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Flavoquinones: Occurrence, Synthesis and Biological Activity

Flavoquinonas: Ocorrência, Síntese e Atividade Biológica

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Flavonoids are an important class of natural metabolites having diverse biological activities, and are therefore the focus of many phytochemical, synthetic and biological studies. Among the flavonoids is a group of compounds having a quinone nucleus in their structure, generically named flavoquinones. While that group of compounds has not yet been intensively explored, they demonstrate significant potential biological activity that indicates their importance to investigative work. As such, this review presents a collection of studies encountered in the literature that discuss the occurrence, synthesis, and biological activities of flavoquinones.

Keywords: Flavonoids; quinones; flavoquinones.

1. Introduction

A large number of natural chemical compounds have attracted the interest of the scientific community because of their very diverse pharmacological and biological properties. Flavonoids compose one such class of natural products that have been widely studied and investigated. Large numbers of flavonoids have been isolated from different plants, while others have been synthesized. Among the flavonoids, a small group of molecules have within their structures a quinone nucleus. Those flavoquinones are known for their significant synthetic and pharmacological relevance, and were first synthesized in the 1940s by Rao and Balakrishna[1,2] in their work with pedicinin (**1**) (Figure 1), which is a chalcone and its analogues. One of the first reports of those molecules occurring in nature was published by Seshadri, who isolated carthamone (**2**) (Figure 1) from *Carthamus tinctorius* flowers.[3] Many other such molecules were discovered in the following years and had their biological activities examined. (2*S*)-7-methoxy-3',4'-dihydroxy-5,8-quinoflavan (**3**) (Figure 1) isolated from the leaves of *Ilex centrochinensis*, for example, demonstrates promising anti-inflammatory activity.[4] With an eye to their potent utility, there has been increasing interest in flavoquinone extraction, identification and synthesis. There are, however, only a very limited number of published articles examining the principal findings on those themes. It is important to note that in this article the term flavoquinones refers to compounds that have a quinone nucleus in their structure within a flavonoid skeleton, not to be confused with the term flavoquinones used by Lauterwein *et al.*[5] in their work, which uses the term flavoquinones to refer to flavins in their oxidized state.

2. Naturally Occurring Flavoquinones

The number of natural flavonoids with a quinone nucleus in their structure is rather small when compared to the number of known flavonoids. Nonetheless, some of those substances have been intensively studied in terms of their extraction and isolation, structural characterization, and biological properties. Those aspects will be discussed in the following section.

2.1. Flavanones

Allan *et al.* [6] described and structurally characterized three flavanone quinones using NMR and mass spectrometry techniques. The first was remerin (**4**) (Figure 1), isolated from *Remiria maritima*. Those authors also use chemical transformation to confirm its structure. It was possible to obtain **4** starting with 7-OCH_3-hesperetin and utilizing Fremy's salt as an oxidant. The other two flavanone quinones studied were breverin (**5**), isolated from *Cyperus*

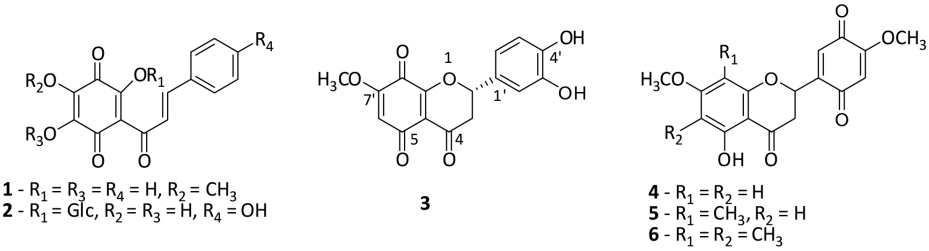
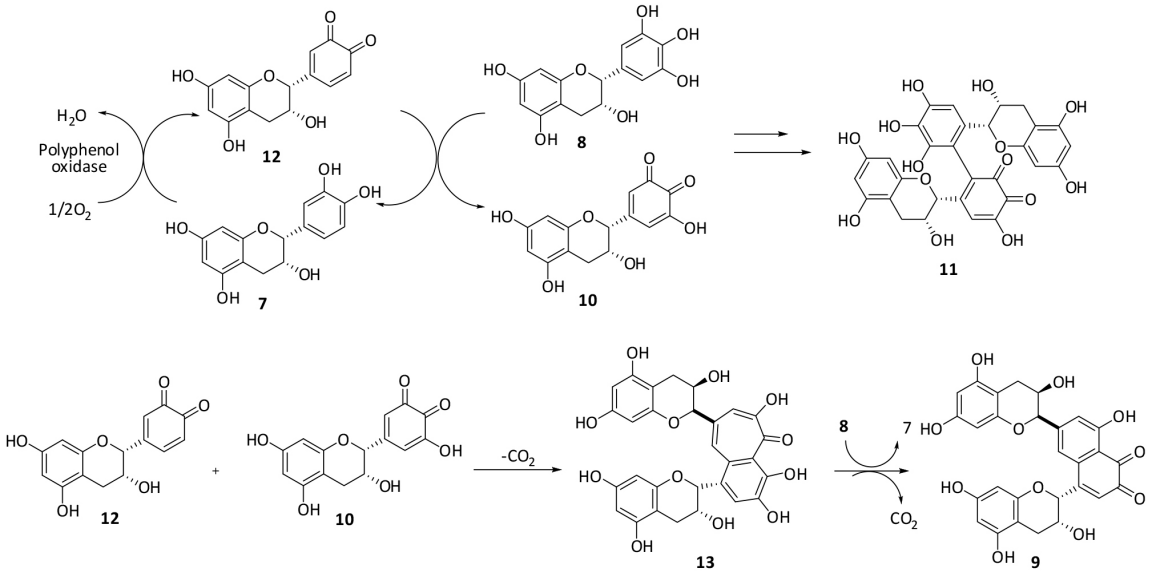


Figure 1. Structures of pedicinin **1**, carthamone **2**, (2*S*)-7-methoxy-3',4'-dihydroxy-5,8-quinoflavan **3**, remerin **4**, breverin **5** and scaberin **6**



Scheme 1. Chemical transformations for obtaining **9** and **11**

brevibracteatus, and scaberin (**6**)**,** isolated from *Cyperus scaber* [6] as shown in Figure 1. Those compounds were also later isolated by Brown and Thomson.[7]

2.2. Flavan-3-ols

Tanaka *et al.* [8–10] treated a mixture of (-)-epicatechin (**7**) and (-)-epigallocatechin (**8**) with an aqueous extract of a fresh tea made from *Camellia sinensis var. assamica* leaves, producing theanaphthoquinone (**9**). Similar results were also obtained by similar reactions with extracts of bananas, apples, potatoes, sweet potatoes, persimmon, "black nespera", mushrooms, and blueberries. All told, 16 plant homogenates were found to furnish **9**, all of them between pH 3.5 and 5.5; the isolated product was yellow and was identified using ^{1}H and ^{13}C NMR techniques, as well as two-dimensional (2D) spectroscopy. Those authors also performed a condensation reaction of **9** with *o*-phenylenediamine, producing a corresponding phenazone. The treatment of **7** and **8** separately with the banana extract did not produce the desired product, indicating that it must be formed in a reaction with both catechins. The oxidation of **8** by the banana homogenate[11] produced not only the expected (-) – epigalocatechinone (**10**) but also a corresponding dimer **11**. The experiments performed by those authors suggested that **7** was rapidly oxidized to stage of quinone **12,** while the oxidation of **8** was very slow. In a mixture of the two, with a banana homogenate, for example, **9** was obtained from the theaflavin (**13**) formed, with the latter compound being oxidized by **12** as, in the absence of **7,** theaflavin is obtained with yields higher than 88%, while less than 3% of **9** is formed. The mechanism proposed by those authors is demonstrated in Scheme 1.

The structure of **11,** as presented in the scheme mentioned above, was confirmed[12] by its capture as a derivative of phenazine **14** (Figure 2) and observed in HPLC. Additionally, as with **9**, **10** and **12**, the product was characterized by ^{1}H and ^{13}C NMR, HMBC and FABMS.

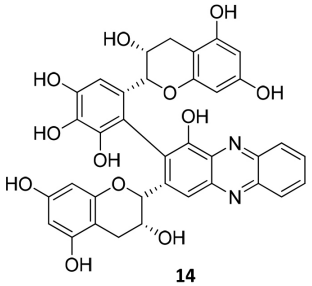
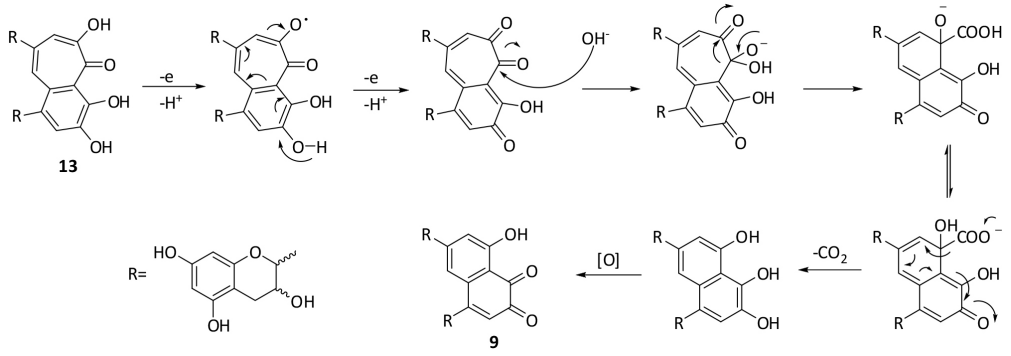


Figure 2. Phenazine **14** structure

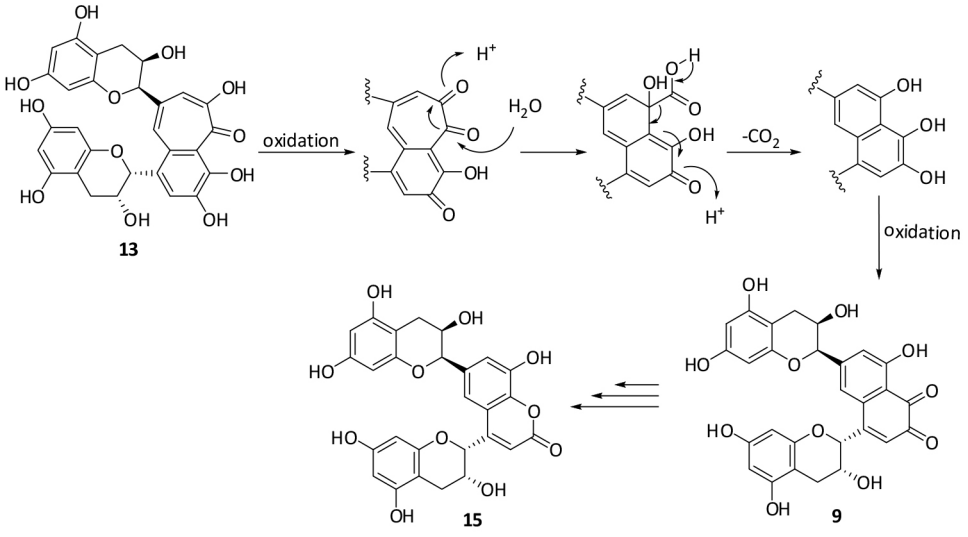
Jhoo *et al.* performed the oxidation of **13** to **9** using two different techniques: the first used 2,2-diphenyl-1-picrylhydrazyl (DPPH), while the second use a system of peroxidase/hydrogen peroxide.[13] In both systems, **9** was the majority product, being isolated using chromatographic techniques and characterized by NMR and EI-MS. Those authors proposed a free radical mechanism to obtain the desired product, in which benzotropolone would be responsible for donating an electron (as it was stabilized by resonance structures), followed by a nucleophilic attack on one of the ketone portions of benzotropolone, thus rearranging the molecule, losing a CO_2, and oxidizing the catechol to form product **9** (Scheme 2).[13] Matsuo *et al.* also observed the formation of **9** in their studies of the synthesis of theaflavins with DPPH, and those authors reported that the heavy use of the free radical reagent resulted in a greater formation of **9** than of **13**.[14]

9 was reported by O'Coinceanainn *et al.* as one of the products obtained from the oxidation of **13** in the presence of Fe^{3+} in an acidic environment. That reaction was followed by liquid chromatography coupled to a mass spectrometer (LC-MS), stopped-flow spectrometry, and multivariate analysis. The authors reported **9** as the principal oxidation product of that reaction, as well as that its concentration was dependent on the amounts of iron used. Analysis by FT-IR and NMR verified the structure of **9**.[15] That same product was also obtained by Kusano *et al.* through the enzymatic oxidation of a mixture of **7** and **8**. Those authors reported that only **12** was obtained in the first 10 min, although after 30 min of reaction time **9** was also observed. At 60 min, it was possible to observe the formation of a new product, **15**, and a decrease in **9**. The formation of **9** is proposed according to the mechanism described in Scheme 3.[16]

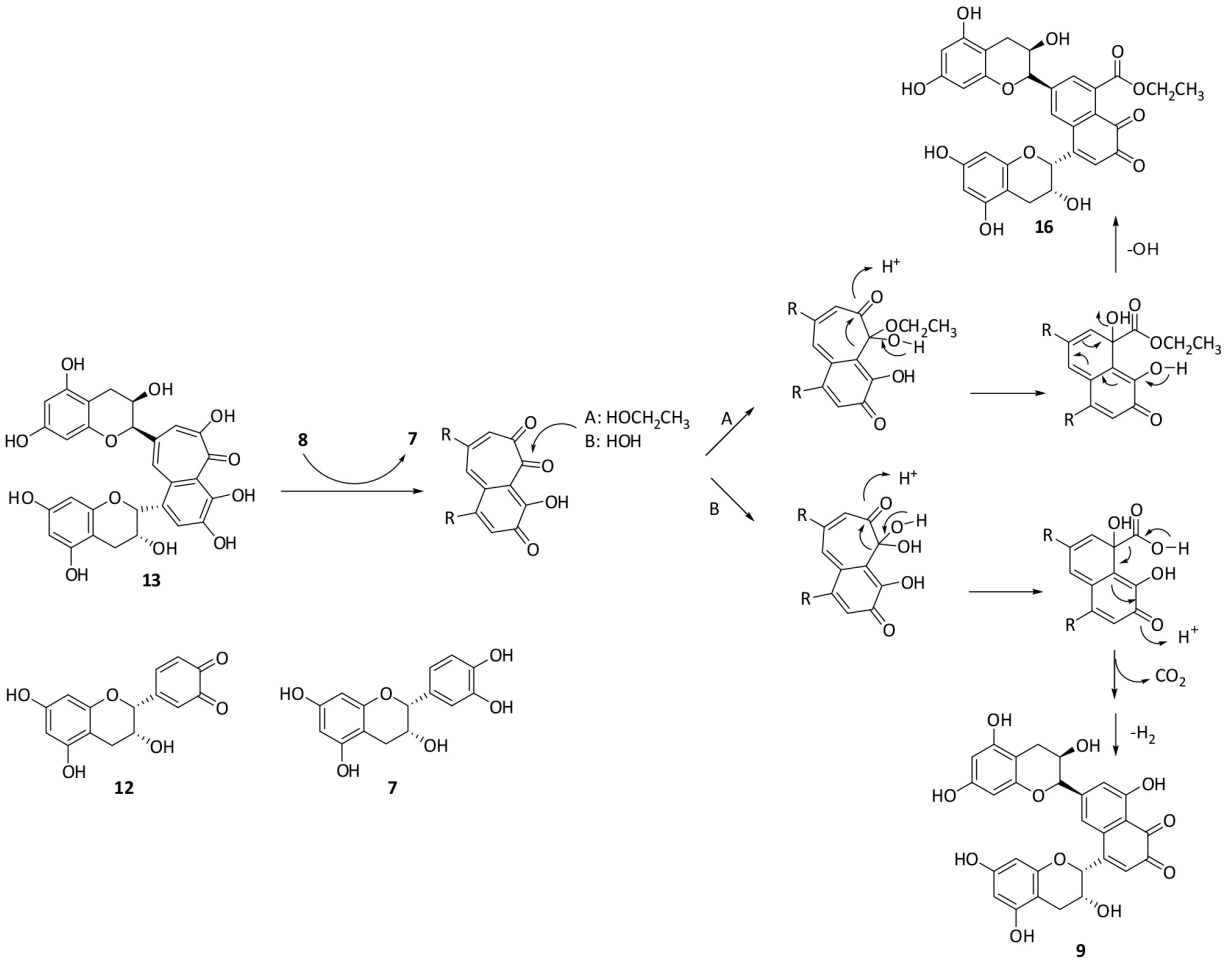
In their studies concerning the oxidation of theaflavin, Li *et al.* observed that by adding ethanol to a mixture of **7** and **8**, together with a homogenate of the *Pyrus pyrifolia*, a new product **16** was formed by oxidation (in addition to the expected product **9**). That product was identified using NMR, UV, MALDI-TOF-MS techniques, and HMQC and HMBC bidimensional correlations. The mechanism (Scheme 4)[17] proposed by those authors is similar to that of Jhoo.[13] The anticancer activity of **9** was evaluated by Weng *et al.*,[18] and it was found to inhibit both epidermal growth factor receptor (EGFR) and ErbB-2 activity induced by Epidermal growth factor (EGF) in breast cancer cells through the suppression of FAS expression in target cells, leading to eventual cell death.



