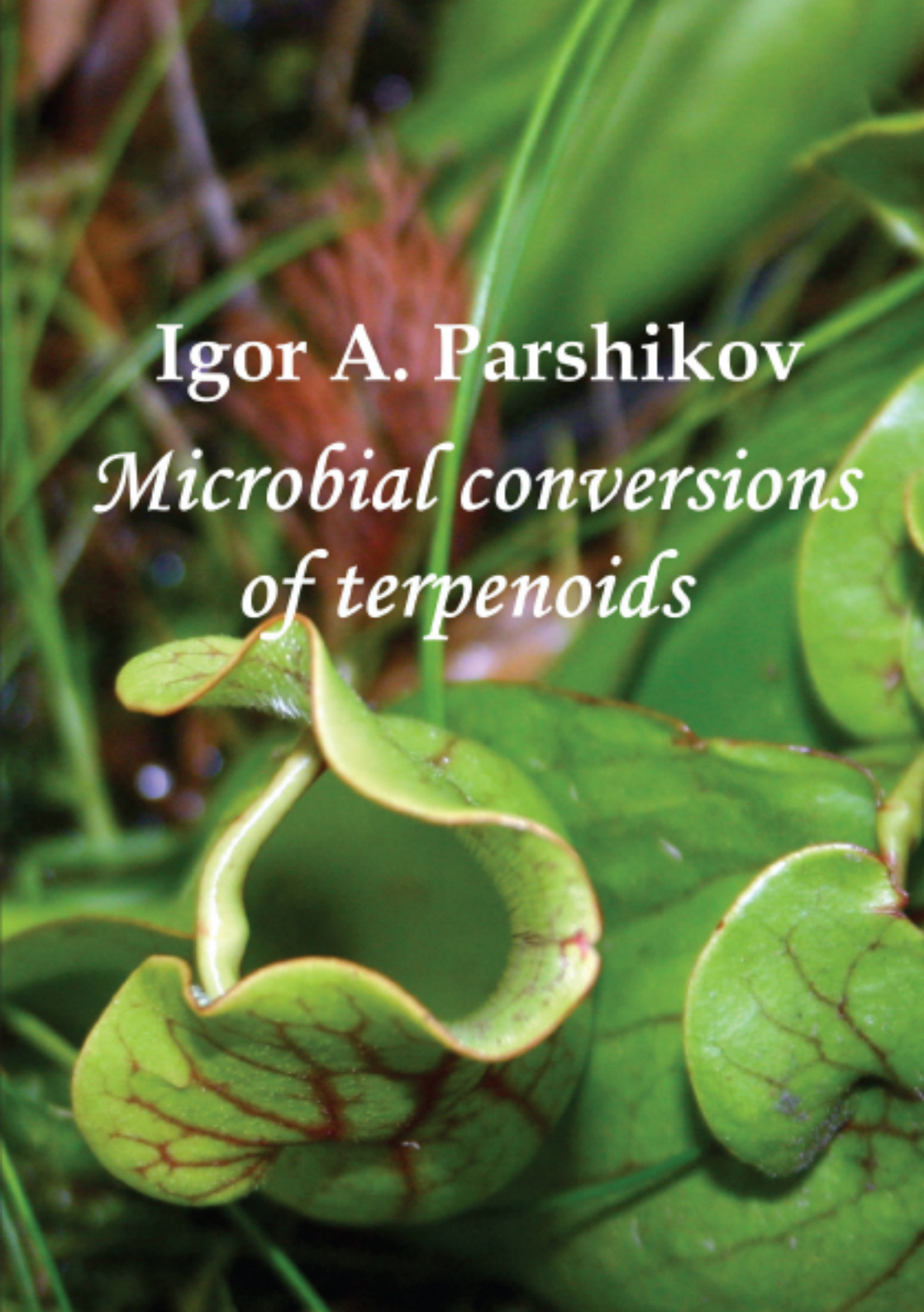


Igor A. Parshikov

Microbial conversions of terpenoids

Igor A. Parshikov

Microbial conversions of terpenoids

Editus

Moscow, 2015

УДК 574.25
ББК 28.072
П18

Reviewers:
Khasaeva F.M., Sc.D.
Zaraisky E.I., Ph.D.

Recommended for publication by the Academic Council of the Institute of Applied Mechanics, Russian Academy of Sciences

Igor A. Parshikov. Microbial conversions of terpenoids. – M.: Editus, 2015. – 100 p.

The monograph describes examples of the application of microbial technology for obtaining of derivatives of terpenoids. Obtaining new derivatives of terpenoids, including artemisinin derivatives with increased antimalarial activity, is an important goal of research in microbial biotechnology and medicinal chemistry.

ISBN 978-5-00058-223-7

© Igor A. Parshikov, 2015

Introduction

The transformation of organic compounds by microbial cultures has long been of interest to the pharmaceutical, chemical and food industries because of numerous advantages compared to chemical synthesis (Pandey et al., 2000; Parshikov et al., 1994; 2010; Parshikov, 2015; Silva et al., 2014).

Terpenoids are components of the essential oils of plants; they are derivatives of terpene hydrocarbons, which are combinations of five-carbon isoprene units (Newman, 1972; Dewick, 2001). They have been classified into monoterpenoids, sesquiterpenoids, diterpenoids, sesterterpenoids, triterpenoids, tetraterpenoids, and polyterpenoids. Several of these groups of terpenoids are found in the essential oils of plants that are used in traditional medicine to treat malaria and other fevers (Titanji et al., 2008; Kaur et al., 2009; Khamsan et al., 2011). The large variety of terpenoids, mostly derived from plants, that have been purified and shown to have antiplasmodial activity in vitro has been discussed extensively in recent review articles (Batista et al., 2009; Bero et al., 2009; Kaur et al., 2009; Chaturvedi, 2011; Harinasuta et al., 1965; Kain, 1995; Klassen, 2009; Nogueira and Lopes, 2011; Snow et al., 2005). Information about the comparative activities of most of these natural terpenoids and their derivatives in different *Plasmodium* spp., however, is difficult to obtain because of data security practices for potential commercial drugs.

Among the sesquiterpenoids, artemisinin and its derivatives are useful and effective drugs against most chloroquine-resistant strains of *P. falciparum* (Klayman, 1985). However, problems associated with artemisinin, including low solubility in water and even in oil (Luo and Shen, 1987; Hien and White, 1993; Vroman et al., 1999), have prompted scientists to seek new artemisinin derivatives. Some of these artemisinin-derived drugs have been reported to be neurotoxic to animals when injected (Vroman et al., 1999; Gordi and Lepist, 2004; Liao, 2009; Medhi et al., 2009; Mannan et al., 2010). There is also evidence of reproductive toxicity of artemisinin derivatives at high doses in animals (Medhi et al., 2009; Clark, 2011). Increasing resistance of malaria parasites to currently used drugs, including *P. vivax* resistance to chloroquine and primaquine in parts of New Guinea, Asia, and Africa (Price et al., 2011) and *P. falciparum* resistance to artemisinin in western Cambodia, eastern Thailand, and some nearby areas (Noedl et al., 2008; Wongsrichanalai and Meshnick, 2008; Dondorp et al., 2010; O'Brien et al., 2011), is another important reason for developing new antimalarial drugs.

Some artemisinin analogs may be obtained by semisynthetic processes; for example, artemisinin can be easily reduced chemically to the more effective, but neurotoxic, dihydroartemisinin (Klayman, 1985; Vroman et al., 1999; Avery et al., 2002). Other structural changes in artemisinin remain a

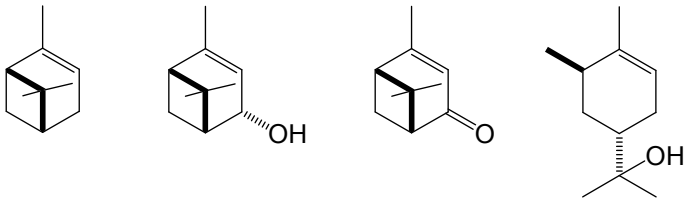
challenge for chemists because of the difficulty of introducing specific functional groups by conventional synthetic methods.

Many microorganisms, especially certain fungi, have the ability to transform terpenoids regioselectively and stereoselectively (Sutherland, 2004; Carvalho and Fonseca, 2006; Simeó and Sinisterra, 2009; Parshikov, 2012). In this book to outline some of the great variety of modifications, that can be expected from the use of microorganisms for the transformation of terpenoids. The biochemical mechanisms have scarcely been investigated, but it seems likely that cytochromes P450 and perhaps dioxygenases will be found to be involved in many of the transformations (Martin et al., 2008; Krings et al., 2009). It is our hope that further developments in microbial biotechnology, including the discovery of new strains with unique enzyme systems for the transformation of terpenoids, may make it possible to derive a variety of newer and more useful drugs from those now available.

1. Transformation of monoterpenoids

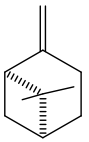
In the leaves of lemon grass, *Cymbopogon citratus*, there is an essential oil that inhibits the growth of *Plasmodium berghei*, a species which does not infect humans, with 86.6% of the activity of chloroquine (Tchoumbougnang et al., 2005). This oil contains several monoterpenoids, with citral (geranial and neral), β-myrcene, geraniol, nerol, citronellal and limonene as the main components (Schaneberg and Khan, 2002). Limonene has been shown to have antimalarial activity because it inhibits the isoprenylation of proteins in *P. falciparum* (Moura et al., 2001).

(+)-α-Pinene (**I**) is a monoterpene, produced by pine trees and many other plants, that acts as an insect repellent. The **(+)-** isomer is oxidized by a strain of *A. niger* to the floral fragrances (+)-*cis*-verbenol (**II**, yield 20-25%) and (+)-verbenone (**III**, yield 2-3%) and the mucolytic agent (+)-*trans*-sobrerol (**IV**, yield 2-3%), in 4-8 h (Bhattacharyya et al., 1960):

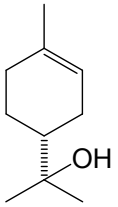


I **II** **III** **IV**

Another strain of *A. niger* produces nonadecanol from (+)-α-pinene and also metabolizes the enantiomer (−)-α-pinene (Divyashree et al., 2006). A different natural isomer, (−)-β-pinene (**V**), is oxidized by *A. niger* ATCC 9642 in liquid cultures to produce the fragrance and flavoring agent α-terpineol (**VI**, yield about 4%) in 3 days (Toniazzo et al., 2005):

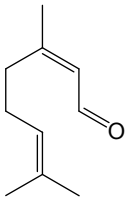


V

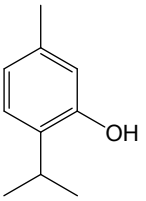


VI

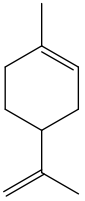
Fungi of the genera *Aspergillus* and *Penicillium* may transform citral and other monoterpenoids to various products (Demyttenaere and De Pooter, 1998; Demyttenaere et al., 2000; Esmaeili and Tavassoli, 2010). For example, a *Penicillium* sp. transformed citral (**VII**) in 21 days to a mixture of six different monoterpenoids with a total yield of 67.4%, including thymol (**VIII**, 21.5%), limonene (**IX**, 3.1%), α-pinene (**I**, 3.7%), geraniol (**X**, 6.8%), geranial (**XI**, 18.6%) and nerol (**XII**, 13.7%) (Esmaeili and Tavassoli, 2010):



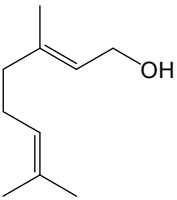
VII



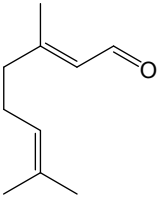
VIII



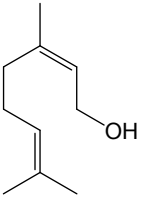
IX



X

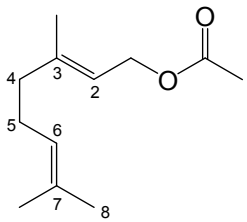


XI



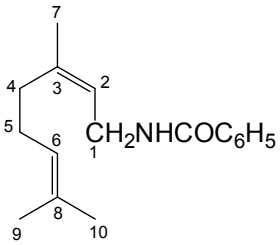
XII

Geranyl acetate **(XIII)** is metabolized by *A. niger* to geraniol (**X**) and 8-hydroxygeraniol, with 50% and 40% yield, respectively (Madyastha et al., 1988):

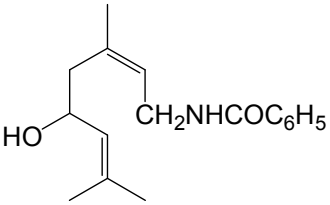


XIII

The transformation of citral benzamide (**XIV**) during 72 hours by fungi *Cunninghamella verticillata* VKPM F-430 and *Beauveria bassiana* VKM F-3111D showed formation of 5-hydroxycitral benzamide (**XV**) in 20% yield (Parshikov et al., 1990a,b):

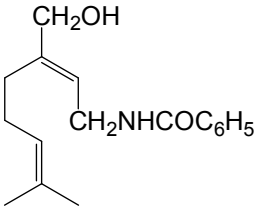


XIV

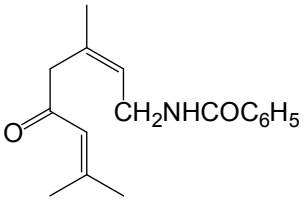


XV

In same time the transformation of citral benzamide (**XIV**) by fungus *Scopulariopsis brevicaulis* VKM F-406 showed formation of 7-hydroxymethyl derivative (**XVI**) in 20% yield and 5-oxo- derivative (**XVII**) in 30% yield (Parshikov et al., 1993):

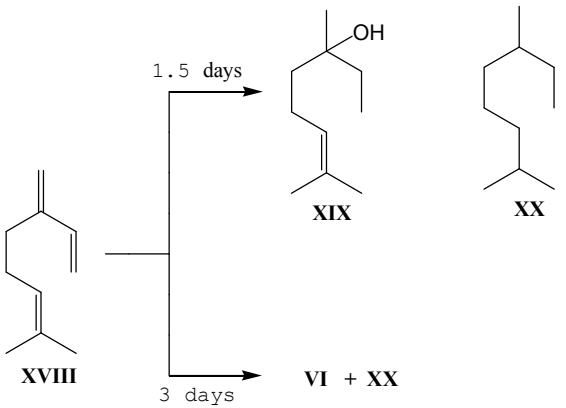


XXVI

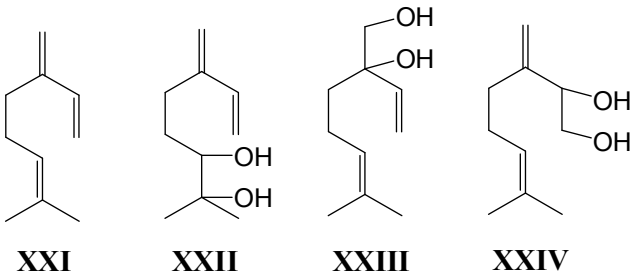


XXVII

In the transformation of myrcene (**XVIII**) by the bacterium *Pseudomonas aeruginosa* PTCC 1074, formation of the products depended on the time of transformation. After 1.5 days the products found were dihydrolinalool (**XIX**, 79.5%) and 2,6-dimethyloctane (**XX**, 9.3%), whereas after 3 days they were α-terpineol (**VI**, 7.7%) and 2,6-dimethyloctane (**XX**, 90.0%) (Esmaeili and Hashemi, 2011):



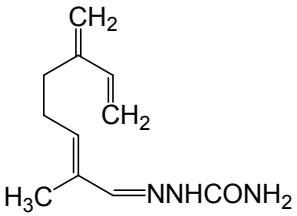
β-Myrcene (**XXI**), an acyclic monoterpene from plant essential oils, is transformed by *A. niger* JTS 191 at each of the three double bonds to produce three fragrant isomeric diols: 2-methyl-6-methylene-7-octene-2,3-diol (**XXII**), 6-methyl-2-ethenyl-5-heptene-1,2-diol (**XXIII**), and 7-methyl-3-methylene-6-octene-1,2-diol (**XXIV**) (Yamazaki al., 1988):



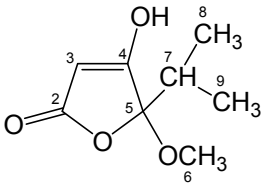
XXI **XXII** **XXIII** **XXIV**

It has been observed that a suspension of non-multiplying *Penicillium simplicissimum* selectively converted myrcenal semicarbazone (**XXV**) into 4-hydroxy-5-isopropyl-5-methoxy-2-

oxo-2,5-dihydrofuran (**XXVI**) with 84% yield (Parshikov et al., 1994, 2010):

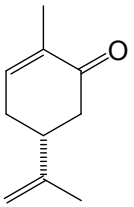


XXV

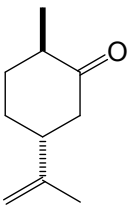


XXVI

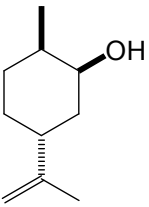
(−)-Carvone (**XXVII**) from spearmint oil is transformed stereoselectively to (+)-dihydrocarvone (**XXVIII**) and (+)-neodihydrocarveol (**XXIX**) by a strain of *A. niger* (Noma and Nonomura, 1974); similar products are produced from (+)-carvone (Noma and Nonomura, 1974):



XXVII



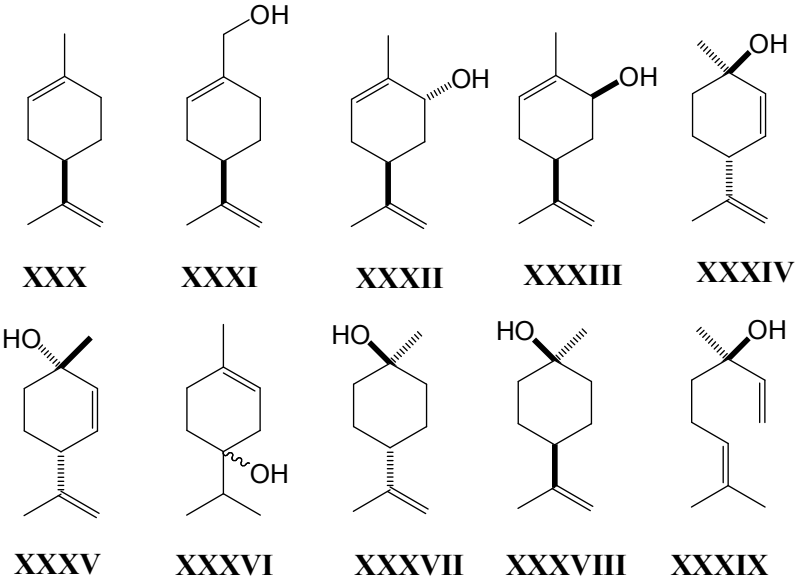
XXVIII



XXIX

(+)-Limonene (**XXX**), a cyclic monoterpene obtained from citrus fruits and many other plants, is metabolized by an *A. niger* strain to perillyl alcohol (**XXXI**) and organic acids (Menéndez et al., 2002). Using two different cultivation systems and two different media, the products include fragrant isomers of *trans*-

carveol (**XXXII**), *cis*-carveol (**XXXIII**), *cis*-*p*-mentha-2,8-dien-1-ol **(XXXIV)**, *trans*-*p*-mentha-2,8-dien-1-ol (**XXXV**), racemic carvone (**XXVII**), perillyl alcohol (**XXXI**), propanoic acid, isobutyric acid, isovaleric acid, the tea tree oil component terpinen-4-ol (**XXXVI**), α-terpineol (**VI**), *cis*-β-terpineol (**XXXVII**), *trans*-β-terpineol (**XXXVIII)**, and the floral scent linalool (**XXXIX**; the (*R*)-(−)-enantiomer is shown) (García-Carnelli et al., 2014):

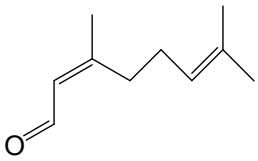


XXX **XXXI** **XXXII** **XXXIII** **XXXIV**

XXXV **XXXVI** **XXXVII** **XXXVIII** **XXXIX**

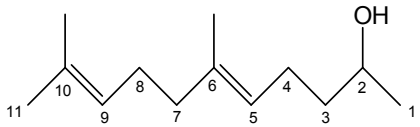
The monoterpenoid alcohol geraniol (**X**), from plant essential oils, is biotransformed by sporulated surface cultures of *A. niger* AN2, mostly to an isomer of linalool (**XXXIX**) with some 6-methyl-5-hepten-2-one. The same strain can also convert the *cis* isomer, nerol (**XII**), or citral, a mixture of the aldehydes geranial

(**XI**) and neral **(XL**), to produce linalool (**XXXIX**) and α-terpineol (**VI**) (Demyttenaere et al., 2000):

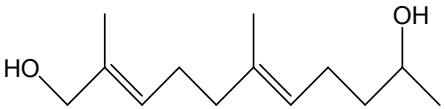


XL

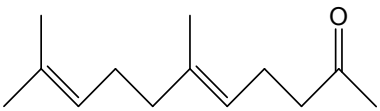
Geranylacetol (**XLI**) is converted by a strain of *A. niger* to 11-hydroxygeranylacetol (**XLII**) and 9,10-dihydroxygeranylacetol, whereas geranylacetone (**XLIII**) is converted to (*S*)-(+)-geranylacetol, 11-hydroxygeranylacetone, and (*S*)-(−)-9,10-dihydroxygeranylacetone, some of which are useful for the synthesis of optically active compounds (Madyastha et al., 1993):



XLI

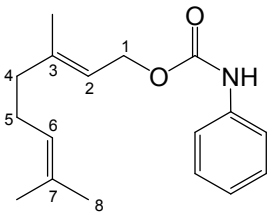


XLII

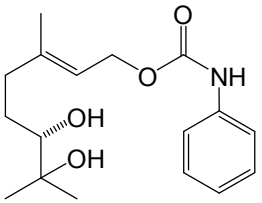


XLIII

The mycelium of *A. niger* LCP 521 hydrolyzes geranyl *N*-phenylcarbamate (**XLIV**) to form (6*R*)-geranyl *N*-phenylcarbamate diol (**XLV**) with an enantiomeric excess over 95% (Fourneron et al., 1989):

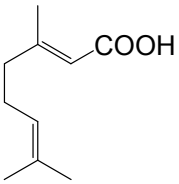


XLIV



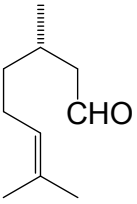
XLV

The bacterium *Rhodococcus* sp. GR3 regioselectively transformed geraniol (**X**) to geranic acid (**XLVI**) in 12.5 h (Chatterjee, 2004):

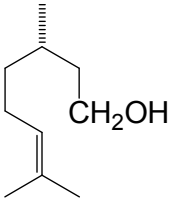


XLVI

The yeast *Rhodotorula minuta* in only 8 h reduced L-(−)-citronellal (**XLVII**) to L-(−)-citronellol (**XLVIII**) with a yield of 78.3% (Velankar and Heble, 2003):

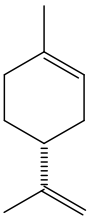


XLVII



XLVIII

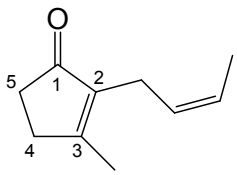
The fungus *Fusarium verticillioides* in 12 h converted R-(+)-limonene (**XLIX**) to R-(+)-perillyl alcohol (**XXXI**) with a yield of 12% (Oliveira and Strapasson, 2000):



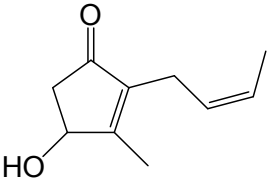
XLIX

Of the microbial transformations of monoterpenoids, those of greatest interest are those producing hydroxylated derivatives (Abraham and Arfmann, 1992; Khor and Uzir, 2011) that can be used in the stereospecific synthesis of valuable compounds, including potential antimalarial drugs.

