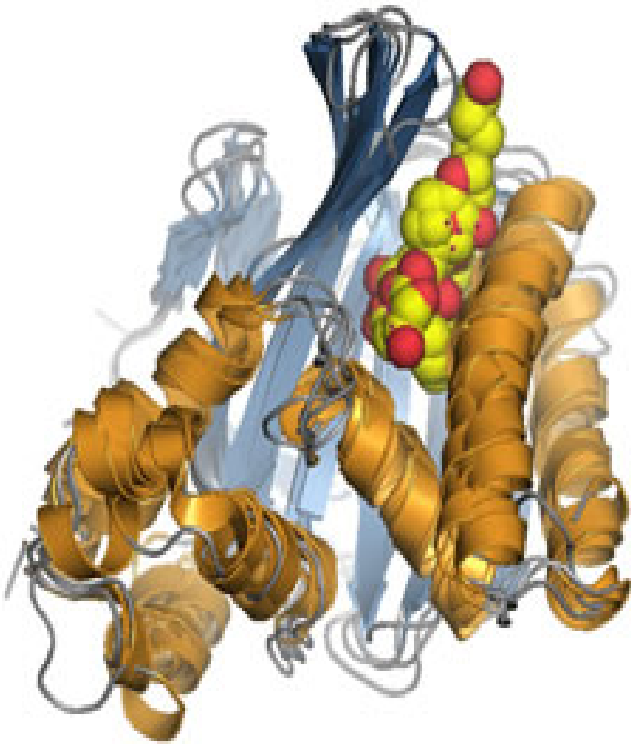
PhytoChem & BioSub Journal

Peer-reviewed research journal on Phytochemistry & Bioactives Substances

ISSN 2170 - 1768



PCBS Journal

Volume 8 N° 1, 2 & 3 2014

PhytoChem & BioSub Journal

Peer-reviewed research journal on Phytochemistry & Bioactives Substances

ISSN 2170 - 1768

PCBS Journal

PCBS Journal

Volume 8 N° 1 2014

Edition LPSO

Phytochemistry & Organic Synthesis Laboratory

http://www.pcbsj.webs.com , Email: phytochem07@yahoo.fr

PhytoChem & BioSub Journal Vol. 8(1) 2014
ISSN 2170-1768
CAS-CODEN:PBJHB3

PCBS Journal
ISSN 2170-1768

PhytoChem & BioSub Journal

2014
Vol. 8 No. 1

Antioxidant activity of Imino-Hesperidin derivatives

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DOI:10.163.pcbsj/2014.8.1.53

Abstract. *DMF solution of imino-Hesperidin derivatives was screened for its antioxidant activity based on their capacity to scavenge the free β-carotene radical after exposure to a UV lamp at 254 nm. In the first time, we have synthesized seven new compounds derived from Hesperidin* ***1*** *based on condensation reactions and nucleophile additions simple and easy to carry. Hesperidin* ***1*** *which is a natural molecule extracted in the laboratory (LPOS) from orange peel (genre Citrus sp.), which is the best known flavanone of citrus and the most studied. The structural elucidation of these new products (mono-iminohesperidin* ***3-4*** *and bis-iminohesperidin* ***5-9*** *derivatives) was achieved by IR, UV, ^{1}H NMR and ^{13}C NMR. The results of antioxidant activity proved that these compounds showed antioxidant activity by means of β-carotene greater than that of Hesperidin* ***1****.*

Key Words**:** Hesperidin, Citrus sp., antioxidant, β-carotene

Introduction

Flavonoids are polyphenolic compounds ubiquitous in plants food and they can be found in a variety of fruits, vegetables, cereals, tea, wine and fruit juices, which are based on 2-phenylchromone or 2-phenylbenzopyrone, they have a C_6–C_3–C_6 carbon skeleton where two benzene rings (A- and B-ring) are linked through a heterocyclic pyran or pyrone ring (C-ring) in the middle. The B-ring is located at the 2-position and the C-ring contains a C2–C3 double (Fig. 1).[1-2] In plants, flavonoids are performing a variety of functions including pollination, seed dispersal, pollen tube growth, resorption of mineral nutrients, tolerance to abiotic stresses, protection against ultraviolet and allelopathic interactions, etc.[3] Natural flavonoids are known for their significant scavenging properties on oxygen radicals in vivo and in vitro.

