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MINI-REVIEW

Biotransformations of organic compounds mediated by cultures of *Aspergillus niger*

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Abstract Many different organic compounds may be converted by microbial biotransformation to high-value products for the chemical and pharmaceutical industries. This review summarizes the use of strains of *Aspergillus niger*, a well-known filamentous fungus used in numerous biotechnological processes, for biochemical transformations of organic compounds. The substrates transformed include monocyclic, bicyclic, and polycyclic aromatic hydrocarbons; azaarenes, epoxides, chlorinated hydrocarbons, and other aliphatic and aromatic compounds. The types of reactions performed by *A. niger*, although not unique to this species, are extremely diverse. They include hydroxylation, oxidation of various functional groups, reduction of double bonds, demethylation, sulfation, epoxide hydrolysis, dechlorination, ring cleavage, and conjugation. Some of the products may be useful as new investigational drugs or chemical intermediates.

Keywords Arenes · *Aspergillus niger* · Biotransformation · Hydrocarbons · Organic compounds

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Introduction

Filamentous fungi are used in numerous biotechnological processes to produce fermented foods, flavorings, and organic acids, as well as enzymes, including phytases, glucoamylases, xylanases, proteases, lipases, α-galactosidases, polygalacturonases, and pectinases (Krishna 2005; Couto and Sanromán 2006; Pandey et al. 2010). One of these fungi, *Aspergillus niger*, has long been used in many processes, including the production of citric acid, other organic acids, and enzymes from natural substrates (Schuster et al. 2002; Betiku and Adesina 2013).

Some of the same strains of fungi that produce citric acid and industrial enzymes have also been used in biotransformations to produce pharmaceuticals and other higher-value products (Borges et al. 2009; Parshikov et al. 2014). The selection of a strain, however, is critical. For instance, different strains of *A. niger* convert ferulic acid either to vanillic acid, which can be further converted to the flavoring compound vanillin, or to 4-vinylguaiacol, a compound that is in much less demand (Zheng et al. 2007; Baqueiro-Peña et al. 2010). Unlike most of the steps in chemical syntheses, fungal biotransformations may be enantioselective. An example is the reduction of ethyl 3-oxohexanoate to the enantiomer ethyl 3-(*R*)-hydroxyhexanoate, with over 99 % enantiomeric excess, by a strain of *A. niger* (Ramos et al. 2011). The chiral product can be used in the synthesis of phytotoxic compounds and anticancer drugs.

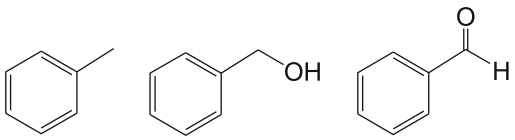
In this review, we will discuss the use of cultures of various strains of *A. niger* to biotransform aromatic hydrocarbons, their derivatives, and other aliphatic and aromatic organic compounds, including heterocycles, epoxides, and chlorinated compounds. Terpenoids, steroids, and flavonoids will not be included because their biotransformations have been reviewed recently

(Parshikov and Sutherland 2014; 2015). Details of the specific conditions used for growth of the cultures and biotransformation of the substrates may be obtained from the original articles cited.

Transformation of aromatic hydrocarbons (arenes) and their derivatives

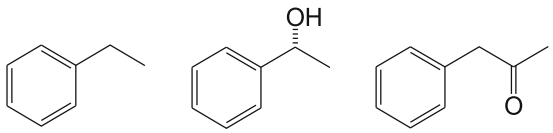
Monocyclic arenes and derivatives

The commonly used solvent toluene (**I**) is oxidized at the methyl group by *A. niger* MTCC-404 to produce 56 % benzyl alcohol (**II**) and 40 % benzaldehyde (**III**) (Yadav et al. 2011). Both products have industrial uses as precursors to various products, including flavors, fragrances, pharmaceuticals, and dyes.



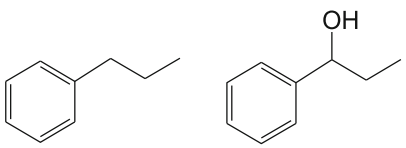
I **II** **III**

Ethylbenzene (**IV**), a precursor in the manufacture of styrene, is hydroxylated stereoselectively by *A. niger* MTCC-404 to 72 % (*R*)-1-phenylethanol (**V**), a valuable intermediate for the synthesis of chiral compounds, in a 99 % enantiomeric excess and 28 % phenylacetone (**VI**) (Yadav et al. 2011), which is also used in chemical synthesis.



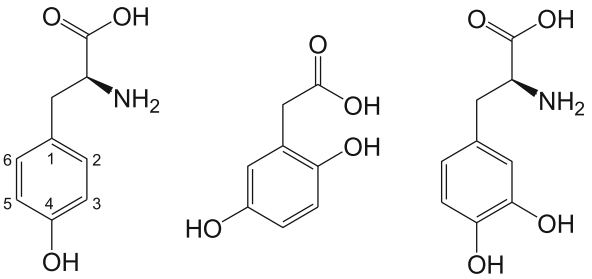
IV **V** **VI**

n-Propylbenzene (**VII**) is oxidized by *A. niger* MTCC-404 to an unspecified enantiomer of 1-phenyl-1-propanol (**VIII**, yield 47 %) (Yadav et al. 2011).



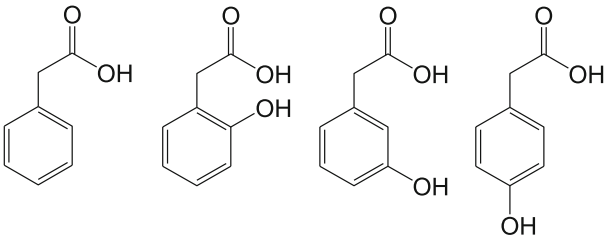
VII **VIII**

One strain of *A. niger* converts the amino acid L-tyrosine (**IX**) via several steps to homogentisic acid (**X**) (Utkin 1950). Another strain, *A. niger* GCBT-8, hydroxylates L-tyrosine at the C-3 position to produce 3,4-dihydroxy-L-phenylalanine (L-dopa, **XI**), a drug used for the treatment of Parkinson's disease (Ali and Haq 2010).



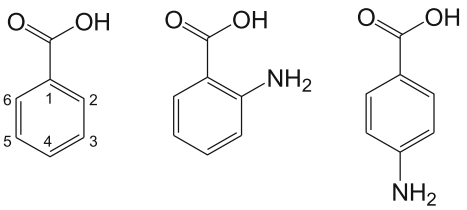
IX **X** **XI**

Phenylacetic acid (**XII**) is metabolized by different strains of *A. niger* to 2-, 3-, and 4-hydroxyphenylacetic acid (**XIII**, **XIV**, and **XV**, respectively) as well as homogentisic acid (**X**) (Kluyver and van Zijp 1951; Bocks 1967b).



XII **XIII** **XIV** **XV**

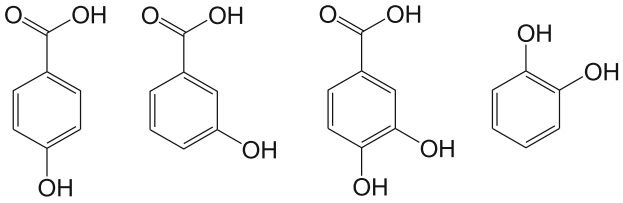
The carboxyl groups of benzoic acid (**XVI**), *o*-aminobenzoic acid (anthranilic acid, **XVII**), and *p*-aminobenzoic acid (**XVIII**) are reduced by *A. niger* Wisc 72-4 to produce the corresponding benzaldehydes (Raman and Shanmugasundaram 1962).



XVI **XVII** **XVIII**

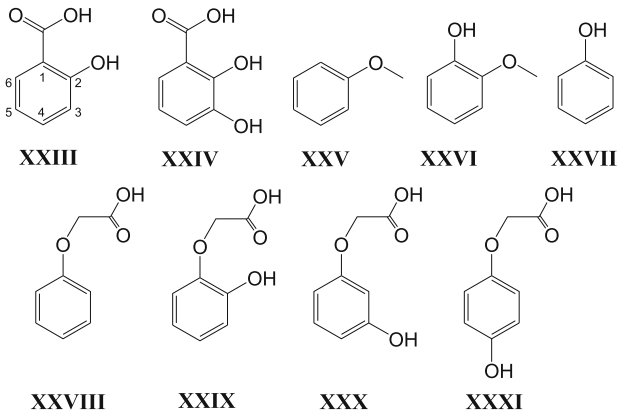
Other strains of *A. niger*, including Wild, 11394, Mulder, and A_2, hydroxylate the ring of benzoic acid (**XVI**) to form *p*-hydroxybenzoic acid (**XIX**) and *m*-hydroxybenzoic acid (**XX**). Both of these metabolites may be hydroxylated to protocatechuic acid (**XXI**),

which then may be decarboxylated to catechol (**XXII**) (Bocks 1967b).



