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Review

Chemistry and pharmacology of oxyprenylated secondary plant metabolites

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Abstract

Oxyprenylated natural products (isopentenyloxy-, geranyloxy- and the less spread farnesyloxy- compounds and their biosynthetic derivatives) represent a family of secondary metabolites that have been considered for years just as biosynthetic intermediates of *C*-prenylated derivatives. Only in the last decade these natural products have been recognized as interesting and valuable biologically active phytochemicals. Up to now about 300 molecules have been isolated from plants mainly belonging to the families of Rutaceae and Compositae, comprising common edible vegetables and fruits. A wide variety of compounds containing a prenyloxy side chain have been isolated and these comprise alkaloids, coumarins, flavonoids, cinnamic acids, benzoic acids, phenols, alcohols, aldehydes, anthraquinones, chalcones, lignans, xanthones, aceto- and benzophenones and other more uncommon skeletons. Many of the isolated oxyprenylated natural products and their semisynthetic derivatives were shown to exert *in vitro* and *in vivo* remarkable anti-cancer, anti-inflammatory, anti-microbial and anti-fungal effects. The aim of this review is to examine in detail the different types of oxyprenylated natural compounds from a phytochemical and pharmacological point of view.

Keywords: Biological activity; Compositae; Oxyprenylated natural products; Rutaceae

Contents

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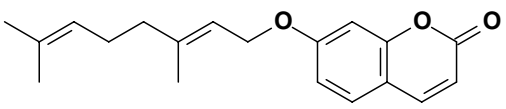
1. Introduction

Prenylation is a chemical or enzymatic addition of an hydrophobic side chain to an accepting molecule (another terpenoid molecule, an aromatic compound, a protein, etc.). In particular, prenylation of aromatic secondary metabolites plays a critical role in the biosynthesis of a wide range of molecules exerting valuable pharmacological effects across phylogenetically different classes of living organisms, from bacteria to mammals and plants. Frequently, the addition of an isoprenoid chain renders the molecule more effective than the parent compound from a pharmacological point of view. These "hybrid" natural products represent nowadays a new frontier for the development of novel drugs, in particular as antimicrobial, anti-oxidant, anti-inflammatory and anti-cancer agents.

Oxyprenylated natural products are compounds of mixed biosynthetic origin for which the final step of the biosynthetic process is the prenylation of an alkaloid or a phenylpropanoid core using prenyl diphosphate as alkylating agent (Kuzuyama et al., 2005), the latter coming in turn from the mevalonate (Haagen-Smit, 1953) or 1-DOXP pathways (Lichtenthaler, 1999). Oxyprenylated secondary metabolites have been considered for decades merely as biosynthetic intermediates of *C*-prenylated compounds and only in the last ten years have been characterized as phytochemicals exerting interesting and valuable biological activities. Considering the length of the carbon chain, three types of prenyloxy skeletons can be identified: C_5 (isopentenyl), C_{10} (geranyl) and C_{15} (farnesyl). Isopentenyloxy and geranyloxy chains are quite abundant in nature, while farnesyloxy ones are less common. The skeleton may consist only of carbon and hydrogen or may contain oxygen atoms, usually in form of alcohols, ethers or ketone functional groups. The first example in the literature of a prenyloxy secondary metabolite is auraptene **1**, isolated in 1930 from *Citrus aurantium* L. (Rutaceae) and structurally characterized by Kariyone and Matsuno (Kariyone and Matsuno, 1953). Although known for a long time, the first study describing a pharmacological effect of auraptene **1** appeared in the literature only in 1991 (Takeuchi et al., 1991). To date about 300 oxyprenylated derivatives have been isolated and/or synthesized and were shown to possess a wide variety of valuable and promising pharmacological activities. In this review, we shall focus our attention on the chemistry and pharmacology of various oxyprenylated natural products, most of which obtained from plants that were long used for proven or supposed medical properties, according to some ancient ethnomedical traditions.



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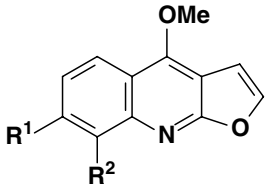
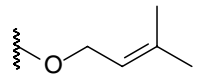
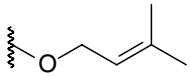
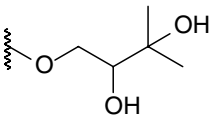
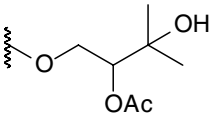
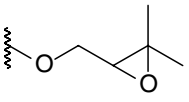


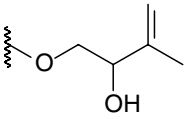
2 R^1 =  R^2 = H

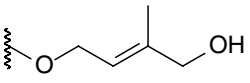
3 R^1 = H R^2 = 

4 R^1 =  R^2 = OMe

5 R^1 =  R^2 = OMe

6 R^1 =  R^2 = OMe

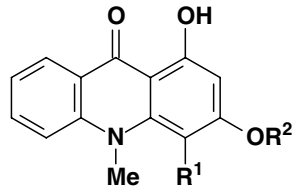
7 R^1 =  R^2 = OMe

8 R^1 =  R^2 = OMe

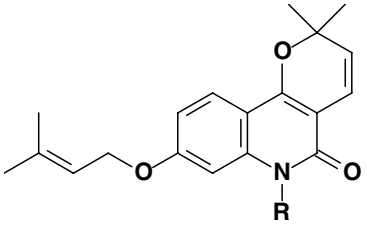
2. Prenyloxyalkaloids

The first example of isolation of an alkaloid containing a prenyloxy side chain dates back to 1974 when Bessonova and co-workers extracted from the above ground parts of *Haplophyllum perforatum* (MB.) Kar. & Kir. (Rutaceae)

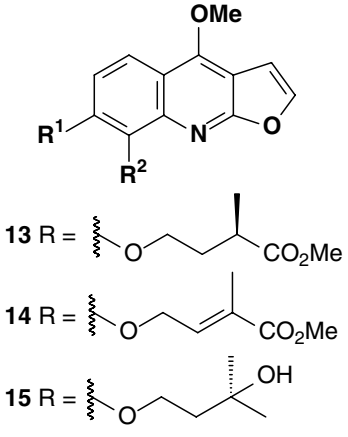
7-isopentenyloxy-γ-fagarine **2** (Bessonova et al., 1974). The same alkaloid has also been isolated from *H. latifolium* Kar. & Kir. (Nesmelova et al., 1977), *H. ferganicum* Vved. (Bessonova and Yunusov, 1982), *Zanthoxylum arborescens* L. (Rutaceae) (Grina et al., 1982), from which it was extracted together with its 8-isomer **3**, *H. glabrum* Bornm. (Rózsa et al., 1986) and *Skimmia reevesiana* R. Fortune (Rutaceae) (Wu, 1987). From these natural sources other furanoquinoline prenyloxyalkaloids, namely evoxine **4** and its acetyl derivative **5**, anhydroevoxine **6**, evodine **7** and haplatine **8**, were isolated (Rózsa et al., 1986; Wu, 1987). The acridone alkaloid 1-hydroxy-1-geranyloxy-4-methoxy-3-methyl-10-acridone **9** has been isolated from wood and bark of the plant of New Caledonia *Sarcomelicope leiocarpa* (P.S. Green) (Rutaceae) (Baudouin et al., 1985). Another acridone alkaloid, having an isopentenyloxy side chain, 1-hydroxy-*N*-methyl-3-isopentenyloxyacridone, named vebilocine **10**, was isolated from *Vepris bilocularis* (Wight & . Arn.) (Rutaceae) (Brader et al., 1996).