Scheme 2. Radical mechanism in the formation of **9** proposed by Jhoo *et al.* [13]



Scheme 3. Mechanism of compound formation of **9** proposed by Kusano *et al.*[16]

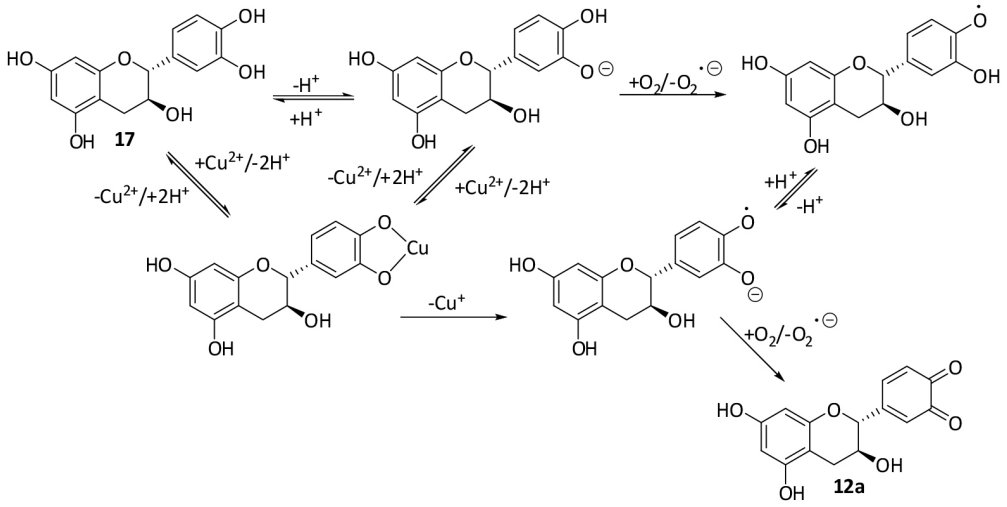


Scheme 4. 9 and **16** formation mechanism proposed by Li *et al*[17]

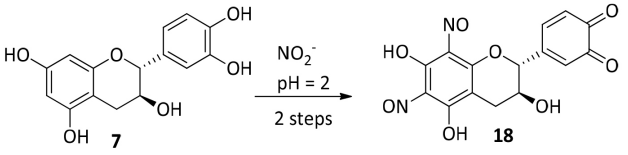
Studies focusing on the primary oxidation of flavan-3-ols, without resulting in the formation of **9**, were also conducted. The compound **12a** was obtained by Yasunaga *et al.*[19] through an enzymatic process utilizing tyrosinase in a Na_2HPO_4/NaH_2PO_4 buffer solution. A study of the reaction conditions of the oxidation of (+)-catechin (**17**) in **12a** with O_2 in a basic solution was performed, evaluating the effects of different conditions on the reaction with the aim of obtaining better synthesis results. Those authors concluded that the quantity of **12a** obtained increased with basicity, and that the monoethanolamine gave the best results among others studied. They also observed that the ideal reaction temperature was 30 °C, that soluble alcohols and water served as good co-solvents, and that the exact water/alcohol proportions depended on the type of alcohol used.[20] Those same authors studied the effects of Cu^{2+} on the oxidation rate of **17**. That reaction was analyzed using UV-Vis spectroscopy, and it was possible to conclude that the formation rate of **12a** increased with increasing pH; in systems in which Cu^{2+} was present, however, the formation rate maximized at pH 8.8, with Cu^{2+} acting in the production of a radical intermediate to be oxidized, thus stabilizing the formation of the (+)-catechin-Cu^{2+} complex.[21,22] The mechanism of oxidation catalyzed (or not) by Cu^{2+} ions (Scheme 5) is proposed based on work by Mochizuki *et al.*, who analyzed the kinetic and mechanistic aspects of the auto-oxidation of the catechins.[23] The importance of that molecule rests in its use as a hair dye. Studies demonstrated that **12a** was not aggressive to rabbit skin, and that the addition of biological material would create a variety of colors.[19,21] Compound **12a** was also obtained by the oxidation of the catechin using an activated periodate resin in acetonitrile.[24]

Morina *et al.* reported the formation of 6,8-dinitrous-catechin-quinone (**18**) during the digestion of foods containing **7** (Scheme 6). Those authors discussed the formation of that compound under conditions similar to those found in stomachs, and the possible health problems that substance could cause if absorbed, as it is formed in the presence of reactive oxygen species.[25]

A computer study of molecular docking, as well as free binding energy calculations, were performed with epigallocatechin-3-gallate (EGCG) and its metabolites to determine if there was any relationship between reports of hepatotoxicity and the consumption of large amounts of green tea (which contains, as its principal component, EGCG).[26] Among the molecules studied, six were catechol-quinones (shown in Figure 3), although only the metabolite



Scheme 5. Oxidation mechanism of (+)-catechin by O_2 in a basic medium catalyzed or not by Cu^{2+}



Scheme 6. Synthesis of **18** by oxidation with HNO_2

19 demonstrated potential inhibitory activity against human NAD[P]H-quinone oxidoreductase 1 (NQO1).

Chen *et al.* synthesized hollow biocompatible spheres through the oxidation of catechins in the presence of Cu^{2+}. The copper ion acted in the oxidation and polymerization of the catechins when heated; those molecules then aggregated at lower temperatures to form spheres. The spheres were then tested as possible vehicles to carry other compounds such as fluorescein and anticancer pharmaceuticals as they were glutathione responsive and alkalis responsive and resistant to acids.[27] The reducing properties of the catechins were also studied in terms of the synthesis of nanoparticles of Fe_3O_4 through the reduction of Fe^{3+} ions and the oxidation of catechins.[28] The catechinones formed can then be used as stabilizers of the nanoparticles. Those reactions have demonstrated advantages over methods of co-precipitation, as they result in the direct formation of monophasic Fe_3O_4 nanoparticles. The catechinones stabilize the nanoparticles in many media, and demonstrate good biocompatibility with epicatechin and epigallocatechin gallate.[28]

Studies by Chen *et al.* of the conversion mechanisms of type B procyanidins to type A in plants obtained, as one of the products of free radical or enzymatic oxidation, the trimer **25** (Figure 4) in which a quinone ring is present on the terminal ring B. That product was characterized using NMR and MS.[29]

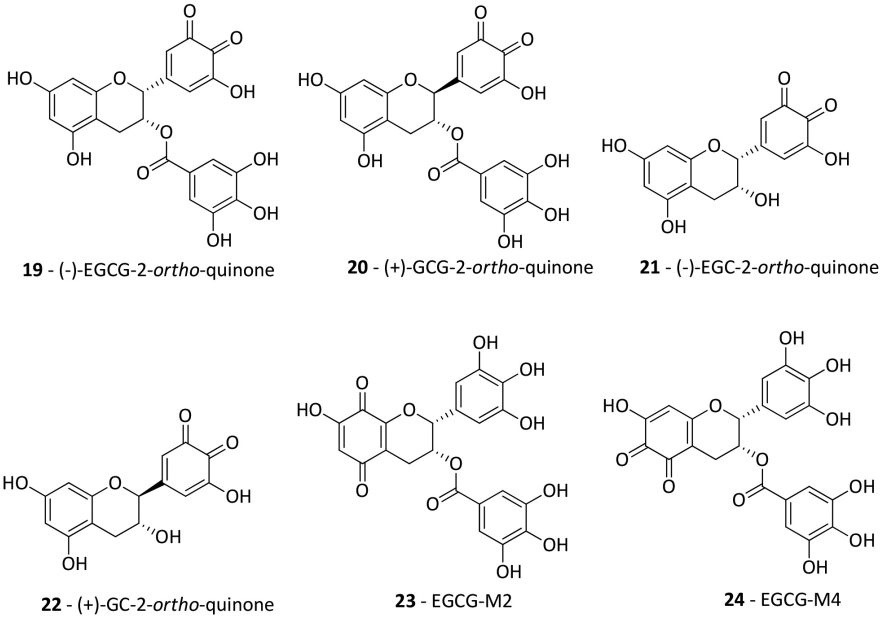
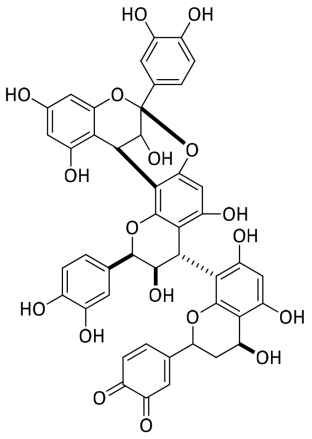


Figure 3. EGCG Derivative Structures



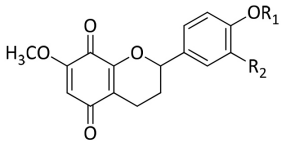
25

Figure 4. Procyanidin trimer structure

2.3. Flavan

In their research with the bioactive compounds of *Ilex*, Li *et al.* encountered two new flavoquinones with flavan nuclei. NMR and MS analyses allowed the elucidation of their structures as (2*R*)-7,3',4'-trimetoxi-5,8-quinoflavan (**26**) and (2*S*)-7-metoxi-4'-hidroxi-5,8-quinoflavan (**27**) (Figure 5). The IV spectra of both evidenced absorption bands attributable to aromatic rings and carbonyl functional groups. ^{1}H and ^{13}C NMR spectra analysis allowed the identification of a flavan nucleus. A benzoquinone nucleus was also identified through HMBC correlations. Both flavoquinones were isolated from *I. centrochinensis* leaves. Cytotoxic activities of both compounds against HuH7 human liver cancer cells and CaCO-2 human colon cancer cells were observed. Both demonstrated weak activity against cell line HuH7, but no activity against CaCO-2 cells.[30] Hu *et al.* published (in 2014) the isolation and the structural identification of a new flavoquinone (hindsiiquinoflavan B) (**28**) (Figure 5) extracted from the stem of *Celastrus hindsii* with an *S* configuration.

The structure of that flavoquinone was elucidated using



(2S) 3 - R_1 = H, R_2 = OH
(2R) 26 - R_1 = CH_3, R_2 = OCH_3
(2S) 27 - R_1 = R_2 = H
(2S) 28 - R_1 = H, R_2 = OCH_3

Figure 5. Structure of flavoquinones **3**, **26, 27** e **28**

IF and NMR techniques. Compound **28** was isolated with a yield of 0.00012%. The cytotoxicity was evaluated against cell lines BC-1 and HuH7, and only moderate to weak activities were observed respectively. Its cytotoxicity against cell lines NCI-H187 and HCT116 were also evaluated, but it was found to be inactive against them.[31]

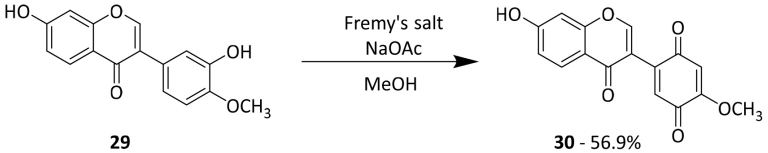
More recently, Hui *et al.* reported the identification of a new flavoquinone, also in an *S* configuration, that contains a flavan nucleus. Compound **3** (Figure 5) was isolated from the leaves of *I. centrochinensis* and characterized using IV, UV, NMR, and HR-ESIMS techniques. That flavoquinone was evaluated in terms of its cytotoxicity and anti-inflammatory activity against RAW264.7 cells. It did not demonstrate cytotoxicity at concentrations below 8 μM, but significantly reduced NO production in that cell line, and demonstrated promising *in vitro* anti-inflammatory activity.[4]

2.4. Isoflavones

Brown and Thomson reported the isolation of bowdichione (**30**) from *Bowdichia nitida* wood, obtaining it from 3'-hydroxy-formononetin (**29**) utilizing Fremy's salt as an oxidant (Scheme 7).[7]

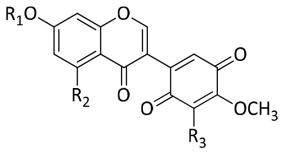
Yahara *et al.* reported the isolation of **30** from *Dalbergia odorifer*.[32] Chan *et al.* similarly isolated **30** from the same plant and evaluated its ability to inhibit the formation of superoxide induced by PMA in rat neutrophils; that substance had an IC_{50} of 0.9 μM. Additionally, the compound demonstrated the ability to reduce exaggerated inflammatory reactions by strongly inhibiting the formation of superoxides induced by PMA.[33] Umehara *et al.* isolated **30** from *Dalbergia parviflora* and reported its activity against the MCF-7 tumor cell line (with an EqE_{10} of 0.7 μM and an EqE_{100} of 0.9 μM), although it did not demonstrate any activity against T47D.[34,35]

In their study of the chemical composition of *Dalbergia canrienatenszs*, Hamburger and Cordell isolated a new isoflavone quinone called 5-hydroxybowdichione (**31**) (Figure 6). That new isoflavone quinone was characterized using UV and IR spectroscopy, mass spectrometry, and ^{1}H and ^{13}C NMR. The compound was evaluated in terms of its *in vitro* antifungal and bactericide activities, although the results were not positive. The authors associated that result with the possible instability of the molecule in solution. It was also not found to be active against *Candida albicans*, *Aspergillus niger*, or *Penicillium expansum*.[36] Brazilian researchers isolated from the resin of *Amburana cearensis* a new substance (**32**) characterized with the techniques of IR, EI-MS, HR-ESI-MS and NMR.[37]



29 **30** - 56.9%

Scheme 7. Synthesis of bowdichione **30**



31 - $R_1 = R_3 = H$, $R_2 = OH$
32 - $R_1 = CH_3$, $R_2 = H$, $R_3 = OCH_3$

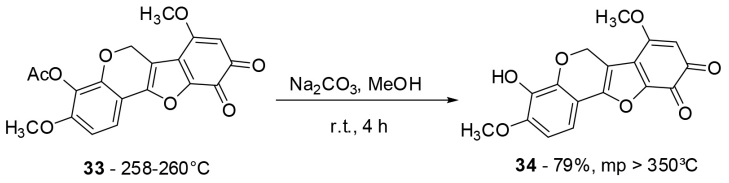
Figure 6. Structures of **31** (5-hydroxybowdichione) and **32**

Bryaquinone (**34**), a pterocarpene (a subclass of isoflavonoids), was isolated from *Brya ebenus*.[37] The authors reported the necessity of its acetylation to be able to separate and isolate it from the plant extract. The acetylated derivative (**33**) was characterized by NMR and mass spectrometry. The product was subsequently hydrolyzed in methanol with sodium carbonate in a reflux operation to give **34** (Scheme 8), which was also characterized by NMR and mass spectroscopy. A second quinone identified 4-deoxybryaquinone (**35**)[38] was isolated together with **33**.

34 and **35** were synthesized by Antus *et al.* (Scheme 9) in a series of reactions that led to the formation of **36,** which was then reduced to produce **37**, followed by a debenzylation and cyclization that was subsequently oxidized to produce **34** utilizing the Fetizon reagent. **35** was obtained using a similar technique.[39]

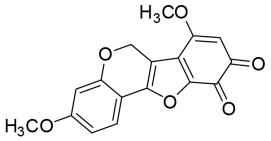
2.5. Isoflavan

The abruquinones A, B and C (**40-42**) (Figure 7) were first isolated by Lupi *et al.* in 1979 from the roots



33 - 258-260°C

34 - 79%, mp > 350°C



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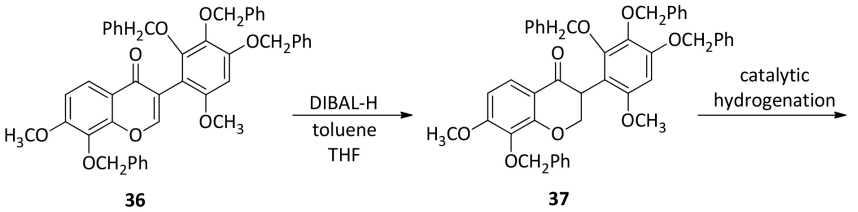
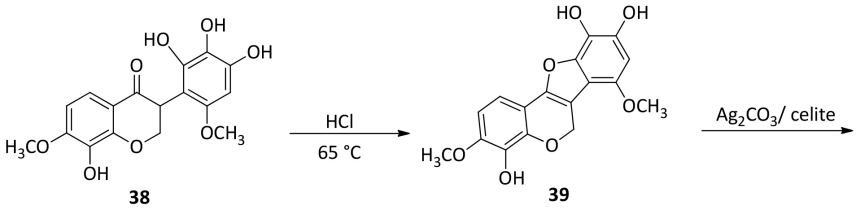
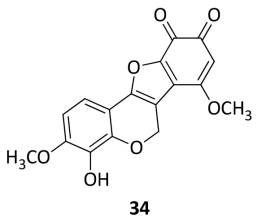
Scheme 8. Structural modification of **34** and structure **35**







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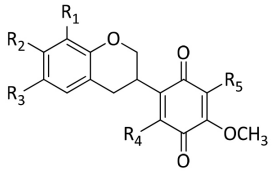
Scheme 9. Synthesis of **34** by Antus *et al* [39]

of *Abrus precatorius*. Kuo *et al.* later reported another three new isoflavanquinones called abruquinones D, E and F (**43-45**) (Figure 7). A study of their pharmaceutical properties indicated the potential activity of (3*S*)- **40** and **41** to inhibit platelet aggregation induced by arachidonic acid (AA) and collagen, while (3*S*)-**44** demonstrated PAF inhibition.

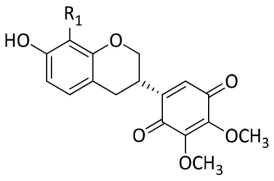


(3S) - 40 - $R_1 = R_4 = H$, $R_2 = R_3 = R_5 = OCH_3$
(3S) - 41 - $R_1 = R_2 = R_3 = R_5 = OCH_3$, $R_4 = H$
(3S) - 42 - $R_1 = R_2 = R_5 = OCH_3$, $R_3 = OH$, $R_4 = H$
(3S) - 43 - $R_1 = R_3 = R_5 = OCH_3$, $R_2 = OH$, $R_4 = H$
(3S) - 44 - $R_1 = R_2 = R_3 = R_4 = R_5 = OCH_3$
(3S) - 45 - $R_1 = OH$, $R_2 = R_3 = R_5 = OCH_3$, $R_4 = H$
(3R) - 46 - $R_1 = R_3 = R_5 = H$, $R_2 = R_4 = OCH_3$
(3S) - 47 - $R_1 = R_2 = R_4 = OCH_3$, $R_3 = R_5 = H$
(3S) - 48 - $R_1 = OH$, $R_2 = R_3 = OCH_3$, $R_4 = R_5 = H$
(3S) - 49 - $R_1 = R_5 = H$, $R_2 = R_4 = OH$, $R_3 = OCH_3$
(3R) - 50 - $R_1 = R_3 = OCH_3$, $R_2 = R_4 = R_5 = H$
(3R) - 51 - $R_1 = R_2 = R_3 = OCH_3$, $R_4 = R_5 = H$
(3S) - 52 - $R_1 = R_4 = OH$, $R_2 = OCH_3$, $R_3 = R_5 = H$

