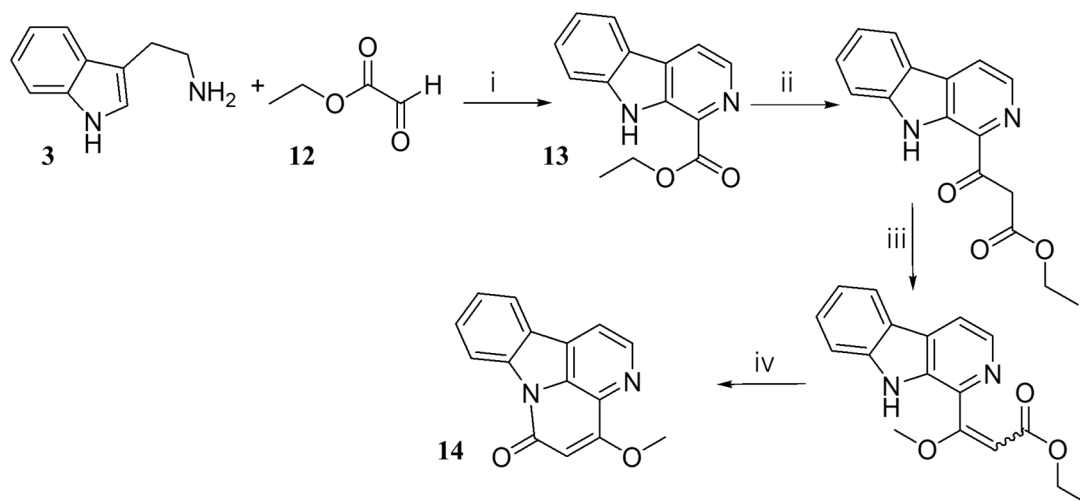
Schema 3. Synthesis based on the strategy $C_{10}N_2 + C_2 + C_2$.



Reagents and conditions : (i) $(CH_3CO)_2O$ (excess), reflux, 3 h, (72 %) ; (ii) Ph_3PCHCO_2Et , toluene, reflux (29%); (iii) DABCO, *t.a.* ; (iv) K_2CO_3 , DMF, *t.a.*

With similar reagents and conditions, Fang *et al.* proposed a way to synthesis 4-methoxycanthin-6-one, named cordatanine (**14**), in four steps via a Pictet–Spengler reaction using tryptamine (**3**) and ethyl glyoxylate (**12**) with a total yield of 8% (Schema 4) [124].

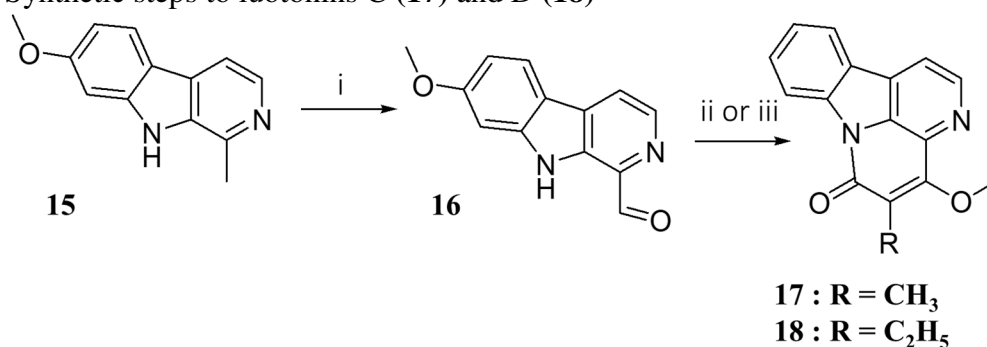
Schema 4. Synthetic steps to cordatanine (**14**).



177 **Reagents and conditions:** (i) HCl, EtOH, Pd/C, toluene, reflux; (ii) NaHDMS, EtOAc, **13**, THF, $-78\text{ }^{\circ}\text{C}$; (iii)
 178 Cs_2CO_3 , MeOMs; (iv) NaH, THF (8%)[124]

180
 181 Ma *et al* [76] proposed a way to synthesis alkylated canthin-6-one in two steps from harmine (**15**) via
 182 1-formyl-7-methoxy- β -carboline (**16**) by slightly modified procedures of Settimj and colleagues [106].
 183 The reaction between compound (**16**) and propionic anhydride or butyric anhydride afforded luotonins
 184 C (**17**) and D (**18**) with a yield of 15% and 13% respectively (schema 5).
 185

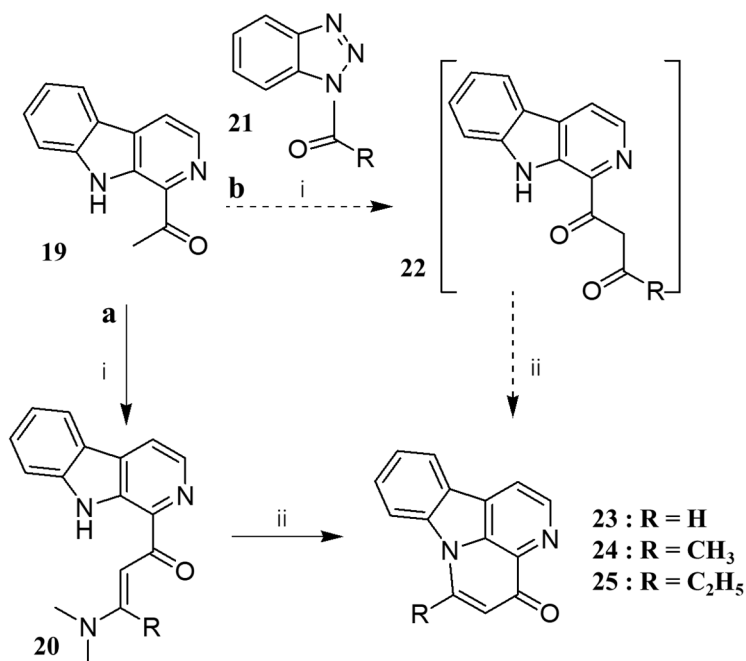
186 **Schema 5.** Synthetic steps to luotonins C (**17**) and D (**18**)



187 **Reagents and conditions:** (i) EtOH, SeO₂, reflux, 3h; (ii) Et₃N, (C₂H₅CO)₂O, reflux, 2 h, (15%) or (iii) Et₃N,
 188 (C₃H₇CO)₂O, reflux, 2 h, (13%)[76]
 189

190
 191 Starting from the same type of intermediate, Tremmel group developed a versatile approach to the
 192 canthin-4-one ring system via a condensation of 1-acyl- β -carboline (**19**) with Bredereck's reagent
 193 (*tert*-butoxy-bis(dimethylamino)methane) or amide acetals to give enaminoketones (**20**), which
 194 undergo cyclization under the reaction conditions resulting the compounds (**23**) and (**24**) with a yield
 195 of 80% and 52% respectively [125] (Schema 6, a route). They proposed also a new approach based on
 196 a Claisen type condensation of 1-acyl- β -carboline (**19**) with a carbonyl derivative (**21**) in basic
 197 medium giving an intermediate (**22**) which cyclizes to the canthin-4-one ring system in a similar
 198 manner. Via this pathway, compounds (**24**) and (**25**) are obtained with a yield of 80% and 52%
 199 respectively [126] (Schema 6, b route).
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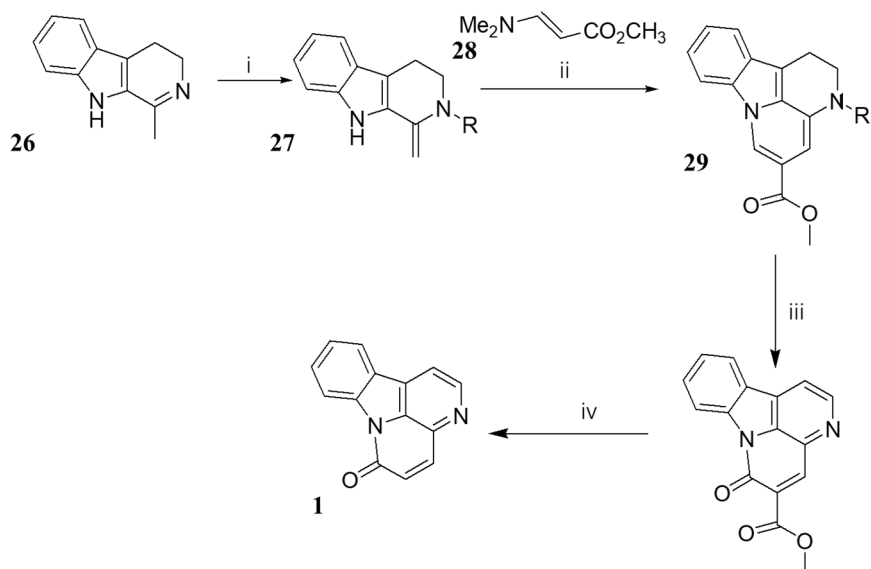
201 **Schema 6.** Synthetic steps to canthin-4-one derivatives (**23**), (**24**) and (**25**).