In addition to these important effects, several beneficial properties have been attributed to these dietary compounds, including antioxidant, anti-inflammatory, anti-allergic, anti-viral, anti-bacterial, anti-protozoal, anti-fungal and anti-carcinogenic effects. The best described property of almost every group of flavonoids is their capacity to act as antioxidants able to scavenge free radicals and reactive oxygen

species which are associated with several forms of tissue damage and disease, including cancer, atherosclerosis, neuronal degeneration, rheumatoid arthritis as well as with aging.[4] In antitumor area, flavonoids can inhibit the metabolism of the benze[α]pyrene by hamster embryo cells in tissue culture.[5]

In particular, flavanones (2,3-dihydro-2-phenyl-*4H*-1-benzopyran-4-one derivatives) are a class of flavonoids mainly present in citrus fruits such as orange, grapefruit and lemon;[6-8] called citroflavonoids.[9] they are present in solid wastes and residues obtained during their industrial processing. They are usually found as flavanone-7-*O*-glycosides (Fig.1).[10-12]

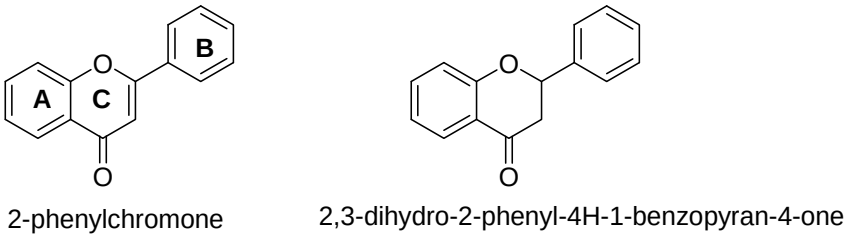
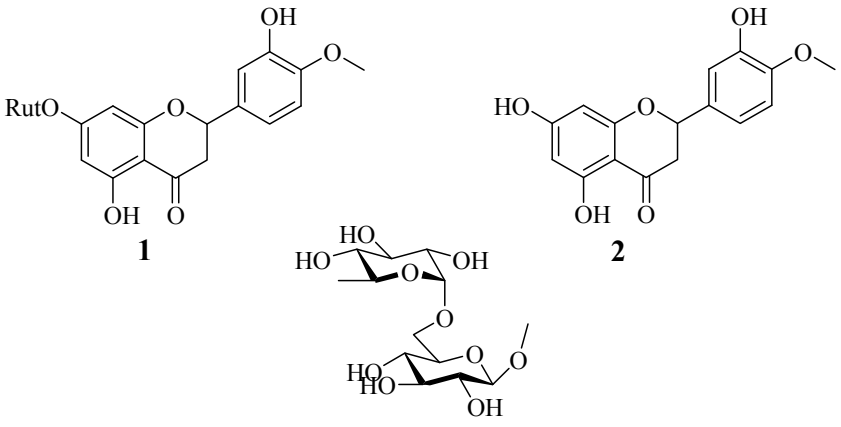


Figure 1: Basic Skeleton of flavanones.

From citroflavonoids, Hesperidin **1** (3',5,7-trihydroxy-4-methoxyflavanone-7-*O*-rutinoside; $C_{28}H_{34}O_{15}$) is the best studied flavanone, and it's a major citroflavonoids isolated in large numbers of fruits and vegetables.[13-16] Hesperidin **1** is a flavanone glycoside contain a chiral center in position C-2, and composed of the flavanone Hesperetin **2** ($C_{16}H_{14}O_6$); and the disaccharide Rutinoside ($C_{12}H_{22}O_{10}$) consisting of an α-*L*-rhamnose linked to a β-*D*-glucose by a connection (α1-6) glycoside. [17-18]The rutinoside is related to Hesperetin **2** by a bond *O*-heterosidic in position 7 [18-21] (Fig.2). The pure Hesperidin **1** obtained as long needles, bronze or pale yellow in colour. Its melting point is located at 258°C to 262°C (softens at 250°C). It has a molecular weight of 610.57 g/mol, it's tasteless and odourless.[18] Normal intake of Hesperidin **1** has been observed to show no signs of toxicity.[22]