XIX **XX** **XXI** **XXII**

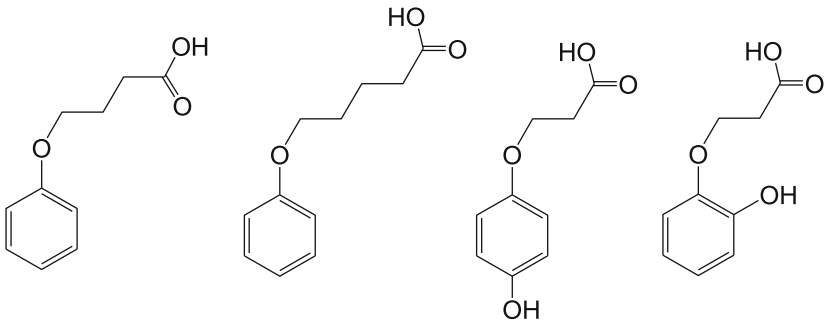
The same strains of *A. niger* also hydroxylate salicylic acid (**XXIII**) to 2,3-dihydroxybenzoic acid (**XXIV**); anisole (**XXV**) to guaiacol (**XXVI**) and phenol (**XXVII**); and phenoxyacetic acid (**XXVIII**) to *o*-hydroxyphenoxyacetic acid (**XXIX**) with small amounts of *m*-hydroxyphenoxyacetic acid (**XXX**) and *p*-hydroxyphenoxyacetic acid (**XXXI**) (Woodcock 1964; Bocks 1967b).



XXIII **XXIV** **XXV** **XXVI** **XXVII**

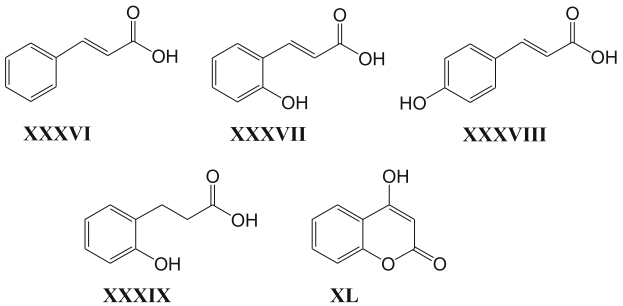
XXVIII **XXIX** **XXX** **XXXI**

Using hydroxylation and β-oxidation, *A. niger* strains convert 4-phenoxy-*n*-butyric acid (**XXXII**) to *p*-hydroxyphenoxyacetic acid (**XXXI**); and 5-phenoxy-*n*-valeric acid (**XXXIII**) to mostly *p*-hydroxyphenoxypropionic acid (**XXXIV**) with some *o*-hydroxyphenoxypropionic acid (**XXXV**) (Woodcock 1964).



XXXII **XXXIII** **XXXIV** **XXXV**

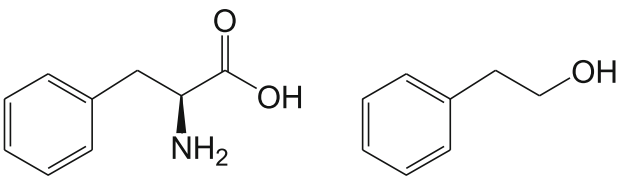
trans-Cinnamic acid (**XXXVI**) is metabolized by *A. niger* strain Mulder to small quantities of *o*-coumaric acid (**XXXVII**) and *p*-coumaric acid (**XXXVIII**), *p*-hydroxybenzoic acid (**XIX**), and melilotic acid (3-(2-hydroxyphenyl)propanoic acid, **XXXIX**). *o*-Coumaric acid (**XXXVII**) is metabolized to 4-hydroxycoumarin (**XL**) (Bocks 1967a).



XXXVI **XXXVII** **XXXVIII**

XXXIX **XL**

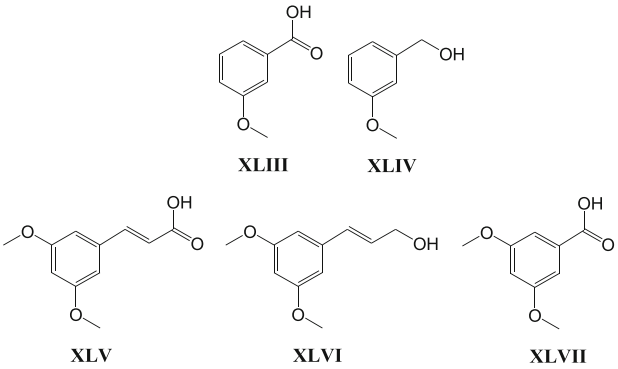
The amino acid L-phenylalanine (**XLI**) is metabolized by *A. niger* CMICC 298302 to a single aromatic product, the valuable fragrance compound 2-phenylethanol (phenethyl alcohol, **XLII**) (Lomascolo et al. 2001).



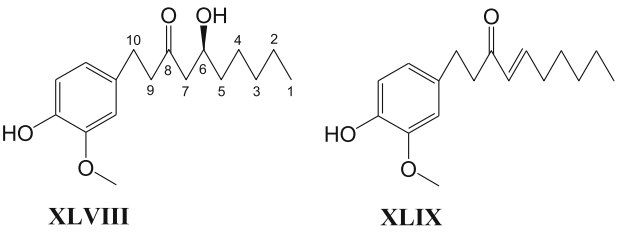
XLI **XLII**

The carboxyl group of 3-methoxybenzoic acid (*m*-anisic acid, **XLIII**) is reduced by *A. niger* ATCC 9142, producing 3-methoxybenzyl alcohol (**XLIV**); and that of 3,5-dimethoxycinnamic acid (**XLV**) is also reduced, producing 3,5-dimethoxycinnamyl alcohol (**XLVI**) (Arfmann and Abraham 1993). Additional products may result from the demethylation of 3-methoxybenzoic acid to produce *p*-hydroxybenzoic acid (**XIX**) or from β-oxidation

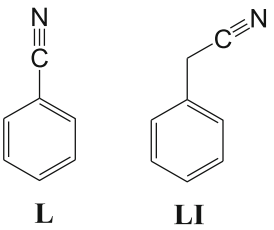
of the side chain of 3,5-dimethoxycinnamic acid to produce 3,5-dimethoxybenzoic acid (**XLVII**) (Arfmann and Abraham 1993).



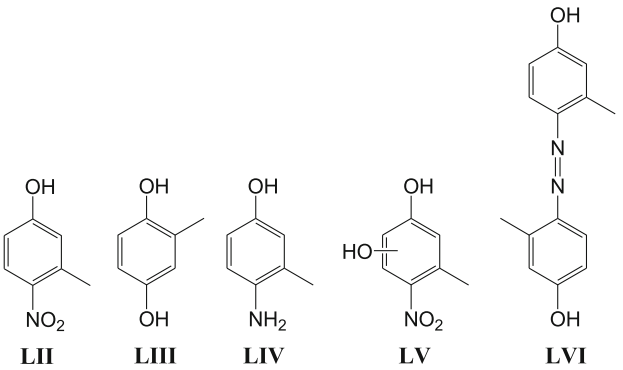
The principal flavoring component of ginger, 6-gingerol (**XLVIII**), is hydroxylated by a strain of *A. niger* in either the 1- or 2-position of the side chain to form two isomeric derivatives (Takahashi et al. 1993). Another component of ginger, 6-shogaol (**XLIX**), is hydroxylated in the 1-position of the side chain and reduced at the 6,7-double bond, and then reduced at the 8-carbonyl group. The ring is not metabolized in either compound (Takahashi et al. 1993).



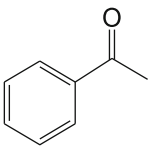
Benzonitrile (**L**) and 2-phenylacetonitrile (benzyl cyanide, **LI**), which are used as precursors in chemical synthesis, are metabolized by *A. niger* K10 to benzoic acid (**XVI**) and phenylacetic acid (**XII**), respectively (Šnajdrová et al. 2004).



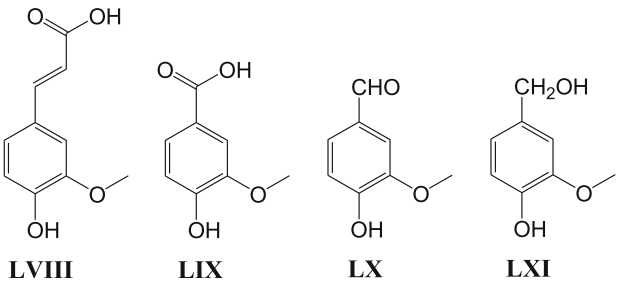
Transformation of 3-methyl-4-nitrophenol (**LII**), an environmental pollutant that inhibits corticosterone production, by *A. niger* VKM F-1119 produces 2-methyl-1,4-benzenediol (**LIII**), 4-amino-3-methylphenol (**LIV**), which is used in hair dyes, two isomers of hydroxy-3-methyl-4-nitrophenol (**LV**), and 4,4′-azo-3-methylphenol (**LVI**) (Kanaly et al. 2005).



