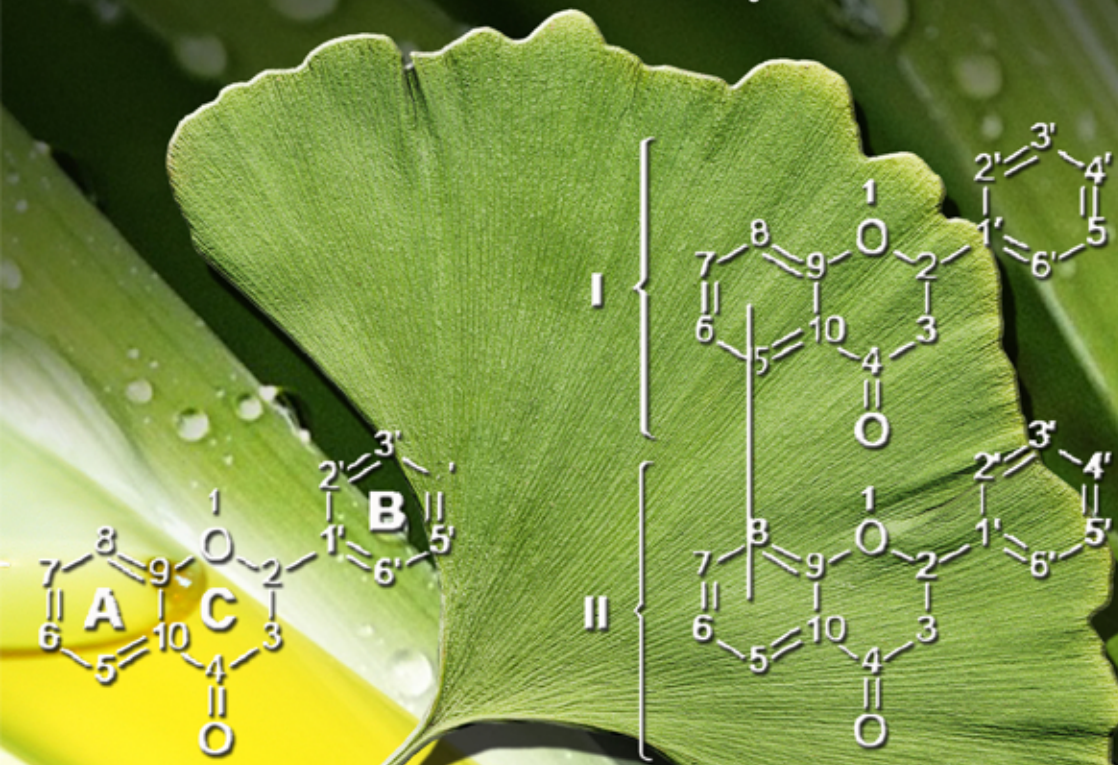
Biflavonoids

Occurrence, Structural Features and Bioactivity



Andrew G. Mercader
Alicia B. Pomilio
Editors

Chemistry Research and Applications

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CHEMISTRY RESEARCH AND APPLICATIONS

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BIFLAVONOIDS: OCCURRENCE, STRUCTURAL FEATURES AND BIOACTIVITY

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PREFACE

Biflavonoids comprise a group of the flavonoid family that possesses a variety of structures, and biological activities of high relevance, such as anticancer, antibacterial, antifungal, antiviral, anti-inflammatory, antinociceptive, antioxidant, vasodilator, anticlotting, among others, regardless of the bioactivity of each monomer unit. The chemistry of biflavonoids is very important in many fields of research, especially because these compounds are structurally different bioactive molecules with potential for biomedical application.

This book aims to highlight the structural biflavonoid variability, rearrangements, and different stereochemistry through about 470 structures distributed in some species of Angiosperms (monocots and dicots), Gymnosperms, ferns (Pteridophyta), and mosses (Bryophyta). Their distribution is shown to provide the latest picture of their natural sources, biological activities, and traditional uses. Chemical structures include simple dimers, complex biflavonoids, rearranged biflavonoids, natural Diels-Alder type adducts, and spirobiflavonoids.

The most important general characteristics, structures and nomenclature of the biflavonoids have been covered, and biological activities are carefully displayed. The structural aspects of the biflavonoids are shown in a detailed list of figures, thus providing an overview of their structural features. The current status and future prospects of the structure-activity studies of these compounds are also discussed.

Chapter 1

INTRODUCTION

Biflavonoids are flavonoid-flavonoid dimers linked by a C-C or C-*O*-C bond, with a variety of chemical structures. Many different combinations of the flavonoid dimers are possible. For example, flavanone-flavone, flavone-flavone, flavone-flavonol are some of the possible structures. Moreover, the connecting linkage may have different positions. In natural biflavonoids, many hydroxy and/or methoxy groups are the substituents at different positions. Therefore, in theory an incredibly high number of biflavonoids may exist. However, plants that contain biflavonoids as main constituents are not widely distributed. Nevertheless, biflavonoids occur in many fruits, vegetables, and plants; and since Furukawa extracted the leaves of maidenhair tree, *Ginkgo biloba* L., to obtain a yellow pigment, which later turned out to be a biflavonoid (II-4′,I-5,II-5,II-7-tetrahydroxy-I-4′,I-7-dimethoxy[I-3′,II-8]-biflavone), the so-called ginkgetin (**7**),[1] the number of isolated and identified biflavonoids in nature keeps growing.[2]

The biological/pharmacological activities of biflavonoids are diverse, including anticancer, antibacterial, antifungal, antiviral, anti-inflammatory, analgesic, antioxidant, vasorelaxant, anticlotting, among others.[3] Brief examples of the most relevant activities are shown in the following sections.

The main purpose of this book is to highlight the structural variability, different rearrangements and stereochemistry of biflavonoids through 466 structures that are distributed in some species of Angiosperms (monocots and dicots), Gymnosperms, ferns (Pteridophyta), and mosses (Bryophyta). Their distribution accompanied with the corresponding biological activities and traditional uses is thoroughly shown, intending to offer the latest picture of their natural sources. The most important general characteristics, structures

and nomenclature of the biflavonoids have been covered, and biological activities are carefully displayed. The structural aspects of the biflavonoids are shown in a detailed list of figures, to provide an overview of their structural features. The current status and future prospects for structure-activity studies of these compounds are also discussed.

Chapter 2

NOMENCLATURE OF THE BIFLAVONOIDS

There is no commonly accepted trivial nomenclature for bi- and triflavonoids, and higher oligomeric forms. Full systematic names, not to mention the often complex common names, are extremely cumbersome. The rapid growth of the literature on biflavonoids led to several systems for naming these compounds. Geiger and Quinn have proposed a system[4-7] that requires frequent reference for understanding and has become increasingly difficult to implement as the number of new compounds has grown. The nomenclature of this class of compounds is messy and disordered and depends on active researchers working in the field to select a simple, but logical system, and then, to use it consistently.

To rationalize and standardize the nomenclature, Locksley proposed some general rules.[8] Locksley standardized nomenclature for the rings and the positions on the rings. Each monomer unit is assigned a Roman numeral (I) and above in a sequential manner. The inter-monomer linkage is identified using a Roman numeral, which corresponds to the flavonoid unit, and an Arabic numeral, which corresponds to the position of the linkage. The two numerals for both flavonoid monomers constituting the dimer are coupled with a hyphen and enclosed in brackets. This represents the inter-monomer linkage. The numbering of the substituents in the monomeric units follows the IUPAC system for flavones, in which the three rings are known as A, B, and C (Fig. 1). As an example, biflavonoid morelloflavone heptamethylether (**161**) would be named I-5,7,4′,II-5,7,3′,4′-hepta-*O*-methylmorelloflavone under the rules of Locksley.

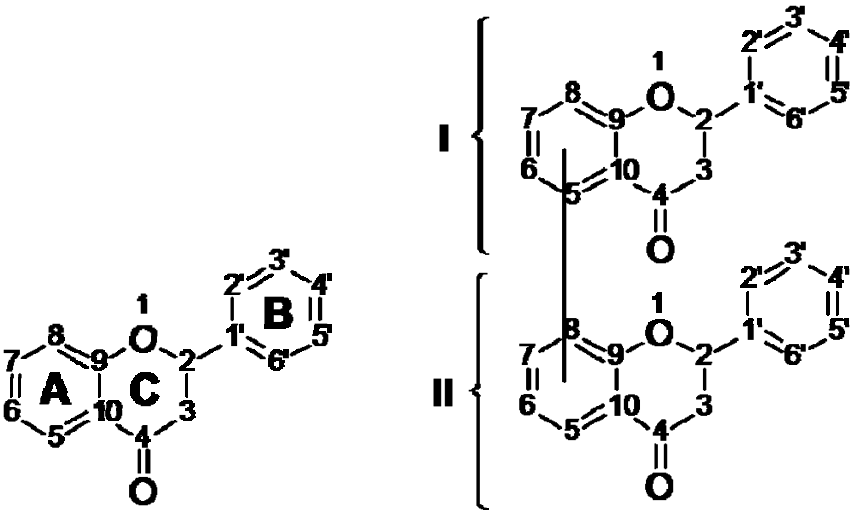


Figure 1. Basic scaffold of flavonoids and biflavonoids.

IUPAC has also devised its own system of nomenclature for biflavonoids, which in comparison with the rules of Locksley is more complicated; the same biflavone (**161**) would be called 5,7,5′,7′-tetramethoxy-2-(4-methoxyphenyl)-2′-(3,4-dimethoxyphenyl)-2,3-dihydro[3,8′]- bichromenyl-4,4′-dione.

The fundamental difference between the system of Locksley and the IUPAC system is the skeleton of reference. While the IUPAC system considers that most biflavonoids are derived from chromene structure, Locksley system uses the flavonoid structure. It is important to take into account that very few scientists use either system, especially since the common names, e.g., amentoflavone, cupressuflavone, and morelloflavone, are easier. These names, however, are limited because they do not contain any structural description. Locksley system is intuitive, logical, and structure-explicit, therefore, the systematic implementation of this method should be strongly encouraged. However, in order to facilitate the search for additional information regarding any of the biflavonoids presented in this review we also utilize the name most commonly used in the literature.

Chapter 3

BIFLAVONOID STRUCTURES

The units of the simple biflavonoid structures are flavones, flavanones, isoflavones, flavanols, chalcones, aurones and dihydrochalcones.[7, 9] Two identical or non-identical units of flavonoids conjoined in a symmetrical or asymmetrical manner through an alkyl- (C-C) or an alkoxy-based (C-*O*-C) linkage of varying length comprise the biflavonoid structure (Fig. 1). Many variations are possible in the parent flavonoid units, along with the large number of permutations possible in the position and nature of the inter-flavonoid linkage. The linkage can take place between different rings of the units, for example, the ring A (of unit 1) and A' (of unit 2), which is indicated as A-A, also could be: A-B, A-C, B-B, B-C and C-C (Fig. 2). This introduces significant structural diversity in biflavonoids, which is further amplified by the variably located functional groups, e.g., OH, MeO, C=O groups, or C=C bonds, and stereogenic centers in the skeleton of the flavonoids.

In combination, the class of biflavonoids represents a library of over 20,000 different molecules, each of which is capable of multiple H-bondings and hydrophobic interactions. Not all these have been found to exist in nature so far. However, biflavonoid theoretical library covers a wide range of the configurational and conformational space, thus suggesting that the scope of interesting biological activities may be extraordinary.[2]

The structure of a given biflavonoid is typically elucidated using intensive 1D and 2D NMR (COSY, NOESY).[10, 11] Circular dichroism (CD) is used to determine the absolute configuration in molecules that possess stereocenters.[12] Occasionally, additional spectroscopic techniques are used (MS, IR, UV and single crystal X-ray).

In the present chapter, the structures of the biflavonoids are represented and included in diverse figures to illustrate their variability, rearrangements, and different stereochemistry. A number was assigned to each structure for further references. Due to the large number of molecules, the structures were classified and divided into series, each series shares a similar backbone, containing a variety of different substituents.

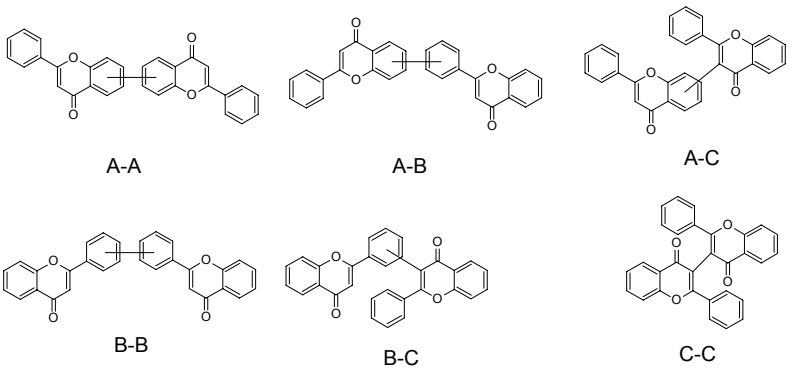
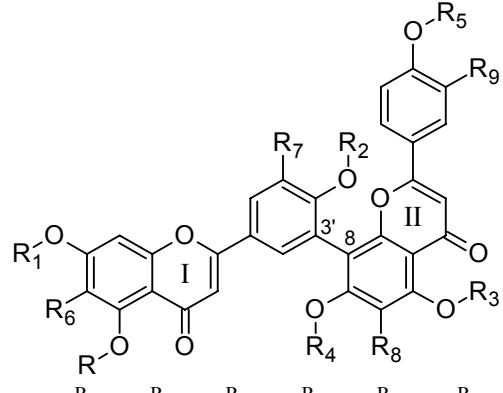


Figure 2. Biflavonoid backbone with different linkage between the flavones units.

SIMPLE DIMERS

The first main group of structures includes simple dimers *with* C-C, C-*O*-C and C-CH_2-C linkages of known flavonoid monomers. The combination of two flavone units through a (I-3′,II-8) bond comprises what is called Amentoflavone series. This series is further divided: in the first subsection structures consist of two identical flavone units, (I-3′,II-8)-biflavones (**1-27**); the structures of the second subsection include a flavone and a flavonol units, e.g., (I-3′,II-8)-flavone-flavonol dimers (**28-30**); the third kind of structures in this series has a flavanone and a flavone units, e.g., (I-3′,II-8)-flavanone-flavone (**31-43**); the following subsection contains structures made by a flavone and a flavanone units, e.g., (I-3′,II-8)-flavone-flavanone (**44**); the next subsection contains structures with a flavone and a flavanonol units, e.g., (I-3′,II-8)-flavone-flavanonol (**45**); then, two units of flavanones are linked together, e.g., (I-3′,II-8)-biflavanones (**46-58**), and finally, the structures contain a flavone and a pyranoflavone units, e.g., (I-3′,II-8)-pyranobiflavones (**59-63**).

(I-3′,II-8)-BIFLAVONES

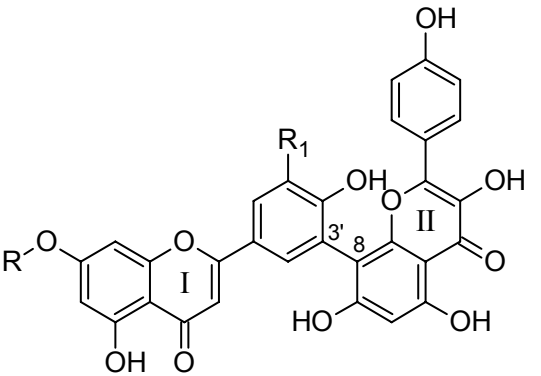


		R	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9
Amentoflavone	**(1)**	H	H	H	H	H	H	H	H	H	H
Sequoiaflavone	**(2)**	H	Me	H	H	H	H	H	H	H	H
Bilobetin	**(3)**	H	H	Me	H	H	H	H	H	H	H
I-5′-Methoxybilobetin	**(4)**	H	H	Me	H	H	H	H	OMe	H	H
Sotetsuflavone	**(5)**	H	H	H	H	Me	H	H	H	H	H
Podocarpusflavone A	**(6)**	H	H	H	H	H	Me	H	H	H	H
Ginkgetin	**(7)**	H	Me	Me	H	H	H	H	H	H	H
I-6-Methyl-I-7,4′-di-*O*-methylamentoflavone	**(8)**	H	Me	Me	H	H	H	Me	H	H	H
II-7-*O*-β-*D*-Glucopyranosylginkgetin	**(9)**	H	Me	Me	H	Glu	H	H	H	H	H
I-7,II-7-Di-*O*-methylamentoflavone	**(10)**	H	Me	H	H	Me	H	H	H	H	H
I-7,II-4′-Di-*O*-methylamentoflavone	**(11)**	H	Me	H	H	H	Me	H	H	H	H
I-4′,II-7-Di-*O*-methylamentoflavone	**(12)**	H	H	Me	H	Me	H	H	H	H	H

(Continued).

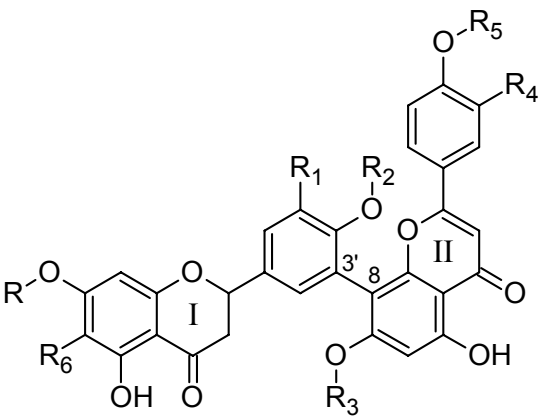
II-7,4′-Di-*O*-methylamentoflavone	**(12a)**	H	H	H	H	Me	Me	H	H	H	H
Isoginkgetin	**(13)**	H	H	Me	H	H	Me	H	H	H	H
II-7-*O*-β-*D*-Glucopyranosylisoginkgetin	**(14)**	H	H	Me	H	H	Me	H	H	H	H
Sciadopitysin	**(15)**	H	Me	Me	H	Glu	Me	H	H	H	H
I-7,4′,II-7-Tri-*O*-methylamentoflavone	**(16)**	H	Me	Me	H	Me	H	H	H	H	H
Kayaflavone	**(17)**	H	H	Me	H	Me	Me	H	H	H	H
Heveaflavone	**(18)**	H	Me	H	H	Me	Me	H	H	H	H
I-7,4′,II-7,4′-Tetra-*O*-methylamentoflavone	**(19)**	H	Me	Me	H	Me	Me	H	H	H	H
II-6-Hydroxyamentoflavone	**(20)**	H	H	H	H	H	H	H	H	OH	H
Oliveriflavone	**(21)**	H	Me	Me	Me	Me	Me	H	H	H	H
I-5,7,4′,II-5,7,4′-Hexa-*O*-methylamentoflavone	**(22)**	Me	Me	Me	Me	Me	Me	H	H	H	H
I-5′-Hydroxyamentoflavone	**(23)**	H	H	H	H	H	H	H	OH	H	H
I-5′,II-3′-Dihydroxyamentoflavone	**(24)**	H	H	H	H	H	H	H	OH	H	OH
(I-5′,II-8)-Biluteolin	**(25)**	H	H	H	H	H	H	H	OH	H	OH
II-6-Isoprenylamentoflavone	**(26)**	H	H	H	H	H	H	H	H		H
II-6-(2-Hydroxy)-isopentenylamentoflavone	**(27)**	H	H	H	H	H	H	H	H		H

(I-3′,II-8)-FLAVONE-FLAVONOL DIMERS



		R	R_1
II-3-Hydroxyamentoflavone	**(28)**	H	H
I-5′,II-3-Dihydroxyamentoflavone	**(29)**	H	OH
I-7-*O*-Methyl-II-3-hydroxyamentoflavone	**(30)**	Me	H

(I-3′,II-8)-FLAVANONE-FLAVONE DIMERS

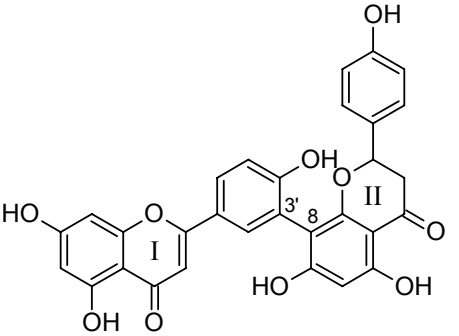


		R	R_1	R_2	R_3	R_4	R_5	R_6
I-2,3-Dihydroamentoflavone	**(31)**	H	H	H	H	H	H	H
I-7-*O*-Methyl-I-2,3-dihydroamentoflavone	**(32)**	Me	H	H	H	H	H	H
I-6-Methyl-I-7-*O*-methyl-I-2,3-dihydroamentoflavone	**(33)**	Me	H	H	H	H	H	Me
I-4′-*O*-Methyl-I-2,3-dihydroamentoflavone	**(34)**	H	H	Me	H	H	H	H
I-6-Methyl-I-4′-*O*-methyl-I-2,3-dihydroamentoflavone	**(35)**	H	H	Me	H	H	H	Me

(Continued).

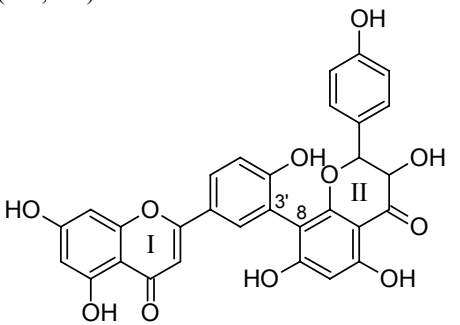
I-6-Methyl-I-7,4′-di-*O*-methyl-I-2,3-dihydroamentoflavone	**(36)**	Me	H	Me	H	H	H	Me
I-7,4′-Di-*O*-methyl-I-2,3-dihydroamentoflavone	**(37)**	Me	H	Me	H	H	H	H
I-7,II-7-Di-*O*-methyl-I-2,3-dihydroamentoflavone	**(38)**	Me	H	H	Me	H	H	H
I-2,3-Dihydrosciadopitysin	**(39)**	Me	H	Me	H	H	Me	H
Podocarpusflavanone	**(40)**	Me	H	H	Me	H	Me	H
I-7,4′,II-7-Tri-*O*-methyl-I-2,3-dihydroamentoflavone	**(41)**	Me	H	Me	Me	H	H	H
I-5′-Hydroxy-I-2,3-dihydroamentoflavone	**(42)**	H	OH	H	H	H	H	H
I-5′,II-3′-Dihydroxy-I-2,3-dihydroamentoflavone	**(43)**	H	OH	H	H	OH	H	H

(I-3′,II-8)-FLAVONE-FLAVANONE DIMER



II-2,3-Dihydroamentoflavone **(44)**

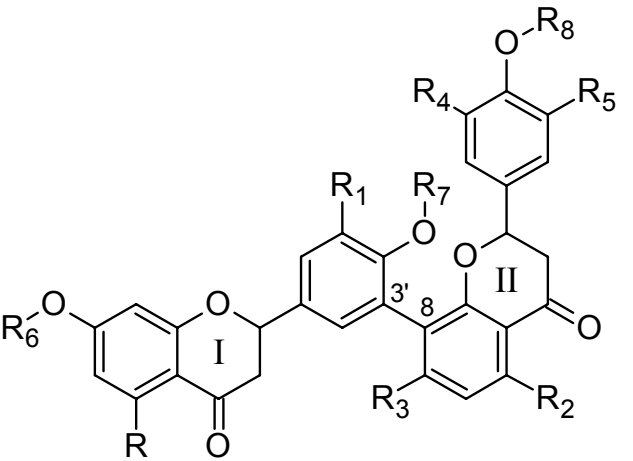
(I-3′,II-8)-FLAVONE-FLAVANONOL DIMER



II-3-Hydroxy-II-2*R*,3*R*-

dihydroamentoflavone **(45)**

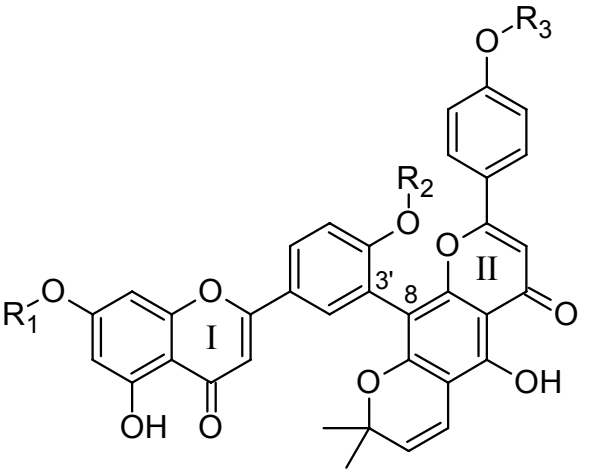
(I-3′,II-8)-BIFLAVANONES



		R	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
(I-3′,II-8)-Biliquiritigenin	**(46)**	H	H	H	OH	H	H	H	H	H
I-2,3,II-2,3-Tetrahydro-amentoflavone	**(47)**	OH	H	OH	OH	H	H	H	H	H
Semecarpuflavanone	**(49)**	H	H	H	OH	OH	OH	H	H	H
Jeediflavanone	**(50)**	OH	H	OH	OH	OH	H	H	H	H
Galluflavanone	**(51)**	H	OH	H	OH	OH	OH	H	H	H
I-4′-*O*-Methyl- I-2,3,II-2,3-tetrahydro-amentoflavone	**(52)**	OH	H	OH	OH	H	H	H	Me	H
II-4′-*O*-Methyl-I-2,3,II,2,3-tetrahydro-amentoflavone	**(53)**	OH	H	OH	OH	H	H	H	H	Me
Tetrahydroisoginkgetin	**(54)**	OH	H	OH	OH	H	H	H	Me	Me
Anacarduflavanone*	**(55)**	OH	OMe	OH	OMe	H	*-*O*-	Me	Me	*-CH_2-
I-7,II-7-Di-*O*-methyl-I-2,3,II-2,3-tetrahydro-amentoflavone	**(56)**	OH	H	OH	OMe	H	H	Me	H	H
Semecarpetin	**(57)**	H	H	H	OH	OMe	H	Me	Me	Me
Nallaflavone	**(58)**	OH	OMe	OH	OMe	OMe	OMe	Me	Me	H

*II-3′,4′ substituent: -O-CH_2-O- (methylenedioxyl).

(I-3′,II-8)-PYRANOBIFLAVONES

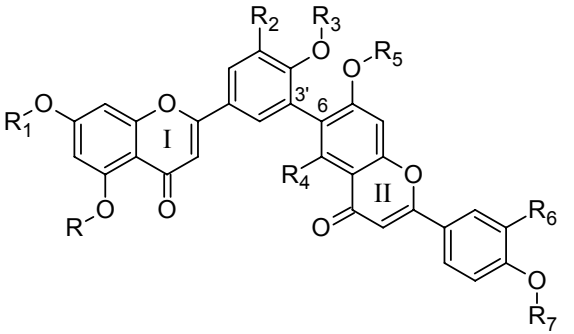


		R_1	R_2	R_3
Pyranoamentoflavone	**(59)**	H	H	H
I-7-*O*-Methylpyranoamentoflavone	**(60)**	Me	H	H
I-4′-*O*-Methylpyranoamentoflavone	**(61)**	H	Me	H
II-4′-*O*-Methylpyranoamentoflavone	**(62)**	H	H	Me
I-7,4′-Di-*O*-methylpyranoamentoflavone	**(63)**	Me	Me	H

Figure 3. SIMPLE BIFLAVONOIDS: (I-3′,II-8)-Biflavones, (I-3′,II-8)-Flavone-flavonol dimers, (I-3′,II-8)-Flavanone-flavone dimers, (I-3′,II-8)-Flavone-flavanone dimer, (I-3′,II-8)-Flavone-flavanonol dimer, (I-3′,II-8)-Biflavanones, (I-3′,II-8)-Pyranobiflavones.

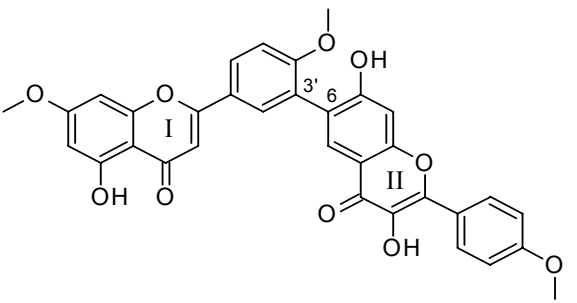
Robustaflavone series consists of two flavonoid units linked by a (I-3′,II-6) bond. This series was also subdivided into the following sets: structures containing two flavone units, (I-3′,II-6)-biflavones (**64**-**73**); a flavone and a flavonol unit, (I-3′,II-6)-flavone-flavonol (**74**); a flavanone and a flavone unit, (I-3′,II-6)-flavanone-flavone (**75**-**79**); a flavone and a flavanone unit, (I-3′,II-6)-flavone-flavanone (**80**-**82**); and finally, a set containing structures with two flavanone units or two flavanonol units, (I-3′,II-6)-biflavanones and (I-3′,II-6)-biflavanonols (**83**-**85**).

(I-3′,II-6)-BIFLAVONES



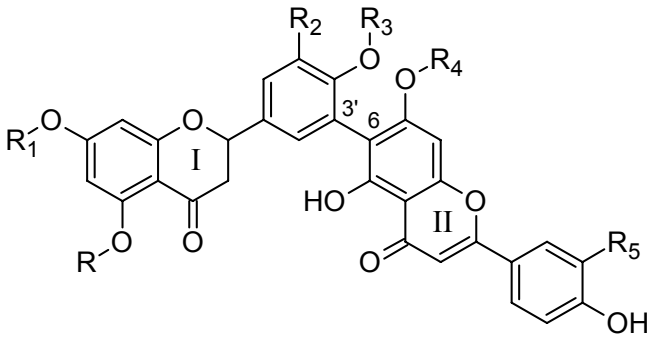
		R	R_1	R_2	R_3	R_4	R_5	R_6	R_7
Robustaflavone	**(64)**	H	H	H	H	OH	H	H	H
I-4′-*O*-Methyl-robustaflavone	**(65)**	H	H	H	Me	OH	H	H	H
II-7-*O*-Methyl-robustaflavone	**(66)**	H	H	H	H	OH	Me	H	H
I-4′,II-7-Di-*O*-methyl-robustaflavone	**(67)**	H	H	H	Me	OH	Me	H	H
I-7,II-4′-Di-*O*-methyl-robustaflavone	**(68)**	H	Me	H	H	OH	H	H	Me
I-4′,II-4′-Di-*O*-methyl-robustaflavone	**(69)**	H	H	H	Me	OH	H	H	Me
I-7,4′,II-4′-Tri-*O*-methyl-robustaflavone	**(70)**	H	Me	H	Me	OH	H	H	Me
I-5,7,4′,II-5,7,4′-Hexa-*O*-methyl-robustaflavone	**(71)**	Me	Me	H	Me	OMe	Me	H	Me
I-5′-Hydroxy-robustaflavone	**(72)**	H	H	OH	H	OH	H	H	H
I-5′,II-3′-Dihydroxy-robustaflavone	**(73)**	H	H	OH	H	OH	H	OH	H

(I-3′,II-6)-Flavone-flavonol dimer



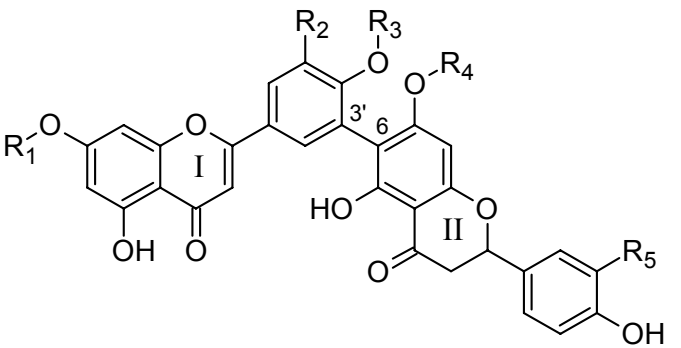
Abiesin **(74)**

(I-3′,II-6)-Flavanone-flavone dimers



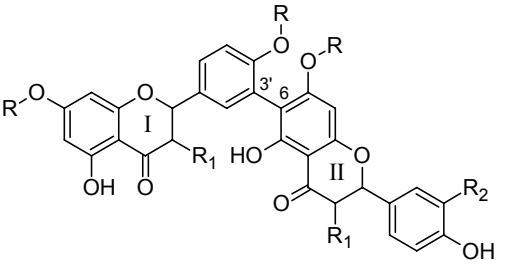
		R	R_1	R_2	R_3	R_4	R_5
I-2,3-Dihydrorobustaflavone	**(75)**	H	H	H	H	H	H
I-5-*O*-Methyl-I-2,3-dihydrorobustaflavone	**(76)**	Me	H	H	H	H	H
I-7,I-4′,II-7-Tri-*O*-methyl-I-2,3-dihydrorobustaflavone	**(77)**	H	Me	H	Me	Me	H
I-5′-Hydroxy-I-2,3-dihydrorobustaflavone	**(78)**	H	H	OH	H	H	H
I-5′,II-3′-Dihydroxy-I-2,3-dihydroamentoflavone	**(79)**	H	H	OH	H	H	OH

(I-3′,II-6)-Flavone-flavanone dimers



		R_1	R_2	R_3	R_4	R_5
(I-3′,II-6)-II-2,3-Dihydrobiluteolin	**(80)**	H	OH	H	H	OH
I-7,I-4′-Di-*O*-methyl-II-2,3-dihydrorobustaflavone	**(81)**	Me	H	Me	H	H
I-7,I-4′,II-7-Tri-*O*-methyl-II-2,3-dihydrorobustaflavone	**(82)**	Me	H	Me	Me	H

(I-3′,II-6)-Biflavanones and a (I-3′,II-6)-biflavanonol

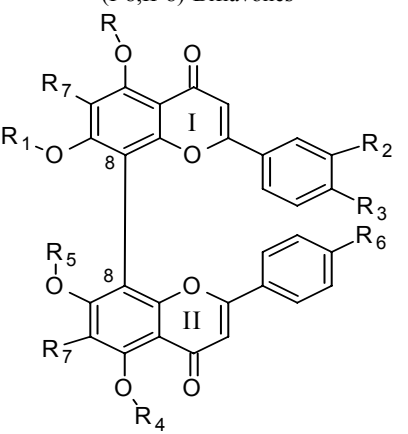


		R	R_1	R_2
I-2,3,II-2,3-Tetrahydrorobustaflavone	**(83)**	H	H	H
I-7,4',II-7-Tri-*O*-methyl-I-2,3,II-2,3-tetrahydrorobustaflavone	**(84)**	Me	H	H
I-3,5,7,4′,II-3,5,7,3′,4′-Nonahydroxy- (I-3′,II-6)-biflavanone	**(85)**	H	OH	OH

Figure 4. SIMPLE BIFLAVONOIDS: (I-3′,II-6)-Biflavones , (I-3′,II-6)-Flavone-flavonol dimer , (I-3′,II-6)-Flavanone-flavone dimers, (I-3′,II-6)-Flavone-flavanone dimers, (I-3′,II-6)-Biflavanones and a (I-3′,II-6)-Biflavanonol.

Two flavonoid units linked by a (I-8,II-8) bond were included in the Cupressuflavone series. The subdivision of this series is as follows: structures with two flavone units, (I-8,II-8)-biflavones (**86-96**); two flavone units and a glucose substituent, (I-8,II-8)-biflavone glucosides (**97**); a flavone and a flavanone unit, (I-8,II-8)-flavone-flavanone (**98**); a flavone and an isoflavone unit, (I-8,II-8)-flavone-isoflavone (**98a**) and finally, two flavanone units, (I-8,II-8)-biflavanone (**99**).

(I-8,II-8)-Biflavones

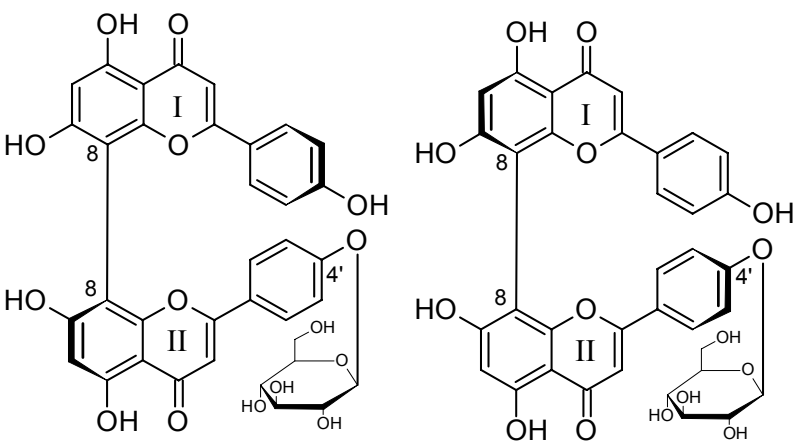


		R	R_1	R_2	R_3	R_4	R_5	R_6	R_7
Cupressuflavone	**(86)**	H	H	H	OH	H	H	OH	H
Mogathin	**(87)**	H	H	OH	OH	H	H	OH	H

(Continued).

I-7-*O*-Methylcupressuflavone	**(88)**	H	Me	H	OH	H	H	OH	H
I-4′-*O*-Methylcupressuflavone	**(89)**	H	H	H	OMe	H	H	OH	H
I-7,4′-Di-*O*-methylcupressuflavone	**(90)**	H	Me	H	OMe	H	H	OH	H
I-7,II-4′-Di-*O*-methylcupressuflavone	**(91)**	H	Me	H	OH	H	H	OMe	H
I-7,II-7-Di-*O*-methylcupressuflavone	**(92)**	H	Me	H	OH	H	Me	OH	H
I-4′,II-4′-Di-*O*-methylcupressuflavone	**(93)**	H	H	H	OMe	H	H	OMe	H
I-7,4′,II-7-Tri-*O*-methylcupressuflavone	**(94)**	H	Me	H	OMe	H	Me	OH	H
I-7,4′,II-7,4′-Tetra-*O*-methyl-cupressuflavone	**(95)**	H	Me	H	OMe	H	Me	OMe	H
(I-8,II-8)-Bibaicalein	**(96)**	H	H	H	H	H	H	H	OH

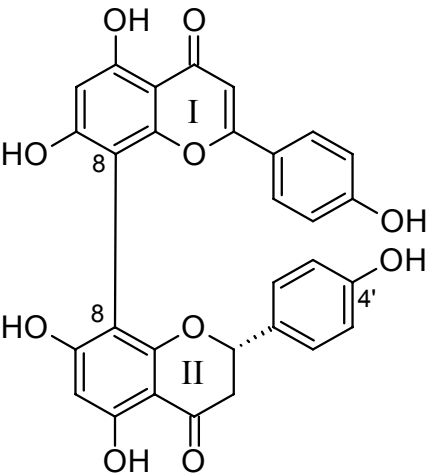
(I-8,II-8)-Biflavone glucosides



M P

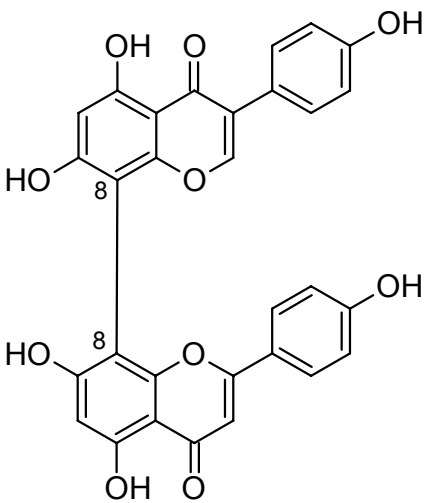
(*M*)- and (*P*)-Cupressuflavone II-4′-*O*-β-*D*-glucopyranosides **(97)**

(I-8,II-8)-Flavone -flavanone dimer



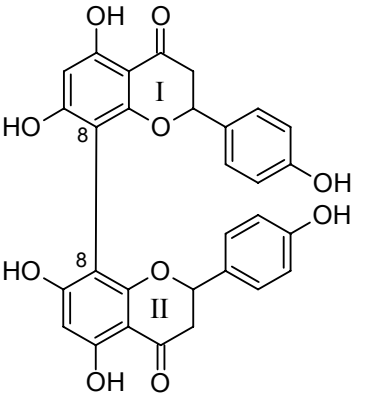
Mesuaferrone B **(98)**

(I-8,II-8)-Flavone -isoflavone dimer



8,8”-Biapigeninyl **(98a)**

(I-8,II-8)-Biflavanones

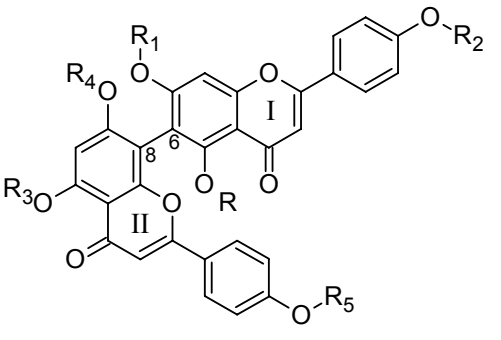


Mesuaferrone A **(99)**

Figure 5. SIMPLE BIFLAVONOIDS: (I-8,II-8)-Biflavones, (I-8,II-8)-Biflavone glucosides, (I-8,II-8)-Flavone-flavanone dimer, (I-8,II-8)-Flavone -isoflavone dimer, (I-8,II-8)-Biflavanone.

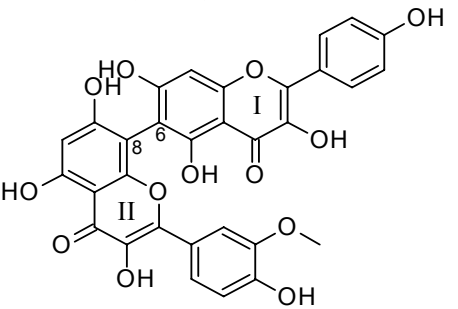
Agathisflavone series contains biflavonoids linked by a (I-6,II-8) bond. The series is further divided into structures with two flavone units (**100-110**), two flavonol units (**111**); flavanone-flavone dimers (**112**); and two flavanone units (**113-114a**). Succedaneaflavone series comprises (I-6, II-6)-biflavones (**115-116b**); (I-6, II-6)-biflavanones (**117-118**) and a (I-6,II-6)-benzofuran-naphthopyranobiflavone (**119**). Afzelone series includes (I-6,II-3)-biflavanone (**120**). Two flavonoid units linked by a (I-3,II-3) bond were included in the Chamaejasmin series. The subdivision of this series is as follow: (I-3,II-3)-biflavones (**121**); a (I-3,II-3)-flavone-flavanone dimer (**122**), and (I-3,II-3)-biflavanones that have different stereochemistry (**123-144**).