Reagents and conditions: **a** : with Bredereck's reagent ($R = H$) (i) Bredereck's reagent wet DMF, reflux; (ii) *tert.*-BuOK (cat.), anhydrous DMF, reflux (80%). With amide acetal ($R = CH_3$) (i) *N,N*-dimethylacetamide dimethylacetal anhydrous DMF, 130 °C (52%) [125] **b** : i) $MgBr_2 \cdot OEt_2$, *i*-Pr₂NEt, methylene chloride, microwave 100 W, 70 °C ii) LDA, THF, 0 °C to rt, (34 and 16%) [126].

In 1999, an innovative way of canthin-6-one synthesis was proposed by R bler *et al.* using a single electron transfer (SET) induced radical cationic hetero [4+2] cycloaddition as high yielding key step [127]. They used harmalan (**26**) as starting reagent. The SET induced cycloaddition between intermediate (**27**) and methyl E-3-(*N,N*-dimethylamino)-acrylate (**28**) was carried out electrochemically at a potential of 400 mV giving an high yield of 87% of compound (**29**). Few more steps are needed to obtain canthin-6-one (**1**) with an overall synthetic yield of 18% at that time (schema 7).

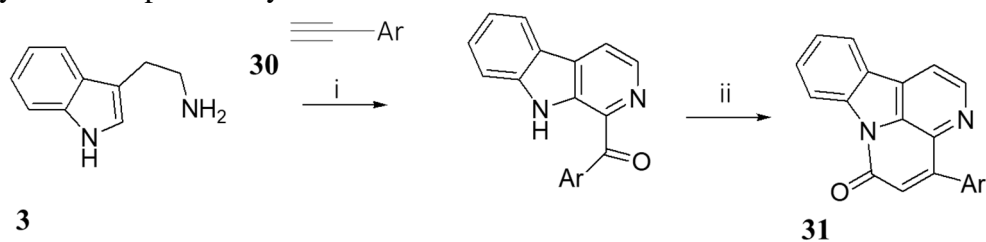
Schema 7. Total synthesis of canthin-6-one using a SET induced hetero [4+2] cycloaddition



218
 219 **Reagents and conditions:** With $R = \text{SO}_2\text{CF}_3$ i) $(\text{CF}_3\text{SO}_2)_2\text{O}$, Et_3N , CH_2Cl_2 at 0°C (94%); ii) ratio (27) 5 : 1
 220 (28), $E = 400 \text{ mV}$ in $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ (1/4:0.1 M LiClO_4), rt (87%); iii) Na/naphthalene , DME at 0°C , MnO_2 ,
 221 CH_2Cl_2 , rt (74%); iv) HCl , Cu/pyridine (50%).
 222

223 Instead of using a carbonyl intermediates with tryptamine (**3**), Dighe *et al.* have developed an
 224 alternative route to the synthesis of canthin-6-one aryl derivatives (**31**) via iodine-mediated oxidative
 225 Pictet-Spengler reaction choosing terminal alkynes as the 2-oxoaldehyde surrogate [128]. Lower
 226 loading of iodine and better yields of products as compared to the reported methodologies where
 227 acetophenones have been used as the 2-oxoaldehyde source are attractive attributes of this protocol.
 228 The protocol is amenable to aryl terminal alkynes (**30**) whereas alkyl-based terminal alkynes failed to
 229 react. This way of synthesis lead to a high yield of 83% (schema 8).
 230

231 **Schema 8.** Synthetic steps to 4-arylcathin-6-ones



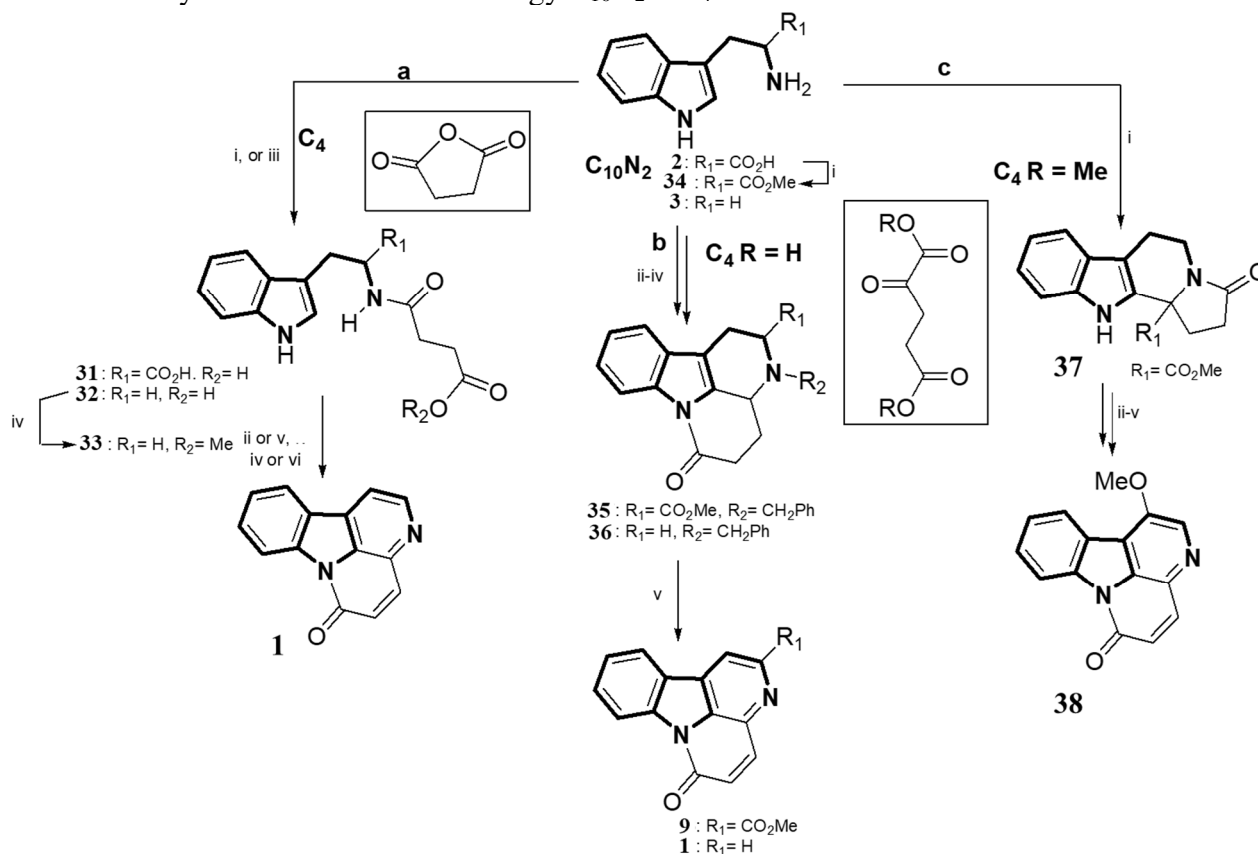
232
 233 **Reagents and conditions:** (i) I_2 (0.5 equiv), DMSO , 100°C , 4-5h (ii) Ac_2O (1.5 equiv), NaH (2.0 equiv), THF ,
 234 70°C , 12h (83%)
 235
 236

237 **4.2. Synthesis based on the strategy $\text{C}_{10}\text{N}_2 + \text{C}_4$**