9 R^1 = OMe, R^2 = geranyl
10 R^1 = H, R^2 = isopentenyl



11 R = H
12 R = Me

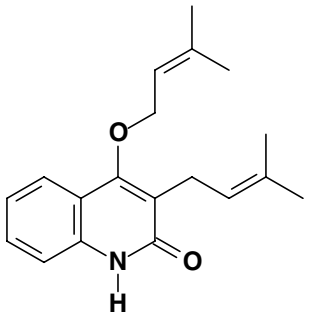


This latter plant yielded also two pyrano-2-quinolone alkaloids, such 7-isopentenyloxyflindersine **11** and its *N*-methyl derivative **12**. The roxiamine family (A–C) **13**–**15** comprises three furanoquinoline alkaloids with functionalized side chains and were isolated from the aerial parts of the Thai plant *Euodia roxburghiana* Benth. (Rutaceae) (McCormick et al., 1996). From the same plant 3-isopentenyl-4-isopentenyloxyquinolin-2-one **16** was isolated. The latter compound protected human lymphoblastoid (CEM-SS) host cells from the cytopathic effects of HIV-1 *in vitro* ($EC_{50} = 1.64$ μM), while roxiamines were not active. Compound **16** showed also an inhibitory effect on HIV-1 reverse transcriptase ($IC_{50} =$ 8.0 μM).

3. Prenyloxyphenylpropanoids

3.1. Acetophenones

Geranyloxyacetophenones have been isolated to date only from one plant, *Euodia merrilli* Kanehira & Sasaki ex Kanehira, a Taiwanese small tree belonging to the family of Rutaceae. In 1992 and 1993, Chen and co-workers reported the characterization of six geranyloxyacetophenones, 4-(1′-geranyloxy)-2,6-dihydroxy-3-isopentenylacetophenone **17**, 2-(1′-geranyloxy)-4,6-dihydroxyacetophenone **18**, 4-(1′-geranyloxy)-2,6-dihydroxyacetophenone **19**, 4-(1′-geranyloxy)-2,6,β-trihydroxyacetophenone **20**, 4-(1′-geranyloxy)-2,6,β-trihydroxy-3-dimethylallylacetophenone **21** and 2-(1′-geranyloxy)-4,6,β-trihydroxyacetophenone **22** (Chou et al., 1992; Lin et al., 1993). Compounds **17** and **18** have been synthesized by Tsukayama and co-workers by palladium coupling processes of suitably substituted functionalized iodophenols with alcohols (Tsukayama et al., 1993, 1994). The only example of acetophenone containing an isopentenyloxy side chain is 4′-isopentenyloxy-2′,6′-dihydroxy-3′-isopentenylacetophenone **23**, that was isolated by Kumar and co-workers in 1990 from root bark of *Euodia lunuankenda* (Gaertn.) Miq. LS. (Kumar et al., 1990) and the structure of which was unambiguously attributed by Tsukayama and co-workers (Tsukayama et al., 1994), by comparison of a sample obtained by chemical synthesis with a pure compound isolated from the plant. Also for farnesyloxyacetophenones only one example has been reported in the literature. In 1994, Waterman and co-workers isolated 4-farnesyloxy-2,6-dihydroxyacetophenone **24** from aerial parts of *Boronia ramosa* (Lindl.) Benth. (Rutaceae) (Ahsan et al., 1994). This latter compound has been also synthesized by Li and co-workers in 1999 in five steps starting from commercially available 2,4,6-trihydroxyacetophenone (Huang et al., 1999).



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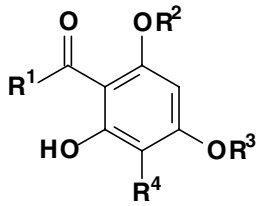
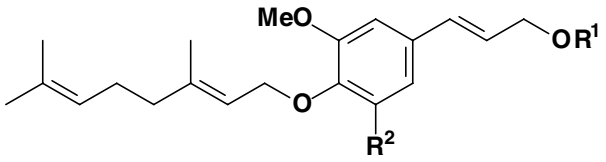


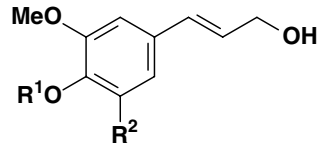
17 $R^1 = R^2 = H$, R^3 = geranyl, R^4 = isopentenyl
18 $R^1 = H$, R^2 = geranyl, $R^3 = R^4 = H$
19 $R^1 = R^2 = H$, R^3 = geranyl, $R^4 = H$
20 $R^1 = CH_2OH$, $R^2 = H$, R^3 =geranyl, $R^4 = H$
21 $R^1 = CH_2OH$, $R^2 = H$, R^3 = geranyl, R^4 = isopentenyl
22 $R^1 = CH_2OH$, R^2 = geranyl, $R^3 = R^4 = H$
23 $R^1 = H$, R^2 = isopentenyl, $R^3 = H$, R^4 = isopentenyl
24 $R^1 = R^2 = H$. R^3 = farnesyl, $R^4 = H$

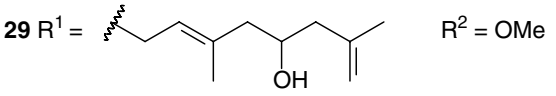


25 $R^1 = H$, R^2 = OMe
26 R^1 = Ac, R^2 = OMe
27 $R^1 = H$, $R^2 = H$

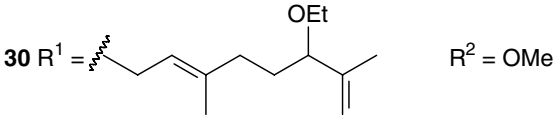
3.2. Alcohols and esters

Alcohols of phenylpropanoid biosynthetic origin containing a prenyloxy chain are all derivatives of cinnamyl alcohol. The first example reported in the literature is the isolation of two sinapyl alcohols, namely 3,5-dimethoxy-4-*O*-geranylcinnamyl alcohol **25** and its acetate **26**, respectively, from aerial parts of *Verbesina glabrata* Hook et Arn (Compositae) (Bohlmann et al., 1980) and *Senecio longifolius* L. (Boraginaceae) (Bohlmann et al., 1978). Compound **25** together with *O*-geranylconiferyl alcohol **27** have been isolated some years later from *Fagara rhetza* (Roxb.) DC. (Rutaceae) (Shibuya et al., 1992). Compound **25** has been also isolated from stem bark of *Zanthoxylum rhesta* DC. (Ahsan et al., 2000). *Ligularia nelumbifolia* [(Bur. et Franch) Hand.-Mazz.] (Compositae) has been shown as a natural source of a wide variety of substituted sinapyl alcohols such **25** and the novel ester **28** (Zhao et al., 1994). In 2002, Zhao and co-workers along with compound **25** reported the isolation from the latter plant five new sinapyl alcohol derivatives having different functionalities in the geranyloxy side chain, namely 4-*O*-[(2*E*)-3,7-dimethyl-2,7-octadien-5-ol]sinapyl alcohol **29**, 4-*O*-[(2*E*)-3,7-dimethyl-6-ethoxy-2,7-octadien]sinapyl alcohol **30**, 4-*O*-[(2*E*,5*E*)-3,7-dimethyl-5-ethoxy-2,5-octadien-7-ol]sinapyl alcohol **31**

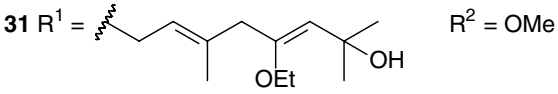




29 R^1 = R^2 = OMe



30 R^1 = R^2 = OMe



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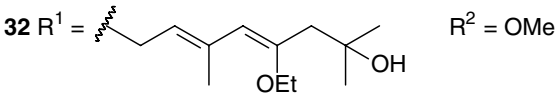
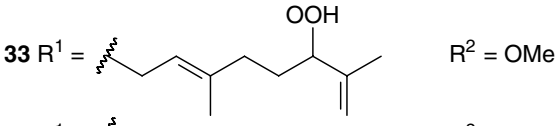
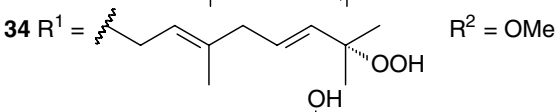