(I-6,II-8)-Biflavones



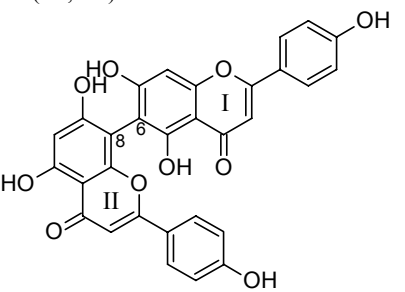
		R	R_1	R_2	R_3	R_4	R_5
Agathisflavone	**(100)**	H	H	H	H	H	H
I-7-*O*-Methylagathisflavone	**(101)**	H	Me	H	H	H	H
I-4′-*O*-Methylagathisflavone	**(102)**	H	H	Me	H	H	H
II-4′-*O*-Methylagathisflavone	**(102a)**	H	H	H	H	H	Me
II-7-*O*-Methylagathisflavone	**(103)**	H	H	H	H	Me	H
I-7,II-7-Di-*O*-methylagathisflavone	**(104)**	H	Me	H	H	Me	H
I-7,II-4′-Di-*O*-methylagathisflavone	**(105)**	H	Me	H	H	H	Me
I-4′, II-4′-Di-*O*-methylagathisflavone	**(106)**	H	H	Me	H	H	Me
I-7,4′,II-7-Tri-*O*-methylagathisflavone	**(107)**	H	Me	Me	H	Me	H
I-7, II-7,4′-Tri-*O*-methylagathisflavone	**(108)**	H	Me	H	H	Me	Me
I-7,4′,II-7,4′-Tetra-*O*-methylagathisflavone	**(109)**	H	Me	Me	H	Me	Me
I-5,7,4′,II-5,7,4′-Hexa-*O*-methylagathisflavone	**(110)**	Me	Me	Me	Me	Me	Me

(I-6,II-8)-Biflavonol



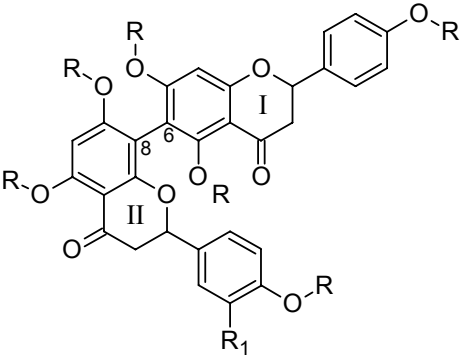
I-5,7,4'-Tri-*O*-methylkaempferol-(I-6,II-8)-II-5,7,3',4'-tetra-*O*-methylquercetin **(111)**

(I-6,II-8)-Flavanone-flavone dimer



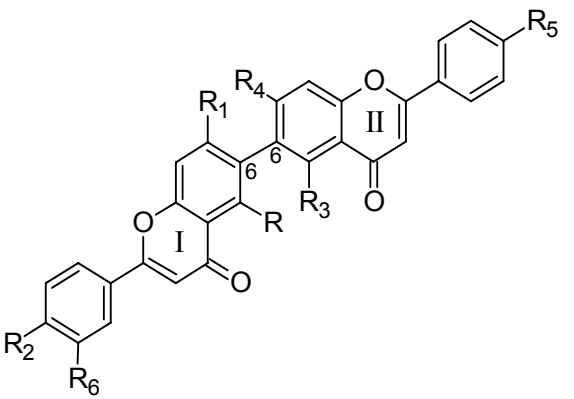
Rhusflavone (**112**)

(I-6,II-8)-Biflavanones



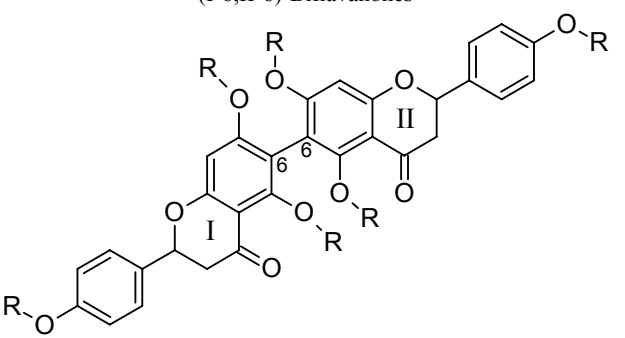
Rhusflavanone	**(113)**	R=H, R_1=H
Rhusflavanone I-5,7,4′,II-5,7,4′-hexa-*O*-acetate	**(114)**	R=Ac, R_1=H
Lateriflavanone	**(114a)**	R=H, R_1=OH

(I-6,II-6)-Biflavones



		R	R_1	R_2	R_3	R_4	R_5	R_6
(I-6,II-6)-Bigenkwanin	**(115)**	OH	OMe	OH	OH	OMe	OH	H
(I-6,II-6)-Biflavone	**(115a)**	H	H	H	H	H	H	H
I-5,7-Dihydroxy-(I-6,II-6)-biflavone	**(115b)**	OH	OH	H	H	H	H	H
I-5-Hydroxy-I-7,4′-dimethoxyflavone-(I-6,II-6)-II-5-hydroxy-II-7,3′,4′-trimethoxyflavone	**(116)**	OH	OMe	OMe	OH	OMe	OMe	OMe
I-5,7,4′,II-5,7,4′-Hexa-*O*-methyl-biapigenin	**(116b)**	OMe	OMe	OMe	OMe	OMe	OMe	H

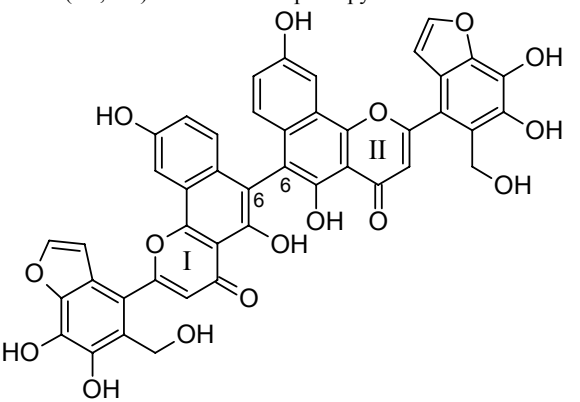
(I-6,II-6)-Biflavanones



Succedaneaflavone **(117)** R=H

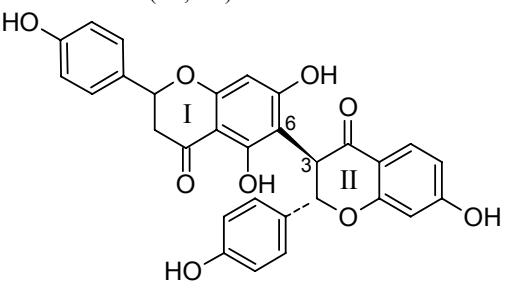
Succedaneaflavone I-5,7,4′,II-5,7,4′-hexa-*O*-acetate **(118)** R=Ac

(I-6,II-6)-Benzofuran-naphthopyranobiflavone



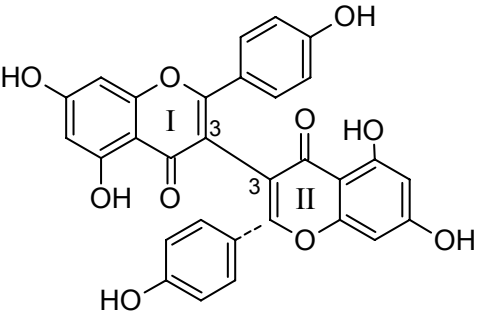
Albiproflavone **(119)**

(I-6,II-3)-Biflavanone



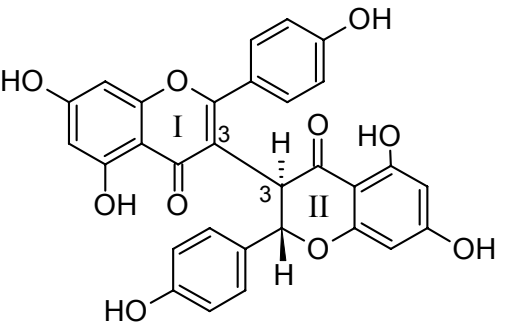
Afzelone B **(120)**

(I-3,II-3)-Biflavones



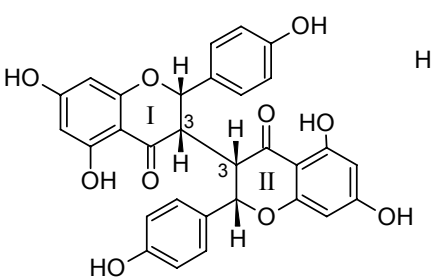
I-5,7,4′,II-5,7,4′-Hexahydroxy-(I-3,II-3)-biflavone (**121**)

(I-3,II-3)-Flavone-flavanone dimer

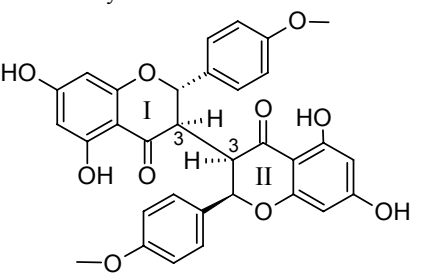


Apigeninyl-(I-3,II-3)-naringenin (**122**)

(I-3,II-3)-Biflavanones of the Chamaejasmin Series
Relative Stereochemistry

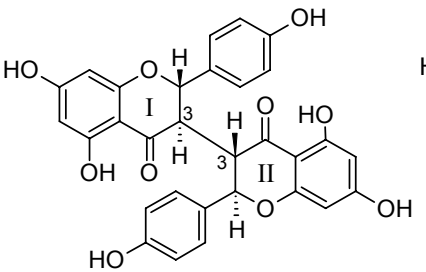


Neochamaejasmin A

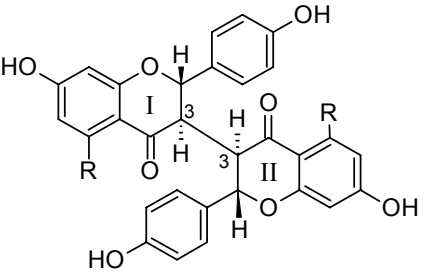


Sikokianin B

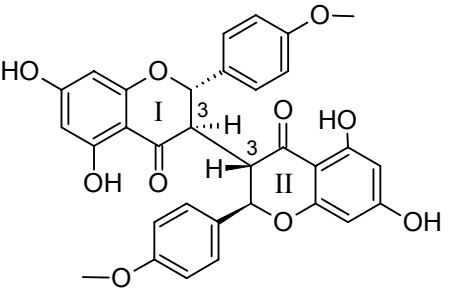
(I-2*S*,3*S*;II-2*S*,3*S*)



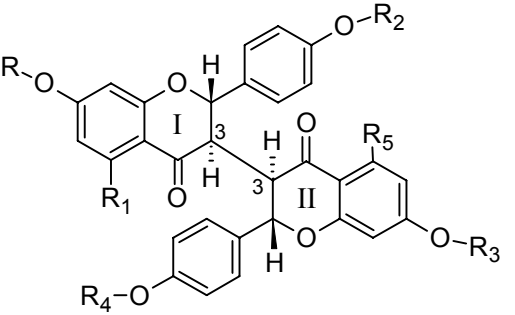
Isochamaejasmin
(I-2*S*,3*R*;II-2*R*,3*S*)



R=H Campylospermone A
R=OH Chamaejasmin



Sikokianin C



Chamaejasmin-type (I-2*S*,3*R*;II-2S,3R)

		R	R_1	R_2	R_3	R_4	R_5
Chamaejasmin (I-2*S*,3*R*;II-2*S*,3*R*)	**(123)**	H	OH	H	H	H	OH
II-7-*O*-β-*D*-Glucopyranosylchamaejasmin	**(124)**	H	OH	H	Glu	H	OH
I-7,II-7-Di-*O*-β-*D*-glucopyranosylchamaejasmin	**(125)**	Glu	OH	H	Glu	H	OH
Campylospermone A	**(126)**	H	H	H	H	H	H
Campylospermone B	**(127)**	H	OH	H	H	H	H
Liquiritigeninyl-(I-3,II-3)-naringenin (I-2*S*,3*R*;II-2*R*,3*S*)	**(128)**	H	H	H	H	H	OH
(I-3,II-3)-Biliquiritigenin (I-2*S*,3*R*;II-2*R*,3*S*)	**(129)**	H	H	H	H	H	H
Isochamaejasmin (I-2*S*,3*R*;II-2*R*,3*S*)	**(130)**	H	OH	H	H	H	OH
I-7,4′,II-7,4′-Tetra-*O*-methylisochamaejasmin	**(131)**	Me	OH	Me	Me	Me	OH

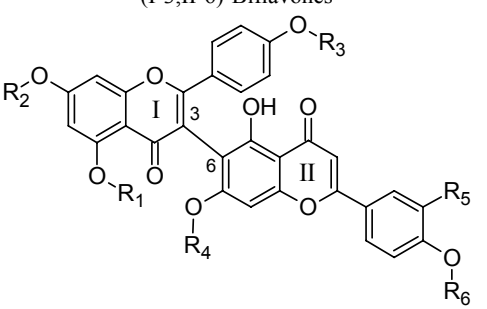
(Continued).

Neochamaejasmin A (I-2*S*,3*S*;II-2S,3S)	**(132)**	H	OH	H	H	H	OH
Neochamaejasmin B (I-2*S*,3*S*;II-2*R*,3*S*)	**(133)**	H	OH	H	H	H	OH
I-7-*O*-Methylneochamaejasmin A (I-2*S*,3*S*;II-2*S*,3*S*)	**(134)**	Me	OH	H	H	H	OH
Sikokianin A (I-2*S*,3*S*;II-2*R*,3*R*)	**(135)**	H	OH	Me	H	H	OH
Sikokianin B (I-2*S*,3*R*;II-2*R*,3*R*)	**(136)**	H	OH	Me	Me	H	OH
Sikokianin C (I-2*S*,3*R*;II-2*R*,3S)	**(137)**	H	OH	Me	Me	H	OH
Chamaejasmenin A (I-2*S*,3*R*;II-2*R*,3*S*)	**(138)**	H	OH	Me	H	Me	OH
Chamaejasmenin B (I-2*S*,3*S*;II-2*R*,3*R*)	**(139)**	H	OH	Me	H	Me	OH
Isochamaejasmenin B (I-2*S*,3*S*;II-2*S*,3*S*)	**(140)**	H	OH	Me	H	Me	OH
Chamaejasmenin C (I-2*S*,3*S*;II-2*R*,3S)	**(141)**	Me	OH	Me	H	Me	OH
Chamaejasmenin D (I-2*S*,3*S*;II-2*S*,3*S*)	**(142)**	Me	OH	Me	H	H	OH
Ruixianglangdusu A (I-2*R*,3*R*;II-2*R*,3*R*)	**(143)**	H	OH	Me	Me	Me	OH
Ruixianglangdusu B (I-2*S*,3*R*;II-2*R*,3*S*)	**(144)**	Me	OH	Me	H	Me	OH

Figure 6. SIMPLE BIFLAVONOIDS: (I-6,II-8)-Biflavones, (I-6,II-8)-Biflavonol, (I-6,II-8)-Flavanone-flavone dimer, (I-6,II-8)-Biflavanones, (I-6,II-6)-Biflavones, (I-6,II-6)-Biflavanones, (I-6,II-6)-Benzofuran-naphthopyranobiflavone, (I-6,II-3)-Biflavanone, (I-3,II-3)-Biflavones, (I-3,II-3)-Flavone-flavanone dimer, (I-3,II-3)-Biflavanones of the Chamaejasmin Series, Relative Stereochemistry.

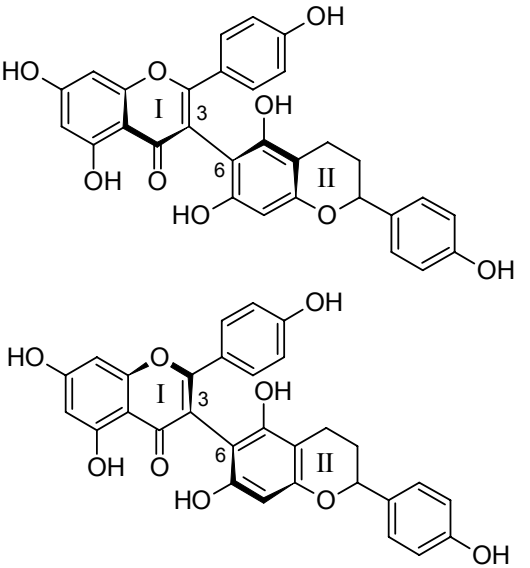
The (I-3,II-6)-biflavonoids were included in Stephaflavone series, which contains structures with two flavone units (**145**-**151**), and (I-3,II-6)-flavone-flavan dimers (**152**) that are formed by a mixture of two atropisomers. GB-Flavone series has structures with flavonoid units linked by a (I-3,II-8) bond. The series consists of the following structures: (I-3,II-8)-biflavone (**153**); (I-3,II-8)-flavanone-flavone dimers (**154**-**164**); (I-3,II-8)-flavanone-flavonol dimers (**165**-**166**); (I-3,II-8)-biflavanones (**167**-**175b**); (I-3,II-8)-flavanone-flavanonol dimers (**176**-**183**); (I-3,II-8)-flavanone-chromene dimer (cleaved biflavonoid) (**184**); (I-3,II-8)-flavone-flavan dimers (**185**-**186**), and (I-3,II-8)-flavone-flavans (**187**-**188**); the latter two containing a mixture of atropisomers.

(I-3,II-6)-Biflavones



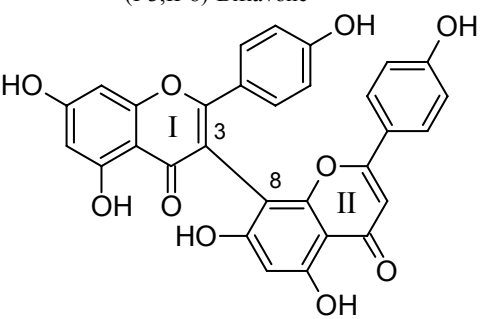
		R_1	R_2	R_3	R_4	R_5	R_6
Ridiculuflavone A	**(145)**	H	H	H	H	OH	H
Ridiculuflavone B	**(146)**	Me	H	H	H	OH	H
Ridiculuflavone D	**(147)**	H	Me	H	H	OH	H
I-7,4′-Di-*O*-methyl-apigeninyl-(I-3,II-6)-II-3′-methoxyapigenin	**(148)**	H	Me	Me	H	OMe	H
Ridiculuflavone C	**(149)**	Me	H	Me	H	OMe	H
Stephaflavone A	**(150)**	H	Me	H	Me	H	Me
Stephaflavone B	**(151)**	H	Me	Me	Me	H	Me

(I-3,II-6)-Flavone-flavan dimers



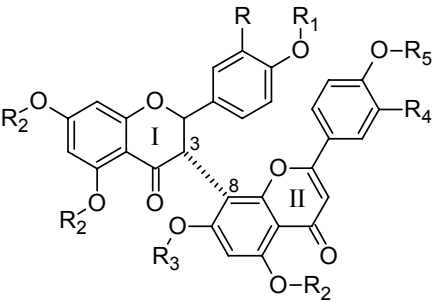
Daphnodorin K (= mixture of two atropisomers as shown above) **(152)**

(I-3,II-8)-Biflavone



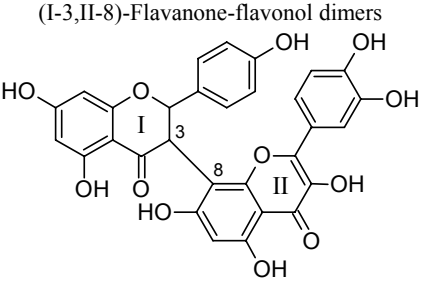
(I-3,II-8)-Biapigenin **(153)**

(I-3,II-8)-Flavanone-flavone dimers

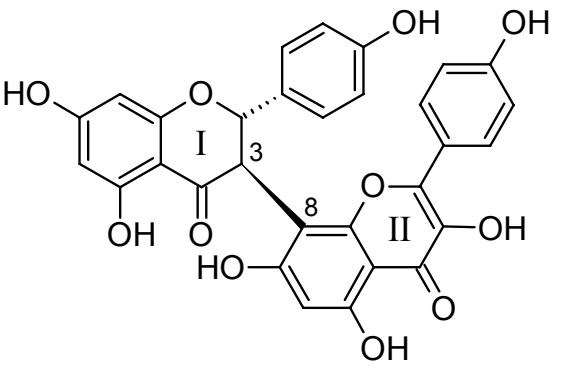


		R	R_1	R_2	R_3	R_4	R_5
(+)-Volkensiflavone	**(154)**	H	H	H	H	H	H
(+)-Volkensiflavone-II-7-sulfate	**(155)**	H	H	H	SO_3H	H	H
Spicataside (volkensiflavone-II-7-*O*-*D*-glucoside)	**(156)**	H	H	H	Glu	H	H
Spicataside nona-*O*-acetate	**(157)**	H	Ac	Ac	2,3,4,6-Tetra-*O*-acetylGlu	H	Ac
I-5,7,4′,II-5,7,4′-Hexa-*O*-methylvolkensiflavone	**(158)**	H	Me	Me	Me	H	Me
Fukugetin	**(159)**	H	H	H	H	OH	H
(+)-Morelloflavone-II-7-sulfate	**(160)**	H	H	H	SO_3H	OH	H
I-5,7,4′,II-5,7,3′,4′-Hepta-*O*-methyl-morelloflavone	**(161)**	H	Me	Me	Me	OMe	Me
Fukugiside	**(162)**	H	H	H	Glu	OH	H
Morelloflavone I-5,7,4′,II-5,7,3′,4′-hepta-*O*-acetate	**(163)**	H	Ac	Ac	Ac	OAc	Ac
I-5,7,3′,4′,II-5,7,4′-Heptahydroxy-(I-3,II-8)-flavanonylflavone	**(164)**	OH	H	H	H	H	H

(I-3,II-8)-Flavanone-flavonol dimers

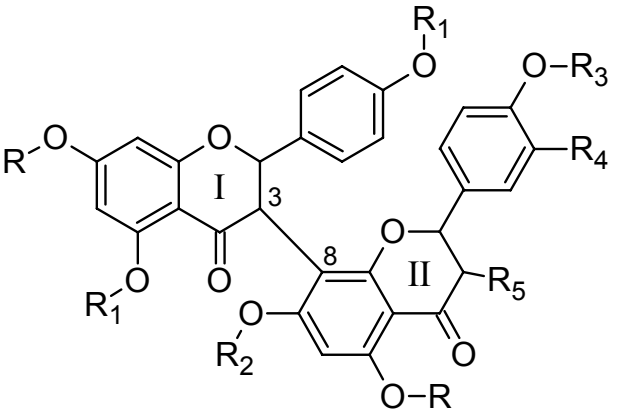


Pancibiflavonol **(165)**



Garcinianin (atropisomers) **(166)**

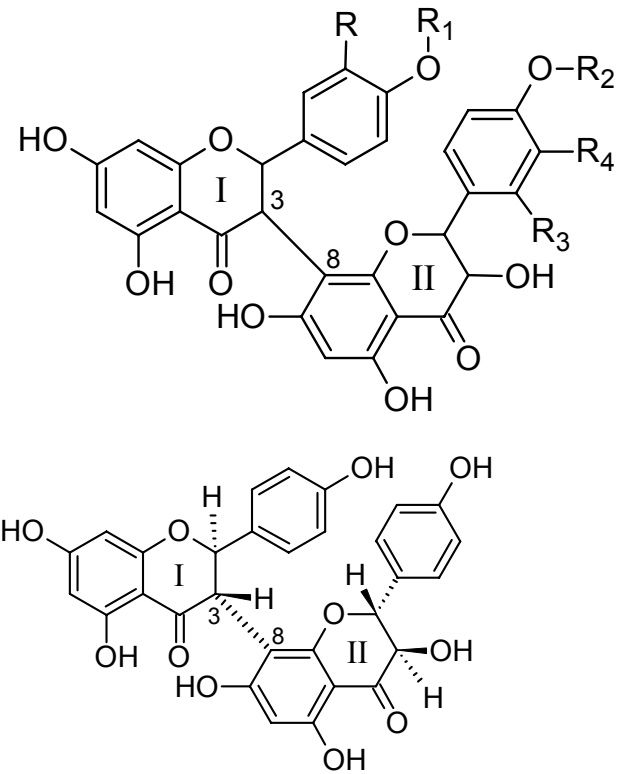
(I-3,II-8)-Biflavanones



		R	R_1	R_2	R_3	R_4	R_5
GB_{1a}*	**(167)**	H	H	H	H	H	H
I-5,7,4′,II-5,7,4′-Hexa-*O*-methyl-GB_{1a}	**(168)**	Me	Me	Me	Me	H	H
GB_{1a}-II-7-*O*-β-*D*-glucopyranoside	**(169)**	H	H	Glu	H	H	H
(+)-GB_{1b}*	**(170)**	H	H	H	H	H	H
ent-Naringeninyl-(I-3α,II-8)-II-4'-*O*-methylnaringenin	**(171)**	H	H	H	Me	H	H
GB_{2a}	**(172)**	H	H	H	H	OH	H
GB_{2a}-I-7-*O*-β-*D*-glucopyranoside	**(173)**	Glu	H	H	H	OH	H
GB_{2a}-II-7-*O*-β-*D*-glucopyranoside (xanthochymuside)	**(174)**	H	H	Glu	H	OH	H
II-4′-*O*-Methyl-GB_{2a}*	**(175)**	H	H	H	Me	OH	H
I-5,7,4',II-3,5,7,3′,4′-Octahydroxy-(I-3,II-8)-biflavanone	**(175a)**	H	H	H	H	OH	OH

*Different stereochemistry.

(I-3,II-8)-Flavanone-flavanonol dimmers

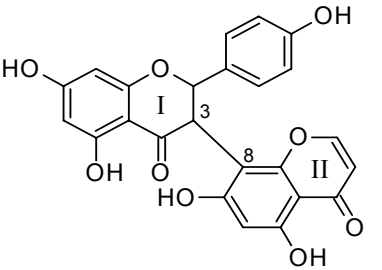


GB_1

		R	R_1	R_2	R_3	R_4
GB_1	**(176)**	H	H	H	H	H
GB_2	**(177)**	H	H	H	H	OH
Kolaflavanone	**(178)**	H	H	Me	H	OH
Manniflavanone*	**(179)**	OH	H	H	H	OH
Garciniflavanone*	**(180)**	OH	H	H	H	OH
GB_3	**(181)**	OH	Me	H	H	OH
GB_4	**(182)**	H	H	H	OH	OH
GB_{4a} (stereoisomer of GB_4)	**(183)**	H	H	H	OH	OH

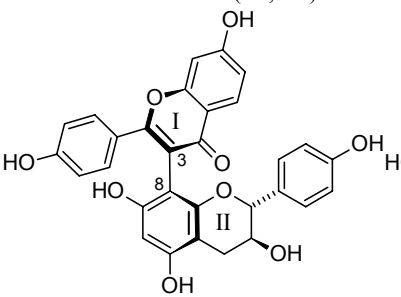
* Different stereochemistry.

(I-3,II-8)-Flavanone-chromene dimer
(cleaved biflavonoid)

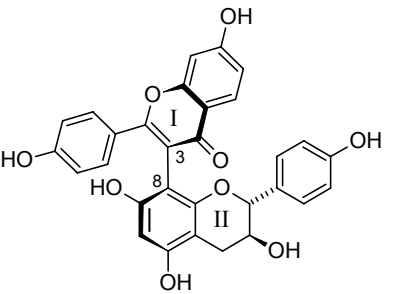


GD IV (184)

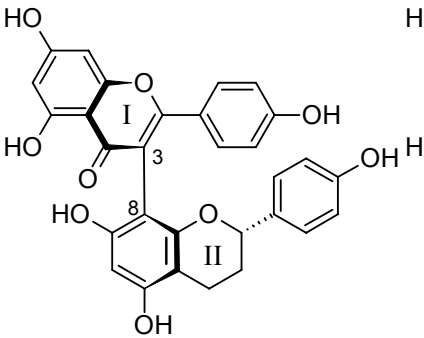
(I-3,II-8)-Flavone-flavan dimers



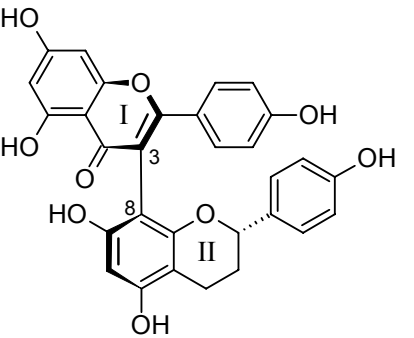
Wikstrol A **(185)**



Wikstrol B **(186)**



Daphnodorin D_1 **(187)**

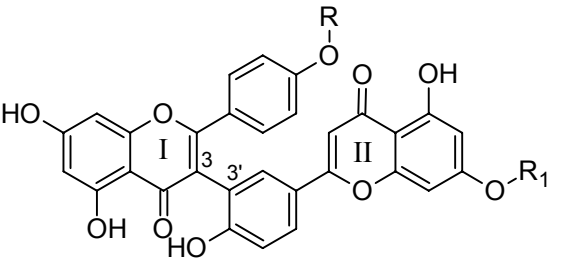


Daphnodorin D_2 **(188)**

Figure 7. SIMPLE BIFLAVONOIDS: (I-3,II-6)-Biflavones, (I-3,II-6)-Flavone-flavan dimers, (I-3,II-8)-Biflavone, (I-3,II-8)-Flavanone-flavone dimers, (I-3,II-8)-Flavanone-flavonol dimers, (I-3,II-8)-Biflavanones, (I-3,II-8)-Flavanone-flavanonol dimers, (I-3,II-8)-Flavanone-chromene dimer (cleaved biflavonoid), (I-3,II-8)-Flavone-flavan dimers.

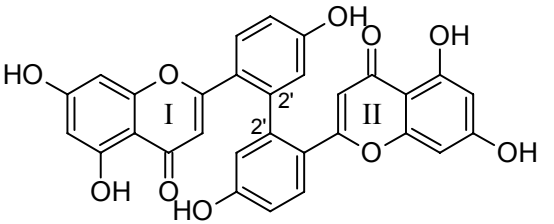
Taiwaniaflavone series has (I-3,II-3′)-biflavones (**189-191**). The following series possesses a (I-2′,II-2′)-biflavone (**192**) and a (I-2′,II-2′)-biflavonol (**193**). Biflavonoids linked by a (I-2′,II-6) bond were included in the Dicranolomin series, which has the following subsections: (I-2′,II-6)-biflavones (**194**,**195**); (I-2′,II-6)-flavanone-flavone dimers (**196,197**); (I-2′,II-6)-flavone-flavanone dimers (**198**,**199**); (I-2′,II-6)-biflavanone (**200**); and (I-2′,II-6)-benzopyranobenzofuranbiflavone (**201**).

(I-3,II-3′)-Biflavones



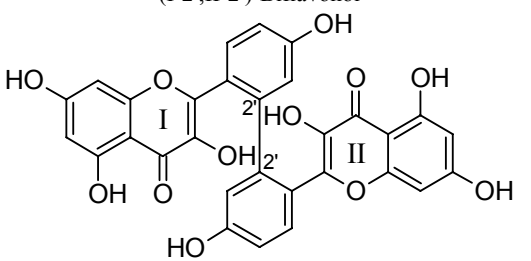
		R	R_1
Taiwaniaflavone	**(189)**	H	H
II-7-*O*-Methyltaiwaniaflavone	**(190)**	H	Me
I-4′,II-7-Di-*O*-methyltaiwaniaflavone	**(191)**	Me	Me

(I-2′,II-2′)-Biflavone



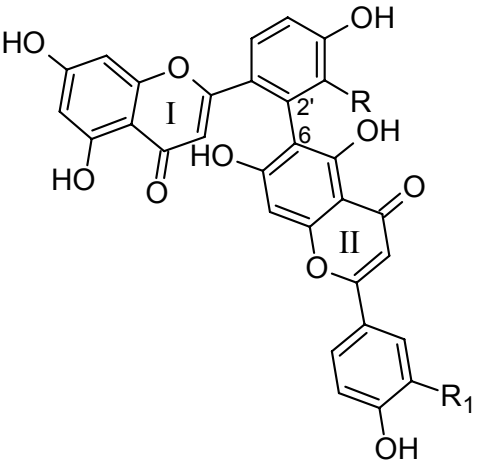
(I-2′,II-2′)-Biapigenin **(192)**

(I-2′,II-2′)-Biflavonol



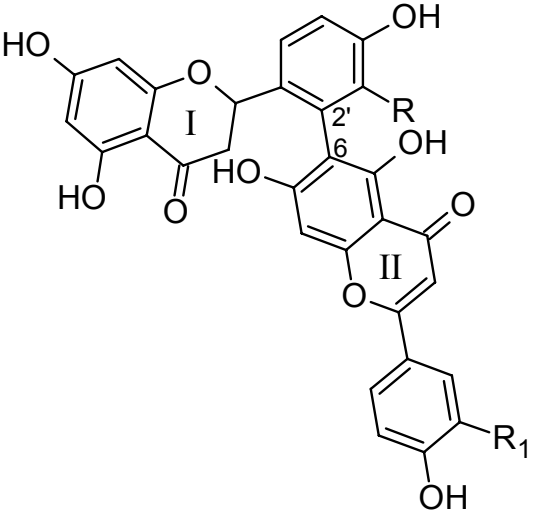
(I-2′,II-2′)-Bikaempferol **(193)**

(I-2′,II-6)-Biflavones



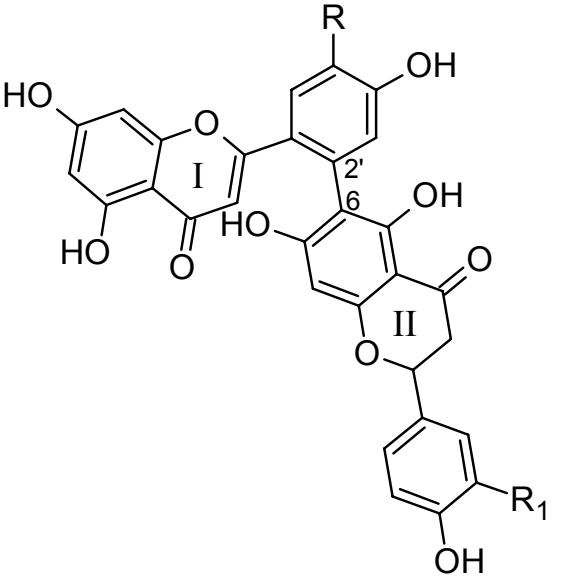
		R	R_1
Dicranolomin	**(194)**	OH	OH
II-3′-Deoxydicranolomin	**(195)**	OH	H

(I-2′,II-6)-Flavanone-flavone dimers



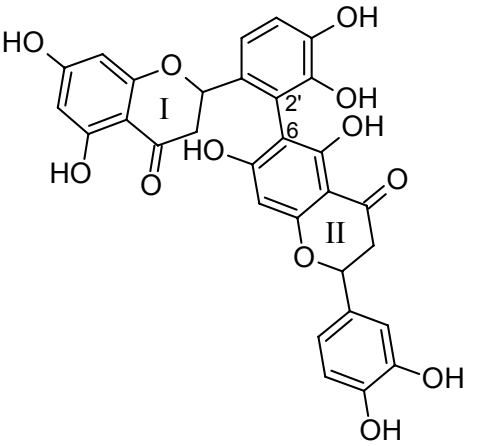
		R	R_1
II-3′-Deoxy-I-2,3-dihydrodicranolomin	**(196)**	OH	H
I-2,3-Dihydrodicranolomin	**(197)**	OH	OH

(I-2′,II-6)-Flavone-flavanone dimers



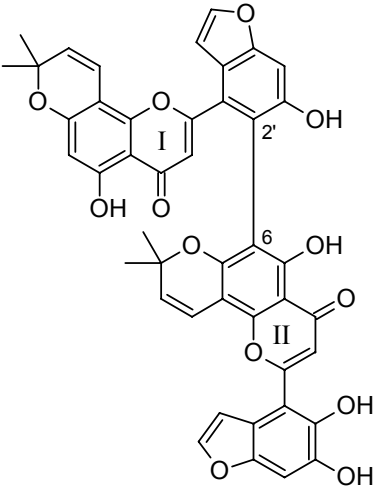
		R	R_1
Hegoflavone A	**(198)**	OH	H
Hegoflavone B	**(199)**	OH	OH

(I-2′,II-6)-Biflavanone



I-2,3,II-2,3-Tetrahydrodicranolomin (I-2*S*) **(200)**

(I-2′,II-6)-Benzopyranobenzofuranbiflavone

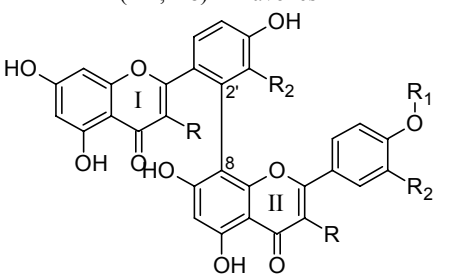


Leucaediflavone **(201)**

Figure 8. SIMPLE BIFLAVONOIDS: (I-3,II-3′)-Biflavones, (I-2′,II-2′)-Biflavone, (I-2′,II-2′)-Biflavonol, (I-2′,II-6)-Biflavones, (I-2′,II-6)-Flavanone-flavone dimers, (I-2′,II-6)-Flavone-flavanone dimers, (I-2′,II-6)-Biflavanone, (I-2′,II-6)-Benzopyrano-benzofuranbiflavone.

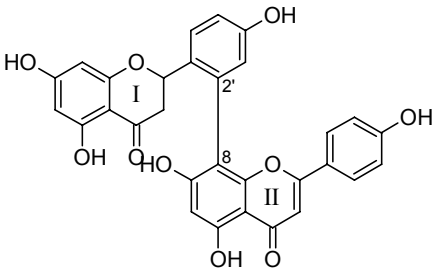
Philonotisflavone series is made by biflavonoids linked by a (I-2′, II-8) bond. This series is divided into (I-2′,II-8)-biflavones (**202**-**205**); a (I-2′,II-8)-flavanone-flavone dimer (**206**); a (I-2′,II-8)-flavone-flavanone dimer (**207**); and a (I-2′,II-8; I-8,II-2′)-doubly linked flavone-flavanone dimer (**208**).

(I-2′,II-8)-Biflavones



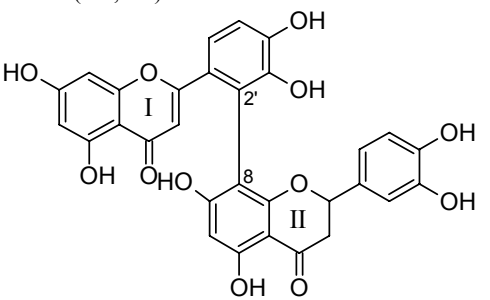
		R	R_1	R_2
(I-2′,II-8)-Biapigenin	**(202)**	H	H	H
Strychnobiflavone	**(203)**	OMe	H	OH
Philonotisflavone	**(204)**	H	H	OH
II-4′-*O*-Methylphilonotisflavone	**(205)**	H	Me	OH

(I-2′,II-8)-Flavanone-flavone dimer



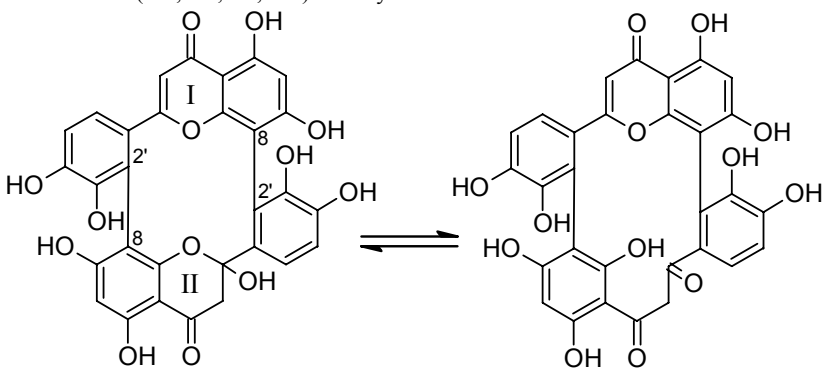
I-2,3-Dihydrophilonotisflavone **(206)**

(I-2′,II-8)-Flavone-flavanone dimer



II-2,3-Dihydrophilonotisflavone **(207)**

(I-2′,II-8; I-8,II-2′)-Doubly linked Flavone-flavanone dimer

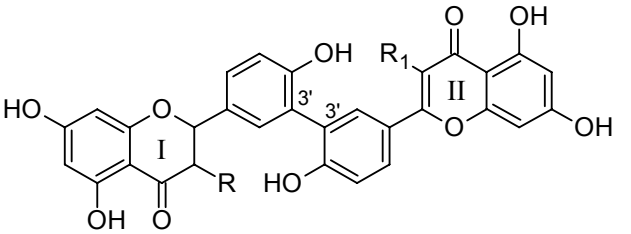


Bartramiaflavone **(208)**

Figure 9. SIMPLE BIFLAVONOIDS: (I-2′,II-8)-Biflavones, (I-2′,II-8)-Flavanone-flavone dimer, (I-2′,II-8)-Flavone-flavanone dimer, (I-2′,II-8; I-8,II-2′)-Doubly linked Flavone-flavanone dimer.

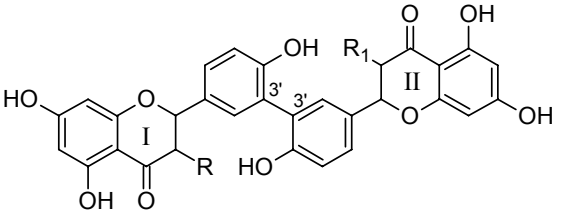
Hypnogenol series includes (I-3′,II-3″)-biflavonoids. Flavanone-flavone and flavanonol-flavonol dimers (**209**,**210**) were included in this series. Biflavanones, flavanonol-flavanones and biflavanonols (**211**-**213**) were incorporated as well.

(I-3′,II-3′)-Flavanone-flavone / Flavanonol-flavonol dimers



		R	R_1
I-2,3-Dihydro-(I-3′,II-3′)-biapigenin	**(209)**	H	H
Hypnogenol B1	**(210)**	OH	OH

(I-3′,II-3′)-Biflavanone / Biflavanonol / Flavanonol-flavanone dimer

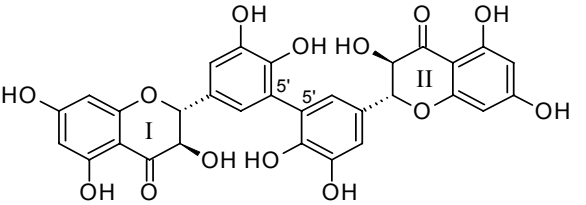


		R	R_1
(I-3′,II-3′)-Binaringenin	**(211)**	H	H
Hypnogenol B	**(212)**	OH	H
Hypnogenol A	**(213)**	OH	OH

Figure 10. SIMPLE BIFLAVONOIDS: (I-3′,II-3′)-Flavanone-flavone / Flavanonol-flavonol dimers, (I-3′,II-3′)-Biflavanone / Biflavanonol / Flavanonol-flavanone dimer.

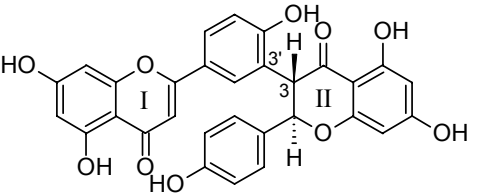
The biflavonoid (I-5′,II-5′)-bisdihydroquercetin presents a (I-5′,II-5′) link (**214**) and lanceolatin A presents a (I-3′,II-3) link (**215**). Lophirone series has (I-3′,II-7)- (**216**) and (I-3′,*O*,II-7)-biflavonoids (**217**). The Ochnaflavone series of (I-3′,*O*,II-4′)-biflavonoids includes (I-3′,*O*,II-4′)-biflavones (**218**-**220**); (I-3′,*O*,II-4′)-flavanone-flavone dimers (**221**-**224**); (I-3′,*O*,II-4′)-flavone-flavanone dimers (**225**-**226**); (I-3′,*O*,II-4′)-biflavanones (**227**-**229**); (I-3′,*O*,II-4′)-biflavanonol (**230**).

(I-5′,II-5′)-Biflavanonol



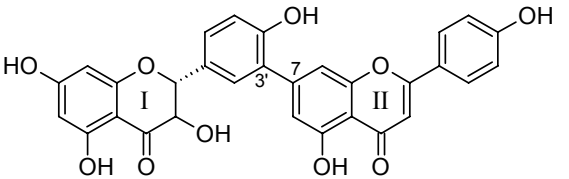
(I-5′,II-5′)-Bis-I-2,3,II-2,3-dihydroquercetin **(214)**

(I-3′,II-3)-Flavone-Flavanone



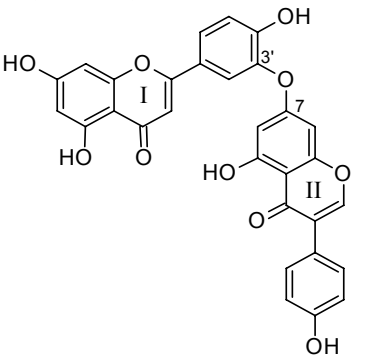
Lanceolatin A **(215)**

(I-3′,II-7)-Flavononol-flavone



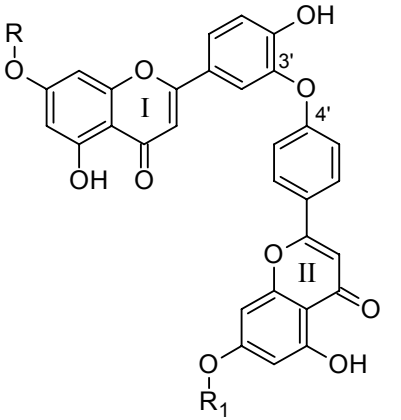
Lophirone M **(216)**

(I-3′,*O*,II-7)-Flavone-isoflavone



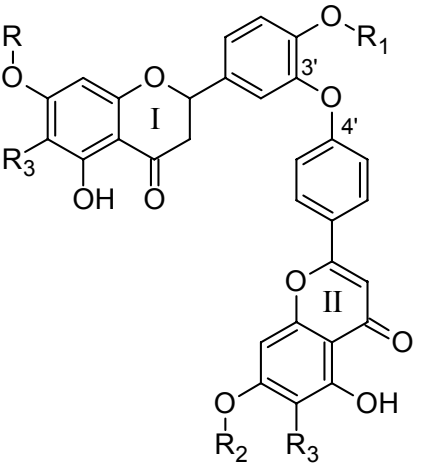
Lophirone L **(217)**

(I-3′,*O*,II-4′)-Biflavones



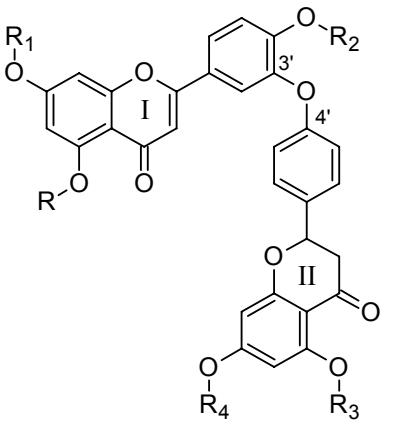
		R	R_1
Ochnaflavone	**(218)**	H	H
I-4′-*O*-Methylochnaflavone	**(219)**	Me	H
II-7-*O*-Methylochnaflavone	**(220)**	H	Me

(I-3′,*O*,II-4′)-Flavanone-flavone dimers



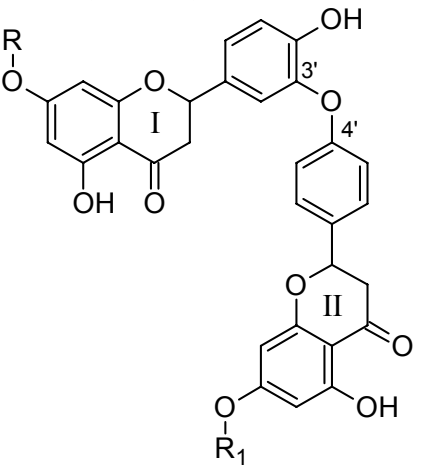
		R	R_1	R_2	R_3
I-2,3-Dihydroochnaflavone	**(221)**	H	H	H	H
I-6,II-6-Dimethyl-I-2,3-dihydroochnaflavone	**(222)**	H	H	H	Me
I-7-*O*-Methyl-I-2,3-dihydroochnaflavone	**(223)**	Me	H	H	H
I-7,I-4′,II-7-Tri-*O*-Methyl-I-2,3-dihydroochnaflavone	**(224)**	Me	Me	Me	H

(I-3′,*O*,II-4′)-Flavone-flavanone dimers



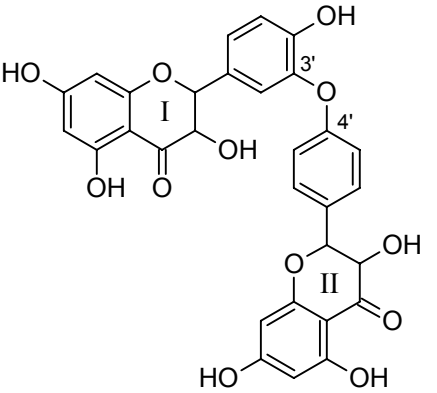
		R	R_1	R_2	R_3	R_4
II-2,3-Dihydroochnaflavone	**(225)**	H	H	H	H	H
I-5,7,4′,II-5,7-*O*-Pentacetyl-II-2,3-dihydroochnaflavone	**(225a)**	Ac	Ac	Ac	Ac	Ac
I-7,4′,II-7-*O*-Trimethyl-II-2,3-dihydroochnaflavone	**(225b)**	H	Me	Me	H	Me
II-7-*O*-Methyl-II-2,3-dihydroochnaflavone	**(226)**	H	H	H	H	Me

(I-3′,*O*,II-4′)-Biflavanones



		R	R_1
I-2,3,II-2,3-Tetrahydroochnaflavone	**(227)**	H	H
I-7-*O*-Methyl-I-2,3,II-2,3-tetrahydroochnaflavone	**(228)**	Me	H
I-7,II-7-Di-*O*-methyl-I-2,3,II-2,3-tetrahydroochnaflavone	**(229)**	Me	Me

(I-3′,*O*,II-4′)-Biflavanonol

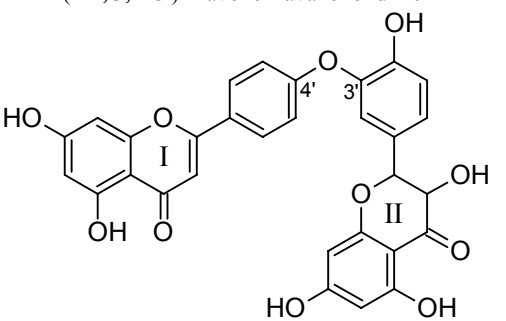


I-5,7,4′,II-5,7-Pentahydroxy-(I-3′,*O*,II-4′)-biflavanonol **(230)**

Figure 11. SIMPLE BIFLAVONOIDS: (I-5′,II-5′)-Biflavanonol, (I-3′,II-3)-Flavone-Flavanone, (I-3′,II-7)-Flavononol-flavone, (I-3′,*O*,II-7)-Flavone-isoflavone, (I-3′,*O*,II-4′)-Biflavones, (I-3′,*O*,II-4′)-Flavanone-flavone dimers, (I-3′,*O*,II-4′)-Flavone-flavanone dimers, (I-3′,*O*,II-4′)-Biflavanones, (I-3′,*O*,II-4′)-Biflavanonol.

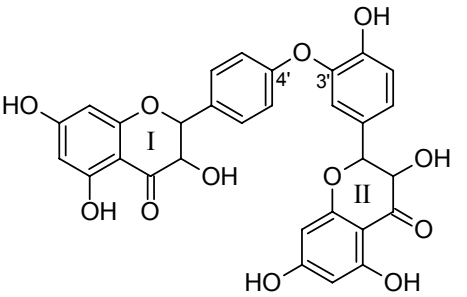
The (I-4′,*O*,II-3′)-series includes a (I-4′,*O*,II-3′)-flavone-flavanonol dimer (**231**); and a (I-4′,*O*,II-3′)-biflavanonol (**232**). Loniflavone shows a (I-4′,*O*,II-4′) connection (**233**,**234**). Hinokiflavone series with (I-4′,*O*,II-6)-biflavonoids contains (I-4′,*O*,II-6)-biflavones (**235-240**), (I-4′,*O*,II-6)-flavanone-flavone dimers (**241,242**), (I-4′,*O*,II-6)-flavone-flavanone dimers (**243-246**), and (I-4′,*O*,II-6)-biflavanones (**247**,**248**). (I-4′,*O*,II-8)-Biflavones were included in the Lanaroflavone series (**249-251**). (I-3,*O*,II-4′)-Biflavones were presented in structures **252** and **253**; (I-6,*O*,II-7)-biflavones in **253a** and **254**; and (I-6,*O*,II-8)-biapigenins in **255**. A (I-8,CH_2,II-8)-biflavonol is shown in **256**.