Cinerone (**L**), a cyclopentenone monoterpenoid, is hydroxylated at the 4-position by *A. niger* ATCC 9142 to produce cinerolone (**LI**), an intermediate in the synthesis of insecticides (Tabenkin et al., 1969):

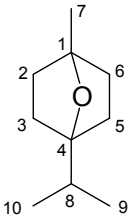


L

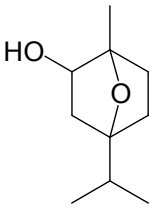


LI

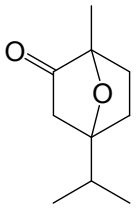
The cyclic ether 1,4-cineole (**LII**) from lime juice is transformed by *A. niger* UI 172 to (±)-2-exo-hydroxy-1,4-cineole (**LIII**), a key precursor in herbicide synthesis, and (±)-2-oxo-1,4-cineole (**LIV**) (Rosazza et al., 1987):



LII

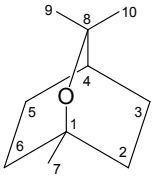


LIII

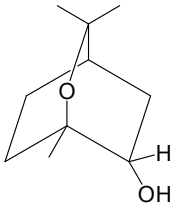


LIV

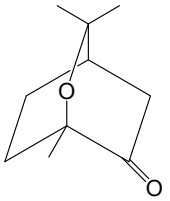
1,8-Cineole (**LV**), also known as eucalyptol, has many uses as a flavoring, fragrance, and insecticide. It is transformed by a strain of *A. niger* to five metabolites, (±)-2-*endo*-hydroxycineole (**LVI**), (±)-2-oxocineole (**LVII**), (±)-3-*endo*-hydroxycineole (**LVIII**), (±)-3-*exo*-hydroxycineole **LIX**), and (±)-3-oxocineole (**LX**). Two of these metabolites, 3-*exo*-hydroxycineole and 3-*endo*-hydroxycineole, are used to synthesize mosquito repellents (Nishimura et al., 1996):



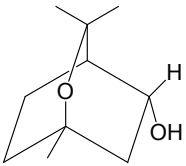
LV



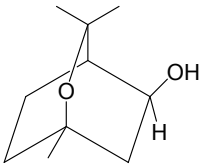
LVI



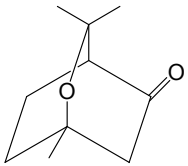
LVII



LVIII

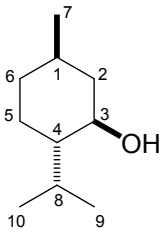


LIX

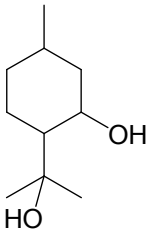


LX

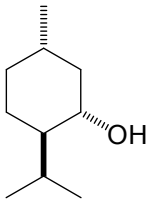
(−)-Menthol (**LXI**), a monoterpenoid flavoring compound from peppermint, is also used as a local anesthetic. It can be biotransformed with a strain of *A. niger* to produce the 1-, 2-, 6-, 7-, 8-, and 9-hydroxymenthols (Asakawa et al., 1991). 8-Hydroxymenthol (**LXII**), also known as *p*-menthane-3,8-diol, is a mosquito repellent. The same strain transforms another isomer, (+)-menthol (**LXIII**), mostly to the 7-hydroxy derivative but also to the 1-, 6-, 8-, and 9-hydroxymenthols (Asakawa et al., 1991):



LXI

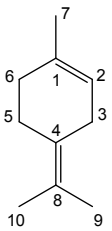


LXII

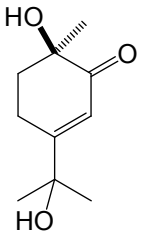


LXIII

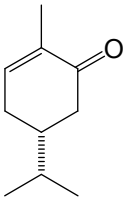
Terpinolene (δ-terpinene, **LXIV**), a monoterpene used for making plastics and resins, is transformed to 1,8-dihydroxy-*p*-menth-3-ene-2-one (**LXV**) and two minor metabolites by the same strain of *A. niger*, which also metabolizes (−)-carvotanacetone (**LXVI**) to *p*-menthane-2,9-diol (**LXVII**) (Asakawa et al., 1991):



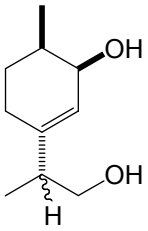
LXIV



LXV

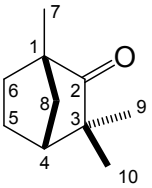


LXVI

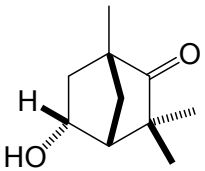


LXVII

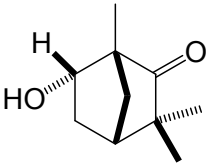
(+)-Fenchone (**LXVIII**), from the essential oil of fennel, is transformed to (+)-5α-hydroxyfenchone (**LXIX**) and (+)-6α-hydroxyfenchone (**LXX**) by a strain of *A. niger* (Noma et al., 1995):



LXVIII



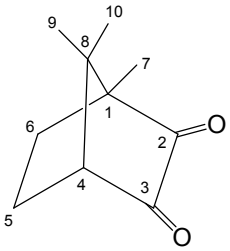
LXIX



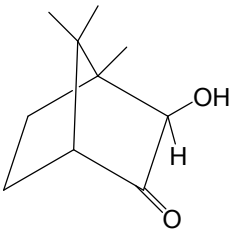
LXX

(+)-Camphorquinone (**LXXI**), used in dental composite resins, is transformed by a strain of *A. niger* mostly to (+)-(2*R*)-*exo*-hydroxyepicamphor (**LXXII**), and (−)-camphorquinone

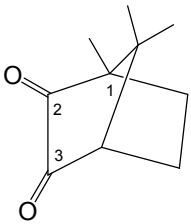
(**LXXIII**) is transformed mostly to (+)-(2*R*)-*endo*-hydroxycamphor (**LXXIV**) (Miyazawa et al., 1995a):



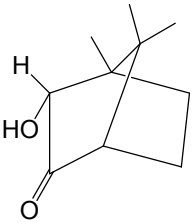
LXXI



LXXII

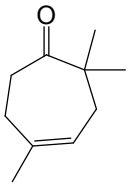


LXXIII

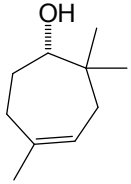


LXXIV

Karahanaenone (**LXXV**), derived from the hop plant, is transformed to a mint aroma compound, (*S*)-karahanaenol (**LXXVI**), by a strain of *A. niger* (Miyazawa et al., 1995b):



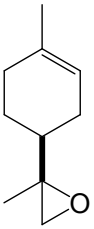
LXXV



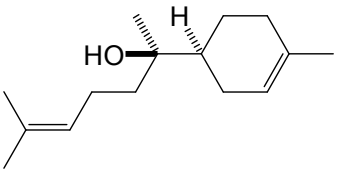
LXXVI

The other enantiomer, (−)-limonene, is also metabolized to carveols and other products by a strain of *A. niger* (Divyashree et al., 2006). The (8*R*) enantiomers in (4*S*,8*RS*)-limonene epoxides

(**LXVII**) and (4*R*,8*RS*)-limonene epoxides, which have two chiral carbons, are hydrolyzed by *A. niger* LCP 521, producing the (4*S*,8*R*) and (4*R*,8*R*) diols, respectively. The (8*S*)-limonene epoxide enantiomers are unchanged by the fungus, so the two epoxides and the two diols can be used in processes to synthesize all four stereoisomers of the sesquiterpenoid alcohol α-bisabolol, including the high-value product (−)-(4*S*,8*S*)-α-bisabolol **(LXVIII)**, for different uses in cosmetics and fragrances (Chen et al., 1993):

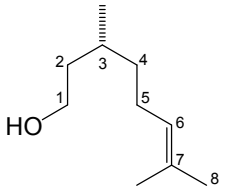


LXVII

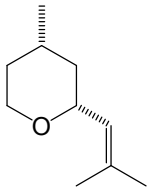


LXVIII

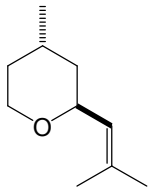
(*R*)-(+)-Citronellol (**LXIX**), an enantiomerically pure monoterpenoid alcohol, is transformed by *A. niger* ANA, mostly to the optical isomers (+)-*cis*-rose oxide (**LXX**) and (+)-*trans*-rose oxide (**LXXI**). In contrast, the isomer (*S*)-(−)-citronellol (**LXXII**) is transformed to (−)-*cis*-rose oxide (**LXXIII**) and (−)-*trans*-rose oxide (**LXXIV**), with 6-methyl-5-hepten-2-one and nerol oxide (**LXXV**) produced as minor metabolites (Demyttenaere et al., 2004):



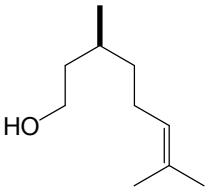
LXIX



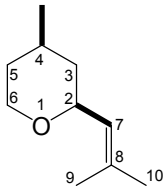
LXX



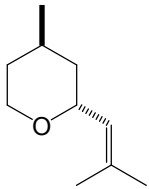
LXXI



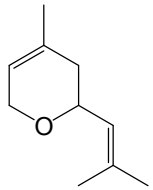
LXXII



LXXIII

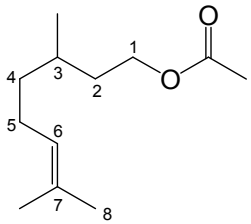


LXXIV



LXXV

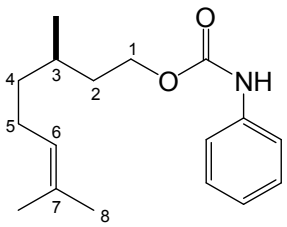
A fragrance ingredient, citronellyl acetate (**LXXVI**), incubated with a strain of *A. niger* produces citronellol (**LXIX**) and 8-hydroxycitronellol**,** with 38 and 60% yield, respectively, in 72 h (Madyastha et al., 1988):



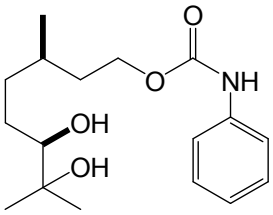
LXXVI

(3*R*)-(+)-Citronellyl *N*-phenylcarbamate (**LXXVII**) is converted by a strain of *A. niger* to either (3*R*,6*R*)-citronellyl *N*-phenylcarbamate diol (**LXXVIII**) or the (3*R*,6*S*)-diol, depending

on the pH; the corresponding (3*S*)-(−)-enantiomer also undergoes similar pH-dependent reactions (Zhang et al., 1992):



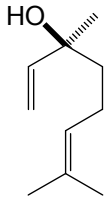
LXXVII



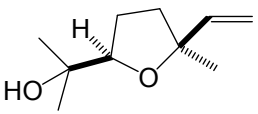
LXXVIII

(−)-*cis*-Rose oxide (**LXX**), a component of the fragrance of roses, is hydroxylated regiospecifically by *A. niger* IFO 4414 in 5 days to (−)-*cis*-9-hydroxy-7*E*-rose oxide, the major product, which may be further oxidized to (−)-*cis*-7*E*-rose oxide-8-carboxylic acid. The analogous (−)-*trans*-metabolites are produced from (−)-*trans*-rose oxide (**LXXI**) (Miyazawa et al., 1995).

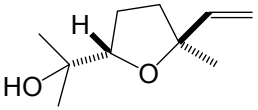
(*S*)-(+)-Linalool (**LXXIX**), one of the isomers of linalool produced by plants, is transformed by *A. niger* DSM 821 to the fragrance ingredients *cis*-(2*S*,5*R*)-furanoid linalool oxide (**LXXX**, yield 30%), *trans*-(2*S*,5*S*)-furanoid linalool oxide (**LXXXI**, yield 5%), and *cis*-(3*S*,6*S*)-pyranoid linalool oxide (**LXXXII**, yield 14%) (Demyttenaere et al., 2001). The other isomer, (*R*)-(−)-linalool (**XXXIX**), is transformed to *trans*-(2*R*,5*R*)-furanoid linalool oxide (**LXXXIII**) and *trans*-(3*S*,6*R*)-pyranoid linalool oxide (**LXXXIV**), but the yields are only 3.3 and 1.1%, respectively (Demyttenaere et al., 2001):



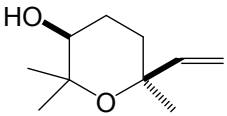
LXXIX



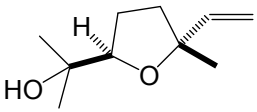
LXXX



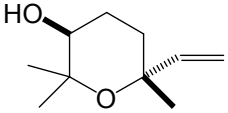
LXXXI



LXXXII

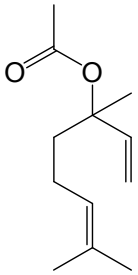


LXXXIII



LXXXIV

Linalyl acetate **(LXXXV)** is metabolized to linalool (**LXXIX**) and 8-hydroxylinalool with 25% and 45% yield, respectively, by a strain of *A. niger*, plus small amounts of geraniol (**X**) and α-terpineol (**VI**) (Madyastha et al., 1988):



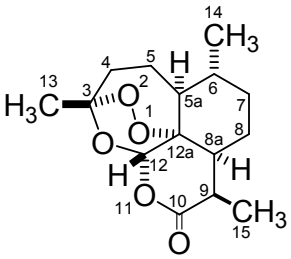
LXXXV

2. Transformation of sesquiterpenoids

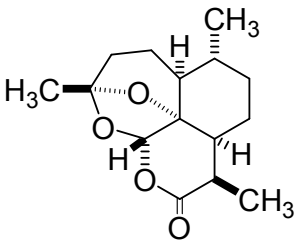
Artemisinin (**LXXXVI**) is the most important antimalarial sesquiterpenoid obtained from plants (Klayman, 1985; Luo and

Shen, 1987; Liao, 2009), although several others have been described (Elmarakby et al., 1987; Chaturvedi et al., 2010; Rustaiyan et al., 2011). Biotransformation of artemisin has been aided by studies of QSAR (quantitative structure-activity relationships), which suggest modifications of artemisinin that are likely to increase antimalarial activity (Avery et al., 2002). Although many terpenoid biotransformations produce metabolites with less antimalarial activity, the products nevertheless may be useful for further modification (Liu et al., 2006). Occasionally, inactive compounds may be transformed to active metabolites by microbial processes (Musharraf et al., 2010).

The bacterium *Nocardia corallina* ATCC 19070 transformed artemisinin to deoxyartemisinin (**LXXXVII**, yield 24%), which lacks antimalarial activity, in 14 days (Lee et al., 1989). Cultures of *Aspergillus flavus* in 48 h transformed artemisinin to deoxyartemisinin (**LXXXVII**) with a yield of 30.5% (Srivastava et al., 2009):

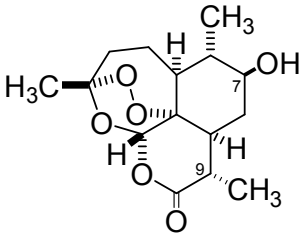


LXXXVI

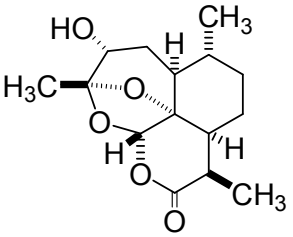


LXXXVII

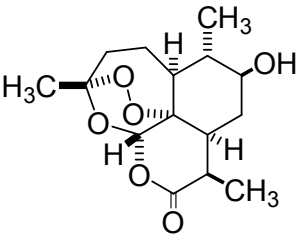
The fungus *Cunninghamella elegans* ATCC 9245 transformed artemisinin to four different hydroxylated derivatives, 7β-hydroxy-9α-artemisinin (**LXXXVIII**, yield 6.0%), 4α-hydroxydeoxyartemisinin (**LXXXIX**, yield 5.4%), 7β-hydroxyartemisinin (**XC**, yield 21.0%) and 6β-hydroxyartemisinin (**XCI**, yield 6.5%). The 7β-hydroxyartemisinin product (**XC**), which cannot be produced chemically, is valuable for further synthesis of candidate antimalarial compounds (Parshikov et al., 2004a, b):



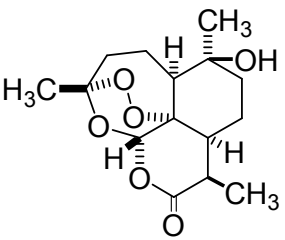
LXXXVIII



LXXXIX



XC



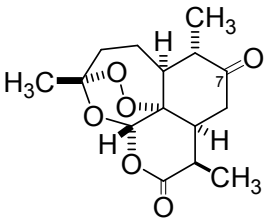
XCI

Penicillium chrysogenum ATCC 9480 transformed artemisinin to two inactive compounds, deoxyartemisinin (**LXXXVII**, yield 1.0%) and 4α-hydroxydeoxyartemisinin (**LXXXIX**, yield 3.6%) in 13 days (Lee et al., 1989). *Cunninghamella echinulata* AS 3.3400 and *Aspergillus niger* AS 3.795 in four days transformed artemisinin to 6β-hydroxyartemisinin (**XCI**, yield 50%) and 4α-hydroxydeoxyartemisinin (**LXXXIX,** yield 15%), respectively (Zhan et al., 2002a), and *Mucor polymorphosporus* AS 3.3443 produced 7β-hydroxyartemisinin (**XC**) and two other hydroxylated products (Zhan et al., 2002b).

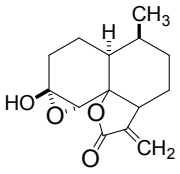
Three strains of *Umbelopsis ramanniana* (*Mucor ramannianus*) hydroxylated artemisinin in 14 days to 7β-hydroxyartemisinin (**XC**, yield 51–88%), 6β-hydroxyartemisinin (**XCI**, yield 1–51%), and two other isomers (Parshikov et al., 2005a, b). *Aspergillus niger* VKM F-1119 hydroxylated artemisinin to 5β-hydroxyartemisinin (yield 80%) and 7β-hydroxyartemisinin (**XC**, yield 19%) (Muraleedharan et al., 2003; Parshikov et al., 2003; 2005c; 2006a, b).