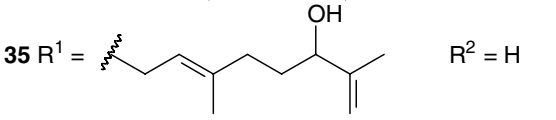
32 R^1 = R^2 = OMe



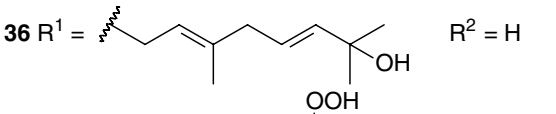
33 R^1 = R^2 = OMe



34 R^1 = R^2 = OMe



35 R^1 = R^2 = H



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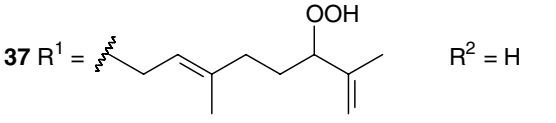
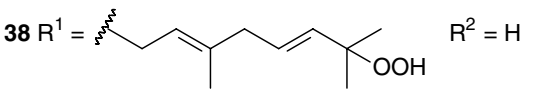
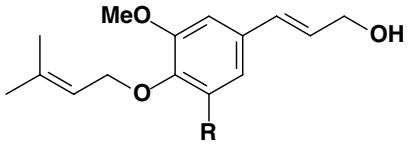


37 R^1 = R^2 = H

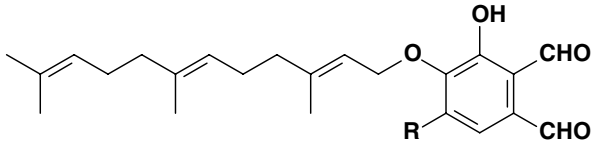


38 R^1 = R^2 = H

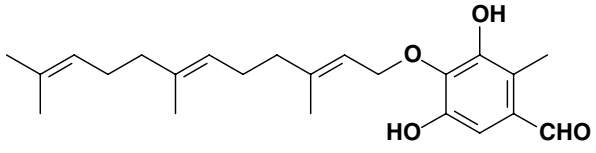
and 4-*O*-[(2*E*,4*E*)-3,7-dimethyl-5-ethoxy-2,4-octadien-7-ol]-sinapyl alcohol **32** (Zhao et al., 2002a). From another plant belonging to genus *Ligularia*, *L. intermedia* Nakai, two other substituted sinapyl alcohols having a hydroperoxy function in the geranyloxy chain, namely (*E*)-4-(6-hydroperoxy-3,7-dimethylocta-2,7-dienyloxy)sinapyl alcohol **33** and (*E*,*E*)-4-(7-hydroperoxy-3,7-dimethylocta-2,5-dienyloxy)sinapyl alcohol **34** have been isolated (Ma et al., 1997). Extracts of roots of *L. dulciformis* afforded, along with compounds **33** and **34**, four novel coniferyl alcohols derivatives such 4-*O*-[6-hydroxy-7(9)-dehydro-6,7-dihydrogeranyl]coniferyl alcohol **35**, 4-*O*-[7-hydroxy-5,6*E*-dehydro-6,7-dihydrogeranyl]coniferyl alcohol **36**, 4-*O*-[6-hydroperoxy-7(9)-dehydro-6,7-dihydrogeranyl]coniferyl alcohol **37** and 4-*O*-[7-hydroperoxy-5,6*E*-dehydro-6,7-dihydrogeranyl]-coniferyl alcohol **38** (Gao et al., 1997). Compounds **34**, **35**, **37** and **38** are the only ones among geranyloxyphenylpropanoids derivatives to have a hydroperoxy function. Sinapyl alcohols derivatives having an isopentenyloxy side chain have been isolated from the roots of *Boronia pinnata* Sm. and named boropinol A **39** and C **40** (Ito et al., 2000). Some of these natural products were obtained also by chemical synthesis: Zhao and co-workers synthesized compound **25** in three steps starting from commercially available sinapic acid (Zhao et al., 1994, 2002b). In this way **25** was made in such a quantity to carry out detailed pharmacological test: this natural product was shown to be cytotoxic to KB cells, whereas exhibited no significative activity against A-549 and HL-60 cell lines (Table 1). These results prompted synthesis of several derivatives and structural analogues of **25** designed with the aim to improve its anti-cancer activity (Zou et al., 2006).



39 R = H
40 R = OMe



41 R = OMe
42 R = OH



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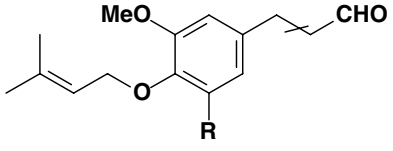


44 R = H
45 R = OMe

Table 1
Cytotoxic activity of compounds **25** and **45** against selected cancer cell lines

Cell line	IC_{50} (M)	
	25	**45**
A-549	3.4×10^{-5}	2.2×10^{-5}
HL-60	6.7×10^{-6}	1.2×10^{-6}
KB	3.0×10^{-6}	2.6×10^{-6}

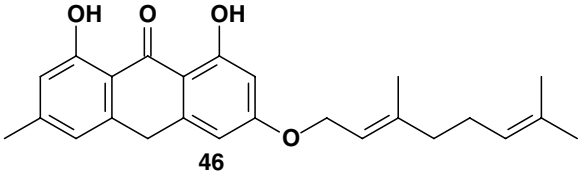
3.3. Aldehydes

Aldehydes of phenylpropanoid biosynthetic origin having a prenyloxy side chain can be divided in two classes: (a) benzaldehyde derivatives and (b) cinnamic aldehyde derivatives. Examples of prenyloxybenzaldehydes belonging to the family of asperugins comprise asperugin A **41**, B **42** and C **43**. These are secondary metabolites of fungal origin containing a farnesyloxy side chain. Compound **41** was first isolated from culture of *Aspergillus rugulosus* by Ballantine and co-workers (Ballantine et al., 1965). The same research group 2 years later isolated from the same natural source **42** (Ballantine et al., 1967) and finally in 1971 **43** (Ballantine et al., 1971), that may represent a shunt metabolite in the biosynthetic pathway of asperugin A. Compound **41** has been also obtained by chemical synthesis starting from gallic acid and was seen to exert a moderate anti-fungal activity (Hayashi et al., 1982). If compared to cinnamic alcohol derivatives, few examples of prenyloxycinnamic aldehydes have been reported. The first compound was isolated from *Boronia pinnata* (Ito et al., 2000) and named boropinal **44**. Geranyloxy sinapyl aldehyde **45** has been obtained from roots of *Ligularia nelumbifolia* (Zhao et al., 2002a) and obtained by chemical synthesis (Zhao et al., 2002b). Compound **45** showed a good cytotoxic activity against KB and A-549 cells, while was less efficient towards HL-60 cell line (Table 1).

3.4. Anthraquinones

Several natural compounds containing an anthraquinone core linked to a prenyloxy chain have been reported in the literature. The first paper dealing with this kind of secondary metabolites appears in 1981 when Amonkar

and co-workers reported the isolation of 3-geranyloxy-6-methyl-1,8-dihydroxyanthrone **46** from root extracts of *Psorospermum febrifugum* Spach var. *ferrugineum* (Hook. fil) (Guttiferae) (Amonkar et al., 1981). This compound showed only a borderline, but reproducible activity in the P-388 mouse leukaemia system. Further investigations on other parts of the latter plant led to the isolation of vismione D **47** (Botta et al., 1983). A complete anthranoid secondary metabolites profile of *P. febrifugum* was finally depicted by Marston anc co-workers in 1986: a reinvestigation on root bark extracts in fact led to the isolation of two novel compounds, acetylvismione D **48**, 3-geranyloxy-6-methyl-1,8-dihydroxyanthraquinone **49** and 3-(19-hydroxygeranyloxy)-6-methyl-1,8-dihydroxyanthraquinone **50** (Marston et al., 1986). Compounds **47** and **48** exhibited a valuable cytotoxic activity *in vitro* against Co-115 human colon carcinoma cell line with LD_{50} values of 0.15 μg/mL and 0.38 μg/mL, respectively (Table 2). Four new emodin derivatives, namely 3-*O*-(2-hydroxy-3-methyl-but-3-enyl)-emodin **51**, 3-*O*-(2-methoxy-3-methyl-but-3-enyl)emodin **52**, 3-*O*-(3-hydroxymethyl-but-2-enyl)emodin **53** and 3-*O*-(3-hydroxymethyl-4-hydroxy-2-enyl)emodin **54** were isolated in 2000 by Morelli and co-workers from roots of the African shrub *Vismia guineensis* (L.) Choisy (Hypericaceae) (Bilia et al., 2000). Along with **49** and **47**, a symmetric dianthrone containing a double geranyloxy chain, named bianthrone A_1 **55**, has been isolated from another plant belonging to the genus *Vismia*, *V. orientalis* Engl. (Mbwambo et al., 2004). In the same study it has been put in evidence that **47** exhibited a broad spectrum of antiprotozoal activities against *Tripanosoma brucei rhodesiense*, *T. cruzi*, *Leishmania donovani* and *Plasmodium falciparum* strain K1, even if it was seen to be only slightly cytotoxic to human L6 cells. **55** was active against *T. brucei rhodesiense* and *P. falciparum* and **49** against *T. brucei rhodesiense*, *L. donovani* and *P. falciparum* (Table 3). Finally, compound **49** was also recently isolated from the stem bark of *Cratoxylum arborescens* (Vahl.) Blume (Fabaceae) (Pattanaprateeb et al., 2005).