Acetophenone (**LVII**), a ketone used to synthesize fragrances, is reduced stereoselectively by *A. niger* strain EBK-9 and others to produce (*R*)-1-phenylethanol (**V**) with up to an 87 % enantiomeric excess. Some substituted acetophenones are converted with higher stereoselectivity (Kurbanoglu et al. 2007).

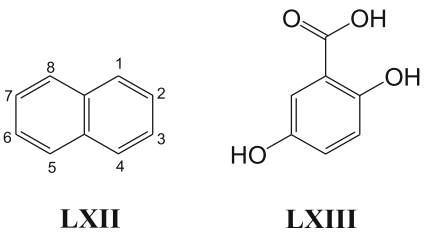


Ferulic acid (**LVIII**) is converted by *A. niger* CGMCC 0774 to vanillic acid (**LIX**), which can be reduced to the flavoring compound vanillin (**LX**) (Zheng et al. 2007). Transformation of vanillin by *A. niger* GC-4 reduces it to vanillyl alcohol (**LXI**), an antioxidant, with a yield of 12 % (Shahwar et al. 2011).

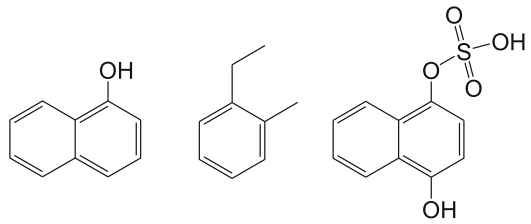


Bicyclic arenes and derivatives

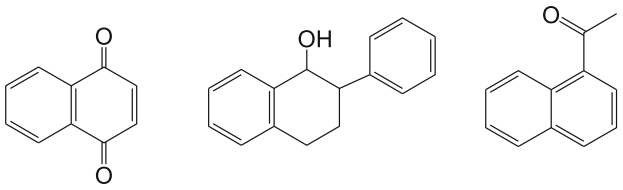
Naphthalene (**LXII**) is reportedly metabolized by *A. niger* in several steps ending in gentisic acid (**LXIII**) (Yogambal and Karegoudar 1997).



α-Naphthol (**LXIV**), a toxic insecticide degradation product, is metabolized by *A. niger* PTCC 5011 in 5 days. The metabolites are reported to be 1-ethyl-2-methylbenzene (**LXV**, yield 41 %), 4-hydroxy-1-naphthyl sulfate (**LXVI**), 1,4-naphthoquinone (**LXVII**), 2-phenyl-1,2,3,4-tetrahydro-1-naphthol (**LXVIII**), and 1-acetonaphthone (**LXIX**, yield 7 %) (Esmaeili et al. 2012).

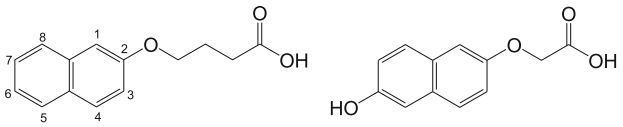


LXIV **LXV** **LXVI**



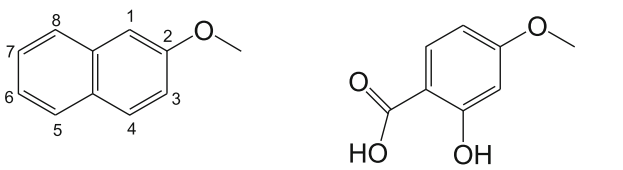
LXVII **LXVIII** **LXIX**

The fungitoxic compound γ-(2-naphthyloxy)-*n*-butyric acid (**LXX**) is converted by *A. niger* strain Mulder via hydroxylation and β-oxidation to produce (6-hydroxy-2-naphthyloxy) acetic acid (**LXXI**) (Byrde et al. 1956).

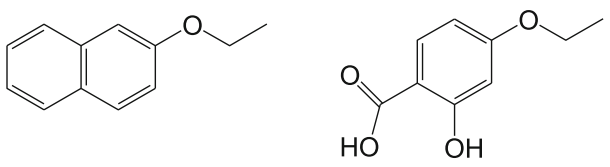


LXX **LXXI**

2-Methoxynaphthalene (**LXXII**) is metabolized by a strain of *A. niger* that opens the unsubstituted ring to produce 4-methoxysalicylic acid (**LXXIII**), whereas 2-ethoxynaphthalene (**LXXIV**) is metabolized similarly to produce 4-ethoxysalicyclic acid (**LXXV**) (Byrde et al. 1959).

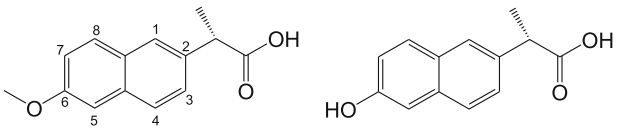


LXXII **LXXIII**

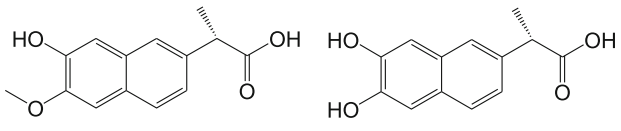


LXXIV **LXXV**

A nonsteroidal anti-inflammatory drug, *S*-naproxen (**LXXVI**), is transformed by *A. niger* ATCC 9142 by *O*-demethylation and hydroxylation to *O*-desmethylnaproxen (**LXXVII**), 7-hydroxynaproxen (**LXXVIII**), and 7-hydroxy-*O*-desmethylnaproxen (**LXXIX**) (He and Rosazza 2003).



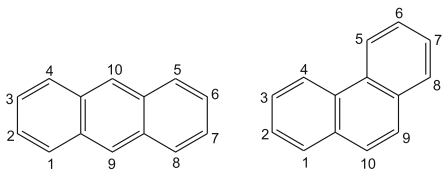
LXXVI **LXXVII**



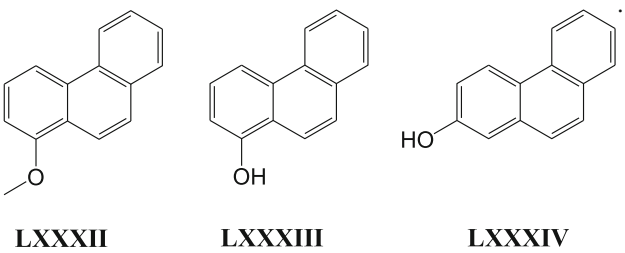
LXXVIII **LXXIX**

Polycyclic aromatic hydrocarbons

Some polycyclic aromatic hydrocarbons are metabolized by *A. niger* (Cerniglia and Sutherland 2010). Anthracene (**LXXX**) is metabolized by a strain of *A. niger* in several steps leading to gentisic acid (**LXIII**) (Yogambal and Karegoudar 1997). Phenanthrene (**LXXXI**) is metabolized by *A. niger* DSM 11167 to 1-methoxyphenanthrene (**LXXXII**), 1-hydroxyphenanthrene **(LXXXIII),** and 2-hydroxyphenanthrene (**LXXXIV**) (Sack et al. 1997). A different strain is reported to metabolize phenanthrene to protocatechuic acid (**XXI**) (Yogambal and Karegoudar 1997).



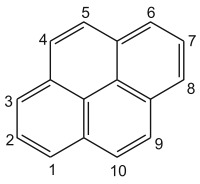
LXXX **LXXXI**



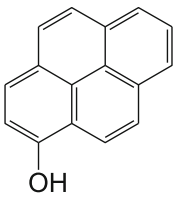
LXXXII **LXXXIII** **LXXXIV**

Pyrene (**LXXXV**) is metabolized by *A. niger* strains SK 9317 and DSM 11167 to eight different products: 1-hydroxypyrene (**LXXXVI**), 1-methoxypyrene (**LXXXVII**),

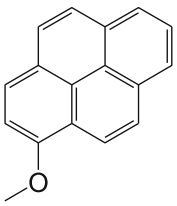
1,6- and 1,8-pyrenequinone (**LXXXVIII** and **LXXXIX**), 1,6- and 1,8-dihydroxypyrene (**XC** and **XCI**), 1-pyrenyl sulfate (**XCII**), and 1-hydroxy-8-pyrenyl sulfate (**XCIII**) (Wunder et al. 1994; Sack et al. 1997).