238
 239 The synthetic approach based on intermediates type $\text{C}_{10}\text{N}_2 + \text{C}_4$ to yield the canthinone scaffold,
 240 employ as starting material compounds that have the same number of carbons as the canthin-6-one (**1**).
 241 The group of Rosenkranz [118] reported the synthesis of canthin-6-one (**1**) in two steps from
 242 tryptophan (**2**) through the formation of the intermediate (**31**) (Schema 9, a route). In 2006, Soriano-

Agatón *et al.* designed a synthetic pathway utilizing a similar strategy, based on the addition of the four carbon atoms from succinic anhydride, through a four steps reaction sequence to tryptamine (**3**) [80]. In the presence of succinic anhydride, tryptamine (**3**) is easily converted into tryptamide (**32**), protecting the carboxylic acid form of methyl ester (**33**), and employing this molecule as substrate of the Bischler-Napieralski cyclization resulting in a β -carboline that will undergo an intramolecular cyclization. A final spontaneous oxidation of the resulting tetracyclic system led directly to the canthin-6-one (**1**) with an overall yield of about 60% (Schema 9, a route). Shelar *et al.* described a similar pathway of 4-methoxycanthin-6-one (**14**) synthesis starting from tryptamine (**3**) and methoxymaleic anhydride [129]. They proposed an efficient total synthesis of cordatanine (**14**) via regioselective reduction of methoxymaleimide, acid-catalyzed intramolecular cyclization of the formed lactamol, in situ stepwise oxidations leading to aromatization, and intramolecular cyclization with the exchange of N-regioselectivity. Cook and coworkers were able to synthesize similar compounds by two different synthetic routes [99,102,108-110,114]. They also synthesized canthin-6-one (**1**) in four steps from tryptamine (**3**). A final oxidation step showed very low yields (Schema 9, b route). Few years later, Czerwinski and collaborators reported a methodology that would improve the yield of this oxidation step [105] (Schema 9, c route) synthesizing 1-methoxycanthin-6-one (**38**).

Schema 9. Synthesis based on the strategy $C_{10}N_2 + C_4$.

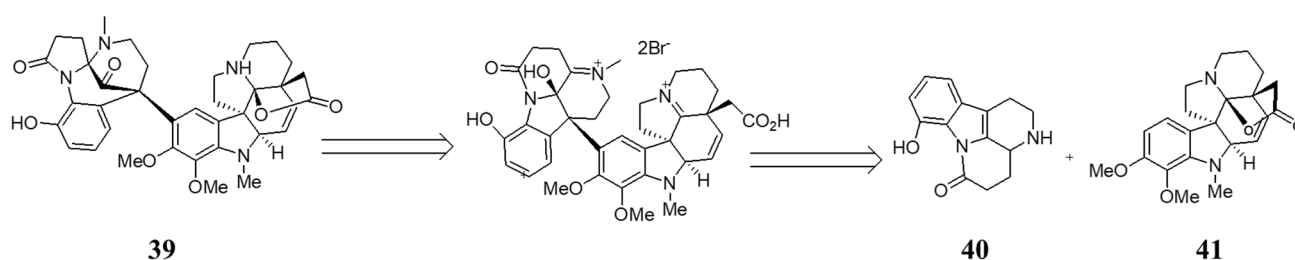


Reactives and conditions: **a:** (i) Succinic acid (1.1 equiv.), sol. 2N K_2CO_3 , 30 min, t.a., (60 %); (ii) polyphosphoric acid, V_2O_5 , $POCl_3$ (excess), 1 h, 115 °C, (25 %); (iii) succinic anhydride (1.1 equiv.), CH_2Cl_2 , 18 h, r.t., (>97 %); (iv) Amberlyst® H-15 (20 % m/m), MeOH reflux, 18 h, (>97 %); (v) $POCl_3$ (3 equiv.), benzene, 1 h, reflux; (vi) DBU (3 equiv.), CH_2Cl_2 , 18 h, r.t., (60 % + 80 %). **b:** (i) Na/NH₃, MeI, 30 min, -70 °C, (80 %); (ii) PhCHO, MeOH, 6 h, r.t.; (iii) NaBH₄, MeOH, 0-5 °C, 3 h, (two steps, 95 %); (iv) 2-

cetoglutaric acid (1.1 equiv.), benzene, 7 days, reflux, (82 %); (v) SeO_2 (1.5 equiv.), dioxane, reflux, 24 h, (30 %). **c** : (i) Dimethyl 2-ketoglutarate (1.5 equiv.), MeOH, 20 h, reflux, (92 %) ; (ii) DDQ (excess), THF / H_2O , r.t., (75 %) ; (iii) HCl, AcOH, reflux, 3 h, (88 %) ; (iv) MeOH, $\text{CH}(\text{OCH}_3)_3$, PTSA, reflux 24 h, (82 %) ; (v) DDQ (excess), dioxane, 10 h, reflux, (70 %).

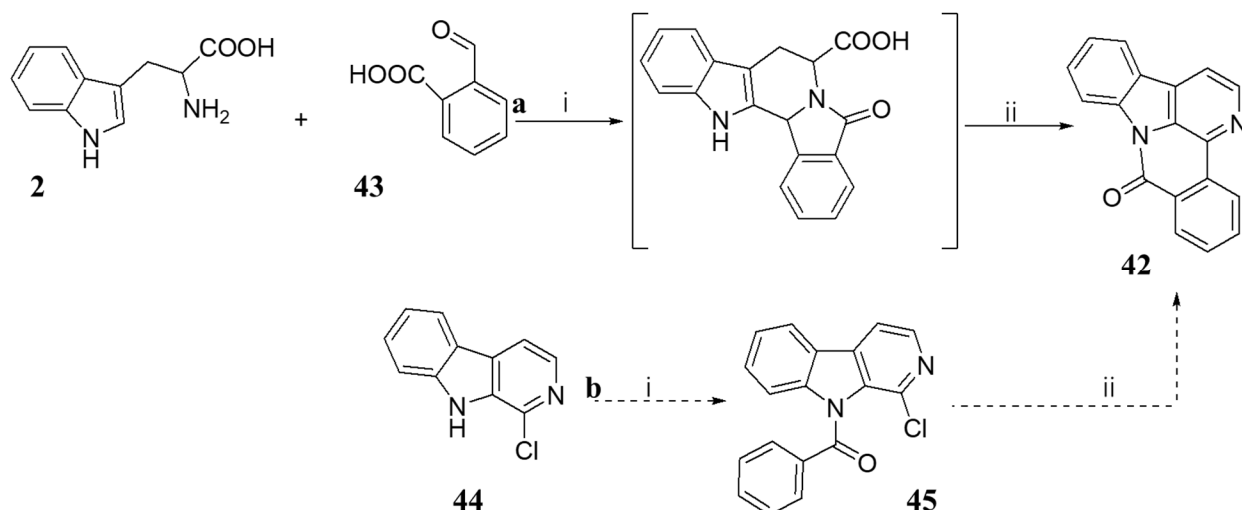
Between 2006 and 2009 the laboratories of Corey [117] and Nicolaou [115,116] described the synthesis of (+)-haplophytine (**39**), based on a similar approach. (+)-haplophytine (**39**) is a potent insecticidal alkaloid which derive from two indoles, aspidophytine (**41**) coupling with a canthiphytine (**40**) derivative which is very similar in structure to canthin-6-one (Schema 10).

Schema 10. Retrosynthesis of (+)-haplophytine (**39**).



Synthetic approach type $\text{C}_{10}\text{N}_2 + \text{C}_4$ may also be employed for building benzocanthin-6-one (**42**) and derivatives. This type of approach included Bischler–Napieralski cyclization of tryptamine (**3**) and phthalic anhydride used by Soriano-Agatón *et al.* [80] or Pictet–Spengler cyclization of tryptophan (**2**) and *o*-formylbenzoic acid (**43**) [130] both followed by intramolecular *N*-acylation of the pyrrole N and dehydration (schema 11, a route). The same year, Zimmerman’s group published a versatile route to synthesize benzocanthinone (**42**) by Suzuki coupling as well [113]. This compound were prepared by radical-induced cyclizations of halo *N*-aroyl derivatives of β -carboline (**45**). 1-chloro- β -carboline (**44**) was converted to compound (**45**), which afforded the benzocanthinone (**42**) as the only observed product (Scheme 11, b route).