Figure 7 . Structure of some isoflavanquinones

In addition to those activities, (3*S*)- **40**, **41**, **43** and **45** demonstrated anti-inflammatory and anti-allergenic activities.[40] (3*S*)-**41** was isolated by Limmatvapirat witch showed antitubercular activity at a minimum inhibitory concentration (MIC) of 12.5 $\mu g.mL^{-1}$; it also showed antiplasmodial activity (IC_{50}: 1.5 $\mu g.mL^{-1}$) and was cytotoxic to cell lines KB and BC (IC_{50}: 9.9 and 5.7 $\mu g.mL^{-1}$ respectively).[41] In 2013, Hata *et al.* reported the isolation of 3 isoflavanquinones from the seeds and roots of *A. precatorius* that demonstrated strong antiprotozoal activities against *T.b. rhodesiense*. Those compounds therefore became strong candidates for *in vivo* trials against that Trypanosome due to their low cytotoxicity to L-6 cell lines and high selectivity index. (3*R*)- abruquinone I (**46**) (Figure 7), (3*R*)-**41** and (3*S*)-7,8,3‘,5‘-tetramethoxyisoflavan-1‘,4‘-quinone (**47**) (Figure 7) were characterized and their absolute configurations determined. HMBC and COSY correlations were performed to corroborate the connectivity of their rings and the positions of their substitutions.[42] Those same authors reported in the following year the extraction of (3*R*)- **40** and (3*R*) -**43** from the same plant from the same locality, although in a different period of the year. Those molecules had their absolute configurations confirmed using electronic circular dichroism (ECD). Their strong antiprotozoal activities against *Trypanosoma brucei rhodesiense* were also confirmed, with low cytotoxicity to the L-6 cell line and high selectivity – making them promising objects of studies of *in vivo* activity.[43] (3*S*)-**40** and (3*S*)-**41** were extracted from the roots of *Abrus precatorius* from Nigeria by Okoro *et al.*, and they demonstrated *in vitro* antifungal and leishmanicidal activities. Both also demonstrated strong activity against *Leishmania major* and *L. tropica* and moderate antifungal activity against *M. canis* and *F. solani*.[44] More recently, 4 new coumpounds (Figure 7) called abruquinones M, N, O and P (**48**-**51**) were isolated by Okoro and collaborators from the roots of *A. precatorius*. The four molecules were characterized with ^1H and ^{13}C NMR techniques as well as HRESI-MS, UV, IR and HMBC. In addition to these previously unpublished abruquinones, the authors isolated the already know **40**, **41**, **42**, **43**, **44**, **45**, **46** and **52**. The authors evaluated the cytotoxic activity of abruquinones **40**, **41**, **48** and **49** against human squamous cell carcinoma (CAL-27), human colorectal adenocarcinoma (Caco-2) lines and human lung cell carcinoma (NCI – H460) where the compounds significantly reduced cell proliferation, with **41** being the most active against the proliferation of CAL-27 and NCI–H460 cells and **40** being the most active. active against Caco-2. These substances also had their anti-inflammatory activity evaluated, showing good activity in inhibiting reactive oxygen species.[45]

Amorphaquinone (**53**) was isolated for the first time from *Amorpha fruticosa* seeds by Shibata *et al.*;[46] some years later, Ohyama *et al.*[47] extracted isoflavone quinone from the same plant whose structure was elucidated using ^1H and ^{13}C NMR techniques. In 2011, Rahman *et al.* published a study of the extraction and characterizations of (3*S*)-**53** and (3*S*)-pendulone (**54**) (Figure 8), as well as their leishmanicidal, antiplasmodial, antimicrobial, and cytotoxic activities. Isoflavone quinones were also extracted from the leaves of *A. schimperi*. The both molecules were identified using HRESIMS, UV, and ^1H and ^{13}C NMR techniques as well as 2-D (HMBC and HMQC) correlations. Their absolute configurations (3*S*) were defined by studies of circular dichroism (CD) spectroscopy and by optical rotatory dispersion curves (ORD). Both compounds demonstrated potent leishmanicidal activities against promastigotes of *L. donovani,* and against *L. donovani* axenic amastigotes, and amastigotes in macrophage THP1 cultures. Those compounds also demonstrated antiplasmodial activities, although they were less accentuated than the chloroquine standard. (3*S*)-**54** demonstrated moderate bactericidal activity against *S. aureus* and *S. aureus* resistant to methicillin. Both also demonstrated moderate anticancer activity against human tumor cell lines, including SKMEL, KB, BT-549, and SK-OV-3. According to those authors, their report was the first description of the extraction of those types of molecules from the *genus Abrus,* with the determination of their absolute configurations and the evaluation of the leishmanicidal activity of (3*S*)-amorphaquinone (**53**).[48] **53** and **49** were also isolated from the roots of *Apoplanesia paniculata*, and their antiplasmodial and antiproliferative activities were examined. Both demonstrated inhibitory activity in terms of the growth of Dd2 strains resistant to drugs against *P. falciparum*, with IC_{50} of 6 ± 2 μM and

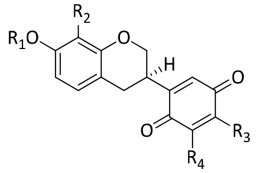


53 - $R_1 = OCH_3$
54 - $R_1 = H$

Figure 8. Structure of (3*S*)-amorphaquinone (**53**) and (3*S*)-pendulone (**54**)

7 ± 1 μM, respectively, and activity against the tumor cell line A2780 (human ovarian cancer), with IC_{50} 6.6 and 19.6 μM respectively.[49]

In their studies of the egyptian species *Astragalus alexandrinus* and *A. trigonus*, El-Sebakhy *et al.* isolated (3*R*)-astragaluquinone (**55**), (3*R*)-mucroquinone (**56**), and (3*R*)-claussequinone (**57**).[50] Those authors reported **55** as being isolated from that species for the first time, while the isolation of the two other substances had already been reported in the literature (Figure 9).[36,51,52]



55 - R_1 = Me, R_2 = OMe, R_3 = H, R_4 = OH
56 - R_1 = H, R_2 = R_3 = OMe, R_4 = H
57 - R_1 = R_2 = R_4 = H, R_3 = OMe
60 - R_1 = Ac, R_2 = R_4 = H, R_3 = OMe

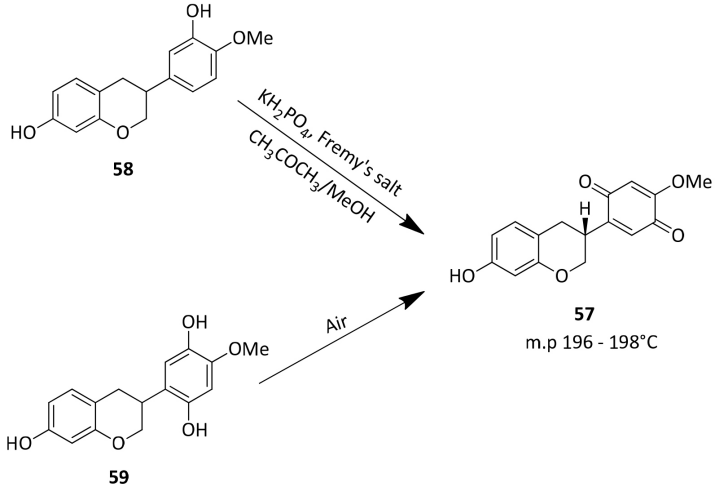
Figure 9. Structure of (3*R*)-astragaluquinone (**55**), (3*R*)-mucroquinone (**56**) and (3*R*)-claussequinone (**57**) and acetyl derivative of claussequinone (**60**)

Farkas synthesized **57** by two different pathways in 1974. The first pathway involved as its first step the cyclization of the corresponding chalcone to obtain an isoflavone, followed by catalytic hydrogenation to obtain **58**, and then oxidation to claussequinone (**57**). The second pathway was similar to the first except for the oxidation step, which occurred using atmospheric oxygen to form the corresponding compound **57** from the hydroquinone **59**. The authors did not dismiss the possibility of obtaining the claussequinone from the oxidation of the corresponding hydroquinone during the isolation of the natural product. Scheme 10 demonstrates the oxidation step in the synthesis of **57**.[53]

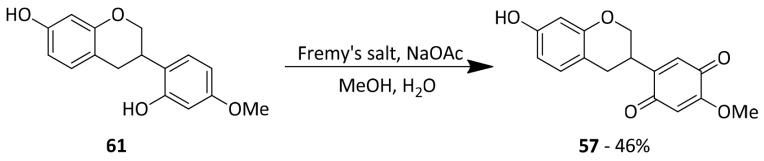
(3*R*)-**57** and (3*R*)-**56** were also isolated by brazilian researchers in 1975 (Gottlieb *et al.* [54]) from *Cyclolobium clausseni* from Minas Gerais State. (3*R*)- **57** was also isolated from *C. vecchii* collected in the Rio de Janeiro Botanic Garden. Those molecules had their structures confirmed using classical techniques of structural elucidation; the absolute configurations were analyzed by ORD curves. Additionally, those authors reported the identification of a mono-acetylated (3*R*)-claussequinone (**60**).[54]

Those same authors undertook the synthesis of (±)-**57** from (±)-vestitol (**61**) (Scheme 11) using Fremy's salt as an oxidizing agent with MeOH/H_2O as a solvent. The precise molecular conformation of the heterocyclic ring of **57** was defined by x-ray diffraction performed by Gambardella *et al*.[55] As was already cited, Hamburger and Cordell isolated (3*R*)-**57** from *Dalbergia canrienatenszs* Prain. They evaluated the *in vitro* antifungal and bactericidal activities against, for example, *Trichophyton mentagrophytes*, although it was not promising; neither did it demonstrate activity against *Candida albicans*, *Aspergillus niger*, or *Penicillium expansum*.[36] According to Goulart *et al.*, (3*R*)-**57** shows potent antimalarial activity. Those authors studied the electrochemical reduction of that molecule and its acetylated derivative in mixed solvents (H_2O/DMF) and in dry DMF.

The authors observed a single reversible transfer of two electrons in the mixed solvent; in dry DMF, they reported two transfers of one electron each, with the second transfer being irreversible. Comparing the results obtained in that study with the acetylated derivative of claussoquinone, the authors concluded that there was an auto-protonation in one of the steps.[56] Emim *et al.* evaluated the anti-inflammatory activity of **57** isolated from *Machaerium villosum* Vog and



Scheme 10. Isoflavan oxidation to obtain claussequinone (**57**)

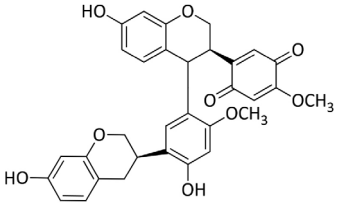


61 **57** - 46%

Scheme 11. Synthesis of (±)-claussoquinone (**57**) from vestitol (**61**)

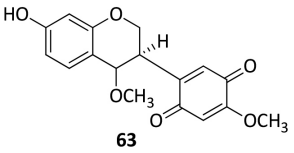
Cyclolobium clausseni, and found it ineffective.[57] Choi *et al.* isolated **57** from *Dalbergia odorifera*, and it demonstrated moderate cytotoxicity against some lines of tumor cells (MES-AS, MES-SA/DX5, HCT15, HTC15/CL02).[58,59]

Yahara *et al.* isolated (3*R*)-**57** from *Dalbergia odorífera* and reported the isolation of a new biflavonoid **62** (Figure 10) that contained a quinone nucleus in its structure. The dimer appeared as a yellow solid, and represented a fusion of **57** and **61**. The structure was characterized using ^{1}H and ^{13}C NMR as well as EI-MS; its absolute configuration was determined by the analyses of the CD Cotton effect.[32,60]



62

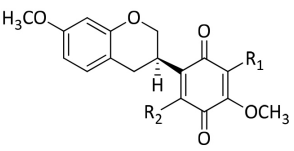
Figure 10. Chemical structure of biflavonoid isolated from *Dalbergia odorífera*



63

Figure 11. Millettilone A (**63**) compound isolated from *M. pendula*

by spectral CD, and that of (3*R*)-**65** by comparisons of its CD curve with those of (3*R*)-**64** and (3*R*)-**57**. The antifungal activities of both colutequinones were evaluated, demonstrating moderate activities against *S. cerevisiae* and *Candida albicans*.[62,63]



64 - R_1 = H. R_2 = OCH_3
65 - R_1 = OCH_3, R_2 = H

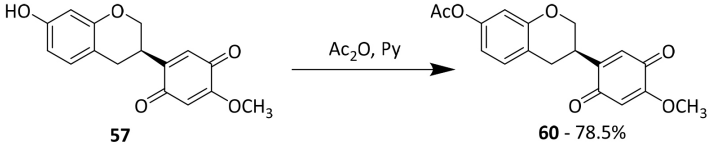
Figure 12. Colutequinone structures

Those authors also reported the synthesis of **60** by classical procedures (Scheme 12).

Takahashi *et al.* isolated, in 2006, an isoflavan-quinone named millettilone A **63** (Figure 11) from the wood of *Millettia pendula,* together with the already known compound, (3*R*)-**57**. The leishmanicidal activities of those compounds were tested against promastigotes of *Leishmania major*, with **59** demonstrating the best results, with an IC_{50} of 0.07 $mg.mL^{-1}$; the other isoflavan-quinones demonstrated only moderate activities [IC_{50} 9.3 $mg.mL^{-1}$ with **58**, and IC_{50} 1.2 $mg.mL^{-1}$ with (3*R*)-**52**]. The isoflavanquinones demonstrated greater activities than molecules containing only the isoflavone nucleus.[61]

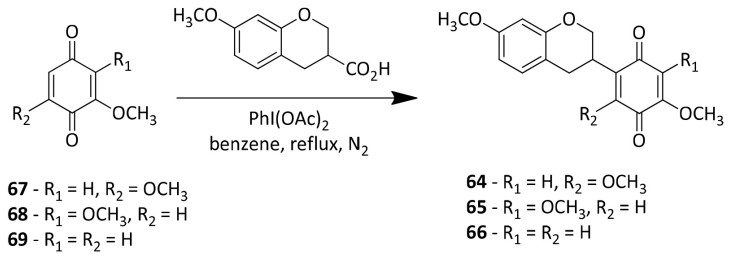
(3*R*)-colutequinone (**64**) (Figure 12) was isolated from *Colutea arborescens* by Grosvenor and Gray. Those same authors later isolated (3*R*)-colutequinone B (**65**) (Figure 12) from the same. Both molecules had their structures elucidated using ^{1}H and ^{13}C NMR as well as EI-MS, HMQC and DEPT-90 and UV-Vis techniques. The absolute configuration of (3R)-**64** was determined

Kraus and Kim[64] synthetically produced **64** and **65** as a racemic mixture. Those isoflavan-quinones were obtained from the reaction of a corresponding quinone (1 eq) with an chroman acidic carboxylic (3 eq) and the hypervalent iodine reagent phenyliodoso diacetate [$PhI(OAc)_2$] (1 eq). The mixture was heated under reflux, and **64** was obtained with a 92% yield, with a conversion rate of 24%; **65** was obtained with an 87% yield and a conversion rate of 11%. The authors synthesized *O*-methyl claussequinone (**66**) with an 84% yield and a conversion rate of 9% using the same methodology and purification by CC (Scheme 13). The authors studied the synthesis of those molecules using ammonia persulfate and catalytic quantities of silver nitrate, although they were unsuccessful even when the quantity of ammonia persulfate was increased or if stoichiometric quantities of silver nitrate were added. As such, the authors concluded that the techniques using ammonia persulfate were incompatible with acids containing aromatic systems rich in electrons, as their tests using either aromatic acids or unsubstituted aromatics gave good results.



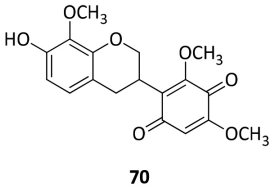
57 **60** - 78.5%

Scheme 12. Synthesis of acetilated derivate of claussequinone (**57**)



Scheme 13. Synthesis of colutequinones (**64** and **65**) and *O*-methyl claussequinone (**66**)

Laurentiquinone (**70**) (Figure 13) was isolated from the wood of *Millettia laurentii* and characterized using IR, UV ^{1}H NMR, and MS techniques. That data demonstrated that **70** was an isomer of **53**, an isoflavanquinone isolated from *Amorpha fructicosa*; the only difference between them being the position of the two methoxyl groups on ring B.[65]

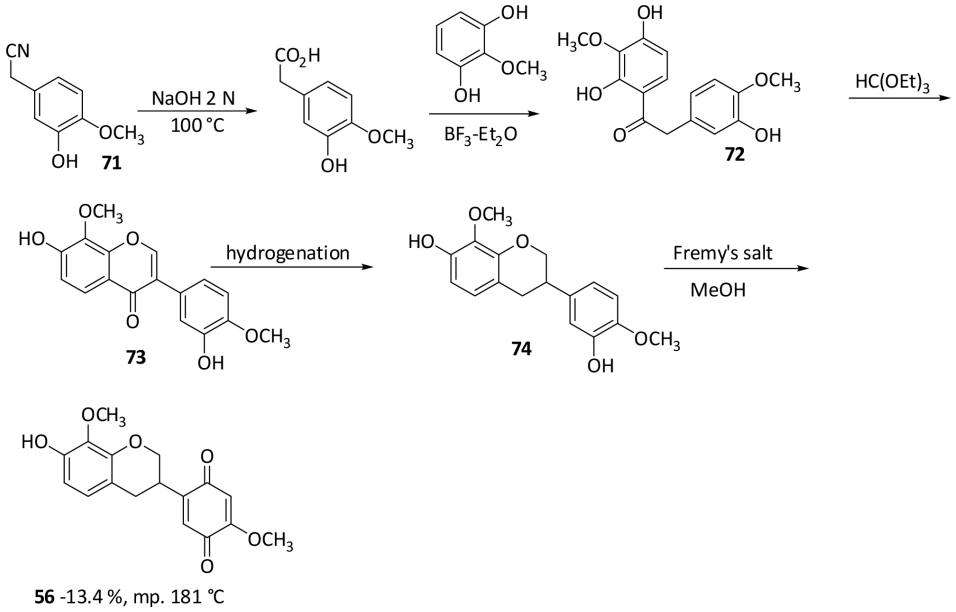


70

Figure 13. Structure of laurentiquinone (**70**)

Kurosawa *et al.* reported the absolute configurations of some natural and synthetic isoflavanquinones. (3*S*)-**56** isolated from *Machaerium mucronulatum*, (3*R*)-**56** isolated from *Cyclolobium claussenii*, and (3*R*)-**57** isolated from both *C. claussenii* and *Cyclolobium vecchi* had their absolute configurations determine based on ORD curve analyses.[66,67] (3*S*)-**56** was similarly isolated by Brown *et al.* from *M. mucromulatum*.[7] Those authors also reported the synthesis of (±)-**56** (Scheme 14), which initially involved hydrolysis in a basic media of the nitrile present in **71** to obtain the corresponding carboxylic acid in a reaction in which pyrogallol-2-methyl-ether furnished 1-(2,4-dihydroxy-3-methoxyphenyl)-3-(3-hydroxy-4-methoxyphenyl)propan-1-one **72**. After that, a condensation reaction resulted in **73**, which was then hydrogenated to form isoflavan **74** and then oxidized to isoflavanquinone by using Fremy's salt, resulting in a racemic product of mucroquinone, with a yield of 13.4%.[68]

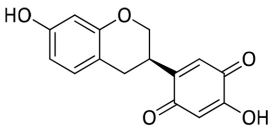
Kaneko *et al.* isolated pendulone (**54**) for the first time from galls and the wood of *Wisteria brachybotrys*, characterizing its spectroscopic properties based on previously published data.[69] The substance was analyzed by Konoshima *et al.* in terms of its antitumor activity, and was found to have inhibitory activity in terms of the activation of EBV-EA induced by TPA in Raji cells with more than 85% of inhibition.[70,71] Chen *et al.* confirmed the structure of **54** isolated from the roots of *Oxytropis falcata* in 2008 by x-ray diffraction analysis, which allowed the determination of bond lengths and their angles. Those authors were also able to determine that the quinone ring is linked to the chromeno ring by the C-3 in an equatorial position. Its absolute configuration was determined by CD.[72,73] (3*R*)-**54** was also isolated from *C. istria* by Radwan *et al.*,[74] by



Scheme 14. Synthesis of (±)-mucroquinone (**56**)

Zhang *et al.* from *Astragali Radix*,[75] and by Maamria *et al.* from *Astragalus depressus*.[76] Its antibacterial activity was tested against methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Mycobacterium intracellulare,* and *Escherichia coli*; it demonstrated activity against methicillin-resistant *Staphylococcus aureus* (with IC_{50} 20 µg/mL). Its antimalarial activity against *Plasmodium falciparum* and *P. falciparum* was also evaluated, as well as its cytotoxicity to Vero cells, although that isoflavanquinone did not demonstrate activity in any of those cases.[74]

Park [77] *et al.* sought to identify new natural products that could aid in promoting hair growth, and isolated a new isoflavanquinone from the bark of *Dalbergia oliveri*. That compound was characterized using classic techniques of spectrometry, HMBC, and COSY. The CD spectra allowed the authors to determine its absolute configuration as (3*R*)-7,4'-dihydroxy-isoflavanquinone (**75**) (Figure 14).