The bacterium *Streptomyces griseus* ATCC 13273 oxidized artemisinin to a less active ketone, artemisitone (**XCII**, yield 12.5%), in 3.5 days (Liu et al., 2006). *Penicillium simplicissimum* modified artemisinin to produce 4β-acetoxy and 4α-hydroxy derivatives (Goswami et al., 2010).

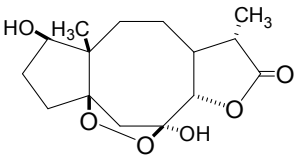
A few other natural sesquiterpenoids have been investigated for possible biotransformations. Arteannuin B (**XCIII**), another terpenoid produced by *Artemisia annua*, is transformed by the fungi *Aspergillus flavipes* and *Beauveria bassiana* to three different products (Elmarakby et al., 1987). A *Microbacterium trichotecenolyticum* extract transformed arteannuin B to artemisinin (Tatineni et al., 2006). Artediffusin (**XCIV**), a recently discovered sesquiterpene lactone produced by *Artemisia diffusa* (Rustaiyan et al., 2011), has antimalarial activity and may also be amenable to biotransformation:



XCII



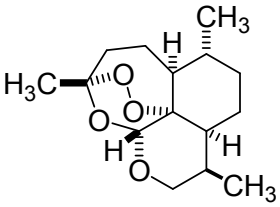
XCIII



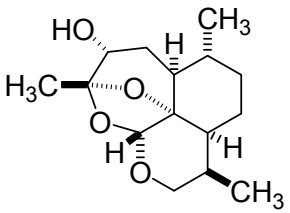
XCIV

Semisynthetic derivatives of artemisinin also have interested researchers seeking possible microbiological modifications. For example, *U. ramanniana* 1839 transformed the semisynthetic antimalarial drug 10-deoxoartemisinin (**XCV**) to the inactive 4α-hydroxydeoxy-10-deoxoartemisinin (**XCVI**, yield 7.0%) and the partially active 7β-hydroxy-10-deoxoartemisinin (**XCVII**, yield 10.9%) in 14 days (Khalifa et al., 1995). Medeiros et al. (2002) optimized the conditions and obtained a 45% yield of

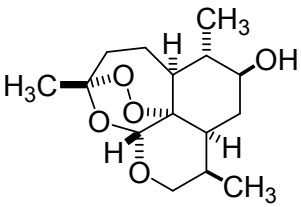
XCVII, which despite its lower antimalarial activity may be useful for further transformations, in 14 days. *Aspergillus niger* hydroxylated 10-deoxoartemisinin (**XCV**) to 7β-hydroxy-10-deoxoartemisinin (**XCVII**, yield 69%) and 15-hydroxy-10-deoxoartemisinin (yield 26%) (Parshikov et al., 2004a). *Cunninghamella elegans* ATCC 9245 transformed 10-deoxoartemisinin (**XCV**) to three hydroxylated derivatives, 5β-hydroxy-10-deoxoartemisinin (**XCVIII**, yield 8.8%), 4α-hydroxydeoxy-10-deoxoartemisinin (**XCVI**, yield 4.6%) and 7β-hydroxy-10-deoxoartemisinin (**XCVII**, yield 83.9%) (Parshikov et al., 2004c):



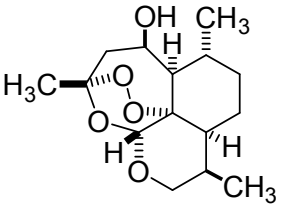
XCV



XCVI



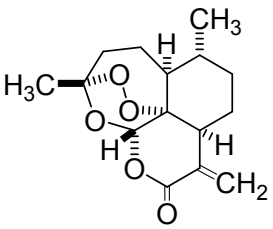
XCVII



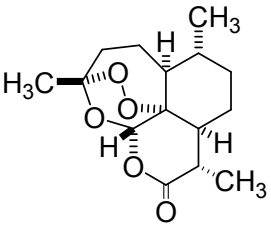
XCVIII

A minor sesquiterpene of *Artemisia annua*, artemisitene (**XCIX**), can also be produced chemically from artemisinin (Chaturvedi et al., 2010). Artemisitene was transformed by *A.*

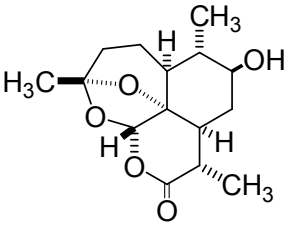
niger NRRL 599 to 9α-artemisinin (**C**), 7β-hydroxydeoxy-9α-artemisinin (**CI**) and 7β-hydroxy-9α-artemisinin (**LXXXVIII**), which has antimalarial activity (Orabi et al., 1999):



XCIX



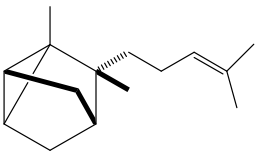
C



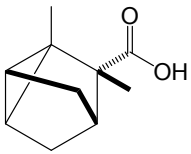
CI

Three isoprene units are used to make up the sesquiterpenoids, many of which have anti-inflammatory and other medicinal properties. Sesquiterpenoid drugs have been used in the treatment of diseases including cancer, cardiovascular disease, and malaria (Bhatti et al., 2009; Huang et al., 2012).

α-Santalene (**CII**), a fragrant sesquiterpene from sandalwood essential oil, is metabolized by a strain of *A. niger*, mostly to the monoterpenoid teresantalic acid (**CIII**), which is used as a flavoring ingredient (Prema et al., 1962):

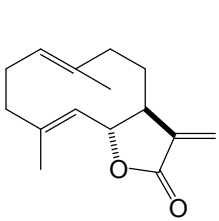


CII

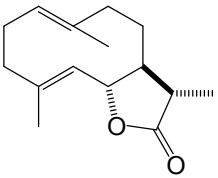


CIII

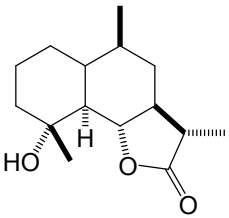
Costunolide (**CIV**), a sesquiterpenoid lactone from magnolia trees that is cytotoxic to tumor cells *in vitro*, is converted *by A. niger* ATCC 16888 to dihydrocostunolide (**CV**), colartin (**CVI**), 11,13-dihydrosantamarine (**CVII**), 11,13-dihydroreynosin (**CVIII**), and tetrahydrovulgarin (**CIX**); all of these metabolites, however, lack cytotoxicity to tumor cells (Clark et al., 1979):



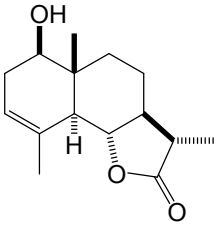
CIV



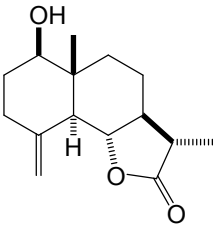
CV



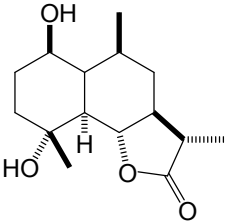
CVI



CVII

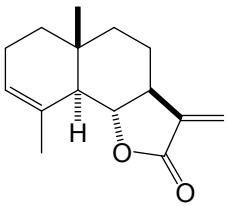


CVIII

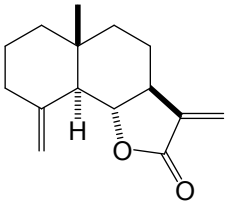


CIX

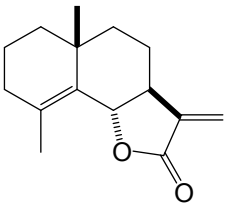
The sesquiterpenoids α-cyclocostunolide (**CX**), β-cyclocostunolide (**CXI**), and γ-cyclocostunolide (**CXII**) are transformed by another strain of *A. niger* by double-bond reduction, hydroxylation, methylene oxidation, and conjugation to form several metabolites (Hashimoto et al., 2001):



CX

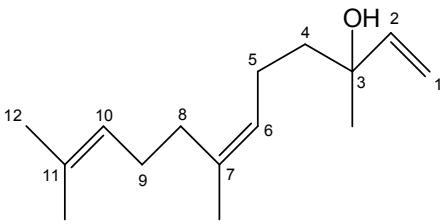


CXI

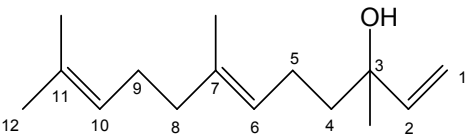


CXII

The nerolidols are sesquiterpenoids from plant essential oils that are used in flavors and perfumes. *cis*-nerolidol (**CXIII**) is transformed by *A. niger* ATCC 9142 to a major product, 10,11-dihydroxy-10,11-dihydro-*cis*-nerolidol, and a minor product, 12-hydroxy-*cis*-nerolidol (Arfmann et al., 1988). *trans*-nerolidol (**CXIV**) is transformed by the same strain to all-*trans*-12-hydroxynerolidol, 10,11-dihydroxy-10,11-dihydro-*trans*-nerolidol, 1,2,12-trihydroxy-1,2-dihydro-*trans*-nerolidol, *trans*-nerolidol 12-carboxylic acid, *trans*-12-acetoxynerolidol, and 6*E*,10*Z*-12-hydroxynerolidol (Arfmann et al., 1988):

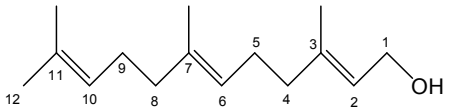


CXIII

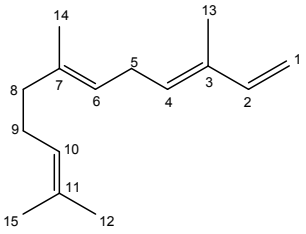


CXIV

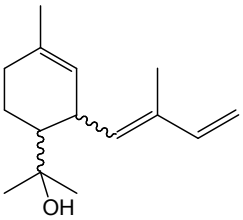
Farnesol (**CXV**), a sesquiterpenoid alcohol from plant essential oils, is used in perfumes, tobacco flavoring, and pesticides. A mixture of farnesol isomers is hydroxylated by *A. niger* DSM 63263 to produce 12-hydroxyfarnesol (Arfmann et al., 1988); and by another strain of *A. niger* to produce 12-hydroxyfarnesol (yield 35%) and 10,11-dihydroxyfarnesol (yield 48%) [33]. α-Farnesene (**CXVI**), a sesquiterpene found in the essential oils of fruits, is transformed by *A. niger* LB 2025 to four terpenoid alcohols: two diastereomers of *p*-menth-1-en-3-[2-methyl-1,3-butadienyl]-8-ol (**CXVII**) and two diastereomers of 2,6,10-trimethyldodeca-2,7,9,11-tetraen-6-ol (Krings et al., 2006):



CXV

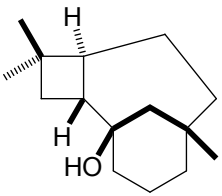


CXVI

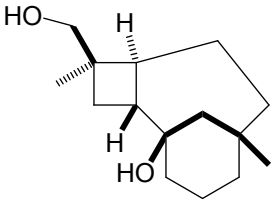


CXVII

(*R*)-Caryolan-1-ol (**CXVIII**) is transformed by *A. niger* MMP 521, forming caryolan-1,14-diol (**CXIX**) with a yield of 26% (Lamare et al., 1989):

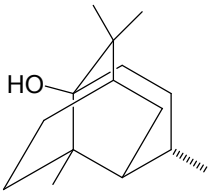


CXVIII

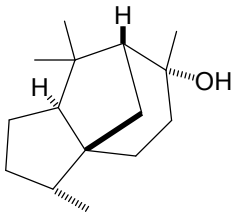


CXIX

The fragrance compound patchoulol (**CXX**), from patchouli oil, is hydroxylated by a strain of *A. niger* to form a diol (Lamare et al., 1990). Cedrol (**CXXI**), from cedarwood oil, is hydroxylated by *A. niger* ATCC 9142 to form another diol (Lamare et al., 1990):

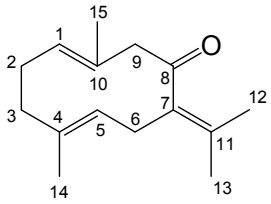


CXX

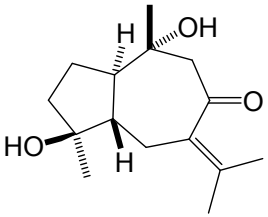


CXXI

Germacrone (**CXXII**), a sesquiterpenoid produced by several plants, is transformed by a strain of *A. niger* to the anti-inflammatory drug zedoarondiol (**CXXIII**) and 3β-hydroxygermacrone (Asakawa et al., 1991; Cho et al., 2009):

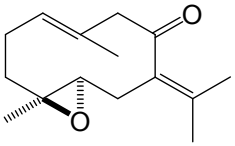


CXXII

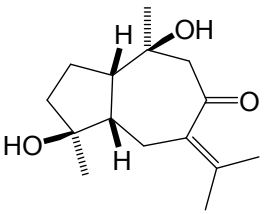


CXXIII

(+)-Germacrone-4,5-epoxide (**CXXIV**), a sesquiterpenoid epoxide derived from a species of turmeric, is transformed by a strain of *A. niger* into zedoarondiol (**CXXIII**) and isozedoarondiol (**CXXV**) (Asakawa et al., 1991):

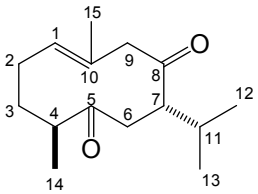


CXXIV

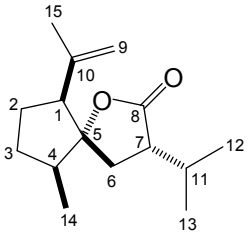


CXXV

(+)-Curdione (**CXXVI**), from a traditional Chinese medicine, is transformed by growing cells of *A. niger* AS 3.739 to several metabolites, including 3α-hydroxycurdione, 2β-hydroxycurdione, curcumalactone (**CXXVII**), 3α-hydroxycurcumalactone, (10*S*)-9,10-dihydroxycurcumalactone, and (10*R*)-9,10-dihydroxycurcumalactone (Asakawa et al., 1991; Chen et al., 2014):

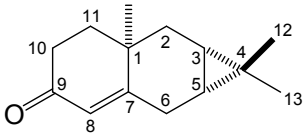


CXXVI



CXXVII

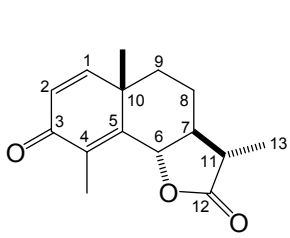
A sesquiterpenoid ketone, 1,4,4-trimethyltricyclo[5.4.0.0^{3,5}]undec-7-en-9-one (**CXXVIII**), is hydroxylated at the 13- and 12-methyl groups by *A. niger* ATCC 9142 to produce 4(*S*)- and 4(*R*)-(hydroxymethyl)-1,4-dimethyltricyclo[5.4.0.0^{3,5}]undec-7-en-9-one, respectively (Hebda et al., 1991):



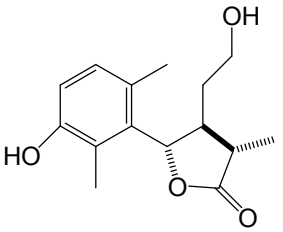
CXXVIII

(−)-α-Santonin (**CXXIX**), a sesquiterpenoid lactone from the sandalwood plant, was formerly used as an anthelmintic. It is transformed by one strain of *A. niger* to 1,2-dihydro-α-santonin (Atta-ur-Rahman et al., 1998) and by a different strain to 1-hydroxy-α-santonin, 13-hydroxy-α-santonin, 3,6,9-trihydroxy-9,10-*seco*-selina-1,3,5(10)-trien-12-oic acid-12,6-lactone (**CXXX**), and the photoproduct lumisantonin (**CXXXI**) (Hashimoto et al., 2001). Another strain, *A. niger* ATCC 9142, transforms (−)-α-

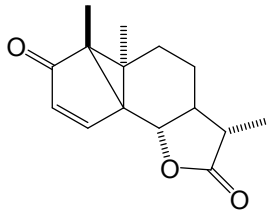
santonin (**CXXIX**) to 11β-hydroxy-α-santonin, 14-hydroxy-α-santonin, and 3,6-dihydroxy-9-keto-9,10-*seco*-selina-1,3,5(10)-trien-12-oic acid-12,6-lactone (**CXXXII**) (Lamm et al., 2009):



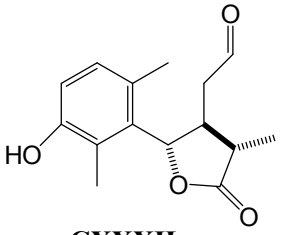
CXXIX



CXXX



CXXXI

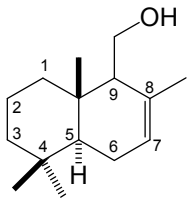


CXXXII

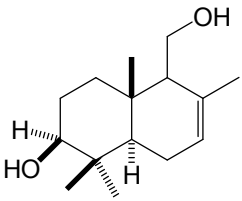
11,13-Dehydro-(−)-α-santonin is transformed by *A. niger* MIL 5024 to produce the metabolites (−)-α-santonin (**CXXIX**), 11β-hydroxy-(−)-α-santonin, 13-hydroxy-(−)-α-santonin, 3,6,9-trihydroxy-9,10-*seco*-selina-1,3,5(10)-trien-l2-oic acid-12,6-lactone (**CXXX**), and 8β-hydroxy-(−)-α-santonin (Iida et al., 1993).

(−)-Drimenol (**CXXXIII**), a sesquiterpenoid alcohol from the Winter's bark tree of Chile and Argentina, is useful for chiral synthesis. Hydroxylation by a strain of *A. niger* produces 3β-hydroxy-(−)-drimenol (**CXXXIV**); drimenyl acetate (**CXXXV**) is

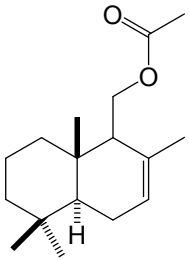
also transformed to the corresponding 3β-hydroxy derivative (Ramirez et al., 1993):



CXXXIII

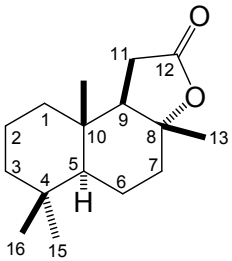


CXXXIV



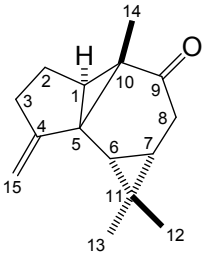
CXXXV

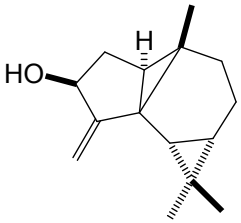
Sclareolide (**CXXXVI**), a sesquiterpenoid lactone obtained from sage plants and used as a fragrance, is transformed by *A. niger* ATCC 10549 to five metabolites: 3-ketosclareolide, 1β- and 3β-hydroxysclareolide, and 1α,3β- and 1β,3β-dihydroxysclareolide (Atta-ur-Rahman et al., 1997):



CXXXVI

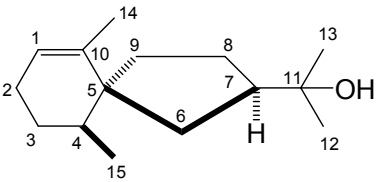
Myli-4(15)-en-9-one (**CXXXVII**) and myliol (**CXXXVIII**), two sesquiterpenoids derived from a liverwort, are hydroxylated by *A. niger* IFO 4407 at the 12-methyl group (Hayashi et al., 1998):





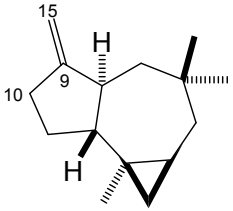
CXXXVII **CXXXVIII**

(−)-Hinesol (**CXXXIX**), a sesquiterpenoid alcohol from a Chinese medicinal plant, is transformed by a strain of *A. niger* to eight metabolites: 2-ketohinesol, 2α- and 2β-hydroxyhinesol, two *trans*-1,2-dihydrodiols, 3α,13- and 3α,12-dihydroxyhinesol 10,11-ethers, and 3α,13-dihydroxy-1,2-epoxyhinesol 10,11-ether (Hashimoto et al., 1999):



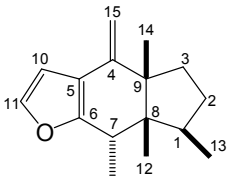
CXXXIX

The tricyclic sesquiterpene $\Delta^{9(15)}$-africanene (**CXL**), incubated with *A. niger* ATCC 9642 for 8 days, produces 10α-hydroxy-$\Delta^{9(15)}$-africanene and 9α,15-epoxyafricanane (Venkateswarlu et al., 1999):