Schema 11. Synthetic steps to benzocanthin-6-one (**42**).

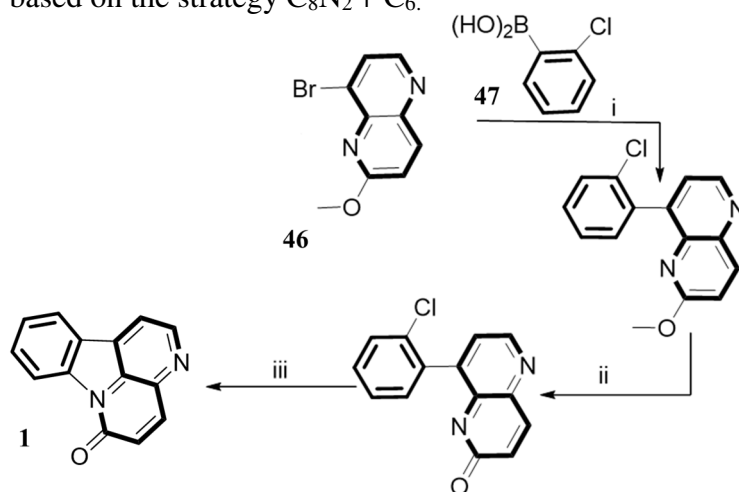


Reagents and conditions: **a** : (i) AcOH, 100°C, reflux, 30-40h; (ii) O₂ (35-56%)¹³⁰. **b** : (i) NaH, DMF, r.t., benzoyl chloride, DMAP, DMF, 120°C; (ii) Bu₃SnH, ACN, toluene, reflux (74%)[113]

4.3. Synthesis based on the strategy C₈N₂ + C₆

Koutentis group presented a total synthesis of canthin-6-one (**1**) using a strategy totally independent of the biosynthesis of the β-carboline alkaloids [107,111]. This newest pathway did not exploit starting materials derived from tryptophan (**2**) and instead used novel original strategy type C₈N₂ + C₆. This work reported a revolutionary synthesis of canthin-6-one (**1**) in two steps from 8-bromo-2-methoxynaphthyridine (**46**) and 2-chlorophenylboronic acid (**47**) by one-pot reaction sequence using Pd-catalyzed Suzuki-Miyaura coupling followed by Cu-catalyzed C-N coupling [122] (Schema 12).

Schema 12. Synthesis based on the strategy C₈N₂ + C₆.

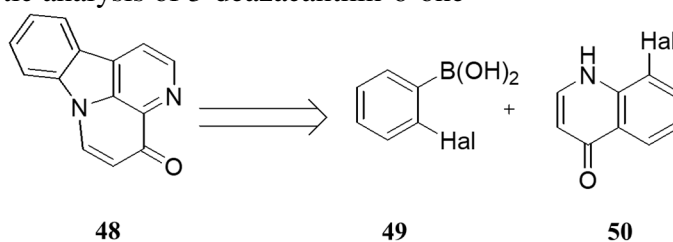


Reagents and conditions: (i) ArB(OH)₂, Pd(dppf)Cl₂, K₂CO₃, dioxane:H₂O, reflux; (ii) HCl_(aq), dioxane, reflux; (iii) CuI, DMEDA, Cs₂CO₃, H₂O, dioxane, reflux, (99%)[107]

More recently, Broumidis and Koutentis still used this strategy by developing a one-pot, two-step

synthesis of 3-deazacanthin-4-one (**48**) involving readily available 2-chloro-arylboronic acids (**49**) and 8-iodoquinolin-4(1*H*)-one (**50**) (Schema 13). The procedure takes advantage of transition metal-catalyzed Suzuki-Miyaura and Buchwald-Hartwig coupling strategies to construct the 3-deazacanthin-4-one central B ring [131]. The route successfully provides a rapid route towards 8-, 9-, and 10-substituted 3-deazacanthin-4-ones.

Schema 13. Retrosynthetic analysis of 3-deazacanthin-6-one



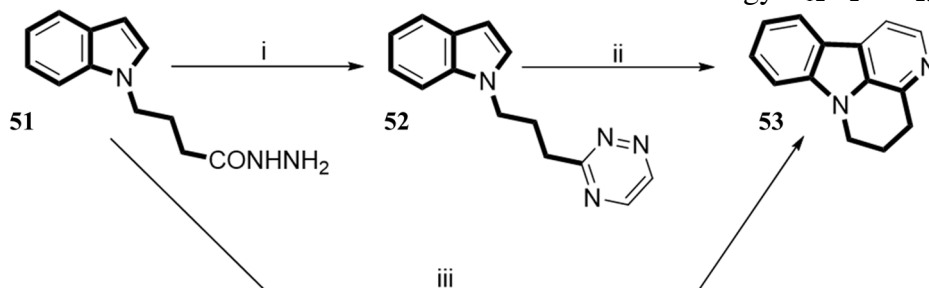
261 4.4. Synthesis of unnatural canthine alkaloids based on the strategy $C_{12}N_2 + C_2$

262

263 The synthetic approach based on intermediates type $C_{12}N_2 + C_2$ to obtain the basic canthine
 264 scaffold (**53**) was put for the by the Snyder group [120,132] disclosing an elegant entry to canthine
 265 skeleton utilizing indole as dienophile in an intramolecular inverse electron demand Diels-Alder
 266 reaction (Schema 14). An additional oxidation step is necessary to obtain the canthin-6-one alkaloid
 267 [133]. Treatment of acyl-hydrazine-tethered indole (**51**) with a 1,2-diketone and excess of ammonium
 268 acetate in refluxing acetic acid for several hours provided the triazine-tethered indole (**52**) which was
 269 refluxed in triisopropylbenzene to provide the basic canthine skeleton (**53**). Recently, Lindsley *et al.*
 270 reported the synthesis of the basic canthine core by the Snyder synthesis on *one pot* microwave-
 271 assisted protocol [112,123].

272

273 **Schema 14.** Synthesis of unnatural canthine alkaloids based on the strategy $C_{12}N_2 + C_2$.



274

275 **Reagents and conditions** : **a** : (i) NH_4OAc (excess), $AcOH$, reflux 6-4 h, (50-60 %); (ii) triisopropylbenzene,
 276 reflux, 232 °C, (72-92 %); (iii) NH_4OAc (excess), $AcOH$, 180 °C, 5 min, MWI, (6 %).

277

278

279 5. Pharmacological and toxicological study

280

281 5.1. Antileishmanial activity

282

283 The antileishmanial activity demonstrated by *Zanthoxylum chiloperone* is attributed to the
284 presence of canthin-6-one and 5-methoxycanthin-6-one [14]. The effect of canthin-6-one *in vivo* is
285 stronger than the molecule of reference, the meglumine antimoniate, used as a positive control. The 5-
286 methoxycanthin-6-one showed activity, but less than canthin-6-one [14,134].

287 Silva's group exposed antileishmanial activity of synthetic benzocanthin-6-one derivatives
288 [135]. Compound bearing an N-methylpiperazylcarboxamide at C-2, showed the highest activity
289 towards *Leishmania amazonensis* parasite with the half maximal inhibitory concentration (IC₅₀) of
290 $0.90 \pm 0.13 \mu\text{M}$.

291 5.2. Antimalarial activity

292 The antimalarial activities of canthin-6-one and some derivatives (9-hydroxycanthin-6-one, 5-
293 methoxycanthin-6-one) were studied [27,49,136,137], with mixed results. Kuo *et al.* showed that
294 canthin-6-one and 9-hydroxycanthin-6-one exhibited low antimalarial activity against the W2
295 *Plasmodium falciparum* clone with IC₅₀ values 2238 and 2336 ng/mL, respectively [27]. We report a
296 good antiplasmodial effect on chloroquine resistant and sensitive strains of *Plasmodium falciparum* for
297 the canthinone alkaloids with IC₅₀ of 2.0-5.3 $\mu\text{g/mL}$ and 5.1-10.4 $\mu\text{g/mL}$ for canthin-6-one and 5-
298 methoxycanthin-6-one, respectively [136]. *In vivo* data (unpublished) in our hands did not match the *in*
299 *vitro* activity. This discrepancy is likely due to *in vivo* metabolism of the canthinones.