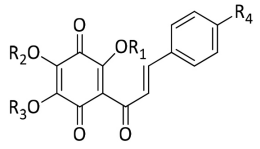


75

Figure 14. Structure of isoflavanquinone (**75**) isolated from the bark of *Dalbergia oliveri*

2.6. Chalcones

Balakrishn *et al.* reported the properties of dimethyl-pedicinin (**76**) that could be obtained by the methylation of pedicinin (**1**) and recrystallization in chloroform.[78,79] Those substances were isolated from *Didymocarpus pedicellata*.[7,80] Seshadri reported that the flowers of *Carthamus tinctorius* yielded a small quantity of a red chalcone quinone glycoside that was obtained by the oxidation (with peroxidase) of a corresponding chalcone glycoside. That compound was named carthamone (**2**).[3,7] Biswas *et al.* isolated isomethyl pedicinin (**77**) (as well as **1** and **76**) from the leaves of *D. pedicellata.* **77** (Figure 15) demonstrated inhibitory activity of the growth of *Rhizopus artocarpii* sporangiospores at a concentration of 50 ppm; the other two compounds demonstrated similar activities at concentrations of 100 ppm. Isomethyl-pedicinin was the only compound of the three, however, to demonstrate inhibitory activity against the growth of *Fusarium* at a concentration of 500 ppm. Pedicinin



1 - $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$
2 - R_1 = Gc, $R_2 = R_3 = H$, $R_4 = OH$
76 - $R_1 = R_2 = R_3 = CH_3$, $R_4 = H$
77 - $R_1 = R_3 = CH_3$, $R_2 = R_4 = H$

Figure 15. Structures of pedicinin (**1**), carthamone (**2**), dimethyl-pedicinin (**76**) and isomethyl pedicinin (**77**)

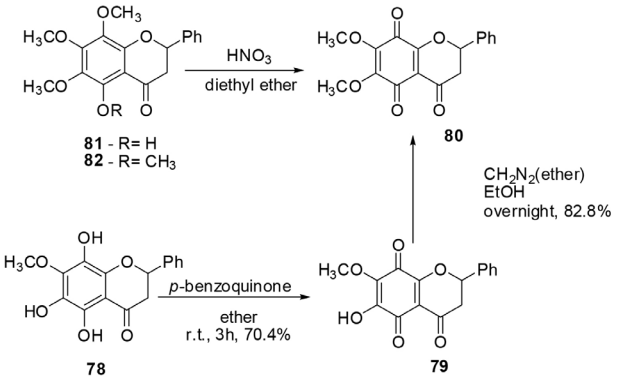
demonstrated inhibitory activity against the germination of *Rhizopus oryzae* at 100 ppm, while the other compounds demonstrated that same activity but at 250 ppm.[81]

3. Synthetical and Semi-synthetical Flavoquinones

3.1. Flavanone

The number of published studies reporting the synthesis of flavoquinones derived from flavanones is still quite small. We listed below the reports encountered up until the publication of this review.

Rao *et al.* reported the synthesis of two flavanone quinones, one of which was obtained from the treatment of **78** with p-benzoquinone in ether and named allo-pedicinin (**79**). That reaction was maintained for 3h at room temperature and the crude yield was filtered. The product was then purified by crystallization in benzene. That allo-pedicinin was used to obtain the methylated derivative **80** using diazomethane in ether that was added in small portions while holding the reaction in an ice bath. The reaction was maintained overnight, and the product purified by crystallization in ethyl acetate. **80** was also obtained by the oxidation of **81** and **82** in anhydrous ether using HNO_3 as the oxidant. The flavanone quinone was crystallized in ethyl acetate, producing the desired product (Scheme 15).[82,83]

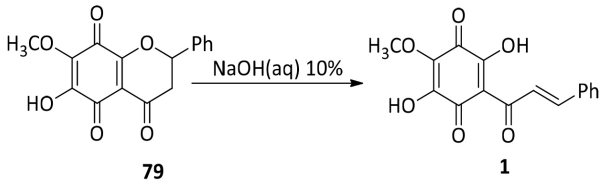


Scheme 15. Synthesis of **79** and **80**

Pedicinin **1** was obtained by Rao *et al.* from **79** through hydrolysis in a basic medium (Scheme 16). The product was separated by filtration and purified by crystallization in benzene.[82]

80 was reported by Gény *et al.* as a product of the spontaneous oxidation of didymocarpin-A (**83**) (Figure 16) - extracted from *F. latifolium var. ovoideum* - after two days of exposure to air at room temperature. The resulting substance was characterized by ^1H NMR.[84]

Mukerjee *et al.* obtained flavoquinone **85** from 5,7,8-trimethoxyflavanone (**84**) using HNO_3 in a water-cooled system (Scheme 17). Those authors reported that



Scheme 16. Basic hydrolysis of **79** providing **1**

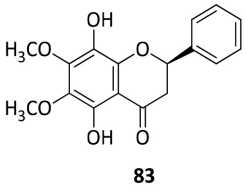
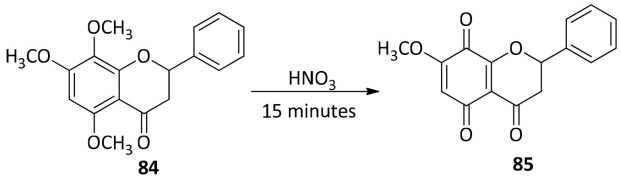


Figure 16. Structure of didymocarpin-A (**83**)

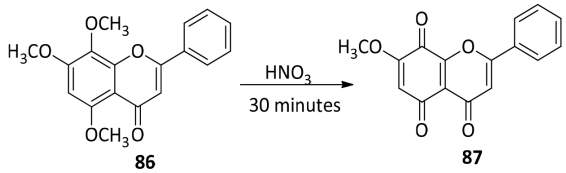
after five minutes of reaction time a color change could be observed to reddish yellow. The reaction was maintained for 15 minutes, after which the product was isolated and purified by crystallization in benzene.[85]



Scheme 17. Oxidation of 5,7,8-trimethoxyflavanone (**84**)

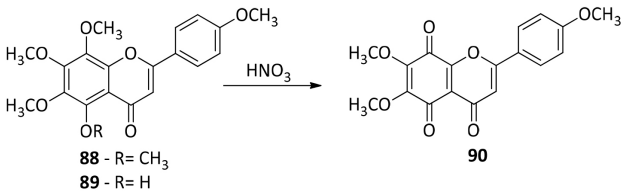
3.2. Flavones

During their studies of flavone oxidation, Rao *et al.* synthesized 7-methoxy-2-phenyl-4*H*-chromen-4,5,8-trione (**87**), a flavoquinone derived from 5,7,8-trimetoxiflavone (**86**) by an established methodology using HNO_3 (Scheme 18).[86]



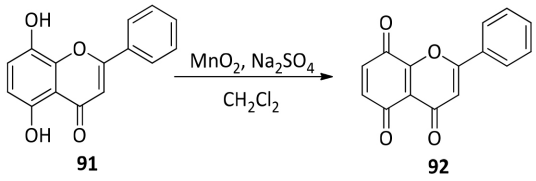
Scheme 18. Synthesis of 7-methoxy-2-phenyl-4*H*-chromene-4,5,8-trione (**87**)

In their studies of the phenolic compounds found in the lemon peels of *Citrus jambhiri*, Rao reported that when those fruits were collected in the Nagaland region in India, in addition to hesperidin, they also yielded tangeretin (**88**) and 5-hidroxyl-tangeretin (**89**). The authors then synthesized a flavoquinone derived from those flavonoids using the same synthetic methodology presented earlier in this review. In both cases the products were obtained after 30 min of reaction time and purified by crystallization in ethanol. Flavoquinone **90** was obtained from **88** with a yield of 65.3%, and from **89** was obtained with a yield of 68% (Scheme 19).[87]



Scheme 19. Synthesis of the flavoquinone **90**

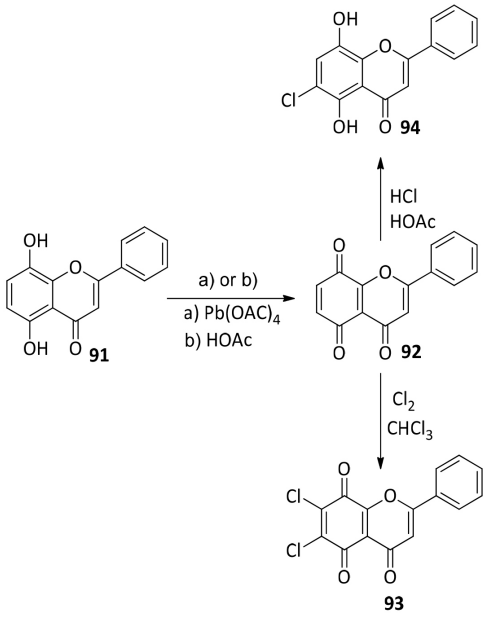
Hausen *et al.* studied the allergenic natures of the cells of *Primula mistassinica* plants and isolated primetin (**91**) using petroleum ether - ether (1:1). The allergenic nature of *Primula obconica* Hance caused by primin, a *p*-benzoquinone, had previously been reported in the literature. Therefore, to verify if the sensitization capacity of *P. mistassinica* was in fact caused by **91**, or its oxidative form, the authors oxidized it using magnesium dioxide to obtain primetinquinone (**92**) after a 30-minute reaction time, with the yield of 65% (Scheme 20). The product demonstrated absorption in the UV region at 261 nm, the wavelength expected for that type of substrate. The experiments to determine the sensitization capacities of **91** and **92** were performed using white female guinea pigs of the *Pirbright-white* line in the open epicutaneous test (OET) and Freund's complete adjuvant test (FCAT). Both methods demonstrated a high sensitization potential for both substrates, although flavoquinone was observed to produce stronger reactions in guinea pigs sensitive to flavones than to animals sensitized to primetinquinone itself. [88]



Scheme 20. Synthesis of primetinquinone (**92**)

Looker *et al.* likewise obtained **92** from **91**, although using lead acetate in benzene as the oxidizing agent (with a 37% yield) or using acetic acid (with a 68% yield). To prove the formation of a quinone, those authors studied reactions following the addition of halides to the flavoquinone. The addition of chlorine led to the probable formation of 6,7-dichloro-primentiquinone (**93**). The addition of bromine occurred, although the authors suggested that the bromine derivative had already become reduced to **91**. When dry HCl in acetic acid and chloroform was used, it led to the formation of chlorodihydroxyflavone **94** (Scheme 21). That same reaction, however, using only chloroform at 400 °C, gave a mixture of products that were not isolated or identified by those authors. **92** was tested with $FeCl_3$ and gave negative results, reinforcing the probability of the formation of flavoquinone. Additionally, the product was analyzed using the IR technique, and it was possible to observe the absence of a stretching peak related to the -OH

bond, although there were peaks related to the carbonyls of the quinone and flavonoid portions.[89]



Scheme 21. Synthetic analysis of the (**92**)

Laroche *et al.*, in their search for meroterpene derivatives, synthesized flavoquinone **96** using AgO and HNO_3 in the presence of a 1:1 acetone-dioxane mixture, obtaining a product purified by column chromatography with a 24% yield. That product was then used to obtain the product **97** through Diels Alder reactions (Scheme 22).[90]

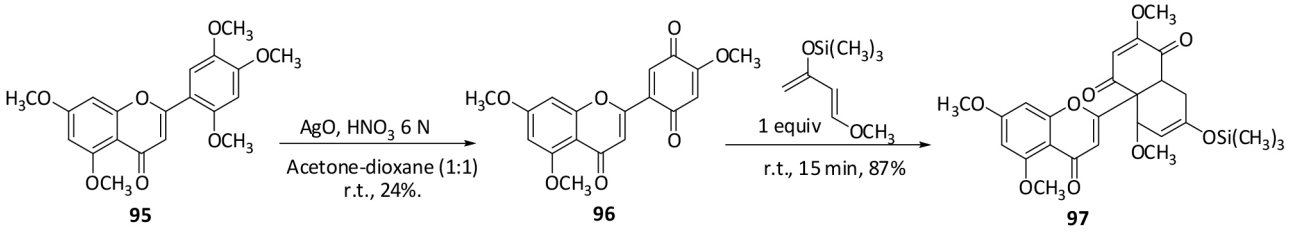
Compton *et al.* studied the use of dimethyldioxirane (DMDO) to oxidize flavones, and reported obtaining flavoquinone **102** while attempting to synthesize 8-hydroxy-5,7-dimethoxyflavone (**101**). Those authors reported that the reaction of 5-hydroxy-7-methoxyflavone (**98**) with DMDO at a 1:4 ratio at 15° C during 19h led to the formation of 5,6-di-hydroxy-7-methoxyflavone (**100**) (4 % yield) and **99** (30 % yield) (Scheme 23).[91]

3.3. Flavonol

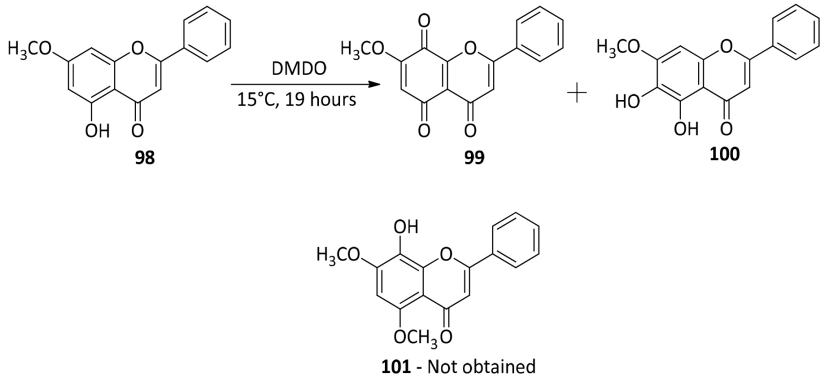
Rao *et al.* reported the synthesis of **103** from 3,5,7,8-tetramethoxyflavone (**102**) in 1947, using nitric acid as the oxidizing agent. According to those authors, the reaction proceeded for 15 minutes until the yellow solution became completely red. The product was crystallized twice in ethanol and was subsequently reduced with sodium sulfite in acetic acid to obtain isognaphaliin (**104**), as illustrated in Scheme 24.[92]

In the same year of 1947, Rao and Seshadri published the synthesis of **108**, derived from a gossypetin nucleus. That flavoquinone was obtained from 8-hydroxy-3,3',4',5,7-pentamethyl-gossypetin (**105**), 5-hydroxy-3,3',4',7,8-pentamethyl-gossypetin (**106**), and hexamethyl-gossypetin (**107**). All of those reactions were performed in nitric acid for 15 minutes, with the exception of reaction with **107**, which required twice that time. **108** was crystallized from acetic acid. That product was obtained with an 83.45% yield from **105** (Scheme 25). The data for the yields of the other reactions were not published by those authors.[93]

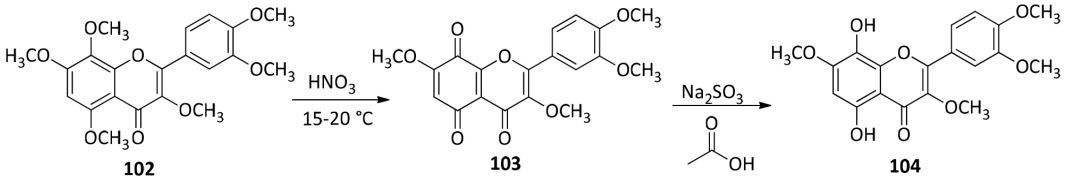
Continuing their studies of the oxidation of flavonoids to flavoquinones, Rao *et al.* synthesized flavoquinone **111,** derived from mono and dimethylated calycopterin (Scheme 26). Those reactions were performed under the same experimental conditions as described above and crystallized in benzene.[94]



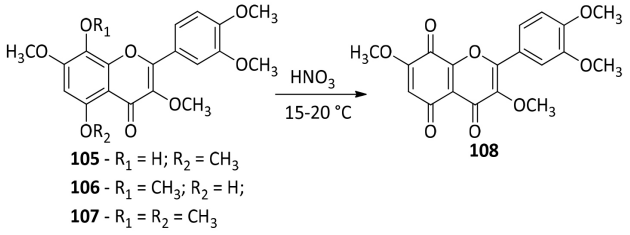
Scheme 22. Synthetic route of **97** having as intermediate **96**



Scheme 23. Synthesis of flavoquinone **99** by using DMDO



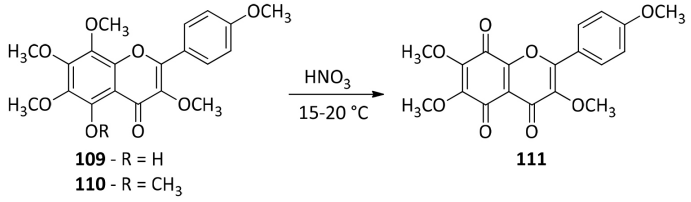
Scheme 24. Synthesis of 3,7-dimethoxy-2-phenyl-4*H*-chromene-4,5,8-trione **103**



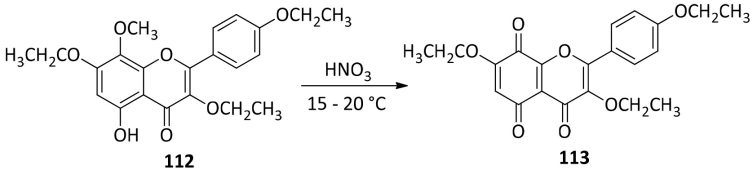
Scheme 25. Reaction scheme for obtaining flavoquinone derived from the gossypetin nucleus

During a study of the synthesis of *O*-tetraethyl tambuletin, Balakrishna reported the synthesis of 3,7-diethoxy-2-(4-ethoxiphenyl)-4*H*-chromen-4,5,8-trione (**113**), a flavoquinone derived from *O*-triethyl tambuletin (**112**) that was obtained using nitric acid as an oxidant and crystallized in diluted acetic acid (Scheme 27).[2]