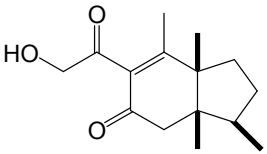


CXL

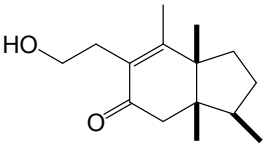
Dehydropinguisenol (**CXLI**), a furanosesquiterpenoid alcohol obtained from a liverwort, is metabolized by a strain of *A. niger* to two metabolites, 10-oxolejeuneapinguisenol (**CXLII**) and lejeuneapinguisenol (**CXLIII**), in 3 to 5 days of incubation (Lahlou et al., 2000):



CXLI

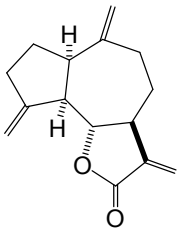


CXLII

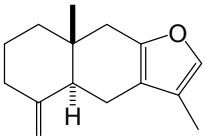


CXLIII

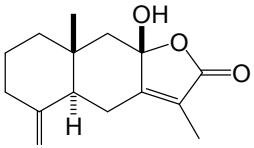
Dehydrocostus lactone (**CXLIV**), a drug derived from an Asian plant, inhibits the activation of NF-κB, a protein complex which regulates immune responses. It is transformed regio- and stereospecifically by a strain of *A. niger* via double-bond reduction, epoxidation, ring hydroxylation, and epoxide hydrolysis to six metabolites (Hashimoto et al., 2001. Atractylon (**CXLV**), found in a Chinese herbal medicine, is transformed by the same strain to produce atractylenolide III (**CXLVI**), which inhibits vascular permeability (Hashimoto et al., 2001):



CXLIV

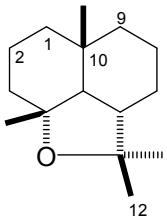


CXLV



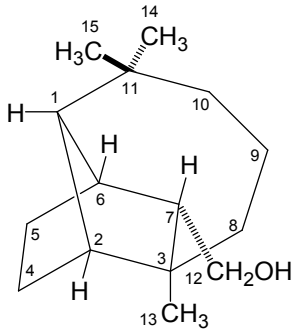
CXLVI

A sesquiterpenoid cyclic ether from a liverwort, (−)-maalioxide (**CXLVII**), is hydroxylated by a strain of *A. niger* to three metabolites: 1β-hydroxy-(−)-maalioxide, 1β,9β-dihydroxy-(−)-maalioxide, and 1β,12-dihydroxy-(−)-maalioxide (Hashimoto et al., 2004):



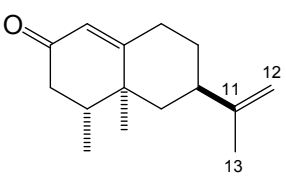
CXLVII

(−)-Isolongifolol (**CXLVIII**), a derivative of a sesquiterpene from Himalayan pine resin, is transformed by *A. niger* ATCC 10549 to the metabolites 10α- and 9α-hydroxyisolongifolol, which inhibit butyrylcholinesterase activity and have been investigated for the treatment of diseases of the nervous system (Choudhary et al., 2005):

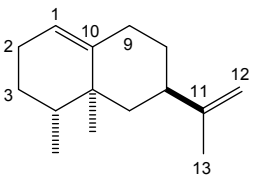


CXLVIII

Nootkatone (**CXLIX**), a sesquiterpenoid ketone from grapefruits, is biotransformed by a strain of *A. niger* to three metabolites, 12-hydroxy-11,12-dihydronootkatone (yield 10.6%) and a mixture of (11*R*)- and (11*S*)-nootkatone-11,12-diol (combined yield 51.5%) (Furusawa et al., 2005). The related sesquiterpene valencene (**CL**), from orange oil, can be biotransformed by the same strain to the same three metabolites as nootkatone plus four minor metabolites. The ratio of (11*R*)- and (11*S*)-diols from valencene was found by derivatization and HPLC analysis to be 3:1 (Furusawa et al., 2005):

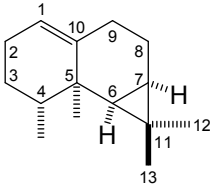


CXLIX

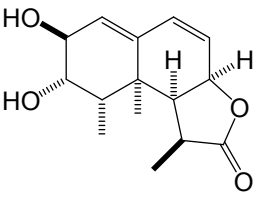


CL

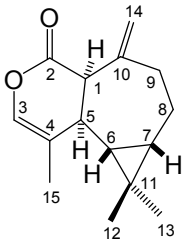
A tricyclic sesquiterpene, (+)-1(10)-aristolene (**CLI**), from a Chinese medicinal plant, is transformed by a strain of *A. niger* to 2-oxo-1(10)-aristolen-12-oic acid, 3β-hydroxy-1(2),9(10)-aristoladien-13-oic acid, 3-oxo-1(2),9(10)-aristoladien-13-oic acid, and 2β,3α-dihydroxynardosinan-1(10),8(9)-dien-11β-methyl-12,7-olide (**CLII**) (Furusawa et al., 2006). The same strain also transforms plagiochilide (**CLIII**), a sesquiterpenoid from a liverwort, to 12-hydroxyplagiochilide and plagiochilid-12-oic acid (Furusawa et al., 2006):



CLI

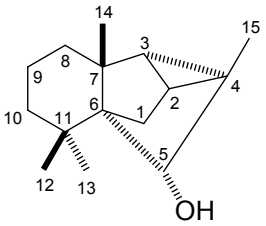


CLII

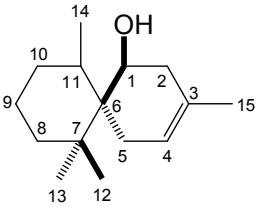


CLIII

Cyclomyltaylan-5α-ol (**CLIV**), another sesquiterpenoid from a liverwort, is biotransformed by a strain of *A. niger* in 5 days to four metabolites: cyclomyltaylane-5α,9β-diol, cyclomyltaylane-5α,10β-diol, cyclomyltaylane-5α,9β,15-triol, and 5-oxocyclomyltaylane-9β,15-diol (Furusawa et al., 2006). *ent*-β-Chamigren-1β-ol (**CLV**) is transformed to β-chamigren-1β,9α-diol, β-chamigren-1β,8α-diol, and β-chamigren-1β,8α,15-triol (Furusawa et al., 2006):

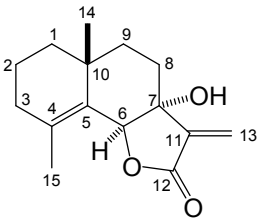


CLIV



CLV

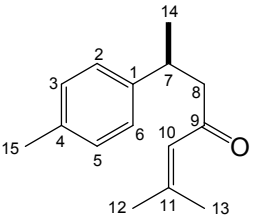
7α-Hydroxyfrullanolide (**CLVI**), a sesquiterpenoid lactone from the East Indian globe thistle, inhibits growth of Gram-positive bacteria and the production of pro-inflammatory cytokines. *A. niger* ATCC 1004 transforms it to three metabolites: 11,13-dihydro-7α-hydroxyfrullanolide, 13-acetyl-7α-hydroxyfrullanolide, and 2α,7α-dihydroxyfrullanolide, which are much less antibacterial (Ata et al., 2009):



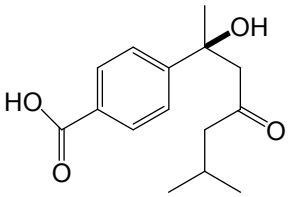
CLVI

A sesquiterpenoid, (+)-(*S*)-*ar*-turmerone (**CLVII**), from the rhizomes of black turmeric, inhibits acetylcholinesterase activity. It is oxidized by *A. niger* NBRC 4414 to four metabolites: (+)-(7*S*)-hydroxydehydro-*ar*-todomatuic acid (**CLVIII**), (+)-(7*S*,10*E*)-

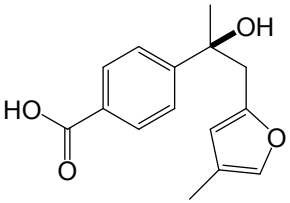
12-hydroxydehydro-*ar*-todomatuic acid, (+)-(7*S*,10*E*)-7,12-dihydroxydehydro-*ar*-todomatuic acid, and (+)-(7*S*)-15-carboxy-9,13-epoxy-7-hydroxy-9,13-dehydro-*ar*-curcumene (**CLIX**) (Fujiwara et al., 2011). The same strain also metabolizes (+)-(*S*)-dihydro-*ar*-turmerone (**CLX**) to (+)-7,11-dihydroxy-*ar*-todomatuic acid (Fujiwara et al., 2011):



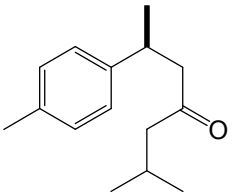
CLVII



CLVIII

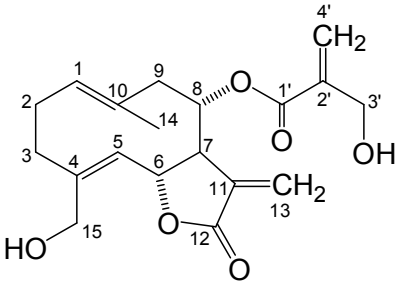


CLIX



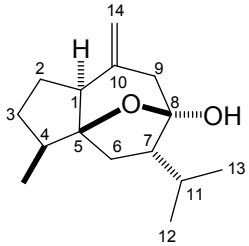
CLX

Onopordopicrin (**CLXI**), an antibacterial but cytotoxic sesquiterpenoid lactone produced by several plants, is transformed by *A. niger* PTCC 5011 to 11αH-dihydroonopordopicrin, 11βH-dihydroonopordopicrin, 3β-hydroxy-11βH-dihydroonopordopicrin, and 14-hydroxy-11βH-dihydroonopordopicrin (Esmaeili et al., 2012):

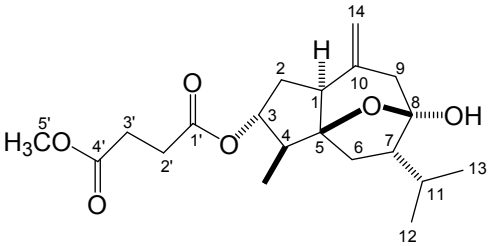


CLXI

Curcumol (**CLXII**), a sesquiterpenoid with antitumor and antivirus activity, is derived from a species of turmeric used in Chinese traditional medicine. It is transformed by *A. niger* AS 3.739 to 3α-hydroxycurcumol and 3α-(4'methoxysuccinyloxy)-curcumol (**CLXIII**) (Chen et al., 2013):

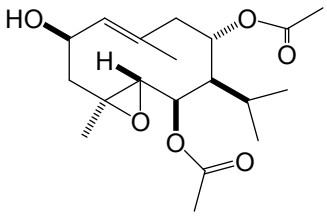


CLXII



CLXIII

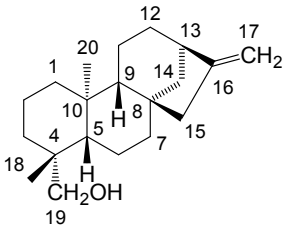
Shiromodiol diacetate, a sesquiterpenoid epoxide obtained from an Asian tree, is hydroxylated by *A. niger* IFO 4407 to produce 2β-hydroxyshiromodiol diacetate (**CLXIV**), with a 59% yield in 4 days (Hayashi et al., 1998):



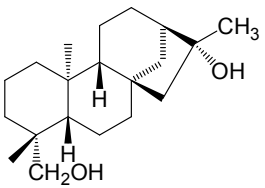
CLXIV

3. Transformation of diterpenoids

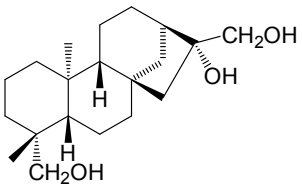
Many diterpenoids from medicinal plants have antimalarial activity (García et al., 2007; Titanji et al., 2008; Kaur et al., 2009). Cultures of the fungus *Cephalosporium aphidicola* CCT 2163 hydroxylate the kaurane diterpenoid *ent*-kaur-16-en-19-ol (**CLXV**) with formation of two products, *ent*-kauran-16b,19-diol (**CLXVI**, yield 54%) and *ent*-kauran-16b,17,19-triol (**CLXVII**, yield 18.6%), in 13 days (Rocha et al., 2009):



CLXV

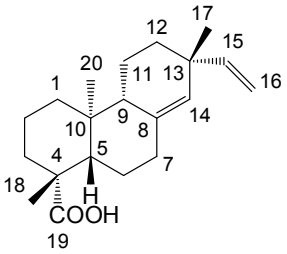


CLXVI

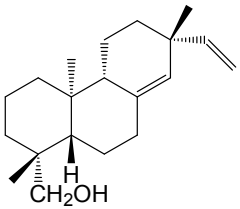


CLXVII

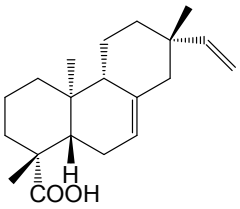
Because plants containing pimarane diterpenoids, such as *Kaempferia marginata*, have been used as antimalarials in traditional medicine, the pimaranes have also been investigated for antimalarial activity (Thongnest et al., 2005). Although the reduction of specific carboxyl groups to alcohols is not always possible by chemical methods, the fungus *Glomerella cingulata* regioselectively transformed *ent*-pimara-8(14),15-dien-19-oic acid (**CLXVIII**) to *ent*-8(14),15-pimaradien-19-ol (**CLXIX,** yield 18.3%) in 10 days (Severiano et al., 2010). *Mucor rouxii* converted **CLXVIII** to *ent*-pimara-7,15-dien-19-oic acid (**CLXX**, yield 2.8%) and 7-keto-*ent*-pimara-8,15-dien-19-oic acid (**CLXXI**, yield 2.1%) in 7 days (Severiano et al., 2010):



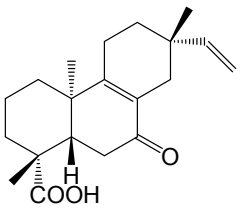
CLXVIII



CLXIX

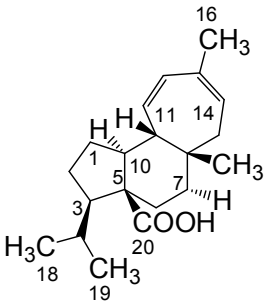


CLXX

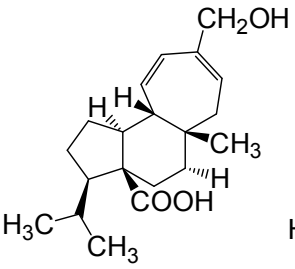


CLXXI

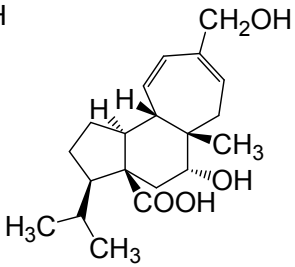
Some mulinane derivatives from the medicinal plant *Azorella compacta* have been shown to have antiplasmodial activity (Loyola et al., 2004). *Mucor plumbeus* IMI 116688 transformed mulin-11,13-dien-20-oic acid (**CLXXII**) to two metabolites, 16-hydroxymulin-11,13-dien-20-oic acid (**CLXXIII**, yield 0.8%) and 7α,16-dihydroxymulin-11,13-dien-20-oic acid (**CLXXIV**, yield 0.75%) in 15 days (Areche et al., 2008):



CLXXII



CLXXIII

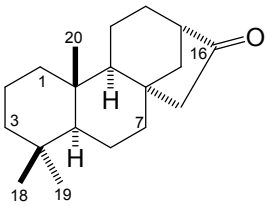


CLXXIV

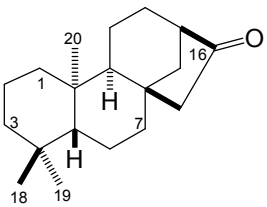
The diterpenoids found in plant resins consist of four isoprene units in a variety of arrangements. They are not used as fragrances, but several of them have medicinal properties, especially the taxoids produced by yew trees, which have valuable anticancer activity. Biotransformation processes have been developed for many diterpenoids (Bhatti et al., 2014).

17-Norkauran-16-one (**CLXXV**) and *ent*-17-norkauran-16-one (**CLXXVI**), which are tetracyclic diterpenoids that are

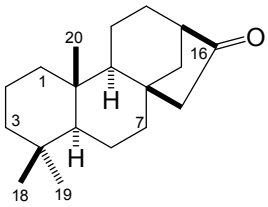
possible gibberellin precursors in plants, are biotransformed by *A. niger* ATCC 26693 to the 3β-hydroxy and 3α-hydroxy derivatives, respectively (Anderson et al., 1975). In contrast, 17-norphyllocladan-16-one (**CLXXVII**) is biotransformed to the 3β-hydroxy and the 3-keto derivatives (Anderson et al., 1975):



CLXXV

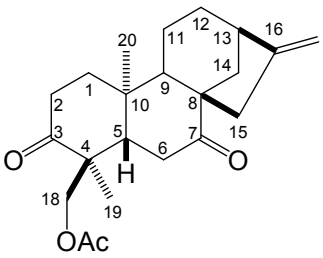


CLXXVI

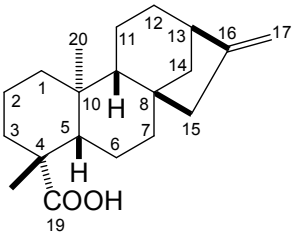


CLXXVII

A similar diterpenoid, *ent*-18-acetoxykaur-16-en-3,7-dione (**CLXXVIII**), can be transformed by *A. niger* CECT 2091. Acetoxyl hydrolysis produces *ent*-18-hydroxykaur-16-en-3,7-dione in 2 days; *ent*-16β,18- and *ent*-17,18-dihydroxykauran-3,7-dione; and *ent*-l6α,17,18- and *ent*-16β,17,18-trihydroxykauran-3,7-dione can also be isolated after 6 days (García-Granados et al., 1986). *ent*-Kaur-16-en-19-oic acid (kaurenoic acid, **CLXXIX**), a diterpenoid from the roots of a medicinal plant, has antispasmodic and anti-inflammatory properties. It is transformed by *A. niger* AN-1 to two dihydroxylated metabolites, *ent*-7α,11β-dihydroxy-kaur-16-en-19-oic acid (20% yield) and *ent*-1β,7α-dihydroxy-kaur-16-en-19-oic acid (5.8% yield) in 13 days (Marquina et al., 2009):

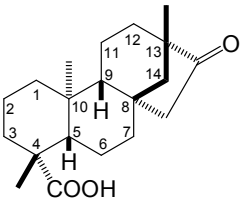


CLXXVIII

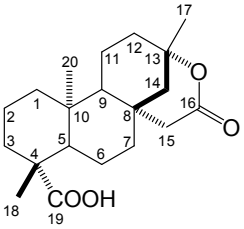


CLXXIX

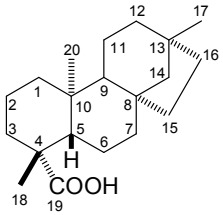
Isosteviol (**CLXXX**), an *ent*-beyer-19-oic acid derivative with a variety of biological effects, is biotransformed by *A. niger* CMI 17454 to form 7β-hydroxyisosteviol and 1α,7β-dihydroxyisosteviol (Oliveira et al., 1999). Another strain, *A. niger* IFO 4414, metabolizes isosteviol not only to 7β-hydroxyisosteviol but also to 11β- and 12β-hydroxyisosteviol; all three of these metabolites have antitumor activity (Akihisa et al., 2004). Isosteviol lactone (**CLXXXI**) is biotransformed by *A. niger* BCRC 31130 to seven different hydroxylated diterpenoids, some of which inhibit the activator protein-1 transcription factor (Chou et al., 2009). Isostevic acid (**CLXXXII**) is hydroxylated by *A. niger* BCRC 32720 to eight metabolites with anti-inflammatory properties (Yang et al.,2012):



CLXXX

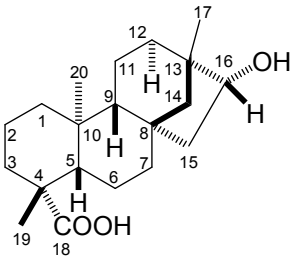


CLXXXI

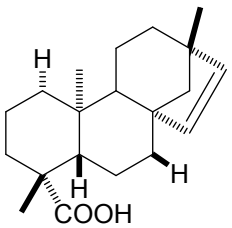


CLXXXII

The tetracyclic diterpenoid *ent*-16β-hydroxybeyeran-19-oic acid (**CLXXXIII**) is hydroxylated by *A. niger* CCRC 32720 to *ent*-1β,7α,16β-trihydroxybeyeran-19-oic acid and *ent*-1β,7α-dihydroxy-16-oxobeyeran-19-oic acid, both of which have greater antihypertensive activity than the starting drug [81]. A similar diterpenoid from a Mexican plant, *ent*-beyer-15-en-19-oic acid (**CLXXXIV**), is hydroxylated by *A. niger* AN-1 to *ent*-1β,7α-dihydroxy-beyer-15-en-19-oic acid (yield 40%) (Marquina et al., 2009):