(I-4′,*O*,II-3′)-Flavone-flavanonol dimer



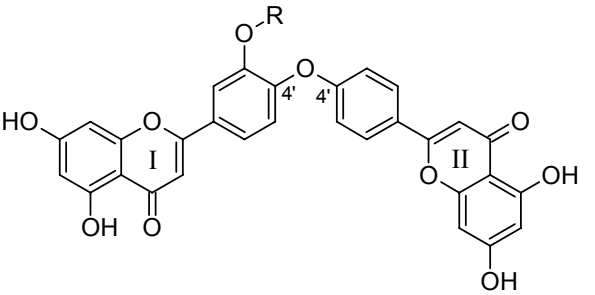
Sulcatone A **(231)**

(I-4′,*O*,II-3′)-Biflavanonol



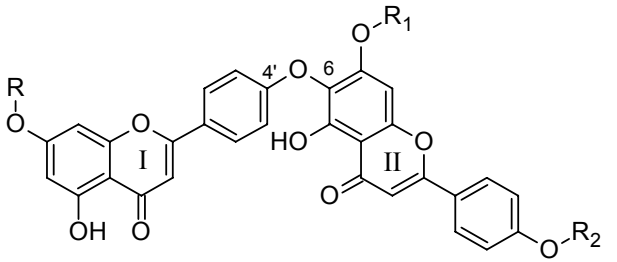
I-2,3-Dihydrokaempferol-(I-4',*O*,II-3')-II-2,3-dihydrokaempferol **(232)**

(I-4′,*O*,II-4′)-Biflavones



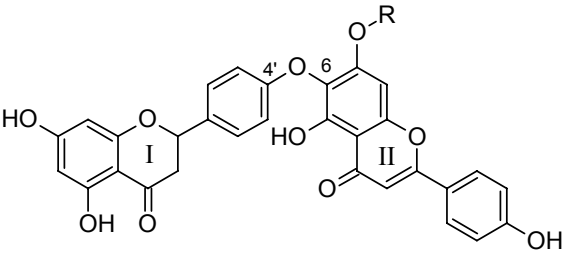
		R
Loniflavone	**(233)**	H
I-3′-*O*-Methylloniflavone	**(234)**	Me

(I-4′,*O*,II-6)-Biflavones



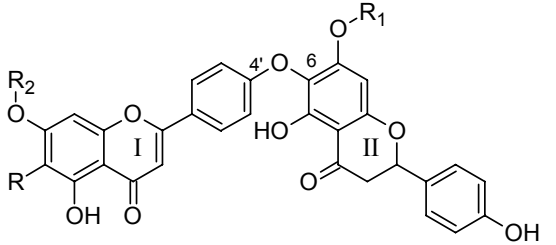
		R	R_1	R_2
Hinokiflavone	**(235)**	H	H	H
I-7-*O*-Methylhinokiflavone	**(236)**	Me	H	H
Isocryptomerin	**(237)**	H	Me	H
Cryptomerin A	**(238)**	H	H	Me
Cryptomerin B	**(239)**	H	Me	Me
Chamaecyparin	**(240)**	Me	Me	H

(I-4′,*O*,II-6)-Flavanone-flavone dimers



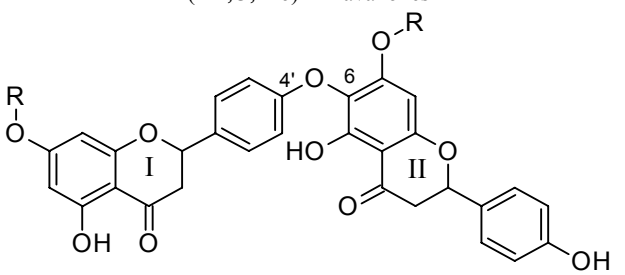
		R
I-2,3-Dihydrohinokiflavone	**(241)**	H
I-2,3-Dihydroisocryptomerin	**(242)**	Me

(I-4′,*O*,II-6)-Flavone-flavanone dimers



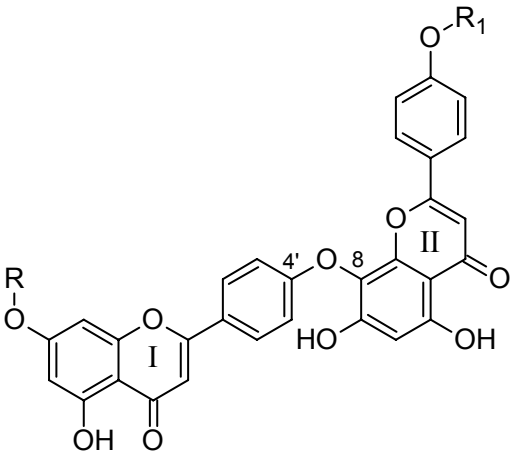
		R	R_1	R_2
I-7-*O*-Methyl-II-2,3-dihydroisocryptomerin	**(243)**	H	Me	Me
II-2,3-Dihydrohinoki-flavone	**(244)**	H	H	H
II-2,3-Dihydroisocryptomerin	**(245)**	H	Me	H
I-6-Methyl-II-2,3-dihydrocryptomerin	**(246)**	Me	Me	H

(I-4′,*O*,II-6)-Biflavanones



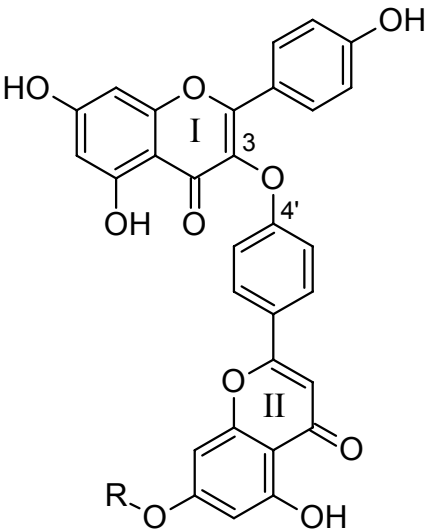
		R
I-2,3,II-2,3-Tetrahydrohinokiflavone	**(247)**	H
I-7,II-7-Di-*O*-methyl-I-2,3,II-2,3-tetrahydrohinokiflavone	**(248)**	Me

(I-4′,*O*,II-8)-Biflavones



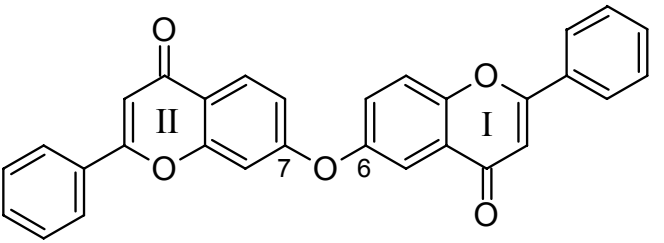
		R	R_1
Lanaroflavone	**(249)**	H	H
I-7-*O*-Methyllanaroflavone	**(250)**	Me	H
I-7,II-4′-Di-*O*-methyllanaroflavone	**(251)**	Me	Me

(I-3,*O*,II-4′)-Biflavone



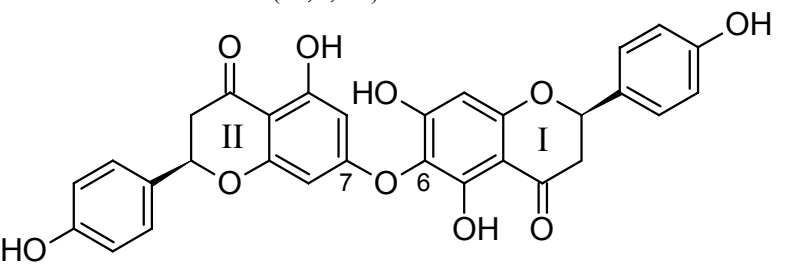
		R
Delicaflavone	**(252)**	H
I-5,7,4',II-5-Tetrahydroxy-II-7-methoxy-(I-3,*O*,II-4')-biflavone	**(253)**	Me

(I-6,*O*,II-7)-Biflavone



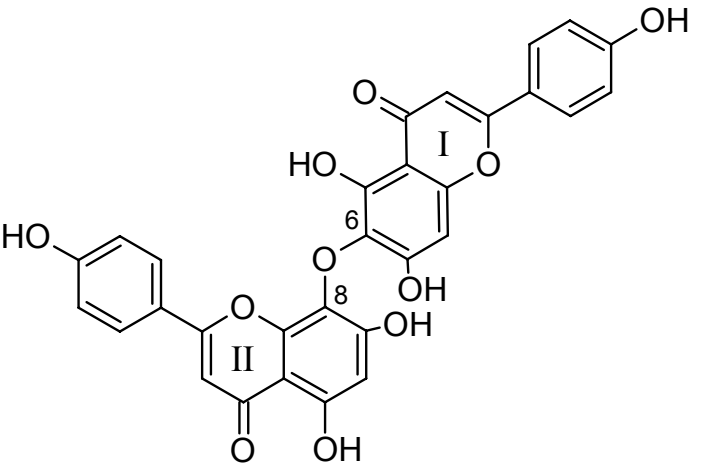
(I-6,*O*,II-7)-Biflavone **(253a)**

(I-6,*O*,II-7)-Biflavanone



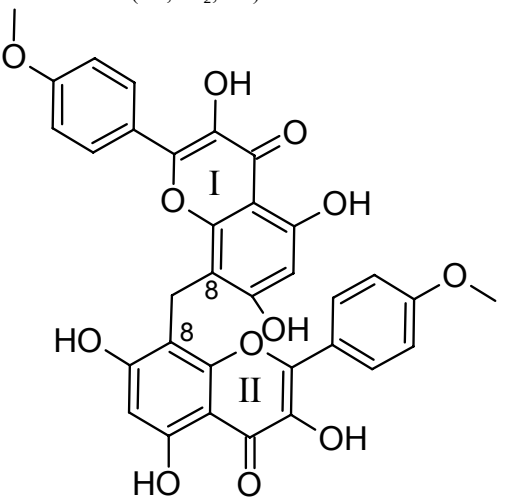
Masazinoflavanone **(254)**

(I-6,*O*,II-8)-Biflavone



(I-6,*O*,II-8)-Biapigenin **(255)**

(I-8,CH_2,II-8)-Biflavonol



Pentagrametin **(256)**

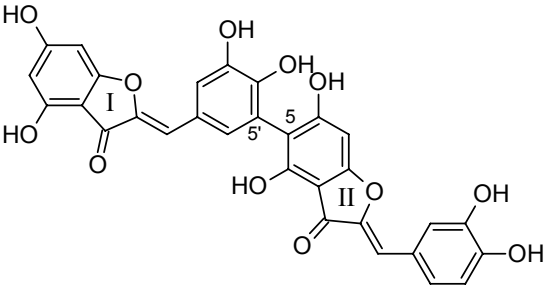
Figure 12. SIMPLE BIFLAVONOIDS: (I-4′,*O*,II-3′)-Flavone-flavanonol dimer, (I-4′,*O*,II-3′)-Biflavanonol, (I-4′,*O*,II-4′)-Biflavones, (I-4′,*O*,II-6)-Biflavones, (I-4′,*O*,II-6)-Flavanone-flavone dimers, (I-4′,*O*,II-6)-Flavone-flavanone dimers, (I-4′,*O*,II-6)-Biflavanones, (I-4′,*O*,II-8)-Biflavones, (I-3,*O*,II-4′)-Biflavone, (I-6,*O*,II-7)-Biflavone, (I-6,*O*,II-7)-Biflavanone, (I-6,*O*,II-8)-Biflavone, (I-8,CH_2,II-8)-Biflavonol.

COMPLEX BIFLAVONOIDS

The second main group of structures includes complex biflavonoids, which are biaurones, bi-isoflavonoids, cumarin-flavonoid dimers, bineoflavonoids, derivatives of furochromen-4-one, furo[2,3-*f*]chromanone, furo[2,3-*h*]benzopyran, naphthalene, dihydronaphthalene, and tetrahydronaphthalene, substituted cyclobutane, substituted tetrahydrofuran, substituted benzofuran and benzodihydrofuran, and related compounds.

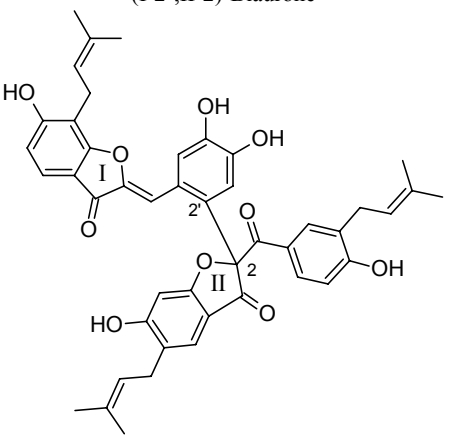
The Biaurone series includes (I-5’,II-5)-, (I-2’,II-2)- and (I-α,II-α)-biaurones (**257-259**). Aurone-auronol series consist of three (I-2,II-7)-aurone-auronol dimers (**260-263**). Aurone-flavanone series presents a (I-2’,II-6)-aurone-flavanone dimer (**264**) and a (I-5’,II-6)-aurone-flavanone dimer (**265**). (I-3,II-5)-Flavanone-auronol dimers (**266**, **267**) and (I-3,II-7)-flavanone-auronol dimers (**268**, **269**) form the flavanone-auronol series.

(I-5',II-5)-Biaurone



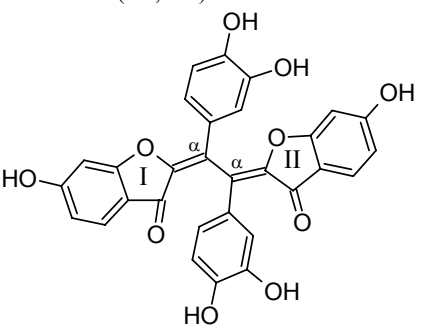
Aulacomniumbiaureusidin **(257)**

(I-2',II-2)-Biaurone



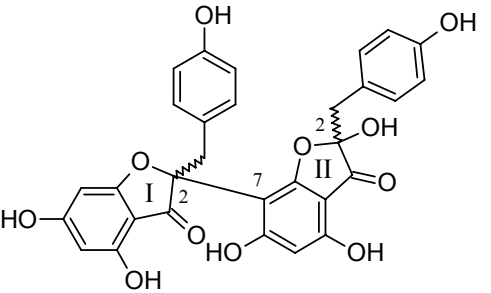
Licoagrone **(258)**

(I-α,II-α)-Biaurone



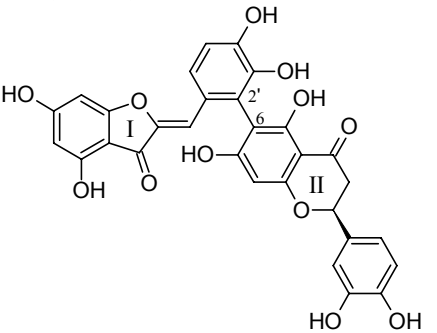
Disulfuretin **(259)**

(I-2,II-7)-Aurone-auronol dimers



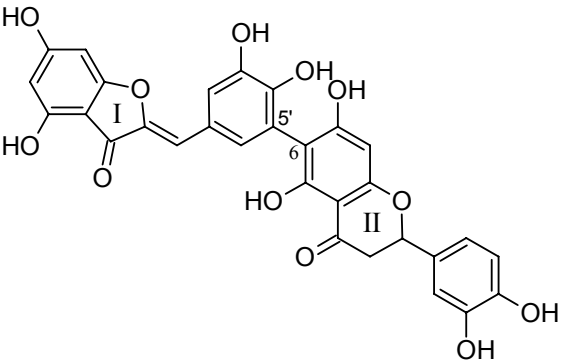
(I-2*S*)-I-2-Deoxymaesopsin-(I-2,II-7)-(II-2*R*)-maesopsin	**(260)**	(I-2*S*,II-2*R*)-isomer
(I-2*R*)-I-2-Deoxymaesopsin-(I-2,II-7)-(II-2*S*)-maesopsin	**(261)**	(I-2*R*,II-2*S*)-enantiomer
(I-2*R*)-I-2-Deoxymaesopsin-(I-2,II-7)-(II-2*R*)-maesopsin	**(262)**	(I-2*R*,II-2*R*)-isomer
(I-2*S*)-I-2-Deoxymaesopsin-(I-2,II-7)-(II-2*S*)-maesopsin	**(263)**	(I-2*S*,II-2*S*)-enantiomer

(I-2',II-6)-Aurone-flavanone dimer



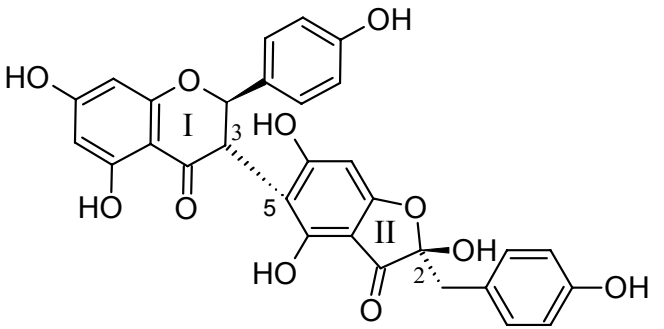
Pilotrichellaaurone **(264)**

(I-5',II-6)-Aurone-flavanone dimer



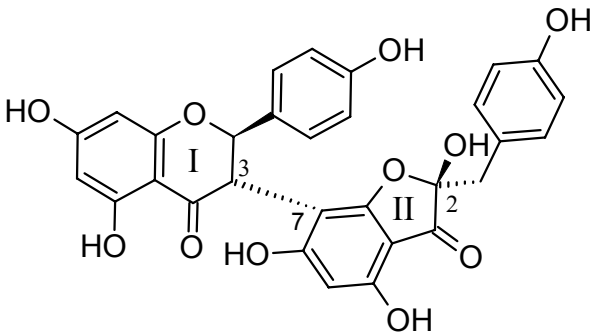
Campylopusaurone **(265)**

(I-3,II-5)-Flavanone-auronol dimmers



(I-2*R*,3*S*)-Naringenin-(I-3α,II-5)-(II-2*R*)-maesopsin (266)
(I-2*R*,3*S*)-Naringenin-(I-3α,II-5)-(II-2*S*)-maesopsin (267)

(I-3,II-7)-Flavanone-auronol dimmers

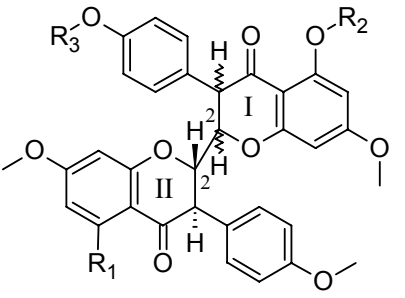


(I-2*R*,3*S*)-Naringenin-(I-3α,II-7)-(II-2*R*)-maesopsin **(268)**
(I-2*R*,3*S*)-Naringenin-(I-3α,II-7)-(2*S*)-maesopsin **(269)**

Figure 13. COMPLEX BIFLAVONOIDS: (I-5',II-5)-Biaurone, (I-2',II-2)-Biaurone, (I-α,II-α)-Biaurone, (I-2,II-7)-Aurone-auronol dimers, (I-2',II-6)-Aurone-flavanone dimer, (I-5',II-6)-Aurone-flavanone dimer, (I-3,II-5)-Flavanone-auronol dimers, (I-3,II-7)-Flavanone-auronol dimers.

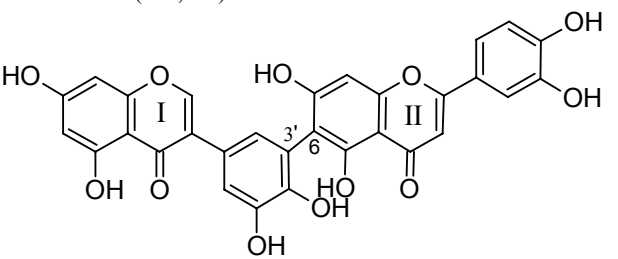
The Bi-isoflavonoid series is formed by (I-2,II-2)-bi-isoflavanones (**270**-**273**); a (I-3',II-6)-isoflavone-flavone dimer (**274**); a (I-3',II-8)-isoflavone-flavone dimer (**275**); (I-2,II-5)-isoflavanone-auronol dimers (**276**, **277**); (I-2,II-7)-isoflavanone-auronol dimers (**278**, **279**).

(I-2,II-2)-Bi-isoflavanones



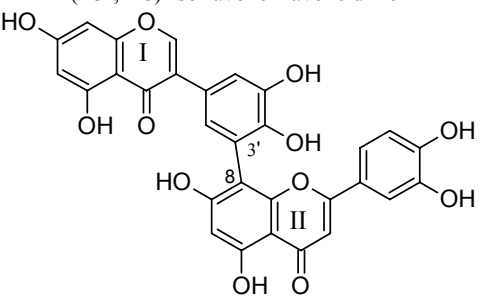
		R_1	R_2	R_3
Hexaspermone A (I-2βH, I-3αH)	**(270)**	OH	H	Me
Hexaspermone B (I-2βH, I-3αH)	**(271)**	OH	Me	H
Hexaspermone C (I-2βH, I-3αH)	**(272)**	OH	H	H
Dehydroxyhexaspermone C (I-2αH, I-3βH)	**(273)**	H	H	H

(I-3',II-6)-Isoflavone-flavone dimer



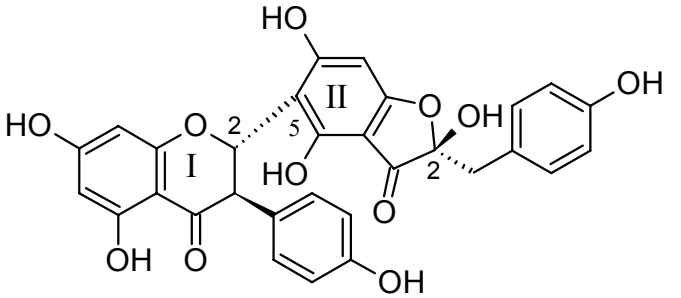
Heterobryoflavone **(274)**

(I-3',II-8)-Isoflavone-flavone dimer



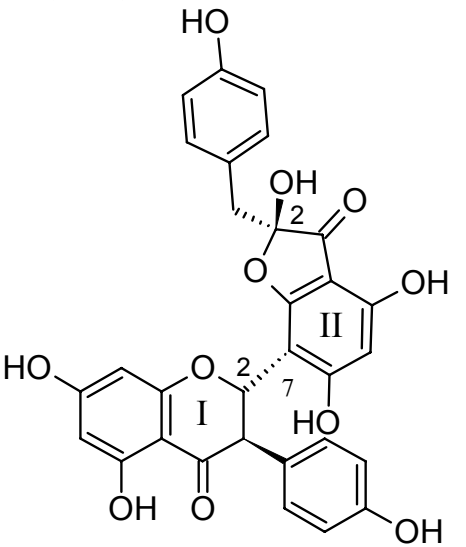
Bryoflavone **(275)**

(I-2,II-5)-Isoflavanone-auronol dimers



(I-2*S*,3*R*)-Dihydrogenistein-(I-2α,II-5)-(II-2*R*)-maesopsin **(276)**
(I-2*S*,3*R*)-Dihydrogenistein-(I-2α,II-5)-(II-2*S*)-maesopsin **(277)**

(I-2,II-7)-Isoflavanone-auronol dimers

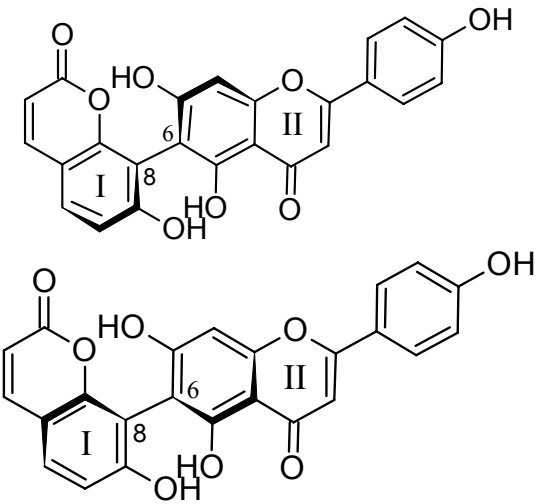


(I-2*S*,3*R*)-Dihydrogenistein-(I-2α,II-7)-(II-2*R*)-maesopsin **(278)**
(I-2*S*,3*R*)-Dihydrogenistein-(I-2α,II-7)-(II-2*S*)-maesopsin **(279)**

Figure 14. COMPLEX BIFLAVONOIDS: (I-2,II-2)-Bi-isoflavanones, (I-3',II-6)-Isoflavone-flavone dimer, (I-3',II-8)-Isoflavone-flavone dimer, (I-2,II-5)-Isoflavanone-auronol dimers, (I-2,II-7)-Isoflavanone-auronol dimers.

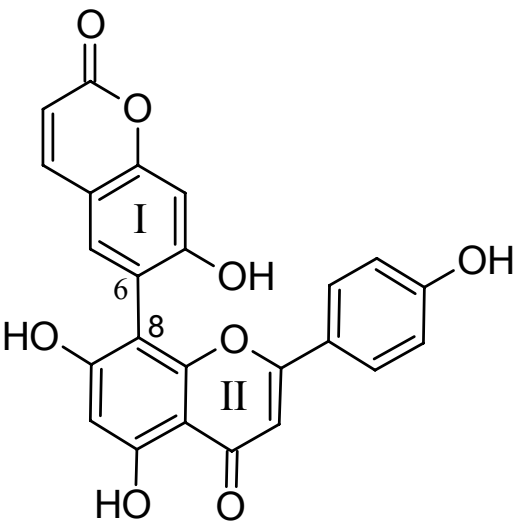
The (I-8,II-6)-coumarin-flavone dimer (**280**) and the (I-6,II-8)-coumarin-flavone dimer (**281**) are shown in the Coumarin-Flavone series. The Bineoflavonoid series include five (I-3,II-3)-bi-4-aryldihydrocoumarins (**282-286**).

(I-8,II-6)-Coumarin-flavone dimer



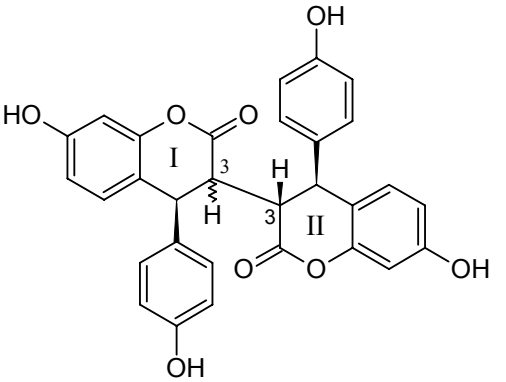
(I-8,II-6)-Umbelliferyl-apigenin **(280)**
(with optical activity) (free rotation at the biaryl axis is hindered: atropisomer)

(I-6,II-8)-Coumarin-flavone dimer

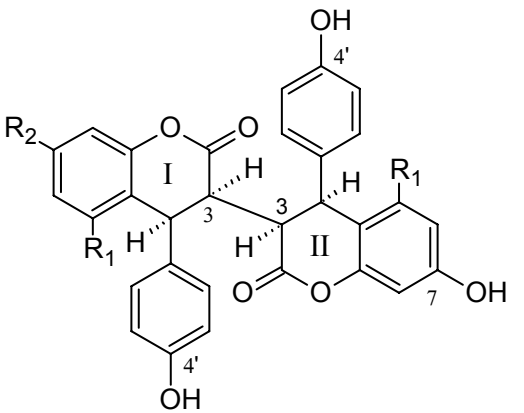


(I-6,II-8)-Umbelliferyl-apigenin **(281)**
(without optical activity)

(I-3,II-3)-Bi-4-aryldihydrocoumarins



(I-3*R*,II-3*S*)-*bis*-4-(4'-hydroxy)phenyl-7-hydroxy-3,4-dihydrocoumarin **(282)**
(I-3*S*,II-3*S*)-*bis*-4-(4'-hydroxy)phenyl-7-hydroxy-3,4-dihydrocoumarin **(283)**

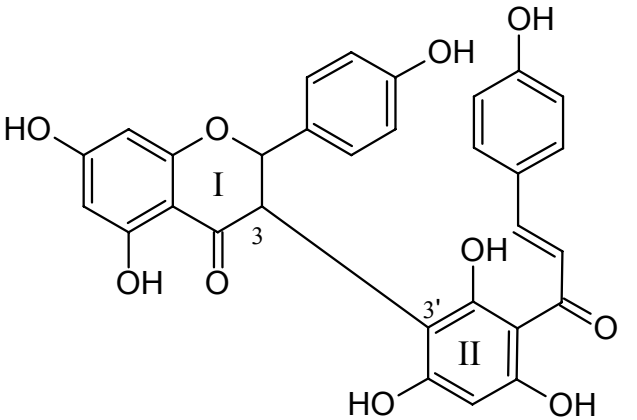


		R_1	R_2
Diphysin	**(284)**	OH	OH
I-7-*O*-β-*D*-Glucopyranosyldiphysin	**(285)**	OH	OGlu
I-5,II-5-Di-*O*-methyldiphysin	**(286)**	OMe	OH

Figure 15. COMPLEX BIFLAVONOIDS: (I-8,II-6)-Coumarin-flavone dimer, (I-6,II-8)-Coumarin-flavone dimer, (I-3,II-3)-Bi-4-aryldihydrocoumarins.

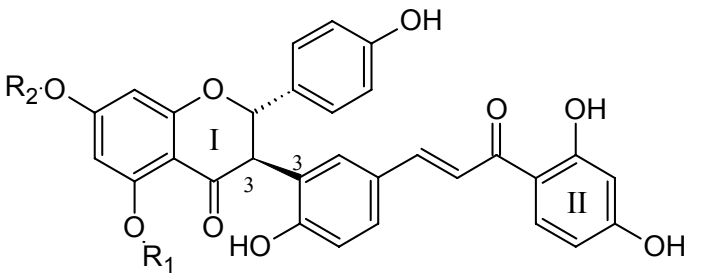
The simple Flavonoid-Chalcone series contains a (I-3,II-3')-flavanone-chalcone dimer (**287**); (I-3,II-3)-flavanone-chalcone dimers (**288**- **290**); and a (I-3,II-3)-flavan-chalcone dimer (**291**).

(I-3,II-3')-Flavanone-chalcone dimer

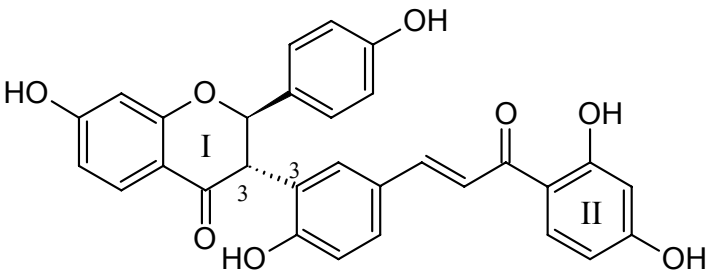


I-5,7,4'-Trihydroxyflavanone-(I-3,II-3')-II-4,2',4',6'-tetrahydroxychalcone **(287)**

(I-3,II-3)-Flavanone-chalcone dimers

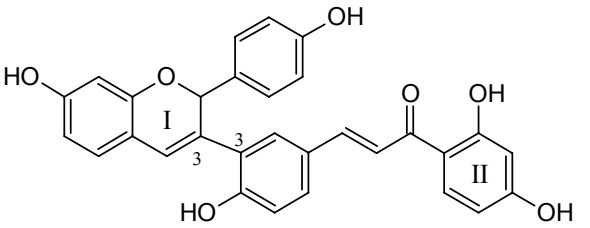


		R_1	R_2
I-5-Hydroxylophirone B	**(288)**	H	H
I-5-Hydroxylophirone B I-7-*O*-β-*D*-glucopyranoside	**(289)**	H	β-*D*-Glu



Lophirone B **(290)**

(I-3,II-3)-Flavan-chalcone dimer

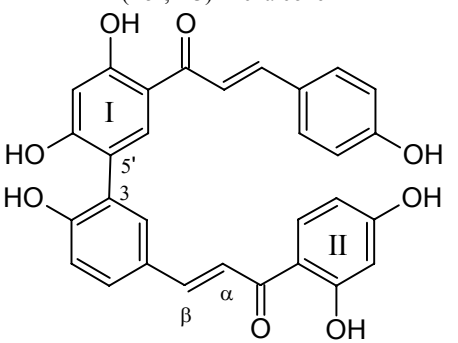


Bongosin **(291)**

Figure 16. COMPLEX BIFLAVONOIDS: (I-3,II-3')-Flavanone-chalcone dimer, (I-3,II-3)-Flavanone-chalcone dimers, (I-3,II-3)-Flavan-chalcone dimer.

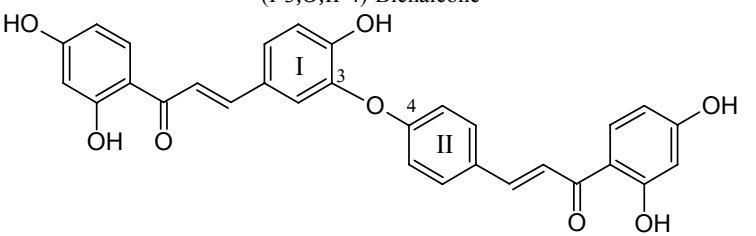
The Bichalcone series encloses a (I-5',II-3)-bichalcone (**292**); a (I-3,*O*,II-4)-bichalcone (**293**); (I-4,*O*,II-5')-bichalcones (**294**-**296**) and a (I-5',*O*,II-4')-bichalcone (**297**).

(I-5',II-3)-Bichalcone



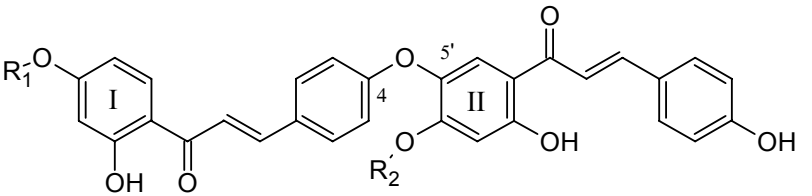
Rhuschalcone VI **(292)**

(I-3,*O*,II-4)-Bichalcone



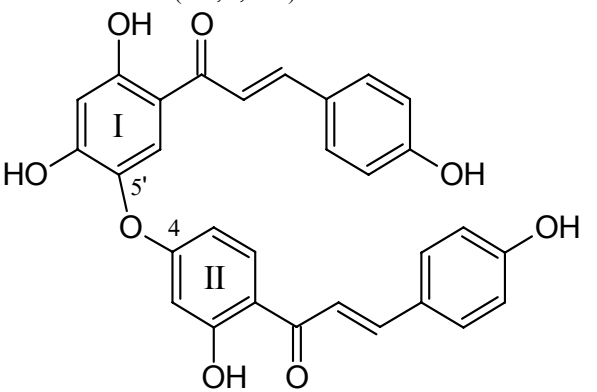
Luxenchalcone **(293)**

(I-4,*O*,II-5')-Bichalcones



		R_1	R_2
Rhuschalcone I	**(294)**	Me	Me
Rhuschalcone II	**(295)**	H	H
Rhuschalcone III	**(296)**	Me	H

(I-5',*O*,II-4')-Bichalcone

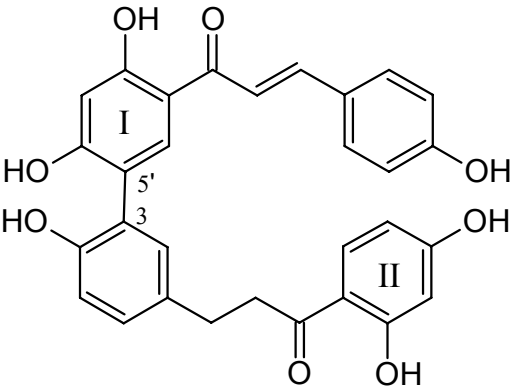


Rhuschalcone IV **(297)**
(Rhuschalcones I–IV are combinations of isoliquiritigenin and its 4'-methyl ether)

Figure 17. COMPLEX BIFLAVONOIDS: (I-5',II-3)-Bichalcone, (I-3,*O*,II-4)-Bichalcone, (I-4,*O*,II-5')-Bichalcones, (I-5',*O*,II-4')-Bichalcone.

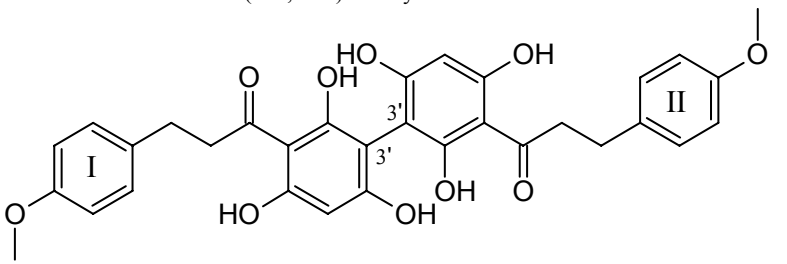
The Bidihydrochalcone series contains a (I-5',II-3)-chalcone-dihydrochalcone dimer (**298**); a (I-3',II-3')-bidihydrochalcone (**299**); (I-α,II-α)-bidihydrochalcone (**300**); a (I-4,*O*,II-4)-bidihydrochalcone (**301**); a (I-3,*O*,II-4)-bidihydrochalcone (**302**) and a (I-5,II-5)-bi-I-2,II-2-isoprenyldihydrochalcone (**303**). The Methylene-linked bidihydrochalcone series includes a (I-5',CH_2,II-5')-bidihydrochalcone (**304**); a (I-3', CH_2,II-8)-dihydrochalcone-flavonol (**305**, **307**, **308**) and (I-3',CH_2,II-8)-dihydrochalcone-II-3-methoxyflavone dimers (**306**, **309**).

(I-5',II-3)-Chalcone-dihydrochalcone dimer



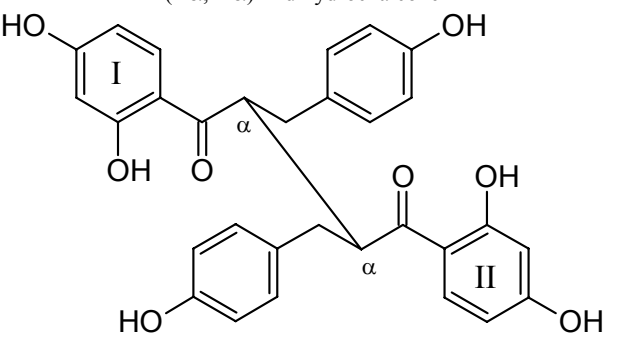
Rhuschalcone V **(298)**

(I-3',II-3')-Bidihydrochalcone



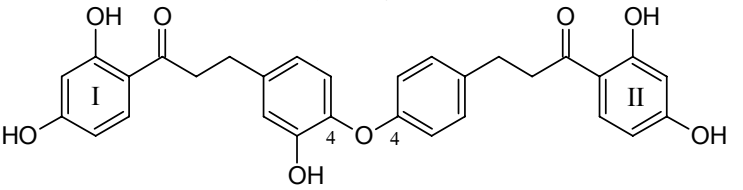
(I-3',II-3')-*Bis*-2',4',6'-trihydroxy-4-methoxy-α,β-dihydrochalcone **(299)**

(I-α,II-α)-Bidihydrochalcone



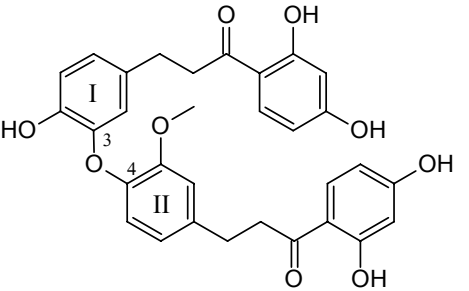
Brackenin **(300)**

(I-4,*O*,II-4)-Bidihydrochalcone



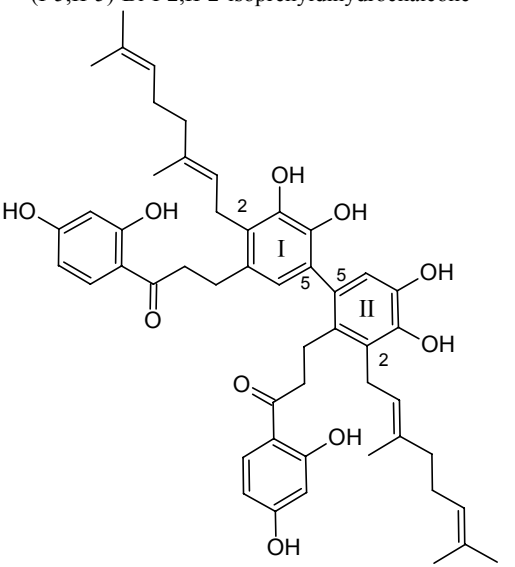
Littorachalcone **(301)**

(I-3,*O*,II-4)-Bidihydrochalcone



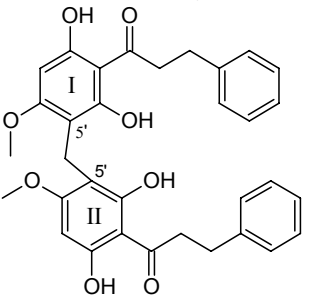
Verbenachalcone **(302)**

(I-5,II-5)-Bi-I-2,II-2-isoprenyldihydrochalcone



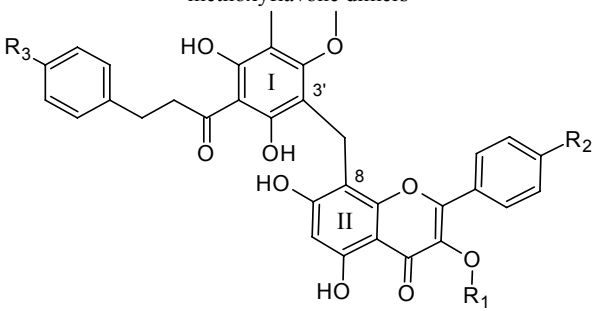
Cycloaltilisin 6 **(303)**

(I-5',CH_2,II-5')-Bidihydrochalcone



Piperaduncin C **(304)**

(I-3',CH_2,II-8)-Dihydrochalcone-flavonol and (I-3',CH_2,II-8)-Dihydrochalcone-II-3-methoxyflavone dimers

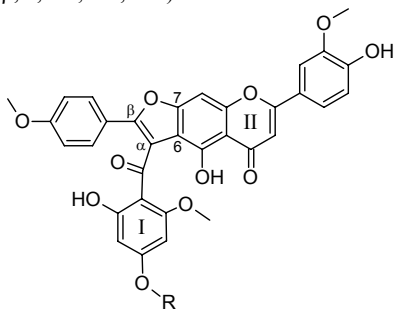


		R_1	R_2	R_3
Trianguletin	**(305)**	H	OMe	H
I-2',6'-Dihydroxy-I-4'-methoxy-I-5'-methyl-I-α,β-dihydrochalcone-(I-3',CH_2,II-8)-II-5,7-dihydroxy-II-3-methoxyflavone	**(306)**	Me	H	H
I-4,2',6'-Trihydroxy-I-4'-methoxy-I-5'-methyl-I-α,β-dihydrochalcone-(I-3',CH_2,II-8)-II-4'-*O*-methylkaempferol	**(307)**	H	OMe	OH
I-4,2',6'-Trihydroxy-I-4'-methoxy-I-5'-methyl-I-α,β-dihydrochalcone-(I-3',CH_2,II-8)-II-5,7-dihydroxy-II-3,4'-dimethoxyflavone	**(308)**	Me	OMe	OH
I-4,2',6'-Trihydroxy-I-4'-methoxy-I-5'-methyl-I-α,β-dihydrochalcone-(I-3',CH_2,II-8)-II-5,7-dihydroxy-II-3-methoxyflavone	**(309)**	Me	H	OH

Figure 18. COMPLEX BIFLAVONOIDS: (I-5',II-3)-Chalcone-dihydrochalcone dimer, (I-3',II-3')-Bidihydrochalcone, (I-α,II-α)-Bidihydrochalcone, (I-4,*O*,II-4)-Bidihydrochalcone, (I-3,*O*,II-4)-Bidihydrochalcone, (I-5,II-5)-Bi-I-2,II-2-isoprenyldihydrochalcone, (I-5',CH_2,II-5')-Bidihydrochalcone, (I-3',CH_2,II-8)-Dihydrochalcone-flavonol and (I-3',CH_2,II-8)-Dihydrochalcone-II-3-methoxyflavone dimers.

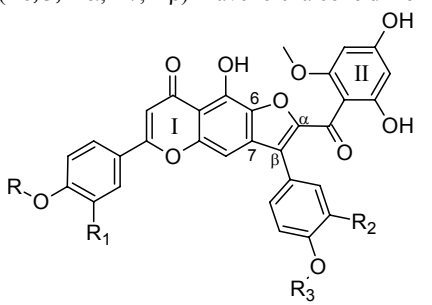
Furobenzo-γ-pyrone (furochromen-4-one) derivatives are shown in the chalcone-flavone and flavone-chalcone series. These series includes (I-β,*O*,II-7; I-α, II-6)-chalcone-flavone dimers (**310, 311**); (I-6,*O*,II-α; I-7,II-β)-flavone-chalcone dimers (**312-314**); and (I-6,*O*,II-β; I-7,II-α)-flavone-chalcone dimers (**315**). Furo[2,3-*f*]chromanone derivatives comprise a (I-6,II-α; I-5,*O*,II-β)-flavanone-chalcone dimer (**316**); dihydrofuro[3,2-*g*]chromanone derivatives comprise (I-7,*O*,II-β; I-6,II-α)-flavanone-dihydrochalcone dimers (**317**); and furo[2,3-*h*]benzopyran derivatives (I-α,II-8; I-β,*O*,II-7)-chalcone-flavan dimers (**318, 319**).

(I-β,*O*,II-7; I-α, II-6)-Chalcone-flavone dimers



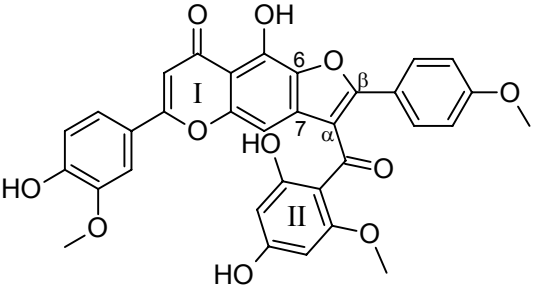
		R
Ridiculuflavonylchalcone B	**(310)**	H
Cissampeloflavone	**(311)**	Me

(I-6,*O*,II-α; I-7,II-β)-Flavone-chalcone dimer



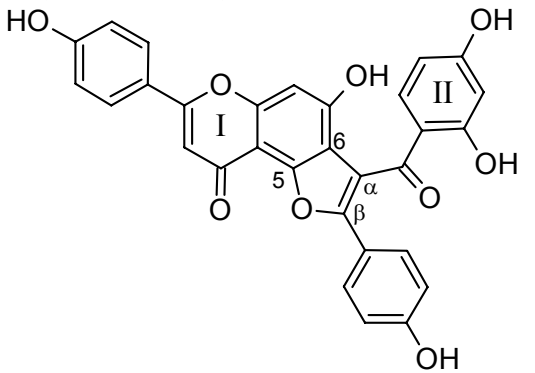
		R	R_1	R_2	R_3
I-5-Hydroxy-I-4′-methoxyflavone (I-6,*O*,II-α; I-7,II-β)-II-4,2′,4′-trihydroxy-II-3,6′-dimethoxychalcone	**(312)**	Me	H	OMe	H
I-5,4′-Dihydroxy-I-3′-methoxyflavone (I-6,*O*,II-α; I-7,II-β)-II-2′,4′-dihydroxy-II-4,6′-dimethoxychalcone	**(313)**	H	OMe	H	Me
I-5-Hydroxy-I-4′-methoxyflavone (I-6,*O*,II-α; I-7,II-β)-II-3,2′,4′-trihydroxy-II-4,6′-dimethoxychalcone	**(314)**	Me	H	OH	Me

(I-6,*O*,II-β; I-7,II-α)-Flavone-chalcone dimer



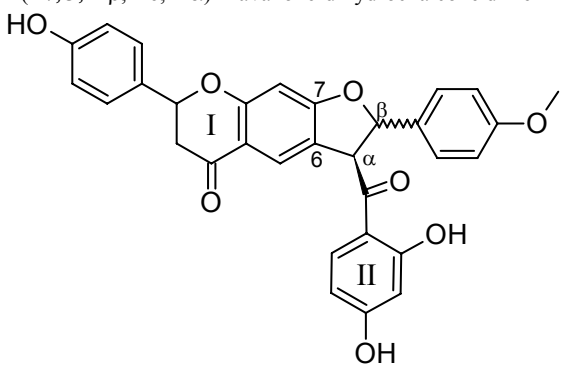
I-5,4′-Dihydroxy-I-3′-methoxyflavone (I-6,*O*,II-β;I-7,II-α)-II-2′,4′-dihydroxy-II-4,6′-dimethoxychalcone **(315)**

(I-6,II-α; I-5,*O*,II-β)-Flavanone-chalcone dimer



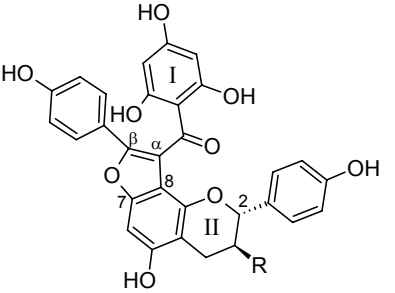
Flavumone B **(316)**

(I-7,*O*,II-β; I-6,II-α)-Flavanone-dihydrochalcone dimer



Afzelone A **(317)**

(I-α,II-8; I-β,*O*,II-7)-Chalcone-flavan dimers

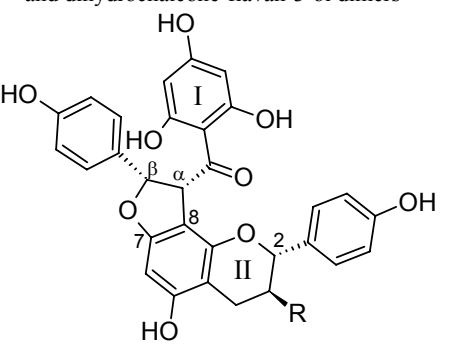


		R
Daphnodorin A	**(318)**	H
Daphnodorin B	**(319)**	OH

Figure 19. COMPLEX BIFLAVONOIDS: (I-β,*O*,II-7; I-α, II-6)-Chalcone-flavone dimers, (I-6,*O*,II-α; I-7,II-β)-Flavone-chalcone dimer, (I-6,*O*,II-β; I-7,II-α)-Flavone-chalcone dimer, (I-6,II-α; I-5,*O*,II-β)-Flavanone-chalcone dimer, (I-7,*O*,II-β; I-6,II-α)-Flavanone-dihydrochalcone dimer, (I-α,II-8; I-β,*O*,II-7)-Chalcone-flavan dimers.