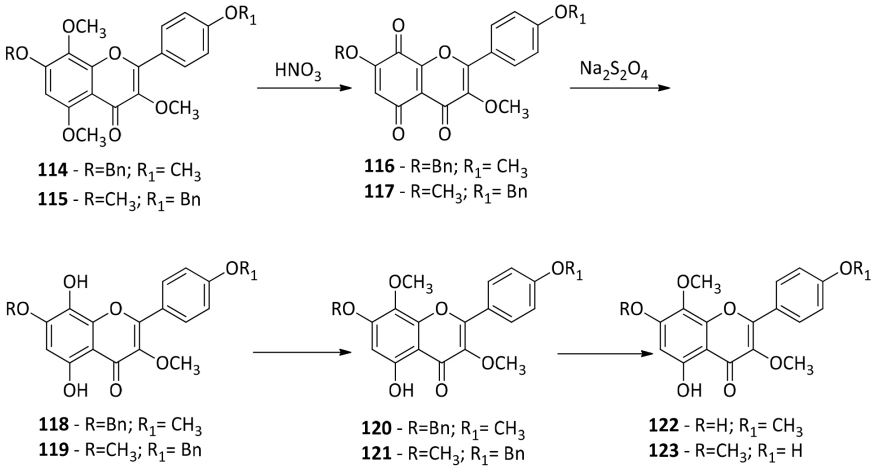
Farkas and Nógrádi examined the synthesis of compounds synthesized by the *Euphorbiaceae* family, and obtained two flavoquinones (**116** and **117**) as intermediates during the synthesis of 3,8,4‘-trimethylherbacetin (**122**) and 3,7,8-trimethylherbacetin (**123**), as can be seen in scheme 28. The starting flavonoids were initially oxidized using HNO_3, followed by reduction to obtain the corresponding hydroquinones. They were then partially methylated, followed by debenzylation, to produce the molecules of interest (Scheme 28). The authors extended that synthetic pathway for flavonoids by substitutions at positions C-3’ and C-4’, although the yields were low, stimulating the authors to find other pathways to obtain other flavonoids of the *Euphorbiaceae* family.[95,96]



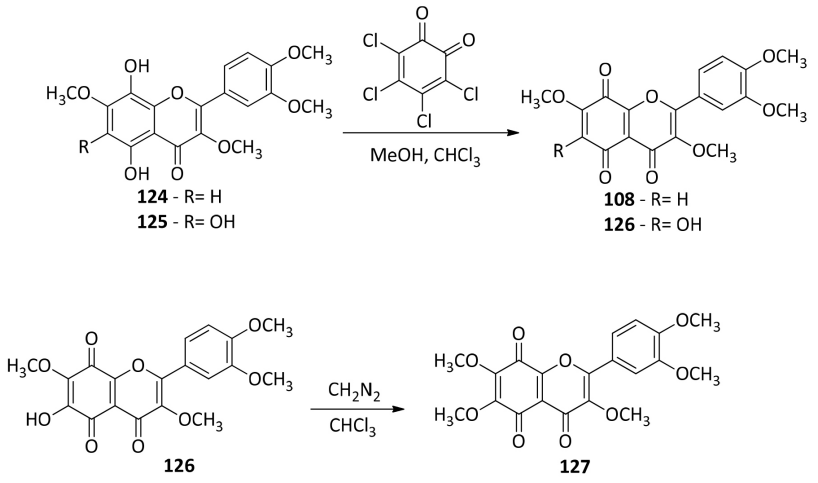
Scheme 26. Oxidation of calycopterin derivatives



Scheme 27. Synthesis of 3,7-diethoxy-2-(4-ethoxyphenyl)-4*H*-chromene-4,5,8-trione **113**



Scheme 28. Synthetic route of flavonoids components of Euphorbiaceae



Scheme 29. Synthesis of flavoquinones **108**, **126** e **127**

In a study of the Elbs oxidation method to obtain the ether 3,3‘,4‘,7-*O*-tetramethyl from gossypetin **127** starting with retusin **124**, Rao and Owoyale observed that independent of the quantities of base and potassium peroxydisulfate used, the product **124** was obtained together with **125,** and that the separation of the two was quite difficult due to their similar solubilities. The authors therefore decided to oxidize those flavonoids, obtaining the flavoquinones **108** and **126** that were more easily separable. Once separated, the flavoquinones were reduced to obtain flavonoids **124** and **125** separately. Flavoquinones **108** and **126** were obtained through the oxidation of a mixture of **124** and **125** in a methanol/chloroform (20%/80%) solution with tetrachloro-*o*-quinone as the oxidant. Flavoquinone **108** was then crystallized in methanol/chloroform, while **126** was crystallized in methanol. The flavoquinone **126** was subsequently methylated with an excess of diazomethane to yield the flavoquinone **127** (Scheme 29).[97]

Studies of the amine derivative of combretastatin A4 analog **128** (Figure 17), a powerful inhibitor of tubulin assembly, was clinically investigated as a pro-pharmaceutical in its phosphate form, which had a slightly greater activity. After the observation that 5-hidroxy-2-(3-hidroxy-4-methoxiphenyl)-3,6,7,8-tetramethoxy-4*H*-chromen-4-one (**130**) was structurally similar to that molecule, Lewin *et al.* investigated the synthesis of various analogues of flavonoids **130**. While searching for a pathway with fewer steps, those authors decided to begin with calycopterin (**132**). As one of the molecular targets was the 3‘-amino analog of flavonoid **130**, the first synthetic step was therefore the nitration of **132** using nitric acid (1 equiv). However, instead of the expected 3‘-nitro-calycoperin, they obtained a mixture of reddish-orange flavoquinones (Scheme 30). The results of ^{1}H NMR and EIMS analyses demonstrated that the products were mixture of the isomers 3‘-nitro-5,6-*p*-flavaquinone (**133**) and 3‘-nitro-5,8-*o*-flavoquinone (**134**). Those isomers were crystallized in MeOH and separated by preparative tlc (CH_2CH_2/MeOH - 97.5/2.5).[98]

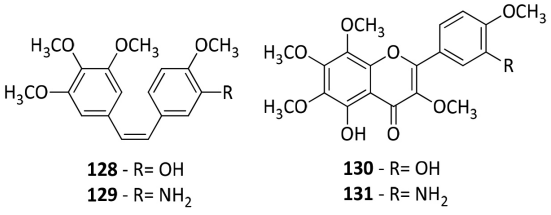
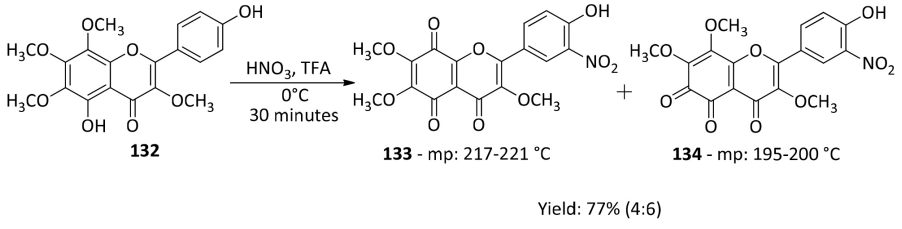
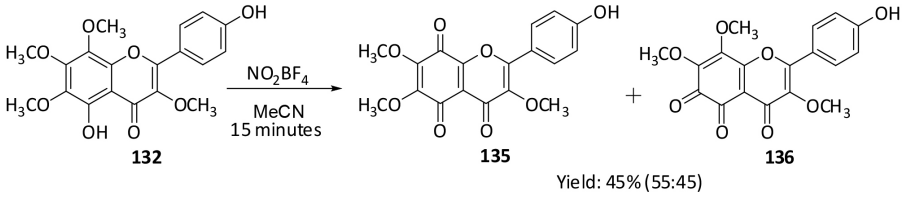


Figure 17. Structure of combretastatin A4 (**128**) and its amino analog as well as flavonoid **130** and its analog

In an attempt to obtain the desired product, those authors altered the nitration agent to NO_2BF_4 (1 equiv) in acetonitrile under an inert atmosphere. Those reaction conditions, however, once again produced a mixture of a pair of *ortho*- and *para*-flavoquinone isomers, although they were not nitrated (Scheme 31). It is interesting to note, in terms of those results, that oxidation in trifluoroacetic acid (TFA) using HNO_3 is selective in the formation of *ortho*-flavoquinone, while the use of NO_2BF_4 in acetonitrile favors the formation of *para*-flavoquinone. Additionally, those results demonstrated



Scheme 30. Attempted to nitrate calycopterin using HNO_3/TFA



Scheme 31. Oxidation of calycopterin with NO_2BF_4

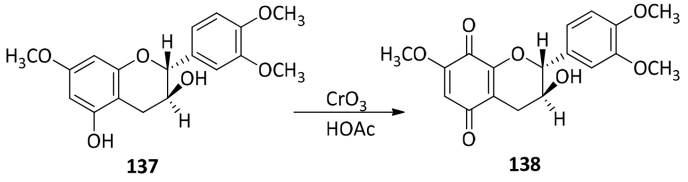
that the oxidation of ring A of a flavonoid to flavoquinone occurred before the nitration of ring B.

3.4. Flavan-3-ols

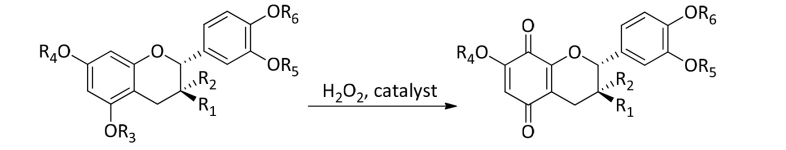
With the intent of being able to structurally distinguish two catechins, Weinges and Wild obtained, in 1970, a flavoquinone with a catechin nucleus. Starting with catechin **137** and using chromic anhydride in acetic acid, the authors obtained flavoquinone **138** with a yield of 9.6% (Scheme 32). The product was crystallized in ethanol and characterized using the IR technique.[99]

Bernini *et al.* studied the catalytic oxidation of catechins to flavoquinones (Scheme 33) using hydrogen peroxide (H_2O_2) as a source of oxygen with methyltrioxorhenium (CH_3ReO_3, MTO - **146**), a catalyst that is stable in air, efficient in many organic solvents, and commercially available. As they were interested in studying the effectiveness of that catalytic agent under both homogeneous and heterogeneous conditions, MTO was bound to polyvinylpyrrolidone (PVP) to act as a support for the organometallic. The reaction of **7** and **17** with that catalytic system showed it to be incompatible (due to the condensation reaction between the MTO and the catechol system on ring B of the catechins). The authors then used catechins methylated in those positions to direct the oxidation. Various tests were then performed under different experimental conditions, and the best results in terms of conversion, reaction time, and yields were obtained using acetic acid as the solvent. Under homogeneous conditions, the best results obtained were the 98% conversion of catechin **7** with a 42% yield. Similar results were also obtained using a heterogeneous catalytic system with PVP-2%/MTO, PVPN-2%/MTO, and PVP-25%/MTO; the latter gave the best results (98% conversion of catechin **138**, with a 38% yield). The absence of that catalytic agent resulted in conversion rates below 5%. The catalyst yielding the best results (PVP-25%/MTO) was recuperated by filtration, and could be washed and re-utilized under the same conditions – demonstrating that catalytic efficiency could be maintained until the fifth cycle of reuse. There was selective oxidation in all of the reactions tested, with the formation of *p*-flavoquinones. The products were identified using ^1H and ^{13}C NMR techniques, as well as HMQC, HMBC, and NOESY.[100]

In their study of the oxidation of ring A of the catechins, and influences that their substitutions had on the reactions, Boyer *et al.* reported the synthesis of 4 flavoquinones. In their attempts to oxidize compound **147** to obtain a hydroxylated product in position 6, the authors observed traces of the flavoquinones **148** and **149** while using



Scheme 32. Synthesis of flavoquinone **138**



7 - R_1= R_3= R_4= R_5= R_6= H; R_2=OH
17 - R_1= OH; R_2= R_3= R_4= R_5= R_6= H
139 - R_1= H; R_2= OH; R_3= R_4= R_5= R_6= CH_3
140 - R_1= OH; R_2= H; R_3= R_4= R_5= R_6= CH_3
141 - R_1= H; R_2= OAc; R_3= R_4= R_5= R_6= CH_3
142 - R_1= OAc; R_2= H; R_3= R_4= R_5= R_6= CH_3

143 - R_1= H; R_2= OH; R_4= R5= R_6= CH_3
138 - R_1= OH; R_2= H; R_4= R_5= R_6= CH_3
144 - R_1= H; R_2= OAc; R_4= R_5= R_6= CH_3
145 - R_1= OAc; R_2= H; R_4= R_5= R_6= CH_3

146 - Catalyst structure

Scheme 33. Catalytic oxidation of catechin nucleus to flavoquinones

meta-chloroperoxybenzoic acid (m-CPBA) and DMDO as oxidants (Scheme 34).[101]

Those authors also observed that (+)-elephantorrhizol (**150**) was not stable in acetone-MeOH, undergoing spontaneous oxidation to form flavoquinone **151**, a dark red compound whose structure was elucidated using HSQC / HMBC techniques (Scheme 35).

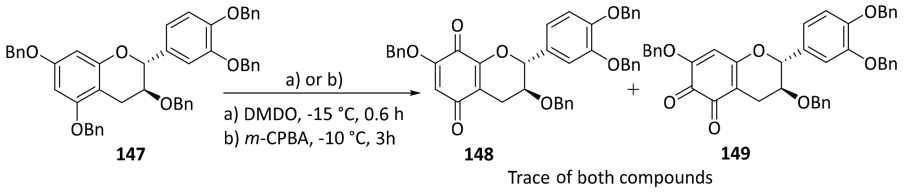
Similarly, it was observed that compound **152** was oxidized spontaneously into flavoquinone **153**. In terms of the formation of that flavoquinone, the authors suggested that there was first the formation of an *o*-flavoquinone that then had a C ring opened by the addition of a water molecule, followed by a rearrangement that led to the formation of product **153** as a solid orange compound (Scheme 36). It was reported that the formation of an intermediary methyl quinone, which would have involved the methylbenzil group, did not occur, as that exchange was not observed when a deuterated solvent was used. The authors observed that this rearrangement could be explained by the formation of flavoquinone **148**, even in trace amounts. The structure of compound **153** was elucidated using the HSQC / HMBC techniques.

3.5. Isoflavones

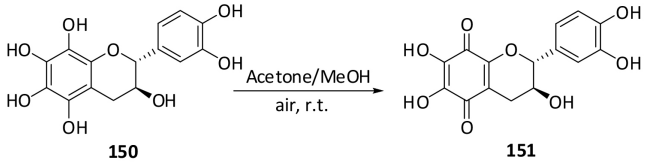
Chang *et al.* reported the synthesis of a number of flavoquinones. The first step of the synthesis of isoflavan-quinones and isoflavone-quinones involves the condensation of 2-hidroxy-4-substituted acetophenones with 2-benzyloxy-4-substituted benzaldehydes in a base. That reaction yields a chalcone that was acetylated and subsequently treated with thallium nitrate in trimethyl orthoformate followed by a treatment with heated and diluted HCl to obtain the corresponding isoflavones. Those isoflavones were then submitted to two different synthetic pathways: the first involved catalytic hydrogenation followed by oxidation by Fremy's salt to obtain the corresponding isoflavan-quinone; the second involved the debenzylation of the isoflavones using HBr followed by oxidation with Fremy's salt (Scheme 37). The flavoquinones were purified using column chromatography.[102]

Flavan quinone and flavone quinone were synthesized using the same pathway described above, although starting with chalcone **156c**, which, surprisingly, did not form the desired isoflavone but rather a corresponding flavone (Scheme 38).

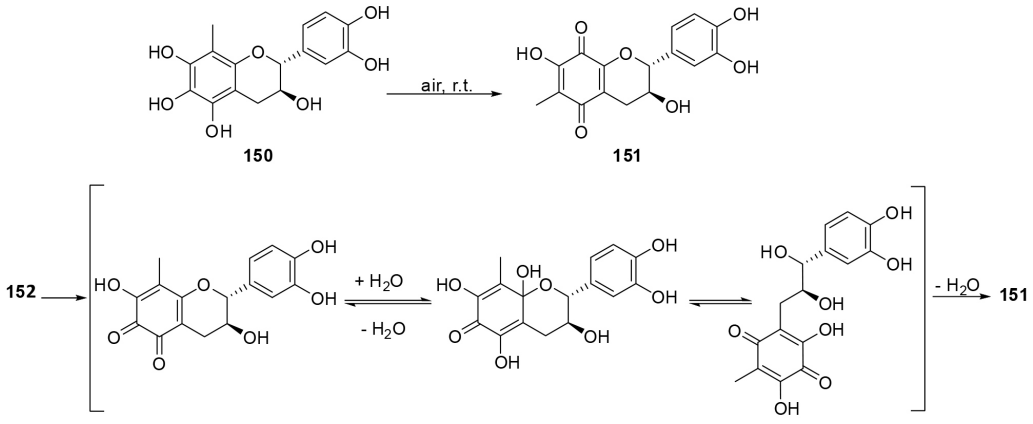
Those molecules were evaluated in terms of their anti-inflammatory activities. All of them demonstrated good potential activity, with **159c** being the most active (IC_{50} = 0.19 μM), which was 30 times greater than the trifluoperazine control. That compound also demonstrated



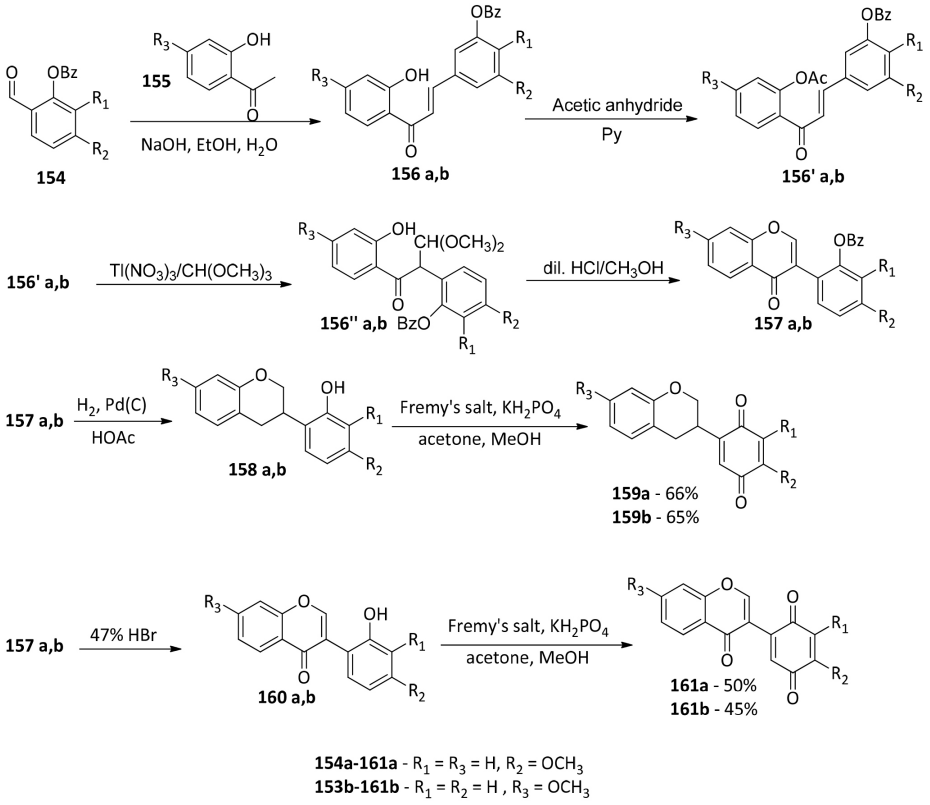
Scheme 34. Flavoquinones observed in the oxidation of catechin **147**