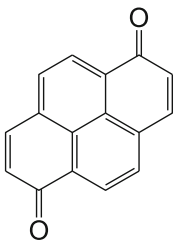
LXXXV



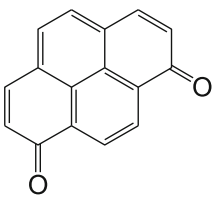
LXXXVI



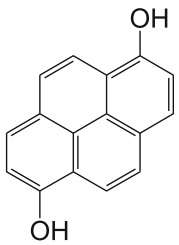
LXXXVII



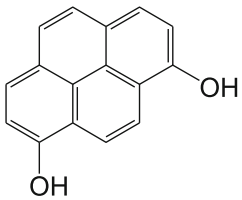
LXXXVIII



LXXXIX



XC



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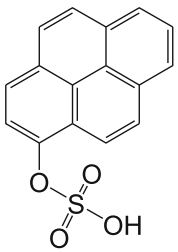
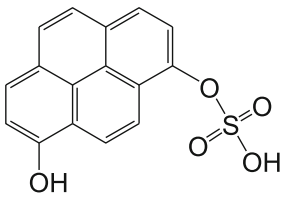


XCII

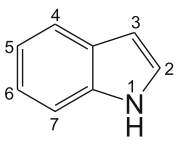


XCIII

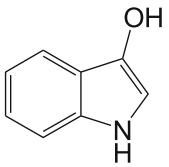
Transformation of azaarenes

Many nitrogen-containing aromatic compounds have been shown to be metabolized by fungi (Parshikov et al. 2012). Strains of *A. niger* have been used for some of these biotransformations.

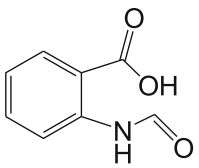
Indole (**XCIV**), which is used for the synthesis of pharmaceuticals and fragrances, is transformed successively by a strain of *A. niger* to 3-hydroxyindole (indoxyl, **XCV**), 2-(formylamino)benzoic acid (**XCVI**), anthranilic acid (**XVII**), 2,3-dihydroxybenzoic acid (**XXIV**), and finally to catechol (**XXII**) (Kamath and Vaidyanathan 1990).



XCIV

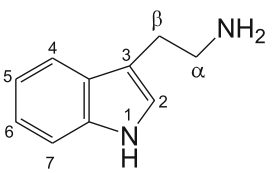


XCV

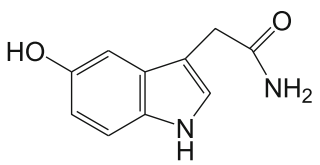


XCVI

Tryptamine (**XCVII**), a monoamine alkaloid that has physiological roles in many organisms, is oxidized by *A. niger* NRRL 4026 on both the 5-carbon of the benzo ring and the α-carbon of the side chain to produce 5-hydroxyindole-3-acetamide (**XCVIII**) (Boaventura et al. 2004).

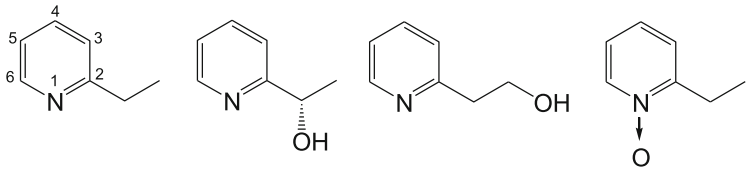


XCVII



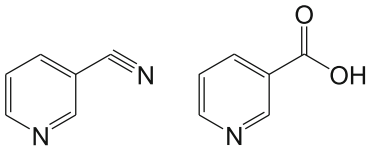
XCVIII

A. niger VKM F-1119 biotransforms 2-ethylpyridine (**XCIX**) to produce (−)-2-(1-hydroxyethyl)pyridine (**C**), a small amount of 2-(2-hydroxyethyl)pyridine (**CI**), and traces of 2-ethylpyridine *N*-oxide (**CII**) (Vorobyeva et al. 1990).



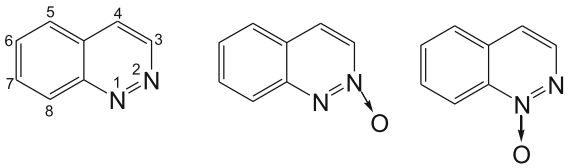
XCIX **C** **CI** **CII**

3-Cyanopyridine (**CIII**) is metabolized by *A. niger* K10 to produce 3-nicotinic acid (niacin, **CIV**) (Šnajdrová et al. 2004).



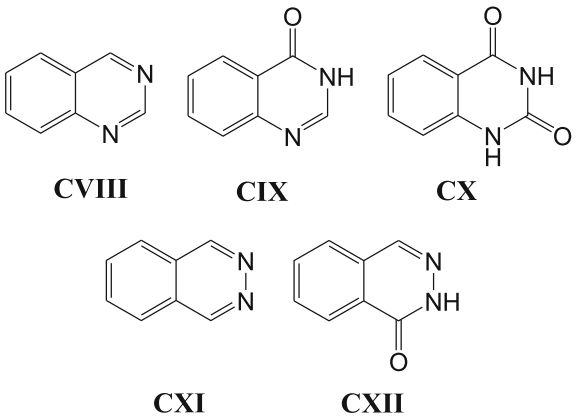
CIII **CIV**

Cinnoline (**CV**), a toxic benzodiazine found in diesel exhaust, is metabolized by *A. niger* NRRL-599 via N-oxidation to both cinnoline 2-oxide (**CVI**) and cinnoline 1-oxide (**CVII**) (Sutherland et al. 1998).



CV **CVI** **CVII**

In other benzodiazines, the carbon atoms are oxidized. Quinazoline (**CVIII**) is oxidized by *A. niger* NRRL-599 to 4-quinazolinone (**CIX**) and 2,4-quinazolinedione (**CX**); and phthalazine (**CXI**) is oxidized to 1-phthalazinone (**CXII**) (Sutherland et al. 2011).



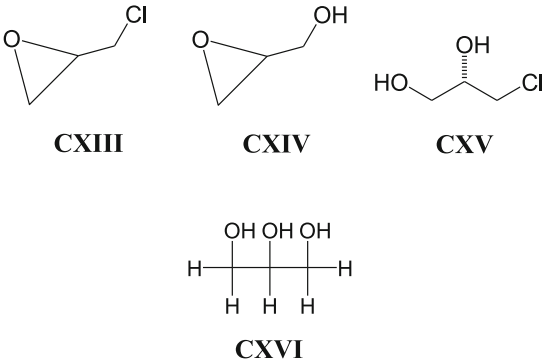
CVIII **CIX** **CX**

CXI **CXII**

Transformation of epoxides

A. niger strains produce a broad-spectrum epoxide hydrolase, which has been purified commercially and used to catalyze many reactions that are not discussed here. However, whole mycelia of this species are frequently used to resolve racemic mixtures of epoxides (Choi et al. 1998; Goswami et al. 1999). The diols and triols produced by hydrolysis, as well as the chiral epoxides that remain unhydrolyzed, may be used in the production of pharmaceutical drugs (Choi et al. 1998).

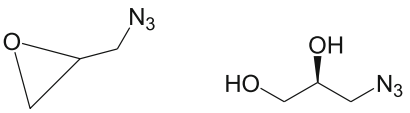
The epoxides (±)-epichlorohydrin (**CXIII**) and (±)-glycidol (**CXIV**) are hydrolyzed by a strain of *A. niger* to (*R*)-(−)-3-chloro-1,2-propanediol (**CXV**) and glycerol (**CXVI**), respectively (Choi et al. 1998). Several aromatic epoxides are also hydrolyzed enantioselectively (Choi et al. 1998).



CXIII **CXIV** **CXV**

CXVI

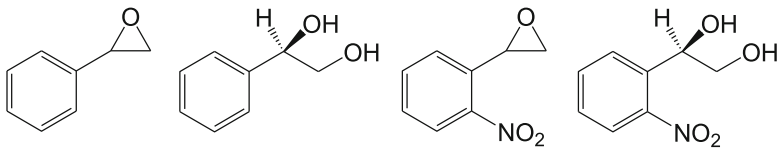
The (*S*)-enantiomer of (±)-glycidyl azide (**CXVII**) is hydrolyzed by *A. niger* ZJUTZQ208 to (2*S*)-3-azido-1,2-propanediol (**CXVIII**). The (*R*)-enantiomer of glycidyl azide, which is not hydrolyzed, can be used in the chemical synthesis of the antimicrobial agent linezolid (Chen et al. 2013).