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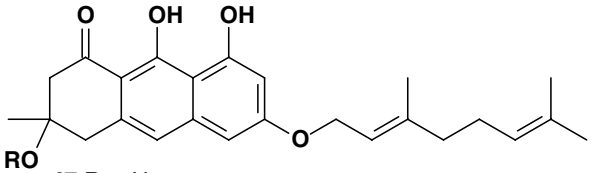
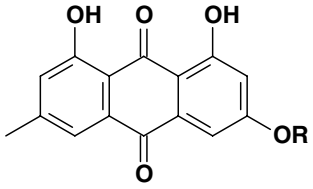


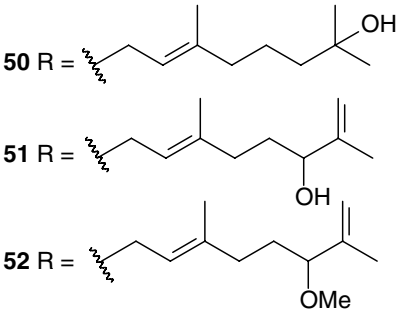
47 R = H
48 R = Ac

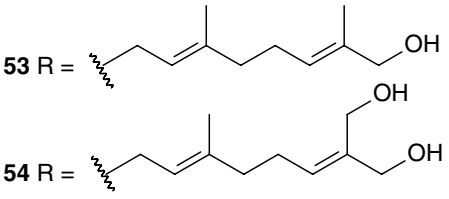
Table 2
Cytotoxic activity of compounds **47** and **48** against human colon carcinoma cell line Co-115 after a 5 day incubation period

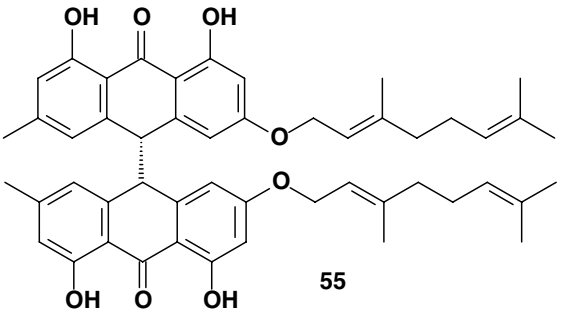
Compound	LD_{50} (μg/ml)
47	0.15
48	0.38



49 R = geranyl







55

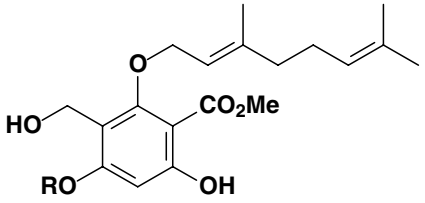
3.5. Benzoic acids

Benzoic acid derivatives have been found in nature to date always in form of methyl esters. The first compound of this series has been isolated in 1965 by Ritchie and co-workers from wood and bark of *Melicope broadbentiana* F.M. Bail. (Rutaceae). This secondary metabolite containing a geranyloxy chain was named melicopol **56** and was extracted together with its 5-methyl ether (methylmelicopol **57**) (Ritchie et al., 1965). About 30 years later Perry and

Table 3
Antiprotozoal activity of compounds **47, 49** and **55**

Entry	IC_{50} (μg/ml)				
	Tripanosoma brucei	*T. cruzi*	*Leishmania donovani*	*Plasmodium falciparum*	Cytotoxicity
47	9.0. ± 3.5	4.6 ± 1.6	0.37 ± 0.03	1.01 ± 0.13	4.1 ± 1.0
49	14.4 ± 8.1	> 90	12.0 ± 1.0	21.6 ± 1.42	>90
55	53.5 ± 18.4	> 90	> 30	41.1 ± 6.61	>90

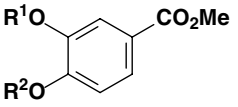
co-workers isolated eleven novel benzoic acid derivatives (**58**–**68**) from some liverworts of the genus *Trichocolea* (Trichocoleaceae), namely *T. mollissima* (Hook. f. and Tayl.) Gott., *T. tomentella* (Ehrh.) Dumort, *T. lanata* (Ehrh.) Dumort and *T. hatchery* Evans (Perry et al., 1996; Baek et al., 1998). These natural products are characterized by a different degree of oxidation in the prenyloxy chain leading to the presence of keto groups. Moreover compounds **60** and **68** are the only examples of prenyloxyphenylpropanoids having a neryloxy side chain. Compounds **58** and **61** were shown to be effective cytotoxic agents *in vitro* against monkey kidney (BSC) cells at a concentration of 15 μg/disk. The observed cytotoxic activity may be due to metabolic transformation of compounds leading to the breakdown of the ethereal linkage and formation of β-ocimenone that was seen to be cytotoxic against several cell lines (Perry et al., 1996). The cleavage of the carbon–oxygen bond of allyl ether function of the substituted geranyloxy chain could be facilitated by formation of thermodynamically stable allyl and phenoxy radicals prior to the formation of β-ocimenone and the parent phenol. The Claisen rearrangement of aryl allyl ether leading to *o*-allyl phenols is an example of how an allyl side chain could be cleaved in a relatively easy way in this kind of substrates (March, 1992). Natural products **58** and **61** were also mildly anti-fungal against the dermatophytic fungi *Trichophyton mentagrophytes* and *Candida albicans*.



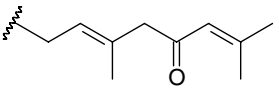
56 R = H
57 R = Me

3.6. Benzophenones

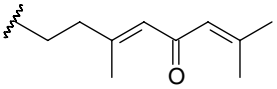
Only one geranyloxybenzophenone, namely 4-geranyloxy-2,6-dihydroxybenzophenone **69** has been described in the literature and isolated from two *Tovomita* species, *T. krukovii* A.C. and *T. longifolia* (Rich.) Hochr. (Clusiaceae) (Bohlmann and Subita, 1978) and from some plants belonging to *Leontonyx* species (Asteraceae) (Pecchio et al., 2006). Compound **69** showed a valuable cytotoxic activity against the human cancer cell line MCF-7 (IC_{50} = 4.8 μg/ml), H-460 (IC_{50} = 6.5 μg/ml) and SF-265 (IC_{50} = 5.6 μg/ml) and anti-microbial activity against *Staphylococcus aureus* (IC_{50} = 12.5 μg/mL) and *Mycobacterium smegmatis* (IC_{50} = 12.5 μg/ml).