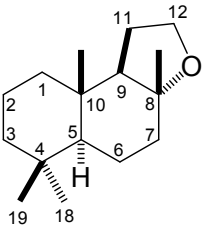
CLXXXIII



CLXXXIV

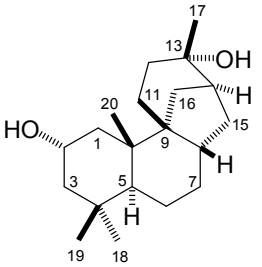
(−)-Ambroxide (Ambrox, **CLXXXV**), a diterpenoid used in fragrances, is transformed by a strain of *A. niger*, by oxidation at

the C3 and C18 positions and hydrolysis of the furan ring, to produce four metabolites (Hashimoto et al., 2001):

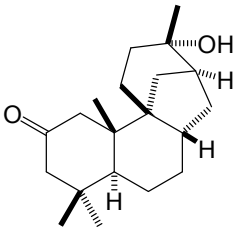


CLXXXV

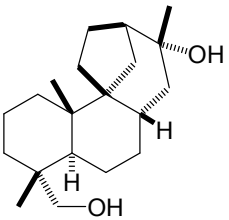
Stemodin (**CLXXXVI**), a tetracyclic diterpenoid produced by the seaside twintip plant of Jamaica, is biotransformed in cultures of *A. niger* ATCC 9142 to 2α,3β,13-, 2α,7β,13-, and 2α,13,16β-trihydroxystemodane (Furusawa et al., 2005). The same strain also transforms stemodinone (**CLXXXVII**) to 13,18- and 13,16β-dihydroxystemodan-2-one; and it transforms stemarin (**CLXXXVIII**) to four metabolites, including three carboxylic acids (Chen et al., 2002):



CLXXXVI

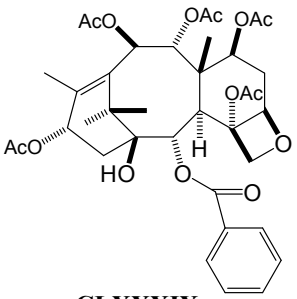


CLXXXVII

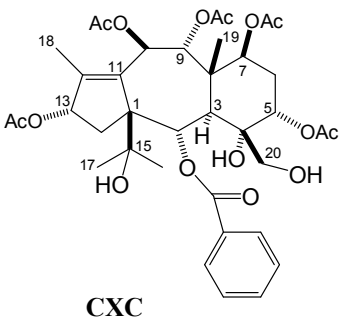


CLXXXVIII

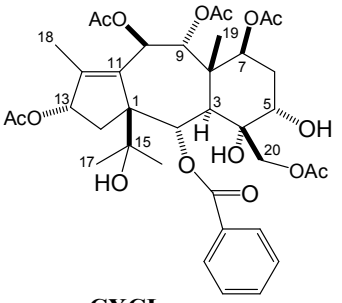
Baccatin VI (**CLXXXIX**), a taxoid diterpenoid from a Chinese yew tree, can be biotransformed with *A. niger* BCRC 31130 to produce the diterpenoids taxumairol S_1 (**CXC**) and taxumairol T_1 (**CXCI**), which have been used in antitumor research (Shen et al., 2003):



CLXXXIX

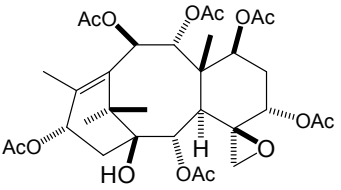


CXC

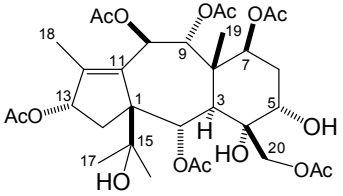


CXCI

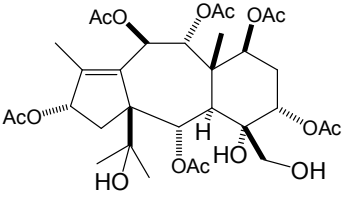
Similarly, the biotransformation of 1β-hydroxybaccatin I (**CXCII**), a polyacetylated diterpenoid epoxide from the Chinese yew, by *A. niger* BCRC 31130 produces a mixture of taxumairol S (**CXCIII**) and taxumairol T (**CXCIV**) (Shen et al., 2003):



CXCII

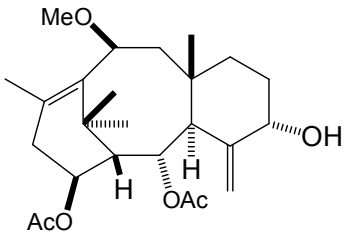


CXCIII



CXCIV

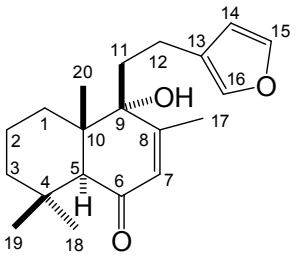
5α-Hydroxy-10β-methoxy-2α,14β-diacetoxytaxa-4(20),11(12)-diene (**CXCV**), a taxadiene diterpenoid, is transformed by *A. niger* CGMCC 3.1858 by demethylation, acetylation, deacetylation, and O-alkylation to seven metabolites. One of them, 2α-hydroxy-5α,10β,14β-triacetoxytaxa-4(20),11(12)-diene, has the potential to prevent resistance to chemotherapeutic drugs in some tumor cells (Liu et al., 2012):



CXCV

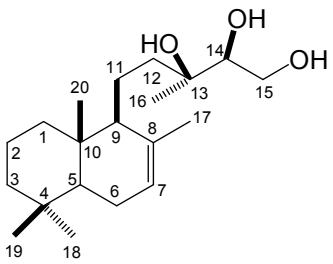
Solidagenone (**CXCVI**), a diterpenoid found in Chilean goldenrod rhizomes, is hydroxylated to 3β-hydroxy- and 19-

hydroxysolidagenone, which have gastroprotective effects on cultured epithelial cells, when incubated with *A. niger* ATCC 16404 (Schmeda-Hirschmann et al., 2004):

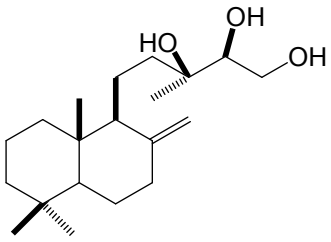


CXCVI

A diterpenoid from a tarweed plant, 13*R*,14*R*,15-trihydroxylabd-7-ene (**CXCVII**), is transformed by a strain of *A. niger* to produce 3β,13*R*,14*R*,15-tetrahydroxy-labd-7-ene; and 13*R*,14*R*,15-trihydroxylabd-8(17)-ene (**CXCVIII**) is transformed by the same strain to produce 7α,13*R*,14*R*,15-tetrahydroxylabd-8(17)-ene and 13*R*,14*R*,15-trihydroxy-3-oxo-labd-8(17)-ene (Haridy et al., 2006):

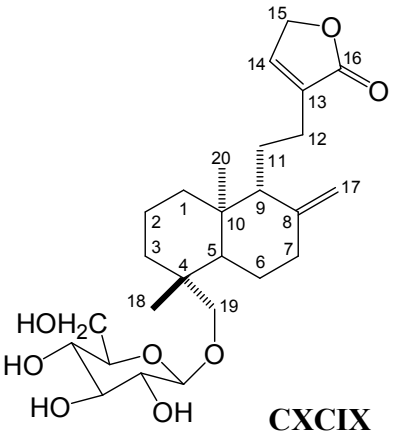


CXCVII



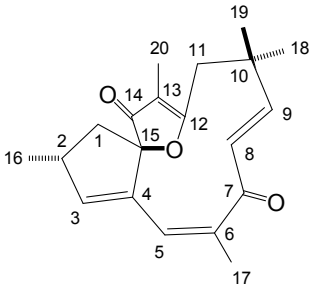
CXCVIII

Neoandrographolide (**CXCIX**), a diterpenoid from a Chinese traditional medicinal plant, is biotransformed by *A. niger* AS 3.739 to five products: 8(17),13-*ent*-labdadien-16,15-olid-19-oic acid, 19-hydroxy-8(17),13-*ent*-labdadien-16,15-olide, 18-hydroxy-8(17),13-*ent*-labdadien-16,15-olid-19-oic acid, 3α-hydroxy-8(17),13-*ent*-labdadien-16,15-olid-19-oic acid, and 8β,19-dihydroxy-*ent*-labd-13-en-16,15-olide (Chen et al., 2007):

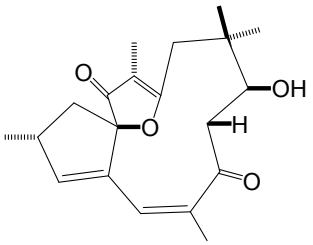


CXCIX

Jatrophone (**CC**), a relatively toxic antiprotozoal and antileukemic diterpenoid from a plant native to Middle and South America, is regioselectively converted by *A. niger* ATCC 16404 to a small amount of the much less cytotoxic 9β-hydroxyisabellione in 25 days (**CCI**, yield 0.65%) (Pertino et al., 2007):

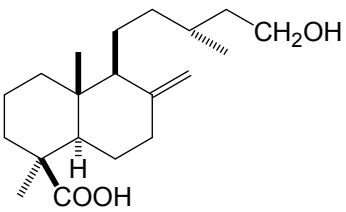


CC

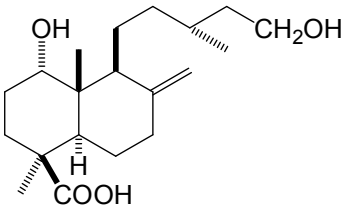


CCI

Imbricatolic acid (**CCII**), a diterpenoid obtained from the common juniper, is regioselectively transformed by cultures of *A. niger* ATCC 16404 to 1α-hydroxyimbricatolic acid (**CCIII**) in 15 days (Schmeda-Hirschmann et al., 2007):

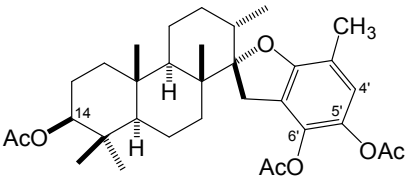


CCII

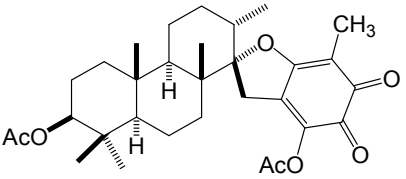


CCIII

Stypotriol triacetate (**CCIV**), a derivative of a compound found in brown algae, is converted by *A. niger* ATCC 16404 to 6',14-diacetoxystypol-4',5'-dione (**CCV**) in 20 days, with a 1.7% yield after purification (Areche et al., 2011):

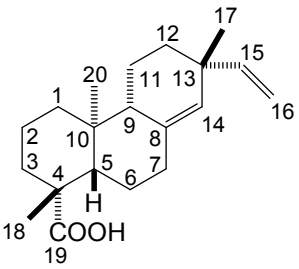


CCIV



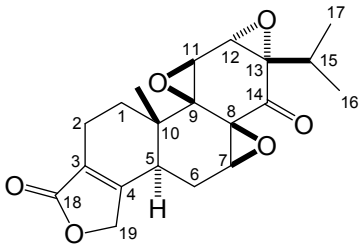
CCV

ent-Pimaradienoic acid (**CCVI**), an antibacterial diterpenoid from a Chinese yew tree, is derivatized by biotransformation with a strain of *A. niger* to 7α-hydroxy-*ent*-pimara-8(14),15-dien-19-oic acid, 1β-hydroxy-*ent*-pimara-6,8(14),15-trien-19-oic acid, 1α,6β,14β-trihydroxy-*ent*-pimara-7,15-dien-19-oic acid, and 1α,6β,7α,11α-tetrahydroxy-*ent*-pimara-8(14),15-dien-19-oic acid (Severiano et al., 2013):



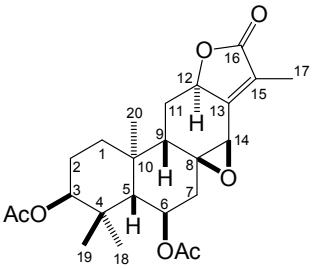
CCVI

Triptonide (**CCVII**), a diterpenoid triepoxide lactone from a Chinese medicinal vine, has anti-inflammatory and antitumor activity but also significant toxicity. *A. niger* AS 3.739 transforms it to the less toxic metabolites 5α-hydroxytriptonide, triptolide (with a 14β-hydroxyl group), 17-hydroxytriptonide, and 16-hydroxytriptonide without hydrolyzing any of the three epoxide groups (Ning et al., 2003):

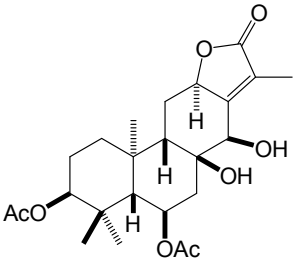


CCVII

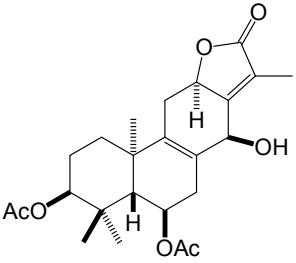
Gelomulide G (3β,6β-diacetoxy-8β,14β-epoxyabiet-13(15)-en-16,12-olide, **CCVIII**), a diterpenoid epoxy lactone from a tropical Asian plant with antileishmanial activity, when incubated with *A. niger* ATCC 10549 produces two metabolites, 3β,6β-diacetoxy-8β,14β-dihydroxyabiet-13(15)-en-16,12-olide (**CCIX**) and 3β,6β-diacetoxy-14β-hydroxyabiet-8(9),13(15)-dien-16,12-olide (**CCX**) (Choudhary et al., 2005):



CCVIII



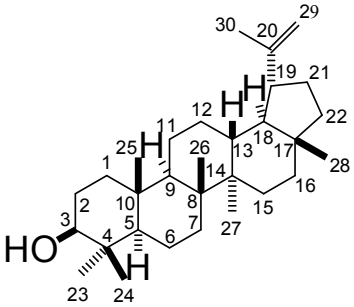
CCIX



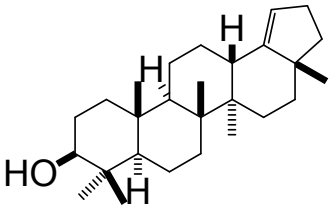
CCX

4. Transformation of triterpenoids

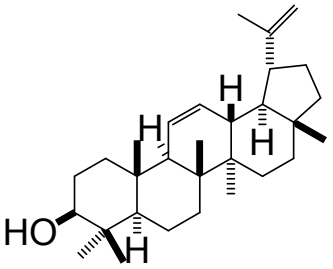
Several triterpenoids from plant essential oils are potential antimalarial drugs (Kaur et al., 2009). The lupanes are a group of pentacyclic triterpenoids that contain compounds with antimalarial activity (Suksamrarn et al., 2006; Kaur et al., 2009). *Aspergillus ochraceus* converted lupeol (**CCXI**) to two metabolites, **CCXII** (yield 19.0%) and **CCXIII** (yield 11.1%) in 10 days (Carvalho et al., 2010):



CCXI

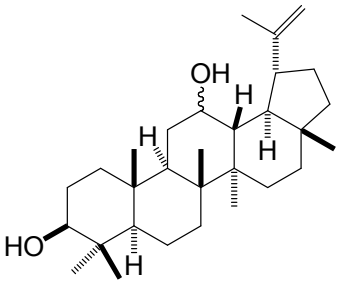


CCXII

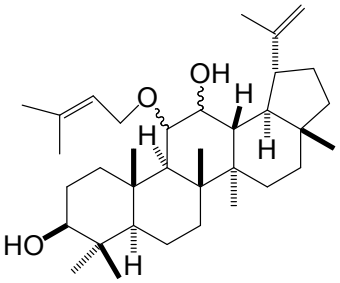


CCXIII

Also, *M. rouxii* transformed lupeol (**CCXI**) to two metabolites, **CCXIV** (yield 26.5%) and **CCXV** (yield 16.0%) in 10 days (Carvalho et al., 2010):

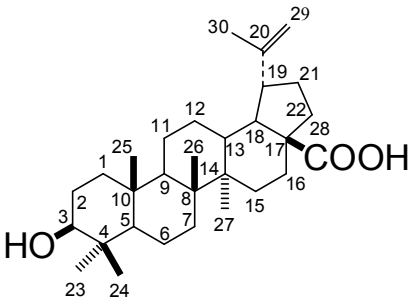


CCXIV

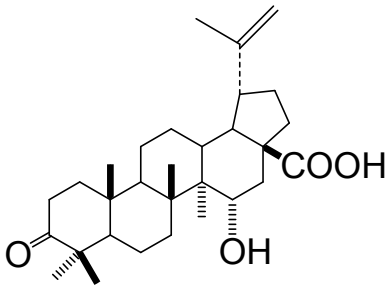


CCXV

The triterpenoids betulinic acid and betulonic acid are known to have antimalarial activity (Sá et al., 2009). Several fungi have been investigated for their ability to biotransform these compounds. For instance, *Colletotrichum* sp. transformed betulinic acid (**CCXVI**) to 3-oxo-15α-hydroxylup-20(29)-en-28-oic acid (**CCXVII**, yield 2.34%) (Bastos et al., 2007):

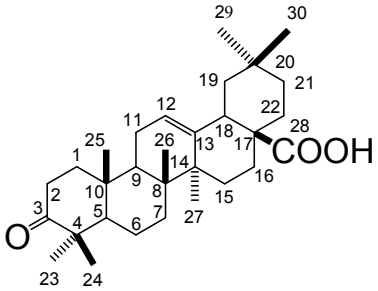


CCXVI

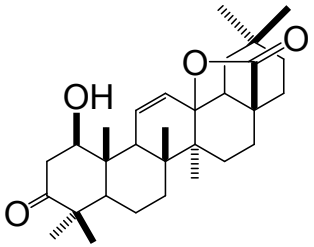


CCXVII

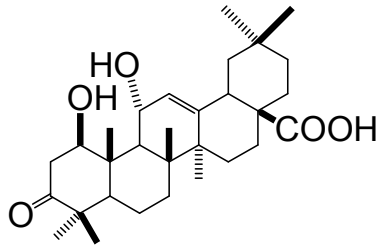
Some oleanolic acids from medicinal plants have been reported to be antimalarial (Cimanga et al., 2006; Kaur et al., 2009). The fungus *Absidia glauca* CGMCC 3.67 transformed 3-oxo-oleanolic acid (**CCXVIII**) to three new derivatives, 1β-hydroxy-3-oxo-olean-11-eno-28,13-lactone (**CCXIX**, yield 0.74%), 1β,11α-dihydroxy-3-oxo-olean-12-en-28-oic acid (**CCXX**, yield 2.3%) and 1β,11α,21β-trihydroxy-3-oxo-olean-12-en-28-oic acid (**CCXXI**, yield 0.23 %) (Guo et al., 2010):



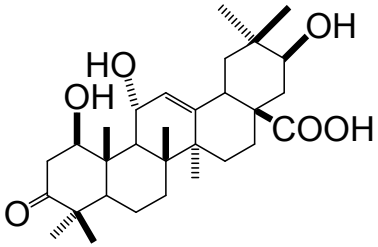
CCXVIII



CCXIX

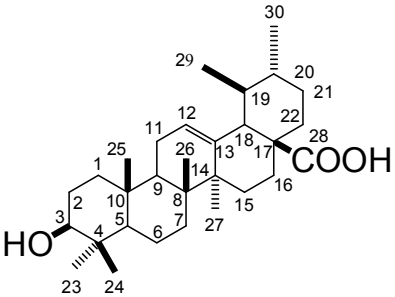


CCXX

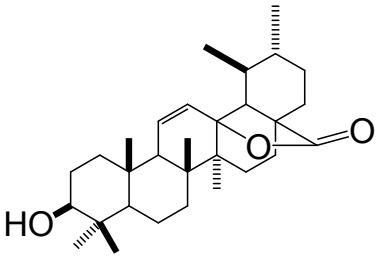


CCXXI

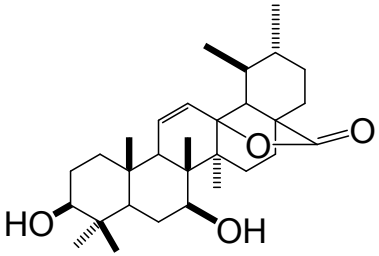
The triterpenoid ursolic acid, from the medicinal plant *Morinda lucida*, has been shown to have antimalarial activity (Cimanga et al., 2006). The soil fungus *Umbelopsis isabellina* converted ursolic acid (**CCXXII**) to three metabolites, 3β-hydroxy-urs-11-eno-28,13-lactone (**CCXXIII**, yield 0.69%), 3β,7β-dihydroxy-urs-11-eno-28,13-lactone (**CCXXIV**, yield 0.5%) and 1β,3β-dihydroxy-urs-11-eno-28,13-lactone (**CCXXV**, yield 0.88%) (Fu et al., 2011):