Rut ≡Rutinoside

Figure 2: Structure of Hesperidin **1** and Hesperetin **2**

Hesperidin **1** has been long recognized to possess a wide range of pharmacological properties such as: anticholesterol, antioxidant,[16] anti-inflammatory,[23] antimutagenic and antihypertensive, diuretic,[24] antidiabetic,[25] vasoprotective, antiallergenic, antimicrobial,[26] anticarcinogenic.[27] has shown beneficial effects in the treatment of hyperglycemic disease;[1] it Other reported activities of the Hesperidin **1** include the loss of bone density.[20] Hesperidin is known to improve vascular integrity and to decrease capillary permeability, and is used as supplementation for patients of blood vessel fragility and permeability complaints.[15]

Because of reactive sites interest of Hesperidin **1** and pharmacological activity, we are interested to the extraction and synthesis of derivatives of this molecule in order to give a deep research to the antioxidant activity of these derivatives by means of β-carotene.

Materials and Methods

Extraction of Hesperidin 1:

Orange peels were air-dried at room temperature. Extracts of *Citrus sinensis* (40 g) were extracted using Soxhlet extractor with 500 ml of petroleum ether (40-60°C) until the siphoned material become colorless for 2 hours. After, the extraction was continued in 2nd time by adding 300 ml of methanol over a period of 2 hours. The methanol extract was dried in vacuo at 65°C, and recrystallized with aqueous acetic acid. The flavanone glycoside, Hesperidin **1**, was separated as beige needles, mp 261-262°C; the total yield quantity was 33.2 g (83%).

Synthesis of Imino-Hesperidin derivatives 3-9:

We reported here the synthesis of imino-Hesperidin derivatives. We have synthesized seven compounds derived from Hesperidin **1** regarding the effect of different reagents (primary amine, diamine). We include a simple and cost effective synthesis of these derivatives.

The imino-Hesperidin **3-9** are purified and characterized by spectroscopic methods. These derivatives of Hesperidin obtained after 24 h of reflux in methanol with excellent yields and without catalyst.

Extraction of β-carotene

10 g of crushed carrot were mixed with 40 ml of 99.8% ethanol and 100 ml of 10% potassium hydroxide (weight/volume) at reflux. After 30 min, the mixture was cooled to room temperature. After, we put the mixture with 50 ml of n-hexane in a separating funnel. The organic portion was removed with a pipette and collected in a beaker, and we re-extract the ethanolic portion twice with 50 ml of n-hexane. Phenolphthalein solution (1%) was added to the hexanolic extract to check any alkali. Next, the extract hexanolic was then filtered through anhydrous sodium sulfate. The residue was removed under reduced pressure at 45 ° C using a rotary evaporator.

Test the antioxidant activity through β-carotene

The detection of antioxidant substances in our various products was performed using the test through β-carotene; the principle is to capture free radicals provided by the β-carotene after exposure to a UV lamp. We proceeded as follows: DMF solution was used to dissolve the synthesized product (0.01 g of each product was dissolved in 1 ml of DMF). Then, deposits spots of our products are done using a capillary tube on a

TLC plate. After drying in ambient air, the TLC plate was sprayed with a chloroform solution containing 5 mg / ml of β-carotene, then, the plate under UV light at 254 nm is allowed to discoloration. Areas of antioxidant activity were determined by the appearance of a yellow color on white background. We used as reference vitamin C (or ascorbic acid).