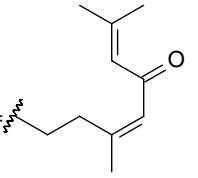
58 R^1 = Me, R^2 =



59 R^1 = Me, R^2 =

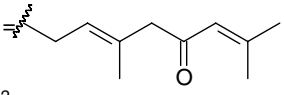


60 R^1 = Me, R^2 =



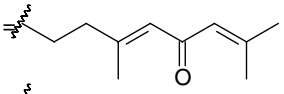
61 R^1 = Me, R^2 = geranyl

62 R^1 = H, R^2 =

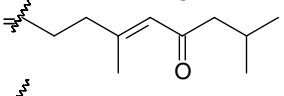


63 R^1 = Me, R^2 = isopenteny l
64 R^1 = H, R^2 = geranyl

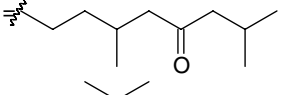
65 R^1 = H, R^2 =



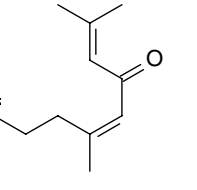
66 R^1 = H, R^2 =



67 R^1 = H, R^2 =

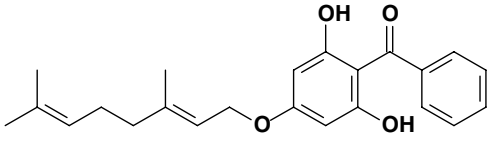


68 R^1 = H, R^2 =



3.7. Chalcones

The first example of a chalcone containing a prenyloxy side chain is derricidin **70** that was isolated from the root bark of *Derris sericea* (syn. *Lonchocarpus sericea*) (Poiret) Duche (Papilionaceae) in 1972 (Do Nascimento and Mors, 1972). From a plant belonging to the same genus, *L. muehlbergianus* Hassl., Magãlhaes and co-workers isolated a novel furanochalcone, 2′,5′,6′-trimethoxy-9-(1,1-dimethylallyloxy)-[2″,3″,3′,4′]- furanochalcone **71** (Magalhães et al., 2004). Chalcones **72** and **73** were obtained from aerial parts and roots of *Helichrysum athrixiifolium* (Kuntze) Moser (Bohlmann and Ates, 1984). Other chalcones were isolated from the genus *Millettia* (Leguminosae). In 1990, Noguchi and co-workers isolated 4′-*O*-geranylisoliquiritigenin **74**, the first example of a chalcone containing a geranyloxy chain (Dagne et al., 1990). From pods of *M. erythrocalix* Gagnep. 2,3′-dihydroxy-4-methoxy-4′-γ, γ-dimethylallyloxychalcone **75** was isolated by Sritularak and Likhitwitayawuid (Sritularak and Likhitwitayawuid, 2006). The only example of pyranochalcone has been reported by Suarez and Vargas in 2005, that isolated 2′, 6′-dihydroxy-4-isoprenyloxy-3,4(3‴,3⁗-dimethylpyran)chalcone **76** from wood of *Beilschmiedia tovarensis* (Meisn.) Sa. Nishida (Lauraceae) (Suarez and Vargas, 2005).



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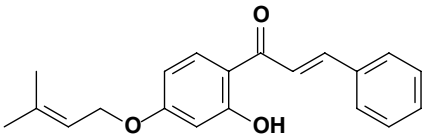

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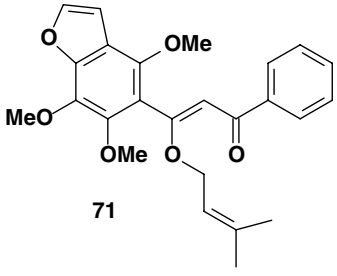

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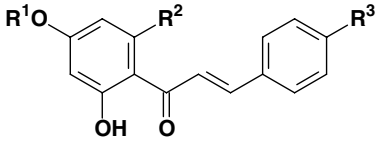
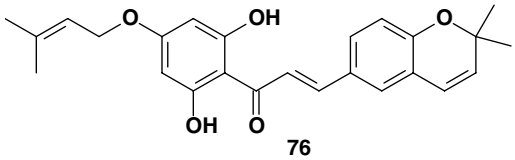


72 R^1 = isopentenyl, R^2 = OH, R^3 = H
73 R^1 = isopentenyl, R^2 = R^3= OH
74 R^1 = geranyl, R^2 = H, R^3 OH
75 R^1 = isopentenyl, R^2 = OH, R^3 = OMe

3.8. Cinnamic acids

Prenyloxy secondary metabolites having a cinnamic acid core are all derivatives of *trans-p*-coumaric acid and/or ferulic acid and of their 2,3-dihydro analogues. The most investigated compound is 3-(4′-geranyloxy-3′-methoxyphenyl)-2-*trans* propenoic acid **77**, isolated together with the *p*-coumarate derivative **78** in 1966 from the Australian small tree *Acronychia baueri* Schott (Rutaceae) (Prager and Thredgold, 1966). The properties of **77** and its semisynthetic derivatives have been recently reviewed by Curini and co-workers (Curini et al., 2006a). The isopentenyloxy derivative of ferulic acid **79**, named boropinic acid has been isolated from roots of an Australian shrub, *Boronia pinnata* (Ito et al., 2000). This compound was seen to inhibit Epstein-Barr virus early antigen (EBV-VA) activation induced by 12-*O*-tetradecanoylphorbol-13-acetate in Raji cells (Ito et al., 1999) and to effectively inhibit *in vitro* growth of *Helicobacter pylori* with a MIC value of 1.62 μg/mL (Epifano et al., 2006). Another plant belonging to genus *Boronia*, *B. megastigma* Nees., yielded methyl ester of acid **78** and methyl 4-(5′-geranyloxy)-cinnamate **80** (Weyerstahl et al., 1994). Methyl 4-isopentenyloxy-*trans*-cinnamate **81** has been isolated by Delle Monache and co-workers from the leaves of *Esenbechia hieronimi* (Rutaceae) (Delle Monache et al., 1995). Derivatives of dihydrocinnamic acid, namely methyl 4-isopentenyloxydihydrocinnamate **82** and methyl 4-geranyloxydihydrocinnamate **83** were isolated by Chen and co-workers in 2004 from the leaves of the Taiwanese shrub *Zanthoxylum pistaciflorum* Hayata (Chen et al., 2004). Compound **83** had a weak cytotoxic effect *in vitro* against P-388 cancer cell line (ED_{50} = 9.38 μg/ml).



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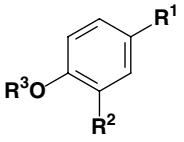
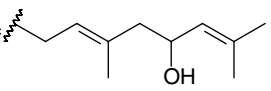


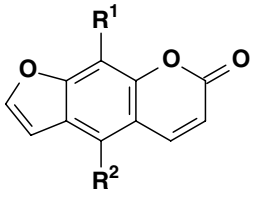
77 R^1 = -CH=CH-COOH, R^2 = OMe, R^3 = geranyl
78 R^1 = -CH=CH-COOH, R^2 = H, R^3 = geranyl
79 R^1 = -CH=CH-COOH, R^2 = OMe, R^3 = isopentenyl
80 R^1 = -CH=CH-COOMe, R^2 = H, R^3 = 
81 R^1 = -CH=CH-COOMe, R^2 = H, R^3 = isopentenyl
82 R^1 = -CH_2CH_2-COOMe, R^2 = H, R^3 = isopentenyl
83 R^1 = -CH_2CH_2-COOMe, R^2 = H, R^3 = geranyl