302 5.3. Antifungal

303 The activity against *Candida albicans* is the first activity attributed to the canthin-6-one, this
304 activity was described in *Zanthoxylum elephantiasis* [9]. Recently, bark and root extracts of
305 *Zanthoxylum usambarensis* and *Zanthoxylum chiloperone* antifungal activities against different mycelia
306 and yeasts were evaluated with promising results [15,138].

307 The antifungal activity of canthin-6-one and some analogues against *Candida albicans*,
308 *Aspergillus fumigatus*, *Trichophyton mentagrophytes*, *Cryptococcus neoformans* and *Saccharomyces*
309 *cerevisiae*, among others, is not so far away to the reference drug, ketoconazole [80]. Later, a
310 mechanism of action of antifungal canthin-6-one N-oxide was investigated in *Saccharomyces*
311 *cerevisiae* and found to affect fatty acid metabolism [139].

312 Dejos *et al.* screened a yeast genomic library in *Saccharomyces cerevisiae* to isolate high-copy-
313 number suppressors of canthin-6-one sensitivity [140]. Among the genes selected with this strategy,
314 they isolated the yeast AP1 homologue (*YAPI*), a gene involved in cell response to various stress,
315 more particularly oxidative stress and pleiotropic drug resistance in high-copy number. In this study
316 they showed that plasmid-borne overexpression of *YAPI* leads to canthin-6-one resistance via the
317 major-facilitator-superfamily (MFS) transporter Flr1 involved in the efflux of a broad range of
318 cytotoxic molecules.

319 Recently, Gazoni *et al.* presented the phytochemical analysis by high performance liquid
320 chromatography (HPLC), toxicological potential of canthin-6-one, using the cytotoxicity, genotoxicity
321 assays with CHOK1 cells and *in vivo* acute test in mice [141]. They evaluated potent *in vitro*
322 antifungal activity of canthin-6-one against clinically important *Aspergillus niger* and *Candida* species

325 showing a minimal fungicidal concentration between 3.12 to 25 $\mu\text{g/mL}$. They also studied the
326 antifungal mode of action on *Saccharomyces cerevisiae* and *Neurospora crassa* highlighting that
327 canthin-6-one inhibited growth and altered cell membrane respectively.

328 In Zhao *et al.* researches, a novel series of ester derivatives of 10-hydroxycanthin-6-one were
329 synthesized and evaluated for their bioactivity against three phytopathogenic fungi (*Alternaria solani*,
330 *Fusarium graminearum*, and *Fusarium solani*) and four bacterial strains (*Bacillus cereus*, *Bacillus*
331 *subtilis*, *Ralstonia solanacearum*, and *Pseudomonas syringae*) [142]. The aliphatic ester derivatives of
332 10-hydroxycanthin-6-one had much higher antifungal activity than did the aromatic ester derivatives.
333

334 **5.4. Antitumor activity**

335
336 Canthin-6-one and derivatives (hydroxylated and methoxylated) were tested for cytotoxic
337 activity against different cell lines exhibiting weaker antitumor activity than the reference compound,
338 cisplatin [31,82,143-145].

339 Peduto *et al.* described some β -carboline derivatives which are potent agent against prostate
340 cancer [146]. In this work, the authors highlight the relationship between structure and cytotoxic
341 activities. The in vitro experiments showed that the shift of methoxy group in position 4 of harmine led
342 to enhanced cytotoxic activity and substituents at position 1 were essential for high activity towards
343 specific tumor types. 3N substitution of 1-methoxycanthin-6-one with benzyl group increased activity
344 against most of the cell lines tested.

345 Leite silva's group confirmed the previous results by synthesizing benzo[4,5] canthin-6-ones
346 derivatives substituted on position 3 with N-alkylcarboxamide and analyzing the antitumor activities
347 [135]. Several compounds exhibited moderated to significant activity especially the N-
348 methylpiperazylcarbohydrazide at C-2 derivative, which displayed IC_{50} values in the range of 1.15–
349 8.46 μM for all cell lines tested. The highest cytotoxicity was observed towards ovarian cancer cell
350 lines (OVCAR-3) with IC_{50} of 1.15 μM . It seems that the interaction with DNA, enzymatic or receptor
351 systems are the most commonly mode of action observed for antitumor β -carboline compounds.

352 Interestingly, some canthin-5,6-dione derivatives showed antitumor activity against P-388
353 murine leukemia cells and P-6 human lung carcinoma cells [147]. The antiproliferative effect of a
354 commercially available canthin-6-one was examined dose-dependently on six cancer cell lines (human
355 prostate, PC-3; human colon, HT-29; human lymphocyte, Jurkat; human cervix, HeLa; rat glioma, C6;
356 and mouse embryonic fibroblasts, NIH-3T3)¹⁴⁸. Strong antiproliferative effects of the compound were
357 observed in all cell lines, whereas cytotoxic effects were very dependent on cell type. The data
358 suggested that the primary effect of canthin-6-one is antiproliferative, possibly by interfering with the
359 G2/M transition.

360 The activity of *Z. chiloperone* var. *angustifolium* alkaloids (canthin-6-one, 5-methoxycanthin-
361 6-one and canthin-6-one N-oxide) and some close analogues ((4,5-dihydrocanthin-6-one, 10-
362 methoxycanthin-6-one and 10-benzyloxycanthin-6-one) were evaluated against malignant
363 glioblastoma cells [149]. 10-benzyloxycanthin-6-one revealed an effect of 40% of maximal viability
364 loss in TG1 cells and 85% of maximal viability loss in TG10 cells when at the same time no viability
365 changes were observed on NSC24 making this compound the most selective of the series.

366 The de Feo group utilizing *in vitro* bioassay studies, investigated the antiproliferative and
367 cytotoxic effects of the 1-methoxycanthin-6-one isolated from *Ailanthus altissima* (Tree-of-Heaven)
368 [150,151]. They also showed that 1-methoxy-canthin-6-one induced apoptosis *via* a *c-jun* NH₂-
369 terminal kinase (JNK) [152].

370 The AKT is a serine/threonine kinase that recently garnered attention as a promising target for
371 cancer therapy due to its critical role as a regulator of the cell's apoptotic machinery. A series of
372 synthetic canthine alkaloids were shown to be potent and selective AKT kinase inhibitors that induced
373 apoptosis in LnCaP cells [153].

374 Recently, quassidine E, a unique derivative of canthin-6-one, showed potent inhibitory activity
375 on the production of nitric oxide (NO), tumor necrosis factor α (TNF α), and interleukin 6 (IL-6) in
376 mouse monocyte-macrophage RAW264.7 cells stimulated by lipopolysaccharide (LPS) [64].

377 A bioassay-guided purification on the root extract yielded two alkaloids canthin-6-one and
378 bruceolline J which were further investigated for their bioactivity in representative human cancer lines
379 and normal phenotypic counterparts [154]. Canthin-6-one was able to synergize the cytotoxic effect of
380 cisplatin when used in combination, suggesting the potential of combination therapy for those less
381 responsive lesions to standard chemotherapy.

382 Recently, a biochemical study showed that canthin-6-one inhibited basal soluble guanylate
383 cyclase (sGC) activity in a dose dependent manner at micromolar range [155]. The electrochemical
384 analysis of sGC-canthin-6-one interactions was achieved by the solution-phase and solid-state
385 voltammetry. The electrochemical data suggest that deactivation of sGC by canthin-6-one operates via
386 a coordinating pathway rather than a direct oxidation of the metal center, the canthin-6-one
387 coordination possibly does not affect the Fe-His bond, but involves binding to the sGC active site in
388 different orientations. Such mechanisms appear to be strongly influenced by structural/conformational
389 constraints allowing for the occurrence of that oxidative pathway under determined circumstances.

390 Vieira Torquato *et al.* showed that canthin-6-one could affect Kasumi-1 cells by promoting cell death,
391 cell cycle arrest and cell differentiation depending on concentration used [156]. Canthin-6-one also
392 promoted differentiation of Kasumi-1, evidenced by an increase in the expression of myeloid markers
393 (CD11 b and CD15) and the transcription factor PU.1.