Dihydrofurobenzopyran derivatives include (I-α,II-8; I-β,*O*,II-7)-dihydrochalcone-flavan and dihydrochalcone-flavan-3-ol dimers (**320, 321**); and (I-3,II-α;I-4,*O*,II-β)-flavan-dihydrochalcone dimers (**322**). A (I-3,II-α;I-4,*O*,II-β)-bidihydrochalcone was included in the tetrahydrofuro[3,2-c]benzopyran derivatives (**323**). A naphthalene derivative (I-2,II-β;I-α,II-α)-bichalcone was presented in **324**; dihydronaphthalene derivatives (I-2,II-β;I-α,II-α)-chalcone-dihydrochalcone dimers were presented in **325**, **326** and **327**; and tetrahydronaphthalene derivatives (I-2,II-β;I-α,II-α)-bi-dihydrochalcone was presented in **328**.

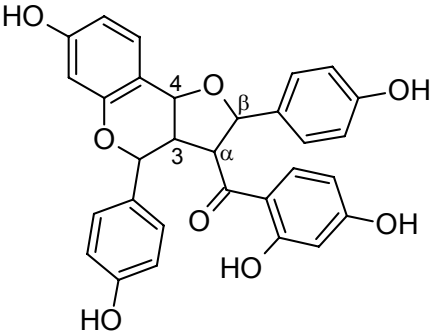
(I-α,II-8; I-β,*O*,II-7)-Dihydrochalcone-flavan
and dihydrochalcone-flavan-3-ol dimers*



		R
Daphnodorin J	**(320)**	H
I-α,β-Dihydrodaphnodorin B	**(321)**	OH

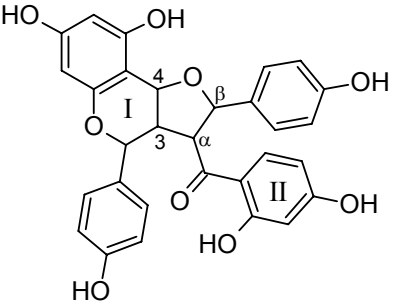
*Compounds derived from the condensation of chalconaringenin with apigeniflavan (5,7,4′-trihydroxyflavan), followed by internal cyclization reactions.

(I-3,II-α;I-4,*O*,II-β)-Flavan-dihydrochalcone dimer



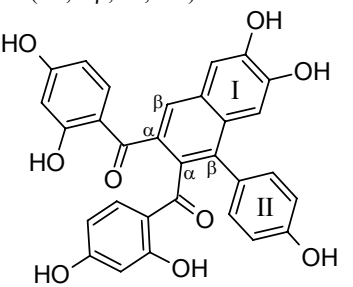
Lophirone H **(322)**

(I-3,II-α;I-4,*O*,II-β)-Bidihydrochalcones



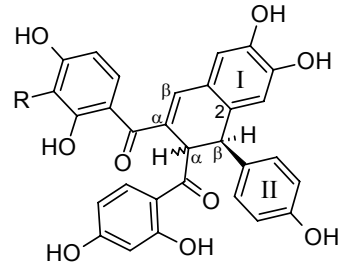
Cordigol **(323)**

(I-2,II-β;I-α,II-α)-Bichalcone

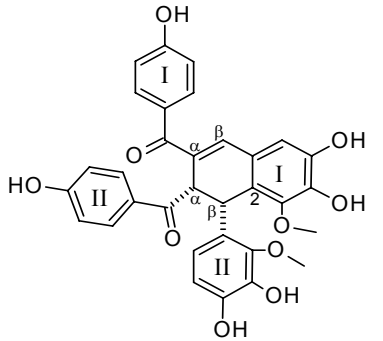


Urundeuvine B **(324)**

(I-2,II-β;I-α,II-α)-Chalcone-dihydrochalcone dimers

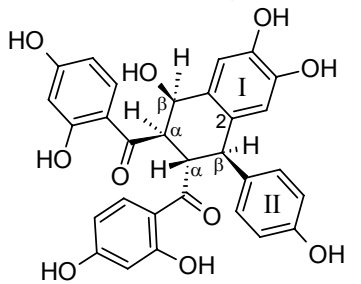


		R
Urundeuvine A	**(325)**	H
Urundeuvine C	**(326)**	OH



Licobichalcone **(327)** (Coupling of two moieties of libochalcone B and further rearrangement)

(I-2,II-β;I-α,II-α)-Bi-dihydrochalcone

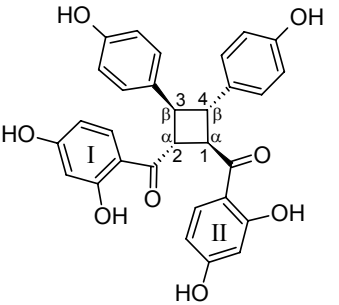


Matosine **(328)**

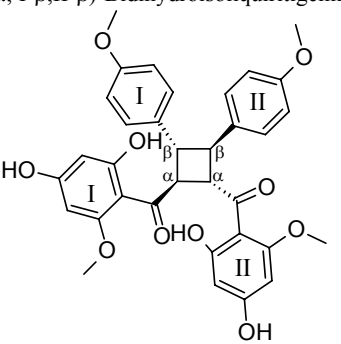
Figure 20. COMPLEX BIFLAVONOIDS: (I-α,II-8; I-β,*O*,II-7)-Dihydrochalcone-flavan and dihydrochalcone-flavan-3-ol dimers, (I-3,II-α;I-4,*O*,II-β)-Flavan-dihydrochalcone dimer, (I-3,II-α;I-4,*O*,II-β)-Bidihydrochalcones, (I-2,II-β;I-α,II-α)-Bichalcone, (I-2,II-β;I-α,II-α)-Chalcone-dihydrochalcone dimers, (I-2,II-β;I-α,II-α)-Bi-dihydrochalcone.

Substituted cyclobutanes (I-α,II-α; I-β,II-β)-Bidihydrochalcones were included in **329-332**; and substituted tetrahydrofurans (I-β,*O*,II-β; I-α,II-α)-Bidihydrochalcones in **333-337**.

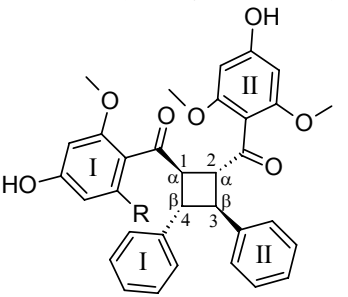
(I-α,II-α; I-β,II-β)-Bidihydrochalcones



(I-α,II-α; I-β,II-β)-Bidihydroisoliquiritigenin **(329)**

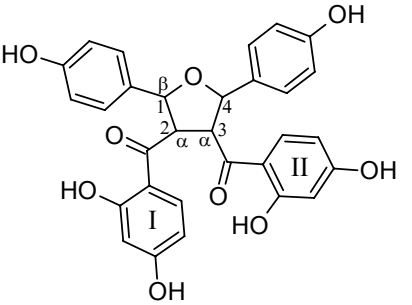


(I-α,II-α; I-β,II-β)-Bidihydrochalcone **(330)**

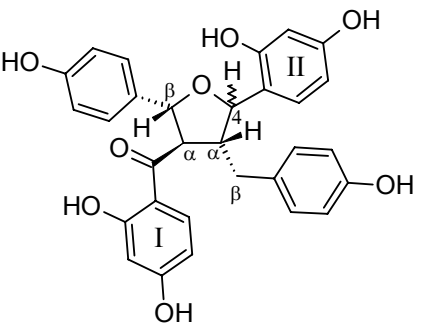


		R
rel-1β-(2,4-Dihydroxy-6-methoxy)benzoyl-*rel*-2α-(2,6-dimethoxy-4-hydroxy)benzoyl-*rel*-(3β,4α)-diphenylcyclobutane	**(331)**	OH
rel-(1α,2β)-Di-(2,6-dimethoxy-4-hydroxy)benzoyl-*rel*-(3α,4β)-diphenylcyclobutane	**(332)**	OMe

(I-β,*O*,II-β; I-α,II-α)-Bidihydrochalcones



Lophirone F **(333)**
Lophirone G **(334)**
Cordigone **(335)**

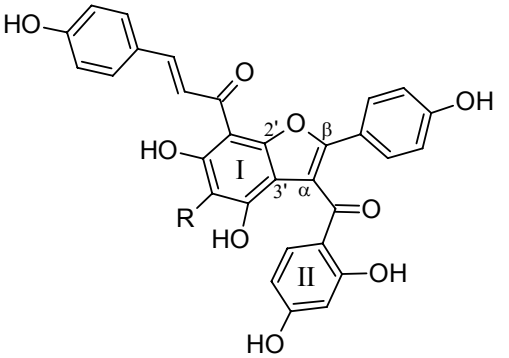


Mbamichalcone (II-4*R*) **(336)**
Isombamichalcone (II-4*S*) **(337)**

Figure 21. COMPLEX BIFLAVONOIDS: (I-α,II-α; I-β,II-β)-Bidihydrochalcones, (I-β,*O*,II-β; I-α,II-α)-Bidihydrochalcones.

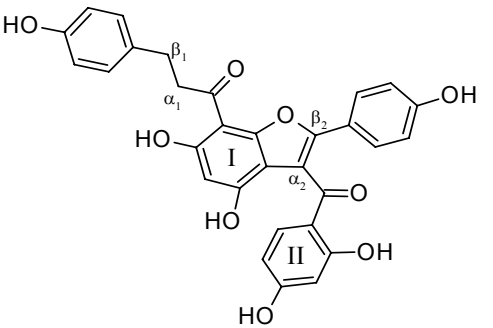
Trisubstituted benzofurans include (I-2′,*O*,II-β; I-3′,II-α)-bichalcones (**338**, **339**); a (I-α,II-3′; I-β,*O*,II-2′)-chalcone-dihydrochalcone dimer (**340**); and a (I-3,II-α;I-4,*O*,II-β)-dihydrochalcone-chalcone dimer (**341**). Trisubstituted benzodihydrofurans contain (I-3,II-α; I-4,*O*,II-2)-chalcone-dihydrochalcone dimers (**342**, **343**); a (I-3,II-α; I-4,*O*,II-β)-chalcone-dihydrochalcone dimer (**344**); and a (I-2′,*O*, II-β;I-3′,II-α)-chalcone-dihydrochalcone dimer (**345**). The structures of related compounds were also illustrated: (I-3,II-α; I-4,*O*,II-β)-dihydrochalcone (**346**); (I-3,II-5)-bi-isoflavonoid (**347**); and (I-3,II-8)-bi-isoflavonoid (**348**).

(I-2′,*O*,II-β; I-3′,II-α)-Bichalcones



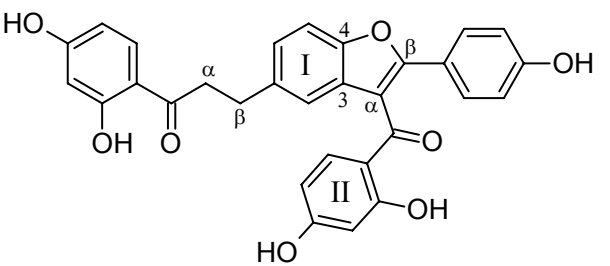
		R
Calodenin B	**(338)**	H
Flavumone A	**(339)**	OH

(I-α,II-3′; I-β,*O*,II-2′)-Chalcone-dihydrochalcone dimer



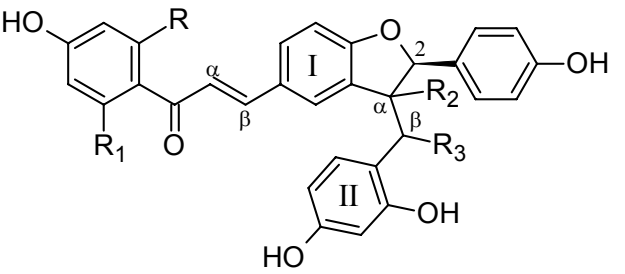
Calodenin A **(340)**

(I-3,II-α;I-4,*O*,II-β)-Dihydrochalcone-chalcone dimer



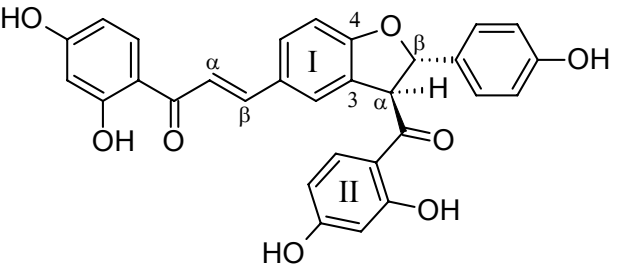
Isolophirone C **(341)**

(I-3,II-α; I-4,*O*,II-2)-Chalcone-dihydrochalcone dimmers



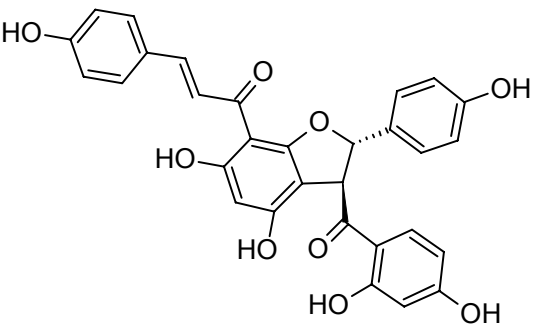
		R	R_1	R_2	R_3
Lophirone K	**(342)**	OH	H	βOH	=O
Azobechalcone	**(343)**	H	OH	H	OMe

(I-3,II-α; I-4,*O*,II-β)-Chalcone-dihydrochalcone dimer



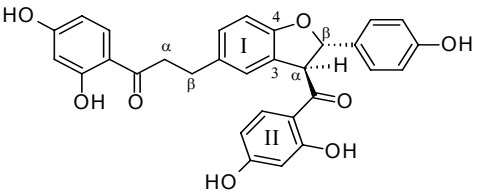
Lophirone C **(344)**

(I-2′,*O*, II-β;I-3′,II-α)-Chalcone-dihydrochalcone dimer



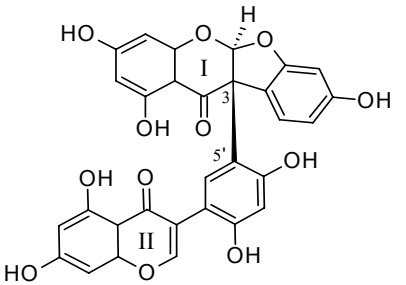
Afzelone C **(345)**

(I-3,II-α; I-4,*O*,II-β)-Dihydrochalcone



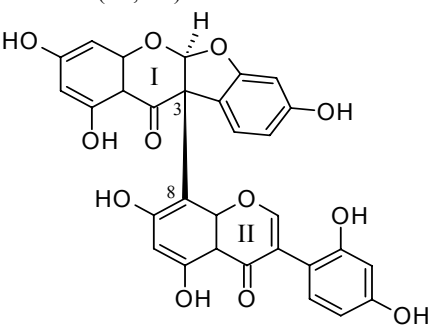
Dihydrolophirone C (I-α,β-dihydro) **(346)**

(I-3,II-5)-Bi-isoflavonoid



Lupinus albus (I-3,II-5)-bi-isoflavonoid **(347)**

(I-3,II-8)-Bi-isoflavonoid

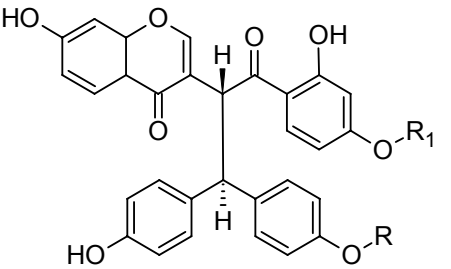


Lupinus albus (I-3,II-8)-bi-isoflavonoid **(348)**

Figure 22. COMPLEX BIFLAVONOIDS: (I-2′,*O*,II-β; I-3′,II-α)-Bichalcones, (I-α,II-3′; I-β,*O*,II-2′)-Chalcone-dihydrochalcone dimer, (I-3,II-α;I-4,*O*,II-β)-Dihydrochalcone-chalcone dimer, (I-3,II-α; I-4,*O*,II-2)-Chalcone-dihydrochalcone dimers, (I-3,II-α; I-4,*O*,II-β)-Chalcone-dihydrochalcone dimer, (I-2′,*O,* II-β;I-3′,II-α)-Chalcone-dihydrochalcone dimer, (I-3,II-α; I-4,*O*,II-β)-Dihydrochalcone, (I-3,II-5)-Bi-isoflavonoid, (I-3,II-8)-Bi-isoflavonoid.

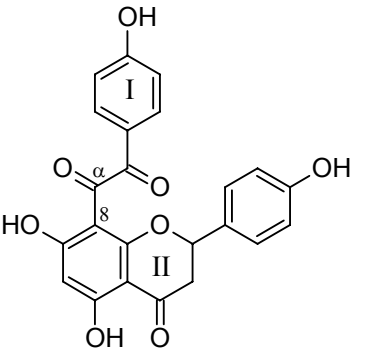
REARRANGED BIFLAVONOIDS

The third main group of structures includes rearranged biflavonoids (**349-354**); cleaved biflavonoids: (I-5,II-7′)-Dihydrochalcone-deoxodihydrochalcone (**355**), (I-4,*O*,II-4)-Prenylbiflavan (**356**), (I-4,*O*,II-4)-Isopropenyldihydrofuranbiflavan (**357**), doubly-linked biflavonoids (Tetrahydrofuran-2-one[5,6-f]tetrahydrochromanones) (**358-365**); ketalized (I-2,*O*,II-7; I-3,II-8)-Flavanonol-Flavan dimers (**366-374**); ketalized prenylflavanone-prenylisoflavan dimers (**375**); and rearranged ketalized dimers (**376-392**).

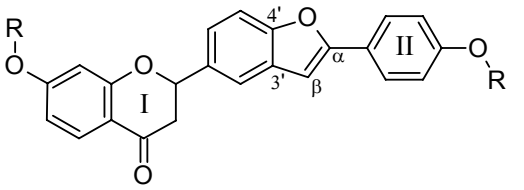


		R	R_1
Afzelone D	**(349)**	Me	Me
Calodenone	**(350)**	H	Me
Lophirone A	**(351)**	H	H

Cleaved Biflavonoids

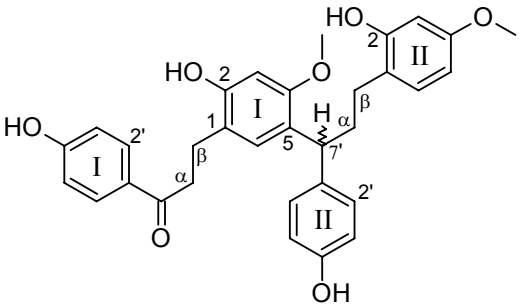


Daphnodorin L **(352)**
(*Daphne odora* cleaved-chalcone-flavan dimer)



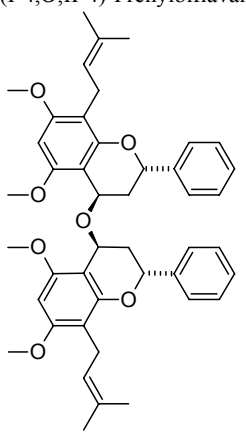
		R
Lophirone I	**(353)**	H
Lophirone J	**(354)**	Me

(I-5,II-7′)-Dihydrochalcone-deoxodihydrochalcone
(C-7′ accounts for the carbon that used to be that of a carbonyl group in a chalcone)



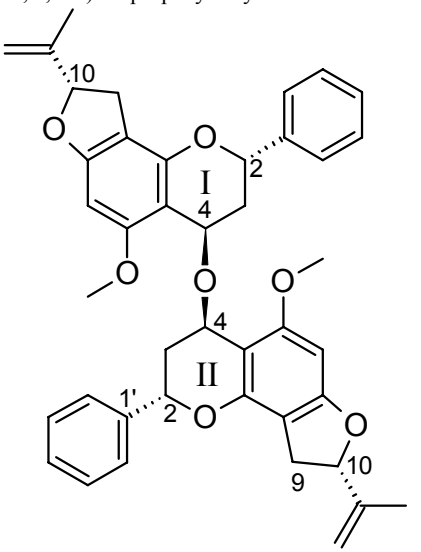
Cinnabarone **(355)**

(I-4,*O*,II-4)-Prenylbiflavan



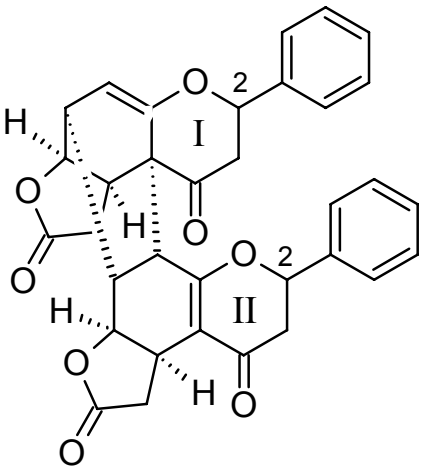
Tepicanol A **(356)**

(I-4,*O*,II-4)-Isopropenyldihydrofuranbiflavan

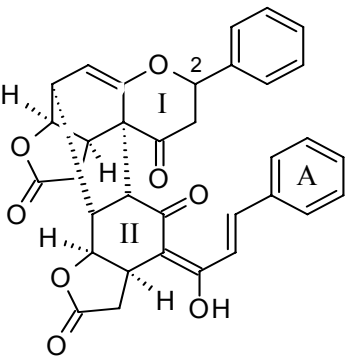


Crassifolin A **(357)**

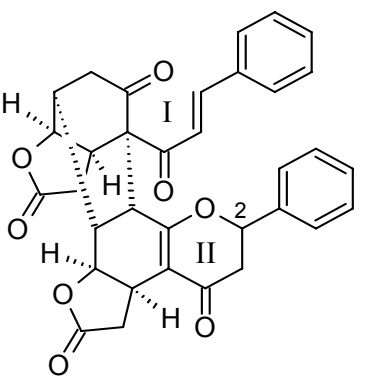
Doubly-Linked Biflavonoids



Bicaryone A (I-2*S*, II-2*S*) **(358)**
Bicaryone B (I-2*S*, II-2*R*) **(359)**
Bicaryone C (I-2*R*, II-2*S*) **(360)**
Bicaryone D (I-2*R*, II-2*R*) **(361)**

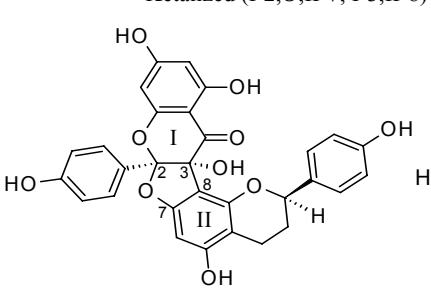


Chalcocaryanone A (I-2*R*) **(362)**
Chalcocaryanone B (I-2*S*) **(363)**

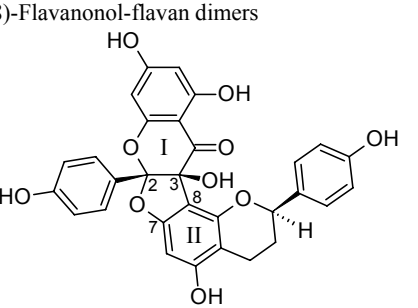


Chalcocaryanone C (I-2*S*) **(364)**
Chalcocaryanone D (I-2*R*) **(365)**

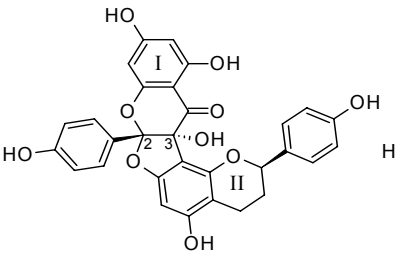
Ketalized (I-2,*O*,II-7; I-3,II-8)-Flavanonol-flavan dimers



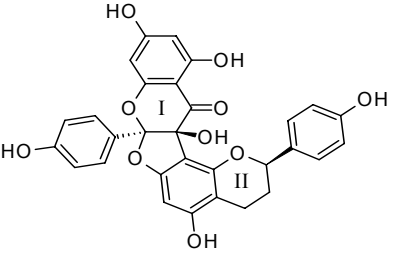
A



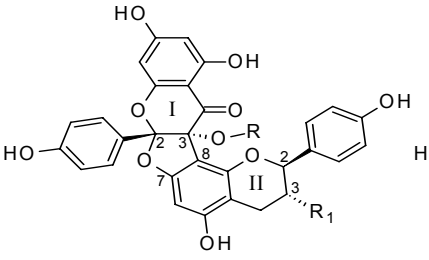
B



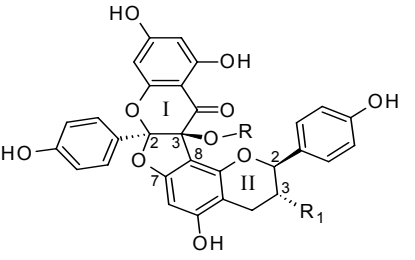
E



F



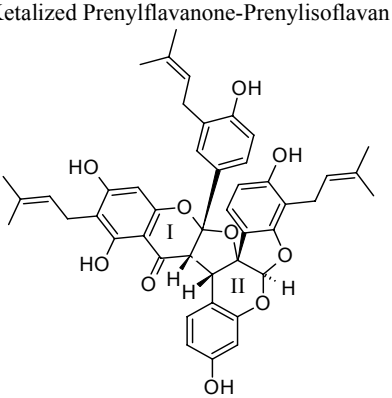
G



H

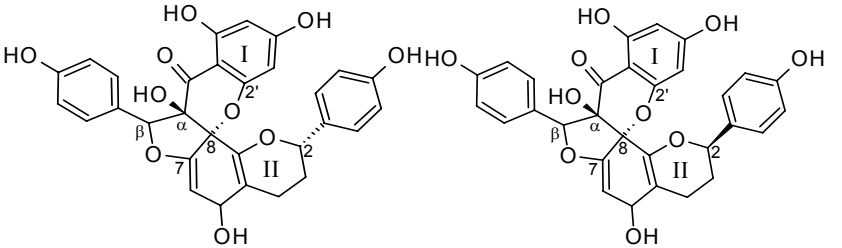
		R	R_1
Daphnogirin A (I-2*S*,3*R*, II-2*R*)	**(366)**	H	H
Daphnogirin B (I-2*R*,3*S*, II-2*R*)	**(367)**	H	H
Daphnogirin E (I-2*R*,3*R*, II-2*R*)	**(368)**	H	H
Daphnodorin F (I-2*S*, 3*S*, II-2*R*)	**(369)**	H	H
Daphnodorin G (I-2*R*,3*R*, II-2*R*,3*R*)	**(370)**	H	OH
II-3-*O*-Methyldaphnodorin G	**(371)**	H	OMe
Daphnodorin H (I-2*S*,3*S*, II-2*R*,3*R*)	**(372)**	H	OH
I-3-*O*-Methyldaphnodorin H	**(373)**	Me	OH
II-3-*O*-Methyldaphnodorin H	**(374)**	H	OMe

Ketalized Prenylflavanone-Prenylisoflavan



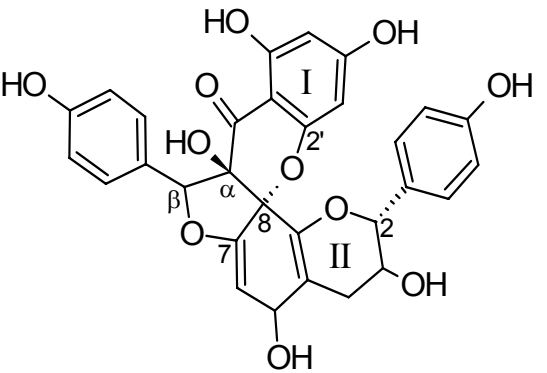
Licoagrodin **(375)**

Rearranged Ketalized Dimers

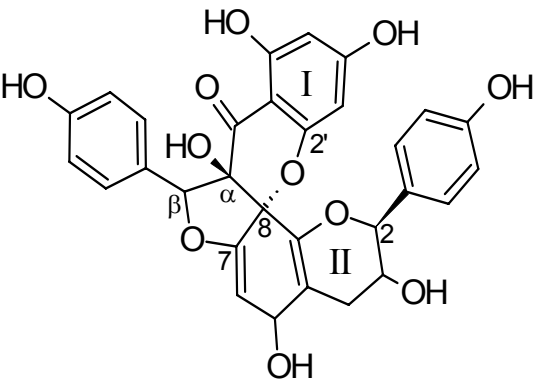


Daphnodorin M (II-2*S*)* **(376)**
Daphnodorin N (II-2*R*)* **(377)**

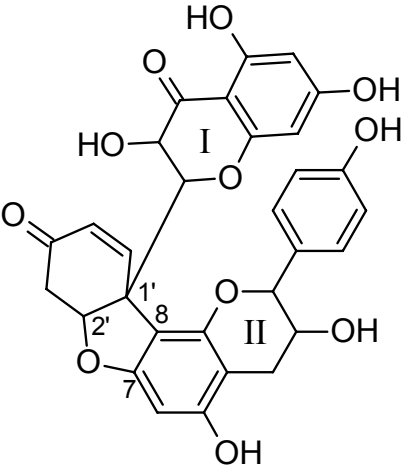
*Compounds derived from the condensation of chalconaringenin with apigeniflavan (5,7,4′-trihydroxyflavan), followed by internal cyclization reactions.



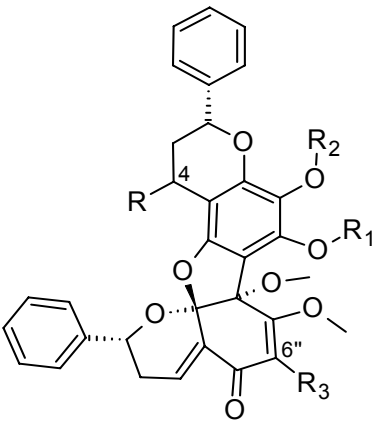
Genkwanol B (II-2*S*) **(378)**



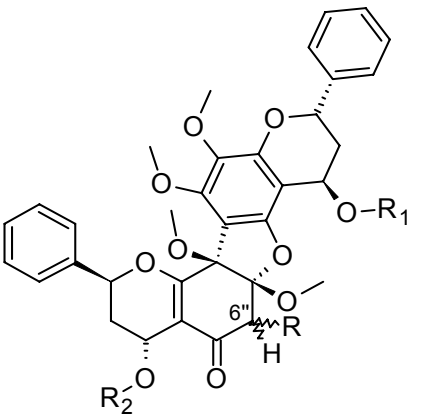
Genkwanol C (II-2*R*) **(379)**



Hypnumbiflavonoid A **(380)**



		R	R_1	R_2	R_3
Calycopterone (I-4*S* = I-4-βOMe)	**(381)**	βOMe	H	Me	OMe
Isocalycopterone (I-4*S* I-4-βOMe)	**(382)**	βOMe	Me	H	OMe
I-4-Demethylcalycopterone (I-4*S* = I-4-βOH)	**(383)**	βOH	H	Me	OMe
Neocalycopterone (I-4*S* = I-4-βOH)	**(384)**	βOH	Me	Me	OMe
I-4-Methylneocalycopterone (I-4*S* = I-4-βOMe)	**(385)**	βOMe	Me	Me	OMe
II-6-Demethoxyneocalycopterone (I-4*R* = I-4-αOH)	**(386)**	αOH	Me	Me	H



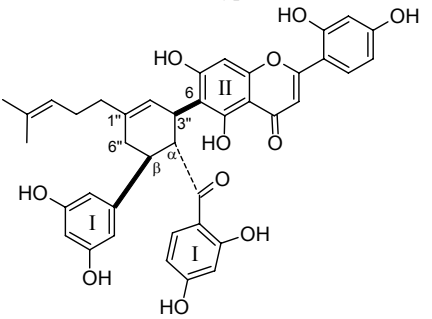
		R	R_1	R_2
Calyflorenone A (II-6-βOMe)	**(387)**	βOMe	Me	Me
Calyflorenone B (II-6-βOMe)	**(388)**	βOMe	H	Me
Calyflorenone C (II-6-βOMe)	**(389)**	βOMe	H	H
Calyflorenone D (abs. config.)	**(390)**	H	H	H
II-6-*epi*-Calyflorenone B (II-6-αOMe)	**(391)**	αOMe	H	Me
II-6-*epi*-Calyflorenone C (II-6-αOMe)	**(392)**	αOMe	H	H

Figure 23. REARRANGED BIFLAVONOIDS: Cleaved Biflavonoids, (I-5,II-7′)-Dihydrochalcone-deoxodihydrochalcone, (I-4,*O*,II-4)-Isopropenyldihydrofuran-biflavan, Doubly-Linked Biflavonoids, Ketalized (I-2,*O*,II-7; I-3,II-8)-Flavanonol-flavan dimers, Ketalized Prenylflavanone-Prenylisoflavan, Rearranged Ketalized Dimers.

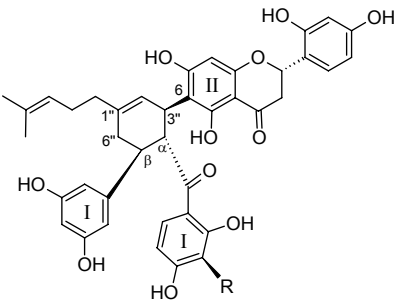
NATURAL DIELS-ALDER-TYPE ADDUCTS

Natural Diels-Alder-type adducts, including substituted cyclohexene derivatives, prenylbiflavonoids (ketalized Diels-Alder-type adducts), and 2-arylbenzofuran-ketalized Diels-Alder adducts, comprise the fourth main group of structures. Substituted cyclohexene derivatives include (I-α,II-3”,I-β,II-6”)-dihydrochalcone-dehydrogeranylflavone (**393**); and (I-α,II-3”,I-β,II-6”)-dihydrochalcone-dehydrogeranylflavanone (**394**, **395**).

(I-α,II-3”,I- β,II-6”)-Dihydrochalcone-dehydrogeranylflavone
Diels-Alder-type adduct



Multicaulisin **(393)**



Sanggenol M **(394)** R

Sanggenon G **(395)** H

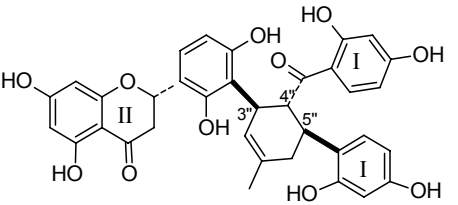
Figure 24**.** NATURAL DIELS-ALDER-TYPE ADDUCTS: (I-α,II-3”,I- β,II-6”)-Dihydrochalcone-dehydrogeranylflavone, (I-α,II-3”,I- β,II-6”)-Dihydrochalcone-dehydrogeranylflavanone.

KETALIZED DIELS-ALDER-TYPE ADDUCTS

Ketalized Diels-Alder-type adducts comprise prenylflavanone-dihydrochalcones (**396**); prenylflavanone-prenyldihydrochalcones (**397**); (prenyl)dihydrochalcone-diprenylflavones (**398-399**); (I-3′,II-3)-biprenylchalcones (**400**); (I-3”,II-α;I-6”,II-β)-prenylchalcone-prenyldihydrochalcone (**401**); (I-3”,II-α;I-6”,II-β)-prenylchalcone-prenyldihydrochalcone (**402**); (I-α,II-3”,I-β,II-6”)-prenyldihydrochalcone-prenylchalcones (**403-407**); (I-3”,II-3′)-dihydrochalcone-prenylchalcone dimer

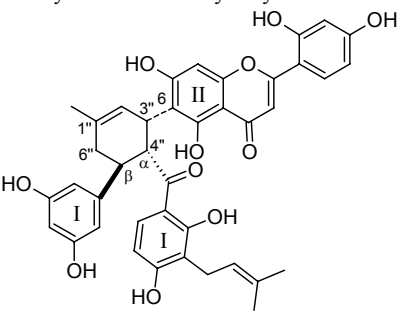
(**408**) a Diels-Alder-type adduct made of a chalcone and a dehydroprenylflavone; (I-3′,II-5;I-4′,*O*,II-1)- prenyldihydrochalcone-prenylchalcone (ketalized Diels-Alder adduct) (**409**); dihydrochalcone-prenylflavonol dimer (**410-411**); a (I-3″,II-8)- prenyldihydrochalcone-prenylflavanone dimer (**412**); (I-α,II-1”,I-β,II-4”)- prenyldihydrochalcone-prenylflavanonol dimers (**413-415**); a (I-3”,II-3′)-prenyldihydrochalcone-prenylflavanonol dimers (**416-417**); and (I-3”,II-α,I-6”,II-β)-prenylflavanonol-prenyldihydrochalcone (**418-421**).

Prenylflavanone-Dihydrochalcone



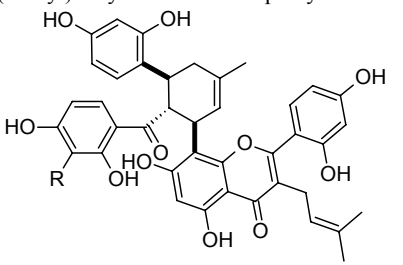
Kuwanon L **(396)**

Prenylflavanone-Prenyldihydrochalcone



Artonin I **(397)**

(Prenyl)Dihydrochalcone-Diprenylflavone

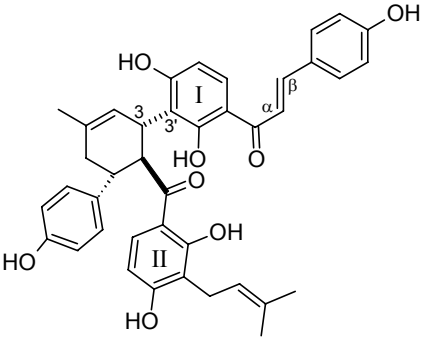


R

Kuwanon G **(398)** H

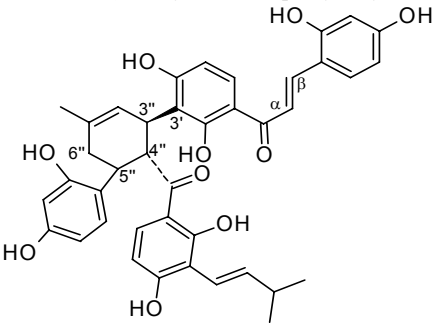
Kuwanon H **(399)**

(I-3′,II-3)-Bi-Prenylchalcone



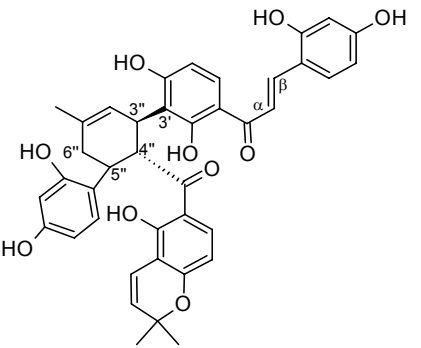
Dorstenone **(400)**

(I-3”,II-α;I-6”,II-β)-Prenylchalcone-prenyldihydrochalcone



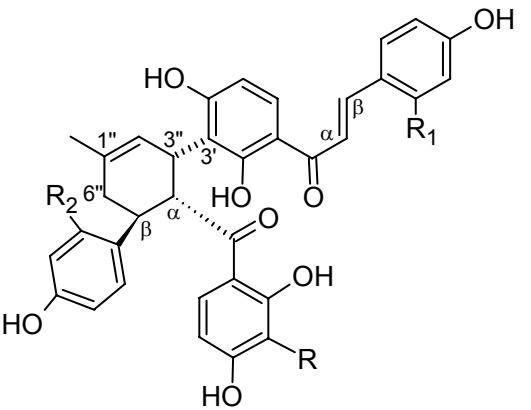
Artonin C **(401)**

(I-3”,II-α;I-6”,II-β)-Prenylchalcone-prenyldihydrochalcone ketalized DielS-Alder adduct



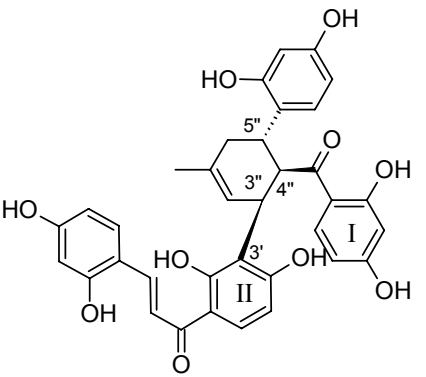
Artonin D **(402)**

(I-α,II-3”,I- β,II-6”)-Prenyldihydrochalcone-prenylchalcone



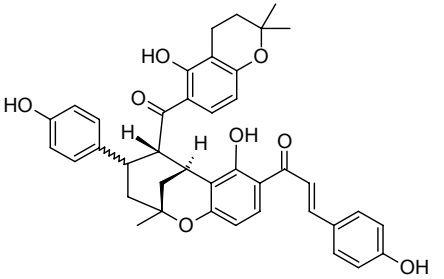
		R	R_1	R_2
Artonin X	**(403)**		H	OH
Kuwanon R	**(404)**		H	OH
Kuwanon J	**(405)**		OH	OH
Kuwanon Q	**(406)**		OH	H
Kuwanon V	**(407)**		H	H

(I-3”,II-3′)-Dihydrochalcone-prenylchalcone dimer
(Diels-Alder type adducts of a chalcone and a dehydroprenylflavone)



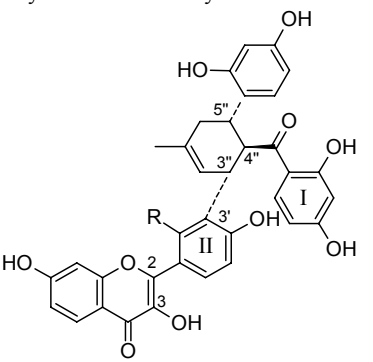
Kuwanon I **(408)**

(I-3′,II-5; I-4′,*O*,II-1)-Prenyldihydrochalcone-prenylchalcone ketalized Diels-Alder adduct



Dorstenia zenkeri prenyldihydrochalcone-prenylchalcone **(409)**

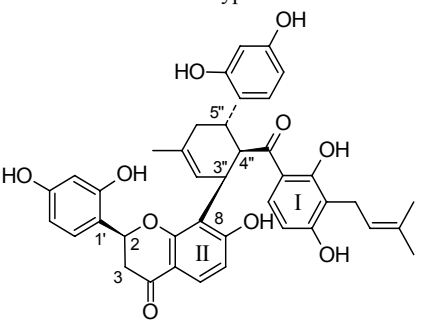
Dihydrochalcone-Prenylflavonol Dimer



		R
Guangsangon G*	**(410)**	H
Guangsangon I*	**(411)**	OH

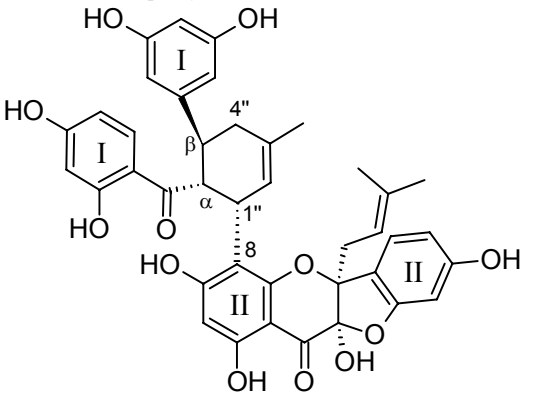
*Equilibrium mixture of conformational isomers in solution

(I-3″,II-8)-Prenyldihydrochalcone-prenylflavanone dimer Diels–Alder type adduct

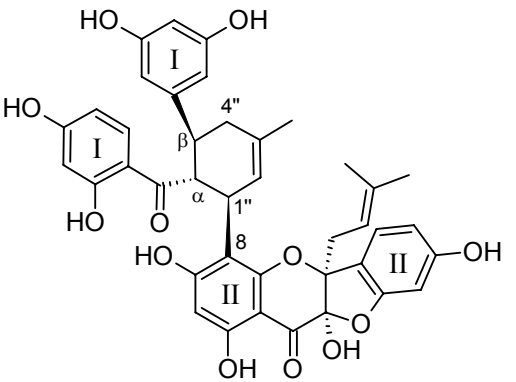


Wittiorumin G **(412)**

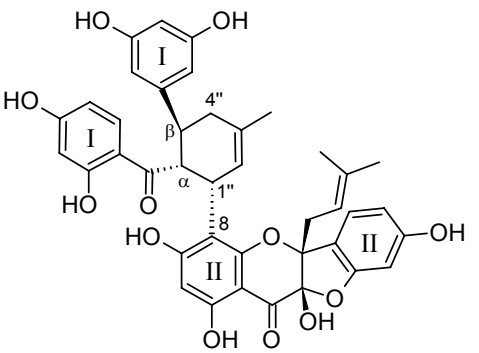
(I-α,II-1",I-β,II-4")-Prenyldihydrochalcone-prenylflavanonol dimers



Cathayanon A (= 2*S*, 3*R*,14*S*, 19*S*, 20*R*) **(413)**

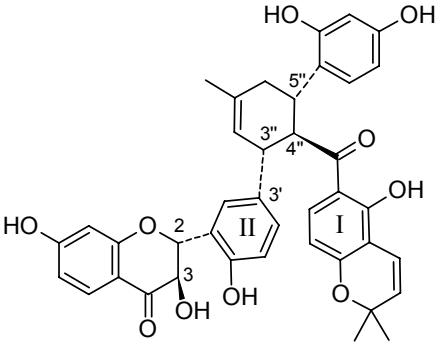


Cathayanon B (= 2*S*, 3*R*, 14*R*, 19*S*, 20*R*) **(414)**



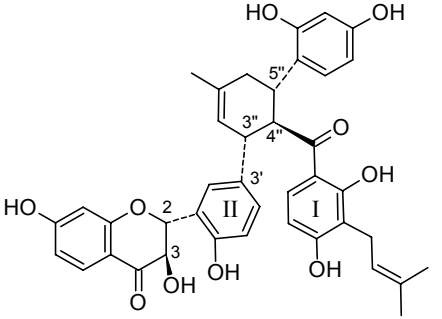
Sanggenon O **(415)**

(I-3”,II-3′)-Prenyldihydrochalcone-prenylflavanonol dimer



Guangsangon F* **(416)**

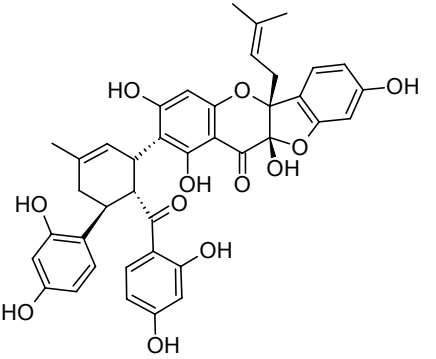
*Equilibrium mixture of conformational isomers in solution



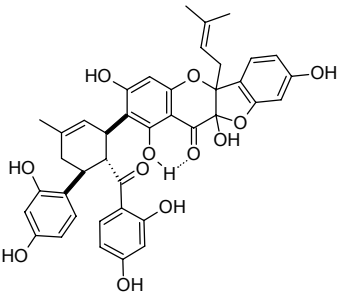
Guangsangon H* **(417)**

*Equilibrium mixture of conformational isomers in solution

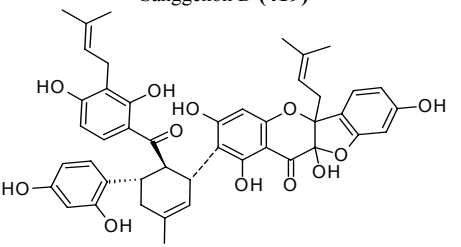
(I-3”,II-α,I-6”,II-β)-Prenylflavanonol-prenyldihydrochalcone dimers



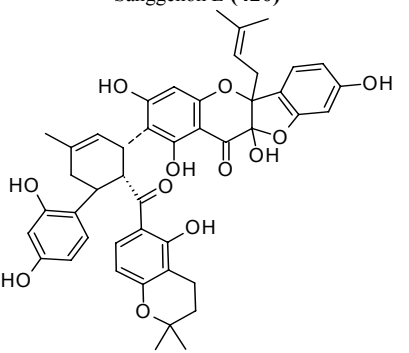
Sanggenon C **(418)**



Sanggenon D **(419)**



Sanggenon E **(420)**



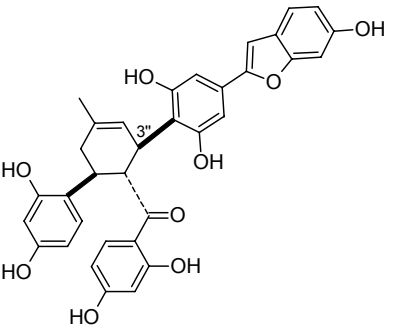
Sanggenon J **(421)**

Figure 25. KETALIZED DIELS-ALDER-TYPE ADDUCTS: Prenylflavanone-Dihydrochalcone, Prenylflavanone-Prenyldihydrochalcone, (Prenyl)Dihydrochalcone-Diprenylflavone, (I-3′,II-3)-Bi-Prenylchalcone, (I-3”,II-α;I-6”,II-β)-Prenylchalcone-prenyldihydrochalcone, (I-3”,II-α;I-6”,II-β)-Prenylchalcone-prenyldihydrochalcone, (I-α,II-3”,I- β,II-6”)-Prenyldihydrochalcone-prenylchalcone, (I-3”,II-3′)-Dihydrochalcone-prenylchalcone dimer, (I-3′,II-5; I-4′,*O*,II-1)-Prenyldihydrochalcone-prenylchalcone, Dihydrochalcone-Prenylflavonol Dimer, (I-3″,II-8)-Prenyldihydrochalcone-prenylflavanone dimer, (I-α,II-1”,I-β,II-4”)-Prenyldihydrochalcone-prenylflavanonol dimers, (I-3”,II-3′)-Prenyldihydrochalcone-prenylflavanonol dimer, (I-3”,II-α,I-6”,II-β)-Prenylflavanonol-prenyldihydrochalcone dimers.