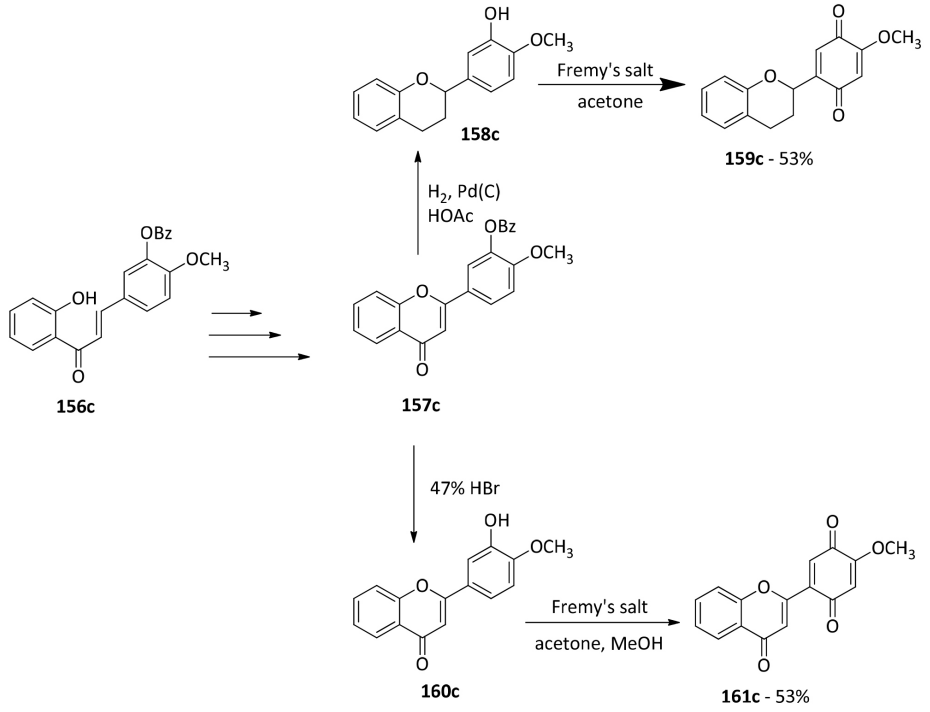
Scheme 35. Spontaneous oxidation of (+) – elephantorrhizol (**150**)



Scheme 36. Spontaneous oxidation of **152** and mechanism proposed by Boyer *et al* [101]



Scheme 37. Synthesis of isoflavanquinones **159a/159b** and isoflavonequinones **161a/161b**



Scheme 38. Synthesis of flavanquinone **159c** and flavonequinone **161c**

a potent inhibitory effect against the formation of superoxide neutrophils induced by formyl-Met-Leu-Phe (fMLP), with an IC_{50} of 0.44 μM. The other flavoquinones did not exhibit any such activity. Those researchers then evaluated the anti-allergic activities of those compounds. Once again, those molecules were found to be very active in that sense, with **159c** once again being the most effective, with an IC_{50} = 1.59 μM (three times more potent than the mepacrine control). Those authors also reported that flavanquinone and flavoquinone (**159c** and

161c) were more potent than their isoflavanquinone and isoflavoquinone counterparts.

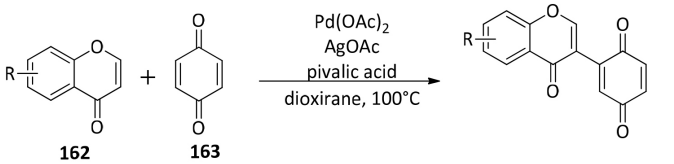
Moon *et al.* (Schemes 39 and 40) undertook an extensive study of the synthesis of isoflavoquinones based on direct cross coupling of chromones and quinones. The syntheses were evaluated using $Pd(OAc)_2$ and Cu(OAc) in pivalic acid, although coupled products were not observed. By exchanging Cu^{2+} for Ag^{+}, those authors observed the formation of the desired product, with a 20% yield. While performing reaction optimization studies they observed that using $Pd(OAc)_2$ as a catalyzer, AgOAc as an oxidant, pivalic acid as an additive, and dioxane as the solvent resulted in better results (89% yields). Once the reaction was optimized, they were able to successfully undertake reactions with diverse substituted chromones and quinones, with yields varying from 55 – 93%.[103]

When studying efficient routes for coupling maleimides with chromones at the C-5 position, Zhou *et al.* [104] developed a methodology using a Ru(II) catalyst for this coupling reaction. As a synthetic application, one of the products obtained was **166** with 52% by column chromatography. The reaction is shown in Scheme 41 below.

3.5. Isoflavan

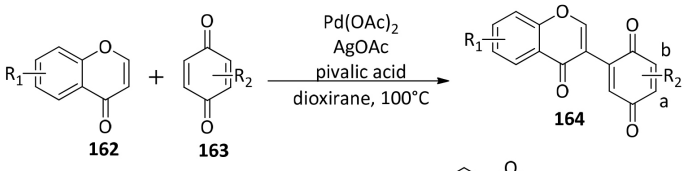
Kurosawa *et al.* reported the synthesis of four new isoflavanquinones and their absolute configurations. The isoflavanquinones (**170** - **172**) were obtained through the oxidation of the corresponding isoflavan using Fremy's salt as the oxidizing agent. **173** was obtained by methylation of **171** (Scheme 42).[66,67]

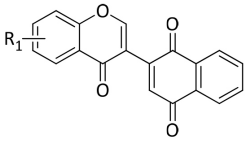
The synthesis of **66** (Scheme 43) was undertaken in three steps. Starting with chromene **174**, BH_3 and benzoquinone, it was possible to obtain **175**, which was then treated with $HgCl_2$ and I_2 to obtain the desired product **176** with a yield of 70%. In order to obtain **66**, those authors altered the



164a - R= H (74%)
164b - R= 6-NO_2 (66%)
164c - R= 6-F (71%)
164d - R= 6-Cl (92%)
164e - R= 6-Br (93%)
164f - R= 7-OCH_3 (73%)
164g - R= 7-OAc (90%)
164h - R= 7-OTf (85%)
164i - R= 7-OH (63%)

Scheme 39. Synthesis of isoflavoquinone via cross coupling

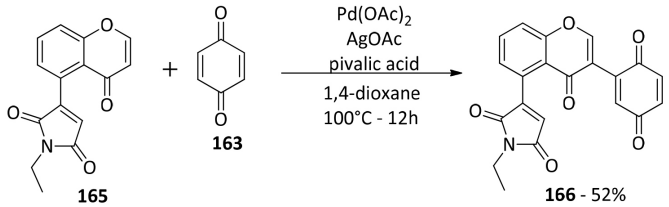




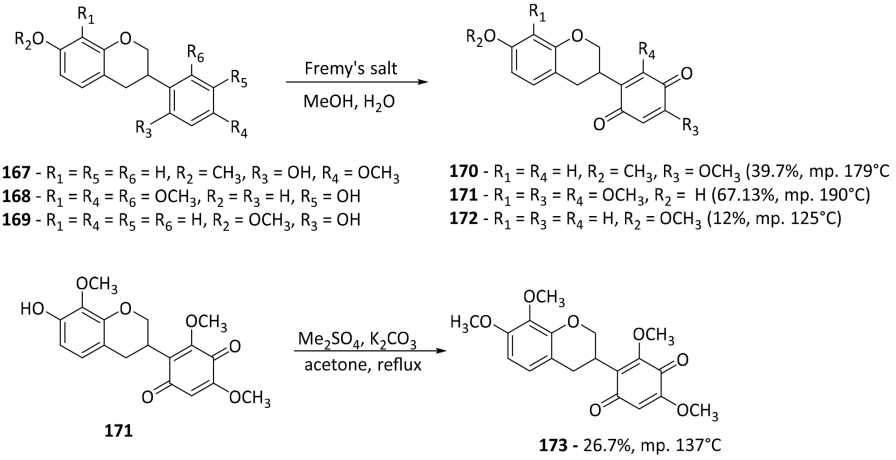
164j - R_1= 6-CH_3, R_2= CH_3 (81%; a/b 1:1)
164k - R_1= 6-CH_3, R_2= OCH_3 (77%; a/b 3:1)
164l - R_1= 6-CH_3, R_2= tBu (92%; a/b 1:1,4)
164m - R_1= 6-CH_3, R_2= Cl (69%; a/b 1,5:1)
164n - R_1= 6-CH_3. R_2= Br (55%; a/b 1,5:1)
164o - R_1= 6-CH_3, R_2= Ph (71%; a/b 1:1,1)
164p - R_1= 6-CH_3, R_2= C_6H_{11} (88%; a/b 1:1,2)

164q - R_1= H (76%)
164r - R_1= 6-CH_3 (87%)
164s - R_1= 7-OCH_3 (56%)

Scheme 40. Other isoflavoquinones obtained by Moon *et al.*



Scheme 41. Synthesis of 4-(3-(3,6-Dioxocyclohexa-1,4-dyenyl)-4-oxo-4*H*-chromen-5-yl)-1- ethyl-1*H*-pyrrole-2,5-dione (**166**)



167 - $R_1 = R_5 = R_6 = H$, $R_2 = CH_3$, $R_3 = OH$, $R_4 = OCH_3$
168 - $R_1 = R_4 = R_6 = OCH_3$, $R_2 = R_3 = H$, $R_5 = OH$
169 - $R_1 = R_4 = R_5 = R_6 = H$, $R_2 = OCH_3$, $R_3 = OH$

170 - $R_1 = R_4 = H$, $R_2 = CH_3$, $R_3 = OCH_3$ (39.7%, mp. 179°C
171 - $R_1 = R_3 = R_4 = OCH_3$, $R_2 =$ H (67.13%, mp. 190°C)
172 - $R_1 = R_3 = R_4 = H$, $R_2 = OCH_3$ (12%, mp. 125°C)

171

173 - 26.7%, mp. 137°C

Scheme 42. Synthesis of isoflavanquinones by Kurosawa *et al.*

synthetic pathway, reacting **175** with thiophenol and PTSA, followed by oxidation with AgO, resulting in a mixture of the regioisomers **177** and **178** in the proportion of 5:1, with a yield of 93%. **177** was mixed with *m*-CPBA and allowed to reflux with MeOH, producing the desired quinone isoflavane **66**, with a yield of 70%.[105]

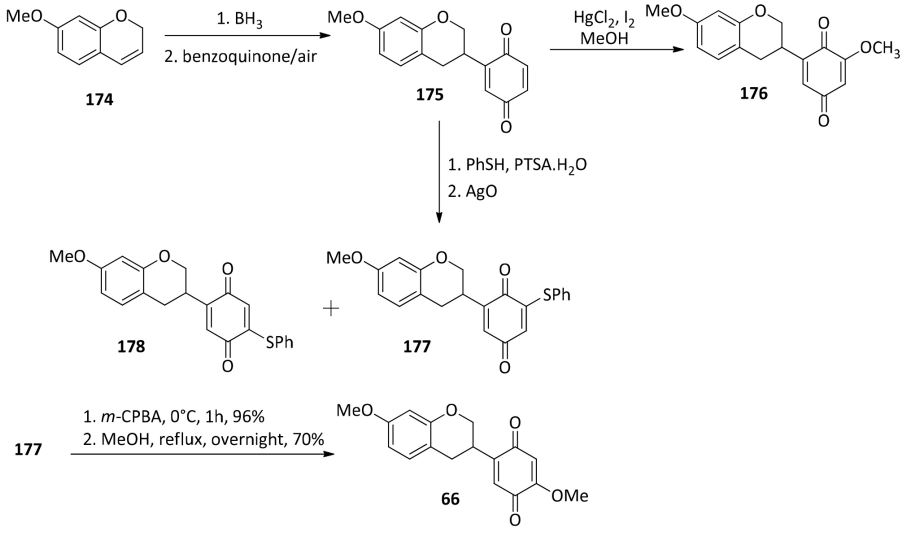
Gafner *et al.* reported that during the process of isolating licoridicin (**179**) and licorisoflavan A (**180**) from the roots of *Glycyrrhiza uralensis*, two new isoflavanquinones were formed and isolated. The ^{1}H and ^{13}C spectra, as well as ultraviolet absorption, evidenced the presence of a quinone ring in the isoflavan structure, which was corroborated by HMBC studies. Those new isoflavanquinones were named licoriquinone A **181** and licoriquinone B (**182**) (Scheme 44). The authors could not determine whether those substances were natural or the results of oxidative degradation processes during the gel filtration phase. Nonetheless, the authors reported that the isoflavanquinones were obtained when the plant extract contained licoridicin and licoriso-flavan A and was held in a basic medium. The possibility that catalyzation was promoted by copper II ions in the sephadex column during product isolation could not, however, be eliminated [106]. The bactericide activity of **181** was tested, but it demonstrated no effects against *S. mutans* or *S. sobrinus*, and was also inefficient in inhibiting the growth of *P. gingivalis*; it did, however, demonstrate moderate inhibitory activity of the growth of *P. intermedia*, a bacteria that attacks periodontal tissue.[106]

Those authors proposed an oxidation mechanism (Scheme 45) based on the work of Philipp and Schinkn [107] and Liu[108] *et al*.

3.6. Chalcones

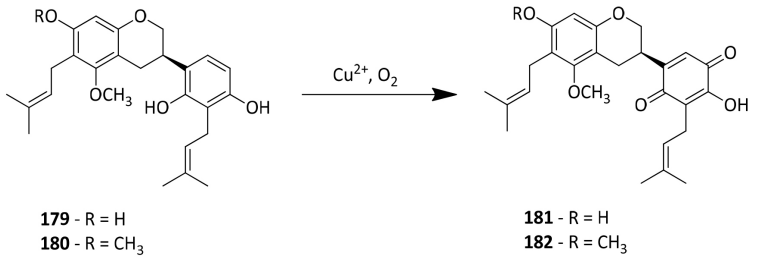
The synthesis of **1** and its analogues was reported by Rao. Starting with tetraethyldihydropedicinin (**183**) in acetic acid, and exposure to nitric acid, resulted in the crystallization of two solids (**1** and **184**) in benzene and ligroin. **1** could also be obtained from hydrolysis under basic conditions of ethylpedicinin (**184**) (Scheme 46).[109]

In 1979, Obara *et al.* reported the synthesis of a series of chalcone quinones. **186** was obtained from chalcone

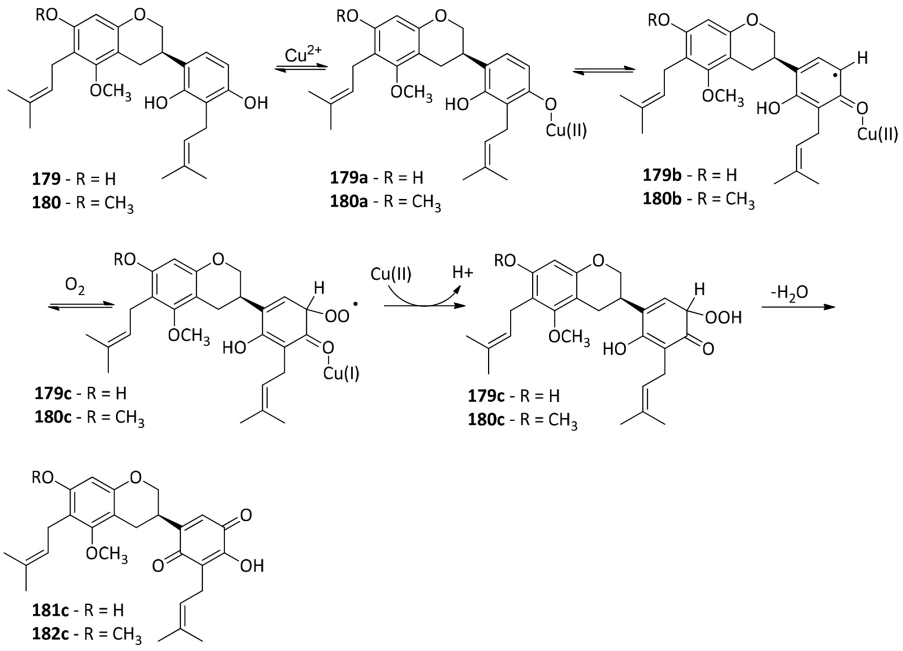


174 **175** **176** **178** **177** **177** **66**

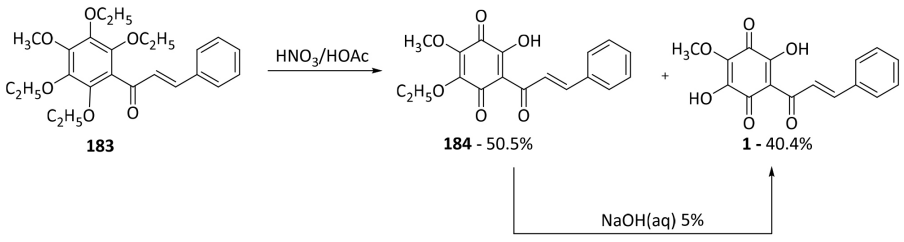
Scheme 43. Synthesis of *O*-methyl-claussoquinone **66**



Scheme 44. Oxidative degradation of licoricidin (**179**) and licorisoflavan A (**180**)

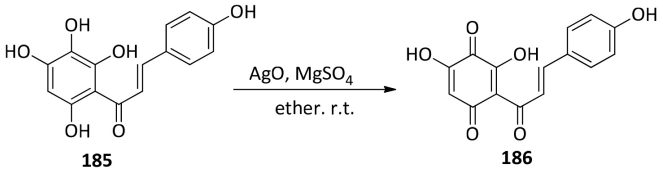


Scheme 45. 179 and **180** oxidation proposal

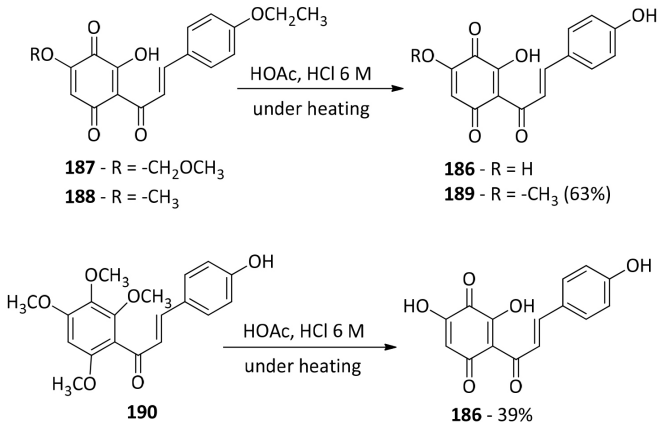


Scheme 46. Synthesis of **184** and **1**

185 (Scheme 47) by oxidation with AgO in ether that was purified through column chromatography. The product could also be obtained from chalcone quinone **187** through demethoxymethylation in HOAc/HCl under heating, and from **190** using the same methodology (Scheme 48). The products **186**, **194** and **195** were obtained from the corresponding chalcones **191**, **192** and **193** oxidized with HNO_3 and purified by recrystallization in HOAc/ether. Those reactions are presented in Scheme 49.[110]