3.9. Coumarins

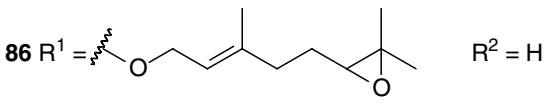
Chemistry and pharmacology of prenyloxycoumarins up to 2005 has been exhaustively reviewed by Curini and co-workers (Curini et al., 2006b). However, further insights on some prenyloxycoumarin derivatives have been recently reported in the literature, in particular about geranyloxyfuranocoumarins. Recent studies were done on the interaction of bergamottin (BG) **84**, 8-geranyloxypsoralen **85** and their semisynthetic derivatives with cytochromes P450. Hollenberg and co-workers studied the interaction of **84** with cytochrome P450 2B6 and 3A5 (Kent et al., 2006). They found that P450 2B6 metabolized **84** primarily to 5′-hydroxy, 6′-hydroxy and 7′-hydroxy-BG and to bergaptol to a lesser extent, while metabolism of **84** by P450 3A5 resulted in three main metabolites, bergaptol, 5′-hydroxy-BG and 2′-hydroxy-BG and three minor ones, 6′,7′-dihydroxy-BG, 6′-hydroxy and 7′-hydroxy-BG. These findings suggested that P450 2B6 preferentially oxidized the geranyloxy chain of **84**, while P450 3A5 metabolized BG mainly by cleaving the geranyloxy chain. This hypothesis was supported by molecular modelling technique studies. Lennard and co-workers synthesized a series of 8-geranyloxypsoralen analogues as novel CYP 3A4 inhibitors. Using commercially available xanthotoxin and xanthotoxol as starting materials, they made compounds **85**–**89** differently functionalized in the geranyloxy side chain. IC_{50} values for the inhibition of CYP 3A4 of these derivatives and the parent natural compounds are summarized in Table 4 (Row et al., 2006). All compounds showed a moderate to good inhibition of CYP 3A4. The absence of the alkoxy chain resulted in loss of activity, addition of polar substituents at the 6′ and 7′ position led to an increase of activity and finally saturation of the furan ring gave a 4-fold decrease of activity. From these data Lennard and co-workers depicted a detailed pharmacophore model for the inhibition of CYP 3A4 by natural and semisynthetic prenyloxyfuranocoumarins.

3.10. Flavonoids

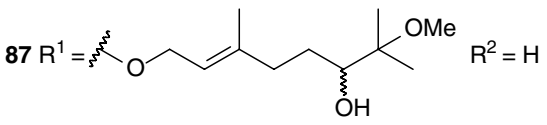
Several prenyloxyflavonoids have been isolated from different species. The first example reported in the literature has been reported by Bohlmann and Ates in 1984 (Bohlmann and Ates, 1984). These authors isolated 4′5-dihydroxy-7-isopentenyloxyflavanone **90** and 5-hydroxy-7-isopentenyloxyflavanone **91** from roots and aerial parts of *Helichrysum athrixiifolium*. Subsequently, two other prenyloxyflavonoids, 7-*O*-geranylformonetin **92** and nordurlettone **93** have been isolated from root bark and seeds of *Millettia ferruginea* (Hochst.) Bak. subsp. *darassana* (Cuf.) Gillett by Noguchi and co-workers in 1990 (Dagne et al., 1990). Among methoxyflavones obtained from leaves of *Ficus*



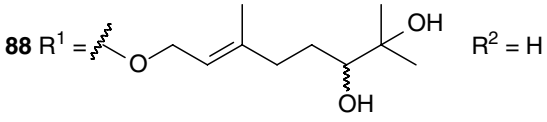
84 R^1 = H, R^2 = *O*-geranyl
85 R^1 = *O*-geranyl, R^2 = H



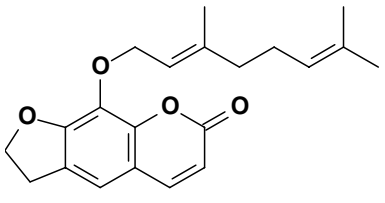
86 R^1 = R^2 = H



87 R^1 = R^2 = H



88 R^1 = R^2 = H



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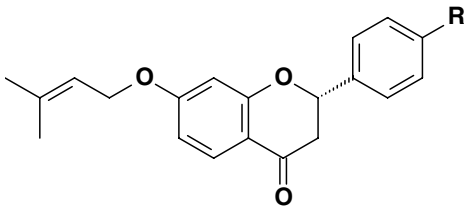
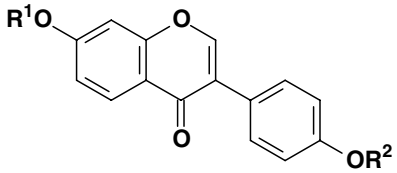
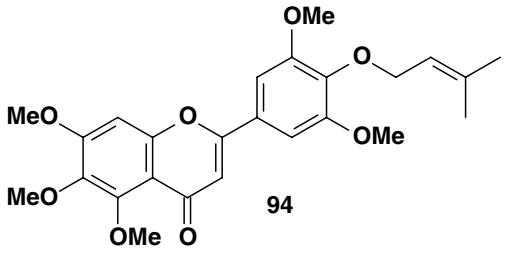


90 R = OH
91 R = H



92 R^1 = geranyl, R^2 = Me
93 R^1 = H, R^2 = isopentenyl



94

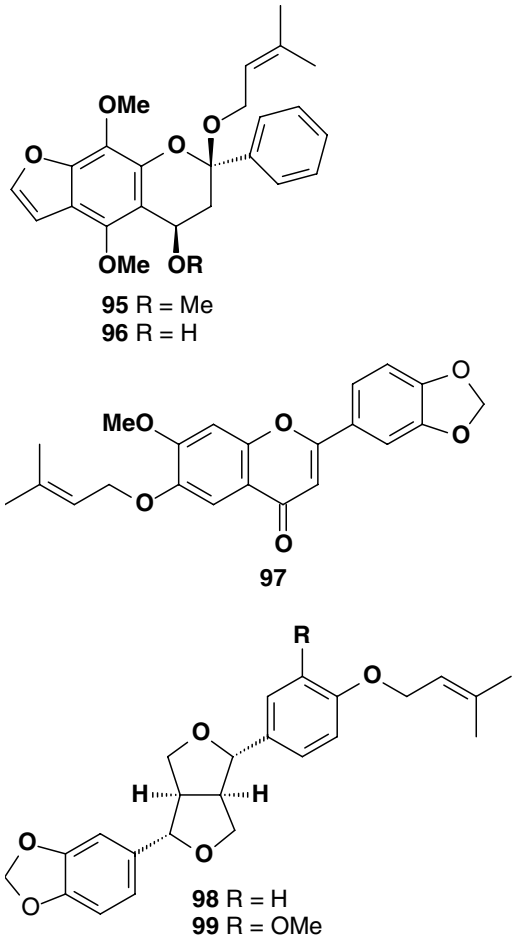
Table 4
IC_{50} values for the inhibition of CYP 3A4 activity in human liver (HL-7) cells

Compound	IC_{50} (μM)
84	4.48 ± 0.42
85	3.93 ± 0.53
86	0.78 ± 0.11
87	1.89 ± 0.31
88	0.92 ± 0.03
89	15.6 ± 0.5

maxima P. Miller (Moraceae), Arruda and co-workers isolated 5,6,7,3′,5′-pentamethoxy-4′isopentenyloxyflavone **94** (Gaspar et al., 1997). This compound represented the first and only example of isolation of a prenyloxyphenylpropanoid derivative from plants belonging to the family of Moraceae. Compound **94** was also isolated from *F. benghalensis* L. (Elgindi, 2004). Two novel furanoflavones, 2,4-*cis*-2-isopentenyloxy-4,5,8-trimethoxy-(2″,3″:6,7)-furanoflavan **95** and 2,4-*cis*-2-isopentenyloxy-4-hydroxy-5,8-dimethoxy-(2″,3″:6,7)-furanoflavan **96** have been purified from light petroleum extract of roots of *Lonchocarpus muehlbergianus* and these compounds represented the first example of occurrence in nature of a prenyloxyfuranoflavan (Magalhães et al., 2004). Finally millettocalyxin B **97** was isolated from the stem bark of *Millettia erythrocalix* (Sritularak et al., 2002).