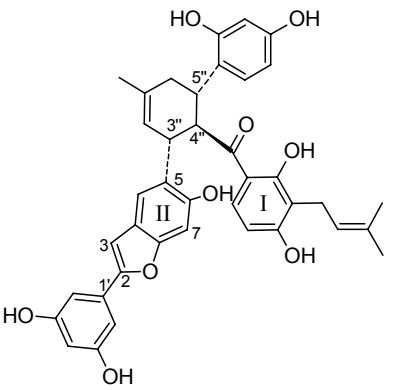
2-ARYLBENZOFURAN-KETALIZED DIELS-ALDER ADDUCTS AND REARRANGED KETALIZED DIELS-ALDER ADDUCTS

2-Arylbenzofuran-ketalized Diels-Alder adducts include (I-3",II-5)-dihydrochalcone-prenyl-2-arylbenzofuran dimers (**422-426**); a (I-α,II-3"; I-β,II-6")-dihydrochalcone-prenyl-2-arylbenzofuran dimer, a Diels-Alder adduct of a dehydroprenyl-2-arylbenzofuran with a chalcone (**427**); a (I-α,II-3"; I-β,II-6")-dihydrochalcone-prenyl-2-arylbenzofuran dimer (**428**); a 2-arylbenzofuran-prenyldihydrochalcone dimer (**429**); 2-arylbenzofuran-ketalized Diels-Alder adducts (**430-431**); Diels-Alder-type adducts of a chalcone and a dehydroprenylstilbene (**432-433**); and stilbene and diprenyldihydrochalcone dimers (**434-438**).

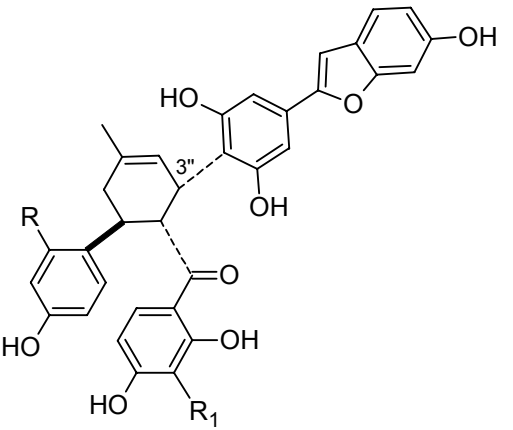
(I-3",II-5)-Dihydrochalcone-prenyl-2-arylbenzofuran dimers



Mulberrofuran J (H-3" α) **(422)**

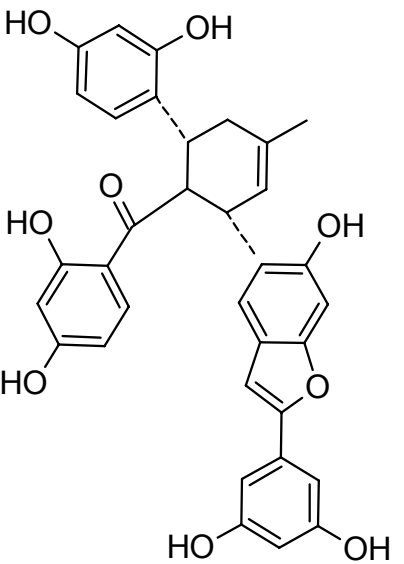


Guangsangon J **(423)**



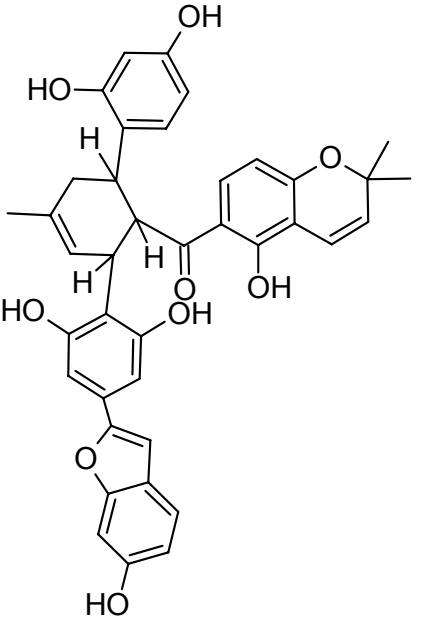
		R	R_1
Mulberrofuran C	**(424)**	OH	H
Chalcomoracin	**(425)**	OH	
Mulberrofuran E	**(426)**	H	

(I-α,II-3”; I-β,II-6”)-Dihydrochalcone-prenyl-2-arylbenzofuran dimer



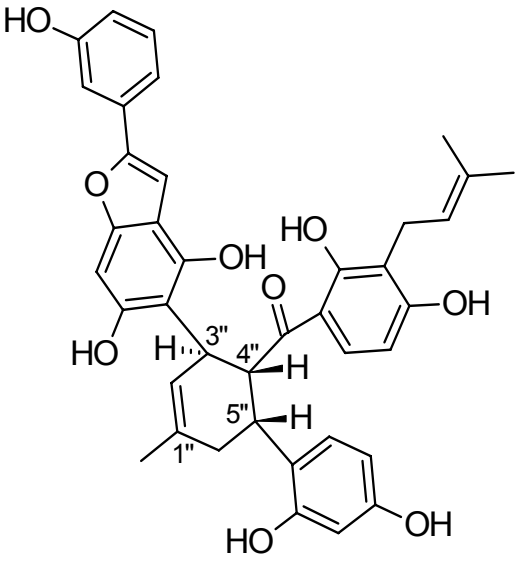
Albafuran C **(427)**

(I-α,II-3"; I-β,II-6")-Dihydrochalcone-prenyl-2-arylbenzofuran dimer



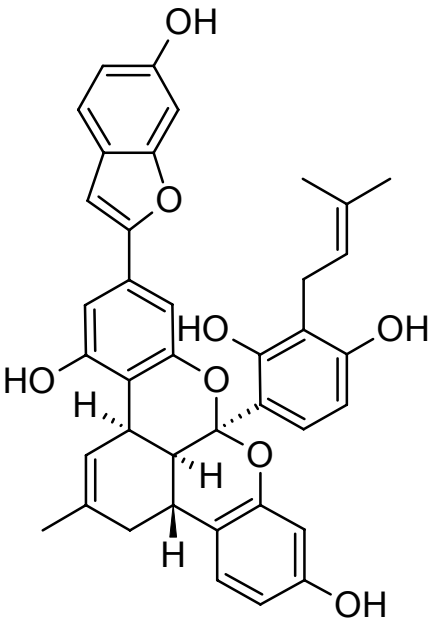
Mulberrofuran O **(428)**

2-Arylbenzofuran-prenyldihydrochalcone dimer

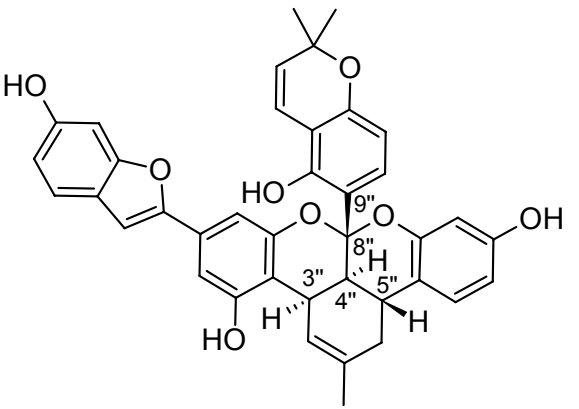


Sorocenol H **(429)**

2-Arylbenzofuran-ketalized Diels-Alder adducts

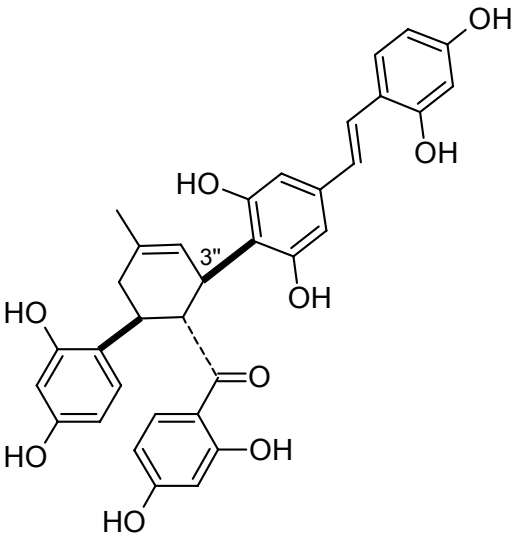


Mulberrofuran F **(430)**



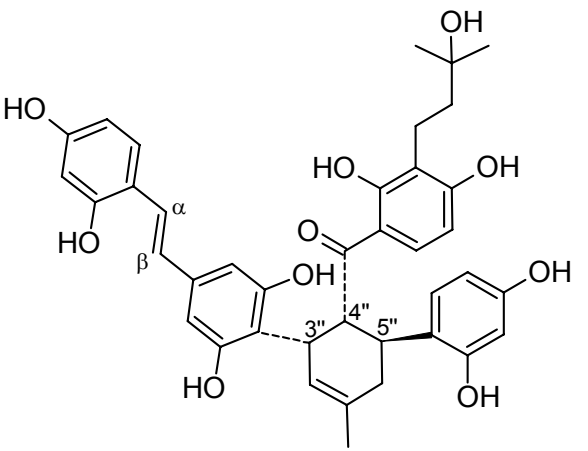
Sorocenol G **(431)**

Diels-Alder type adducts of a chalcone and a dehydroprenylstilbene



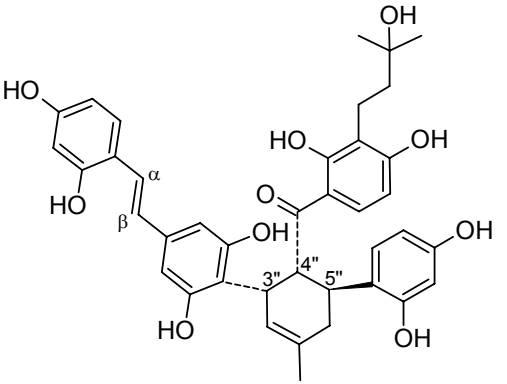
		H-3”
Kuwanon X	**(432)**	α
Kuwanon Y	**(433)**	β

Stilbene and diprenyldihydrochalcone dimmers

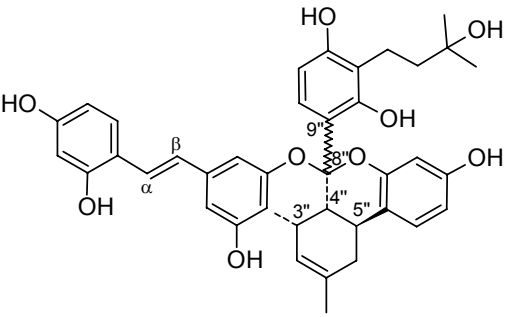


Sorocein M* **(434)**

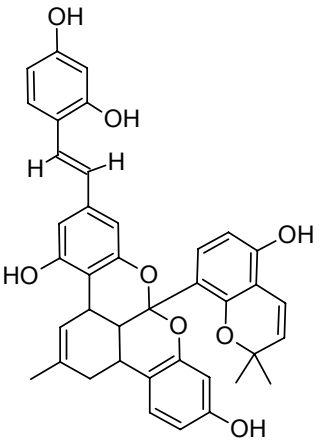
*Addition of one molecule of water to the prenyl group of kuwanol E.



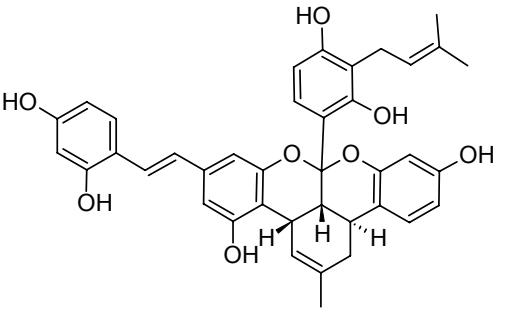
Kuwanol E* **(435)**
* Prenyl derivative of kuwanon Y



Sorocein L* **(436)**
*Ketalized derivative of sorocein M



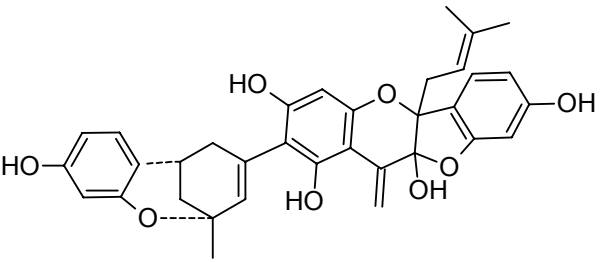
Sorocein A **(437)**



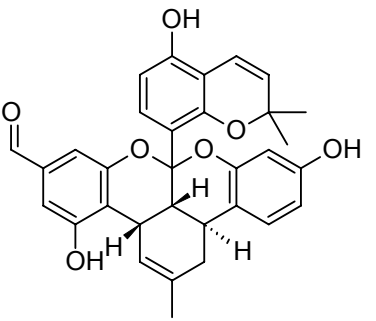
Sorocein I **(438)**

Figure 26. 2-ARYLBENZOFURAN-KETALIZED DIELS-ALDER ADDUCTS: (I-3",II-5)-Dihydrochalcone-prenyl-2-arylbenzofuran dimers, (I-α,II-3"; I-β,II-6")-Dihydrochalcone-prenyl-2-arylbenzofuran dimer, (I-α,II-3"; I-β,II-6")-Dihydrochalcone-prenyl-2-arylbenzofuran dimer, 2-Arylbenzofuran-prenyldihydrochalcone dimer, 2-Arylbenzofuran-ketalized Diels-Alder adducts, Diels-Alder type adducts of a chalcone and a dehydroprenylstilbene, Stilbene and diprenyldihydrochalcone dimers.

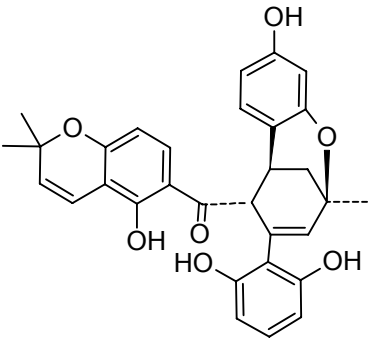
Rearranged ketalized Diels-Alder adducts are schematized in **439**-**441**.



Sanggenon B **(439)**



Soroceal **(440)**



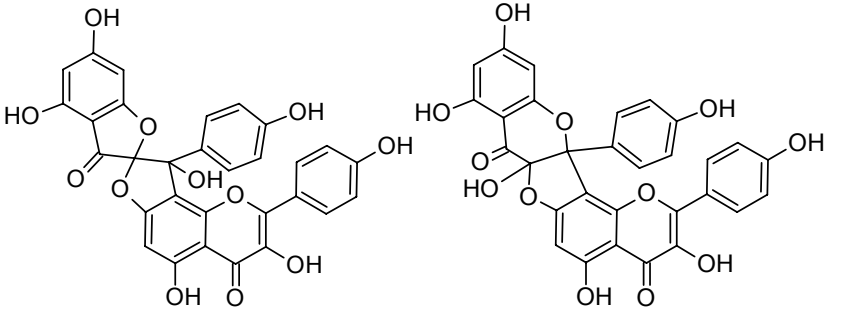
Sorocenol B * **(441)**

*Derived from the Diels-Alder type adduct between a chalcone derivative and a dehydroprenylated resorcinol by the oxidative reaction.

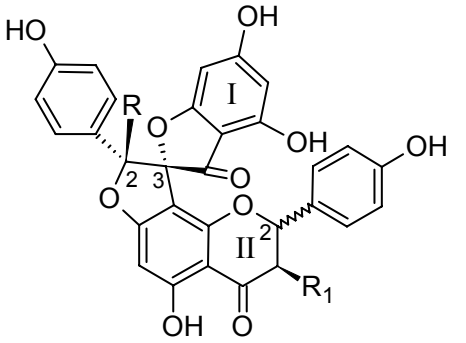
Figure 27. Rearranged ketalized Diels-Alder adducts.

SPIROBIFLAVONOIDS

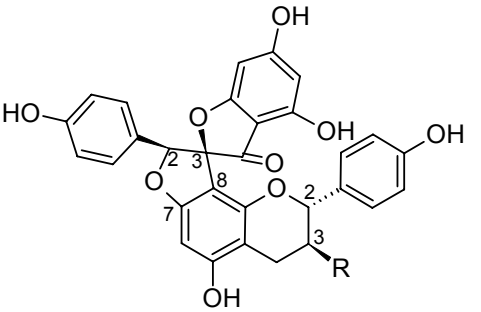
The final main group of structures is composed of spirobiflavonoids (**442-447**); spirobiflavonoids made up of two C_{15} units (**448-449**); phenolic spiro derivatives derived from C_{15} and C_{14} units (**450**); a C_{15} moiety of flavonoid origin and a C_{14}-stilbene substructure linked *via* a γ-lactone ring (attachment of the stilbene derivative to the carbocation intermediate of the oxidation of flavanone to flavanol, and subsequent rearrangement of this intermediate) (**451-452**); and a C_{15} moiety of flavonoid origin and a C_{14}-stilbene substructure linked *via* a γ-lactone ring (**453-455**).



Posible structures for:
VC-15B (Vahlia biflavone) **(442)**

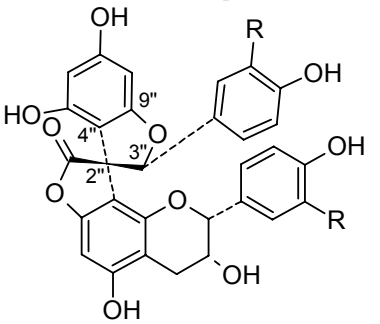


		R	R_1
2”β-Methoxydaphnodorin C (II-2*R*)	**(443)**	OMe	H
2”β-Methoxy-II-2-*epi*-daphnodorin C (II-2*S*)	**(444)**	OMe	H
Genkwanol A (II-2*S*)	**(445)**	H	OH



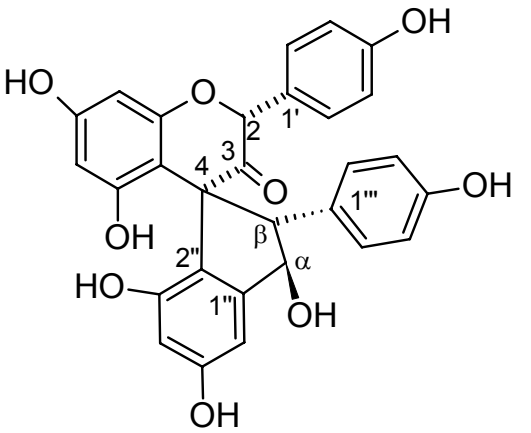
		R
Daphnodorin C	**(446)**	H
Daphnodorin I	**(447)**	OH

Spirobiflavonoids made up of two C_{15} units



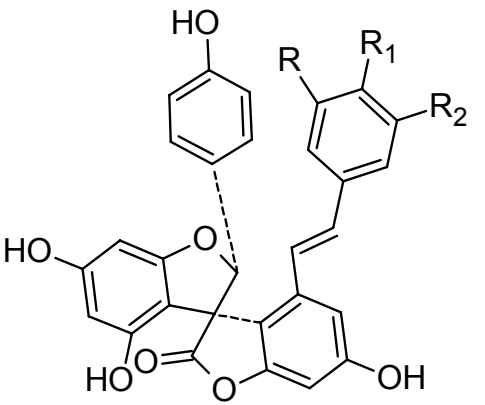
		R
Larixirol	**(448)**	H
Vitisinol	**(449)**	OH

Phenolic Spiro Derivative made up of a C_{15} and a C_{14} units



Yuccaone A **(450)**

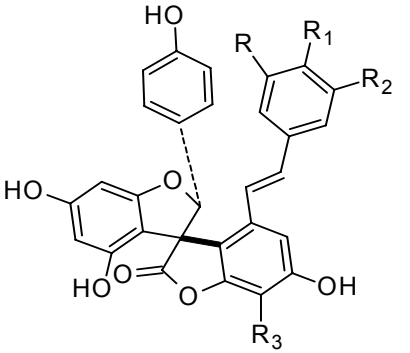
A C_{15} moiety of flavonoid origin and a C_{14}-stilbene substructure linked *via* a γ-lactone ring



		R	R_1	R_2
Yuccaol A *	**(451)**	H	OH	H
Yuccaol D**	**(452)**	OH	OMe	OH

*Flavonoid and resveratrol substructures linked *via* a γ-lactone ring

** Flavonoid and *trans*-3,3',5,5'-tetrahydroxy-4'-methoxystilbene linked *via* a γ-lactone ring



		R	R_1	R_2	R_3
Yuccaol B*	**(453)**	H	OH	H	H
Yuccaol C**	**(454)**	OH	OMe	OH	H
Yuccaol E***	**(455)**	OH	H	OH	OMe

*Flavonoid and resveratrol linked *via* a γ-lactone ring

**Flavonoid and *trans*-3,3',5,5'-tetrahydroxy-4'-methoxystilbene linked *via* a γ-lactone ring

***Flavonoid and *trans*-3,3',5,5'-tetrahydroxy-4'-methoxystilbene linked *via* a γ-lactone ring

Figure 28. SPIROBIFLAVONOIDS: Spirobiflavonoids made up of two C_{15} units, Phenolic Spiro Derivative made up of a C_{15} and a C_{14} units, A C_{15} moiety of flavonoid origin and a C_{14}-stilbene substructure linked *via* a γ-lactone ring, A C_{15} moiety of flavonoid origin and a C_{14}-stilbene substructure linked *via* a γ-lactone ring.

The main purpose of structure analysis is that in the search for new powerful bioactive compounds it is incredibly valuable to be able to predict in advance the biological activity of candidates for synthesis. These predictions are achievable through structure-activity studies.

STRUCTURE-ACTIVITY STUDIES OF BIFLAVONOIDS

The structure-activity relationships (SAR) are the traditional practices of medicinal chemistry that try to associate the effect or potency (i.e. activity) of bioactive chemical compounds to a particular attribute of the chemical structure.

This enables the identification and determination of the chemical groups responsible for evoking a target biological effect in the organism. This method was later refined to establish mathematical relationships between chemical

structure and biological activity, known as quantitative structure-activity relationships (QSAR).

SAR studies are usually based on a small set of molecules with an important known activity measured under similar conditions. Structural features are calculated by a geometry optimization of the compounds. Then a qualitative analysis is carried out with the aim of linking the known measured biological activity to any of the structural features. As an example of a SAR study of biflavonoids Pan *et al.* [13] reported a SAR and binding mechanism study of three biflavones, amentoflavone (**1**) (AMF1), II-4′-*O*-methylamentoflavone (4‴-methylamentoflavone) (**6**) (AMF2) and 7",4‴-dimethylamentoflavone (II-7,4′-di-*O*-methyl-amentoflavone) (**12a**) (AMF3). The compounds were isolated from *Taxodium mucronatum* as novel natural inhibitors of human cathepsin B (CatB), which is a member of the papain superfamily of cysteine proteases and has been implicated in the pathology of many diseases, including arthritis and cancer. All three compounds showed strong inhibitory activities with IC_{50} values of 1.75, 1.68 and 0.55 μM, respectively. The method of Density Functional Theory (DFT) was applied to optimize the geometry of the structures of the three biflavonoids. Through the geometry and electronic structure analysis of the biflavonoids, it was observed that the CH_3 substituent at 7″ and 4‴ positions could not vary the difference in the geometry structure significantly, but increased the electron density of A-ring, HOMO energy, hydrophobic property, and improved inhibitory activity.

Since this sort of study does not require many experimental data it is possible to apply it to the biflavonoid family with the aim of finding relevant links between structure and biological activities.

QUANTITATIVE-STRUCTURE ACTIVITY RELATIONSHIPS OF BIFLAVONOIDS

Studies using the theory of Quantitative Structure-Activity Relationships (QSAR) are intended to suggest mathematical models capable of estimating the relevant properties of interest, especially when those cannot be experimentally determined for some reason. Such studies rely on the basic assumption that the structure of a compound completely determines its properties, which can therefore be translated into the so-called molecular descriptors. These parameters are calculated through mathematical formulae derived from several theories, such as Chemical Graph Theory, Information

Theory, Quantum Mechanics, etc.[14, 15] QSAR model then has the ability to predict an activity using only structural information of the compound, therefore, the activity can be calculated for any possible structure, including compounds not found in nature and not yet synthesized. Consequently, this type of study is generally accepted as a remedy for overcoming the lack of experimental data on complex chemical phenomena.[16] Accordingly, there is a permanently renewed interest focused on the development of such kind of predictive techniques.[14, 15, 17, 18]

Currently there are no QSAR studies performed exclusively in the biflavonoid group. The main reason is that the number of bioactivities measured under the same conditions for this family of compounds is not high enough to perform such studies. It is expected that in the near future when more experimental information is available this kind of studies will be feasible providing powerful tools for finding new bioactive biflavonoids.

Nevertheless, there are some QSAR studies that include biflavonoids as a mixture of flavonoids and biflavonoids to increase the number of data. As examples Farkas *et al.*[19] have reported a QSAR study based on 36 different types of flavonoids, including 2 biflavonoids, to predict their antioxidant activity, which is characterized by the ability to inhibit heat-induced oxidation in a model-system of β-carotene-linoleic acid.[20] In our laboratory[17] we developed a predictive model of a very important property of flavonoids, which is the inhibition (IC_{50}) of neuraminidase (NA) of H1N1 influenza virus using a set of 25 different flavonoids, including 3 biflavonoids.[21-25] Experimental influenza virus (H1N1) NA inhibitory activity of the data set was measured using a standard fluorimetric assay.[26] Even though these studies are very useful, prediction of the bioactivity based on a set of biflavonoids alone will be more reliable, usually QSAR studies based on compounds of the same family give models with higher predictive ability.

Chapter 4

DISTRIBUTION

The natural sources, biological activities, and traditional uses of all biflavonoids mentioned above are compressed in Table 1. In this way a current picture of their distribution is achieved, thus providing an important tool for future biflavonoid studies. The structures are mainly distributed in some species of Angiosperms (monocots and dicots), Gymnosperms, ferns (Pteridophyta), and mosses (Bryophyta).

Table 1. Occurrence of biflavonoids in fruits, vegetables and plants; along with their corresponding bioactivity and traditional use

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
ANGIOSPERMAE			
DICOTS			
Adoxaceae (The genus *Viburnum* was formerly included in the family Caprifoliaceae)			
Viburnum cotinifolium D. Don. (leaves)	(I-6,*O*,II-8)-Biapigenin (**255**).		Muhaisen et al., 2002[123].
Viburnum jucundum Morton (aerial parts)	Amentoflavone (**1**).	Amentoflavone is an agonist of the central $GABA_A$-R benzodiazepine receptor, hence exhibiting ***anticonvulsant and anxiolytic activity***.	Rios et al., 2001[124].
Viburnum pichinchense Benth. (leaves)	Amentoflavone (**1**).	Amentoflavone showed to be a potent inhibitor of nucleotide phosphodiesterase and a cyclooxygenase inhibitor. Also showed ***antifungal activity***.	Lobstein et al., 2003[125].
Anacardiaceae			
Anacardium occidentale L. (leaves). Cashew plant.	Agathisflavone (**100**).	*Cytotoxic activity*. An ethanolic extract elicited lymphopenia in rats. and *induced apoptosis* in Jurkat cells. Agathisflavone (**100**) showed a high anti-proliferative effect in Jurkat cells (IC_{50} = 4.45 μM). Agathisflavone *induced apoptosis* in Jurkat cells.	Konan et al., 2010 [45].

Plant (Part of the plant)	**Compounds**	**Bioactivity. Traditional uses.**	**Author, References**
Campnosperma panamense Standl. (leaves)	Lanaroflavone (**249**).	***Antiprotozoal activity***: ***antimalarial and leishmanicidal activities***, but inactive against Chagas disease vector, *Trypanosoma cruzi*.	Weniger et al., 2001[126], 2004 [70], 2006[86].
Cotinus coggygria Scop. (whole plant)	***Biaurone***: Disulfuretin (**259**).	***Antioxidant properties***.	Westenburg et al., 2000[127].
Myracrodruon urundeuva Fr.All. (syn. *Astronium urundeuva* Engl.) (heartwood)	Urundeuvine A (**325**); urundeuvine B (**324**); urundeuvine C (**326**); matosine (**328**).	Traditional medicinal plant of Brazil. ***Analgesic and antiinflammatory effects.***	Bandeira et al., 2003[128]; Viana et al., 2003[129].
Pistacia chinensis Bunge (twigs) (The genus *Pistacia* usually is included in this family, but has sometimes been placed in the family Pistaciaceae).	***(I-3,II-3)-Bineoflavonoids***: (I-3*R*,II-3*S*)-*Bis*-4-(4′-hydroxy)phenyl-7-hydroxy-3,4-dihydrocoumarin (**282**); (I-3*S*,II-3*S*)-*bis*-4-(4′-hydroxy)phenyl-7-hydroxy-3,4-dihydrocoumarin (**283**).	***Estrogen-like activity***.	Nishimura et al., 2000[130].
Rhus alata Thunb. (leaves)	Amentoflavone (**1**); agathisflavone (**100**); robustaflavone (**64**); hinokiflavone (**235**); I-5,7,4′,II-5,7,4′-hexa-*O*-methylagathisflavone (**110**); I-5,7,4′,II-5,7,4′-hexa-*O*-methylrobustaflavone (**71**).	Hinokiflavone inhibited the interleukin-1β-induced procoagulant activity of adherent human monocytes.	Parveen and Khan, 1987[131]; Lale et al., 1996[121].
Rhus dentata Thunb. (leaves)	***Biflavone***: Agathisflavone (**100**).	Extracts of *Rhus dentata* were not as active as those of *Rhus pyroides* in the affinity for the $GABA_A$/ benzodiazepine receptor.	Svenningsen et al., 2006[132].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
*Rhus pentheri*A. Zahlbr. (leaves)	***Biflavone***: Agathisflavone (**100**).	Extracts of *Rhus pentheri* were not as active as that of *Rhus pyroides* in the affinity for the $GABA_A$/ benzodiazepine receptor.	Svenningsen et al., 2006[132].
Rhus pyroides Burch. (syn. *Rhus tridentata*) (leaves)	***Biflavones***: Amentoflavone (**1**); agathisflavone (**100**).	Traditionally used in South Africa for the treatment of epilepsy. ***Affinity for the $GABA_A$/ benzodiazepine receptor.***	Svenningsen et al., 2006[132].
Rhus pyroides Burch. (syn. *Rhus tridentata*) (root bark)	***Bichalcones***: Rhuschalcone I (**294**); rhuschalcone II (**295**); rhuschalcone III (**296**); rhuschalcone IV (**297**); rhuschalcone V (**298**); rhuschalcone VI (**292**).	***Insect antifeedant, cytotoxic and antiproliferative activities.*** All bichalcones exhibited selective ***cytotoxic activity*** against the HT29 and HCT-116 colon tumor cell lines.	Abegaz, 2002[133]; Mdee et al., 2003[134].
Rhus pyroides Burch. (twigs)	***Bichalcone***: Rhuschalcone I (**294**).		Masesane et al., 2000[135].
Rhus retinorrhoea Steud. ex Olive (leaves)	***Biflavanone***: (I-2*S*,II-2*S*)-I-7,II-7-di-*O*-methyl-I-2,3,II-2,3-tetrahydroamento-flavone (**56**).	Used in traditional medicine because of the antimicrobial and cytotoxic properties. ***Insecticidal activities against aphids.*** Moderate ***antimalarial activity*** against *Plasmodium falciparum* (W2 Clone); weak activity against *P. falciparum* (D6 Clone).	Ahmed et al., 2001[68].

Plant (Part of the plant)	**Compounds**	**Bioactivity. Traditional uses.**	**Author, References**
Rhus succedanea L. (drupes)	Hinokiflavone (**235**); amentoflavone (**1**); agathisflavone (**100**); robustaflavone (**64**); cupressuflavone (**86**); rhusflavone (**112**); volkensiflavone (**154**); I-5,7,4′,II-5,7,4′-hexa-*O*-methylvolkensiflavone (**158**); spicataside (**156**); spicataside I-5,7,4`,II-5,7,4′-nona-*O*-acetate (**157**); morelloflavone (**159**); I-5,7,4′,II-5,7,3′,4′-hepta-*O*-methylmorelloflavone (**161**); morelloflavone I-5,7,4′,II-5,7,3′,4′-hepta-*O*-acetate (**163**); rhusflavanone (**113**); rhusflavanone I-5,7,4′,II-5,7,4′-hexa-*O*-acetate (**114**); succedaneaflavone (**117**); succedaneaflavone I-5,7,4′,II-5,7,4′-hexa-*O*-acetate (**118**); GB-1a (**167**); GB-1a II-7-*O*-β-glucopyranoside (**169**); I-5,7,4′,II-5,7,4′-hexa-*O*-methyl-GB-1a (**168**); GB-2a (**172**); neorhusflavanone (**99**).	***Antiviral activities***, including potent inhibition of hepatitis B virus (HBV) replication, influenza A and influenza B, VZV, measles, HSV-1 and HSV-2 viruses. ***Cytotoxic activity.*** ***Anti-HIV activity***: agathisflavone, robustaflavone and hinokiflavone have shown HIV-1 reverse transcriptase activity. Hexa-*O*-methylvolkensiflavone showed ***antituberculosis activity***.	Lin et al., 1989[38], 1997[82], 1999[136]; Zembower et al., 1998[80]; Lin et al., 2001[67].
Rhus tripartitum (Ucria) DC (aerial parts: leaves, stems, and fruits)	***(I-6,O,II-7)-Biflavanone:*** Masazinoflavanone (**254**). ***Bi-isoflavonoid***: Calodenone (**350**).	***Anti-inflammatory activity.***	Mahjoub et al., 2005[137], 2010[138].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Schinus terebinthifolius Raddi (drupes) (stem bark)	Amentoflavone (**1**); II-2.3-dihydroamentoflavone (**44**); I-2,3,II-2,3-tetrahydroamentoflavone (**47**).	The extract of stem bark is widely used by population of northeastern Brazil as an anti-inflammatory agent and to cicatrize wounds. ***Anti-inflammatory and antifungal activity. Mutagenic activity.***	Skopp and Schwenker, 1986[139]; Furones Mourelle et al., 1993[140]; Ribeiro Dantas de Carvalho et al., 2003[141]; Braga et al., 2007[142].
Semecarpus anacardium L. (nuts)	(***I-3',II-8-biflavanones:*** Nallaflavone (**58**); semecarpuflavanone (**49**); galluflavanone (**51**); jeediflavanone (**50**); semecarpetin (**57**); anacarduflavanone (**55**); biflavanones A_1, A_2, B (*O*-methyl derivatives of I-3′,II-8-binaringenin (**47**); biflavanone C (*O*-methyl derivative of I-3′,II-8-biliquiritigenin (**46**); I-2,3-II-2,3-tetrahydrorobustaflavone (**83**); I-2,3-II-2,3-tetrahydroamentoflavone (**47**). Amentoflavone (leaves) (**1**).	Many applications in the Ayurvedic and Siddha systems of medicine. Applications in Indian medicine in the treatment of gout, rheumatic pain and cancer. Nut extract preparations are effective against arthritis, tumours, infections etc. and are not toxic. ***Anti-cancer, anti-inflammatory, antispermatogenic, neuroprotective, antiatherogenic, hypoglycemic, and fungistatic activities***. Nut preparations were used for treatment of angina, hypertension, and myocardial dysfunctions. A rise in glycolytic enzyme activities and a simultaneous fall in gluconeogenic enzyme activities were found in breast carcinoma in rats;	Prakasa Rao et al., 1973[143]; Murthy, 1983[144, 145], 1984[146], 1985[147], 1988[148], 1992[149]; Premalatha, 2000[150]; Selvam and Jachak, 2004[28]; Mathivadhani et al., 2006[151]; Majumdar et al., 2008[152];

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
		nut extract administration returned these enzyme activities to the respective activities. Protective effect in maintaining the glutathione redox status by restoring the associated enzymes against oxidative stress in experimental breast carcinoma.	Basheeruddin Asdaq and Prasannakumar, 2009[153].
Semecarpus anacardium L. (seed)	I-2,3-II-2,3-Tetrahydroamentoflavone (**47**).	*Widely used in Indian traditional medicine; Ayurveda and Sidha, for treatment of inflammatory disorders and gout*. Tetrahydroamentoflavone (**47**) is a potent xanthine oxidase inhibitor (IC_{50} = 92 nM; Ki = 0.982 μM) .	Arimboor et al., 2011[107].
Annonaceae			
Goniothalamus gardneri Hook. f. & Thoms. (aerial parts)	**(I-α,II-α; I-β,II-β)-Bidihydrochalcone:** *rel*-(1β,2α)-Di-(2,4-dihydroxy-6-methoxy)benzoyl-(3β,4α)-di-(4-methoxy)phenyl-cyclobutane (**330**).	Used in traditional medicine as post-partum protective remedies, abortifacients and insects repellents.	Seidel et al., 2000[154].
Aristolochiaceae			
Aristolochia contorta Bge. (fruits)	***(I-3',II-8)-Flavone-flavonols***: II-3-Hydroxyamentoflavone (**28**); I-7-O-methyl-II-3-hydroxyamentoflavone (**30**); ***(I-3',II-8)-Flavone-flavanonol***: (±)-II-3-Hydroxy-II-2*R*,3*R*-dihydroamento-flavone (**45**).		Chen et al., 2005[155]; Yu et al., 2005[156].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Aristolochia ridicula H.B.K. (stems)	***(I-3,II-6)-Biflavones***: I-7,4′-Di-*O*-methyl-apigeninyl-(I-3,II-6)-II-3′-methoxy-apigenin (**148**); ridiculuflavone C (**149**). ***(I-6,O,II-α; I-7,II-β)-Flavone-chalcones:*** I-5-Hydroxy-I-4′-methoxyflavone (I-6,*O*,II-α; I-7,II-β)-II-4,2′,4′-trihydroxy-II-3,6′-dimethoxychalcone (**312**); I-5,4′-dihydroxy-I-3′-methoxyflavone (I-6,*O*,II-α; I-7,II-β)-II-2′,4′-dihydroxy-II-4,6′-dimethoxychalcone (**313**); I-5-hydroxy-I-4′-methoxyflavone (I-6,*O*,II-α; I-7,II-β)-II-3,2′,4′-trihydroxy-II-4,6′-dimethoxychalcone (**314**). ***(I-6,O,II-β; I-7,II-α)-Flavone-chalcone:*** I-5,4′-Dihydroxy-I-3′-methoxyflavone (I-6,*O*,II-β;I-7,II-α)-II-2′,4′-dihydroxy-II-4,6′-dimethoxychalcone (**315**). ***(I-β,O,II-7; I-α, II-6)-Chalcone-flavone dimer:*** Ridiculuflavonylchalcone B (**310**).	*Used in Brazilian traditional medicine as anti-inflammatory, antiasthmatic and abortifacient, as well as an antidote for snakebite, to cure several types of cancer.*	Carneiro et al., 2000[157]; Machado and Lopes, 2010[158].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Aristolochia ridicula H.B.K. (leaves)	***(I-3,II-6)-Biflavones***: Ridiculuflavone A (**145**); ridiculuflavone B (**146**); ridiculuflavone C (**149**); ridiculuflavone D (**147**); ***(I-β,O,II-7; I-α, II-6)-Chalcone-flavone dimers:*** Ridiculuflavonylchalcone B (**310**).	Used in Brazilian traditional medicine as anti-inflammatory, antiasthmatic and abortifacient, as well as an antidote for snakebite, to cure several types of cancer.	Machado and Lopes, 2005[159], 2008[160].
Asteraceae (or Compositae)			
***Saussurea eopygmaea* Hand.-Mazz.**	I-4′,II-4′-Di-*O*-methylrobustaflavone (**69**).	Tibetan medicine. *Antitumor activity*.	Zhang et al., 2011[161].
Boraginaceae			
Cordia goetzei Gürke (stem bark)	***Bidihydrochalcones (tetrahydrofuro[3,2-c]benzopyran and tetrasubstituted tetrahydrofuran derivatives):*** Cordigone (**335**); cordigol (**323**).	***Antifungal bichalcones***.	Marston et al., 1988[162].
Capparaceae (or Capparidaceae)			
Capparis spinosa L. (fuits)	Isoginkgetin (**13**); ginkgetin (**7**).	*Widely used as food and folk medicine in the Mediterranean basin and in central and west Asia*. *Anti-inflammatory effects* were evaluated by secreted placental alkaline phosphatase (SEAP) reporter assay, which was designed to measure NF-κB activation. Isoginkgetin (**13**) and ginkgetin (**7**) showed inhibitory effects in initial screen at 20 μM, while the effect of ginkgetin was much greater than that of isoginkgetin.	Zhou et al., 2011[163].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Caprifoliaceae		In a dose-response experiment, the IC_{50} value of ginkgetin (**7**) was estimated at 7.5 μM, suggesting it could be a strong NF-κB inhibitor and worthy of study *in vivo*.	
Lonicera japonica Thunb. (= *Lonicera chinensis* Wats, *Lonicera brachypoda* DC. var. *repens* Sieb.) (leaves)	***(I-4',O,II-4')-Biflavones***: Loniflavone (**233**); I-3′-*O*-methylloniflavone (**234**). ***(I-3',O,II-4')-Biflavones:*** Ochnaflavone (**218**); I-4′-*O*-methylochnaflavone (**219**).	***Neuroprotective effects*** on oxidative stress-induced and amyloid β peptide-induced cell death in neuronal cells. ***Ochnaflavone showed inhibitory activity against phospholipase A_2 (PLA2).***	Kang et al., 2005[164]; Kumar et al., 2005[165]; Chen et al., 2006[166].
Chloranthaceae			
Sarcandra hainanensis (Pei) Swamy et Bailey (whole plants)	Two flavan-chalcone dimers; two flavan-flavanone dimers.	The flavan-chalcone dimers showed HIV-1 integrase inhibition activities (IC_{50} = 18.05 and 25.27 μM, respectively).	Cao et al., 2009[167], 2010[168].
Clusiaceae or Guttiferae Juss. (nom. alt. et cons.)			
Calophyllum brasiliense Camb. (leaves) (stem bark) (heartwood)	Amentoflavone (**1**); podocarpusflavone A (**6**).	Some species are used to treat gastric ulcers, infections, pain, tumors, and inflammatory processes. Preparations from stem bark are popular remedies for the treatment of chronic ulcers.	da Silva et al., 2001[169]; Abe et al., 2004[170]; Reyes-Chilpa et al., 2008[171];