Scheme 47. Oxidation of **185** with AgO to obtain **186**



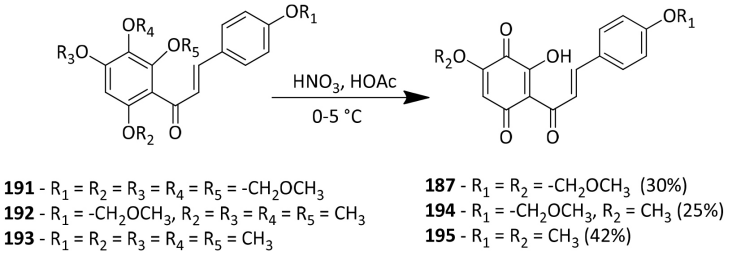
Scheme 48. Obtaining chalcoquinones via demethoxymethylation

Lee *et al.* reported the synthesis of **197** (Scheme 50) as one of the steps, and the synthesis of lucidones. The product was obtained from the corresponding hydroquinone utilizing a HOAc/HNO_3 oxidant system with heating. The product was purified by crystallization in benzene.[111]

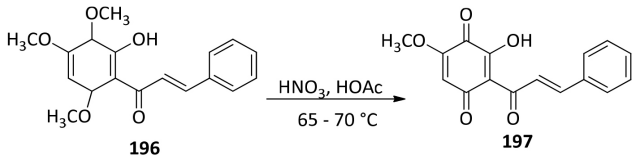
Alias *et al.* produced two amino-chalcoquinones from **198a** and **198b** by treating both with NH_4OH at room temperature for three hours, yielding solid violet crystals by crystallization in MeOH. Those authors also reported the possibility of obtaining **199a** from the chalcoquinone **76**, previously prepared by the oxidation of **198a** with AgO (Scheme 51).[112]

4. Conclusion

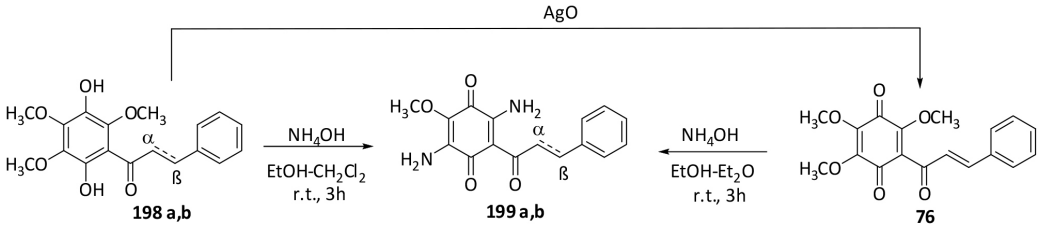
This review explored a group of substances frequently reported in the literature, this being the first attempt at gathering works involving flavonoids with quinone nuclei in their structures. We presented a wide diversity of natural molecules that possess that structure, with flavans being the class of flavonoids that have a greater presence of quinone groups incorporated in their structures. It was observed that, except for chalcones, the quinone groups in those natural molecules appear in ring B of the flavonoids. Very few reports have investigated the synthesis of those substances, which, in their majority, represent synthesized reaction



Scheme 49. Obtaining chalcoquinones via oxidation with HNO_3



Scheme 50. Oxidation of **196** to obtain **197**



Scheme 51. Oxidation reactions of **198** performed by Alias *et al.* [112]

intermediates (or were investigated to confirm certain structures). It was possible, however, to observe that those compounds demonstrated diverse biological activities, even though there is a scarcity of studies investigating them. It could therefore be seen that the phytochemical, synthetic, and biological studies of that class of molecules are of scientific relevance and could contribute greatly to obtaining new bioactive molecules.

Acknowledgments

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References

1. Rao, K. V.; Seshadri, T. R.; Nuclear oxidation in the flavone series - Part I. A new synthesis of gossypetin and 8-hydroxy-galangin. *Proceedings of the Indian Academy of Sciences - Section A* **1947**, *25*, 417. [Crossref]
2. Balakrishna, K. J.; Seshadri, T. R.; Colouring matter of tambul seeds - Part II. Constitution of tambuletin: Synthesis of O-tetraethyl tambuletin. *Proceedings of the Indian Academy of Sciences - Section A* **1947**, *26*, 72. [Crossref]
3. Seshadri, T. R.; Thakur, R. S.; The colouring matter of the flowers of *Carthamus tinctorius*. *Current Science* **1960**, *29*, 54. [Link]
4. Long, H.; Yan, Q.-F.; Hu, Z.-H.; Zhang, Q.; Chen, Y.; Li, L.-J.; A new para-quinone-type flavan from the leaves of *Ilex centrochinensis* and its anti-inflammatory activities. *Journal of Asian Natural Products Research* **2019**, *21*, 86. [Crossref] [PubMed]
5. Lauterwein, J.; Hemmerich, P.; Lhoste, J. M.; Flavoquinone-Metal Complexes. I. Structure and Properties. *Inorganic Chemistry* **1975**, *14*, 2152. [Crossref]
6. Allan, R. D.; Wells, R. J.; MacLeod, J. K.; Flavanone quinones from *Cyperus species*. *Tetrahedron Letters* **1973**, *14*, 7. [Crossref]
7. Brown, P. M.; Thomson, R. H.; Hausen, B. M.; Simatupang, M. H.; Natürlich vorkommende Chinone, XXIV1) Über die Inhaltsstoffe von *Bowdichia nitida* Benth.: Erstmalige Isolierung eines Isoflavonchinons. *Justus Liebigs Annalen der Chemie* **1974**, *1974*, 1295. [Crossref]
8. Tanaka, T.; Inoue, K.; Betsumiya, Y.; Mine, C.; Kouno, I.; Two types of oxidative dimerization of the black tea polyphenol theaflavin. *Journal of Agricultural and Food Chemistry* **2001**, *49*, 5785. [Crossref] [PubMed]
9. Tanaka, T.; Betsumiya, Y.; Mine, C.; Kouno, I.; Theanaphthoquinone, a novel pigment oxidatively derived from theaflavin during tea-fermentation. *Chemical Communications* **2000**, 1365. [Crossref]
10. Tanaka, T.; Kouno, I.; Oxidation of Tea Catechins: Chemical Structures and Reaction Mechanism. *Food Science and Technology Research* **2003**, *9*, 128. [Crossref]
11. Tanaka, T.; Mine, C.; Inoue, K.; Matsuda, M.; Kouno, I.; Synthesis of theaflavin from epicatechin and epigallocatechin by plant homogenates and role of epicatechin quinone in the synthesis and degradation of theaflavin. *Journal of Agricultural and Food Chemistry* **2002**, *50*, 2142. [Crossref] [PubMed]
12. Tanaka, T.; Mine, C.; Watarumi, S.; Fujioka, T.; Mihashi, K.; Zhang, Y.-J.; Kouno, I.; Accumulation of epigallocatechin quinone dimers during tea fermentation and formation of theasinensins. *Journal of Natural Products* **2002**, *65*, 1582. [Crossref] [PubMed]
13. Jhoo, J.-W.; Lo, C.-Y.; Li, S.; Sang, S.; Ang, C. Y. W.; Heinze, T. M.; Ho, C.-T.; Stability of Black Tea Polyphenol, Theaflavin, and Identification of Theanaphthoquinone as Its Major Radical Reaction Product. *Journal of Agricultural and Food Chemistry* **2005**, *53*, 6146. [Crossref] [PubMed]
14. Matsuo, Y.; Oowatashi, R.; Saito, Y.; Tanaka, T.; Nonenzymatic Biomimetic Synthesis of Black Tea Pigment Theaflavins. *Synlett* **2017**, *28*, 2505. [Crossref]
15. O'Coinceanainn, M.; Bonnely, S.; Baderschneider, B.; Hynes, M. J.; Reaction of iron(III) with theaflavin: Complexation and oxidative products. *Journal of Inorganic Biochemistry* **2004**, *98*, 657. [Crossref] [PubMed]
16. Kusano, R.; Matsuo, Y.; Saito, Y.; Tanaka, T.; Oxidation mechanism of black tea pigment theaflavin by peroxidase. *Tetrahedron Letters* **2015**, *56*, 5099. [Crossref]
17. Li, Y.; Shibahara, A.; Matsuo, Y.; Tanaka, T.; Kouno, I.; Reaction of the Black Tea Pigment Theaflavin during Enzymatic Oxidation of Tea Catechins. *Journal of Natural Products* **2010**, *73*, 33. [Crossref]
18. Weng, M.-S.; Ho, C.-T.; Ho, Y.-S.; Lin, J.-K.; Theanaphthoquinone inhibits fatty acid synthase expression in EGF-stimulated human breast cancer cells *via* the regulation of EGFR/ErbB-2 signaling. *Toxicology and Applied Pharmacology* **2007**, *218*, 107. [Crossref] [PubMed]
19. Hidekazu, Y.; Akiko, T.; Kazue, I.; Masahisa, U.; Hiroshi, U.; Hair Dyeing by Using Catechinone Obtained from (+)-Catechin. *Journal of Cosmetics, Dermatological Sciences and Applications* **2012**, *2*, 158. [Crossref]
20. Matsubara, T.; Wataoka, I.; Urakawa, H.; Yasunaga, H.; Effect of Reaction Conditions on Production of Catechinone Hair Dyestuff in Water/Alcohol Mixed Solution. *Advances in Chemical Engineering and Science* **2014**, *4*, 292. [Crossref]
21. Matsubara, T.; Seki, C.; Yasunaga, H.; The Relationships between Dyeing Methods and Dyeability in Hair Colouring by Utilising Enzymatic Oxidation of (+)-Catechin. *American Journal of Plant Sciences* **2016**, *7*, 1058. [Crossref]
22. Matsubara, T.; Wataoka, I.; Urakawa, H.; Yasunaga, H.; Effect of reaction pH and $CuSO_4$ addition on the formation of catechinone due to oxidation of (+)-catechin. *International Journal of Cosmetic Science* **2013**, *35*, 362. [Crossref]
23. Mochizuki, M.; Yamazaki, S.-I.; Kano, K.; Ikeda, T.; Kinetic analysis and mechanistic aspects of autoxidation of catechins. *Biochimica et Biophysica Acta - General Subjects* **2002**, *1569*, 35. [Crossref] [PubMed]

24. Ma, L.; Waterhouse, A. L.; Flavanols react preferentially with quinones through an electron transfer reaction, stimulating rather than preventing wine browning. *Analytica Chimica Acta* **2018**, *1039*, 162. [Crossref] [PubMed]
25. Morina, F.; Takahama, U.; Mojović, M.; Popović-Bijelić, A.; Veljović-Jovanović, S.; Formation of stable radicals in catechin/nitrous acid systems: Participation of dinitrosocatechin. *Food Chemistry* **2016**, *194*, 1116. [Crossref] [PubMed]
26. Pandey, P.; Avula, B.; Khan, I. A.; Khan, S. I.; Navarro, V. J.; Doerksen, R. J.; Chittiboyina, A. G.; Potential Modulation of Human NAD[P]H-Quinone Oxidoreductase 1 (NQO1) by EGCG and Its Metabolites - A Systematic Computational Study. *Chemical Research in Toxicology* **2020**, *33*, 2749. [Crossref] [PubMed]
27. Chen, Z.; Wang, C.; Chen, J.; Li, X.; Biocompatible, functional spheres based on oxidative coupling assembly of green tea polyphenols. *Journal of the American Chemical Society* **2013**, *135*, 4179. [Crossref] [PubMed]
28. Xiao, L.; Mertens, M.; Wortmann, L.; Kremer, S.; Valldor, M.; Lammers, T.; Kiessling, F.; Mathur, S.; Enhanced *in vitro* and *in vivo* cellular imaging with green tea coated water-soluble iron oxide nanocrystals. *ACS Applied Materials and Interfaces* **2015**, *7*, 6530. [Crossref] [PubMed]
29. Chen, L.; Yuan, P.; Chen, K.; Jia, Q.; Li, Y.; Oxidative conversion of B- to A-type procyanidin trimer: Evidence for quinone methide mechanism. *Food Chemistry* **2014**, *154*, 315. [Crossref] [PubMed]
30. Li, L.-J.; Zhang, Y.; Zhang, P.; Pi, H.-F.; Ruan, H.-L.; Wu, J.-Z.; Two new 5,8-quinoflavans from the leaf of *Ilex centrochinensis*. *Journal of Asian Natural Products Research* **2011**, *13*, 341. [Crossref]
31. Hu, X.-Q.; Han, W.; Han, Z.-Z.; Liu, Q.-X.; Xu, X.-K.; Fu, P.; Li, H.-L.; A new macrocyclic lactone and a new quinoflavan from *Celastrus hindsii*. *Phytochemistry Letters* **2014**, *7*, 169. [Crossref]
32. Yahara, S.; Ogata, T.; Saijo, R.; Konishi, R.; Yamahara, J.; Miyahara, K.; Nohara, T.; Isoflavan and related compounds from *Dalbergia odorifera*. I. *Chemical and Pharmaceutical Bulletin* **1989**, *37*, 979. [Crossref]
33. Chan, S.-C.; Chang, Y.-S.; Wang, J.-P.; Chen, S.-C.; Kuo, S.-C.; Three new flavonoids and antiallergic, anti-inflammatory constituents from the heartwood of *Dalbergia odorifera*. *Planta Medica* **1998**, *64*, 153. [Crossref] [PubMed]
34. Umehara, K.; Nemoto, K.; Matsushita, A.; Terada, E.; Monthakantirat, O.; De-Eknamkul, W.; Miyase, T.; Warashina, T.; Degawa, M.; Noguchi, H.; Flavonoids from the heartwood of the Thai medicinal plant *Dalbergia parviflora* and their effects on estrogenic-responsive human breast cancer cells. *Journal of Natural Products* **2009**, *72*, 2163. [Crossref] [PubMed]
35. De-Eknamkul, W.; Umehara, K.; Monthakantirat, O.; Toth, R.; Frecer, V.; Knapic, L.; Braiuca, P.; Noguchi, H.; Miertus, S.; QSAR study of natural estrogen-like isoflavonoids and diphenolics from Thai medicinal plants. *Journal of Molecular Graphics and Modelling* **2011**, *29*, 784. [Crossref] [PubMed]
36. Hamburger, M. O.; Cordell, G. A.; Tantivatana, P.; Ruangrungsi, N.; Traditional medicinal plants of Thailand, VIII: Isoflavonoids of *Dalbergia candenatensis*. *Journal of Natural Products* **1987**, *50*, 696. [Crossref] [PubMed]
37. Bandeira, P. N.; de Farias, S. S.; Lemos, T. L. G.; Braz-Filho, R.; Santos, H. S.; Albuquerque, M. R. J. R.; Costa, S. M. O.; New isoflavone derivative and other flavonoids from the resin of *Amburana cearensis*. *Journal of the Brazilian Chemical Society* **2011**, *22*, 372. [Crossref]
38. Ferreira, M. A.; Moir, M.; Thomson, R. H.; Naturally occurring quinones. Part XXV. Pterocarpenequinones (6*H*-benzofuro[3,2-c][1]benzopyranquinones) from *Brya ebenus*. *Journal of the Chemical Society, Perkin Transactions 1* **1975**, 1113. [Crossref]
39. Antus, S.; Gottsegen, A.; Kolonits, P.; Nagy, Z.; Nógrádi, M.; Vermes, B.; Synthesis of some pterocarpenes obtained from *Brya ebenus*. *Journal of the Chemical Society, Perkin Transactions 1* **1982**, 1389. [Crossref]
40. Kuo, S.-C.; Chen, S.-C.; Chen, L.-H.; Wu, J.-B.; Wang, J.-P.; Teng, C.-M.; Potent antiplatelet, anti-inflammatory and antiallergic isoflavanquinones from the roots of *Abrus precatorius*. *Planta Medica* **1995**, *61*, 307. [Crossref] [PubMed]
41. Limmatvapirat, C.; Sirisopanaporn, S.; Kittakoop, P.; Antitubercular and antiplasmodial constituents of *Abrus precatorius*. *Planta Medica* **2004**, *70*, 276. [Crossref] [PubMed]
42. Hata, Y.; Raith, M.; Ebrahimi, S. N.; Zimmermann, S.; Mokoka, T.; Naidoo, D.; Fouche, G.; Maharaj, V.; Kaiser, M.; Brun, R.; Hamburger, M.; Antiprotozoal isoflavan quinones from *Abrus precatorius ssp. africanus*. *Planta Medica* **2013**, *79*, 492. [Crossref] [PubMed]
43. Hata, Y.; Ebrahimi, S. N.; De Mieri, M.; Zimmermann, S.; Mokoka, T.; Naidoo, D.; Fouche, G.; Maharaj, V.; Kaiser, M.; Brun, R.; Potterat, O.; Hamburger, M.; Antitrypanosomal isoflavan quinones from *Abrus precatorius*. *Fitoterapia* **2014**, *93*, 81. [Crossref] [PubMed]
44. Okoro, E. E.; Ahmad, M. S.; Osoniyi, O. R.; Onajobi, F. D.; Antifungal and antileishmanial activities of fractions and isolated isoflavanquinones from the roots of *Abrus precatorius*. *Comparative Clinical Pathology* **2020**, *29*, 391. [Crossref]
45. Okoro, E. E.; Maharjan, R.; Jabeen, A.; Ahmad, M. S.; Azhar, M.; Shehla, N.; Zaman, W.; Shams, S.; Osoniyi, O. R.; Onajobi, F. D.; Choudhary, M. I.; Isoflavanquinones from *Abrus precatorius* roots with their antiproliferative and anti-inflammatory effects. *Phytochemistry* **2021**, *187*, 112743. [Crossref] [PubMed]
46. Sibata, H.; Simizu, S.; Amorphaquinone, a New Isoflavanquinone from *Amorpha fruticos*a L. *Heterocycles* **1978**, *10*, 85. [Crossref]
47. Ohyama, M.; Tanaka, T.; Linuma, M.; A prenylated flavonone from roots of *Amorpha fruticosa*. *Phytochemistry* **1998**, *48*, 907. [Crossref]
48. Rahman, A. A.; Samoylenko, V.; Jain, S. K.; Tekwani, B. L.; Khan, S. I.; Jacob, M. R.; Midiwo, J. O.; Hester, J. P.; Walker, L. A.; Muhammad, I.; Antiparasitic and antimicrobial isoflavanquinones from *Abrus schimperi*. *Natural Product Communications* **2011**, *6*, 1645. [Crossref] [PubMed]
49. Su, Q.; Krai, P.; Goetz, M.; Cassera, M. B.; Kingston, D. G. I.; Antiplasmodial Isoflavanes and Pterocarpans from *Apoplanesia paniculata*. *Planta Medica* **2015**, *81*, 1128. [Crossref] [PubMed]