CXVII **CXVIII**

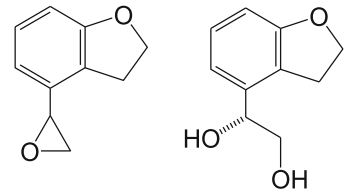
The (*R*)-enantiomer of (±)-styrene oxide (**CXIX**), a toxic derivative of styrene, is hydrolyzed enantioselectively in a racemic mixture to (*R*)-(−)-1-phenyl-1,2-ethanediol (**CXX**) by *A. niger* LCP 521 and another unnumbered strain, leaving the (*S*)-enantiomer unchanged (Pedragosa-Moreau et al. 1993; Choi et al. 1998). (*R*)-(−)-1-Phenyl-1,2-ethanediol has been used to synthesize antiviral nucleoside analogs, calcimimetic compounds, and neurokinin-1 receptor

antagonists. The (*R*)-enantiomer of (±)-2-nitrostyrene oxide (**CXXI**) is hydrolyzed similarly by *A. niger* CGMCC 0496, which produces (*R*)-1-(2-nitrophenyl)-1,2-ethanediol (**CXXII**), a chemical that is used for the synthesis of pharmaceutical and agricultural products, while leaving the (*S*)-enantiomer unchanged (Jin and Li 2002).



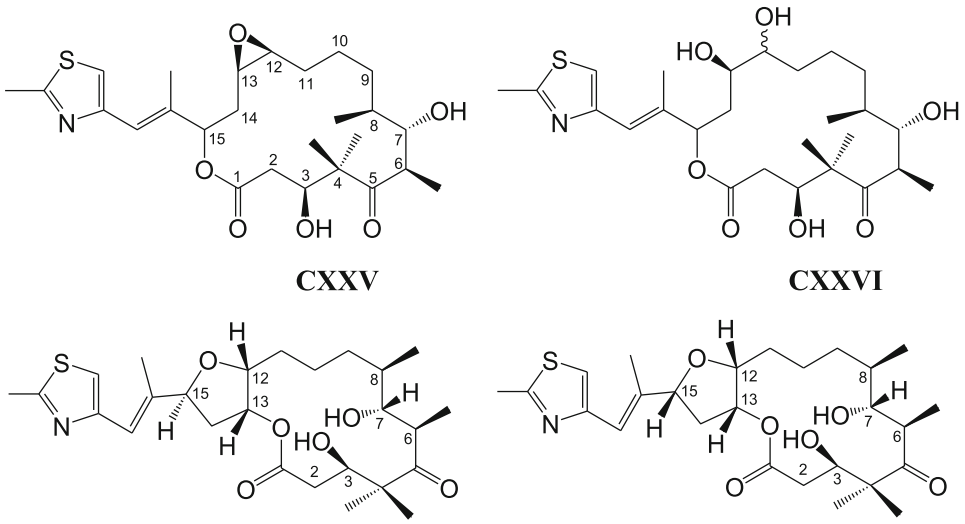
CXIX **CXX** **CXXI** **CXXII**

In metabolizing (±)-1-(2′,3′-dihydrobenzo[*b*]furan-4′-yl)-1,2-oxirane (**CXXIII**), *A. niger* SC 16311 enantiospecifically hydrolyzes only the (*R*)-epoxide, forming (*R*)-1-(2′,3′-dihydrobenzo[*b*]furan-4′-yl)-ethane-1,2-diol (**CXXIV**) and leaving the (*S*)-epoxide unreacted (Goswami et al. 1999).



CXXIII **CXXIV**

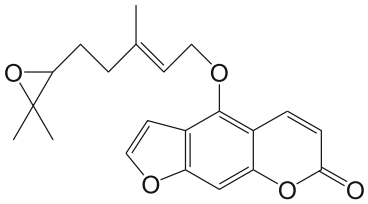
Epothilone A (**CXXV**), a cytotoxic bacterial metabolite that binds to the same β-tubulin site in microtubules as the drug paclitaxel, is transformed by *A. niger* AS 3.739 to *trans*- and *cis*-12,13-dihydroxyepothilone A (**CXXVI**), *trans*-12,15-epoxyepothilone A (**CXXVII**), and *cis*-12,15-epoxyepothilone A (**CXXVIII**), all of which have cytotoxic activity against human cancer cell lines (Wang et al. 2009).



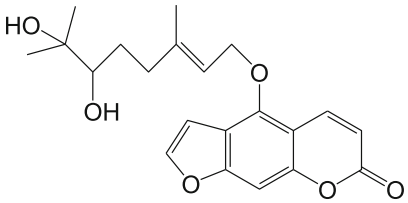
CXXV **CXXVI**

CXXVII **CXXVIII**

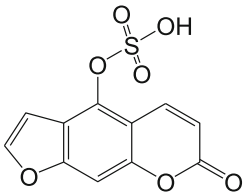
6′,7′-Epoxybergamottin (**CXXIX**), a furanocoumarin epoxide found in grapefruit, inhibits cytochrome P450 3A4. It is metabolized by *A. niger* NRRL 326 to two metabolites by epoxide hydrolysis to form 6′,7′-dihydroxybergamottin (**CXXX**) and by removal of the side chain and sulfation to form bergaptol 5-sulfate (**CXXXI**) (Myung et al. 2008).



CXXIX

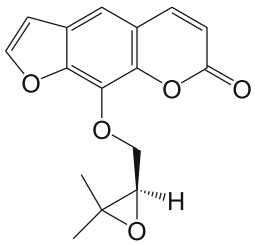


CXXX

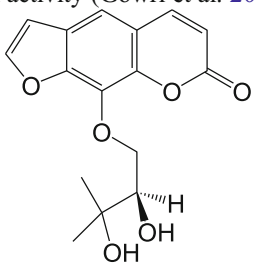


CXXXI

(+)-Heraclenin (**CXXXII**), a furanocoumarin epoxide found in the fruits of the medicinal bael tree of India as well as in other plants, shows antimalarial activity and inhibition of T cell proliferation in vitro. It is hydrolyzed stereospecifically by *A. niger* NCIM 620 to a much less antimalarial diol, (−)-heraclenol (**CXXXIII**). This demonstrates the necessity of the oxirane ring for antimalarial activity (Gowri et al. 2011).



CXXXII

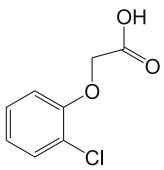


CXXXIII

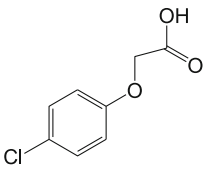
Transformation of chlorinated aromatic compounds

Several chlorinated compounds, which may be used as pesticides or be found as environmental pollutants (Faulkner and Woodcock 1961; Shailubhai et al. 1984; Bhalerao and Puranik 2007), are transformed by cultures of *A. niger*.

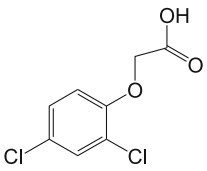
Both 2-chlorophenoxyacetic acid (**CXXXIV**) and 4-chlorophenoxyacetic acid (**CXXXV**) may be hydroxylated at any of the unsubstituted ring carbon atoms by *A. niger* strain Mulder. The detection of o-hydroxyphenoxyacetic acid (**XXIX**) as an additional metabolite shows that even the chlorine atom may be replaced by a hydroxyl group (Faulkner and Woodcock 1961). The herbicide 2,4-dichlorophenoxyacetic acid (2,4-D, **CXXXVI**) also is hydroxylated, presumably by the same strain of *A. niger*, to 2,4-dichloro-5-hydroxyphenoxyacetic acid (**CXXXVII**) and small amounts of two other metabolites. In one of them, 2,5-dichloro-4-hydroxyphenoxyacetic acid (**CXXXVIII**), a chlorine atom has been shifted from the 4- to the 5-position (Faulkner and Woodcock 1964).



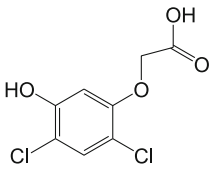
CXXXIV



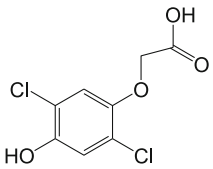
CXXXV



CXXXVI

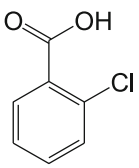


CXXXVII

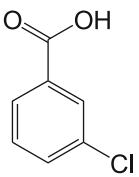


CXXXVIII

Another strain of *A. niger* metabolizes 2-chlorobenzoic acid (**CXXXIX**) and 3-chlorobenzoic acid (**CXL**) by hydroxylation, dechlorination, and ring cleavage. The intermediate products include *p*-hydroxybenzoic acid (**XIX**) and protocatechuic acid (**XXI**) (Shailubhai et al. 1984).