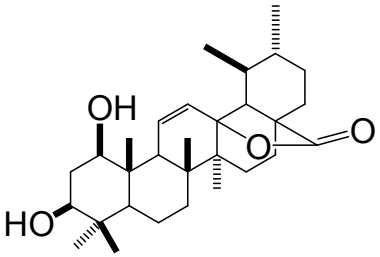
CCXXII



CCXXIII

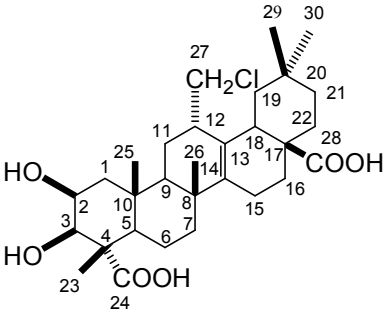


CCXXIV

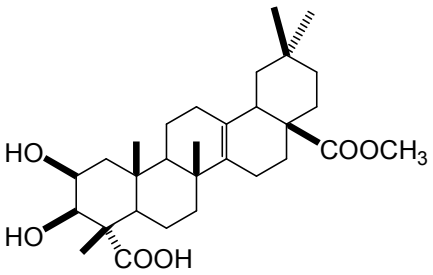


CCXXV

Transformation of another triterpenoid, senegenin (**CCXXVI**), by *Nocardia* sp. NRRL 5646 was accompanied by the formation of senegenic acid 28-methyl ester (**CCXXVII**) (Zhang et al., 2005):

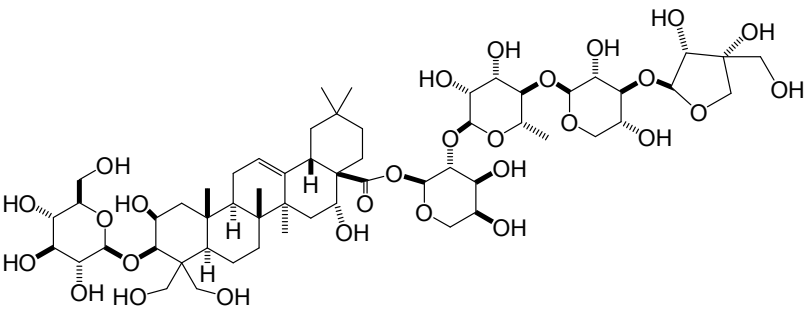


CCXXVI



CCXXVII

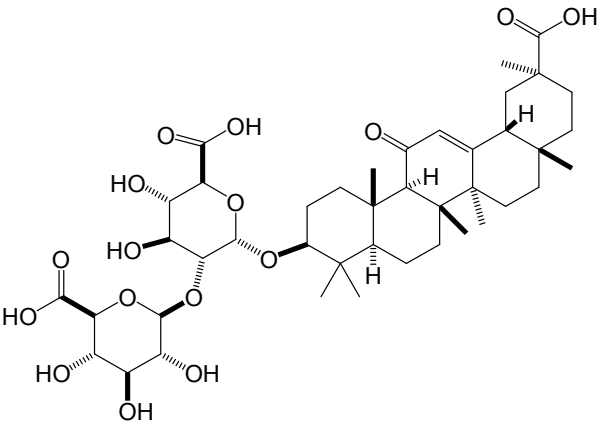
Platycodin D (**CCXXVIII**), a triterpenoid saponin with two side chains, from the root of the Asian bellflower, is transformed by a crude enzyme preparation from *A. niger* KCTC 6906 to a saponin lacking the terminal apiose and xylose of one side chain. This derivative has greater nitrite-scavenging activity and less toxicity (Wie et al., 2007):



CCXXVIII

A triterpenoid saponin derived from licorice, glycyrrhizic acid (glycyrrhizin, **CCXXIX**), is metabolized by a strain of *A. niger* that removes two glucuronic acid residues to produce the triterpenoids 7β,15α-dihydroxy-3,11-dioxo-oleana-12-en-30-oic

acid and 15α-hydroxy-3,11-dione-oleana-12-en-30-oic acid (Kang et al., 2008):

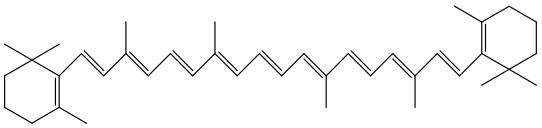


CCXXIX

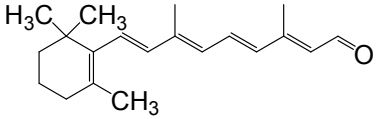
5. Transformation of tetraterpenoids

Carotenoids, an important group of tetraterpenoids found in nearly all plants, are often biotransformed for preparation of food additives and flavorings (Uenojo and Pastore, 2010). Biotransformation of β-carotene may produce retinoids, which can be used as raw materials for drugs and cosmetics (Jang et al., 2011), and some retinoids, including retinol, have antimalarial activity (Hamzah et al., 2003). A recombinant strain of *Escherichia coli* expressing β-carotene 15,15'-mono(di)oxygenase and the mevalonate pathway transformed β-carotene (**CCXXX**) to

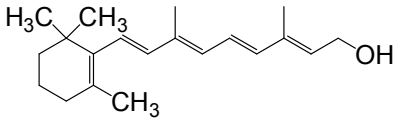
retinal (**CCXXXI**), the antimalarial retinol (**CCXXXII**) and retinyl acetate (**CCXXXIII**) (Jang et al., 2011):



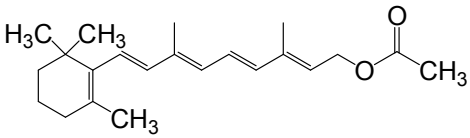
CCXXX



CCXXXI

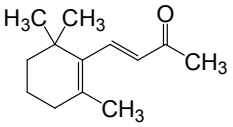


CCXXXII

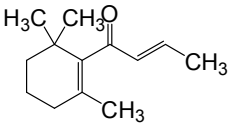


CCXXXIII

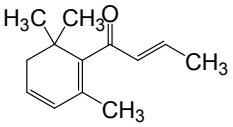
For the biotransformation of β-carotene, over 300 strains of microorganisms (bacteria, yeasts and filamentous fungi) were tested and seven unidentified strains showed transformation activity (Uenojo and Pastore, 2010). The isoprenoid chain of β-carotene (**CCXXX**) was cleaved with the formation of several products, including the principal product β-ionone (**CCXXXIV**), β-damascone (**CCXXXV**), β-damascenone (**CCXXXVI**), pseudoionone (**CCXXXVII**) and probably 1,1,6-trimethyl-1,2,3,4-tetrahydronaphthalene (**CCXXXVIII**) (Uenojo and Pastore, 2010):



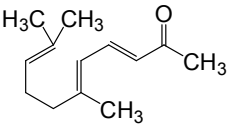
CCXXXIV



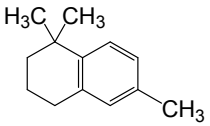
CCXXXV



CCXXXVI



CCXXXVII



CCXXXVIII

Conclusion

A work with terpenoids may suggest new biotransformation experiments that use fungi to produce new drug candidates. The most useful biotransformations should be amenable to improved methods and scale-up so that larger quantities of new metabolites may be made available for investigation.

Currently, artemisinin derivatives appear to be the most promising sources of new terpenoid antimalarial drugs. The main route selected by most researchers for the preparation of derivatives begins with chemical reduction of the carbonyl at position 10 of artemisinin to produce the toxic antimalarial compound dihydroartemisinin (Klayman, 1985; Li et al., 1998; Chaturvedi, 2011).

Arteether can be converted to several metabolites, not only by mammalian systems but also by fungi and bacteria (Vroman et al., 1999). Other chemical derivatives of artemisinin may be useful in the future for the microbial biosynthesis of new drugs with novel therapeutic properties. The combination of artemether with the unrelated drug lumefantrine is one of five artemisinin-based combinations currently recommended by the World Health Organization (WHO) for treatment of malaria (Omari et al., 2004; O'Brien et al., 2011). Various laboratories now are conducting research on hybrid trioxaquine molecules that have two different modes of action (Chauhan et al., 2010), such as a drug combining the structures of artemisinin and quinine that is highly effective against *P. falciparum* (Walsh et al., 2007).

The mechanisms of action of artemisinin and its derivatives on malaria parasites have not been completely studied, but there is evidence that the endoperoxide group plays an important role in antimalarial activity (Vroman et al., 1999; Muraleedharan and Avery, 2009; Fernández and Robert, 2011). The endoperoxide linkage breaks down under the influence of heme iron, with formation of an oxy free radical and then a carbon free radical, which interacts with proteins of the parasite to cause its death (Chaturvedi et al., 2010).

Some of the artemisinin derivatives, especially the trioxane dimers, are selectively cytotoxic; they have been shown not only

to target cancer cells by inducing apoptosis but also to prevent tumor growth by antiangiogenesis (Beekman et al., 1998; Posner et al., 2006; Nakase et al., 2008). The endoperoxide moiety required for antimalarial activity also appears to be required for cytotoxicity toward tumor cell lines (Beekman et al., 1998; Meunier and Robert, 2010). Therefore, in the development of microbial biotransformation processes for the derivatization of artemisinin, the endoperoxide group should be preserved.

Among the microbial biotransformation processes described here, the ones of greatest interest are those for the regiospecific and stereospecific hydroxylation of artemisinin and other antimalarial terpenoids because they increase solubility and provide sites for further modification (Medeiros et al., 2002; Parshikov et al., 2006). Microbial biotransformation procedures can be used to obtain terpenoid derivatives hydroxylated in almost any position, including some not obtainable by organic synthesis, such as 7β-hydroxyartemisinin (Parshikov et al., 2004b; Khor and Uzir, 2011). These metabolites may be used for further chemical or biological transformations that yield many potential candidate drugs from one compound.

Future research on antimalarial terpenoids should include studies of the biochemistry of the most useful biotransformations and of the antiplasmodial efficacy and toxicity of each of the metabolites. The compounds that are most effective against drug-

resistant strains of *P. falciparum* or *P. vivax* may be produced in higher yields by the use of biotechnology. New biotransformations of terpenoids, perhaps combined with chemical derivatization, may provide ways to overcome parasite resistance to currently used antimalarial drugs.

Hydroxylated derivatives of artemisinins obtained by microbial techniques may be used to create hybrid molecules based on molecules of nitrogenous heterocycles (Dovgilevich et al., 1991; Khasaeva et al., 2014; Modyanova et al., 1999, 2010; Parshikov et al., 1992, 1994, 1997, 1999a,b,c, 2000a,b,c,d, 2001a,b,c,d, 2002a,b,c,d, 2010b,c,d,e ; Sutherland et al., 2001; Terentyev et al., 1989, 1997, 2010; Williams et al., 2001, 2004; Williamson et al., 2007).

References

Abraham W-R., Arfmann H-A. Microbial hydroxylation of activated acyclic monoterpene hydrocarbons. Tetrahedron 1992;48:6681–8.

Akihisa T., Hamasaki Y., Tokuda H., Ukiya M, Kimura Y., Nishino H. Microbial transformation of isosteviol and inhibitory effects on Epstein-Barr virus activation of the transformation products. J Nat Prod 2004;67:407–410.

Anderson A.B., McCrindle R., Turnbull J.K. Microbiological transformations of 17-norkauran-16-one, *ent*-17-norkauran-16-one, and 17-norphyllocladan-16-one by *Aspergillus niger*. Can J Chem 1975;53:1181–1188.

Areche C., Loyola L.A., Borquez J., Rovirosa J., San-Martin A. Microbial transformation of the diterpene mulin-11,13-dien-20-oic acid by *Mucor plumbeus*. Magn Reson Chem 2008;46:765–8.

Areche C., Vaca I., Labbe P., Soto-Delgado J., Astudillo L., Silva M., Rovirosa J., San-Martin A. Biotransformation of stypotriol triacetate by *Aspergillus niger*. J Mol Struct 2011;998:167–170.

Arfmann H-A., Abraham W-R., Kieslich K. Microbial ω-hydroxylation of *trans*-nerolidol and structurally related sesquiterpenoids. Biocatalysis 1988;2:59–67.

Asakawa Y., Takahashi H., Toyota M., Noma Y. Biotransformation of monoterpenoids, (−)- and (+)-menthols, terpinolene and carvotanacetone by *Aspergillus* species. Phytochemistry 1991;30:3981–3987.

Asakawa Y., Takahashi H., Toyota M. Biotransformation of germacrane-type sesquiterpenoids by *Aspergillus niger*. Phytochemistry 1991;30:3993–3997.

Ata A., Betteridge J., Schaub E., Kozera D.J., Holloway P., Samerasekera R. Microbial reactions on 7α-

hydroxyfrullanolide and evaluation of biotransformed products for antibacterial activity. Chem Biodivers 2009;6:1453–1462.

Atta-ur-Rahman, Choudhary M.I., Shaheen F., Rauf A., Farooq A. Microbial transformation of some bioactive natural products. Nat Prod Lett 1998;12:215–222.

Atta-ur-Rahman, Farooq A., Choudhary M.I. Microbial transformation of sclareolide. J Nat Prod 1997;60:1038–1040.

Avery M.A., Alvim-Gaston M., Rodrigues C.R., Barreiro E.J., Cohen F.E., Sabnis YA, et al. Structure-activity relationships of the antimalarial agent artemisinin. 6. The development of predictive in vitro potency models using CoMFA and HQSAR methodologies. J Med Chem 2002;45:292–303.

Bastos D.Z.L., Pimentel I.C., Jesus D.A., Oliveira B.H. Biotransformation of betulinic and betulonic acids by fungi. Phytochemistry 2007;68:834–9.

Batista R., Silva A.J., Oliveira A.B. Plant-derived antimalarial agents: new leads and efficient phytomedicines. Part II. Non-alkaloidal natural products. Molecules 2009;14:3037–72.

Beekman A.C., Wierenga P.K., Woerdenbag H.J., van Uden W., Pras N., Konings A.W.T., et al. Artemisinin-derived sesquiterpene lactones as potential antitumour compounds: cytotoxic action against bone marrow and tumour cells. Planta Med 1998;64:615–9.

Bero J., Frédérich M., Quetin-Leclercq J. Antimalarial compounds isolated from plants used in traditional medicine. J Pharm Pharmacol 2009;61:1401–33.

Bhattacharyya PK, Prema BR, Kulkarni BD, Pradhan SK. Microbiological transformation of terpenes: hydroxylation of α-pinene. Nature 1960;187:689–690.

Bhatti H.N., Khera R.A. Biotransformations of diterpenoids and triterpenoids: a review. J Asian Nat Prod Res 2014;16:70–104.

Bhatti H.N., Zubair M., Rasool N., Hassan Z., Ahmad V.U. Microbial transformation of sesquiterpenoids. Nat Prod Commun 2009;4:1155–1168.

Carvalho C.C.C.R., Fonseca M.M.R. Biotransformation of terpenes. Biotechnol Adv 2006;24:134–42.

Carvalho T.C., Polizeli A.M., Turatti I.C.C., Severiano M.E., Carvalho C.E., Ambrósio S.R., et al. Screening of filamentous fungi to identify biocatalysts for lupeol biotransformation. Molecules 2010;15:6140–51.

Chatterjee T. Biotransformation of geraniol by *Rhodococcus* sp. strain GR3. Biotechnol Appl Biochem 2004;39:303–6.

Chaturvedi D., Goswami A., Saikia P.P., Barua N.C., Rao P.G. Artemisinin and its derivatives: a novel class of anti-malarial and anti-cancer agents. Chem Soc Rev 2010;39:435–54.

Chaturvedi D. Sesquiterpene lactones: structural diversity and their biological activities. In: Tiwari VK, Mishra BB, editors. Opportunity, challenge and scope of natural products in medicinal chemistry. Trivandrum: Research Signpost; 2011. p. 313–34.

Chauhan S.S., Sharma M., Chauhan P.M.S. Trioxaquines: hybrid molecules for the treatment of malaria. Drug News Perspect 2010;23:632–46.

Chen A.R.M., Reese P.B. Biotransformation of terpenes from *Stemodia maritima* by *Aspergillus niger* ATCC 9142. Phytochemistry 2002;59:57–62.

Chen L-X., Qiu F., Qu G-X., Yao X-S. Microbial transformation of neoandrographolide by *Aspergillus niger* (AS 3.739). J Asian Nat Prod Res 2007;9:493–499.

Chen L-X., Zhang H., Zhao Q., Yin S-Y., Zhang Z., Li T-X., Qiu F. Microbial transformation of curcumol by *Aspergillus niger*. Nat Prod Commun 2013;8:149–152.

Chen X-J., Archelas A., Furstoss R. Microbiological transformations. 27. The first examples for preparative-scale enantioselective or diastereoselective epoxide hydrolyses using microorganisms. An unequivocal access to all four bisabolol stereoisomers. J Org Chem 1993;58:5528–5532.

Chen Y., Zhang L., Qin B., Zhang X., Jia X., Wang X., Jin D., You S. An insight into the curdione biotransformation pathway by *Aspergillus niger*. Nat Prod Res 2014;28:454–460.

Cho W., Nam J-W., Kang H-J., Windono T., Seo E-K., Lee K-T. Zedoarondiol isolated from the rhizoma of *Curcuma heyneana* is involved in the inhibition of iNOS, COX-2 and pro-inflammatory cytokines via the downregulation of NF-κB pathway in LPS-stimulated murine macrophages. Int Immunopharmacol 2009;9:1049–1057.

Chou B-H, Yang L-M, Chang S-F, Hsu F-L, Lo C-H, Lin W-K, Wang L-H, Liu P-C, Lin S-J. Fungal transformation of isosteviol lactone and its biological evaluation for inhibiting the AP-1 transcription factor. Phytochemistry 2009;70:759–764.

Choudhary MI, Gondal HY, Abbaskhan A, Atta-ur-Rahman. Microbial transformations of gelomulide G: a member of the rare class of diterpene lactones. Chem Biodivers 2005;2:1401–1408.

Choudhary MI, Musharraf SG, Nawaz SA, Anjum S, Parvez M, Fun H-K, Atta-ur-Rahman. Microbial transformation of (−)-isolongifolol and butyrylcholinesterase inhibitory activity of transformed products. Bioorg Med Chem 2005;13:1939–1944.

Cimanga RK, Tona GL, Mesia GK, Kambu OK, Bakana DP, Kalenda PDT, et al. Bioassay-guided isolation of antimalarial triterpenoid acids from the leaves of *Morinda lucida*. Pharm Biol 2006;44:677–81.

Clark AM, Hufford CD. Microbial transformations of the sesquiterpene lactone costunolide. J Chem Soc Perkin Trans I 1979;3022–3028.

Clark RL. Effects of artemisinins on reticulocyte count and relationship to possible embryotoxicity in confirmed and unconfirmed malarial patients. Birth Defects Res Part A 2012;94:61–75.

Demyttenaere JCR, Adams A, Vanoverschelde J, De Kimpe N. Biotransformation of (*S*)-(+)-linalool by *Aspergillus niger*: an investigation of the culture conditions. J Agric Food Chem 2001;49:5895–5901.

Demyttenaere JCR, De Pooter HL. Biotransformation of citral and nerol by spores of *Penicillium digitatum*. Flavour Fragr J 1998;13:173–6.

Demyttenaere JCR, Herrera MdC, De Kimpe N. Biotransformation of geraniol, nerol and citral by sporulated surface cultures of *Aspergillus niger* and *Penicillium* sp. Phytochemistry 2000;55:363–373.

Demyttenaere JCR, Vanoverschelde J, De Kimpe N. Biotransformation of (*R*)-(+)- and (*S*)-(−)-citronellol by *Aspergillus* sp. and *Penicillium* sp., and the use of solid-phase microextraction for screening. J Chromatogr A 2004;1027:137–146.

Dewick PM. The mevalonate and deoxyxylulose phosphate pathways: terpenoids and steroids. In: Medicinal natural products: a biosynthetic approach, second edition. Chichester: Wiley; 2001. p. 167–289.

Divyashree MS, George J, Agrawal R. Biotransformation of terpenic substrates by resting cells of *Aspergillus niger* and

Pseudomonas putida isolates. J Food Sci Technol 2006;43:73–76.

Dondorp AM, Yeung S, White L, Nguon C, Day NPJ, Socheat D, et al. Artemisinin resistance: current status and scenarios for containment. Nature Rev Microbiol 2010;8:272–80.

Dovgilevich E.V., Modyanova L.V., Parshikov I.A., Terentyev P.B., Duduchava M.R. Microbial synthesis of *N*-oxide of 9 amino-1,2,3,4,5,6,7,8-octahydroacridine: All-Union Conference on Chemistry of *N*-containing heterocyclic compounds. Chernogolovka, Moscow region, Russia, 1991, part 1, P. 118.