50. El-Sebakhy, N. A.; Asaad, A. M.; Abdallah, R. M.; Toaima, S. M.; Abdel-Kader, M. S.; Stermitz, F. R.; Antimicrobial isoflavans from *Astragalus* species. *Phytochemistry* **1994**, *36*, 1387. [Crossref] [PubMed]
51. Agrawal, P. K.; *Carbon-13 NMR of Flavonoids, Volume 39* - 1a. ed., Elsevier Science: Amsterdã, 1989. [Crossref] [Link]
52. Wang, D.-W.; Xiao, C.-J.; Qiu, L.; Tian, X.-Y.; Dong, X.; Jiang, B.; Two new 8-isopentenyl isoflavane derivatives from *Astragalus dolichochaete* Diels. *Natural Product Research* **2021**, *35*, 1323. [Crossref] [PubMed]
53. Farkas, L.; Gottsegen, À.; Nóagrádi, M.; Antus, S.; Synthesis of sophorol, violanone, lonchocarpan, claussequinone, philenopteran, leiocalycin, and some other natural isoflavonoids by the oxidative rearrangement of chalcones with thallium(III) nitrate. *Journal of the Chemical Society, Perkin Transactions 1* **1974**, 305. [Crossref]
54. Gottlieb, O. R.; de Oliveira, A. B.; Gonçalves, T. M. M.; de Oliveira, G. G.; Pereira, S. A.; Isoflavonoids from *Cyclolobium species*. *Phytochemistry* **1975**, *14*, 2495. [Crossref]
55. Gambardella, M. T. P.; Mascarenhas, Y. P.; Santos, R. H. A.; 7-Hydroxy-4'-methoxyisoflavanquinone (claussequinone), $C_{16}H_{14}O_5$. *Acta Crystallographica Section C Crystal Structural Chemistry* **1983**, *C39*, 741. [Crossref]
56. Goulart, M. O. F.; Soares, N. A.; Sant'Ana, A. E. G.; Tonholo, J.; Boodts, J. F. C.; Investigation of the Electrochemical Reduction of 3*R*-Claussequinone, in "Dry" DMF and Mixed Water-DMF Solvent: A system Involving Self-Protonation. *Journal Of The Brazilian Chemical Society* **1993**, *4*, 47. [Crossref]
57. Emim, J. A. S.; Oliveira, A. B.; Lapa, A. J.; Pharmacological Evaluation of the Anti-inflammatory Activity of a Citrus Bioflavonoid, Hesperidin, and the Isoflavonoids, Duartin and Claussequinone, in Rats and Mice. *Journal of Pharmacy and Pharmacology* **1994**, *46*, 118. [Crossref] [PubMed]
58. Choi, C. W.; Choi, Y. H.; Cha, M.-R.; Kim, Y. S.; Yon, G. H.; Kim, Y.-K.; Choi, S. U.; Kim, Y. H.; Ryu, S. Y. Antitumor Components Isolated from the Heartwood Extract of *Dalbergia odorifera*. *Journal of the Korean Society for Applied Biological Chemistry* **2009**, *52*, 375. [Crossref]
59. Choi, C. W.; Choi, Y. H.; Cha, M.-R.; Yoo, D. S.; Kim, Y. S.; Yon, G. H.; Hong, K. S.; Kim, Y. H.; Ryu, S. Y.; Yeast α-glucosidase inhibition by isoflavones from plants of leguminosae as an *in vitro* alternative to acarbose. *Journal of Agricultural and Food Chemistry* **2010**, *58*, 9988. [Crossref] [PubMed]
60. Yahara, S.; Saijo, R.; Nohara, T.; Konishi, R.; Yamahara, J.; Kawasaki, T.; Miyahara, K.; Novel bi-isoflavonoids from *Dalbergia odorifera*. *Chemical & Pharmaceutical Bulletin* **1985**, *33*, 5130. [Crossref]
61. Takahashi, M.; Fuchino, H.; Sekita, S.; Satake, M.; Kiuchi, F.; *In vitro* leishmanicidal constituents of *Millettia pendula*. *Chemical and Pharmaceutical Bulletin* **2006**, *54*, 915. [Crossref] [PubMed]
62. Grosvenor, P. W.; Gray, D. O.; Colutequinone and colutehydroquinone, antifungal isoflavonoids from *Colutea arborescens*. *Phytochemistry* **1996**, *43*, 377. [Crossref] [PubMed]
63. Grosvenor, P. W.; Gray, D. O.; Coluteol and colutequinone B, more antifungal isoflavonoids from *Colutea arborescens*. *Journal of Natural Products* **1998**, *61*, 99. [Crossref]
64. Kraus, G. A.; Kim, I.; A direct route to isoflavan quinones. The synthesis of colutequinones A and B. *Tetrahedron* **2003**, *59*, 7935. [Crossref]
65. Kamnaing, P.; Free, S. N. Y. F.; Nkengfack, A. E.; Folefoc, G.; Fomum, Z. T.; An isoflavan-quinone and a flavonol from *Millettia laurentii*. *Phytochemistry* **1999**, *51*, 829. [Crossref]
66. Kurosawa, K.; Ollis, W. D.; Redman, B. T.; Sutherland, I. O.; Alves, H. M.; Gottlieb, O. R.; Absolute configurations of isoflavans. *Phytochemistry* **1978**, *17*, 1423. [Crossref]
67. Kurosawa, K.; Ollis, W. D.; Redman, B. T.; Sutherland, I. O.; Gottlieb, O. R.; Alves, H. M.; The absolute configurations of the animal metabolite, equol, three naturally occurring isoflavans, and one natural isoflavanquinone. *Chemical Communications (London)* **1968**, 1265. [Crossref]
68. Kurosawa, K.; Ollis, W. D.; Sutherland, I. O.; Gottlieb, O. R.; de Oliveira, A. B.; Mucronulatol, mucroquinone and mucronucarpan, isoflavonoids from *Machaerium mucronulatum* and *M. villosum*. *Phytochemistry* **1978**, *17*, 1405. [Crossref]
69. Kaneko, M.; Nakata, H.; Takada, F.; Matsumura, M.; Kitagawa, C.; Sakashita, S.; Nuno, M.; Saitoh, T.; Isoflavones from the gall and wood of *Wisteria brachybotrys*. *Phytochemistry* **1988**, *27*, 267. [Crossref]
70. Konoshima, T.; Takasaki, M.; Kozuka, M.; Tokuda, H.; Nishino, H.; Matsuda, E.; Nagai, M.; Anti-tumor promoting activities of isoflavonoids from *Wistaria brachybotrys*. *Biological and Pharmaceutical Bulletin* **1997**, *20*, 865. [Crossref] [PubMed]
71. Konoshima, T.; Takasaki, M.; Anti-Tumor-Promoting Activities (Cancer Chemopreventive Activities) of Natural Products, Em *Studies in Natural Products Chemistry*; Atta-ur-Rahman ed.; Elsevier: Amsterdã, 2000, vol.24, part E, pp215. [Crossref]
72. Chen, W.-H.; Ren, Z.-Y.; Wang, R.; Shi, Y.-P.; Crystal Structure and Absolute Configuration of Pendulone. *Analytical Sciences: X-ray Structure Analysis Online* **2008**, *24*, x209. [Crossref]
73. Chen, W.-H.; Wang, R.; Shi, Y.-P.; Flavonoids in the poisonous plant *Oxytropis falcata*. *Journal of Natural Products* **2010**, *73*, 1398. [Crossref] [PubMed]
74. Radwan, M. M.; Isoflavonoids from an Egyptian Collection of *Colutea istria*. *Natural Product Communications* **2008**, *3*, 1491. [Crossref]
75. Zhang, L.-J.; Liu, H.-K.; Hsiao, P.-C.; Kuo, L.-M. Y.; Lee, I.-J.; Wu, T.-S.; Chiou, W.-F.; Kuo, Y.-H.; New isoflavonoid glycosides and related constituents from *Astragali radix* (*Astragalus membranaceus*) and their inhibitory activity on nitric oxide production. *Journal of Agricultural and Food Chemistry* **2011**, *59*, 1131. [Crossref] [PubMed]
76. Maamria, L.; Haba, H.; Lavaud, C.; Harakat, D.; Benkhaled, M.; An isoflavane and saponins from *Astragalus depressus* L. *Journal of the Serbian Chemical Society* **2015**, *80*, 137. [Crossref]
77. Park, S. J.; Nhiem, N. X.; Tai, B. H.; Anh, H. L. T.; Oh, S. H.; Sung, J.-H.; Kim, N.; Yoo, G.; Park, J. H.; Kwak, H. J.; Loan, P. T.; Kim, S. H.; Kiem, P. V.; Proliferation Effects on Hair Growth of Compounds Isolated from the Bark of *Dalbergia oliveri*. *Natural Product Communications* **2017**, *12*, 1729. [Crossref]
78. Balakrishna, K. J.; Seshadri, T. R.; Viswanath, G.; Formation of quinones by oxidative demethylation - Part IV. Isomers of

methyl pedicinin. *Proceedings of the Indian Academy of Sciences - Section A* **1949**, *30*, 163. [Crossref]

79. Balakrishna, K. J.; Seshadri, T. R.; Viswanath, G.; Nuclear oxidation in flavones and related compounds - Part XXV. Isomers of pedicinin. *Proceedings of the Indian Academy of Sciences - Section A* **1949**, *30*, 120. [Crossref]
80. Bennett, G. J.; Lee, H.-H.; Oxidative rearrangement of quinochalcones. Part 2. A facile synthesis of linderone. *Journal of the Chemical Society, Perkin Transactions 1* **1986**, 633. [Crossref]
81. Biswas, P.; Bhattacharyya, A.; Bose, P. C.; Mukherjee, N.; Adityachaudhury, N.; Further studies on the sensitivity of plant pathogenic microorganisms towards some naturally occurring chalcones and flavanones. *Experientia* **1981**, *37*, 397. [Crossref]
82. Rao, G. S. K.; Rao, K. V.; Seshadri, T. R.; A new effect of hydrogen bond formation (chelation) - Part II. Constitution of despedicellin, dihydropedicinin and isopedicin. *Proceedings of the Indian Academy of Sciences - Section A* **1948**, *28*, 198. [Crossref]
83. Rao, K. V.; Seshadri, T. R.; Nuclear oxidation in flavones and related compounds - Part XII. Constitution and Synthesis of Pedicin and Its Allies. *Proceedings of the Indian Academy of Sciences - Section A* **1948**, *27*, 375. [Crossref]
84. Gény, C.; Samra, A. A.; Retailleau, P.; Iorga, B. I.; Nedev, H.; Awang, K.; Roussi, F.; Litaudon, M.; Dumontet, V.; (+)- and (-)-Ecarlottones, Uncommon Chalconoids from *Fissistigma latifolium* with Pro-Apoptotic Activity. *Journal of Natural Products* **2017**, *80*, 3179. [Crossref] [PubMed]
85. Mukerjee, S. K.; Seshadri, T. R.; Varadarajan, S.; Synthetic experiments in the benzopyrone series - Part XXI. Isomerisation of C-(6 or 8)-methyl-5: 7-dihydroxy chromones. *Proceedings of the Indian Academy of Sciences - Section A* **1953**, *37*, 127. [Crossref]
86. Rao, K. V.; Rao, K. V.; Seshadri, T. R.; Nuclear oxidation in the flavone series - Part II. Synthesis of norwogonin and isowogonin. *Proceedings of the Indian Academy of Sciences - Section A* **1947**, *25*, 427. [Crossref]
87. Chaliha, B. P.; Sastry, G. P.; Rao, P. R.; Chemical examination of the peel of *Citrus jambhiri* Lush. Isolation of a new flavone. *Tetrahedron* **1965**, *21*, 1441. [Crossref]
88. Hausen, B. M.; Schmalle, H. W.; Marshall, D.; Thomson, R. H.; 5,8-Dihydroxyflavone (primetin) the contact sensitizer of *Primula mistassinica* Michaux. *Archives of Dermatological Research* **1983**, *275*, 365. [Crossref] [PubMed]
89. Looker, J. H.; Edman, J. R.; Kingsbury, C. A.; 5,8-Quinoflavone. Synthesis and Addition Reactions. *Journal of Organic Chemistry* **1984**, *49*, 645. [Crossref]
90. Laroche, M.-F.; Marchand, A.; Duflos, A.; Massiot, G.; Diels-Alder adducts from flavonoid. *Tetrahedron Letters* **2007**, *48*, 9056. [Crossref]
91. Compton, B. J.; Larsen, L.; Weavers, R. T.; Use of acyl substituents to favour 2,3-epoxidation of 5,7-dioxygenated flavones with dimethyldioxirane. *Tetrahedron* **2011**, *67*, 718. [Crossref]
92. Rao, K. V.; Seshadri, T. R.; Constitution of gossypin-Part I. *Proceedings of the Indian Academy of Sciences - Section A* **1946**, *24*, 375. [Crossref]
93. Rao, K. V.; Seshadri, T. R.; Constitution of gossypin-Part II. *Proceedings of the Indian Academy of Sciences - Section A* **1947**, *25*, 397. [Crossref]
94. Rao, G. S. K.; Rao, K. V.; Seshadri, T. R.; A note on the formation of quinones by oxidative demethylation and the effect of methylating agents on them. *Proceedings of the Indian Academy of Sciences - Section A* **1948**, *27*, 245. [Crossref]
95. Farkas, L.; Nógrádi, M.; Synthesis of some flavone components of the euphorbiaceae. *Tetrahedron Letters* **1966**, *7*, 3759. [Crossref]
96. Farkas, L.; Nógrádi, M.; Vermes, B.; Synthese einiger Flavonkomponenten aus *Ricinocarpos stylosus*. *Chemische Berichte* **1967**, *100*, 2296. [Crossref]
97. Rao, K. V.; Owoyale, J. A.; Nuclear bishydroxylation with peroxydisulfate. *Journal of Heterocyclic Chemistry* **1976**, *13*, 361. [Crossref]
98. Lewin, G.; Shridhar, N. B.; Aubert, G.; Thoret, S.; Dubois, J.; Cresteil, T.; Synthesis of antiproliferative flavones from calycopterin, major flavonoid of *Calycopteris floribunda* Lamk. *Bioorganic and Medicinal Chemistry* **2011**, *19*, 186. [Crossref] [PubMed]
99. Weinges, K.; Wild, R.; Phenolische Naturstoffe, XII - Die Konstitution des Polydins. *Justus Liebigs Annalen der Chemie* **1970**, *734*, 46. [Crossref]
100. Bernini, R.; Mincione, E.; Provenzano, G.; Fabrizi, G.; Catalytic oxidation of catechins to *p*-benzoquinones with hydrogen peroxide/methyltrioxorhenium. *Tetrahedron Letters* **2005**, *46*, 2993. [Crossref]
101. Boyer, F.-D.; Beauhaire, J.; Martin, M. T.; Ducrot, P.-H.; Hydroxylation of ring A of flavan-3-ols: Influence of the ring A substitution pattern on the oxidative rearrangement of 6-hydroxyflavan-3-ols. *Synthesis* **2006**, *2006*, 3250. [Crossref]
102. Chang, C.-Y.; Huang, L.-J.; Wang, J.-P.; Teng, C.-M.; Chen, S.-C.; Kuo, S.-C.; Synthesis and Anti-platelet, Anti-inflammatory and Anti-allergic Activities of Methoxyisoflavanquinone and Related Compounds. *Chemical and Pharmaceutical Bulletin* **2000**, *48*, 964. [Crossref]
103. Moon, Y.; Hong, S.; A facile route to isoflavonequinones *via* the direct cross-coupling of chromones and quinones. *Chemical Communications* **2012**, *48*, 7191. [Crossref] [PubMed]
104. Zhou, Y.; Liang, H.; Sheng, Y.; Wang, S.; Gao, Y.; Zhan, L.; Zheng, Z.; Yang, M.; Liang, G.; Zhou, J.; Deng, J.; Song, Z.; Ruthenium(II)-Catalyzed C-H Activation of Chromones with Maleimides to Synthesize Succinimide/Maleimide-Containing Chromones. *Journal of Organic Chemistry* **2020**, *85*, 9230. [Crossref]
105. Kraus, G. A.; Kim, I.; A direct synthesis of *O*-methyl claussequinone. *Journal of Organic Chemistry* **2003**, *68*, 4517. [Crossref] [PubMed]
106. Gafner, S.; Bergeron, C.; Villinski, J. R.; Godejohann, M.; Kessler, P.; Cardellina, J. H.; Ferreira, D.; Feghali, K.; Grenier, D.; Isoflavonoids and coumarins from *Glycyrrhiza uralensis*: Antibacterial activity against oral pathogens and conversion of isoflavans into isoflavan-quinones during purification. *Journal of Natural Products* **2011**, *74*, 2514. [Crossref] [PubMed]

107. Philipp, B.; Schink, B.; Evidence of two oxidative reaction steps initiating anaerobic degradation of resorcinol (1,3-dihydroxybenzene) by the denitrifying bacterium *Azoarcus anaerobius*. *Journal of Bacteriology* **1998**, *180*, 3644. [Crossref] [PubMed]
108. Ling, K.-Q.; Lee, Y.; Macikenas, D.; Protasiewicz, J. D.; Sayre, L. M.; Copper(II)-mediated autoxidation of *tert*-butylresorcinols. *Journal of Organic Chemistry* **2003**, *68*, 1358. [Crossref] [PubMed]
109. Rao, G. S. K.; Rao, K. V.; Seshadri, T. R.; Formation of quinones by oxidative dealkylation - Part II. Constitution of pedicinin. *Proceedings of the Indian Academy of Sciences - Section A* **1948**, *28*, 103. [Crossref]
110. Obara, H.; Onodera, J.-I.; Abe, S.; The Synthesis of 3'-Methoxy-2',4,4',6'- and 2'-Methoxy-3',4,4',6'-tetrahydroxychalcone and Some Quinochalcones and a Comparison of Them with Carthamin. *Bulletin of the Chemical Society of Japan* **1979**, *52*, 2596. [Crossref]
111. Lee, H.-H.; Que, Y.-T.; Ng, S.; Synthesis of lucidones. *Journal of the Chemical Society, Perkin Transactions 1* **1985**, 453. [Crossref]
112. Alias, Y.; Awang, K.; Hadi, A. H. A.; Thoison, O.; Sévenet, T.; Païs, M.; An antimitotic and cytotoxic chalcone from *Fissistigma lanuginosum*. *Journal of Natural Products* **1995**, *58*, 1160. [Crossref] [PubMed]