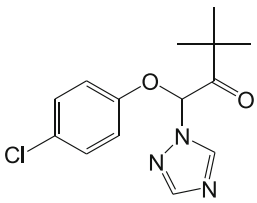


CXXXIX

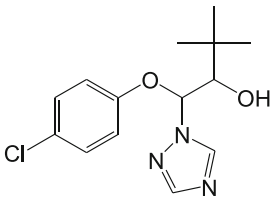


CXL

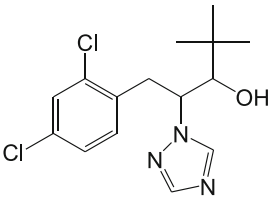
The fungicides triadimefon (**CXLI**), triadimenol (**CXLII**), and diclobutrazol (**CXLIII**) are hydroxylated by *A. niger* CBS 121.49 at the *tert*-butyl groups. Triadimefon is also reduced at the carbonyl group to produce triadimenol (Deas and Clifford 1982).



CXLI

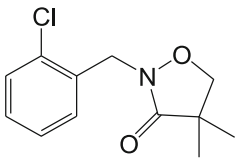


CXLII



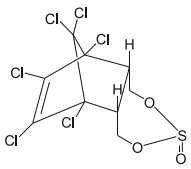
CXLIII

The herbicide clomazone (**CXLIV**) is hydroxylated in at least three different positions by *A. niger* strains UI-X172 and ATCC 10581 (Liu et al. 1996).

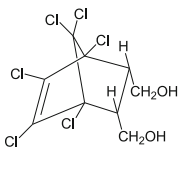


CXLIV

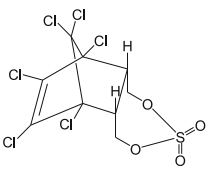
The highly toxic compound endosulfan (**CXLV**), formerly used as an insecticide, is degraded by *A. niger* E-11, producing metabolites that include endosulfan diol (**CXLVI**) and endosulfan sulfate (**CXLVII**). The metabolites appear to be eventually mineralized (Bhalerao and Puranik 2007).



CXLV

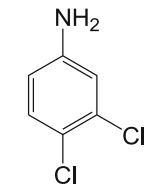


CXLVI

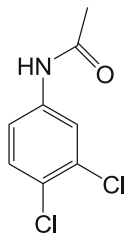


CXLVII

3,4-Dichloroaniline (**CXLVIII**), a chemical industry intermediate that is also found as an environmental pollutant, is converted to 3,4-dichloroacetanilide (**CXLIX**) by *A. niger* F3 (Castillo et al. 2014).



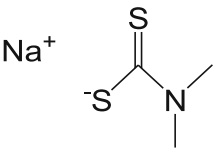
CXLVIII



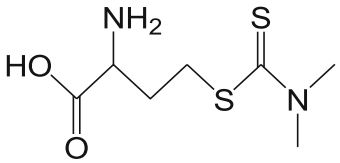
CXLIX

Transformation of other organic compounds

The fungicide sodium dimethyldithiocarbamate (**CL**) is conjugated with α-aminobutyric acid by mycelia of a strain of *A. niger* to produce γ-(dimethylthiocarbamoylthio)-α-aminobutyric acid (**CLI**), which has much less antifungal activity (Kaars Sijpesteijn et al. 1962).

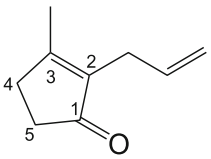


CL

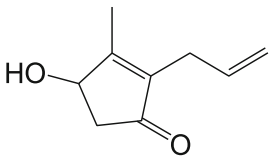


CLI

Allethrone (**CLII**), a synthetic pyrethrin, is hydroxylated at the 4-position by *A. niger* NRRL 3228 to produce allethrolone (**CLIII**), an insecticide precursor (LeMahieu et al. 1970).

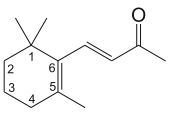


CLII

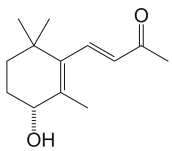


CLIII

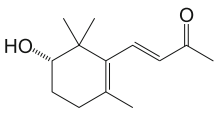
β-Ionone (**CLIV**), from the essential oil of roses, is one of the rose ketones that are used in fragrances. It is hydroxylated by *A. niger* JTS 191 to a variety of products, including (*R*)-4-hydroxy-β-ionone (**CLV**) and (*S*)-2-hydroxy-β-ionone (**CLVI**). β-Methylionone (**CLVII**) is hydroxylated to an analogous set of products. These metabolites have been used in tobacco flavoring (Mikami et al. 1981a).



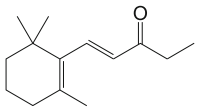
CLIV



CLV

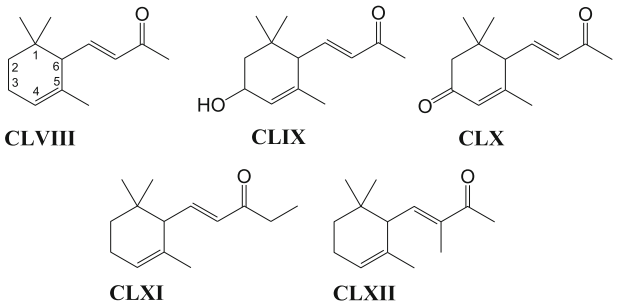


CLVI

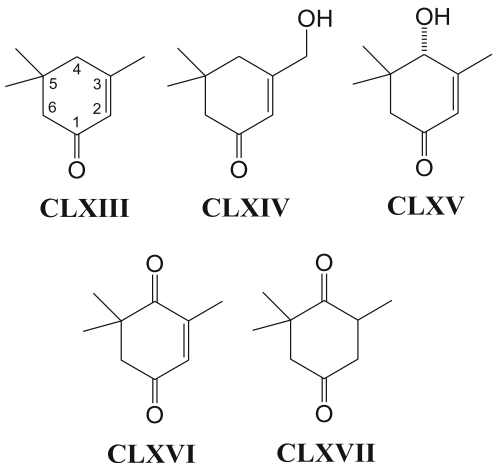


CLVII

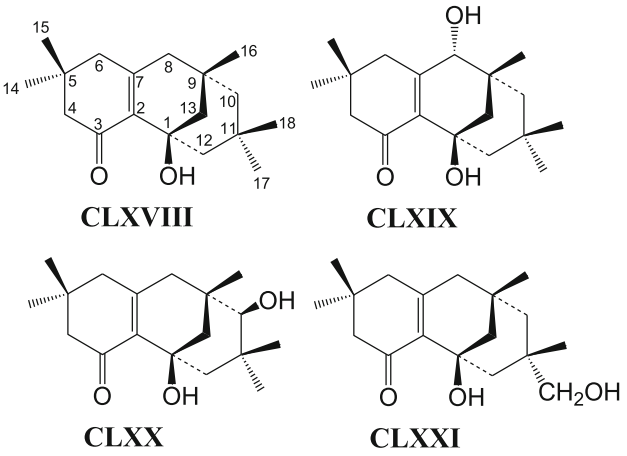
Another rose ketone, (±)-α-ionone (**CLVIII**), is metabolized by *A. niger* JTS 191 to **(±)-***cis*- and (±)-*trans*-3-hydroxy-α-ionone (**CLIX**), (±)-3-keto-α-ionone (**CLX**), and at least three other products. Similarly, (±)-α-methylionone (**CLXI**) and (±)-α-isomethylionone (**CLXII**) are metabolized to analogous products (Yamazaki et al. 1988).



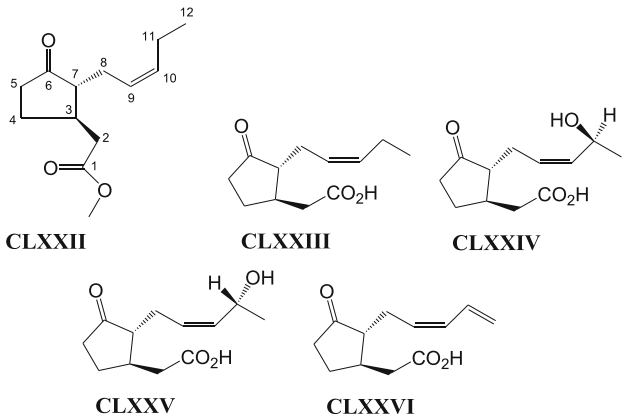
The cyclic ketone isophorone (**CLXIII**), used as a solvent and in chemical synthesis, is hydroxylated by *A. niger* JTS 191, either to 3-hydroxymethyl-5,5-dimethyl-2-cyclohexen-1-one (**CLXIV**) or stereospecifically to (*S*)-4-hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one (**CLXV**). The latter is transformed further to 3,5,5-trimethyl-2-cyclohexene-1,4-dione (**CLXVI**) and 3,5,5-trimethylcyclohexane-1,4-dione (**CLXVII**), which are also used for tobacco flavoring (Mikami et al. 1981b).