Elmarakby SA, el-Feraly FS, Elsohly HN, Croom EM, Hufford CD. Microbial transformation studies on arteannuin B. J Nat Prod 1987;50:903–9.

Esmaeili A, Hashemi E. Biotransformation of myrcene by *Pseudomonas aeruginosa*. Chem Centr J 2011;5:26.

Esmaeili A, Moazami N, Rustaiyan A. Biotransformation of germacranolide from [*Onopordum leptolepis*] by *Aspergillus niger.* Pak J Pharm Sci 2012;25:155–159.

Esmaeili A, Tavassoli A. Microbial transformation of citral by *Penicillium* sp. Acta Biochim Pol 2010;57:265–8.

Fernández I, Robert A. Peroxide bond strength of antimalarial drugs containing an endoperoxide cycle. Relation with biological activity. Org Biomol Chem 2011;9:4098–107.

Fourneron JD, Archelas A, Furstoss R. Microbial transformations. 12. Regiospecific and asymmetric oxidation of the remote double bond of geraniol. J Org Chem 1989;54:4686–4689.

Fu S-B, Yang J-S, Cui J-L, Feng X, Sun D-A. Biotransformation of ursolic acid by an endophytic fungus from medicinal plant *Huperzia serrata*. Chem Pharm Bull 2011;59:1180–2.

Fujiwara M, Marumoto S, Yagi N, Miyazawa M. Biotransformation of turmerones by *Aspergillus niger*. J Nat Prod 2011;74:86–89

Furusawa M, Hashimoto T, Noma Y, Asakawa Y. Biotransformation of citrus aromatics nootkatone and valencene by microorganisms. Chem Pharm Bull 2005;53:1423–1429.

Furusawa M, Hashimoto T, Noma Y, Asakawa Y. Biotransformation of aristolane- and 2,3-secoaromadendrane-type sesquiterpenoids having a 1,1-dimethylcyclopropane ring by *Chlorella fusca* var. *vacuolata*, *Mucor* species, and *Aspergillus niger*. Chem Pharm Bull 2006;54:861–868.

Furusawa M, Hashimoto T, Noma Y, Asakawa Y. Isolation and structures of new cyclomyltaylane and *ent*-chamigrane-type sesquiterpenoids from the liverwort *Reboulia hemisphaerica* and their biotransformation by the fungus *Aspergillus niger*. Chem Pharm Bull 2006;54:996–1003.

García PA, Oliveira AB, Batista R. Occurrence, biological activities and synthesis of kaurane diterpenes and their glycosides. Molecules 2007;12:455–83.

García-Carnelli C, Rodríguez P, Heinzen H, Menéndez P. Influence of culture conditions on the biotransformation of (+)-limonene by *Aspergillus niger*. Z Naturforsch 2014;69c:61–67.

García-Granados A, Martínez A, Onorato ME, Arias JM. Microbial transformation of tetracyclic diterpenes: conversion of *ent*-kaurenones by *Aspergillus niger*. J Nat Prod 1986;49:126–132.

Gordi T, Lepist E-I. Artemisinin derivatives: toxic for laboratory animals, safe for humans? Toxicol Lett 2004;147:99–107.

Goswami A, Saikia PP, Barua NC, Bordoloi M, Yadav A, Bora TC, et al. Bio-transformation of artemisinin using soil microbe: direct C-acetoxylation of artemisinin at C-9 by

Penicillium simpli[ci]ssimum. Bioorg Med Chem Lett 2010;20:359–61.

Guo N, Zhao Y, Fang W-S. Biotransformation of 3-oxo-oleanolic acid by *Absidia glauca*. Planta Med 2010;76:1904–7.

Hamzah J, Skinner-Adams TS, Davis TME. In vitro antimalarial activity of retinoids and the influence of selective retinoic acid receptor antagonists. Acta Tropica 2003;87:345–53.

Haridy MSA, Ahmed AA, Doe M. Microbiological transformation of two labdane diterpenes, the main constituents of *Madia* species, by two fungi. Phytochemistry 2006;67:1455–1459.

Harinasuta T, Suntharasamai P, Viravan C. Chloroquine-resistant falciparum malaria in Thailand. Lancet 1965;286:657–60.

Hashimoto T, Noma Y, Asakawa Y. Biotransformation of terpenoids from the crude drugs and animal origin by microorganisms. Heterocycles 2001;54:529–559.

Hashimoto T, Noma Y, Gotoh Y, Tanaka M, Takaoka S, Asakawa Y. Biotransformation of (−)-maalioxide by *Aspergillus niger* and *Aspergillus cellulosae.* Heterocycles 2004;62:655–666.

Hashimoto T, Noma Y, Kato S, Tanaka M, Takaoka S, Asakawa Y. Biotransformation of hinesol isolated from the crude drug *Atractylodes lancea* by *Aspergillus niger* and *Aspergillus cellulosae.* Chem Pharm Bull 1999;47:716–717

Hayashi K-I, Asano K-I, Tanaka M, Takaoka D, Nozaki H. Biotransformation of shiromodiol diacetate, myli-4(15)-en-9-one and myliol by *Aspergillus niger*. Phytochemistry 1998;48:461–466.

Hebda C, Szykula J, Orpiszewski J, Fischer P. Novel metabolite structures from biotransformation of a sesquiterpenoid ketone by selected fungal strains. Biol Chem Hoppe-Seyler 1991;372:337–344.

Hien TT, White NJ. Qinghaosu. Lancet 1993;341:603–8.

Huang M, Lu J-J, Huang M-Q, Bao J-L, Chen X-P, Wang Y-T. Terpenoids: natural products for cancer therapy. Expert Opinion Investig Drugs 2012;21:1801–1818.

Iida M, Wakuri S, Mineki S, Nishitani K, Yamakawa K. Microbial hydroxylation of 11,13-dehydrosantonin by *Aspergillus niger*. J Ferment Bioeng 1993;76:296–299.

Jang H-J, Yoon S-H, Ryu H-K, Kim J-H, Wang C-L, Kim J-Y, et al. Retinoid production using metabolically engineered *Escherichia coli* with a two-phase culture system. Microb Cell Fact 2011;10:59.

Kain KC. Chemotherapy and prevention of drug-resistant malaria. Wildern Environ Med 1995;6:307–24.

Kang L-P, Zhang J, Yu H-S, Huang H-Z, Wang Y-Z, Ma B-P. One new triterpenoid from biotransformation product of glycyrrhizic acid. J Asian Nat Prod Res 2008;10:463–466.

Kaur K, Jain M, Kaur T, Jain R. Antimalarials from nature. Bioorg Med Chem 2009;17:3229–56.

Khalifa SI, Baker JK, Jung M, McChesney JD, Hufford CD. Microbial and mammalian metabolism studies on the semisynthetic antimalarial, deoxoartemisinin. Pharm Res 1995;12:1493–8.

Khamsan S, Liawruangrath B, Liawruangrath S, Teerawutkulrag A, Pyne SG, Garson MJ. Antimalarial, anticancer, antimicrobial activities and chemical constituents of essential oil from the aerial parts of *Cyperus kyllingia* Endl. Rec Nat Prod 2011;5:324–7.

Khasaeva F.M., Zakharchuk L.M., Netrusov A.I., Parshikov I.A. Biodegradation of pyridine by *Arthrobacter* sp. Natural Science. In: Young Scientist USA. 2014. V.1, P.50-52.

Khor GK, Uzir MH. *Saccharomyces cerevisiae*: a potential stereospecific reduction tool for biotransformation of mono- and sesquiterpenoids. Yeast 2011;28:93–107.

Klassen W. Introduction: development of the sterile insect technique for African malaria vectors. Malaria J 2009;8(Suppl 2):11.

Klayman DL. *Qinghaosu* (artemisinin): an antimalarial drug from China. Science 1985;228:1049–55.

Krings U, Hardebusch B, Albert D, Berger RG, Maróstica M, Pastore GM. Odor-active alcohols from the fungal transformation of α-farnesene. J Agric Food Chem 2006;54:9079–9084.

Krings U, Lehnert N, Fraatz MA, Hardebusch B, Zorn H, Berger RG. Autoxidation versus biotransformation of α-pinene to flavors with *Pleurotus sapidus*: regioselective hydroperoxidation of α-pinene and stereoselective dehydrogenation of verbenol. J Agric Food Chem 2009;57:9944–50.

Lahlou EH, Noma Y, Hashimoto T, Asakawa Y. Microbial transfomation of dehydropinguisenol by *Aspergillus* sp. Phytochemistry 2000;54:455–460.

Lamare V, Archelas A, Faure R, Cesario M, Pascard C, Furstoss R. Microbial transformations. 14. Regioselective hydroxylation of (1*R*)-caryolanol by *Aspergillus niger*. A reexamination of the ^{13}C NMR spectrum of caryolanol. Tetrahedron 1989;45:3761–3768.

Lamare V, Furstoss R. Bioconversion of sesquiterpenes. Tetrahedron 1990;46:4109–4132.

Lamm AS, Chen ARM, Reynolds WF, Reese PB. Fungal hydroxylation of (−)-santonin and its analogues. J Mol Catal B Enzym 2009;59:292–296.

Lee I-S, ElSohly HN, Croom EM, Hufford CD. Microbial metabolism studies of the antimalarial sesquiterpene artemisinin. J Nat Prod 1989;52:337–41.

Li Q-G, Peggins JO, Fleckenstein LL, Masonic K, Heiffer MH, Brewer TG. The pharmacokinetics and bioavailability of

dihydroartemisin, arteether, artemether, artesunic acid and artelinic acid in rats. J Pharm Pharmacol 1998;50:173–82.

Liao F. Discovery of artemisinin (qinghaosu). Molecules 2009;14:5362–6.

Liu J-H, Chen Y-G, Yu B-Y, Chen Y-J. A novel ketone derivative of artemisinin biotransformed by *Streptomyces griseus* ATCC 13273. Bioorg Med Chem Lett 2006;16:1909–12.

Liu X, Chen R, Xie D, Mei M, Zou J, Chen X, Dai J. Microbial transformations of taxadienes and the multi-drug resistant tumor reversal activities of the metabolites. Tetrahedron 2012;68:9539–9549.

Loyola LA, Bórquez J, Morales G, San-Martín A, Darias J, Flores N, et al. Mulinane-type diterpenoids from *Azorella compacta* display antiplasmodial activity. Phytochemistry 2004;65:1931–5.

Luo XD, Shen CC. The chemistry, pharmacology, and clinical applications of qinghaosu (artemisinin) and its derivatives. Med Res Rev 1987;7:29–52.

Madyastha KM, Gururaja TL. Utility of microbes in organic synthesis: selective transformation of acyclic isoprenoids by *Aspergillus niger*. Indian J Chem 1993;32B:609–614.

Madyastha KM, Krishna Murthy NSR. Regiospecific hydroxylation of acyclic monoterpene alcohols by *Aspergillus niger*. Tetrahedron Lett 1988;29:579–580.

Madyastha KM, Krishna Murthy NSR. Regiospecific hydroxylation of acyclic monoterpene alcohols by *Aspergillus niger*. Tetrahedron Lett 1988;29:579–580.

Mannan A, Ahmed I, Arshad W, Asim MF, Qureshi RA, Hussain I, et al. Survey of artemisinin production by diverse *Artemisia* species in northern Pakistan. Malaria J 2010;9:310.

Marquina S, Parra JL, González M, Zamilpa A, Escalante J, Trejo-Hernández MR, Álvarez L. Hydroxylation of the

diterpenes *ent*-kaur-16-en-19-oic and *ent*-beyer-15-en-19-oic acids by the fungus *Aspergillus niger*. Phytochemistry 2009;70:2017–2022.

Martin GDA, Durrant MC, Reese PB. A predictive cytochrome P450 monooxygenase functional model for generic hydroxylation by *Rhizopus oryzae* ATCC 11145. J Theor Comput Chem 2008;7:421–33.

Medeiros SF, Avery MA, Avery B, Leite SGF, Freitas ACC, Williamson JS. Biotransformation of 10-deoxoartemisinin to its 7β-hydroxy derivative by *Mucor ramannianus*. Biotechnol Lett 2002;24:937–41.

Medhi B, Patyar S, Rao RS, Byrav P, Prakash A. Pharmacokinetic and toxicological profile of artemisinin compounds: an update. Pharmacology 2009;84:323–32.

Menéndez P, García C, Rodríguez P, Moyna P, Heinzen H. Enzymatic systems involved in D-limonene biooxidation. Braz Arch Biol Technol 2002;45:111–114.

Meunier B, Robert A. Heme as trigger and target for trioxane-containing antimalarial drugs. Accounts Chem Res 2010;43:1444–51.

Miyazawa M, Nobata M, Hyakumachi M, Kameoka H. Biotransformation of (+)- and (−)-camphorquinones by fungi. Phytochemistry 1995a;39:569–573.

Miyazawa M, Tsuruno K, Kameoka H. Asymmetric reduction of karahanaenone with various microorganisms. Tetrahedron Asymmetry 1995b;6:2121–2122.

Miyazawa M, Yokote K, Kameoka H. Biotransformation of the monoterpenoid, rose oxide, by *Aspergillus niger*. Phytochemistry 1995;39:85–89.

Modyanova L.V., Duduchava M.R., Piskunkova N.F., Grishina G.V., Terentyev P.B., Parshikov I.A. Microbial transformations of piperideine and pyridine derivatives.

Chemistry of Heterocyclic Compounds, 1999, 35, N5, P. 580-586; Chemical Abstracts, v. 132, 166096.

Modyanova L.V., Duduchava M.R., Piskunkova N.F., Grishina G.V., Terent'ev P.B., Parshikov I.A. Microbiological Transformation of Piperidine and Pyridine Derivatives. Cheminform. 2010. V.31, N 12. http://dx.doi.org/10.1002/chin.200012047

Moura IC, Wunderlich G, Uhrig ML, Couto AS, Peres VJ, Katzin AM, et al. Limonene arests parasite development and inhibits isoprenylation of proteins in *Plasmodium falciparum*. Antimicrob Agents Chemother 2001;45:2553–8.

Muraleedharan KM, Avery MA. Progress in the development of peroxide-based anti-parasitic agents. Drug Discov Today 2009;14:793–803.

Muraleedharan, K. M.; Parshikov, I. A.; Bandyopadhyaya, A. K.; Desai, P. V.; Tekwani, B. L.; Avery, M. A. Artemisinin-based antimalarial drugs: Search for new derivatives with improved bioavailability and novel biological activities. Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003.

Musharraf SG, Najeeb A, Khan S, Pervez M, Ali RA, Choudhary MI. Microbial transformation of 5α-hydroxycaryophylla-4(12),8(13)-diene with *Macrophomina phaseolina*. J Mol Catal B Enzym 2010;66:156–60.

Nakase I, Lai H, Singh NP, Sasaki T. Anticancer properties of artemisinin derivatives and their targeted delivery by transferrin conjugation. Int J Pharmaceutics 2008;354:28–33.

Newman AA, editor. Chemistry of terpenes and terpenoids. London: Academic Press; 1972.

Ning L, Qu G, Ye M, Guo H, Bi K, Guo D. Cytotoxic biotransformed products from triptonide by *Aspergillus niger*. Planta Med 2003;69:804–808.

Nishimura H, Noma Y. Microbial transformation of monoterpenes: flavor and biological activity. In: Takeoka GR, Teranishi R, Williams PJ, Kobayashi A, editors. Biotechnology for improved foods and flavors. ACS Symp Ser 1996;637:173–187.

Noedl H, Se Y, Schaecher K, Smith BL, Socheat D, Fukuda MM. Evidence of artemisinin-resistant malaria in western Cambodia. N Engl J Med 2008;359:2619–20.

Nogueira CR, Lopes LMX. Antiplasmodial natural products. Molecules 2011;16:2146–90.

Noma Y, Asakawa Y. *Aspergillus* spp.: biotransformation of terpenoids and related compounds. In: Bajaj WPS, editor. Biotechnology in agriculture and forestry, vol. 33, medicinal and aromatic plants VIII. Berlin: Springer-Verlag; 1995. p.62–96.

Noma Y, Nonomura S. Conversion of (−)-carvone and (+)-carvone by a strain of *Aspergillus niger*. Agric Biol Chem 1974;38:741–744.

O'Brien C, Henrich PP, Passi N, Fidock DA. Recent clinical and molecular insights into emerging artemisinin resistance in *Plasmodium falciparum*. Curr Opin Infect Dis 2011;24:570–7.

Oliveira BH, Santos MC dos, Leal PC. Biotransformation of the diterpenoid, isosteviol, by *Aspergillus niger, Penicillium chrysogenum* and *Rhizopus arrhizus*. Phytochemistry 1999;51:737–741.

Oliveira BH, Strapasson RA. Biotransformation of the monoterpene, limonene, by *Fusarium verticill[i]oides*. Braz Arch Biol Technol 2000;43:11–4.

Omari AA, Gamble C, Garner P. Artemether-lumefantrine for uncomplicated malaria: a systematic review. Trop Med Int Health 2004;9:192–9.

Orabi K.Y., Galal AM, Ibrahim A-RS, El-Feraly FS, Khalifa SI, El-Sohly HN. Microbial metabolism of artemisitene. Phytochemistry 1999;51:257–61.

Pandey A, Soccol CR, Mitchell D. New developments in solid state fermentation: I-Bioprocesses and products. Process Biochem 2000;35:1153–69.

Parshikov I.A., Vorobyeva L.I., Modyanova L.V., Dovgilevich E.V., Terentyev P.B., Khofmann K. Strain of fungus *Cunninghamella verticillata* VKPM F-430 as a transformator for 1-benzoylpyrrolidine and 1-benzoylamino-3,7-dimethyloctadiene 2,6-hydroxylation. USSR Inventor's Certificate N 1 789 557, 1990a (Cl. C12P 17/12, C12N 1/14).

Parshikov I.A., Vorobyeva L.I., Modyanova L.V., Dovgilevich E.V., Terentyev P.B., Khofmann K. Strain of fungus *Beauveria bassiana* VKM F-3111D as a transformator for 1-benzoylpiperidine and 1-benzoylamino-3,7-dimethyloctadiene 2,6-hydroxylation, USSR Inventor's Certificate N 1 822 886, 1990b (Cl. C12P 17/12, C12N 1/14); Chemical Abstracts 1995, v. 122, 289065v.

Parshikov I.A., Modyanova L.V., Dovgilevich E.V., Terentyev P.B., Vorobyeva L.I., Grishina G.V. Microbial transformations of nitrogen heterocycles. III. Microbial synthesis of 1-benzoylpiperidine and 1-benzoylpyrrolidine hydroxy derivatives. Chemistry of Heterocyclic Compounds, 1992 , 28, N 2, P. 159-162; Chemical Abstracts 1993, v. 118, 6835c.

Parshikov I.A. The transformation of nitrogen-containing heterocyclic compounds by some fungi. Thesis of Ph.D. M.: Moscow University. 1993. - 121 p.

Parshikov I.A., Terentyev P.B., Modyanova L.V. Microbiological transformation in a series of nitrogen containing-heterocycles. (Review.) Chemistry of Heterocyclic

Compounds, 1994, 30, N11-12, 1308-1330; Chemical Abstracts 1995, v.122, 290732s.

Parshikov I.A., Terentyev P.B., Modyanova L.V., Duduchava M.R., Dovgilevich E.V., Butakoff K.A. Microbial transformation of 9-amino-1,2,3,4,5,6,7,8-octahydroacridine. Chemistry of Heterocyclic Compounds, 1994, 30, N5, 627-628; Chemical Abstracts 1995, v. 122, 290697j.

Parshikov I.A., Terentyev P.B., Modyanova L.V., Khofmann K., Khaufe G., Vogel M. Microbiological synthesis of 4-hydroxy-5-isopropyl-5-methoxy-2,5-dihydrofuran-2-one. Chemistry of Heterocyclic Compounds, 1994, 30, N5, 626; Chemical Abstracts 1995, v. 122, 290613d.

Parshikov I.A., Terentyev P.B., Piskunkova N.F., Gracheva G.A., Bulakhov G.A. Micobiological transformation of derivatives 4-phenyl-2-pyrrolidone by mycelial fungi. Chemistry of Heterocyclic Compounds, 1997, 33, N5, 523-526.

Parshikov I.A., Freeman J. P., Williams A. J., Moody J. D., Sutherland J. B. Biotransformation of *N*-acetylphenothiazine by fungi. Appl. Microbiol. Biotechnol., 1999a, v. 52, P. 553-557.

Parshikov I.A., Freeman J. P., Lay J. O. Jr., Beger R. D., Williams A. J., Sutherland J. B. Regioselective transformation of ciprofloxacin to *N*-acetylciprofloxacin by the fungus *Mucor ramannianus*. FEMS Microbiol. Lett., 1999b, v. 177, P. 131-135.

Parshikov I.A., Freeman J. P., Williams A. J., Moody J. D., Sutherland J. B. Microbiological transformation of *N*-acetylphenothiazine by fungi. 99th General Meeting of American Society for Microbiology, Chicago, Illinois, May 30 – June 3, 1999c, Q-258.