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
		Cytotoxic activity against several cell lines, inhibition of HIV-1 reverse transcriptase, antisecretory and cytoprotective properties, antinociceptive, molluscicidal and antimicrobial effects. ***Immunostimulatory activity***. Crude extract and hexane fraction of *C. brasiliense* revealed a significant *in vitro* and *in vivo* ***leishmanicide activity*** (leaves). Leaves also showed ***analgesic activity***. ***Antiulcer activity*** of stem barks was due, in part, to its anti-*Helicobacter pylori* action. ***Trypanocidal activity*** (heartwood).	Cechinel Filho, et al., 2009[172]; Souza et al., 2009[173]; Philippi et al., 2010[174]; Honda et al., 2010[175].
Calophyllum inophylloide King (leaves and heartwood)	Pyranoamentoflavone (**59**); amentoflavone (**1**).	Some *Calophyllum* species are used to treat a large number of diseases, including gastric ulcers, infections, pain, tumors, and inflammatory processes. ***Cytotoxic activity*** against several cell lines, inhibition of HIV-1 reverse transcriptase, antisecretory and cytoprotective properties, antinociceptive, molluscicidal and antimicrobial effects.	Goh et al., 1992[176]; Su et al., 2008[177]; Cechinel Filho, et al., 2009[172].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Calophyllum panciflorum A.C. Smith (stem bark)	***GB biflavonoids: (I-3,II-8)-biflavanones:*** GB_{1a} (**167**); GB_{2a} (**172**). ***(I-3,II-8)-biflavanone-flavanonols:*** GB_1 (**176**); GB_2 (**177**). ***(I-3,II-8)-Flavanone-chromone:*** GD-IV (**184**). ***(I-3,II-8)-flavanone-flavones:*** Pancibiflavonol (**165**); garcinianin (**166**).	Pancibiflavonol has ***antitumour-promoting activity***. ***Antibacterial activity.***	Ito et al., 1999[178]; Han et al., 2005[74]; Su et al., 2008[177]; Cechinel Filho et al., 2009[172].
Calophyllum pinetorum Bisse. (stem bark and leaves)	Amentoflavone (**1**).		Alarcón et al., 2008[179].
Calophyllum venulosum Zoll. (leaves)	I-7-*O*-Methylpyranoamentoflavone (**60**); I-4′-*O*-methylpyranoamentoflavone (**61**); II-4′-*O*-methylpyranoamentoflavone (**62**); I-7,4′-di-*O*-methylpyranoamentoflavone (**63**); II-6-isoprenylamentoflavone (**26**); II-6-(2-hydroxy)-isopentenylamentoflavone (**27**).	***Cytotoxic and anti-HIVactivity***, ***cytoprotective properties, antisecretory properties, antinociceptive effects***.	Cao et al., 1997[180], 2001[181]; Cechinel Filho et al., 2009[172].
Clusia columnaris Engl. (branches with leaves and fruits)	***GB biflavonoids:*** GB_{1a} (**167**); GB_{2a} (**172**); GB_{2a}-II-7-*O*-β-*D*-glucopyranoside (**174**); volkensiflavone (**154**); spicataside (volkensiflavone II-7-*O*-glucoside) (**156**); fukugetin (**159**); fukugiside (**162**).		Compagnone et al., 2008[182].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Garcinia dulcis (Roxb.) Kurz. (fruits)	Morelloflavone (**159**).	***Antioxidation effects*** in both Fe^{2+}-mediated and non-metal induced human low-density lipoprotein (LDL) oxidations. Morelloflavone has shown ***antioxidative, antiviral, and anti-inflammatory properties***. Morelloflavone (**159**) showed hypocholesterolemic activity, and *in vitro* inhibition of HMG-CoA reductase, the rate-limiting enzyme of the cholesterol biosynthetic pathway; **159** inhibited the enzyme activity by competing with HMG-CoA, whereas it was non-competitive towards NADPH. The inhibition constants (K_i) with respect to HMG-CoA and NADPH were 80.87 ± 0.06 μm and 103 ± 0.07 μm, respectively. Both flavonoid subunits of this compound, naringenin and luteolin, equally competed with HMG-CoA, and were also non-competitive with NADPH. Therefore, each subunit of **159** would occupied the active site of the enzyme, thereby blocking access of its substrate.	Hutadilok-Towatana et al., 2007[117]; Pang et al., 2009[49]; Pinkaew et al., 2009[183]; Tuansulong et al., 2011[184].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Garcinia gardneriana (Planch. & Triana) Zappi (leaves)	Fukugetin (or morelloflavone) (**159**); 13-naringenin-II 8-eriodictyol (GB_{2a}) (**172**).	Used in folk medicine of Brazil to treat inflammation, pain, and urinary tract and other infections. Important ***anti-inflammatory effects*** of hydroethanolic extract (HEGG) and both biflavonoids through interaction with different intracellular signaling pathways, without interfering with the formation of arachidonic acid metabolites.	Castardo et al., 2008[104].
Garcinia gardneriana (Planch. & Triana) Zappi (leaves, bark and seeds)	Fukugetin (or morelloflavone) (**159**); 13-naringenin-II 8-eriodictyol (GB_{2a}) (**172**).	Popularly used in skin disorders. *Anti-inflammatory effect of leaves for topical usage;* **159** *and* **172** *were responsible for this effect*. The topical application of the leaf extract reduced (70 ± 3%, and ID_{50} 0.33 mg/ear) ear oedema, while the seed (51 ± 5%) and wood (60 ± 12%) extracts were less effective. The leaf extract diminished the myeloperoxidase (MPO) activity in 64 ± 13%, which suggests the inhibition of leucocyte infiltration that was confirmed by histological analysis. Compounds **159** and **172** reduced ear oedema, (ID_{50} = 0.18 and 0.22 mg/ear, respectively), besides inhibited MPO activity (52 ± 6% and 64 ± 5%, respectively).	Otuki et al., 2011[185].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
		The leaf extract, **159** and **172** topically applied to the ear treated with croton oil reduced 52 ± 15%, 63 ± 17% and 83 ± 4%, respectively, the production of reactive oxygen species of the skin.	
Garcinia intermedia Pittier Hammel (leaves)	***Biflavones***: Podocarpusflavone A (**6**); amentoflavone (**1**).	***Trypanocidal activity*** against epimastigotes of *Trypanosoma cruzi*, the etiologic agent of Chagas' disease.	Abe et al., 2004[170].
Garcinia kola Heckel (seeds)	3",4',4'",5,5",7,7"-Heptahydroxy-3,8-biflavanone (GB_1) (**176**); GB_2 (**177**); Kolaviron (KV) [a mixture of (C-3,C-8)-linked biflavonoids; GB_1 (**177**) + GB_2 (**177**) + kolaflavanone (**178**)].	Traditional medicine in the West and Central African sub-region. Poison antidote. Seeds have been used in traditional African medicine to treat diabetes. ***Antioxidant and antihepatotoxic properties.*** KV showed ***antioxidant, hepatoprotective and hypoglycaemic effects.*** KV ***inhibited rat lens aldose reductase*** (RLAR) ***activity***, had ***anti-diabetic and hypolipidaemic effects***, and showed ***immunomodulatory and immunorestorative properties.***	Maurice, 1982[186]; Iwu et al., 1987[187], 1990[101]; Farombi et al., 2000[188]; Adefule-Ositelu et al., 2004[189];Adaramoye and Adeyemi, 2006[190, 191]; Nworu et al., 2008[192]; Okoko, 2009[113].
Garcinia kola Heckel (bark)	GB_1 (176); GB_2 (177); GB_3 (181).	***Antibacterial activity.***	Kabangu et al., 1987[193] ; Han et al., 2005[74].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Garcinia kola Heckel (stem bark)	GB_1 (176).	GB_1 (**176**) exhibited α-glucosidase and aromatase inhibitory activities, as well as antiplasmodial activity, but was not toxic against cell lines tested. GB_1 (**176**) may be a potential dietary supplement or phytomedicine for the prevention of breast cancer and type 2 diabetes mellitus.	Antia et al., 2010[194].
Garcinia kola Heckel (roots)	*GB-flavones* (*(I-3,II-8)-flavanone-flavone:* Garcinianin atropisomers (166); GB_1 (176); GB_2 (177); kolaflavanone (178); manniflavanone (179); garciniflavanone (180).	GB_1 showed ***antibacterial activity*** against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE).	Iwu et al., 1990b; Terashima et al., 1995[195], 1999[196]; Han et al., 2005[74].
Garcinia kola Heckel (stems)	*GB-flavones [(I-3,II-8)-flavanone-flavone]:* (+)-GB_{1b} (170).		Terashima, 1999[196].
Garcinia laterifolia Bl. (stem bark)	Lateriflavanone (114a); morelloflavone (159);	The biflavonoids exhibited proteasome-inhibitory activity. Morelloflavone (**159**) was found to have the highest potency (IC_{50} = 1.3 μM).	Ren et al.[43].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Garcinia livingstonei T. Anderson (root bark)	*ent*-Naringeninyl-(I-3α,II-8)-II-4′-*O*-methylnaringenin (**171**). (+)-volkensiflavone (**154**); (+)-morelloflavone (**159**).	***Antiparasitic activity against Plasmodium falciparum, Leishmania infantum, Trypanosoma brucei brucei, and T. cruzi, and cytotoxicity against MRC-5 cells***.	Mbwambo et al., 2006[85].
Garcinia livingstonei T. Anderson (leaves)	Amentoflavone (**1**); II-4′-O-methylamentoflavone (= podocarpusflavone A) (**6**).	***Antibacterial activity*** against *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus faecalis* and *Pseudomonas aeruginosa*. MTT assay using Vero monkey kidney cells: The compounds had low toxicity against the cell line. 4"-Methoxyamentoflavone was more active and much less toxic than amentoflavone.	Kaikabo et al, 2009[78].
Garcinia livingstonei T. Anderson (fruits)	Amentoflavone (**1**); (I-3,II-8)-biapigenin (**153**); (+)-volkensiflavone (**154**); (+)-morelloflavone (**159**); (+)-fukugiside (**162**).		Yang et al., 2010[197].
Garcinia madruno (Kunth) Hammel (aerial parts: leaves and branches)	***Flavanone-(I-3,II-8)-flavones:*** Morelloflavone (**159**); volkensiflavone (**154**). ***(I-3′,II-8)-flavone:*** Amentoflavone (**1**).	***Antioxidant activity: Inhibitory LDL oxidation potential and free radical stabilization capacity of the biflavonoid fraction.***	Osorio et al., 2009[198].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Garcinia multiflora Champ. (heartwood)	Amentoflavone (**1**); agathisflavone (**100**); robustaflavone (**64**); hinokiflavone (**235**); volkensiflavone (**154**); volkensiflavone-II-7-*O*-glucoside (spicataside) (**157**); morelloflavone (**159**); morelloflavone-II-7-*O*-glucoside (fukugiside) (**162**); rhusflavanone (**113**); succedaneaflavone (**117**); GB_{1a} (**167**); GB_{1a} II-7-*O*-β-glucoside (**169**); GB_{2a} (**172**); GB_{2a}-II-7-*O*-glucoside (xanthochymuside) (**174**) ; I-5,7,4′,II-5,7,4′-hexa-*O*-methylvolkensiflavone (**158**); hepta-*O*-methylmorelloflavone (**161**); I-5,7,4′,II-5,7,4′-hexa-*O*-methyl-GB_{1a} (**168**); rhusflavanone I-5,7,4′,II-5,7,4′-hexa-*O*-acetate (**114**); succedaneaflavone I-5,7,4′,II-5,7,4′-hexa-*O*-acetate (**118**).	***Antiviral activities*** against influenza A and influenza B, measles, VZV, HSV-1 anti-HSV-2 viruses. ***Anti-HIV-1 reverse transcriptase (RT) activity.*** Hexa-*O*-methylvolkensiflavone showed ***antituberculosis activity***.	Lin et al., 1997[82], 1999[136], 2001[67].
Garcinia nervosa Miq. (leaves)	(I-2′,II-2′)-Biapigenin (**192**); I-3,5,7,4′,II-3,5,7,4'-octahydroxy-(I-2', II-2')-biflavonol (**193**); I-5,7,3′,4′,II-5,7,4′-heptahydroxy-(I-3,II-8)-flavanonylflavone (**164**).		Babu et al., 1988[199]; Parveen et al., 2004[200].
Garcinia scortechinii King (fruits)	(+)-Volkensiflavone (**154**); (+)-morelloflavone (**159**).	***Antibacterial activity.***	Sukpondma et al., 2005[201].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Garcinia subelliptica Merr. (leaves)	*Biflavanones*: (2*R*,3*S*)-I-5,7,4',II-5,7,3′,4′-heptahydroxy-(I-3,II-8)-flavanone-flavone (164); GB2a (172).	*Tyrosinase inhibitory activity.*	Masuda et al., 2005[202].
Mesua ferrea L. (stamens)	Mesuaferrone A (99); mesuaferrone B (98).	Ayurvedic therapy. ***Antimicrobial, antiasthmatic, antispasmodic, hypotensive. Antibacterial activity*** a large number of Gram-positive and Gram-negative bacteria.	Raju et al., 1976[203], 1978; Mazumder et al., 2004[204]; Gupta and Shaw, 2009[205].
Pentadesma grandifolia Baker f. (stem bark, roots, leaves and fruits)	Two binaringenin derivatives.	The biflavanones exhibited antifungal activity against *Cladosporium sphaerospermum*.	Djoufack et al., 2010[206].
Rheedia acuminata Tr. & Pl. (twigs and leaves)	***Flavanone-(I-3,II-8)-flavones***: (2*R*,3*S*)-(+)-morelloflavone (**159**); (2*R*,3*S*)-(+)-morelloflavone-II-7-sulfate (**160**); (2*R*,3*S*)-(+)-volkensiflavone-II-7-sulfate (**155**). ***(I-3',II-8)-Biflavone***: Amentoflavone (**1**).	Coexistence of two conformers for morelloflavone in solution at room temperature.	Li et al., 2002[207].
Rheedia edulis (Seem) Triana & Planchon (seeds and rinds)	(+)-Volkensiflavone (**154**); (+)-morelloflavone (**159**).		Acuña et al., 2010[208].
Rheedia gardneriana Planch et Triana (leaves)	***GB-flavones [(I-3,II-8)-flavanone-flavone]:*** II-4′-*O*-Methyl-GB_{2a} (**175**); volkensiflavone (**154**); fukugetin (**159**); fukugiside (**162**); GB_{2a}-I-7-*O*-glucoside (**173**).	Used in traditional medicine for the treatment of inflammation of urinary tract, arthritis and to relieve pain. ***Analgesic activity. Antibacterial and brine shrimp lethality activity.***	Cechinel Filho, et al., 2000[97, 209]; **Rodrigues et al., 2000[210];Verdi et al., 2004[73].**
Symphonia globulifera L. (stem bark)	GB_2 (**177**); manniflavanone (**179**); GB_3 (**181**).	*Antimicrobial activity*.	Mkounga et al., 2009[211].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Combretaceae			
Calycopteris floribunda Lamk.	***Unusual biflavonoids***: Calycopterone (**381**); isocalycopterone (**382**); I-4-demethylcalycopterone (**383**); neocalycopterone (**384**); I-4-methylneocalycopterone (**385**); calyflorenone A (**387**); calyflorenone B (**388**); II-6-demethoxyneocalycopterone (**385**); calyflorenone D (**390**); calyflorenone C (**389**); 6-*epi*-calyflorenone B (**391**); 6-*epi*-calyflorenone C (**392**).	***Cytotoxic biflavonoids***.	Wall et al., 1994[212]; Mayer, 1999[213], 2004[214].
Combretum albopunctatum Suesseng (aerial parts)	***(I-α,II-α; I-β,II-β)-Bidihydrochalcones:*** *rel*-1β-(4,6-Dihydroxy-2-methoxy)-benzoyl-*rel*-2α-(2,6-dimethoxy-4-hydroxy)benzoyl-*rel*-(3β,4α)-diphenylcyclobutane (**331**); *rel*-(1α,2β)-di-(2,6-dimethoxy-4-hydroxy)benzoyl-*rel*-(3α,4β)-diphenylcyclobutane (**332**).		Katerere et al., 2004[215].
Euphorbiaceae			
Chrozophora senegalense (Lam.) A. Juss. ex Spreng.	Amentoflavone (**1**).	***Antimalarial properties.***	Hashim et al., 1990[216]; Benoit-Vical et al., 2008[217].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Senefelderopsis chiribiquetensis (R.E. Schult. & Croizat) Steyerm. (leaves and stems)	Podocarpusflavone A (**6**); podocarpusflavone B (**10**).		Canelón et al., 2005[218].
Fabaceae (or Leguminosae)			
Subfamily Caesalpinioideae			
Caesalpinia pyramidalis Tull. (leaves)	Caesalflavone (**75**); podocarpusflavone A (**6**); agathisflavone (**100**). Biflavonoids were not found in trunk wood.	Leaves are used as diuretic, dyspeptic, digestive, and antipyretic in traditional medicine. Neurogenesis induced by all-trans retinoic acid (RA) was enhanced by agathisflavone (**100**). Agathisflavone (**100**) increased the percentage of nestin-labeled cells by 2.7-fold mouse embryonic stem (mES) and 2.4 mouse induced pluripotent stem (miPS) and β-tubulin III-positive cells by 2-fold (mES) and 2.7 (miPS) in comparison to RA-treated embryoid bodies (EBs) only; **100** increased the expression of RA receptors α and β in mES EBs, suggesting that the availability of RA receptors was limiting RA-induced neurogenesis in pluripotent stem cells.	Bahia et al., 2005[219]; Paulsen et al., 2011[220].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
		First report to describe that naturally occurring biflavonoids regulate apoptosis and neuronal differentiation in pluripotent stem cells.	
Subfamily Faboideae (or Papilionoideae)			
Glycyrrhiza glabra L. (hairy root cultures)	*Prenylbiaurone*: Licoagrone (258). ***Ketalized prenyl flavanone-prenylisoflavan***: Licoagrodin (**375**).		Asada et al., 1999[221]; Li et al., 2000[222].
Glycyrrhiza uralensis Fisch. (roots)	Licobichalcone (**327**).		Bai et al., 2003[223].
Lupinus albus L. (roots)	LA (I-3,II-5)-bi-isoflavonoid (**347**); LA (I-3,II-8)-bi-isoflavonoid (**348**).		Sakasai et al., 2000[224]
Ormocarpum kirkii S. Moore (roots)	***(I-3,II-3)-Biflavonoids***: Ormocarpin (**125**); isochamaejasmin (**130**); (+)-chamaejasmin (**123**); II-7-*O*-β-*D*-glucopyranosylchamaejasmin (**124**); liquiritigeninyl-(I-3,II-3)-naringenin (**128**); (I-3,II-3)-biliquiritigenin (**129**); apigeninyl-(I-3,II-3)-naringenin (**122**). ***(I-3,II-3)-Bineoflavonoids***:	*Tanzanian traditional medicine. Antimalarial use.* ***Antimicrobial activity.*** ***Antiplasmodial activity*** (against *Plasmodium falciparum*). Isochamaejasmin showed the highest antiplasmodial activity. Medicinal plant used in traditional medicine against malaria.	Nyandat et al., 1990[225]; Dhooghe et al., 2010[84]; Xu et al., 2011[226].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
	Diphysin (**284**); I-7-*O*-β-*D*-glucopyranosyldiphysin (**285**); I-5,II-5-di-*O*-methyldiphysin (**286**). 7-*O*-β-*D*-Glucopyranoside of (I-3,II-3)-biliquiritigenin (**129**).	Ormocarpin (**125**) and **129** were some of the compounds responsible for the *antimalarial activity*.	
Tephrosia crassifolia Benth. (roots and aerial parts)	***Isopropenyldihydrofuran biflavan:*** Crassifolin A (**357**).	***Concentration-dependent inhibition of photophosphorylation.***	Gómez-Garibay et al., 1999[227]; Céspedes et al., 2001[228].
Tephrosia tepicana Standl. (roots and aerial parts)	***(I-4,O,II-4)-Prenylbiflavan:*** Tepicanol A (**356**).		Gómez-Garibay et al., 1997[229].
Subfamily Mimosoideae			
Albizia procera (Roxb.) Benth. (leaves)	***Succedaneaflavones [(I-6,II-6)-biflavones]***: Albiproflavone (including benzofuranoid and naphtopyrano groups) (**119**).		Yadav and Bhadoria, 2004[230].
Leucaena diversifolia (Schlecht) Benth. (leaves)	***(I-2',II-6)-Benzopyranobenzofuran-biflavone:*** Leucaediflavone (**201**).		Yadav and Bhadoria, 2004[230].
Hypericaceae			
Hypericum aucheri Jaub. et Spach (leaves)	(I-3,II-8)-Biapigenin (**153**).		Kitanov, 1985[231], 1988[232].
Hypericum confertum Choisy	Amentoflavone (**1**).		Cirak et al., 2010[233].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Hypericum ericoides L. ssp. *Roberti* (Coss. ex Batt.) Maire & Wilczek	(I-3,II-8)-Biapigenin (**153**).		Hosni et al., 2010[234].
Hypericum perfoliatum L.	(I-3,II-8)-Biapigenin (**153**).		Hosni et al., 2010[234].
Hypericum perforatum L.	(I-3,II-8)-Biapigenin (**153**); amentoflavone (**1**).	*Used in the treatment of inflammation and depression*. (I3,II8)-Biapigenin (**153**) was not detected in mice brain (< 5ng/g)), suggesting poor brain-to-blood permeability. Amentoflavone (**1**) crossed the blood-brain barrier *in vitro*, but did not inhibit benzodiazepine binding *in vivo*, suggesting poor brain permeability. Biapigenin (**153**) is neuroprotective against excitotoxic insults. The observed neuroprotection was correlated with prevention of delayed calcium deregulation and with the maintenance of mitochondrial transmembrane electric potential. Biapigenin was also able to significantly affect mitochondrial bioenergetics and decreased the capacity of mitochondria to accumulate calcium. Biflavones **1** and **153** were quantified in human plasma.	Berghoefer and Hoelzl, 1987[235], 1989[236]; Colovic and Caccia, 2008[237]; Colovic et al., 2008[238]; Silva et al., 2008[239]; Hosni et al., 2010[234]; Michler et al., 2011[240].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Lamiaceae (or Labiatae)			
Scutellaria alpina (L.) Moench. (root)	(I-8,II-8)-Bibaicalein (**96**).		Kikuchi et al., 1991[241].
Lauraceae			
Cryptocarya infectoria (Bl.) Miq.	***Rare biflavonoids:*** Bicaryone A (**358**); bicaryone B (**359**); bicaryone C (**360**); bicaryone D (**361**); chalcocaryanone A (**362**); chalcocaryone B (**363**); chalcocaryanone C (**364**); chalcocaryone D (**365**).	***Cytotoxic*** biflavonoids.	Dumontet et al., 2001[242].
Loganiaceae			
Strychnos pseudoquina St. Hil.	Strychnobiflavone (**203**).	Native plant of the Brazilian Savannah, used in popular medicine. ***Antiulcer activity. Mutagenicity.***	Nicoletti et al., 1984[243]; Santos et al., 2006[244].
Melastomataceae			
Miconia cabucu Hoehne (leaves)	***(I-6,II-6)-Biflavone***: I-4′,II-4′-Di-O-methyl-I-3′-methoxy-(I-6,II-6)-bigenkwanin (**116**).		Rodrigues et al., 2007[245].
Meliaceae			
Dysoxylum lenticellare Gillespie (leaves)	***Robustaflavones [(I-3',II-6)-biflavones]:*** I-4′,II-7-Di-*O*-methylrobustaflavone (**67**). ***(I-3',II-8) Biflavonoids:*** Isoginkgetin (**13**); bilobetin (**3**).		He et al., 1996[246].
Menispermaceae			

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Cissampelos pareira L. (aerial parts)	***(I-β,O,II-7; I-α, II-6)-Chalcone-flavone*:** Cissampeloflavone (**311**).	***Antiprotozoal activity***: against *Trypanosoma cruzi* and *T. brucei rhodiense*, and has ***a low cytotoxicity*** in the human KB cell line.	Ramírez et al., 2003[247] ; Maya et al., 2007[248].
Stephania tetrandra S. Moore (aerial parts)	***(I-3,II-6)-Biflavones***: Stephaflavone A (**150**); stephaflavone B (**151**).		Si et al., 2001[249].
Moraceae			
Artocarpus altilis (Parkins.) Fosb. (bud covers)	***(I-5,II-5)-Bi-isoprenyldihydrochalcone***: Cycloaltilisin 6 (**303**).	Traditionally used in Taiwan for the treatment of liver cirrhosis and hypertension. Antiinflammatory and detoxifying effects. ***Potent inhibition of Cathepsin K (cysteine protease that has been implicated in osteoporosis).***	Patil et al., 2002[250].
Artocarpus heterophylla Lamk. (bark)	***Diels-Alder-type adducts:*** Artonin C (**401**); artonin D (**402**); artonin I (**397**) (root bark). ***Prenyldihydrochalcone-chalcone dimers (Diels-Alder-type adducts):*** Artonin X (**403**); kuwanon R (**404**).	Used as a traditional medicine in Southeastern Asia. Ingredient in the preparations of some *Ayurvedic* and *Yunani* medicines. ***Melanin biosynthesis inhibitory activity.***	Hano et al., 1990[251], 1992[252]; Shinomiya et al., 1995[253].
Dorstenia barteri Bureau (whole plants)	***Isoprenylbichalcone:*** Dorstenone (**400**).		Tsopmo et al., 1999[254].
Dorstenia zenkeri Engl. (leaves)	(I-3′,II-5; I-4′,*O*,II-1)-Prenyldihydro-chalcone-prenylchalcone (ketalized Diels-Alder-type adduct) (**409**).		Abegaz et al., 2002[255].

Plant (Part of the plant)	**Compounds**	**Bioactivity. Traditional uses.**	**Author, References**
Morus alba L. (root bark)	***Mulberry Diels-Alder-type adducts:*** Kuwanon L (**396**); kuwanon G (**398**); kuwanon H (**399**); kuwanon I (**408**); kuwanon J (**405**); kuwanon X (**432**); kuwanon Y (**433**); mulberrofuran C (**424**); mulberrofuran J (**422**); sanggenon D (**419**); sanggenon B (**439**); sanggenon G (**395**); sanggenon O (**415**); sanggenon E (**420**); sanggenon C (**418**).	Asian traditional medicine. Japanese mulberry tree. Traditional Chinese medicine for an anti-inflammatory, diuretic, antitussive, expectorant, and anti-pyretic purposes. Kuwanons G and H showed ***hypotensive effect***. ***Antimicrobial and cytotoxic activity. Antioxidant activity. Cardiovascular protection. Inhibition of LDL oxidation, and neurodegenerative disorders. Effective against hyperglycemia and lipid peroxidation in diabetics.*** Natural fungicides effective against *Venturia inaequalis* (Cooke) Winter, the causal agent of apple scab.	Park et al., 2003[256]; Sohn et al., 2004[257]; Rollinger et al., 2006[258]; Butt et al., 2008[259]; Nomura et al., 2009[260].
Chinese crude drug 'Sang-Bai-Pi′ (*Morus* root bark)	Sanggenon C (**418**); sanggenon G (**395**); mulberrofuran C (**424**); kuwanon L (**396**); sanggenon D (**419**); sanggenon B (**439**); sanggenon O (**415**); sanggenon E (**420**).	Asian traditional medicine. ***Inhibitory compounds for protein tyrosine phosphatase 1B (PTP1B).*** (PTP1B inhibitors could not only be used for treating Type 2 diabetes but also obesity). Natural fungicides effective against *Venturia inaequalis* (Cooke) Winter, the causal agent of apple scab.	Cui et al., 2006[261] ; Rollinger et al., 2006[258].
Morus alba L. (cell cultures)	***Mulberry Diels-Alder type adducts:*** Kuwanon J (**405**); kuwanon Q (**406**); kuwanon R (**404**); kuwanon V (**407**); mulberrofuran E (**426**); chalcomoracin (**425**); mulberrofuran C (**424**).	Antibacterial activity against MRSA and moderate cytotoxicity against five human cancer cell lines.	Gunawan and Rizzacasa, 2010[262].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Morus cathayana Hemsl. (root bark)	***Diels-Alder-type adducts:*** Sanggenon C (**418**); sanggenon D (**419**); sanggenon J (**421**); sanggenon O (**413**); cathayanon A (**413**); cathayanon B (**414**).	Root bark, "sang-bai-pi", is used in traditional Chinese medicine as an antiphlogistic, diuretic and expectorant, and in traditional Sino-Japanese medicine in Japan. Sanggenon C is an antihypertensive compound. ***Potent activities on the inhibition of HL-60 cell adhesion to BAEC.***	Fukai et al., 1998[263]; Shen et al., 2001[264].
Morus macroura Miq. (stem bark)	***Diels–Alder type adducts:*** Guangsangon F (**416**); guangsangon G (**410**); guangsangon H (**417**); guangsangon I (**411**); guangsangon J (**423**); mulberrofuran J (**422**); kuwanon J (**405**).	Chinese herbal medicine. ***Anti-oxidant and anti-inflammatory activities***.	Dai et al., 2004[265]
Morus mongolica Schneider (root bark)	***Cycloaddition product of a dehydrogeranylflavanone and a prenylchalcone (Diels-Alder-type adduct):*** Sanggenol M (**394**).	Traditional Chinese herbal medicine. ***Antimicrobial and cytotoxic activity.*** Higher cytotoxicity against human oral tumor cell lines (HSC-2 and HSG) than against normal human gingival fibroblasts (HGF).	Shi et al., 2001[266]; Sohn et al., 2004[257];
Morus multicaulis Perr. (roots)	***(I-α,II-3",I- β,II-6")-Dihydrochalcone-dehydrogeranylflavone Diels-Alder-type adduct:*** Multicaulisin (**393**).		Ferrari et al., 2000[267].
Morus wittiorum Hand.-Mazz. (stem bark)	***Diels–Alder type adducts:*** Wittiorumin G (**412**); albafuran C (**427**); sorocein A (**437**); mulberrofuran E (**426**); mulberrofuran F (**430**); mulberrofuran O (**428**).	***Antioxidant activity, and cytotoxicity against five human cancer cell lines.*** Mulberrofuran F is a hypotensive Diels–Alder type adduct.	Tan et al., 2009[268].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Sorocea bonplandii Baillon (roots)	**Ketalized Diels-Alder type adducts**: Soroceal (**440**); sorocein A (**437**); kuwanol E (**435**).	Brazilian plants. ***Effects on agonist-induced contractions in the rat uterus and in the guinea pig ileum in vitro.***	Messana et al., 1991[269]; Calixto et al., 1993[270].
Sorocea bonplandii Baillon [= *Sorocea bonplandii (*Baill.) W. C. Burger, Lanj. & Wess. Boer]	***Isoprenylated Diels Alder adducts:*** Sorocenol B (**441**); artonin D (**402**).	Paraguayan plants.	Hano et al., 1995[271].
Sorocea ilicifolia Miq. (root bark) (roots)	***Ketalized Diels-Alder type adducts:*** Soroceal (**440**); sorocein A (**437**); sorocein I (**438**); sorocein L (**436**); sorocein M (**434**); chalcomoracin (**425**); kuwanon J (**405**); mulberrofuran O (**428**); kuwanol E (**435**).		Ferrari and Messana, 1995[272]; Ferrari and Delle Monache, 2001[273]; Ferrari et al., 2003[274].
Sorocea muriculata Miq. (roots)	***Diels-Alder-type adducts:*** Sorocenol G (**431**); Sorocenol H (**429**).	Used traditionally to treat inflammation and gastric ulcers. ***Antimicrobial activity*** against methicillin-resistant *Staphylococcus aureus* (MRSA), *Escherichia coli, Pseudomonas aeruginosa*, and *Mycobacterium intracellulare*. ***Antifungal activity.***	Ross et al., 2008[275].
Myristicaceae			
Iryanthera sagotiana (Benth.) Warb. (leaves and inflorescences)	(***I-3',II-3')-Bidihydrochalcone***: (I-3′,II-3′)-*Bis*-2′,4′,6′-trihydroxy-4-methoxy-α,β-dihydrochalcone (**299**).		Silva et al., 1997[276].
Ochnaceae			

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Brackenridgia zanguebarica (bark)	***(I-α,II-α)-Bidihydrochalcone***: Brackenin [= (I-α,II-α)-bidihydroisoliquiritigenin] (**300**); isochamaejasmin (**130**). ***(I-3,II-3′)-flavanone-chalcone***: I-5,7,4′-Trihydroxyflavanone-(I-3,II-3′)-II-4,2′,4′,6′-tetrahydroxy-chalcone (**287**). ***Chalcone-dihydrochalcone dimer:*** Calodenin A (**340**); *trans*-2,3-dihydro-orange pigment (= dihydrolophirone C) (**346**).		Drewes and Hudson, 1983[277]; Drewes et al., 1984[278], 1987[279]
Campylospermum mannii Teigh. (leaves and stem bark)	Azobechalcone (**343**); mbamichalcone (**336**); isombamichalcone (**337**). Amentoflavone (**1**); robustaflavone (**64**); chamaejasmin (**123**); campylospermone A (**126**); campylospermone B (**127**).	Used in the south of Cameroon by the Baka pigmies to remedy heart and stomach disorders. Robustaflavone is a potential non-nucleoside anti-hepatitis B agent.	Tih et al., 1988[280], Murakami et al., 1992[281]; Zembower et al., 1998[80]; Elo Manga et al., 2009[282].
Cespedesia macrophylla Seem. (leaves)	Ochnaflavone (**218**); II-7-*O*-methylochnaflavone (**220**).	Cytotoxic activity *in vitro*. ***Ochnaflavone showed inhibitory activity against phospholipase A_2 (PLA2).***	Lobstein et al., 2004[283] ; Chen et al., 2006[166].

Plant (Part of the plant)	**Compounds**	**Bioactivity. Traditional uses.**	**Author, References**
Cespedesia spathulata (Ruiz & Pav.) Planch. (leaves)	Ochnaflavone (**218**); II-7-*O*-methylochnaflavone (**220**).	***Ochnaflavone showed inhibitory activity against phospholipase A_2 (PLA2).***	Lobstein et al., 2004 [283]; Chen et al., 2006[166].
Lophira alata Banks ex Gaertn (leaves)	Bongosin (290); lophirone L (217); lophirone M (216).	Cameroonian medicinal plant. Anti-tumor promoters.	Tih et al., 1990[284]; Murakami et al., 1992[281]; Tih et al., 2006.
Lophira lanceolata Van Tiegh. ex Kaey (stem) (stem bark)	Lanceolatin A [apigeninyl-(I-3′,II-3)-II-2,3-dihydroapigenin] (**215**); isombamichalcone (**336**); lophirone A (**351**); lophirone B (**290**); lophirone C (**344**); lophirone F (**333**); lophirone G (**334**); lophirone I (**353**); lophirone J (**354**).	Cameroonian medicinal plant.	Ghogomu Tih et al., 1987[285], 1989[285, 286], 1994[287]; Pegnyemb et al., 1994[288], 1998[289].
Luxemburgia nobilis Eichl. (leaves)	***Ochnaflavone (I-3',O,II-4'--flavone-flavanone)***: II-2,3-Dihydroochnaflavone (**225**).	***Inhibitor of DNA topoisomerases***. (**225**) was cytotoxic to murine Ehrlich carcinoma and human leukemia K562 cells. (**225**) inhibited the activity of human DNA topoisomerases I and II-α. (**225**) is a DNA interacting agent, which causes DNA unwinding in an assay with topoisomerase I.	Likhitwitayawuid et al., 2001[290]; De Oliveira et al. 2002[291], 2005[59].
Luxemburgia octandra St. Hil.	***(I-3',O,II-4')Biflavonoids***: II-2,3-dihydroochnaflavone (**225**). ***Bichalcone:*** Luxenchalcone (**293**).	***Antitumoral activity.***	de Carvalho et al. 2004[292].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Ochna afzelii R. Br. ex Oliv. (stem bark)	Isolophirone C (**341**); I-α,β-dihydrolophirone C (**346**); lophirone C (**344**); afzelone A (**317**); afzelone B (**120**); afzelone C (**345**); afzelone D (**349**); calodenin A (**340**); calodenin B (**338**); lophirone A (**351**); calodenone (**350**).	Used in Central African traditional medicine. Cameroonian medicinal plant. ***Anti-β-lactamase activity.***	Pegnyemb et al., 2001[293], 2003[294, 295]; Gangoué-Piéboji et al., 2007[296].
Ochna beddomei Gamble (leaves)	***Ochnaflavones (I-3',O,II-4'-biflavonoids***: I-7-*O*-methyl-I-2,3,II-2,3-tetrahydroochnaflavone (**228**); I-7-*O*-methyl-I-2,3-dihydroochnaflavone (**223**); I-2,3-dihydroochnaflavone (**221**); ochnaflavone (**218**).	***Ochnaflavone showed inhibitory activity agains phospholipase A_2 (PLA2).***	Jayaprakasam et al., 2000[297]; Chen et al., 2006[166].
Ochna beddomei Gamble (stem bark)	***Ochnaflavones (I-3',O,II-4'-biflavonoids; 3',O,4"'-flavanone-flavone)***: I-7,4',II-7-tri-*O*-methyl-I-2,3-dihydroochnaflavone (**224**); I-2,3-dihydroochnaflavone (**221**); ochnaflavone (**218**).	***Ochnaflavone showed inhibitory activity agains phospholipase A_2 (PLA2).***	Jayakrishna et al., 2003[298]; Chen et al., 2006[166].
Ochna calodendron Gilg. et Mildbr. (stem bark)	***Bichalcones***: lophirone C (**344**); lophirone K (**342**); calodenin A (**340**); calodenin B (**338**). ***Bi-isoflavonoid***: Calodenone (**350**).		Messanga et al., 1992[299], 1994[300].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Ochna integerrima (Louri) Merr. (leaves)	***Ochnaflavones (I-3',O,II-4'-biflavonoids)***: Ochnaflavone (**218**); II-7-*O*-methylochnaflavone (**220**); II-2,3-dihydroochnaflavone (**225**); II-7-*O*-methyl-II-2,3-dihydroochnaflavone (**226**).	***Anti HIV-1 activity:*** very active; inhibited HIV-1 reverse transcriptase (RT).	Likhitwitayawuid et al., 2001[290], 2005[301]; Reutrakul et al., 2007[83].
Ochna integerrima (Louri) Merr. (stem bark)	***(I-3,II-3)-Flavanone-chalcones***: I-5-hydroxylophirone B (**288**); I-5-hydroxylophirone B I-7-*O*-β-*D*-glucopyranoside (**289**); lophirone A (**351**); lophirone C (**344**); calodenone (**350**); calodenin A (**340**).	Outer bark: good ***anti-malarial activity***; inner barks: no antimalarial activity.	Kaewamatawong et al., 2002[302]; Ichino et al., 2006[87].
Ochna integerrima (Louri) Merr. (root bark)	I-5-Hydroxylophirone B (**288**); lophirone A (**351**); lophirone C (**344**); calodenone (**350**); calodenin A (**340**).		Likhitwitayawuid et al., 2005[301].
Ochna integerrima (Louri) Merr. (root wood)	I-5-Hydroxylophirone B (**288**); lophirone A (**351**); lophirone C (**344**); calodenone (**350**); calodenin A (**340**).		Likhitwitayawuid et al., 2005[301].
Ochna lanceolata Spreng. (stem bark)	I-7,4',II-7,4′-Tetra-*O*-methylisochamaejasmin (**131**); ochnaflavone (**218**); I-2,3-dihydroochnaflavone (**221**).	Used in Central India in traditional medicine.	Reddy et al., 2008[303].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Ochna macrocalyx Oliv. (bark)	***(I-2,II-2)-Bi-isoflavanones***: Dehydroxyhexaspermone C (**273**); hexaspermone C (**272**). ***(I-3,II-α;I-4,O,II-β)-Bidihydrochalcones (= tetrahydrofuro[3,2-c]benzopyran derivative):*** Cordigol (**323**); calodenin B (**338**); calodenin A (**340**).	***Moderate cytotoxic activity*** on MCF-7 breast cancer cells. ***Strong antibacterial activity*** against three strains of multi-drug resistant (mdr) *Staphylococcus aureus* (RN4220, XU212 and SA-1199-B). The ethanolic extract of the bark also showed NF-*kappa*B inhibitory activity.	Tang et al., 2003[304].
Ochna obtusata DC (leaves)	***Ochnaflavones (I-3',O,II-4'-biflavonoids; 3',O,4"-flavanone-flavone)***: ochnaflavone (**218**); I-7-*O*-methyl-I-2,3-dihydroochnaflavone (**223**); I-2,3-dihydroochnaflavone (**221**).	***Ochnaflavone showed inhibitory activity against phospholipase A_2 (PLA2).***	Rao et al., 1997[305]; Chen et al., 2006[166].
***Ochna squarrosa* L.** (root bark)	Lophirone A (**351**); lophirone L (**217**); lophirone H (**322**); calodenone (**350**).	Used in Indian traditional systems of medicine. ***Analgesic and anti-inflammatory activities.***	**Anuradha et al., 2006[306].**
Ouratea flava Schum and Thon. (stem bark)	***(I-2',O,II-β; I-3',II-α)-Bichalcones (trisubstituted benzofuran derivatives) :*** Calodenin B (**338**); flavumone A (**339**). ***Flavanone-chalcone (furochromanone derivative)***: Flavumone B (**316**). lophirone A (**351**).		Mbing et al., 2003[307].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Ouratea hexasperma Bail (St. Hill) (leaves).	***(I-2,II-2)-Bi-isoflavanones***: Hexaspermone A (**270**); hexaspermone B (**271**); hexaspermone C (**272**). ***Biflavone***: II-7-*O*-Methylagathisflavone (**103**).	Biflavone ***inhibited human DNA topoisomerases I*** at 200 μM, and at 200 μM also ***inhibited DNA topoisomerases II-alpha***. It showed concentration-dependent growth inhibitory activity on Ehrlich carcinoma cells in 45-h culture, and showed 42% growth inhibitory activity at 90 μM against human K562 leukemia cells in 45-h culture. Then, this biflavone is a target for DNA topoisomerases and its cytotoxicity is dependent on tumor cell type.	Moreira et al., 1994[308], 1999[309]; Grynberg et al., 2002[48].
Ouratea multiflora Pohl (leaves)	***Biflavonol***: I-5,7,4'-Tri-*O*-methylkaempferol-(I-6,II-8)-II-5,7,3',4'-tetra-*O*-methylquercetin (**111**); amentoflavone (**1**).	*Ouratea* species are used for treatment of rheumatic and gastric ailments. ***Inhibitory activity on aflatoxin B_1 and B_2 production***, but did not inhibit fungal growth. Therefore, suitable for the control of aflatoxin production.	Felicio et al., 2001[310]; Gonçalez et al., 2001[311].
Ouratea nigroviolacea Gilg. ex Engl. (leaves)	***(I-6,II-8)-Biflavones***: Agathisflavone (**100**); ouratine A (I-4′,II-4′-di-*O*-methylagathisflavone) (**106**); ouratine B (I-4′-*O*-methylagathisflavone) (**102**).		Mbing et al., 2006[312].
Ouratea parviflora (DC.) Baill. (leaves)	***Biflavone***: I-7,II-7-di-*O*-methylagathisflavone (**104**).	***Inhibitory activity on aflatoxin B_1 and B_2 production***, but did not inhibit fungal growth at the concentration tested. Therefore, it can be used for the development of agents to control aflatoxin production.	Gonçalez et al., 2001[311].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Ouratea semiserrata Mart (Engl.) (leaves and branches)	***Biflavones***: I-7-*O*-Methyllanaroflavone (**250**); I-7,II-4′-di-*O*-methyllanaroflavone (**251**); lanaroflavone (**249**); amentoflavone (**1**); podocarpusflavone A (**6**).	Amentoflavone and its acetyl derivative are inhibitors of human DNA topoisomerases I at 200 μM. These biflavonoids showed concentration-dependent growth inhibitory activities on Ehrlich carcinoma cells in 45-h culture. These biflavonoids are targets for DNA topoisomerases and their cytotoxicity is dependent on tumor cell type. Lanaroflavone is an active ***antiplasmodial compound.***	Velandia et al., 2002[313]; Grynberg et al., 2002[48] ; Weniger et al., 2006[86].
Ouratea spectabilis (Mart.) Engl. (leaves)	***Succedaneaflavones [(I-6,II-6)-Biflavones]***: (I-6,II-6)-Bigenkwanin (**115**); I-7,II-7-di-*O*-methylagathisflavone (**104**).	***Biflavones inhibited lens aldose reductase***. The biflavonoids showed ***inhibitory activity on aflatoxin B_1 and B_2 production***, but did not inhibit fungal growth at the concentration tested. Therefore, biflavonoids can be used for the development of agents to control aflatoxin production.	Felício et al., 1995[100]. Gonçalez et al., 2001[311].
Ouratea staudtii Van Tiegh. Ex Keay. (aerial parts)	Lophirone A (**351**); amentoflavone (**1**); ochnaflavone (**218**); bilobetin (**3**); podocarpusflavone A (**6**); agathisflavone (**100**).		Abouem à Zintchem et al., 2007[314].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Ouratea sulcata Van Tiegh (ex Keay) (aerial parts)	***(I-4',O,II-3')-Flavone-flavanonol dimer:*** Sulcatone A [= apigenyl-(I-4',*O*,II-3')-II-2,3-dihydrokaempferol] (**231**). ***(I-4',O,II-3')-Biflavanonol:*** I-2,3-Dihydrokaempferol-(I-4',*O*,II-3')-II-2,3-dihydrokaempferol (**232**). ***Biflavones:*** amentoflavone (**1**); agathisflavone (**100**). ***Cleaved bi-isoflavonoid***: Lophirone A (**351**).	Extracts are used in many African countries, including Cameroon, Nigeria, Congo and Gabon to treat human ailments such as upper respiratory tract infections, dysentery, diarrhoea and toothache. ***Antimicrobial activity.***	Pegnyemb et al., 2005[76].
Paracryphiaceae (or Quintiniaceae)			
Quintinia acutifolia Kirk	***Ether-linked biflavonoids***: I-2,3,II-2,3-Tetrahydroochnaflavone (**227**); I-7,II-7-di-*O*-methyl-I-2,3,II-2,3-tetrahydroochnaflavone (**229**); I-7-*O*-methyl-I-2,3,II-2,3-tetrahydroochnaflavone (**228**); II-2,3-dihydroochnaflavone (**225**).		Ariyasena et al., 2004[315].
Phyllanthaceae	This family is the most closely related to the family Picrodendraceae.		
Phyllanthus sellowianus Müller Arg. (bark)	I-4′,II-4′-Di-*O*-methylcupressuflavone (**93**).	*Antidiabetic agent* in Argentine folk medicine.	Hnatyszyn et al., 1987[316].
Picrodendraceae	This family was previously known as the subfamily Oldfieldioideae of the family Euphorbiaceae.		