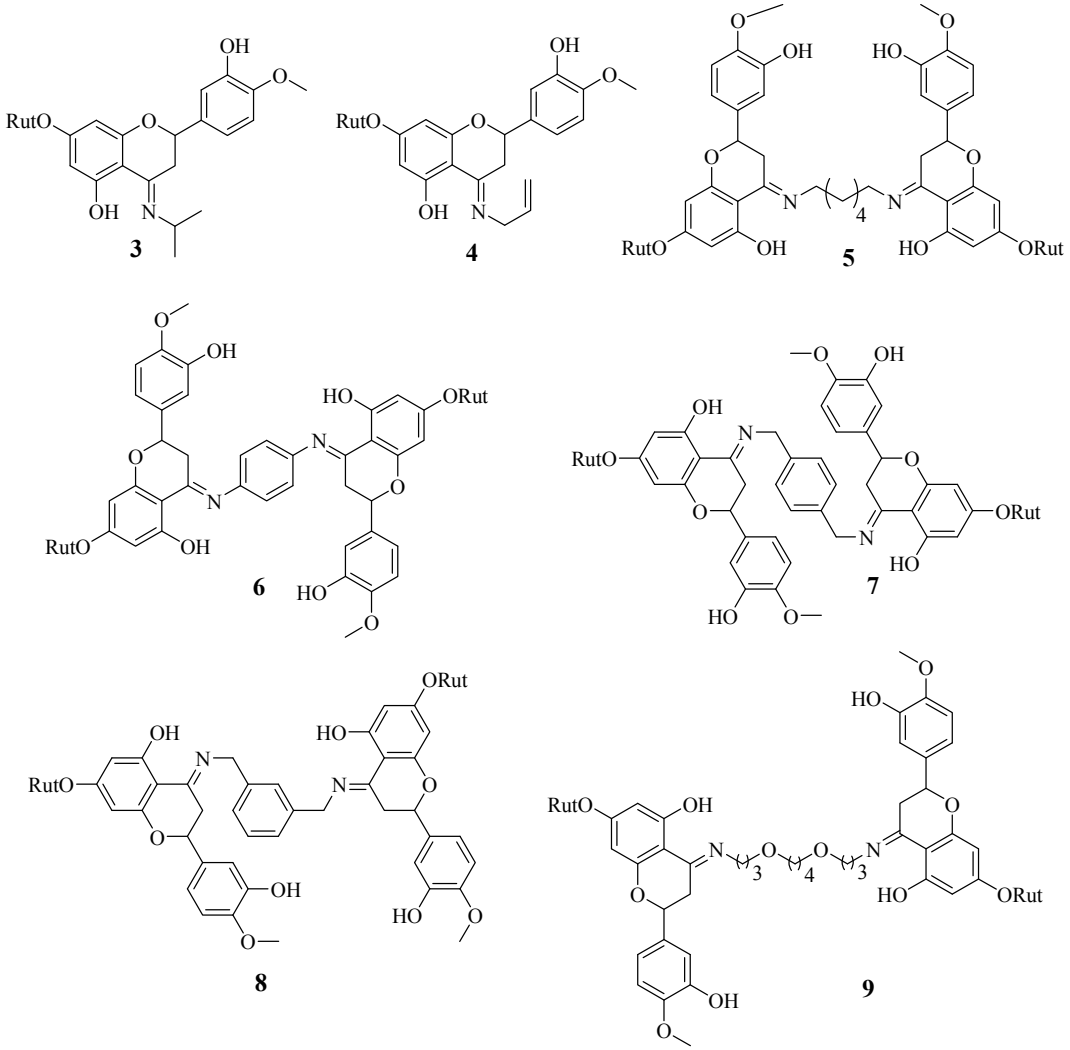


Figure 3: Structure of Imino-Hesperidin synthetizes **3-9**.

Results and Discussion

Table 1 summarizes the results obtained for the antioxidant activity of our products, after the discoloration of the TLC plate under a UV lamp 254 nm.

Our study showed that the derivatives of Hesperidin showed antioxidant activity. All synthesized products presented yellow spots with a different fluorescent using the test using β-carotene (i.e. fading of the β-carotene). The antioxidant activity could be explained by the main skeleton of our products, which is the skeleton of a flavanone, the Hesperidin. According to the literature, flavanones as other flavonoids are

scavengers of free radicals or sensors, numerous studies *in vivo* and *in vitro* have shown the antioxidant property of Hesperidin.

Under our experimental conditions, each of the products synthesized an antioxidant power but with variable intensity. We also observe that the products **3**, **4**, **8** and **9** have darker than the other yellow spots, and then we can consider these compounds as antioxidants.

Table 1: Results of antioxidant test of Imino-Hesperidin **3-9** after the revelation by β-carotene

Compound	Color after exposure to UV lamp 254	Intensity
Vit C	yellow	+++
1	yellow	+
3	yellow	+++
4	yellow	+++
5	yellow	+
6	yellow	++
7	yellow	++
8	yellow	+++
9	yellow	+++

Conclusion

This study, allowed us to show that the imino-Hesperidin synthesized **3-9** has antioxidant properties. By this action, they can contribute to the prevention against certain types of diseases, for example such as skin aging and cancer.

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