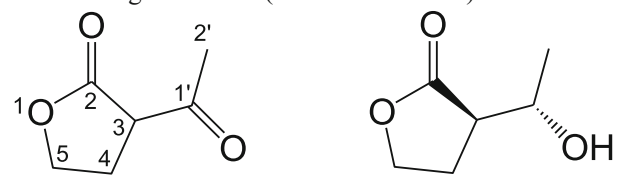
(±)-Diisophorone (**CLXVIII**), which has antifungal activity, is hydroxylated by *A. niger* ATCC 10549 at three different sites to produce the optically active derivatives 8α-hydroxydiisophorone (**CLXIX**), 10-hydroxydiisophorone (**CLXX**), and 17-hydroxydiisophorone (**CLXXI**) (Kiran et al. 2004).



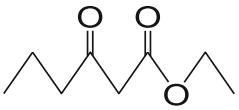
The plant growth regulator methyl (−)-jasmonate (**CLXXII**) is demethylated by *A. niger* i-400 to (−)-jasmonic acid (**CLXXIII**), which is then converted to (11*S*)-(−)-hydroxyjasmonic acid (**CLXXIV**) or (11*R*)-(−)-hydroxyjasmonic acid (**CLXXV**) and (−)-11,12-didehydrojasmonic acid (**CLXXVI**) (Miersch et al. 1999).



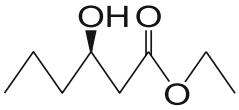
(±)-α-Acetyl-γ-butyrolactone (**CLXXVII**) is reduced stereospecifically at the 1′-carbonyl group by *A. niger* LIV 10 to produce (+)-(3*R*,1′*S*)-α-1′-hydroxyethyl-γ-butyrolactone (**CLXXVIII**), which has been used to synthesize new drug candidates (Ribeiro et al. 2006).



Ethyl 3-oxohexanoate (ethyl butyrylacetate, **CLXXIX**) is reduced stereospecifically by a strain of *A. niger* to ethyl 3-(*R*)-hydroxyhexanoate (**CLXXX**), a food flavoring ingredient that also serves as a precursor for the synthesis of the chiral anticancer compound (+)-neopeltolide (Ramos et al. 2011).

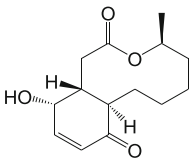


CLXXIX

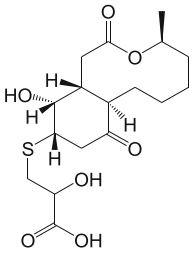


CLXXX

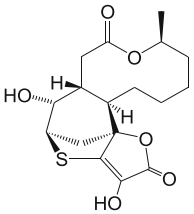
(+)-Sch-642305 (**CLXXXI**), a lactone produced by several fungi, inhibits DNA primase in bacteria. Resting cultures of *A. niger* ATCC 16404 conjugate (+)-Sch-642305 with 3-mercaptolactate to form two different derivatives. One of the derivatives, compound 1 (**CLXXXII**), retains antibacterial activity against *Bacillus subtilis*, but the other, compound 2 (**CLXXXIII**), lacks it (Adelin et al. 2012).



CLXXXI

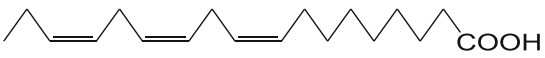


CLXXXII

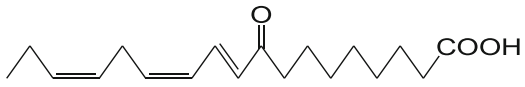


CLXXXIII

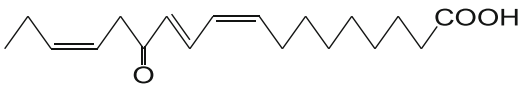
A strain of *A. niger* converts α-linolenic acid (**CLXXXIV**) to 9-keto-10*E*,12*Z*,15*Z*-octadecatrienoic acid (**CLXXXV**) and 13-keto-9*Z*,11*E*,15*Z*-octadecatrienoic acid (**CLXXXVI**), which are being investigated for their anti-inflammatory properties (Petta et al. 2014).



CLXXXIV

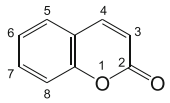


CLXXXV

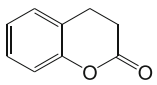


CLXXXVI

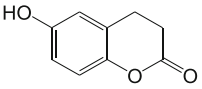
Coumarin (**CLXXXVII**), a compound with a vanilla-like odor found in various plants, is metabolized by *A. niger* strain Mulder to melilotic acid (**XXXIX**) and small amounts of *o*-coumaric acid (**XXXVII**), 4-hydroxycoumarin (**XL**), and catechol (**XXII**) (Bocks 1967a). A different strain, *A. niger* ATCC 11394, reduces coumarin to dihydrocoumarin (3,4-dihydrochromen-2-one, **CLXXXVIII**) and then either to 6-hydroxy-3,4-dihydrochromen-2-one (**CLXXXIX**) or to melilotic acid (**XXXIX**), 3-(2-hydroxyphenyl)propanal (**CXC**), and 2-(3-hydroxypropyl)phenol (**CXCI**) (Aguirre-Pranzoni et al. 2011b). Dihydrocoumarin (**CLXXXVIII**), which is widely used as a flavor and fragrance, is transformed by *A. niger* ATCC 11394 to 2-(3-hydroxypropyl)phenol (**CXCI**), 6-hydroxy-3,4-dihydrochromen-2-one (**CLXXXIX**), 4-hydroxycoumarin (**XL**), and three minor metabolites (Aguirre-Pranzoni et al. 2011a).



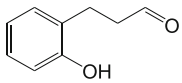
CLXXXVII



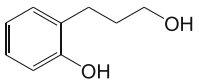
CLXXXVIII



CLXXXIX

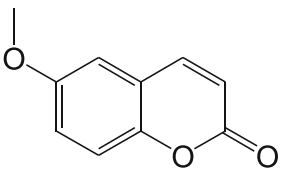


CXC

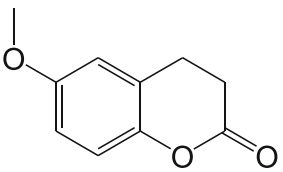


CXCI

6-Methoxycoumarin (**CXCII**) is transformed by *A. niger* ATCC 11394 to 6-methoxy-3,4-dihydrochromen-2-one (**CXCIII**), an unidentified hydroxylated derivative of the same metabolite, and 6-hydroxy-3,4-dihydrochromen-2-one (**CLXXXIX**) (Aguirre-Pranzoni et al. 2011b).

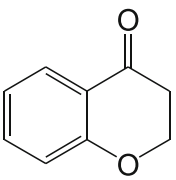


CXCII

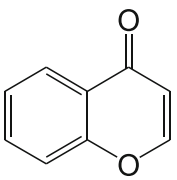


CXCIII

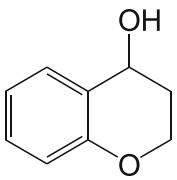
4-Chromanone (**CXCIV**) is oxidized to chromone (**CXCV**) or reduced to chroman-4-ol (**CXCVI**) by *A. niger* NRRL 599 (Ibrahim and Abul-Hajj 1990).



CXCIV

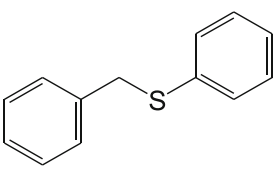


CXCV

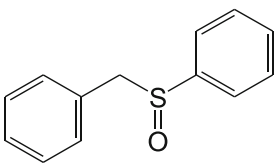


CXCVI

Aromatic thioethers, including benzyl phenyl sulfide (**CXCVII**), are oxidized stereoselectively to benzyl phenyl sulfoxide (**CXCVIII**) and other sulfoxides by *A. niger* NRRL 337 (Auret et al. 1968).

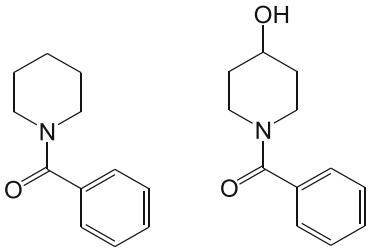


CXCVII



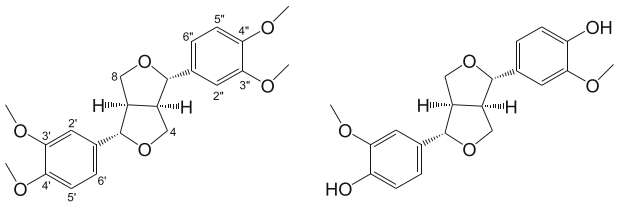
CXCVIII

1-Benzoylpiperidine (**CXCIX**) is hydroxylated regiospecifically by growing cultures of *A. niger* VKM F-1119 to 1-benzoyl-4-hydroxypiperidine (**CC**) with an 80 % yield (Parshikov et al. 1992).