394 The voltammetry of immobilized particles (VIMP) was used to study a possible correlation between
395 the solid-state electrochemistry of canthin-6-one compounds and their anti-proliferative activity
396 against cancer stem cells [157,158]. There was no single, direct correlation between anti-proliferation
397 activity, which is a complex biochemical process, and solid state electrochemistry, where interfacial
398 electron transfer processes are involved, current data suggest that the ability to experience the one-
399 electron reduction of the naphthyridone motif present in the canthin-6-one structure could be a crucial
400 aspect potentially related to biochemical activity.

401 **5.5. Antibacterial activity**

402 Over twenty canthin-6-one alkaloids have been bioassayed for their antimicrobial activity.
403
404 Activities of various canthinones against a number of bacterial strains were minor compared to that of
405 streptomycin. Activity was observed to increase with a hydroxyl group on the canthin-6-one nucleus
406

407 and decrease when the hydroxyl group was substituted for a methoxyl group. Some canthinones,
408 however, were found to inhibit the growth of *Staphylococcus aureus* and its drug-resistant strains [40].
409 The bacterial type II topoisomerase DNA gyrase (GyrA) and topoisomerase IV are validated targets
410 for clinically useful antimicrobial drugs. The canthin-6-one was proposed as highest-scoring GyrA
411 targeted compounds identified by molecular docking [159].

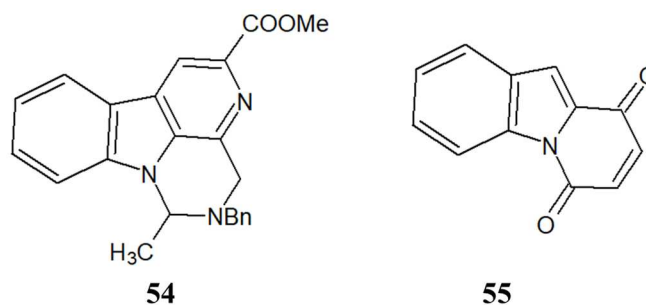
412 Recently, the *in vitro* screening for antimicrobial activity revealed that two 5-substituted canthin-4-
413 ones (3-pyridyl, 2-bromophenyl) exhibit significant activity against *Streptococcus entericus*, coupled
414 with high selectivity and the lack of cytotoxicity against mammalian cells. The intact canthin-4-one
415 ring system was demonstrated to be essential for antibacterial activity [160].

416 Dai *et al.* have synthesized hydrophilic analogs of canthin-6-one via an easier synthetic route and
417 evaluated their *in vitro* antibacterial activities against Gram-positive (*Staphylococcus aureus* and
418 *Bacillus cereus*) and Gram-negative bacteria (*Ralstonia solanacearum* and *Pseudomonas*
419 *solanacearum*) [161]. The data clearly indicated that some compounds such as 3-*N*-benzylated
420 derivatives, were more potent than canthin-6-one and may become lead compounds for further
421 diseases-relevant studies even if the mechanism of these compounds' antibacterial activity is still
422 ongoing to explore.

423 In accordance with previous studies, Li *et al.* developed twenty-two new 3-*N*-benzylated 10-methoxy
424 canthin-6-ones synthesized through quaternization reaction [162]. They discussed the *in vitro*
425 antibacterial activity against three bacteria *R. solanacearum*, *P. syringae* and *B. cereus*. Moreover, the
426 structure–activity relationships (SARs) were carefully summarized in order to guide the development
427 of antibacterial canthin-6-one agents. Two highly active compounds (CH₂Ph(3,4-dichloro) and
428 CH₂Ph(*m*-I) 3-*N* substituents) displayed 8-fold superiority (MIC = 3.91 µg/mL) against agricultural
429 pathogenic bacteria *R. solanacearum* and *P. syringae* compared to agrochemical streptomycin sulfate,
430 and exhibited potential activity against *B. cereus* while showing good “drug-like” properties, low
431 cytotoxicity, and no inhibition on seed germination.

432 Dai and coworkers synthesized, in one hand, C₂, C₅ modified and D rejjiggered ring canthin-6-ones, on
433 the other hand, C₁₀ and truncated canthin-6-ones, in order to study their antibacterial activity and
434 structure-activity relationships [163,164]. The C₂ substituted and D rejjiggered ring (**54**) compound
435 showed a broad spectrum of antibacterial activity, being active against all the tested bacteria such as *S.*
436 *aureus*, *B. subtilis* (MIC = 12.5 nmol/mL), *MRSA*, *B. cereus*, *R. solanacearum* (MIC = 25 nmol/mL)
437 except *E. coli*. (MIC >200 nmol/mL) [163]. Moreover, the C ring-truncated canthin-6-one (**55**)
438 exhibited also a broad spectrum of antibacterial effect (8-fold superiority against *Staphylococcus*
439 *aureus* and 2-fold superiority against *Ralstonia solanacearum*) than fosfomycin sodium and propineb
440 with a minimum inhibitory concentration value of 2 µg/mL (Schema 15). For both compounds, their
441 bactericidal effects occur by damaging bacterial cell membranes, disrupting the function of DNA
442 topoisomerases or influencing the membrane formation, both of which could lead to cell death.

443
444 **Schema 15.** Structure of C₂ substituted and D rejjiggered ring (54) and the C ring-truncated canthin-6-
445 one (55) [163,164].



446

447

448 5.6. Antiviral activity

449

450 Different canthin-6-one analogs were tested against HIV, 1-methoxycanthin-6-one was the first
 451 example of a β -carboline exhibiting anti-HIV activity, its isomer 5-methoxy-canthin-6-one presents a
 452 higher activity [27,53,54].

453 The antiherpes activity of four kinds of canthin-6-one alkaloids was also evaluated. Among these
 454 compounds, some of them have activity on a level with that of acyclovir, the control. It is noticed
 455 however, that the therapeutic index was small [165].

456 In Chen *et al.* works, crude extracts from the wood of *Picrasma quassioides* and all isolated
 457 compounds have been screened for their inhibitory activities against Tobacco Mosaic Virus (TMV)
 458 [166]. Among these compounds, 4, 5-dimethoxycanthin-6-one inhibited TMV accumulation more
 459 effectively than ningnanmycin with the EC_{50} value of 53.0 $\mu\text{g/mL}$ and mixed with the quassinoid,
 460 nigakilactone B (25 $\mu\text{g/mL}$ each), the canthin-6-one derivative reached a lower EC_{50} value of 36.4
 461 $\mu\text{g/mL}$. This study highlighted the synergistic effects between isolated β -carboline alkaloids and the
 462 quassinoid nigakilactone B against TMV.

463 Compounds of the three plants *viz.* *E. harmandiana*, *S. flavescens* and *A. paniculata* were screened for
 464 antiviral activity against the proteases of the SARS CoV-2 by Verma *et al.* [167]. The molecular
 465 docking and ADMET analysis suggested that canthin-6-one 9-*O*- β -glucopyranoside showed a potential
 466 binding to the Mpro/3CLpro and PLpro and tended to inhibit the replication and transcription of the
 467 virus stopping the virus multiplication.

468

469 5.7. Trypanocidal activity

470

471 The canthin-6-one and some of its analogs isolated from *Z. chiloperone* stem bark exhibited interesting
 472 trypanocidal activity *in vivo* in the mouse model of acute or chronic infection. In addition, the total
 473 extract of alkaloids of *Z. chiloperone* stem bark and leaves led to high levels of parasitological
 474 clearance [6,168].

475 To improve the pharmacological effect of the antiprotozoal and antifungal canthin-6-one,
 476 biodegradable poly(octylcyanoacrylate) matrix loaded with the alkaloid nanoparticles (170 nm average
 477 size) have been proposed by Arias *et al.* [169]. The canthin-6-one loading to the polymeric matrix
 478 during the polymerization process yielded very appropriate drug-loading values and a biphasic
 479 (controlled) drug release profile.

480 Silva's group discussed also antiprotozoal activities of synthetic benzocanthin-6-one derivatives with
481 the N-methylpiperazylcarboxamide at C-2 compound showing the best IC₅₀ of 0.40 ± 0.01 μM against
482 *Trypanosoma cruzi* parasite [135].