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Celaenodendron mexicanum Standl. (leaves)	Amentoflavone (**1**); podocarpusflavone A (**6**); podocarpusflavone B (**10**).	***Antiprotozoal and cytotoxic effects.***	Camacho et al., 2000[317].
Podocalyx loranthoides Klotzsch (leaves and stems)	Podocarpusflavone A (**6**); putraflavone (**10**).	***Antiprotozoal activity*** against *Leishmania mexicana* promastigotes.	Suárez et al., 2003[69]; Díaz et al., 2007[318].
Piperaceae			
Piper aduncum L. (leaves)	***(I-5',CH_2,II-5')-Bidihydrochalcone:*** Piperaduncin C (**304**).	Traditional medicine of Papua New Guinea. ***Cytotoxic and antibacterial activities.***	Orjala et al., 1994[319].
Quintiniaceae			
Quintinia acutifolia Kirk. (leaves)	***Ochnaflavones (I-3',O,II-4'-biflavanones)***: I-7,II-7-Di-*O*-methyl-I-2,3,II-2,3-tetrahydroochnaflavone (**229**).		Ariyasena et al., 2004[315].
Rhamnaceae			
Berchemia zeyheri (Sond.) Grubov. (= Phyllogeiton zeyheri *(*Sond.*) Süsseng.) (= Rhamnus* zeyheri Sond.*) (heartwood)*	***(I-3,II-5)-Flavanone-auronols:*** (I-2*R*, 3*S*)-Naringenin-(I-3α,II-5)-(II-2*R*)-maesopsin (**266**); (I-2*R*,3*S*)-naringenin-(I-3α,II-5)-(II-2*S*)-maesopsin [= (II-2)-*S*-diastereomer] (**267**). ***(I-3,II-7)-Flavanone-auronols*:** (I-2*R*,3*S*)-Naringenin-(I-3α,II-7)-(II-2*R*)-maesopsin (= zeyherin) (**268**); (I-2*R*,3*S*)-naringenin-(I-3α,II-7)-(II-2*S*)-maesopsin (= II-2 diastereomer of zeyherin) (**269**).		Bekker et al., 1996[320], 1998[321], 1999[322], 2000[323], 2001[324].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
	(I-2,II-5)-Isoflavanone-auronols: (I-2*S*,3*R*)-Dihydrogenistein-(I-2α,II-5)-(II-2*R*)-maesopsin (**276**); (I-2*S*,3*R*)-dihydrogenistein-(I-2α,II-5)-(II-2*S*)-maesopsin [= (II-2*S*)-diastereomer] (**277**). ***(I-2,II-7)-Isoflavanone-auronols:*** (I-2*S*,3*R*)-Dihydrogenistein-(I-2α,II-7)-(II-2*R*)-maesopsin (**278**); (I-2*S*,3*R*)-dihydrogenistein-(I-2α,II-7)-(II-2*S*)-maesopsin [= (II-2*S*)-diastereomer] (**279**). ***(I-2,II-7)-Aurone-auronols:*** (I-2*S*)-I-2-Deoxymaesopsin-(I-2,II-7)-(II-2*R*)-maesopsin [= (I-2*S*,II-2*R*)-isomer] (**260**); (I-2*R*)-I-2-deoxymaesopsin-(I-2,II-7)-(II-2*S*)-maesopsin [=(I-2*R*,II-2*S*)-enantiomer] (**261**); (I-2*R*)-I-2-deoxymaesopsin-(I-2,II-7)-(II-2*R*)-maesopsin [=(I-2*R*,II-2*R*)-isomer] (**262**); (I-2*S*)-I-2-deoxymaesopsin-(I-2,II-7)-(II-2*S*)-maesopsin[=(I-2*S*,II-2*S*)-enantiomer] (**263**).		
Salicaceae			
Salix alba L. (leaves)	Cupressuflavone (**86**); amentoflavone (**1**).		Khan and Ansari, 1985[325]; Yunes et al., 2005[326].
Salix fragilis L. (leaves)	Cupressuflavone (**86**); amentoflavone (**1**).		Khan and Ansari, 1985[325]; Yunes et al., 2005[326].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Scrophulariaceae			
Verbascum thapsus L. (whole plant)	Amentoflavone (**1**).	Used in temperate Himalaya for the treatment of asthma and other lung complaints. ***Antiviral activity against herpes virus type 1.***	Hussain et al., 2009[327].
Sterculiaceae	This family was previously the subfamily Sterculioideae of the family Malvaceae.		
Glossostemon bruguieri (Desf.) (roots)	***(I-8,II-8)-Cupressuflavones***: Mogathin (**87**).		Meselhy, 2003[328].
Thymelaeaceae			
Daphne acutiloba Rehd. (roots and bark)	***Benzodihydrofuran-biflavones***: Daphnodorin A (**318**); daphnodorin D_1 (**187**); daphnodorin D_2 (**188**); daphnodorin E; daphnodorin F (**369**); daphnodorin J (**320**). ***Benzodihydrofuran-dihydropyran-chalcone-flavan dimers***: daphnodorin M (**376**); daphnodorin N (**377**).	The roots and bark are used in Chinese herbal medicine under the name "jin yao dai" for the treatment of adenochirapsology and bruises.	Taniguchi et al., 1998[329].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Daphne feddei Levl. (stem bark)	2”-Methoxydaphnodorin C (**443**); 2”-methoxy-II-2-*epi*-daphnodorin C (**444**); daphnodorin A (**318**); daphnodorin B (**319**); daphnodorin C (**446**); daphnodorin I (**447**); daphnodorin J (**320**); a mixture of daphnodorins M and N; I-α,β-dihydrodaphnodorin B (**321**); wikstrol A (**185**); wikstrol B (**186**); genkwanol B (**378**); genkwanol C (**379**); neochamaejasmin B (**133**).	Folk medicine for the treatment of injuries from falls and bruises. ***Inhibitory activity against nitric oxide (NO) production.***	Liang et al., 2008[330].
Daphne genkwa Sieb. et Zucc. (roots)	Genkwanol A (**445**); genkwanol B (**378**); genkwanol C (**379**); I-3-*O*-Methyldaphnodorin H (**373**); II-3-*O*-methyl daphnodorin H (**374**); II-3-*O*-methyldaphnodorin G (**371**).		Baba et al., 1987[331], 1992[332], 1993[333]; Zheng and Shi, 2004[334], 2005[335].
Daphne giraldii Nitsche (roots)	Daphnodorin A (**318**); daphnodorin B (**319**); daphnodorin C (**446**); daphnodorin D_1 (**187**); daphnodorin D_2 (**188**). Daphnogirin A (**366**);daphnogirin B (**367**); and the co-crystal of a 1:1 complex of daphnogirins A and B.	Folk herbal medicine in China. ***Antioxidant activity***.	Zhou et al., 2002[336], 2007[337].
Daphne giraldii Nitsche (stem bark)	Daphnodorin A (**318**); daphnodorin B (**319**); daphnogirin E (**368**).	Folk herbal medicine in China.	Zhang et al., 2008[338].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Daphne odora Thunb. (roots)	Daphnodorin A (**318**); daphnodorin B (**319**); I-α,β-dihydrodaphnodorin B (**321**); daphnodorin C (**446**); daphnodorin D_1 (**187**); daphnodorin D_2 (**188**); daphnodorin E; daphnodorin F (**369**); daphnodorin G (**370**); daphnodorin H (**372**); daphnodorin I (**447**); daphnodorin J (**320**); daphnodorin K (**152**); daphnodorin L (**352**).odorins G-I, were		Baba et al., 1995[339]; Taniguchi and Baba, 1996[340]; Taniguchi et al., 1997[341], 1998[329].
Daphne odora Thunb. var. *Margirmt* (whole plant)	Daphnodorin B (**319**); daphnodorin D_1 (**187**).	Used for treatment of arthritis, fever, and mange.	Chen et al., 2009[342].
Daphne tangutica Maxim. (roots)	***Biflavonoids***: daphnodorin D_1 (**187**); daphnodorin D_2 (**188**).	Marked ***antitumor activity*** *in vivo*.	Zhang et al., 2007[343].
Gnidia involucrata Steud. ex A. Rich. (aerial parts)	***GB-flavones [(I-3,II-8)-flavanone-flavone]:*** GB_1 (**176**); GB_2 (**177**); GB_3 (**181**). ***GB-flavones [(I-3,II-8)-biflavanones]:*** diastereoisomers: GB_4 (I-2*R*,3*S*; II-2*R*,3*R*) (**182**); GB_{4a} (I-2 *S*,3 *R*; II-2*R*,3*R*) (**183**).		Ferrari et al., 2003[344].
Gnidia socotrana (Balf. f.) Gilg (leaves and twigs)	***Coumarin-flavone dimers:*** (I-8,II-6)-Umbelliferyl-apigenin (**280**); (I-5,II-8)-umbelliferylapigenin (**281**).	Yemenian plant. Applications as molluscicidal agent, arrow and fish poison.	Franke et al., 2002[345].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Stellera chamaejasme L. (roots)	***Chamaejasmins [(I-3,II-3)-biflavonoids]***: I-5,7,4′,II-5,7,4′-Hexahydroxy-(I-3,II-3)-biflavone (**121**); neochamaejasmin A (**132**); I-7-*O*-methylneochamaejasmin A (**134**); neochamaejasmin B (**133**); chamaejasmin (**123**); isochamaejasmin (**130**); ruixianglangdusu A (**143**); ruixianglangdusu B (**144**); chamaejasmenin A (**138**); chamaejasmenin B (**139**); chamaejasmenin C (**141**); chamaejasmenin D (**142**); isochamaejasmenin B (**140**); sikokianin A (**135**); daphnodorin B (**319**); daphnodorin I (**447**).	Used as "Langdu" in traditional Chinese medicine. ***Potent antimitotic and antifungal activity.*** ***Antiviral effect on Hepatitis B Virus***. ***Antibacterial, and immunomodulatory activities.*** ***Induction of cell cycle arrest and apoptosis by neochamaejasmin A in human prostate LNCaP cancer cells.***	Niwa et al., 1984[346], 1986[347]; Xu et al., 2001[348]; Jiang et al., 2002[349]; Yang et al., 2005[350]; Liu et al. 2008[60]; Zhao et al., 2008[351]; Yang and Chen, 2008[352].
Wikstroemia indica (L.) C. A. Mey. (roots)	***Flavone-flavan dimer:*** Wikstrol B (**186**). ***Chamaejasmins [(I-3,II-3)-biflavonoids]***: Sikokianin B (**136**); sikokianin C (**137**). Neochamaejasmin B (**133**); genkwanol B (II-2*S*) (**378**); genkwanol C (II-2*R*) (**379**); stelleranol (= II-3*R* isomer of **379**).	*Radix Wikstroemiae* is a traditional Chinese herbal medicine. ***Antibacterial, antiviral, anti-inflammatory, anti-tumor and antifertility effects.Potent antimalarial activity.*** ***Good anti-HIV-1 activity***. Genkwanol B (**378**), **379** and the II-3*R* isomer of **379** (stelleranol), which are stereoisomers of spirobiflavonoids, showed *potent anti-respiratory syncytial virus (RSV) activity*, whereas neochamaejasmin B did not.	Nunome et al., 2004[88]; Singh et al., 2005[353]; Li et al., 2009[66]; Huang et al., 2010[354].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Wikstroemia sikokiana Fr. et Sav. (roots)	***Chamaejasmins [(I-3,II-3)-biflavonoids]***: Sikokianin A (**135**); sikokianin B (**136**).		Niwa et al., 1986[355]; Baba et al., 1994[356]; Xu et al., 2001[348].
Vahliaceae			
Vahlia capensis (L.f.) Thunb. (aerial parts)	***Rare biflavonoids***: VC-15B (vahlia biflavone) (**442**).	***Antibacterial properties***.	Majinda et al., 1997[357].
Verbenaceae			
Verbena littoralis H. B. K. (aerial parts)	***(I-3,O,II-4)-Bidihydrochalcone:*** Verbenachalcone (**302**). ***(I-4,O,II-4)-Bidihydrochalcone:*** Littorachalcone (**301**).	A traditional folk medicine in Paraguay. ***Neuritogenic activity (useful for the medical treatment of dementia).*** Littorachalcone caused a significant enhancement of nerve growth factor (NGF)-mediated neurite outgrowth from PC12D cells. Therefore, useful in the treatment of neurological disorders, such as Parkinson′s disease, Alzheimer′s disease, Huntington′s disease, amyotrophic lateral sclerosis, and human immunodeficiency virus associated dementia.	Li et al., 2001[358], 2003[359].
Vitaceae			
Vitis amurensis Rupr. (seeds)	***Spirobiflavonoid (two C_{15} moieties of flavonoid origin):*** Vitisinol (**449**).	Traditional Chinese medicine.	Wang et al., 2000[360].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
MONOCOTS			
AGAVACEAE			
Yucca schidigera Roezl. (bark) (The genus *Yucca* was formerly included in the family Yuccaceae)	***Spiro-compounds (a spiro benzopyran-4-cyclopentan-3-one derivative made up of C_{15} and C_{14} moieties):*** Yuccaone A (**450**); yuccaol A (**451**); yuccaol B (**453**); yuccaol C (**454**); yuccaol D (**452**); yuccaol E (**455**). ***Spirobiflavonoid (two C_{15} moieties of flavonoid origin):*** Larixirol (**448**).	Mexican medicinal plant. ***Anti-inflammatory and anti-arthritic effects. Anti-platelet action. Antioxidant activity. Inhibition of the nuclear transcription factor NFκB.*** NFκB stimulates synthesis of inducible nitric oxide synthase (iNOS), which causes formation of the inflammatory agent nitric oxide.	Oleszek et al., 2001[361, 362]; Piacente et al., 2002[363], 2004[364], 2005[365]; Cheeke et al., 2006.
Amaryllidaceae			
Agapanthus africanus (L.) Hoffmanns. (roots)	***Bidihydrochalcone***: (I-α,II-α; I-β,II-β)-Bidihydroisoliquiritigenin (**329**).	*A. africanus* is used as a traditional medicine by local South African women during pregnancy.	Kamara et al., 2005[366].
Iridaceae			
Isophysis tasmanica (Hook.) T. Moore (leaves)	Amentoflavone (**1**); podocarpusflavone A (**6**); I-2,3-dihydroamentoflavone (**31**); hinokiflavone (**235**).		Williams and Harborne, 1985[367]; Williams et al., 1986[368]; 1987[369].
Patersonia glabrata R. Brown (leaves)	Amentoflavone (**1**).		Williams and Harborne, 1985[367]; Williams et al., 1989[370].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Patersonia pygmaea Lindl. (leaves)	Amentoflavone (**1**).		Williams et al., 1989[370].
Lanariaceae			
Lanaria lanata (L.) Dur. & Schinz (= *L. plumosa* Ait.) (whole plant)	Lanaroflavone (**249**); amentoflavone (**1**).	***Lanaroflavone is an active antiplasmodial compound***.	Dora and Edwards, 1991[371]; Harborne and Williams, 1994[372]; Weniger et al., 2006[86].
Nartheciaceae			
Lophiola aurea Ker-Gawler [= *Lophiola americana* (Pursh) Wood]	***(I-3,II-8)-Flavanone-flavanonol***: GB_{1a} (**167**).		Zavada et al., 1983[373]; Harborne and Williams, 1994[372].
RUSCACEAE (FORMERLY DRACAENACEAE; OR AGAVACEAE)			
DRACAENA CINNABARI BALF.FIL. (resin: Dragon′s blood)	***DIHYDROCHALCONE-DEOXODIHYDROCHALCONE***: CINNABARONE (**355**).		Massaoud et al., 1995[374].
Velloziaceae			
Nanuza plicata (Mart.) L.B. Sm. & Ayensu (leaves)	Amentoflavone (**1**).		Williams et al., 1991[375]; Harborne and Williams,1994[372]

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Xerophyta plicata Spreng. (leaves)	Amentoflavone (**1**).		Williams et al., 1987[369], 1991[375]; Harborne and Williams,1994[372]
BRYOPHYTA (mosses)			
Aulacomniaceae			
Aulacomnium androgynum (Hedw.) Schwaegr. (gametophyte)	***Biaurone***: Aulacommiumbiaureusidin (**257**). ***(I-2',II-8)-Biflavonoids:*** *Philonotisflavone **(204)**; I-2,3-dihydro-philonotisflavone **(206)**.* ***(I-2',II-6)-Biflavonoids:*** I-2,3-Dihydrodicranolomin (**197**).		Hahn et al., 1995[376].
Aulacomnium palustre (Hedw.) Schwaegr. (gametophyte)	***Biaurone***: Aulacommiumbiaureusidin. ***Biflavones:*** I-5',II-3′-Dihydroxyamentoflavone (**24**); I-5',II-3′-dihydroxyrobustaflavone (**73**); I-5',II-3′-dihydroxy-I-2,3-dihydroamentoflavone (**43**); dicranolomin (**194**).		Hahn et al., 1995[376].
Bartramiaceae			

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Bartramia pomiformis Hedw. (gametophyte)	***Doubly linked biflavonoid:*** Bartramiaflavone (= two equilibrating cyclo-oxo tautomers) (**208**). Dicranolomin (**194**); philonotisflavone (**204**); I-2,3-dihydrophilonotisflavone (**206**); (I-5′,II-8)-biluteolin (**25**).	***Antibacterial activity against Gram (+) bacteria***. Enhancement of antibacterial activity against *Staphylococci* by UV-A light irradiation. ***Allelochemical activity*** on spore germination and sporeling growth of the moss *Tortula muralis* and on root development of *Raphanus sativus* L	Seeger et al., 1991 [377]; Basile et al., 1999[378], 2003[379]; Kang et al., 2007[380].
Philonotis fontana (Hedw.) Brid. (gametophyte)	Dicranolomin (**194**); I-5′,II-3′-dihydroxyrobustaflavone (**73**); philonotisflavone (**204**); I-2,3-dihydrophilonotisflavone (**206**); (I-5′,II-8)-biluteolin (**25**); I-5′,II-3′-dihydroxy-I-2,3- dihydroamentoflavone (**43**).		Geiger and Bokel, 1989[381].
Brachytheciaceae			
Homalothecium lutescens Philibert in Husnot) Hedenäs & L. Söderström (gametophyte)	***(I-3',II-3')-Biflavonoids***: I-2,3-Dihydro-(I-3′,II-3′)-biapigenin (**209**); (I-3′,II-3′)-binaringenin (**211**).		Seeger et al., 1993[382].
Bryaceae			
Bryum capillare Hedw.	***Isoflavone-flavone dimers***: Bryoflavone (**275**); heterobryoflavone (**274**).		Geiger et al., 1987[383].
Dicranaceae			

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Dicranoloma robustum (Hook. & Wilson) Paris (gametophyte)	Dicranolomin (**194**); I-2,3-dihydrodicranolomin (**197**); I-5′,II-3′-dihydroxyrobustaflavone (**73**); II-2,3-dihydro-(I-3′,II-6)-biluteolin (**80**); (I-5′,II-8)-biluteolin (**25**).		Markham et al., 1988[384]
Campylopus clavatus (R. Brown) Wils. (gametophyte)	***(I-5′,II-6)-Auroneflavanone dimer:*** Campylopusaurone (**265**). ***Biflavones***: I-5′,II-3′-dihydroxyrobustaflavone (**73**); I-5′,II-3′-dihydroxyamentoflavone (**24**); (I-5′,II-8)-biluteolin (**25**).		Geiger and Markham,1992[385].
Campylopus holomitrium (CM) Jaeg. (gametophyte)	***(I-3′,II-6)-Auroneflavanone dimer:*** Campylopusaurone (**265**). ***Biflavones***: I-5′,II-3′-dihydroxyrobustaflavone (**73**); (I-5′,II-8)-biluteolin (**25**). ***(I-3′,II-8)-Flavone-flavonol:*** I-5′,II-3-dihydroxyamentoflavone (**29**).		Geiger and Markham,1992[385].
Grimmiaceae			
Racomitrium lanuginosum **(Hedw.) Brid. (gametophyte)**	I-5′,II-3′-Dihydroxyrobustaflavone (**73**); (I-5′,II-8)-biluteolin (**25**).		Geiger et al., 1988[6].
Hylocomiaceae			
Rhytidiadelphus squarrosus **(Hedw.) Warnst. (gametophyte)**	I-5′-Hydroxyrobustaflavone (72); I-5′-hydroxyamentoflavone (**23**); (I-5′,II-8)-biluteolin (**25**); I-5′-hydroxy-I-2,3-dihydroamentoflavone (**42**).		Seeger et al., 1990[386].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Hypnaceae			
Hypnum cupressiforme Hedw. **(gametophyte)**	Hypnogenol A (**213**); hypnogenol B (**212**); I-3,5,7,4′,II-3,5,7,3′,4′-nonahydroxy-(I-3′, II-6)-biflavanone (**85**); I-3,5,7,4′,II-3,5,7-heptahydroxy-(I-3′,*O*,II-4′)-biflavanone (**230**). ***(I-3',II-3')-Biflavonoid***: Hypnogenol B1 (**210**). ***Rearranged ketalized dimers:*** Hypnumbiflavonoid A (**380**).		Sievers et al., 1992[387], 1994[388].
Leptostomataceae			
Leptostomum macrocarpon Brid. (gametophyte) (The genus *Leptostomum* is alternately included in the family Bryaceae)	I-5′,II-3′-Dihydroxyamentoflavone (**24**); I-5′,II-3′dihydroxyrobustaflavone (**73**); dicranolomin (**194**); I-5′,II-3′-dihydroxy-I-2,3-dihydroamentoflavone (**43**).		Brinkmeier et al., 1998[389].
Leucodontaceae			
Antitrichia curtipendula Timm ex Hedwig (gametophyte)	I-5′,II-3′-Dihydroxyrobustaflavone (**73**); (I-5′,II-8)-biluteolin (**25**).		Geiger et al., 1988[6].
Meteoriaceae			
Pilotrichella cuspidata Broth. (gametophyte)	(I-3′,II-3′)-Binaringenin (**211**).		Seeger et al., 1992[390].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Pilotrichella flexilis (Hedw.) Ångstr. (gametophyte)	(I-3′,II-3′)-Binaringenin (**211**). ***(I-2',II-6)-Biflavonoid***: I-2,3,II-2,3-Tetrahydrodicranolomin (**200**). ***(I-2',II-6)-Aurone-flavone***: Pilotrichellaaurone (**264**).		Brinkmeier et al., 2000[391].
Mniaceae			
Mnium hornum Hedw. (gametophytes)	***(I-2',II-8)-Biflavone***: Philonotisflavone (**204**); II-4′-*O*-methylphilonotisflavone (**205**); II-2,3-dihydrophilonotisflavone (**207**).		Brinkmeier et al., 1999[392].
Plagiomnium cuspidatum (Hedw.) T. Kop. (gametophyte)	I-5′,II-3′-Dihydroxyrobustaflavone (**73**); I-5′-hydroxy-I-2,3-dihydrorobustaflavone (**78**); I-5′-hydroxy-I-2,3-dihydroamentoflavone (**42**); I-5′,II-3′-dihydroxy-I-2,3-dihydro-amentoflavone (**43**).		Anhut et al., 1989[393].
Plagiomnium elatum (B. & S.) T. Kop.*(gametophyte)*	I-5′-Hydroxyamentoflavone (**22**).		Geiger et al., 1988[6].
Plagiomnium undulatum (Hedw.) T. Kop. (gametophyte)	***(I-2',II-6)-Biflavones***: II-3′-Deoxy-dicranolomin (**195**); II-3′-deoxy-I-2,3-dihydrodicranolomin (**196**); ***(I-3',II-8)-Biflavonoids:*** I-5′-Hydroxy-I-2,3-dihydroamentoflavone (**42**); I-5′,II-3′-dihydroxy-I-2,3-dihydroamentoflavone (**43**).		Geiger et al., 1988[6]; Anhut et al., 1989[393]; Rampendahl et al., 1996[394]; Harris, 2009[395].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
	Robustaflavones [(I-3',II-6)-flavanone-flavone]: I-5′-Hydroxy-I-2,3-dihydrorobustaflavone (**78**) ; I-5′,II-3′-dihydroxy-I-2,3-dihydrorobustaflavone (**79**) .		
PTERIDOPHYTA (ferns)			
Cyatheaceae			
Alsophila spinulosa (Hook.) R.M.Tryon (fronds)	***(I-6,II-2')-Biflavonoids:*** Hegoflavone A (**198**); hegoflavone B (**199**).	*Asian herbal medicine.* ***Immunomodulatory effects***: Immunostimulation of both humoral and cellular immune responses. Chloroplast genome sequence.	Wada et al., 1985[396]; Kao et al., 1994[397]; Gao et al., 2009[398].
Pteridaceae			
Pentagramma triangularis (Kaulfuss) Yatskievych, Windham, & E. Wollenweber spp *triangularis* [= *Pityrogramma triangularis* (Kaulf.) Maxon] (frond exudates)	***(I-8,CH_2,II-8)-Methylene-bridged biflavonol***: Pentagrammetin (**256**). ***(I-3',CH_2,II-8)-Methylene-bridged dihydrochalcone-flavonol***: Trianguletin (**305**).		Roitman et al., 1993[399].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Pentagramma triangularis (Kaulfuss) Yatskievych, Windham, & E. Wollenweber (farinose exudate)	***(I-3',CH_2,II-8)-Methylene-bridged dihydrochalcone-flavonol and methoxyflavone dimers***: Trianguletin (**305**); I-2′,6′-dihydroxy-I-4′-methoxy-I-5′-methyl-I-α,β-dihydrochalcone-(I-3′,CH_2,II-8)-II-5,7-dihydroxy-II-3-methoxyflavone (**306**); I-4,2′,6′-trihydroxy-I-4′-methoxy-I-5′-methyl-I-α,β-dihydrochalcone-(I-3′,CH_2,II-8)-II-4′-*O*-methylkaempferol (**307**); I-4,2′,6′-trihydroxy-I-4′-methoxy-I-5′-methyl-I-α,β-dihydrochalcone-(I-3′,CH_2,II-8)-II-5,7-dihydroxy-II-3,4′-dimethoxyflavone (**308**); I-4,2′,6′-trihydroxy-I-4′-methoxy-I-5′-methyl-I-α,β-dihydrochalcone-(I-3′,CH_2,II-8)-II-5,7-dihydroxy-II-3-methoxyflavone (**309**).		Iinuma et al., 1994[400], 1997[401].
PLYCOPODIOPHYTA (OR LYCOPHYTA)			
Selaginellaceae (club mosses or spike mosses)			

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Selaginella bryopteris (L.) Bak (aerial parts)	Amentoflavone (**1**); I-2,3-dihydroamentoflavone (**31**); II-2,3-dihydroamentoflavone (**44**); I-2,3,II-2,3-tetrahydroamentoflavone (**47**); sciadopitysin (**15**); hinokiflavone (**235**); I-2,3-dihydrohinokiflavone (**241**); II-2,3-dihydrohinokiflavone (**244**); I-2,3,II-2,3-tetrahydrohinokiflavone (**247**); I-4′-*O*-methylamentoflavone (bilobetin) (**3**); I-7-*O*-methylamentoflavone (sequoiaflavone) (**2**); I-7,II-7,4′-tri-*O*-methylamentoflavone (heveaflavone) (**18**); I-7-*O*-methylhinokiflavone (**236**).	Indian medicinal herb. ***Antiprotozoal activity: Antiplasmodial and leishmanicidal activity.***	Swamy et al., 2006[402]; Kunert et al., 2008[89]; Batista et al., 2009[403].
Selaginella delicatula (Desv.) Alston (aerial parts)	**(I-3,O,II-4′)-Biflavone: Delicaflavone (252).** **Robustaflavones [(I-3′,II-6)-biflavonoids]: Robustaflavone (64); I-4'-O-methylrobustaflavone (65); I-7,4'-di-O-methylrobustaflavone (68); I-4′,II-4′-di-O-methylrobustaflavone (69); I-7,4′,II-4′-tri-O-methylrobustaflavone (70);**	***Cytotoxic activity on various tumor cell lines.***	. Meurer-Grimes et al., 1999[404]; Lin and Chou, 2000[405]; Lin et al., 2000[37]; Chen et al., 2005c[58].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
	I-7,4',II-7-tri-O-methyl-2,3-dihydrorobustaflavone (77); I-7,4'-di-O-methyl-II-2,3-dihydrorobustaflavone (81); I-7,4',II-7-tri-O-methyl-II-2,3-dihydrorobustaflavone (82). (I-3′,II-8)-Biflavonoids: Amentoflavone (1); I-7,4′-di-O-methyl-I-2,3-dihydroamentoflavone (37); I-7,4′,II-7-tri-O-methyl-I-2,3-dihydroamentoflavone (41). ***(I-4',O,II-6)-Biflavonoids:*** I-2,3-Dihydroisocryptomerin (**242**); I-7-O-methyl-II-2,3-dihydroisocryptomerin (**243**); chamaecyparin (**240**).		
Selaginella doederleinii Hieron. (whole plant)	I-7,4',II-7-Tri-*O*-methyl-I-2,3,II-2,3-tetrahydrorobustaflavone (**84**); I-7,4',II-7-tri-*O*-methylrobustaflavone (**70**); amentoflavone (**1**); I-7,II-7-di-*O*-methylamentoflavone (**10**); I-7,4',II-7,4'-tetra-*O*-methylamentoflavone (**19**); heveaflavone (**18**).	Use of the plant in traditional Chinese medicine as an anticancer agent. ***Cytotoxic*** biflavonoids **1** and **2** against the three human cancer cell lines, HCT, NCI-H358, and K562.	Lin et al., 1994[406]; Lee et al., 2008[407]

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Selaginella labordei Hieron. ex Christ. (aerial parts)	I-4'-*O*-Methylrobustaflavone (**65**); robustaflavone (**64**); amentoflavone (**1**); I-6,II-6-dimethyl-I-2,3-dihydroochnaflavone (**222**); I-2,3-dihydroochnaflavone (**221**); II-2,3-dihydroochnaflavone (**225**).	Used in traditional Chinese medicine. Medicinal plant used in the Hubei province of China with ***anti-virus and antioxidant activities***. Extracts ***inhibited xanthine oxidase (XOD) and lipoxygenase activities***, and were radical scavengers. Extracts down-regulated cyclooxygenase-2 gene expression in human colon adenocarcinoma CaCo-2 cells. Robustaflavone is ***effective against the hepatitis B virus.***	Chen et al., 2005[408]; Tan et al., 2009[409]; Xu et al., 2009[410].
Selaginella lepidophylla (Hook et Grev.) Spring (aerial parts)	Robustaflavone (**64**); I-2,3-dihydrorobustaflavone (**75**); I-5-*O*-methyl-I-2,3-dihydrorobustaflavone (**76**).	All compounds **inhibited photosynthesis in spinach chloroplasts;** inhibited ATP production. (**64**) and (**75**) behaved as Hill reaction inhibitors; (**64**) interacted with photosystem II, transforming the reaction centers to silent centers at 300 and 600 μM. The interaction and inhibition target of (**75**) was located on Cyt b6f to PC. The three compounds also behaved as energy transfer inhibitors, (**76**) being the most active.	Aguilar et al., 2008[411].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Selaginella moellendorffii Hieron. (whole plant)	Amentoflavone (**1**); hinokiflavone (**235**); ginkgetin (**7**); isoginkgetin (**13**); kayaflavone (**17**); podocarpusflavone A (**6**); bilobetin (**3**); I-4′-*O*-methylrobustaflavone (**65**); I-7,4′,II-7,4′-tetra-*O*-methylamentoflavone (**19**).	Used in folk medicine for the treatment of gonorrhea, jaundice, hepatitis, and bleeding. ***Anti-HBV and cytotoxic activity. Selective cytotoxicity of ginkgetin*** against OVCAR-3 (human ovarian adenocarcinoma) cells (IC_{50} = 1.8 μg/mL). Ginkgetin is an active ***leishmanicidal compound***. Ginkgetin also showed a good ***antitrypanosomal activity***.	Sun et al., 1997[39]; Weniger et al., 2006[86]; Cao et al., 2010[44].
Selaginella rupestris (L.) Spring. (aerial parts)	Amentoflavone (**1**).	Pharmacological activity of amentoflavone on central nervous system, smooth muscles and isolated frog heart preparations.	Chakravarthy et al., 1981[412].
Selaginella sinensis (Desv.) Spring. (aerial parts)	Amentoflavone (**1**); robustaflavone (**64**); I-4′,II-7-di-*O*-methylamentoflavone (**12**); II-7-*O*-methylrobustaflavone (**66**); ginkgetin (**7**); I-2,3-dihydroamentoflavone (**31**); I-4′-*O*-methylrobustaflavone (**65**) and hinokiflavone (**235**).	***Potent antiviral activity*** against respiratory syncytial virus (RSV). *Radical scavenging activity*.	Ma et al., 2001[413] ; Zhang et al., 2011[414].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Selaginella tamariscina (Beauv.) Spring (aerial parts)	Amentoflavone (**1**); II-6-hydroxyamentoflavone (**20**); (I-2′,II-8)-biapigenin (**202**); taiwaniaflavone (**189**); bilobetin (**3**); robustaflavone (**64**); hinokiflavone (**235**); heveaflavone (**18**); II-7-*O*-methylamentoflavone (= podocarpusflavone A) (**6**); isocryptomerin (**237**); cryptomerin B (**239**).	Used extensively in traditional Chinese medicine for the treatment of many kinds of chronic diseases. *Antiinflammatory and tumoricidal activities against leukemia cell lines, and reduction in tumor growth in epithelial cell tumors.* Extracts showed inhibitory effect on the growth and metastasis of Lewis lung carcinoma cells *in vivo*. *Amentoflavone has shown antioxidant, antifungal against several pathogenic fungal strains, anti-HIV, antiinflammatory, anti-phospholipase C γ1, anti-protein tyrosine phosphatase 1B (PTP1B) (proposed as a strategy for the treatment of type 2 diabetes and obesity), and vasorelaxant effects.* *Amentoflavone induced breast cancer apoptosis through blockade of fatty acid synthesis. Sumaflavone and amentoflavone inhibited UV irradiation induced activity of matrix metalloproteinase-1 (MMP-1) in primary fibroblasts from human skin.* *Bilobetin is an active* ***leishmanicidal*** *compound.*	Miao et al., 1996[415]; Lee et al., 1996[416], 1999[417], 2008[55], 2009[51]; Kang et al., 2004[93] ; Woo et al., 2005[418], 2006[419]; Yin et al., 2005[420]; Jung et al., 2006[421], 2007[422]; Weniger et al., 2006[86]; Na et al., 2007[423]; Yang et al., 2007[424]; Cheng et al., 2008[425]; Yuan et al., 2008[426]; Lee et al., 2009[51].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Selaginella uncinata (Desv.) Spring (aerial parts)	Amentoflavone (**1**); hinokiflavone (**235**); I-5,7,4',II-5-tetrahydroxy-II-7-methoxy-(I-3,*O*,II-4')-biflavone (**253**); I-7,4′,II-7,4′-tetra-*O*-methylamentoflavone (**19**); heveaflavone (=I-7,II-7,4′-tri-*O*-methylamentoflavone) (**18**); I-7,II-7-di-O-methylamentoflavone (**10**).	Medicinal plant used to treat acute infectious jaundice including hepatitis, cholecystitis, enteritis. ***Anti-viral activity:*** anti-HSV-1 virus and Cox B3 virus activity. ***Potent anti-anoxic effect.***	Ma et al., 2003[427]; Zheng et al., 2008[428]; Ting et al., 2010[429].
Selaginella willdenowii (Desv. ex Poir.) Baker (leaves)	I-4',II-7-Di-*O*-methylamentoflavone (**12**); II-7-*O*-methylrobustaflavone (**66**); isocryptomerin (**237**); amentoflavone (**1**); bilobetin (**3**); robustaflavone (**64**); II-2,3-dihydroisocryptomerin (**245**).	(**12**), (**66**) and (**237**) were significantly ***cytotoxic*** against a panel of human cancer cell lines; (**3**) is an active ***leishmanicidal*** compound.	Silva et al., 1995[430]; Weniger et al., 2006[86].
GYMNOSPERMAE			
Gymnospermae (leaf exudates) (epicuticular material of a number of species).	***Biflavones***: amentoflavone (**1**); bilobetin (**3**); podocarpusflavone A (**6**); sciadopitysin (**15**); cupressuflavone (**86**).	Bilobetin is an active ***leishmanicidal*** compound.	Wollenweber et al., 1998[431]; Weniger et al., 2006[86].
Araucariaceae			
Agathis alba Rumphius ex Jeffrey (leaves)	Amentoflavone (**1**); hinokiflavone (**222**); cupressuflavone (**86**); I-7-*O*-methylcupressuflavone (**88**); I-7, II-7-di-*O*-methylcupressuflavone (**92**); agathisflavone (**100**); I-7-*O*-methylagathisflavone (**101**); I-7, II-4′-di-*O*-methylagathisflavone (**105**).		Khan et al., 1972[432]; Ofman et al., 1995[433].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Agathis australis (D. Don) Lindl. (leaves)	I-7-*O*-Methylagathisflavone (**101**); I-7,II-7-di-*O*-methylagathisflavone (**104**); I-7,4′-II-7-tri-*O*-methylagathisflavone (**107**); I-7,4',II-7,4′-tetra-*O*-methylagathisflavone (**109**); I-7-*O*-methylcupressuflavone (**88**); I-7,II-7-di-*O*-methylcupressuflavone (**92**); I-7,4′-II-7-tri-*O*-methylcupressuflavone (**94**); I-7,4',II-7,4′-tetra-*O*-methylcupressuflavone (**95**).		Ofman et al., 1995[433].
Agathis atropurpurea B. Hyland (leaves)	I-7-*O*-Methylagathisflavone (**101**); I-7,II-7-di-*O*-methylagathisflavone (**104**); I-7,4′-II-7-tri-*O*-methylagathisflavone (**107**) (in less quantities); I-7-*O*-methylcupressu- flavone (**88**); I-7,II-7-di-*O*-methyl-cupressuflavone (**92**); I-7,4′-II-7-tri-*O*-methylcupressuflavone (**94**) (in less quantities).		Ofman et al., 1995[433].
Agathis ovata (Moore) Warb. (leaves)	I-7-*O*-Methylagathisflavone (**101**); I-7,II-7-di-*O*-methylagathisflavone (**104**) (in higher quantities); I-7,4′-II-7-tri-*O*-methylagathisflavone (**107**); I-7,4',II-7,4′-tetra-*O*-methylagathisflavone (**109**); I-7-*O*-methylcupressuflavone (**88**);		Ofman et al., 1995[433].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
	I-7,II-7-di-*O*-methylcupressuflavone (**92**) (in higher quantities); I-7,4′-II-7-tri-*O*-methyl-cupressuflavone (**94**); I-7,4',II-7,4′-tetra-*O*-methylcupressuflavone (**95**).		
Agathis robusta (F. Muell.) F. M. Bailey (leaves)	I-7-*O*-Methylagathisflavone (**101**); I-7,II-7-di-*O*-methylagathisflavone (**104**); I-7-*O*-methylcupressuflavone (**88**); I-7,II-7-di-*O*-methylcupressuflavone (**92**).		Ofman et al., 1995[433].
Araucaria angustifolia (Bert.) O. Kuntze (leaves)	Bilobetin (**3**); II-7-*O*-methyl-robustaflavone (**66**); cupressuflavone (**86**).	A Brazilian medicinal plant used for the treatment of various diseases, including dry skin, herpes disease, wounds, and sexually transmitted diseases. Bilobetin is an active ***leishmanicidal*** compound. ***Antiviral activity: antiherpes activity*** (Herpes Simplex Virus type 1, HSV-1).	Weniger et al., 2006[86]; Freitas et al., 2009[79].
Araucaria angustifolia (Bert.) O. Kuntze (needles) Brazilian pine.	Amentoflavone (**1**); ginkgetin (**7**); I-7,4′, II-7,4′-tetra-*O*-methylamentoflavone (**19**); bilobetin (**3**); I-4′,II-4′-di-*O*-methyl-amentoflavone (isogingketin) (**13**);I-7,4′,II-7-tri-*O*-methylamentoflavone (**16**); dioonflavone (**22**).	***Photoprotection: Biflavonoids protect against DNA UV-induced damage and lipoperoxidation*** promoved by reactive species (RNOS).	Yamaguchi et al., 2005[111], 2009[434].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Araucaria angustifolia (Bert.) O. Kuntze (seedling stems)	I-7,4′,II-7-Tri-*O*-methylamentoflavone (**16**); I-7,4′,II-4′-tri-*O*-methyl-amentoflavone (sciadopitysin) (**15**); I-4′,II-4′-di-*O*-methylamentoflavone (isogingketin) (**13**).		Fonseca et al., 2000[435].
Araucaria araucana (Molina) K. Koch (leaves)	***Biflavones:*** I-7-*O*-Methylagathisflavone (**101**); I-7,II-7-di-*O*-methylcupressu-flavone (**92**); sotetsuflavone (= II-7-*O*-methylamentoflavone) (**5**); I-7,II-7-di-*O*-methylagathisflavone (**104**); I-4',II-7-di-*O*-methylamentoflavone (**12**); I-7,4',II-7-tri-*O*-methylagathisflavone (**107**); kayaflavone (**17**); I-7,4',II-7-tri-*O*-methylcupressuflavone (**94**).		Parveen et al., 1987[436].
Araucaria bidwillii Hook (leaves)	I-7-*O*-Methylcupressuflavone (**88**); I-7,II-7-di-*O*-methylagathisflavone (**104**); I-7-*O*-methylagathisflavone (**101**); I-7,II-4′-di-*O*-methylagathisflavone (**105**); I-7,II-7-di-*O*-methylcupressuflavone (**92**); bilobetin (**3**).	***Analgesic and anti-inflammatory activity. Neuroprotective potential of biflavones rich fraction against ischemia/reperfusion (I/R) induced oxidative stress.***	Khan et al., 1972[432]; Dhanasekaran et al., 1994[437] ; Mukherjee et al., 2007[438].
Araucaria excelsa (Lamb.) R. Br. [= *A. heterophylla* (Salisb.) Franco] (leaves)	II-7-*O*-Methylamentoflavone (**5**); I-7,II-7-di-*O*-methylamentoflavone (**10**); I-7,4′-di-*O*-methylcupressuflavone (**90**) or I-7,II-4′-di-*O*-methylcupressuflavone (**91**);		Ilyas et al., 1978[439].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
	I-7,II-7,4′-tri-*O*-methylagathisflavone (**108**); I-7,4′, II-7-tri-*O*-methylamentoflavone (**16**); I-7,II-7-di-*O*-methylagathisflavone (**104**); I-7,4′, II-7,4′-tetra-*O*-methylamentoflavone (**19**); I-7,4′,II-7,4′-tetra-*O*-methylcupressuflavone (**95**); amentoflavone (**1**); cupressuflavone (**86**); agathisflavone (**100**).		
Cephalotaxaceae			
Cephalotaxus harringtonia K. Koch var. *fastigiata* Rehder (leaves)	I-6-Methyl-I-2,3-dihydroginkgetin (**36**); I-6-methyl-I-2,3-dihydrobilobetin (**35**); I-6-methyl-I-2,3-dihydrosequoiaflavone (**33**).		Sasaki et al., 2008[224].
Cephalotaxus koreana Nakai (leaves and twigs)	Bilobetin (**3**); ginkgetin (**7**); I-4′,II-7-di-*O*-methylamentoflavone (**12**); I-7,4′-II-7-tri-*O*-methylamentoflavone (**16**); sciadopitysin (**15**); I-7,4′,II-7,4′-tetra-*O*-methylamentoflavone (**19**).	Increased osteoblast differentiation as assessed by alkaline phosphatase activity, collagen synthesis, and mineralization.	Lee et al., 2006[440].
Cephalotaxus oliveri Mast. (leaves)	***Biflavones:*** Sciadopitysin (**15**); I-7,4′,II-7,4′-tetra-*O*-methylamentoflavone (**19**); oliveriflavone (**21**).	***Cytotoxic activity.***	Ma et al., 1986[441].
Cephalotaxus wilsoniana Hayata (stems)	***Biflavones:*** Kayaflavone (**17**); taiwanhomoflavone A (**8**).	***Cytotoxic activity:*** Inhibitory effects against KB, Hepa-3B, and Hela cancer cell lines.	Kuo et al., 2000[40].
Cephalotaxus wilsoniana Hayata (twigs)	***Biflavones:*** I-7,4',II-7-Tri-*O*-methyl-amentoflavone (**16**); taiwanhomoflavone B (**246**).	***Cytotoxic activity:*** Inhibitory effects against KB oral epidermoid carcinoma and Hepa-3B hepatoma cells.	Kuo et al., 2002[36].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Torreya nucifera (L.) Siebold & Zucc. (leaves)	Amentoflavone (**1**).	*Traditionally used as a medicinal plant in Asia.* The ethanol extract showed good SARS-CoV $3CL^{pro}$ inhibitory activity (62% at 100 μg/mL). Amentoflavone (**1**) showed the most potent $3CL^{pro}$ inhibitory effect (IC_{50}=8.3 μM). Inhibitory activity appeared to be associated with the presence of an apigenin moiety at position C-3' of flavones, as biflavone had an effect on $3CL^{pro}$ inhibitory activity.	Ryu et al., 2010[442].
Cycadaceae			
Cycas beddomei Hort. ex Hook f. (cones)	***Hinokiflavone Series [(I-4',O,II-6)-biflavanones]:*** I-2,3,II-2,3-Tetrahydrohinokiflavone (**247**); I-7,II-7-di-*O*-methyltetrahydro-hinokiflavone (**248**). ***Amentoflavone Series [(I-3',II-8)-biflavones]:*** II-4′-*O*-Methyl-I-2,3,II-2,3-tetrahydroamentoflavone (**53**); I-2,3,II-2,3-tetrahydroamentoflavone (**47**); I-2,3-dihydro-amentoflavone (**31**).		Rani et al., 1998[443]; Jayaprakasam et al., 2000[297]; Das et al., 2005[444].