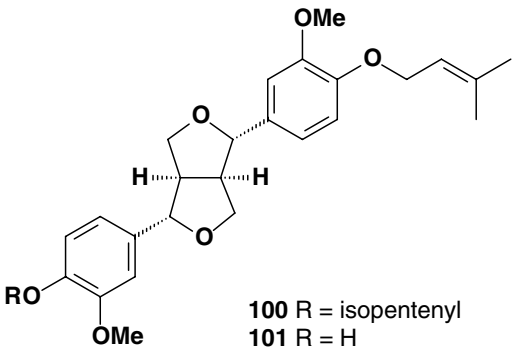
3.11. Lignans

The first report of a prenyloxylignan derivative dates back to 1973 when piperitol-3,3-dimethylallyl ether **98**, a lignan of the furofuran group, was isolated from *Zanthoxylum piperitum* (L.) DC. (Whiting, 1987). Compound **98** has been isolated also from other plants, all belonging to *Zanthoxylum* genus (Arruda et al., 1994; He et al., 2002). The isopentenyl ether of pluviatol **99** was isolated by Whiting from the bark of *Z. podocarpum* Hens. Another plant of *Zanthoxylum* genus, *Z. integrifolium* (Merr.) Merr., afforded two isopentenyloxy pinoresinol derivatives, (+)-pinoresinol-di-3,3-dimethylallyl ether **100** and (+)-pinoresinol-3,3-dimethylallyl ether **101** (Chen et al., 1999). Other prenyloxylignans have been extracted from other genus belonging to the family of Rutaceae. Ulubelen and co-workers isolated two prenylated diarylbutyrolactone lignans **102** and **103** from the aerial parts of *Haplophyllum ptilostylum* Spach- (Ulubelen et al., 1995). An arylnaphtalene lignan containing an isopentenyloxy side chain, namely 7-*O*-(3-methyl-2-butenyl-)-isodaurinol **104** has been isolated by Gözler and co-workers from the Turkish plant *H. myrtifolium* (Saglam et al., 2003). Although lacking of a significative pharmacological activity, this isodaurinol derivative has been used as lead compound for the synthesis of some prenyloxyisodeoxypodophyllotoxin analogues exhibiting cytotoxic properties (Zhao et al., 2006). The finding that prenylation of lignans are found mainly in plants belonging to the family of Rutaceae suggests that *O*-prenyl lignans may be useful chemotaxonomic markers for this family.

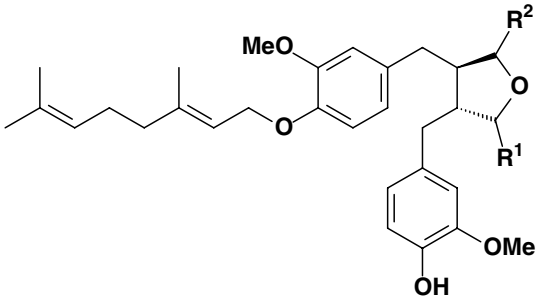


3.12. Terphenyl derivatives

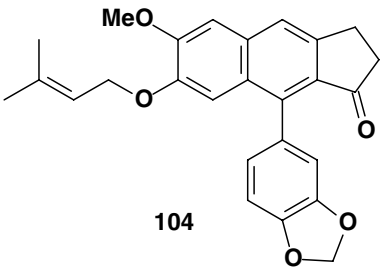
Several *p*-terphenyl derivatives of natural origin have been described in the literature (Tringali et al., 1987), but only one example containing a prenyloxy side chain has been reported. So terprenin **105** has been isolated in the fermentation broth of *Aspergillus candidus* RF-5672 and has also been obtained by chemical synthesis starting from commercially available 3-bromo-2,5-dimethoxybenzaldehyde by a ten steps synthesis (Yonezawa et al., 1998). Compound **105** is a highly potent *in vitro* and *in vivo* immunosuppressive agent able to abolish immunoglobulin E (IgE) antibody production without remarkable side effects (Kawada et al., 1998).



100 R = isopentenyl
101 R = H



102 R^1 = =O, R^2 = H
103 R^1 = H, R^2 = =O



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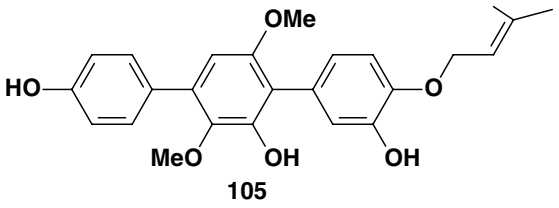
3.13. Xanthones

Seven structures having a differently substituted xanthone core and bearing an isopentenyloxy or geranyloxy side chain have been reported in the literature. The first example has been described by Nguyen and Harrison in 1998: 7-geranyloxy-1,3-dihydroxyxanthone **106** was isolated from *Cratoxylum cochinchinense* (Lour.) Blume (Nguyen and Harrison, 1998). Six xanthones having differently functionalized side chains have been extracted from *Vismia guineensis* by Morelli and co-workers (Bilia et al., 2000), namely 1,8-dihydroxy-3-(2-methoxy-3-methylbut-3-enyloxy)-6-methylxanthone **107**, 1,8-dihydroxy-3-geranyloxy-6-methylxanthone **108**, 1,8-dihydroxy-3-isopentenyloxy-6-methylxanthone **109**, 1,8-dihydroxy-3-(3,7-dimethyl-7-methoxy-oct-2-enyloxy)-6-methylxanthone **110**, 1,8-dihydroxy-3-(*E*-3-hydroxymethyl-but-2-enyloxy)-6-methylxanthone **111** and 1,8-dihydroxy-3-(3-hydroxymethyl-4-hydroxybut-2-enyloxy)-6-methylxanthone **112**. All these compounds were submitted to *in vitro* cytogenetic assay using estramustin and colcemide as reference drugs. Only compound **110** was seen to have a valuable antimitotic activity (cell-cycle arrest ability), although reference drugs were markedly more active compared to the untreated controls. Results are summarized in Table 5.

Table 5
Results of the metaphase-blocking activity assay, expressed as mitotic index (MI), in human lymphocytes treated with xanthone **110** and the reference compounds, estramustin and colcemide

Compound	Dose (μM)	MI
Control	–	20.9 ± 1.9
110	0.5	47.4 ± 3.8
110	1	48.7 ± 4.2
110	25	49.9 ± 4.2
Colcemide	1	70.1 ± 3.6
Estramustin	1	78.7 ± 3.6



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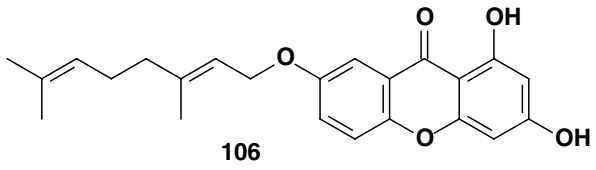

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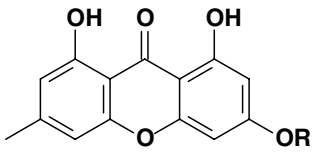
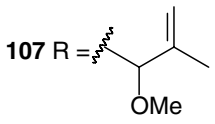
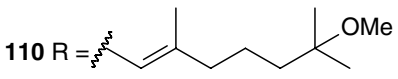
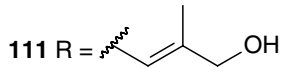
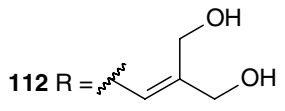




108 R = geranyl
109 R = isopentenyl



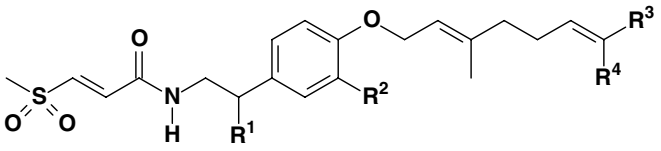




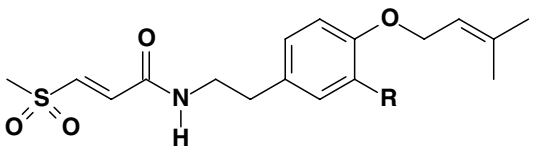
3.14. Miscellaneous

Glycosmis genus (Rutaceae) is characterized to be a rich source of different prenyloxyamides containing sulfur moieties derived from 3-(methylthio)propenoic acid and