483

484 **5.8. Cyclic AMP phosphodiesterase inhibitory activity**

485

486 The inhibitory activities on cyclic AMP phosphodiesterase of canthinones found in *Ailanthus*
487 *altissima* and *Simaba cuspidate* were examined. They showed relatively high inhibitory activities
488 stronger than the control compound, the papaverine [170,171].

489

490 **5.9. Other activities**

491

492 Several quassinoids isolated from *Ailanthus altissima* and *Eurycoma longifolia* showed
493 amoebicidal activity determined by bioassay using *Entamoeba histolytica* [172-174].

494 Some canthinones manifested phototoxicity on bacteria and fungi on irradiation with near-UV light
495 (320-400 nm). These compounds inhibited mitosis of chinese hamster ovary cells and induced
496 chromosomal changes. It was apparent that the two compounds could be photosensitizers, though their
497 activities were weaker than 8-methoxypsoralen, the control [175].

498 The rate of blood flow in the stomach intestine of rabbits was assayed *in vivo* by the hydrogen
499 clearance method. Canthin-6-one and some derivatives (nigakinone and 4, 5-dihydrocanthinone)
500 increased the blood flow rate in the intestine by 15, 25 and 35 %, respectively. In the stomach,
501 however, canthin-6-one increase the rate only 10 % and nigakinone decreased it [165].

502 The pharmacological mechanism of action of the antiulcer effects of the methanol extract of *Simaba*
503 *ferruginea* and its canthin-6-ones were studied. The results of this study indicate that canthinones are
504 the compounds responsible of the antiulcer action of the extract [176].

505 In a recent study, Yuan *et al.* identified canthin-6-one as a potent ubiquitin-proteasome-system (UPS)
506 activity enhancer which promoted alpha-synuclein (α-syn) degradation, a drug target used in the
507 pathology of Parkinson disease [177].

508 *Picrasma quassioides* stems extract with EtOAc revealed potential neuroprotective activities in L-
509 glutamate-stimulated PC12 and Aβ₂₅₋₃₅-stimulated SH-SY5Y cell models and improved memory and
510 cognitive abilities in Alzheimer disease mice induced by amyloid-β peptide in Guo *et al.* research
511 [178]. Among the *Picrasma quassioides* stems extract, nearly twenty compounds have been isolated
512 including seven canthin-6-ones alkaloids. Except for canthin-6-one, all derivatives showed potential
513 neuroprotective activities *in vitro* with a cell proliferation rate of 1.06 % – 56.25 % at the dosage
514 ranging from 10 μM to 40 μM in above cell models.

515 Sasaki *et al.* have screened natural or chemical synthetic canthinone alkaloids and β-carboline
516 alkaloids for their cerebral protective effects at 100 mg/kg (p.o.) in ischemic animal, which provided a
517 disease model of dementia [179]. Picrasidine O was improving learning and memory performance,
518 inhibiting delayed neuronal cell death induced by cerebral ischemia, (reducing neuronal cell death
519 induced by the excitatory neurotransmitter, glutamic acid and the excitotoxin, kainic acid, and
520 decreasing the extent of brain tissue damage. Moreover, picrasidine O was shown to have no effect on
521 heart rate or mean blood pressure.

522 Screening of a natural compound library resulted in six canthinone alkaloids, namely, picrasidine L (3-
 523 methylcanthin-5,6-dione), 3,4-dimethyl-canthin-5,6-dione, 4-ethyl-3-methyl-canthin-5,6-dione,
 524 eurycomine E (3-methyl-9-methoxycanthin-5,6-dione), 5-methoxy-canthin-6-one, and 5-acethoxy-
 525 canthin-6-one, as novel protein tyrosine phosphatase 1B (PTP1B) inhibitors [180]. It is expressed
 526 ubiquitously in the classical insulin-targeted tissues and plays critical roles in negatively regulating
 527 both insulin and leptin signaling cascades [181]. Picrasidine L was found to be the competitive PTP1B
 528 inhibitor with the best inhibitory selectivity between PTP1B and other PTPs.

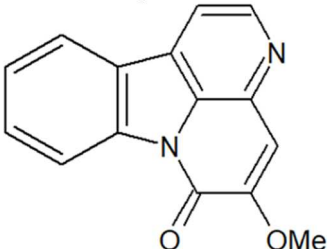
529 Two molecules derivatives from canthin-5,6-dione, amarastelline A and nigakinone, the latter being a
 530 tautomer of 5-hydroxy-canthin-6-one, were isolated as fluorescent natural products from the bark of
 531 *Quassia amara* [182]. They showed respectively strong fluorescence that could stain cytoplasm of
 532 living cells and a solvent-dependent fluorescence properties. By designing and synthesizing canthin-
 533 5,6-dione derivatives, Yokoo *et al.* found that the combination of N^3 - and 10-substituted groups can
 534 regulate the fluorescence properties, and showed that this behavior could be utilized to obtain a
 535 fluorescent sensor responding to a specific range of pH. These findings indicated that the canthin-5,6-
 536 dione moiety could be a valuable scaffold for a range of fluorescent sensors and probes [182].

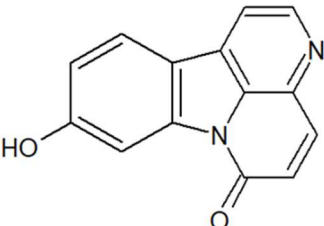
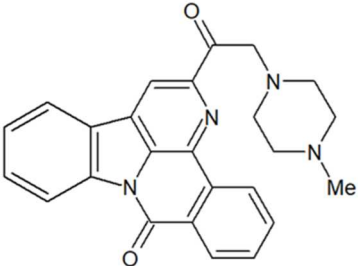
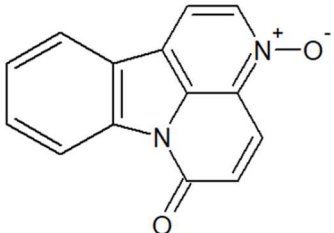
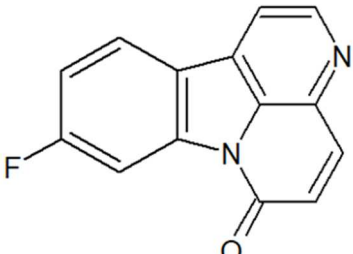
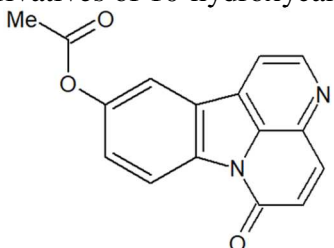
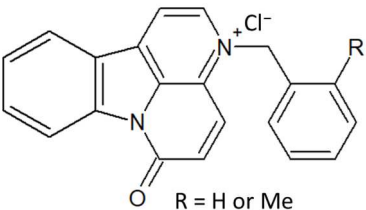
537 Cho *et al.* investigated the anti-inflammatory effects of canthin-6-one and its derivative 5-(1'-
 538 hydroxyethyl)-canthin-6-one both isolated from the stem barks of *Ailanthus altissima* in
 539 lipopolysaccharide (LPS)-stimulated macrophages [183]. These two alkaloids significantly inhibited
 540 the LPS-induced expression of inducible nitric oxide synthase, markedly suppressed the production of
 541 prostaglandin E2 (PGE2) and expression of cyclooxygenase-2, a key enzyme in PGE2 synthesis and
 542 inhibited the phosphorylation of inhibitor kappa B and transcriptional activation of nuclear factor
 543 kappa B (NF- κ B) in LPS-stimulated macrophages. Unlike its derivative, canthin-6-one reduced
 544 monocyte chemotactic protein-1 (MCP-1) and tumor necrosis factor- α (TNF- α) expression and
 545 reduced Akt phosphorylation making it a potential anti-inflammatory agent in LPS-stimulated
 546 macrophages through the downregulation of both the NF- κ B and the Akt pathway.