Plant (Part of the plant)	**Compounds**	**Bioactivity. Traditional uses.**	**Author, References**
Cycas circinalis L. (leaflets) (leaves)	(I-2*S*,II-2*S*)-I-4',II-4'-di-*O*-methyl-I-2,3,II-2,3-tetrahydroamentoflavone (= tetrahydroisoginkgetin) (**54**); I-4'-*O*-methyl- I-2,3,II-2,3-tetrahydroamentoflavone (**52**); I-4'-*O*-methyl-I-2,3-dihydroamentoflavone (**34**).	Used by the Zulus as medicine, the tuberous root for a wide varieties of conditions, and the underground stem as a purgative. Treatment of cholic spasms due to relaxation effect similar to that of atropine, though less potent. ***Moderately active antibacterial biflavonoids*** against *Staphylococcus aureus* and methicillin-resistant *S. aureus.*	Audu Ali et al., 2007[445]; Moawad et al., 2010[77].
Cycas revoluta Thunb. (leaflets) (leaves)	Amentoflavone (**1**); hinokiflavone (**235**); sotetsuflavone (**5**); 2,3-dihydroamentoflavone (**31**); I-2,3-dihydrohinokiflavone (**241**); (I-2*S*,II-2*S*)-I-4',II-4'-di-*O*-methyl-I-2,3,II-2,3-tetrahydroamentoflavone (= tetrahydroisoginkgetin) (**54**); I-4'-*O*-methyl-I-2,3,II-2,3-tetrahydroamentoflavone (**52**); I-4'-*O*-methyl-I-2,3-dihydroamentoflavone (**34**).	***Moderately active antibacterial biflavonoids*** (see *C. circinalis*).	Geiger and de Groot Pfleiderer, 1971[446]; Moawad et al., 2010[77].
Cycas rumphii Miq. (leaves)	Amentoflavone (**1**).	Amentoflavone is an inhibitor of phospholipase C γ1, an irreversible inhibitor of lymphocyte proliferation, and an inhibitor of cytosolic phospholipase A_2 ($cPLA_2$) activity in the epidermis. It has shown inhibitory activity against α-glucosidase (EC 3.2.1.20) and α-amylase (EC 3.2.1.1).	Uddin et al., 2004[447].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
		It shows considerable inhibition of cAMP-phosphodiesterase in rat adipose tissues and inhibits non-enzymic lipid peroxidation. It is a potent scavenger of superoxide and increases the beat rate on isolated atria, stimulates lipolysis and causes a concentration-dependent increase in Ca^{2+} release from the heavy fraction of fragmented sarcoplasmic reticulum of rabbit skeletal muscle.	
Cupressaceae			
Calocedrus microlepic Kurz var. formosana (Florin) Cheng & L. K. Fu (leaves)	Amentoflavone (**1**); taiwaniaflavone (**189**).	***Potent inhibition of the inductions of inducible nitric oxide synthase and cyclooxygenase-2 by taiwaniaflavone.***	Chien et al., 2004[448]; Pokharel et al., 2006[449].
Chamaecyparis obtusa Sieb. & Zucc. (leaves)	Amentoflavone (**1**); hinokiflavone (**235**); sciadopitysin (**15**); ginkgetin (**7**); isoginkgetin (**13**); podocarpusflavone B (**11**); bilobetin (**3**); podocarpusflavone A (**6**); I-7-*O*-methylamentoflavone (**2**); I-7,II-7-di-*O*-dimethylamentoflavone (**10**).		Krauze-Baranowska et al., 2005[450].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Cryptomeria japonica (L.f.) D.Don (leaves)	Cryptomerin A (**238**); cryptomerin B (**239**).		Miura et al., 1966[451]; Gadek and Quinn, 1985[452]; Geiger and Markham,1996 [209].
Cupressocyparis leylandii (Dallim. & AB Jacks.) Dallim. (leaves)	Cupressuflavone (**86**); amentoflavone (**1**); hinokiflavone (**235**); I-4′-*O*-methylcupressuflavone (**89**); I-7-*O*-methylamentoflavone (**2**); II-4′-*O*-methylamentoflavone (**6**).	***Antifungal activity.***	Krauze-Baranowska et al., 1999[453].
Cupressus arizonica L. (leaves)	***Biflavones:*** Amentoflavone (**1**); cupressuflavone (**86**); hinokiflavone (**235**); robustaflavone (**64**); I-4′-methylrobustaflavone (**65**); I-7-*O*-methylamentoflavone (**2**); bilobetin (**3**); II-4′-*O*-methylamentoflavone (**6**); I-7,4′-dimethylcupressuflavone (**90**).		Romani et al., 2002[454].
Cupressus cashmeriana Royle ex Carrière (leaves)	***Biflavones:*** Cupressuflavone (**86**); amentoflavone (**1**); sequoiaflavone (**2**); hinokiflavone (**235**); isocryptomerin (**237**).		Gadek and Quinn, 1985[452]; Khabir et al., 1987[455].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Cupressus glabra L. (leaves)	***Biflavones:*** Amentoflavone (**1**); cupressuflavone (**86**); hinokiflavone (**235**); robustaflavone (**64**); I-4′-methylrobustaflavone (**65**); I-7-*O*-methylamentoflavone (**2**); bilobetin (**3**); II-4′-*O*-methylamentoflavone (**6**); I-7,4′-dimethylcupressuflavone (**90**).		Romani et al., 2002[454].
Cupressus goveniana L. (leaves)	***Biflavones:*** Amentoflavone (**1**); cupressuflavone (**86**); hinokiflavone (**2352**); robustaflavone (**64**); I-4′-methylrobustaflavone (**65**); I-7-*O*-methylamentoflavone (**2**); bilobetin (**3**); II-4′-*O*-methylamentoflavone (**6**); I-7,4′-dimethylcupressuflavone (**90**).		Romani et al., 2002[454].
Cupressus lusitanica L. (leaves)	***Biflavones:*** Amentoflavone (**1**); cupressuflavone (**86**); hinokiflavone (**235**); robustaflavone (**64**); I-4′-methylrobustaflavone (**65**); I-7-*O*-methylamentoflavone (**2**); bilobetin (**3**); II-4′-*O*-methylamentoflavone (**6**); I-7,4′-dimethylcupressuflavone (**90**).		Romani et al., 2002[454].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Cupressus sempervirens L. (leaves)	***Biflavones:*** Amentoflavone (**1**); cupressuflavone (**86**); hinokiflavone (**235**); isocryptomerin (**237**); robustaflavone (**64**); I-4′-methylrobustaflavone (**65**); I-7-*O*-methylamentoflavone (**2**); bilobetin (**3**); II-4′-*O*-methylamentoflavone (**6**); I-7,4′-dimethylcupressuflavone (**90**).	Aerial parts are used in folk medicine. Leaf biflavonoids are involved in the resistance of some plant clones to cypress canker (*Seridium cardinale* fungus attack).	Khabir et al., 1987[455]; Heimler and Pieroni, 1991[456]; Romani et al., 2002[454].
Cupressus sempervirens L. (nuts)	8,8”-Biapigeninyl (**98a**).	The effects of **98a** on murine bone cells *in vitro* and in ovariectomized (OVx) mice showed that **98a** at 10^{-10} M and 10^{-8} M inhibited osteoclastogenesis of bone marrow cells and displayed concentration dependence; **98a** (10^{-10} M) stimulated osteoblast proliferation, differentiation and mineralization. The effect of **98a** in osteoblasts appeared to be mediated *via* estrogen receptors (ER). Microcomputed tomography revealed that **98a** treatment to OVx mice improved parameters of trabecular and cortical architecture. **98a** exhibited no uterine estrogenicity. **98a** showed osteoprotective effect in OVx mice by multiple beneficial effects on bone cells.	Siddiqui et al., 2010[46].
Fitzroya patagonica Hook. f. ex Lindl. (leaves)	***Biflavones:*** Podocarpusflavone A (**6**); isocryptomerin (**237**).		Nagvi et al., 1987[457].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Juniperus communis L. (leaves)	***Biflavones:*** Cupressuflavone (**86**); amentoflavone (**1**); sciadopitysin (**15**); hinokiflavone (**235**); isocryptomerin (**237**).		Ilyas and Ilyas, 1990[458].
Juniperus communis L. (fruits)	***Biflavones:*** Cupressuflavone (**86**); bilobetin (**3**).	Bilobetin is an active ***leishmanicidal*** compound.	Monea and Csedo, 1985[459]; Weniger et al., 2006[86].
Juniperus communis L. var. depressa Pursh (leaves and stems)	(*M*)- and (*P*)-cupressuflavone II-4′-*O*-β-*D*-glucopyranosides (two atropisomers) (**97**) (atropisomerism around the I-8,II-8 linkage)		Inatomi et al., 2005[460].
Libocedrus bidwillii Hook f.	***Biflavones:*** Amentoflavone (**1**); sequoiaflavone (**2**); I-2,3-dihydroamentoflavone (**31**); I-7-*O*-methyl-I-2,3-dihydroamentoflavone (**32**).		Markham et al., 1990[461].
Libocedrus plumosa Druce	***Biflavones:*** Amentoflavone (**1**); sequoiaflavone (**2**); I-2,3-dihydroamentoflavone (**31**); I-7-*O*-methyl-I-2,3-dihydroamentoflavone (**32**).		Markham et al., 1990[461].
Microbiota decussata Stalks (leaves)	***Biflavones:*** Amentoflavone (**1**); I-7-*O*-methylamentoflavone (**2**); cupressuflavone (**86**).		Krauze-Baranowska et al., 2002[462].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Platycladus orientalis (L.) Franco (fruits) (synonym to Biota orientalis Endl; Thuja orientalis L.; Platycladus stricta Spach; Thuja chengii Borderes & Gaussen; and Thuja orientalis var. argyi Lemee & H. Léveillé)	***Biflavones:*** Amentoflavone (**1**); cupressuflavone (**86**); robustaflavone (**64**); hinokiflavone (**235**).	A traditional Chinese herb and food additive. ***Antioxidant and human neutrophil elastase (HNE) inhibitory activities.*** Antibacterial activity (stems and leaves).	Lu et al., 2006[463]; Bissa et al., 2008[464]; Xu et al., 2009[465].
Taiwania cryptomerioides Hayata (leaves)	***Biflavones:*** Amentoflavone (**1**); hinokiflavone (**235**); taiwaniaflavone (**189**); II-7-*O*-methyltaiwaniaflavone (**190**); I-4′,II-7-di-*O*-methyltaiwania-flavone (**191**); I-2,3-dihydrohinoki-flavone (**241**); I-2,3-dihydroamentoflavone (**31**); I-7-*O*-methyl-I-2,3-dihydroamentoflavone (**32**); podocarpusflavone A (**6**); sequoiaflavone (**2**).		Gadek and Quinn, 1985[452], 1989[466].
Thuja javanica Burm. f. [= *Podocarpus javanicus* Burm.f.) Merr.]	***Biflavones:*** Amentoflavone (**1**); hinokiflavone (**235**).		Gadek and Quinn, 1985[452]; Kumar-roy et al., 1987[467] Albernaz et al.[468].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Thuja gigantea Nutt. (= Thuja plicata Donn ex D. Don)	***Biflavones:*** Amentoflavone (**1**); hinokiflavone (**235**); sequoiaflavone (**2**); bilobetin (**3**); cryptomerin A (**238**); cryptomerin B (**239**).		Gadek and Quinn, 1985[452]; Kumar-roy et al., 1987[467]
Ginkgoaceae			
Ginkgo biloba L. (leaves)	***(I-3',II-8-Biflavones:*** Amentoflavone (**1**); ginkgetin (**7**); isoginkgetin (**13**); bilobetin (**3**); sciadopitysin (**15**); I-5′-methoxy-bilobetin (**4**); sequoiaflavone (**2**); podocarpusflavone A (**6**); II-7-*O*-β-*D*-glucopyranosylginkgetin (**9**); II-7-*O*-β-*D*-glucosylisoginkgetin (**14**).	***Antifungal activity.*** Ginkgetin and isoginkgetin were active ***leishmanicidal compounds***. These compounds also showed good ***antitrypanosomal activity***. ***Antioxidant activity.*** ***Anti-influenza virus activity.*** Amentoflavone (1) crossed the blood-brain barrier *in vitro* but did not inhibit benzodiazepine binding *in vivo*, suggesting poor brain permeability.	Joly et al., 1980[469]; Kang et al., 1990[470], 1995[164]; Chang et al., 1993[471]; Krauze-Baranowska and Wiwart, 2003[472]; Krauze-Baranowska et al., 2004[473]; Hyun et al., 2005[474], 2006[475]; Weniger et al., 2006[86]; Miki et al., 2007[24]; Colovic et al., 2008[238].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Pinaceae			
Abies *sachalinensis* (C.F.Schmidt) Mast. (bark)	Spirobiflavonoids (abiesinols).	All compounds exhibited potent inhibitory effects on (±)-(*E*)-methyl-2-[(*E*)-hydroxyimino]-5-nitro-6-methoxyhex-3-enamide (NOR 1) activation. A spirobiflavonoid showed *remarkable anti-tumor-initiating activity* in the *in vivo* two-stage mouse skin carcinogenesis test using peroxynitrite ($ONOO^-$; PN) as the initiator and 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA) as the promoter.	Wada et al., 2010[476].
Abies webbiana Wall. ex D.Don (leaves)	***(I-3′,II-6)-Flavone-flavonol:*** Abiesin (**74**).		Chatterjee et al., 1984[477]; Nayak et al., 2004[478]; Prakash Vishnoi et al., 2007[479]; van Beek and Montoro, 2009[480].
Pseudotsuga menziesii (Mirb.) Franco (bark)	(I-5′,II-5′)-Bisdihydroquercetin (**214**).		Lai et al., 1992[481] ; Dellus et al., 1997[482].

Table 1. (Continued).

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Podocarpaceae			
Podocarpus latifolius (Thunb.) R. Br. ex *Mirb.* (leaves)	***Biflavones:*** Amentoflavone (**1**); I-7,4'-di-*O*-methyl-amentoflavone (= ginkgetin) (**7**); heveaflavone (**18**); I-7,4',II-7,4′-tetra-*O*-methylamentoflavone (**19**).	Used in Zulu traditional medicine. Ginkgetin is an active ***leishmanicidal compound***. Ginkgetin also showed a good ***antitrypanosomal activity***. ***Antimicrobial activity.***	Fozdar et al., 1989[483]; Abdillahi et al., 2008[484], 2010[485].
Podocarpus fleuryi Hickel [= *Nageia fleuryi* (Hickel) de Laub.; *Decussocarpus fleuryi* (Hickel) de Laub.]	***Biflavone:*** II-7-*O*-Methylrobustaflavone (**66**).		Xu and Fang, 1991[486]; Abdillahi et al., 2010[485].
Podocarpus taxifolia H.B.K. [= Prumnopitys montana (Humb. & Bonpl. ex Willd.) de Laub.]	Heveaflavone (**18**); bilobetin (**3**); podocarpusflavone A (**6**); sequoiaflavone (**2**); I-2,3-dihydroamentoflavone (**31**); I-7-*O*-methyl-I-2,3-dihydroamentoflavone (**32**); podocarpusflavanone (**40**); I-5,7,4′,II-5,7,4′-hexa-*O*-methyl-amentoflavone (= dioonflavone) (**22**).	***Antioxidant and anti-inflammatory activities.***	Kumar-roy et al., 1987[467]; Abdillahi et al., 2010[485, 487]
Retrophyllum rospigliosii (Pilger) C.N. Page (leaves)	I-7,4′,II-7,4′-Tetra-*O*-methyl-amentoflavone (**19**); I-7,4′,II-7-tri-*O*-methylamentoflavone (**16**); sciadopitysin (**15**); I-7,II-7-di-*O*-methylamentoflavone (**10**); podocarpusflavone A (**6**); amentoflavone (**1**).		Amaro-Luis et al., 2008[488].

Plant (Part of the plant)	Compounds	Bioactivity. Traditional uses.	Author, References
Taxaceae			
Amentotaxus yunnanensis H. L. Li	***(I-3',II-8)-Biflavonoids***: I-7,II-7-di-*O*-methyl-I-2,3-dihydroamentoflavone (**38**).		Li et al., 2003[489]
Taxus baccata L. (needles)	***Biflavones***: Amentoflavone (**1**); bilobetin (**3**); I-7-*O*-methylamentoflavone (**2**); II-4′-*O*-methylamentoflavone (**6**); I-7,4'-di-*O*-methylamentoflavone (= ginkgetin) (**7**); I-7,4',II-4′-tri-*O*-methylamento-flavone (= sciadopitysin) (**15**).	Ginkgetin is an active ***leishmanicidal compound***. Ginkgetin also showed a good ***antitrypanosomal activity***. ***Antifungal activity.***	Reddy and Krupadanam, 1996[490]; Krauze-Baranowska and Wiwart, 2003[472].
Taxus madia	Ginkgetin (**7**); sciadopitysin (**15**); I-7,4′,II-7-tri-*O*-methylamentoflavone (**16**).		Liu et al., 2008[491].
Taxus wallichiana Zucc. (leaves and branches)	***Biflavones:*** Sequoiaflavone (**2**); ginkgetin (**7**); sciadopitysin (**15**).	Ginkgetin is an active ***leishmanicidal compound***. Ginkgetin also showed a good ***antitrypanosomal activity***.	Qiu et al., 1989[492]; Weniger et al., 2006[86].
Taxodiaceae			
Taxodium mucronatum Ten.	Podocarpusflavone-A (**6**); sciadopitysin (**15**); hinokiflavone (**235**); cryptomerin A (**238**); isocryptomerin (**237**); cryptomerin B (**239**).		Ishratullah et al., 1978[493]; Gadek and Quinn, 1989[466]; Geiger and Markham,1996{Geiger, 1996 #882}.

Chapter 5

BIOLOGICAL ACTIVITY

METABOLISM OF BIFLAVONOIDS

There has been no available data on the absorption and distribution of biflavonoids in animals/humans. Morelloflavone (**159**) and I-2,3,II-2,3-tetrahydroamentoflavone (**47**) showed *in vivo* anti-inflammatory activity by oral administration.[27, 28] However, in some studies, oral treatment produced much reduced or no activity, suggesting that the oral bioavailability of biflavonoids may be very low.[3, 29] In contrast, intraperitoneal administration resulted in higher anti-inflammatory activity. Topical treatment also yielded positive results.[30-33]

EFFECTS OF BIFLAVONOIDS ON CANCER CELLS

Some biflavonoids exhibited cytotoxic/anticancer activity.[34-38] For example, ginkgetin (**7**) was cytotoxic to human ovarian adenocarcinoma (OVCAR)-3 cells, but not to other cells such as Hep G2 and HeLa.[39] Taiwanhomoflavone-A (**8**) showed cytotoxicity against several cancer cell lines.[40] Apoptotic cell death by caspase activation was involved in the cytotoxic effects of ginkgetin.[41] In other studies, several hinokiflavone (**235**)-type biflavonoids such as cryptomerin B (**239**) and isocryptomerin (**237**) exhibited potent cytotoxic effects, probably by apoptotic death at low μM concentrations.[3] In contrast, some biflavones such as ginkgetin (**7**) and sciadopitysin (**15**) enhanced proliferation of normal human skin fibroblasts and increased collagen production.[42]

A new biflavonoid (**114a**) and several known compounds were isolated from the stem bark of *Garcinia lateriflora*, collected in Indonesia. The structure of the new compound was determined by spectroscopic data by analysis of COSY and NOESY NMR and ECD spectra. The biflavonoids exhibited proteasome-inhibitory activity, and the known compound, morelloflavone (**159**) was found to have the highest potency (IC_{50} = 1.3 μM).[43]

The biflavones ginkgetin (**7**), isoginkgetin (**13**) and I-4′-*O*-methylrobustaflavone (**65**), isolated from the herb *Selaginella moellendorffii* Hieron, exhibited selective cytotoxicity against the three human cancer cell lines tested.[44]

The leaves of the Cashew plant (*Anacardium occidentale* L.) are used by the folkmedicine in South America and West Africa. This plant is rich in flavonoids, which have diverse physiological effects. In a sub-acute toxicity it was found that an ethanolic extract of Cashew leaves elicited lymphopenia in rats. The extract was also found to be cytotoxic and to induce apoptosis in Jurkat (acute lymphoblastic leukemia) cells. The crude ethanolic extract was fractionated and resolved by HPLC. One of the four fractions obtained led to the isolation of the biflavonoid agathisflavone. [^{3}H]-Thymidine incorporation assays and flow cytometry analysis showed that the isolated compound displayed a high anti-proliferative effect in Jurkat cells with an IC_{50} of 2.4 μg/mL (4.45 μM). The effect of agathisflavone (**100**) on the acute promyelocytic leukemia cell line HL60, Burkitt lymphoma Raji cells and Hep-2 laryngeal carcinoma cells was also tested. The two latter ones were only mildly affected by agathisflavone. It was also shown that agathisflavone induced apoptosis in Jurkat cells, and it was proposed that this may be the possible mechanism of agathisflavone specific cytotoxicity.[45]

8,8”-Biapigeninyl (BA) (**98a**), a condensation product of two apigenin molecules, was found abundantly in the nuts of *Cupressus sempervirens*. The effects of BA on murine bone cells *in vitro* and in ovariectomized (OVx) mice were investigated. BA at 10^{-10} M and 10^{-8} M inhibited osteoclastogenesis of bone marrow cells (BMCs) and displayed concentration dependence. BA at 10^{-8} M and 10^{-6} M inhibited differentiation of 3T3-L1 and BMCs to mature adipocytes. BA (10^{-10} M) stimulated osteoblast proliferation, differentiation and mineralization. In stimulating osteoblast function, BA was found to be 10^4-fold more potent than apigenin. The effect of BA in osteoblasts appeared to be mediated *via* estrogen receptors (ER) as antiestrogen, ICI-182780 abolished BA-stimulated osteoblast differentiation. In OVx mice BA treatment (at 1.0-, 5.0- and 10.0 $mgkg^{-1}$ day^{-1} doses) given orally for 30 days dose-

dependently inhibited mRNA levels of osteoclastic genes including tartrate-resistant acid phosphatase, receptor activator of nuclear factor (RANK), tumor necrosis factor *alpha* (TNF-α), interleukin-6 and the ratio of RANK ligand/osteoprotegerin ratio in bones compared with OVx mice treated with vehicle. In addition, BA treatment to OVx mice dose-dependently stimulated production of osteoprogenitor cells in the bone marrow and increased mRNA levels of osteogenic genes core binding factor α-1, type I collagen and bone morphogenic protein-2 in bones compared with OVx+ vehicle group. Microcomputed tomography revealed that BA treatment to OVx mice improved parameters of trabecular and cortical architecture. BA exhibited no uterine estrogenicity. From these data, it was concluded that BA exerts osteoprotective effect in OVx mice by multiple beneficial effects on bone cells.[46]

Atrazine (ATR) is a widespread agrochemical contaminant frequently detected in water systems and Kolaviron (KV), a seed-derived mixture of biflavonoids (e.g., mainly GB_1 (**176**), GB_{1a} (**167**), GB_2 (**177**) and Kolaflavanone (**178**)), which has been reported to modulate the effects of many mutagens and carcinogens. The protective effects of KV on ATR-induced cell death in the human neuroblastoma cell line (SHY-SY5Y) were studied. KV prevented ATR-induced generation of reactive oxygen species (ROS), cell death and inhibited cell proliferation by reduction of cell proliferation. Furthermore, ATR-induced levels malondialdehyde (MDA), catalase (CAT), glutathione peroxidase (GSH-Px), glutathione reductase (GR) activities, increased leakage of lactate dehydrogenase (LDH), inhibited cellular LDH activity and depleted glutathione (GSH) levels in SHY-SY5Y cells were blocked by KV. Comparable to the control, KV increased GR but not GSH-Px activities. ATR mediated nuclear changes associated with apoptosis; including nuclear fragmentation, condensation, DNA laddering, and increased caspase-3 activity were blocked on addition of KV. ATR-induced changes in the expressions of p53, Bax, Bcl-2, p21, and mRNA levels of caspase-3 and caspase-9 were prevented by KV. Based on these results, a model was proposed for the protective effect of KV on ATR-induced cell injury in neuronal cell.[47]

II-7-*O*-Methylagathisflavone (7"-*O*-methylagathisflavone) (**103**) and amentoflavone (**1**) showed concentration-dependent growth inhibitory activities on Ehrlich carcinoma cells in 45-h culture, tested by the tetrazolium method, with IC_{50}=24 ± 1 μM for **103**, and 26 ± 1 μM for **1**.[48]

Recent studies have shown that morelloflavone (**159**) exerts an antiangiogenic action targeting the activation of Rho-GTPases and ERK

signaling pathways. [49] Moreover, ochnaflavone (**218**) inhibited the proliferation of HCT-15 cell line of human colon cancer with an IC_{50} value of 4.1 μM.[50]

Fatty acid synthase (FASN) is highly expressed in breast carcinomas to support their continuous growth and proliferation, but has low expression level in normal tissues. Considerable interest has been aroused in the search for novel FASN inhibitors as a therapeutic target for breast cancer. Amentoflavone (**1**) was isolated from *Selaginella tamariscina*, a traditional oriental medicine that has been used to treat cancer for many years, and was found to significantly inhibit the FASN enzymatic activity *in vitro* at concentrations above 50 μM.[51] Amentoflavone (**1**) was also found to decrease fatty acid synthesis by the reduction of [^{3}H]acetyl-CoA incorporation into lipids in FASN-overexpressed SK-BR-3 human breast cancer cells. Growth inhibition of cancer by amentoflavone (**1**) was dose-dependent, showing a slight reduction at 50 μM and a significant reduction at concentrations of 75 and 100 μM. The growth of FASN-nonexpressed NIH-3T3 normal cells was not decreased by treatment with amentoflavone in a dose-time-dependent manner. These data provided evidence that amentoflavone (**1**) isolated from *S. tamariscina* induced breast cancer apoptosis by blocking fatty acid synthesis.[51]

Polyphenolic compounds found in fruits, vegetables, herbs, roots and leaves act as bioactive components, and have been recognized as cancer chemopreventive agents. Guruvayoorappan and Kuttan[52] focused on the regulatory effect of amentoflavone (**1**), a biflavonoid from *Biophytum sensitivum*, on the apoptotic process in B16F-10 melanoma cells, and the production of nitric oxide (NO) and cytokines in B16F-10 cells, tumor-associated macrophages (TAMs) and peritoneal macrophages. Amentoflavone (**1**) at a concentration of 10 μg/mL could significantly ($p < 0.001$) inhibit the production of NO and proinflammatory cytokines (IL-1β, IL-6, GM-CSF and TNF-α) in B16F-10 cells, TAMs and peritoneal macrophages. Incubation of B16F-10 cells with amentoflavone (**1**) showed the presence of apoptotic bodies and induced DNA fragmentation. Furthermore, amentoflavone (**1**) showed inhibitory effects on bcl-2 expression, and upregulated p53 and caspase-3 gene expression in B16F-10 melanoma cells. In conclusion, the observed results suggest that amentoflavone (**1**) stimulates apoptosis by regulating bcl-2, caspase-3 and p53 genes in B16F-10 melanoma cells and regulates nitric oxide and proinflammatory cytokine production in B16F-10 cells, TAMs and peritoneal macrophages.[52]

Membrane-permeable compounds that reversibly inhibit a particular step in gene expression are highly useful tools for cell biological and biochemical/structural studies. In comparison with other gene expression steps where multiple small molecule effectors are available, very few compounds have been described to behave as general inhibitors of pre-mRNA splicing. O′Brien *et al.*[53] reported construction and validation of a set of mammalian cell lines suitable for the identification of small molecule inhibitors of pre-mRNA splicing. Using these cell lines, the authors identified the natural product isoginkgetin (**13**), as a general inhibitor of both major and minor spliceosomes. Isoginkgetin (**13**) inhibited splicing *in vivo* and *in vitro* at similar micromolar concentrations. It appears to do so by preventing stable recruitment of the U4/U5/U6 three-small nuclear ribonucleoprotein complex, resulting in the accumulation of prespliceosomal A complex. As two recently reported general pre-mRNA splicing inhibitors, isoginkgetin (**13**) has been previously described as an antitumor agent. These results suggest that splicing inhibition is the mechanistic basis of the antitumor activity of isoginkgetin (**13**). Therefore, pre-mRNA splicing inhibitors may represent a novel pathway for the development of new anti-cancer agents.[53]

Banerjee *et al.*[54] demonstrated the potential effects of different flavonoids on cytokines mediated cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) expression and activities on A549 cell line using quercetin, amentoflavone and flavanone. These data revealed that quercetin, at a concentration of 50 μM inhibited PGE_2 biosynthesis by A549 very strongly with little effect on COX-2 mRNA and protein expression. Unlike quercetin, amentoflavone (**1**) inhibited both PGE_2 biosynthesis, and COX-2 mRNA and protein expression strongly. In another series of experiments, quercetin inhibited iNOS protein expression completely without affecting iNOS mRNA expression. Although amentoflavone (**1**) exerted no inhibitory effect on iNOS mRNA expression, weakly inhibited iNOS protein expression. Flavanone had no inhibitory effect on either enzyme at the same concentration. Taken together, these data indicated that amentoflavone (**1**) and quercetin differentially exerted supression of PGE_2 biosynthesis *via* downregulation of COX-2/iNOS expression.[54]

A new biflavanone, I-7,4',II-7-tri-*O*-methyl-I-2,3,II-2,3-tetrahydrorobustaflavone (2,2",3,3"-tetrahydrorobustaflavone 7,4',7"-trimethyl ether) (**84**) was isolated from the whole plant of *Selaginella doederleinii* (Selaginellaceae) together with the known biflavonoid, I-7,4′,II-4′-tri-*O*-methylrobustaflavone (robustaflavone 7,4',7"-trimethyl ether) (**70**) as cytotoxic

constituents against the three human cancer cell lines, HCT, NCI-H358, and K562.[55]

Amentoflavone (**1**) has been shown to inhibit tumor metastasis *in vivo*, but its mechanism of action remains unclear. C57BL/6 mice were injected once with B16F-10 melanoma cells *via* tail vein, followed by treatment with amentoflavone (50 mg/kg BW) for 10 consecutive days.[56] Twenty-one days after tumor injection, animals were sacrificed, and tumor metastasis was confined to the lungs. Amentoflavone treatment significantly lowered the number of lung nodules ($p<0.001$) compared with tumor controls. Amentoflavone (**1**) treatment markedly decreased the mRNA expression of MMP-2, MMP-9, prolyl hydroxylase, lysyl oxidase, VEGF, ERK-1, ERK-2, TNF-α, IL-1β, IL-6, and GM-CSF in lung tissues. However, amentoflavone (**1**) treatment increased mRNA expression of STAT-1 and nm23 in lung tissues. *In vitro* studies also indicated that amentoflavone (**1**) treatment inhibited tumor cell invasion and migration. These results showed that treatment with amentoflavone (**1**) reduced experimental tumor metastasis and suggested that such action was associated with attenuation of tumor invasion, proliferation and angiogenesis.[56]

Isoginkgetin (**13**) has been identified as a general inhibitor of pre-mRNA splicing using an *in vivo* screening test.[57] Five new biflavonoids, I-7,4′,II-4′-tri-*O*-methylrobustaflavone (robustaflavone 7,4',4'''-trimethyl ether) (**70**), I-4′,II-4′-di-*O*-methylrobustaflavone (robustaflavone 4',4'''-dimethyl ether) (**69**), 2,3-dihydroamentoflavone 7,4',7''-trimethyl ether (**41**), I-7,4′-di-*O*-methyl-I-2,3-dihydroamentoflavone (2,3-dihydroamentoflavone 7,4'-dimethyl ether) (**37**), and I-7-*O*-methyl-II-2,3-dihydroisocryptomerin (2'',3''-dihydroisocryptomerin 7-methyl ether) (**243**), together with six known compounds have been isolated from the aerial parts of *Selaginella delicatula*.[58] The structures of these new compounds were determined by spectral analysis. Among the isolated compounds, I-4′,II-4′-di-*O*-methylrobustaflavone (robustaflavone 4',4'''-dimethyl ether) (**69**), I-7,4′-di-*O*-methyl-I-2,3-dihydroamentoflavone (2,3-dihydroamentoflavone 7,4'-dimethyl ether) (**37**), and α-tocopheryl quinone showed cytotoxicities (ED_{50} values < 4 μg/mL) against P-388 and/or HT-29 cell lines *in vitro*.[58]

The biflavonoid II-2,3-dihydroochnaflavone (2'',3''-dihydroochnaflavone) (**225**), isolated from the leaves of *Luxemburgia nobilis*, was cytotoxic to murine Ehrlich carcinoma (IC_{50} = 17.2 μM) and human leukemia K562 cells (IC_{50} = 89.0 μM) in a concentration-dependent manner in 45 h cell culture. The acetyl (2'',3''-dihydroochnaflavone 5,7,4',5'',7''-*O*-pentacetyl ether) (I-5,7,4′,II-5,7-*O*-pentacetyl-II-2,3-dihydroochnaflavone) (**225a**) and methyl (2'',3''-

dihydroochnaflavone 7,4',7"-*O*-trimethyl ether) (I-7,4′,II-7-*O*-trimethyl-II-2,3-dihydroochnaflavone) (**225b**) derivatives of 225 were not cytotoxic to these tumor cells at concentrations of 67.0 and 82.0 μM, respectively. Biflavonoids 225 and 225a inhibited the activity of human DNA topoisomerases I and II-α, as observed in relaxation and decatenation assays. In addition, the authors showed that 225 is a DNA interacting agent, thus causing DNA unwinding in a test with topoisomerase I. Also, the spectrophotometric titration of 225 with DNA resulted in a pronounced hypochromic effect.[59]

Neochamaejasmin A (I-2*S*,3*S*;II-2*S*,3*S*) (**132**), a biflavonoid isolated from the roots of a traditional Chinese medicine, *Stellera chamaejasme*, has been shown to inhibit cellular uptake of ^{3}H-thymidine (IC_{50} 12.5 μg/mL) and the subsequent proliferation of human prostate cancer LNCaP cells.[60]

I-7,II-4′-Di-*O*-methyl-amentoflavone (**11**), I-7,4′,II-7-tri-*O*-methyl-amentoflavone (7,4',7"-tri-*O*-methylamentoflavone) (**16**), and II-4′-*O*-methylamentoflavone (4'"-*O*-methylamentoflavone) (**6**) had a moderate cytotoxic activity against human KB (human oral epithelium carcinoma), Hela (human cervical carcinoma), Hepa (human hepatoma), DLD (colon carcinoma), and A-549 (human lung carcinoma) tumor cell lines. [61]

The formation of new capillaries from existing blood vessels is critical for tumor growth and metastasis. Amentoflavone (**1**), a biflavonoid from *Biophytum sensitivum*, could inhibit the process of angiogenesis.[62] Amentoflavone (**1**) at non-toxic concentrations (0.05-0.20 μg/mL) showed a significant inhibition of proliferation, migration and tube formation of endothelial cells, which are key events in the process of angiogenesis.[62]

Guruvayoorappan and Kuttan[63] studied the antimetastatic activity of amentoflavone (**1**) using B16F-10 melanoma-induced experimental lung metastasis in C57BL/6 mice. Amentoflavone (**1**) treatment significantly reduced tumor nodule formation accompanied by reduced levels of lung collagen hydroxyproline, hexosamine, and uronic acid. Serum sialic acid and γ-glutamyl transpeptidase levels were also significantly inhibited after treatment with amentoflavone (**1**). Amentoflavone (**1**) treatment up-regulated the lung tissue inhibitor of metalloprotease-1 and tissue inhibitor of metalloprotease-2 expression.[63]

The modulation of the immune response is highly relevant in tumor cell destruction. The research of Guruvayoorappan and Kuttan[64] focused on the effect of amentoflavone (**1**) on cell-mediated immune responses in normal and tumor-bearing control animals. The treatment with amentoflavone (**1**) significantly enhanced the activity of natural killer cells in normal (42.8% cell lysis) and tumor-bearing animals (48.2% cell lysis) on the fifth day, which was

much earlier compared to tumor-bearing control animals (20.2% cell lysis on day 9). Antibody-dependent cellular cytotoxicity also increased in amentoflavone (**1**)-treated normal (41% cell lysis on day 9) and tumor-bearing animals (43.8% cell lysis on day 9) compared to untreated tumor-bearing control animals (maximum of 15.2% cell lysis on day 13).[64]

Amentoflavone (**1**) is found in a number of plants with medicinal properties, such as *Ginkgo biloba* and *Hypericum perforatum* (St. John's wort). As mentioned earlier Pan *et al*.[13] reported the structure-activity relationship (SAR) and binding mechanism of three biflavones, amentoflavone (**1**) (AMF1), II-4′-*O*-methylamentoflavone (4'''-methylamentoflavone) (**6**) (AMF2) and 7'',4'''-dimethylamentoflavone (II-7,4′-di-*O*-methyl-amentoflavone) (**12a**) (AMF3), isolated from *Taxodium mucronatum* as novel natural inhibitors of human CatB with strong inhibitory activities at IC_{50} values of 1.75, 1.68 and 0.55 μM, respectively.[13]

The root of *Stellera chamaejasme* is a traditional Chinese herb termed Rui Xiang Lang Du and has been used to treat solid tumors, tuberculosis and psoriasis. Exactly how *S. chamaejasme* regulates cellular responses remains unclear. Tian *et al*.[65] examined four biflavonoids isolated from *S. chamaejasme*, including isochamaejasmin (I-2*S*,3*R*;II-2*R*,3*S*) (**130**), two of its stereo-isomers and a methyl derivative, in functional assays originally designed to screen ligands for the G protein-coupled formyl peptide receptor-like 1 (FPRL1). Isochamaejasmin (I-2*S*,3*R*;II-2*R*,3*S*) (**130**) was found to induce the expression of a nuclear factor (NF)-κB-directed reporter gene in transfected HeLa cells with an EC_{50} of 3.23 μM, independently of FPRL1.[65]

All these results indicate that certain biflavonoids strongly affect the cancer cells with little effect on normal cell proliferation, suggesting a therapeutic potential against cancer.

ANTIBACTERIAL, ANTIFUNGAL AND ANTIMYCOBACTERIAL ACTIVITY OF BIFLAVONOIDS

Particular attention has been paid to the antibacterial, antiviral, anti-inflammatory and antifertility effects of *Wikstroemia indica* that contains abundant active constituents, including flavonoids, biflavonoids, coumarins, lignans, volatile oils, polysaccharides, etc.[66]

Several biflavones showed antituberculosis activity.[67] The biflavanone, I-7,II-7-di-*O*-methyl-I-2,3,II-2,3-tetrahydroamentoflavone (7,7"-di-*O*-methyltetrahydroamentoflavone) (**56**), exhibited moderate antimalarial activity with IC_{50} 0.98 μg/mL against *Plasmodium falciparum* (W2 Clone) and weak activity against *P. falciparum* (D6 Clone) with IC_{50} 2.8 μg/mL.[68] I-7,II-4′-di-*O*-methyl-amentoflavone (7,4′-dimethylamentoflavone or putraflavone) (**11**) inhibited *Leishmania mexicana* promastigotes.[69] Furthermore, lanaroflavone (4"',5,5",7,7"-pentahydroxy-4',8"-biflavonyl ether) (**249**) showed antimalarial and leishmanicidal activities.[70] Several ethylene glycol-linked flavonoid dimers based on the apigenin moiety inhibited *Leishmania*.[71] Fatty acid synthase (FAS) has been identified as a potential antifungal target. Morelloflavone (**159**); 3",3"',4',4"',5,5",7,7"-octahydroxy-3,8"-biflavanone (I-5,7,4',II-3,5,7,3′,4′-octahydroxy-(I-3,II-8)-biflavanone (**175a**); amentoflavone (**1**), II-7-*O*-methylamentoflavone (7"-*O*-methylamentoflavone) (**5**) and I-4′,II-7-di-*O*-methyl-amentoflavone (4',7"-*O*-dimethylamentoflavone) (**12**) exhibited IC_{50} values of FAS inhibitory activity of 30, 23, 7, 25 and 47 μg/mL, respectively.[72] Volkensiflavone (**154**), fukugetin (**159**), fukugiside (**162**), GB_{2a}-I-7-*O*-glucoside (**173**) were active against all Gram-positive bacteria.[73] GB_1 (**176**) showed antibacterial activities against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) with MIC of 32 and 128 μg/mL, respectively.[74]

In a recent work the synthesis of natural and synthetic biflavonoids was performed in good overall yields starting from readily available materials *via* high yielding aldol and Ullmann condensations. Some of these compounds, especially bichalcones, displayed an interesting activity against fungi, higher than that of the corresponding monomers.[75]

Sulcatone A (**231**) and I-2,3-dihydrokaempferol-(I-4',*O*,II-3')-II-2,3-dihydrokaempferol (**232**) also showed significant *in vitro* antimicrobial activities against a number of microorganisms (Gram-positive bacteria).[76]

A series of natural and synthetic biflavonoids demonstrated inhibitory activity against *Mycobacterium tuberculosis H37Rv* (*Mtb*). Compounds 6,6″-biapigenin hexamethylether (I-5,7,4′,II-5,7,4′-hexa-*O*-methylbiapigenin) (**116b**), I-5,7,4′,II-5,7,4′-hexa-*O*-methylvolkensiflavone (volkensiflavone hexamethylether) (**158**), and I-5,7,4′,II-5,7,4′-hexa-*O*-methyl-GB_{1a} (GB-1a hexamethylether) (**168**) showed 96, 95, and 87% inhibition, respectively, at a screening concentration of 12.5 μg/mL.[67]

Compounds (I-2*S*,II-2*S*)-I-4′,II-4′-di-*O*-methyl-I-2,3,II-I-2,3,II-2,3-tetrahydroamentoflavone (2,3,2",3"-tetrahydroisoginkgetin) (**54**), 2,3,2",3"-

tetrahydro-4'-*O*-methylamentoflavone (I-4′-*O*-methyl-I-2,3,II-2,3-tetrahydroamentoflavone) (**52**) and I-2,3-dihydroamentoflavone ((2*S*)-2,3-dihydroamentoflavone) (**31**) displayed moderate antibacterial activity against *Staphylococcus aureus* (IC_{50} values of 3.9, 9.7, and 8.2 μM, respectively) and methicillin-resistant *S. aureus* (MRSA; IC_{50} values of 5.9, 12.5, and 11.5 μM, respectively).[77]

The acetone extract of *Garcinia livingstonei* leaves presented antibacterial activity against four nosocomial pathogens. Bioautograms showed that two compounds were primarily responsible for the antibacterial activity, amentoflavone (**1**) and 4′-methoxyamentoflavone (I-4′-*O*-methylamentoflavone) (**3**). The antibacterial activity of the isolated compounds was determined against *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus faecalis* and *Pseudomonas aeruginosa*. Three of the organisms tested were sensitive to both compounds with MIC values ranging from 8-100 μg/mL. *P. aeruginosa* was resistant with MICs > 100 μg/mL. The safety of the two compounds was assessed with a tetrazolium-based colorimetric assay (MTT assay) using monkey kidney cells (Vero line). The compounds had low toxicity against the cell line with cytotoxic concentrations to 50% of the cells (LD_{50}) of 386 μg/mL and > 600 μg/mL for amentoflavone and 4"-methoxyamentoflavone, respectively. Berberine, the positive control, had a CC_{50} of 170 μg/mL. 4"-Methoxyamentoflavone was more active and much less toxic than amentoflavone.[78]

Araucaria angustifolia (Araucariaceae) is a Brazilian medicinal plant traditionally used for the treatment of various diseases including dry skin, wounds, shingles, and sexually transmitted diseases. The ethyl acetate (EA) and *n*-butanol (NB) fractions showed the best results for antiherpetic activity and further fractionation yielded 22 subfractions. Of these subfractions, 14 were active, and the most potent antiherpetic activity was obtained for the subfraction NB1-4 with a selectivity index (SI) of 57.51. Chemical analysis of NB1-4 subfractions revealed the presence of proanthocyanidins and the known biflavonoids bilobetin (I-4′-*O*-methylamentoflavone) (**3**), II-7-*O*-methylrobustaflavone (**66**) and cupressuflavone (**86**).[79]

ANTIVIRAL ACTIVITY

Robustaflavone (**64**), a naturally occurring biflavonoid isolated from *Rhus succedanea*, was found to be a potent inhibitor of hepatitis B virus (HBV) replication in 2.2.15 cells, with an effective concentration (EC_{50}) of 0.25 mM,

and a selectivity index (SI, IC_{50}:EC_{90}) of 153.[80, 81] Robustaflavone (**64**) and hinokiflavone (**235**) showed activity against HIV-1 reverse transcriptase (RT), with similar IC_{50} values of 65 μM.[82]

Ginkgetin-sialic acid conjugates remarkably presented potent anti-influenza virus activities *in vivo*.[24]

Ochnaflavone 7″-*O*-methyl ether (II-7-*O*-methylochnaflavone) (**220**) and II-7-*O*-methyl-II-2,3-dihydroochnaflavone (2",3"-dihydroochnaflavone 7"-*O*-methyl ether) (**226**) were found to inhibit HIV-1 activity and HIV-1 reverse transcriptase activity.[83]

ANTIPROTOZOAL ACTIVITY (ANTIPLASMODIAL, LEISHMANICIDAL AND ANTITRYPANOSOMAL ACTIVITIES)

The preliminary screening of a series of medicinal plants, traditionally used in Tanzania, showed an IC_{50} of 15.6-31.2 μg/mL for the crude extract of the root of *Ormocarpum kirkii* (Papilionaceae) against *Plasmodium falciparum*. A bioguided isolation was performed to isolate the active constituents, compounds comprised seven (I-3,II-3)-biflavonoids among other constituents. Isochamaejasmin (I-2*S*,3*R*;II-2*R*,3*S*) (**130**) was the most active compound with an IC_{50} of 7.3 ± 3.8 μM, but the selectivity was rather limited. Therefore, these constituents may contribute, at least in part, to the antimalarial use of *O. kirkii* in traditional medicine.[84]

A new biflavonoid, *ent*-naringeninyl-(I-3α,II-8)-4'-*O*-methylnaringenin (**171**) was isolated from the root bark of *Garcinia livingstonei* collected in Tanzania. This compound showed moderate activity against *P. falciparum* (IC_{50} 6.7 μM).[85]

The antiplasmodial, leishmanicidal and antitrypanosomal activities of eight natural biflavonoids were estimated *in vitro* on a chloroquine-resistant strain of *Plasmodium falciparum*, axenically grown *Leishmania donovani* amastigotes and *Trypanosoma cruzi* trypomastigotes and *Trypanosoma brucei rhodesiense* bloodstream forms. Lanaroflavone (**249**) showed the highest antiplasmodial activity (IC_{50} = 0.48 μM), isoginkgetin (**13**) was the most active leishmanicidal compound (IC_{50} = 1.9 μM), while ginkgetin (**7**) (IC_{50} = 11 μM) and isoginkgetin (**13**) (IC_{50} = 13 μM) showed the best antitrypanosomal activity. The cytotoxicity and selectivity indices of the most active compounds were also estimated. Lanaroflavone (**249**) exhibited a high

selectivity index value (SI = 159), indicating selective antiplasmodial activity.[86]

Biflavanone (I-3,II-3)-biliquiritigenin (**129**), which had not been previously found in a natural plant source, was isolated as a potent antimalarial active ingredient (IC_{50} value: 80 ng/mL) from the 80% EtOH extract of the outer bark of *Ochna integerrima* (Ochnaceae).[87]

Antimalarial screening of the active *n*-BuOH extract from the root of *Wikstroemia indica* led to the isolation of two biflavonoids, sikokianin B (**136**) and sikokianin C (**137**), with IC_{50} values of 0.54 μg/mL and 0.56 μg/mL, respectively, against the chloroquine-resistant strain of *Plasmodium falciparum*.[88]

A series of eleven biflavonoids containing amentoflavone (**1**) and hinokiflavone (**235**) derived from the Indian medicinal herb *Selaginella bryopteris* (Selaginellaceae) has been investigated for their antiprotozoal activity. The highest antiprotozoal activity was displayed by I-7,4′,II-7-tri-*O*-methyl-amentoflavone (7,4′,7″-tri-*O*-methylamentoflavone) (**16**), which exhibited an IC_{50} of 0.26 μM. This compound showed no significant cytotoxicity (IC_{50} > 150 μM) evaluated using L-6 cells. The strongest activity against *Leishmania* was detected for 2,3-dihydrohinokiflavone (**31b**) (IC_{50} = 1.6 μM).[89]

ANTI-INFLAMMATORY ACTIVITY OF BIFLAVONOIDS

In vivo anti-inflammatory activities of biflavonoids have been demonstrated.[27, 30, 31, 90-103] The *Garcinia* biflavanones, GB_1 (3",4',4"',5,5",7,7"-heptahydroxy-3,8"-biflavanone) (**176**) and GB_2 (**177**), showed *in vivo* anti-inflammatory activity at 50 mg/kg intraperitoneal (i.p.) against CGN-induced edema.[101] When topically applied, the *Ginkgo* biflavonoids, amentoflavone (**1**), ginkgetin (**7**) and sciadopitysin (**15**), showed anti-inflammatory activity against croton-oil-induced ear edema. They exhibited higher anti-inflammatory activity when a liposome formulation was used.[30]

Amentoflavone (**1**), a biflavone also isolated from *Selaginella* species, showed potent anti-inflammatory activity *in vivo*; by i.p. route had approximately 1/2-1/5 of the anti-inflammatory activity of indomethacin or prednisolone against several animal models of acute inflammation, including acetic acid-induced writhings in mice. However, amentoflavone (**1**) did not significantly reduce adjuvant-induced arthritis (AIA) in rats.[31]

Fukugetin (**159**) and GB_{2a} (**172**) prevented the carrageenan-induced paw oedema.[104] The synthetic 7-(4-oxo-2-phenylchromen-6-yl)oxy-2-phenylchromen-4-one ((I-6,*O*,II-7)-biflavone)-biflavone) (**253a**) has potential as a new anti-inflammatory agent.[105] A synthetic biflavone with a C-C (6–6″) linkage ([6,6″]biflavone, BF6-6) (**115a**) having considerable anti-inflammatory activity was enhanced by further substitution of the structure leading to 5,7-dihydroxy[6,6″]biflavone (I-5,7-dihydroxy (I-6,II-6)-biflavone) (G168) (**115b**) that showed a much stronger activity.[106]

The seed of *Semecarpus anacardium* L. is widely used in Indian traditional medicine; Ayurveda and Sidha, for treatment of inflammatory disorders and gout. The activity guided fractionation of *S. anacardium* seed was conducted using liquid–liquid partition and preparative HPLC. The fractions were evaluated for their xanthine oxidase (XO) inhibition, over expression of which lead to inflammation and gout; and antioxidant activity. The ethyl acetate fraction with the highest XO activity yielded a biflavonoid compound tetrahydroamentoflavone (THA) (**47**). IC_{50} values of THA for XO inhibition was 92 nM and its value for Ki was 0.982 μM . As a conclusion, THA is a potent XO inhibitor that could be considered as a drug candidate or chemopreventive agent, after establishing its pharmacological and clinical evaluation. The results support the claim of the traditional medicine with respect to the efficacy of *S. anacardium* seed against inflammation and gout.[107]

Research on anti-inflammatory biflavonoids is in the early stages and in continuous development. Based on initial studies, biflavonoids seem to use multiple anti-inflammatory mechanisms. Affect inflammatory cells such as mast cells and lymphocytes. Inhibit proinflammatory enzymes such as PLA_2 (phospholipase A_2)[108] and COX (cyclooxygenase).[109] Recent research also shows that biflavonoids suppress the expression of proinflammatory molecules. Due to these unique properties, biflavonoids have potential as anti-inflammatory drugs, especially for the treatment of chronic inflammatory disorders. Through more intensive studies with modern pharmacological techniques, new types of anti-inflammatory agents based on biflavonoid structures may be successfully developed.[3]

ANALGESIC ACTIVITY OF BIFLAVONOIDS

Some biflavonoids possess peripheral analgesic activity by i.p. injection. Some research has shown that amentoflavone (**1**) and ginkgetin (**7**) have a potent analgesic activity against writhings by i.p. injection, but not by oral administration.[31, 98] Similarly, GB_{1a} (**167**) showed antinociceptive activity by i.p. injection on writhing test and formalin test.[110] II-4′-*O*-Methyl-GB_{2a} [naringenin-(I-3,II-8)-II-4-*O*-methyleriodictyol] (**175**) isolated from *Rheedia gardneriana* leaves also showed analgesic activity by i.p. injection.[97] The newly synthesized biflavonoid, G168 (**115b**), showed analgesic activity on acetic acid-induced writhing in mice.[106] Therefore, it is clear that some biflavonoids have analgesic activity, which can lead to the development of superior anti-inflammatory agents.

ANTIOXIDANT ACTIVITY OF BIFLAVONOIDS

Another property with potential applicability is the antioxidant property of biflavonoids; their potency appeared to be lower than that of monoflavonoids despite the presence of almost twice the number of phenolic OH groups.[111]

Nevertheless, a recent study showed that Kolaviron, a mixture of biflavonoids (GB_1 (**176**), GB_{1a} (**167**), GB_2 (**177**) and Kolaflavanone (**178**)) extracted from *Garcinia kola* seeds has a protective effect against γ-radiation-induced oxidative stress in the brain of exposed rats.[112] Different studies gave further evidence of the antioxidant potential of biflavonoids from the same source.[113-116] Also, morelloflavone (**159**) showed strong antioxidant effects in both Fe^{2+}-mediated and non-metal-induced human low-density lipoprotein (LDL) oxidations, exhibiting higher potency than the well-known antioxidant vitamin E in the same test systems.[117] It is expected that the number of known biflavonoids with potent antioxidant activity will increase.

ADDITIONAL RELEVANT ACTIVITIES

Biflavonoids also have vasorelaxant,[83, 93, 118, 119] and anticlotting[120, 121] activities.

In addition, the methanolic crude extracts of leaves and stem bark of *C. flavum* and compounds displayed a significant cytotoxicity towards *Artemia*

salina larvae. From the extract it was extracted a new biflavonoid namely 4"'-*O*-methylagathisflavone (**102a**), a chalcone dimer, an alkaloid and 10 known compounds, including three flavonoids, two biflavonoids, two alkaloids, two nitrile glucosides, and glucopyranosyl-β-sistosterol. The structures of these compounds and their relative configurations were established by 1D and 2D NMR experiments.[122]

Chapter 6

CONCLUSION

The structural variability, rearrangements, and different stereochemistry of 466 biflavonoid structures distributed among species of Angiosperms (monocots and dicots), Gymnosperms, ferns (Pteridophyta), and mosses (Bryophyta) were highlighted. Their distribution was presented providing the latest picture of the natural sources, biological activities, and traditional uses; thus offering a compilation that can be an important tool for any future study on biflavonoids.

The chemistry of biflavonoids was discussed getting a current image of their bioactivity confirming their potential biomedical application.

The structure-activity studies of these compounds are scarce due to the shortage of experimental data. It is expected that in future such studies will provide additional tools for the development of biflavonoids with enhanced bioactivity.

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