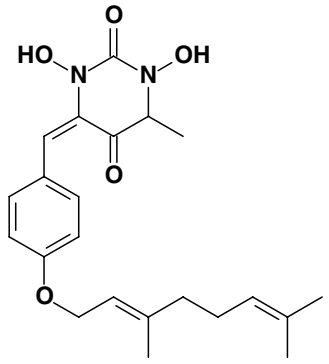
3-(methylsulfonyl)propenoic acid. Hofer and co-workers isolated to date 12 of such amide derivatives: gerambullin **113**, gerambullol **114**, β-hydroxygerambullin **115**, β-hydroxygerambullol **116**, β-hydroxygerambullal **117**, sakarine **118**, sakarinol A **119**, methoxysakarinol A **120**, sakarinol B **121**, dambullin **122** (R = H), sakambullin **123** (R = OH) and methoxysakambullin **124** (R = OMe) (Hofer et al., 2000). Mycelianamide **125** is probably historically the first phenylpropanoid derivative containing a prenyloxy chain to be found in nature. It has been isolated from the mycelium of the fungus *Penicillium griseofulvum* Dierck in 1948 by Oxford and Rastrick (Oxford and Rastrick, 1948). The structure and biosynthesis of **125** were subsequently studied by several authors (Birch et al., 1956, 1958, 1962; Gallina et al., 1966). Compound **125** was shown to inhibit the butyrylcholin esterase of *Pseudomonas* spp. and to have antibiotic effects against some Gram positive bacteria at a concentration range of 0.002–0.005% (Oxford and Rastrick, 1948; Nagasawa et al., 1976). Another natural compound of fungal origin, 3-isobutyl-4-{4-[(3-methyl-2-beutenyl)oxy]phenyl}-1*H*-pyrrole-2,5-dione **126** has been isolated in 2005 by Chen and co-workers from the culture broth of the strain CCRC 35396 of *Antrodia camphorota* Chang & Chou (Shen et al., 2005). The antiviral activity of **126** was evaluated using MS-G2 cells against hepatitis B virus *in vitro*. This compound was seen to suppress both HBsAg and HBeAg expression with the inhibition percentages of 76.5% and 58.2% at the non-cytotoxic dosage of 100 μM and of 35.2% and 12.8% at 50 μM, respectively.



113 $R^1 = R^2 = H$, $R^3 = R^4 = Me$
114 $R^1 = R^2 = H$, $R^3 = CH_2OH$, $R^4 = Me$
115 $R^1 = OH$, $R^2 = H$, $R^3 = R^4 = Me$
116 $R^1 = OH$, $R^2 = H$, $R^3 = CH_2OH$, $R^4 = Me$
117 $R^1 = OH$, $R^2 = H$, $R^3 = CHO$, $R^4 = Me$
118 $R^1 = H$, $R^2 = OH$, $R^3 = Me$, $R^4 = Me$
119 $R^1 = H$, $R^2 = OH$, $R^3 = CH_2OH$, $R^4 = Me$
120 $R^1 = H$, $R^2 = OCH_3$, $R^3 = CH_2OH$, $R^4 = Me$
121 $R^1 = H$, $R^2 = OH$, $R^3 = Me$, $R^4 = CH_2OH$



122 R = H
123 R = OH
124 R = OMe



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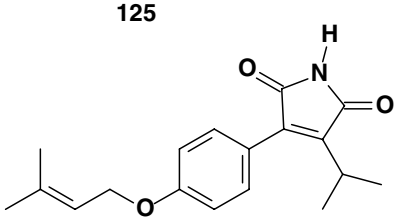

126

4. Conclusions and perspectives

Only in the last decade natural products containing a prenyloxy chain have been recognized as interesting and valuable biologically active phytochemicals. For these reasons research on these secondary metabolites is a field of current and growing interest. Many of the described oxyprenylated derivatives have been found in plants belonging to the family of Rutaceae and by far to a lesser extent in plants of families of Asteraceae, Boraginaceae, Compositae, Fabaceae, Guttiferae, Leguminosae and few others. So prenylation of *O*-functionalities could be considered a peculiar feature and a chemotaxonomic marker of plants of the family of Rutaceae. Another feature of prenyloxy secondary metabolites is the low concentration at which in many cases they can be extracted and isolated from natural sources. This may be the main reason why these class of natural compounds have not been fully considered about their pharmacological properties, being reported in the literature almost exclusively studies about extraction, isolation and structural characterization. Recently, the development of new high yielding procedures made possible the synthesis of some of these compounds in quantities ranging from milligrams to some grams so that more detailed studies on their pharmacological properties could be carried out. Results of these investigations put in evidence how the presence of a lipophilic prenyloxy chain improve the biological activity and data so far reported suggest that these secondary metabolites may represent in the next future a new frontier and a challenge for the development of novel anti-cancer, anti-inflammatory and anti-microbial compounds. As explicative example, in the last 5 years it has been shown that auraptene **1**, other geranyloxycoumarins and 3-(4′-geranyloxy-3′-methoxyphenyl)-2-*trans* propenoic acid **78**

are very good orally active agents in the treatment of benign and malign forms of colon cancer in mice and rats (Curini et al., 2005; Kohno et al., 2006). On the basis of data about the synthesis and pharmacological properties of oxyprenylated derivatives reported in this review article, its hopeful that in the next future more studies could be carried out aimed to the search of prenyloxy phytochemicals from novel natural sources, to develop new environmentally friend, cheap and high yielding synthetic routes to obtain these compounds in large amounts and finally to get further insights and to depict in more detail their pharmacological profile.

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Salvatore Genovese obtained his degree in Pharmacy in July 2004 at University of Perugia. He started his career in September 2004 at the Section of Organic Chemistry of Department of Medicinal Chemistry and Pharmaceutical Technology of University of Perugia under direction of Prof. M. Curini and Dr. F. Epifano, working in the field of use of lanthanide triflates as catalysts of reactions devoted to the synthesis of biologically active natural products. In the same Department, he's currently attending the 3rd year of the Doctorate Course in "Medicinal Chemistry and Pharmaceutical Technology", under the tutorial of Prof. M. Curini, having as a topic of research for the elaboration of doctorate thesis the synthesis and pharmacological activity of 3-(4′-geranyloxy-3′-methoxyphenyl)-2-*trans* propenoic acid, active principle of *Acronychia baueri*, and its derivatives. His work is concerned with extraction, structure elucidation, synthesis and pharmacological properties of plant secondary metabolites, focusing his interest particularly on the synthesis and the study of biological effects as novel cancer chemopreventive and anti-inflammatory agents of natural and semisynthetic prenyloxycinnamic acid derivatives.

Luigi Menghini studied Pharmacy at the University of Perugia and obtained the bachelor in1997 discussing an experimental thesis based on secondary metabolites investigation in *Passiflora* species developed in collaboration with the Laboratory of Pharmacognosy and Bromathology of Universitè Libre de Brussels directed by Prof. M. Vanhaelen,. Achieved the Ph.D. in "Plant Biology and Agroambient Biotechnologies" at the University of Perugia, with a research on quality determination in medicinal plants by chemical and/or genetic approach. From 2001 is employed as researcher at the Faculty of Pharmacy, University G. D'Annunzio" of Chieti-Pescara, where develops teach and research programs. The scientific activity is carried out in the within of scientific disciplinary fields of Pharmaceutical Biology and involved the applied aspects of pharmaceutical botany, phytochemistry and pharmacognosy. The investigation fields concerned the isolation and identification of secondary metabolites, structure characterization of crude extracts and of their biological activity. The main topics of investigation are spontaneous plants using different approach, such as phytochemical or morphofunctional study of secretory structure, in order to understand the biology, the ecology, and the physiology of spontaneous and cultivated plants of medical, dietary or ethnobotanic interest. Part of research work is dedicated to investigate the biological activity of metabolites and extracts, obtained from plants and fungi, *in vivo* and *in vitro* models, and against microorganisms.

Massimo Curini heads the research group of Chemistry of Natural Products at the Section of Organic Chemistry of Department of Medicinal Chemistry and Pharmaceutical Technology of University of Perugia. He took the degree in Chemistry at University of Perugia in 1973. He started working in the School of Pharmacy in the field of isolation and structural determination of secondary metabolites from plants and fungi. From 1990 he started working on synthesis of biologically active natural products, in particular terpenoids. Recently, he changed his focus and is now engaged in the field of isolation, structural determination, synthesis and biological activity as anti-cancer agents of prenyloxyphenylpropanoids.