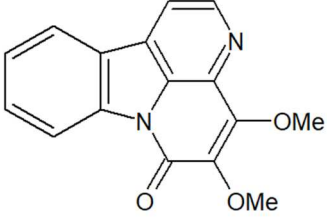
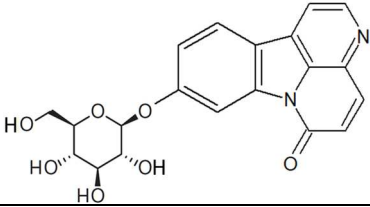
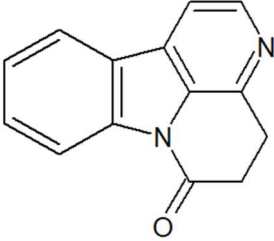
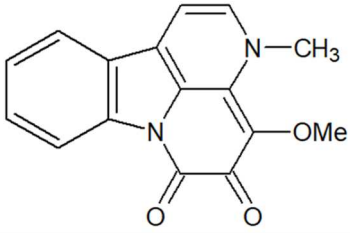
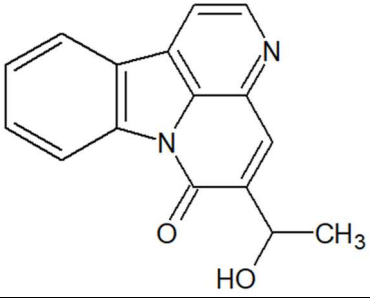
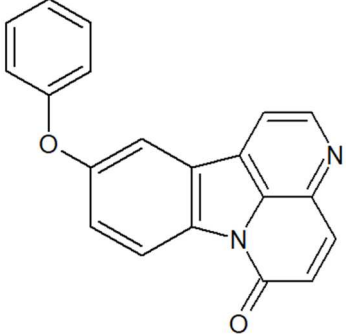
547 Similarly, Zhang *et al.* studied canthin-6-one alkaloids from Thailand *E. longifolia* roots conducted for
 548 searching anti-inflammatory agents [29]. All the isolated alkaloids were evaluated for their inhibitory
 549 effects on lipopolysaccharide (LPS)-induced nitric oxide (NO) production in RAW 264.7 cells at a non
 550 toxic concentration of 50 μ M and exhibited inhibitory effects on NO release significantly comparing
 551 with the control group.

552 Table 2 displays the structure of some natural and synthetic canthin-6-ones derivatives which presents
 553 biological activities.

554 **Table 2.** Structure of few canthin-6-one alkaloids with their biological activities.

Molecules	Biological activities
<p>*5-methoxycanthin-6-one</p> 	<p>antileishmanial [14, 134], antimalarial [136], antiviral [54]</p>

<p>*9-hydroxycanthin-6-one</p> 	antimalarial [27]
<p>**N-methylpiperazyl-6-oxobenzo[4,5]canthine-2-carboxamide</p> 	antileishmanial, antitumor, trypanocidal [135]
<p>*Canthin-6-one-3-N-oxide</p> 	antifungal [80,139]
<p>**9-fluorocanthin-6-one</p> 	antifungal [80]
<p>**ester derivatives of 10-hydroxycanthin-6-one</p> 	antifungal [142]
<p>** 3-N-benzylated canthin-6-ones</p>  <p>R = H or Me</p>	antibacterial [161]
<p>*4,5-dimethoxycanthin-6-one</p>	antiviral [166]

	
<p>* Canthin-6-one-9-O-β-D-glucopyranoside</p> 	antiviral [167]
<p>*4,5-dihydrocanthin-6-one</p> 	Blood flow rate in intestine increasing [165]
<p>* Picrasidine O</p> 	improvement of learning memory performance [179]
<p>*5-(1'-hydroxyethyl)-canthin-6-one</p> 	anti-inflammatory [183]
<p>**10-benzyloxycanthin-6-one</p> 	antitumor [149]

555 * Natural molecules from plants extract; ** synthetic molecules.

556

6. Quantification and optimization of production

Classical methods such as NMR and Mass spectroscopies are used to identify canthinones alkaloids from plants extracts, however, analytical method in separation and quantification of canthin-6-one alkaloids are limited.

Ferreira and coworkers characterized compounds of different organs of *Zanthoxylum chiloperone* by HPLC–UV–MS qualitatively and quantitatively [6]. They investigated the ethanol extracts of stem bark, leaves, fruits, root bark and resin as well as the dichloromethane extracts of stem bark and leaves. Qualitatively, canthin-6-one was identified as the major compound in the stem bark and root bark, while 5-methoxy-canthin-6-one was the major compound in the leaves, fruits and resin, lastly canthin-6-one N-oxide was present in the resin and in the stem bark. Quantitative analysis was performed by external standard method, using a calibration curve constructed utilizing solutions containing different concentrations of the reference samples. Results showed relative compounds concentrations in the different organs. Canthin-6-one concentrations in the ethanol extract of stem and the root bark are 64.7 and 8.2 mg/g extract respectively, while 5-methoxycanthin-6-one concentrations in the ethanol extract of the leaves, the fruits and the resin are 10.8, 3.5 and 5mg/g extracts respectively. Concerning canthin-6-one N-oxide into the ethanol extracts of the stem bark and resin they found concentrations of 8.2 and 1.9 mg/g of extract respectively.

Similarly, Chaingam *et al.* [17] achieved analytical quantification on *Eurycoma longifolia* Jack and *Eurycoma harmandiana* Pierre using high-performance liquid chromatography (HPLC) with UV detection at 354 nm. *E. harmandiana* species contained high amount of total canthin-6-one alkaloids (1.72 ± 0.06 mg/g) compared to *E. longifolia* (0.16 ± 0.01 mg/g). In addition, they tested different solvent extracts (methanol, hydro-methanol (50%), ethanol, and hydro-ethanol (50%)), and showed maximum of canthin-6-one content was observed from 50% methanolic extract followed by 50% ethanolic, methanol and ethanol extracts, respectively. The HPLC method seemed to be a simple, accurate and selective analytical technique for separation and quantification of canthin-6-one alkaloids.

Cebrian and coworkers used another analytical method to estimation amounts of canthin-6-ones alkaloids via cyclic voltammetry [8]. They studied leaves, fruits, seeds, stem barks and roots parts of *Zanthoxylum chiloperone* var. *angustifolium* and estimated the relative amounts of canthin-6-one, 5-methoxycanthin-6-one and trans-avicennol by discussing the peak current values for the corresponding cathodic peaks. Canthin-6-one was the most recurrent compound followed by 5-methoxycanthin-6-one then trans-avicennol in the different parts of the *Zanthoxylum chiloperone* species. Without resorting to sample specific pre-treatment, voltammetry of microparticles methodology appeared to be a relevant tool for phytochemical analysis.

A singular method has been employed by Parikrama *et al.* to increase secondary metabolites content from plant callus culture [184]. Elicitation technique was carried out to evaluate *Eurycoma longifolia* callus culture growth and to analyze its secondary metabolites production after elicitation. Ultraviolet light radiation slightly changed the structure of *Eurycoma longifolia* callus culture without decrease biomass growth. Alkaloids production from *E. longifolia* callus culture, particularly pyrrolidine and canthin-6-one could be increased by 18 hours of ultraviolet exposure daily. GCMS analysis showed that *E. longifolia* callus culture in Murashige-Skoog medium with naphthalene acetic acid and elicited by UV light produced canthin-6-one alkaloid 3.5 times more and pyrrolidine 1.5 times more compared

599 to unelicited culture. It can be concluded that UV elicitation is a useful technique to enhance secondary
600 metabolites production from *E. longifolia* callus culture, by generating protein involved in alkaloids
601 and terpenoids synthesis pathway.

602

603 7. Conclusions

604 A thorough update over the last seventy years have been done on the canthin-6-one alkaloids
605 family. All the canthinone derivatives known to date have been listed and classified according to their
606 taxonomy. Their recurrence and diversity have been compared showing the poor diversity of the
607 largest families. Biosynthesis and synthetic routes have been discussed. The latest were differentiated
608 by C₈N₂ + C₆, C₁₂N₂ + C₂, C₁₀N₂ + C₂ + C₂ and C₁₀N₂ + C₄ strategies. Biological activities of canthin-
609 6-one alkaloids compounds were also enumerated with other activities such as their fluorescence
610 sensor capacity. Finally, recent relevant quantitative methods were quoted as well as a technique
611 allowing production of canthinone derivatives by stimulated plants. Further research, based on
612 calculation methods could be employed for a better understanding of structure-activity relationships
613 and mechanisms.

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620 References

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622

623 References and Notes

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