Parshikov I.A., Freeman J. P., Lay J. O. Jr., Beger R. D., Williams A. J., Sutherland J. B. Microbiological transformation of

enrofloxacin by the fungus *Mucor ramannianus*. Appl. Environ. Microbiol., 2000a, v. 66, No. 6. P. 2664-2667.

Parshikov I.A., Freeman J. P., Lay J. O. Jr., Moody J. D., Williams A. J., Beger R. D., Sutherland J. B. Metabolism of the veterinary fluoroquinolone sarafloxacin by the fungus *Mucor ramannianus*. 100th General Meeting of American Society for Microbiology, Los Angeles, California, May 21–25, 2000b, Q-182.

Parshikov I.A., Freeman J. P., Lay J. O. Jr., Moody J. D., Williams A. J., Sutherland J.B. Formation of unusual ciprofloxacin and norfloxacin conjugates by the fungus *Trichoderma viride*. 100th General Meeting of American Society for Microbiology, Los Angeles,California, May 21–25, 2000c, Q-181.

Parshikov I.A., Freeman J. P., Lay J. O. Jr., Beger R. D., Williams A. J., Sutherland J.B. Microbiological transformation of enrofloxacin by the fungus *Mucor ramannianus*. 100th General Meeting of American Society for Microbiology, Los Angeles, California, May 21-25, 2000d, Q-180.

Parshikov I.A., Freeman J. P., Lay J. O. Jr., Moody J. D., Williams A. J., Beger R. D., Sutherland J. B. Metabolism of the veterinary fluoroquinolone sarafloxacin by the fungus *Mucor ramannianus*. J. Ind. Microbiol. Biotechnol., 2001a, v. 26, P.140-144.

Parshikov I.A., Heinze T. M., Moody J. D., Freeman J. P., Williams A. J., Sutherland J. B. The fungus *Pestalotiopsis guepini* as a model for biotransformation of ciprofloxacin and norfloxacin. Appl. Microbiol. Biotechnol., 2001b, v. 56, No.3/4, P. 474-477.

Parshikov I.A., Heinze T. M., Moody J. D., Freeman J. P., Williams A. J., Sutherland J. B. The fungus *Pestalotiopsis guepini*. as a model for biotransformation of ciprofloxacin and norfloxacin. 101th General Meeting of American

Society for Microbiology, Orlando, Florida, May 20-24, 2001c, Q-191.

Parshikov I.A., Heinze T. M., Moody J. D., Freeman J. P., Williams A. J., Sutherland J. B. Regioselective formation of *N*-oxides from enrofloxacin and ofloxacin by the fungus *Rhizoctonia* sp. 101th General Meeting of American Society for Microbiology, Orlando, Florida, May 20-24, 2001d, Q-192.

Parshikov I.A., Heinze T. M., Williams A. J., Moody J. D., Freeman J. P., Sutherland J. B. Biotransformation of the antibacterial agent cinoxacin by the fungus *Beauveria bassiana.* FEMS Microbiol. Lett., 2002a, v.214, P.133-136.

Parshikov I.A., Moody J. D., Freeman J. P., Lay J. O. Jr., Williams A. J., Heinze T. M., Sutherland J. B. Formation of conjugates from ciprofloxacin and norfloxacin in cultures of *Trichoderma viride*. Mycologia, 2002b, v.94, P.1-5.

Parshikov I.A., Heinze T. M., Williams A. J., Moody J. D., Freeman J. P., Sutherland J. B. Biotransformation of the antibacterial agent cinoxacin by the fungus *Beauveria bassiana*. 102th General Meeting of American Society for Microbiology, Salt Lake City, Utah, May 19-23, 2002c, Q-78.

Parshikov I.A., Heinze T. M., Moody J. D., Williamson J. S. Microbial transformation of the Antimalarial drug Primaquine (8-Aminoquinoline) by *Beauveria bassiana.* 102th General Meeting of American Society for Microbiology, Salt Lake City, Utah, May 19-23, 2002d, Q-83.

Parshikov I.A., Muralieedharan K. M., Avery M. A., Williamson J. S. Novel microbial transformations of artemisinin and 10-deoxoartemisinin. 103th General Meeting of American Society for Microbiology, Washington, D.C., Maryland, May 18-22, 2003, Q-129.

Parshikov I.A., Muraleedharan KM, Avery MA, Williamson JS. Transformation of artemisinin by *Cunninghamella elegans*. Appl Microbiol Biotechnol 2004a;64:782–6.

Parshikov I.A., Miriyala B., Muralieedharan K. M., Avery M. A., Williamson J. S. Fungal transformations of artemisinin. 104th General Meeting of American Society for Microbiology, New Orleans, LA, May 23-27, 2004b, Q-286.

Parshikov I.A., Muraleedharan KM, Miriyala B, Avery MA, Williamson JS. Hydroxylation of 10-deoxoartemisinin by *Cunninghamella elegans*. J Nat Prod 2004c;67:1595–7.

Parshikov I.A., Miriyala B, Avery MA, Williamson JS. Hydroxylation of 10-deoxoartemisinin to 15-hydroxy-10-deoxoartemisinin by *Aspergillus niger*. Biotechnol Lett 2004d;26:607–10.

Parshikov I.A., Miriyala B., Muraleedharan KM, Illendula A, Avery MA, Williamson JS. Biocatalysis of the antimalarial artemisinin by *Mucor ramannianus* strains. Pharm Biol 2005a;43:579–82.

Parshikov I.A., Miriyala B., Avery M. A., Williamson J. S. Transformation of Artemisinin by Different Strains of *Mucor ramannianus*. 105th General Meeting of American Society for Microbiology, Atlanta, GA, June 5-9, 2005b, Q-198.

Parshikov I.A., Miriyala B., Avery M. A., Williamson J. S. Transformations of artemisinin to 5-hydroxyartemisinin. Abstracts of Papers, 229th ACS National Meeting, San Diego, CA, United States, March 13-17, 2005c, #381.

Parshikov I.A., Miriyala B, Muraleedharan KM, Avery MA, Williamson JS. Microbial transformation of artemisinin to 5-hydroxyartemisinin by *Eurotium amstelodami* and *Aspergillus niger*. J Ind Microbiol Biotechnol 2006a;33:349–52.

Parshikov I.A., Miriyala B., Hernandez-Luna C.E., Avery M. A., Williamson J. S. Regiocelective Transformation of Artemisinin by White-Rot Basidiomycetes. 106th General Meeting of American Society for Microbiology, Orlando, FL, May 21-25, 2006b, Q-293.

Parshikov I.A., Terent'ev P.B., Modyanova L.V. Microbiological Transformations of Nitrogen-Containing Heterocycles. Cheminform. 2010, v.26, N 30, http://dx.doi.org/10.1002/chin.199530292

Parshikov I.A., Terentyev P.B., Modyanova L.V., Khofmann K., Khaufe G., Vogel M. Microbiological Synthesis of 4-Hydroxy-5-isopropyl-5-methoxy-2-oxo-2,5- dihydrofuran. Cheminform. 2010a, v.26, N 10, http://dx.doi.org/10.1002/chin.199510251

Parshikov I.A., Modyanova L.V., Dovgilevich E.V., Terentyev P.B., Vorobyeva L.I., Grishina G.V. Microbiological Transformations of Nitrogen-Containing Heterocyclic Compounds. Part 3. Microbiological Synthesis of Hydroxy Derivatives of 1-Benzoylpiperidine and 1-Benzoylpyrrolidine. Cheminform. 2010b, v.24, N 38, http://dx.doi.org/10.1002/chin.199338068

Parshikov I.A., Terentyev P.B., Modyanova L.V., Duduchava M.R., Dovgilevich E.V., Butakoff K.A. Microbiological Transformation of 9-amino-1,2,3,4,5,6,7,8-octahydroacridine. Cheminform. 2010c, v.26, N 10, http://dx.doi.org/10.1002/chin.199510042

Parshikov I.A., Terent'ev P.B., Modyanova L.V. Microbiological Transformations of Nitrogen-Containing Heterocycles. Cheminform. 2010d, v.26, N 30, http://dx.doi.org/10.1002/chin.199530292

Parshikov I.A., Terent'ev P.B., Piskunkova N.F., Gracheva R.A., Bulakhov G.A. Microbial Transformation of 4-Phenylpyrrolidone-2 Derivatives by Micellar Fungi.

Cheminform. 2010e. V. 29. N 1. http://dx.doi.org/10.1002/chin.199801032

Parshikov I.A., Zaraisky E.I. Biotechnology and nanobiotechnology. Volume II. Approaches to the creation of diagnostics and medicines of a new generation to fight malaria (in Russian). – M.: Editus, 2014. − 222 p. (ISBN 978-5-00058-066-0) doi: 10.17686/sced_rusnauka_2014-1382

Parshikov I.A. Microbial conversions of nitrogenous heterocycles. M.: Editus, 2015. - 130 p. (ISBN 978-5-00058-198-8)

Pertino M., Schmeda-Hirschmann G., Santos L.S., Rodríguez J.A., Theoduloz C. Biotransformation of jatrophone by *Aspergillus niger*. Z Naturforsch B 2007;62:275–279.

Posner GH, D'Angelo J, O'Neill PM, Mercer A. Anticancer activity of artemisinin-derived trioxanes. Expert Opin Ther Patents 2006;16:1665–72.

Prema BR, Bhattacharyya PK. 1962. Microbiological transformations of terpenes. III. Transformations of some mono- and sesqui-terpenes. Appl Microbiol 1962;10:529–531.

Price RN, Douglas NM, Anstey NM, von Seidlein L. *Plasmodium vivax* treatments: what are we looking for? Curr Opin Infect Dis 2011;24:578–85.

Ramirez HE, Cortes MM, Agosin E. Bioconversion of drimenol into 3β-hydroxydrimanes by *Aspergillus niger*. Effect of culture additives. J Nat Prod 1993;56:762–764.

Rocha D, Takahashi JA, Boaventura MAD. Di- and tri-hydroxylated kaurane derivatives from microbial transformation of *ent*-kaur-16-en-19-ol by *Cephalosporium aphidicola* and their allelopathic activity on *Lactuca sativa* (lettuce). Ecl Quím, São Paulo. 2009;34:57–62.

Rosazza JPN, Steffens JJ, Sariaslani FS, Goswami A, Beale JM, Reeg S, Chapman R. Microbial hydroxylation of 1,4-cineole. Appl Environ Microbiol 1987;53:2482–2486.

Rustaiyan A, Nahrevanian H, Kazemi M. Isolation of artediffusin (tehranolide) as a new antimalarial agent. Asian J Chem 2011;23:4810–4.

Sá MS, Costa JFO, Krettli AU, Zalis MG, Maia GLA, Sette IMF, et al. Antimalarial activity of betulinic acid and derivatives in vitro against *Plasmodium falciparum* and in vivo in *P. berghei*-infected mice. Parasitol Res 2009;105:275-9.

Schaneberg BT, Khan IA. Comparison of extraction methods for marker compounds in the essential oil of lemon grass by GC. J Agric Food Chem 2002;50:1345-9.

Schmeda-Hirschmann G, Aranda C, Kurina M, Rodríguez JA, Theoduloz C. Biotransformations of imbricatolic acid by *Aspergillus niger* and *Rhizopus nigricans* cultures. Molecules 2007;12:1092–1100.

Schmeda-Hirschmann G, Astudillo L, Palenzuela JA. Biotransformation of solidagenone by *Alternaria alternata, Aspergillus niger* and *Curvularia lunata* cultures. World J Microbiol Biotechnol 2004;20:93–97.

Severiano ME, Simao MR, Porto TS, Martins CHG, Veneziani RCS, Furtado NAJC, et al. Anticariogenic properties of *ent*-pimarane diterpenes obtained by microbial transformation. Molecules 2010;15:8553–66.

Severiano ME, Simão MR, Ramos HP, Parreira RLT, Arakawa NS, Said S, Furtado NAJC, Oliveira DCR de, Gregório LE, Tirapelli CR, Veneziani RCS, Ambrósio SR. Biotransformation of *ent*-pimaradienoic acid by cell cultures of *Aspergillus niger*. Bioorg Med Chem 2013;21:5870–5875.

Shen Y-C, Lo K-L, Lin C-L, Chakraborty R. Microbial transformation of baccatin VI and 1β-hydroxybaccatin I by

Aspergillus niger. Bioorg Med Chem Lett 2003;13:4493–4496.

Silva E.O., Carvalho T.C., Parshikov I.A., Santos R.A., Emery F.S., Furtado N.A.J.C. Cytotoxicity of lapachol metabolites produced by probiotics. Lett. Appl. Microbiol. 2014. V.59. N 1. P. 108–114.

Simeó Y, Sinisterra JV. Biotransformation of terpenoids: a green alternative for producing molecules with pharmacological activity. Mini-Rev Org Chem 2009;6:128–34.

Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI. The global distribution of clinical episodes of *Plasmodium falciparum* malaria. Nature 2005;434:214–7.

Srivastava S, Luqman S, Fatima A, Darokar MP, Negi AS, Kumar JK, et al. Biotransformation of artemisinin mediated through fungal strains for obtaining derivatives with novel activities. Sci Pharm 2009;77:87–95.

Suksamrarn S, Panseeta P, Kunchanawatta S, Distaporn T, Ruktasing S, Suksamrarn A. Ceanothane- and lupane-type triterpenes with antiplasmodial and antimycobacterial activities from *Ziziphus cambodiana*. Chem Pharm Bull 2006;54:535–7.

Sutherland J.B., Freeman J. P., Heinze T. M., Moody J. D., Williams A. J., Parshikov I.A., Zhang D. Oxidation of phenothiazine and phenoxazine by *Cunninghamella elegans*, Xenobiotica, 2001, v. 31, P.799-809.

Sutherland JB. Degradation of hydrocarbons by yeasts and filamentous fungi. In: Arora DK, editor. *Fungal Biotechnology in Agricultural, Food, and Environmental Applications*. New York: Marcel Dekker; 2004. p. 443–55.

Tabenkin B, LeMahieu RA, Berger J, Kierstead RW. Microbiological hydroxylation of cinerone to cinerolone. Appl Microbiol 1969;17:714–717.

Tatineni R, Doddapaneni KK, Dalavayi S, Kulkarni SM, Mangamoori LN. *Microbacterium trichotecenolyticum* enzyme mediated transformation of arteannuin B to artemisinin. Proc Biochem 2006;41:2464–7.

Tchoumbougnang F., Zollo P.H.A., Dagne E., Mekonnen Y. In vivo antimalarial activity of essential oils from *Cymbopogon citratus* and *Ocimum gratissimum* on mice infected with *Plasmodium berghei*. Planta Med 2005;71:20–3.

Terentyev P. B., Parshikov I.A., Dovgilevich E. V., Vorobyeva L. I., Modyanova L. V., Grishina G. V. Microbiological synthesis of isomeric hydroxy-1-benzoylpiperidines: Conference on "Chemistry of physiologically active compounds". Chernogolovka, Moscow region, Russia, November 13-15, 1989. P. 226.

Terentyev P.B., Parshikov I.A., Grishina G.V., Piskunkova N.F., Chumakov T.I., Bulakhov G.A. Hydroxylation of double bond in 1-benzyl-3-methylpiperideine by mycelial fungi. Chemistry of Heterocyclic Compounds, 1997, 33, N5,619-620.

Terentyev P.B., Parshikov I.A., Grishina G.V., Piskunkova N.F., Chumakov T.I., Bulakhov G.A. Hydroxylation of the Multiple Bond in 1-Benzyl-3-methyl-Δ3-piperideine by Micellar Fungi. Cheminform. 2010. V.29. N 1. http://dx.doi.org/10.1002/chin.199801033

Thongnest S., Mahidol C., Sutthivaiyakit S., Ruchirawat S. Oxygenated pimarane diterpenes from *Kaempferia marginata*. J Nat Prod 2005;68:1632–6.

Titanji V.P.K., Zofou D., Ngemenya M.N. The antimalarial potential of medicinal plants used for the treatment of malaria in Cameroonian folk medicine. Afr J Trad Compl Alt Med 2008;5:302–21.

Toniazzo G., Oliveira D., Dariva C., Oestreicher E.G., Antunes O.A.C. Biotransformation of (−)-β-pinene by *Aspergillus*

niger ATCC 9642. Appl Biochem Biotechnol 2005;121:837–844.

Uenojo M., Pastore G.M. β-Carotene biotransformation to obtain aroma compounds. Ciênc Tecnol Aliment, Campinas 2010;30:822–7.

Velankar H.R., Heble M.R. Biotransformation of (L)-citronellal to (L)-citronellol by free and immobilized *Rhodotorula minuta*. Electron J Biotechnol 2003;6:90–103.

Venkateswarlu Y., Ramesh P., Reddy P.S., Jamil K. Microbial transformation of $\Delta^{9(15)}$-africanene. Phytochemistry 1999;52;1275–1277.

Vroman J.A., Alvim-Gaston M., Avery M.A. Current progress in the chemistry, medicinal chemistry and drug design of artemisinin based antimalarials. Curr Pharm Des 1999;5:101–38.

Walsh J.J., Coughlan D., Heneghan N., Gaynor C., Bell A. A novel artemisinin–quinine hybrid with potent antimalarial activity. Bioorg Med Chem Lett 2007;17:3599–602.

Wie H.J., Zhao H.L., Chang J.H., Kim Y.S., Hwang I.K, Ji G.E.. Enzymatic modification of saponins from *Platycodon grandiflorus* with *Aspergillus niger*. J Agric Food Chem 2007;55:8908–8913.

Williams A.J., Parshikov I.A., Moody J.D., Heinze T.M., Freeman J.P., Sutherland J.B. The metabolism of two antibacterial agents, norfloxacin and sarafloxacin by the saprobic fungus *Trichoderma viride*. during growth on the rise hulls. 101th General Meeting of American Society for Microbiology, Orlando, Florida, May 20-24, 2001, Q-195.

Williams A.J., Parshikov I.A., Moody J.D., Heinze T. M., Sutherland J. B. Fungal transformation of the antimicrobial agent during growth on poultry-litter materials. J. Appl. Poultry Res., 2004, v. 13, N 2, P. 235-240.

Wongsrichanalai C., Meshnick S.R. Declining artesunate-mefloquine efficacy against falciparum malaria on the Cambodia-Thailand border. Emerg Infect Dis 2008;14:716–9.

Yamazaki Y., Hayashi Y., Hori N., Mikami Y.. Microbial conversion of β-myrcene by *Aspergillus niger.* Agric Biol Chem 1988;52:2921–2922.

Yang L-M., Chang S-F., Lin W-K., Chou B-H., Wang L-H., Liu P-C., Lin S-J. Oxygenated compounds from the bioconversion of isostevic acid and their inhibition of TNF-α and COX-2 expressions in LPS-stimulated RAW 264.7 cells. Phytochemistry 2012;75:90–98.

Zhan J., Guo H., Dai J., Zhang Y., Guo D. Microbial transformations of artemisinin by *Cunninghamella echinulata* and *Aspergillus niger*. Tetrahedron Lett 2002a;43:4519–21.

Zhan J-X., Zhang Y-X., Guo H-Z., Han J., Ning L-L., Guo D-A. Microbial metabolism of artemisinin by *Mucor polymorphosporus* and *Aspergillus niger*. J Nat Prod 2002b;65:1693–5.

Zhang J., Cheng Z-H., Yu B-Y., Cordell G.A., Qiu S.X.. Novel biotransformation of pentacyclic triterpenoid acids by *Nocardia* sp. NRRL 5646. Tetrahedron Lett 2005;46:2337–2340.

Zhang X-M., Archelas A., Furstoss R. Microbial transformations. 24. Synthesis of chiral building blocks via stereoselective dihydroxylation of citronellol enantiomers. Tetrahedron Asymmetry 1992;3:1373–1376.

CONTENTS

Introduction	3
1. Transformation of monoterpenoids	6
2. Transformation of sesquiterpenoids	23
3. Transformation of diterpenoids	46
4. Transformation of triterpenoids	60
5. Transformation of tetraterpenoids	66
Conclusion	68
References	72

Igor A. Parshikov

Monography

Microbial conversions of terpenoids

Ответственный редактор Калюжин О.В.
Художественный редактор Калюжин О.В.
Компьютерная верстка Паршиков И.А.

Отпечатано в ООО «Эдитус»
129515, г. Москва, ул. Академика Королева, 13
8 (800) 775-30-87
www.editus.ru

Подписано в печать 26.05.15.
Формат 148x210. Гарнитура Таймс. Печ.л. 12,5.
Печать цифровая. Бумага офсетная.
Тираж 36 экз. Заказ № 123911

ISBN 978-5-00058-223-7

Printed at Publishing House Editus.Ltd.
13 Akademik Korolev Str., Moscow, Russia 129515
WWW: http://www.editus.ru/

ISBN 978-5-00058-223-7
www.editus.ru
9 785000 582237 >