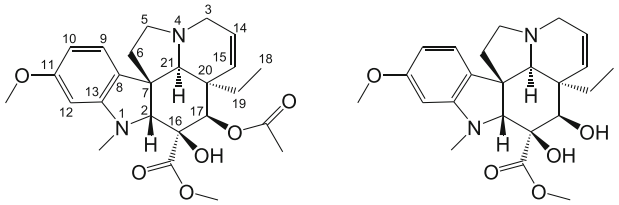
CXCIX **CC**

(±)-Eudesmin (**CCI**), a lignan from plants, is demethylated regioselectively by *A. niger* IFO 4414 at the 4′- and 4″-positions to produce (±)-pinoresinol (**CCII**), another lignan found in several plants. The (+)-isomer of pinoresinol (**CCII**) then is metabolized further, leaving (−)-pinoresinol, which also occurs in nature but is much less common than the (+)-enantiomer (Kasahara et al. 1997).



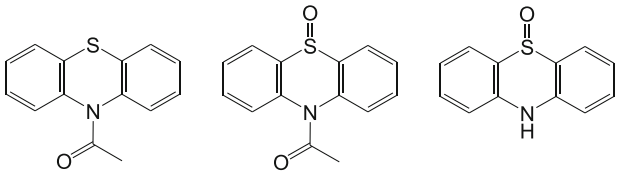
CCI **CCII**

An alkaloid from the Madagascar periwinkle, vindoline (**CCIII**), which is used in the synthesis of the cancer drug vinblastine, is deacetylated by *A. niger* ATCC 105491 to produce 17-deacetylvindoline (**CCIV**) (Atta-ur-Rahman et al. 1998).



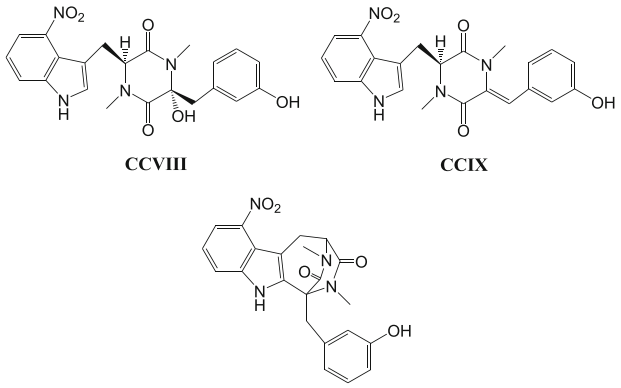
CCIII **CCIV**

N-Acetylphenothiazine (**CCV**), a heterocycle containing both nitrogen and sulfur, is metabolized by *A. niger* VKM F-1119 to two products: *N*-acetylphenothiazine sulfoxide (**CCVI**, yield 13 %) and phenothiazine sulfoxide (**CCVII**, yield 24 %) (Parshikov et al. 1999).



CCV **CCVI** **CCVII**

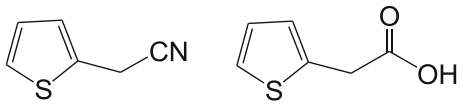
Thaxtomin A (**CCVIII**), a dipeptide phytotoxin produced by a potato pathogenic bacterium, *Streptomyces scabies*, is metabolized by *A. niger* strain F to seven metabolites; the two produced in the highest concentrations, metabolite M-3 (**CCIX**) and metabolite M-5 (**CCX**), have greatly reduced phytotoxicity (Lazarovits et al. 2004).



CCVIII **CCIX**

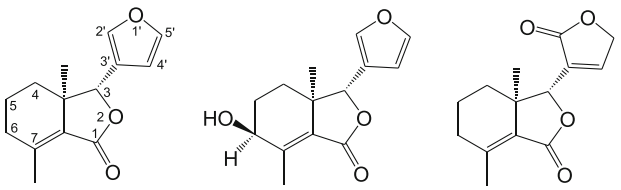
CCX

2-Thiopheneacetonitrile (**CCXI**) is metabolized by cultures of *A. niger* K10 to 2-thiopheneacetic acid (**CCXII**) (Šnajdrová et al. 2004).



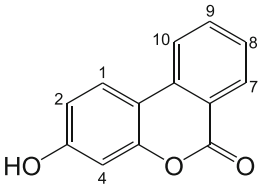
CCXI **CCXII**

Fraxinellone (**CCXIII**), a furan-substituted component of a traditional Chinese medicine, is hydroxylated by a strain of *A. niger* to produce dasycarpol (6β-hydroxyfraxinellone, **CCXIV**), which inhibits cancer cells in culture. It may also be oxidized at the furan ring to produce fraxinigerllone (**CCXV**), which has moderate cytotoxicity (Yang et al. 2005).

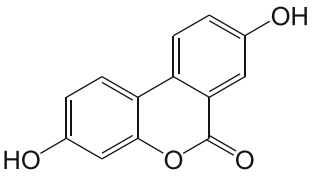


CCXIII **CCXIV** **CCXV**

An antioxidant component from an Indian traditional medicine, 3-hydroxydibenzo-α-pyrone (**CCXVI**), is hydroxylated by an *A. niger* strain to 3,8-dihydroxydibenzo-α-pyrone (**CCXVII**), which stabilizes coenzyme Q_{10}. This metabolite may then be conjugated with glycine or arginine (Islam et al. 2008).

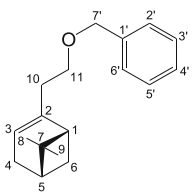


CCXVI

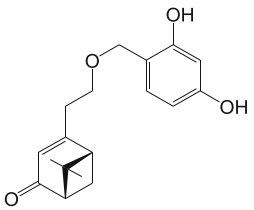


CCXVII

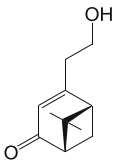
(−)-Nopol benzyl ether (**CCXVIII**) is hydroxylated by *A. niger* strains TBUYN-2 and CBSYN on both the cyclohexene ring and the benzene ring, then dehydrogenated to produce the antioxidant (−)-4-oxonopol-2′4′-dihydroxybenzyl ether (**CCXIX**) and hydrolyzed to produce (−)-4-oxonopol (**CCXX**) (Noma and Asakawa 2010).



CCXVIII

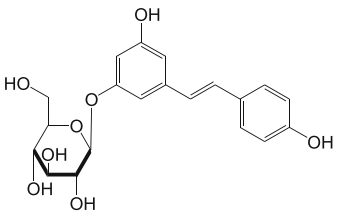


CCXIX

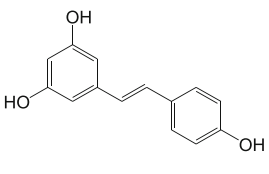


CCXX

Polydatin (*trans*-piceid, resveratrol 3-*O*-β-D-glucopyranoside, **CCXXI**) from Japanese knotweed roots may be hydrolyzed to resveratrol (**CCXXII**) by *A. niger* M85 co-immobilized together with a yeast (Jin et al. 2013).

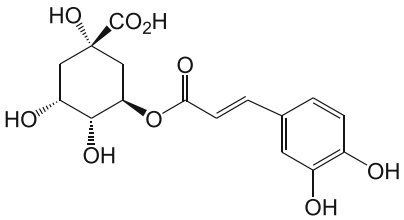


CCXXI

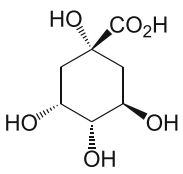


CCXXII

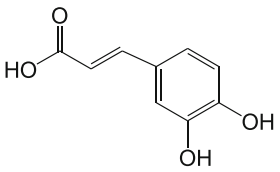
Chlorogenic acid (**CCXXIII**), an antioxidant ester found in green coffee beans and other plants, is hydrolyzed by *A. niger* C23308 to its components, D-(−)-quinic acid (**CCXXIV**) and caffeic acid (**CCXXV**). The latter is then transformed to protocatechuic acid (**XXI**) (Torres-Mancera et al. 2013).



CCXXIII



CCXXIV



CCXXV

Conclusions

Many organic compounds can be transformed by cultures of fungi, including strains of *A. niger*, to metabolites that may have value for organic synthesis. The compounds that already have been investigated as substrates include derivatives of benzene and naphthalene, polycyclic aromatic hydrocarbons, nitrogen-containing heterocycles, epoxides, chlorinated compounds, and other aliphatic and aromatic compounds. Numerous biotransformations have produced new molecules for pharmaceutical investigation. To obtain new drug candidates, especially chiral compounds, the strains of *A. niger* and other fungi that have been shown to catalyze particular types of reactions should be tested with additional alkaloids, antibiotics, and other bioactive compounds.

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Conflict of interest The authors declare that they have no competing interests.

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