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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 nitrogenous heterocycles. – M.: Editus, 2015. – 130 p.

The monography describes examples of the application of microbial technologies for obtaining of derivatives from a series of nitrogen heterocycles (saturated nitrogen heterocycles, azaarenes and quinolones). It is proposed alternative ways for synthesize substances that are difficult to obtain by the methods of organic chemistry. Microbial technologies of synthesis of organic compounds may find out a practical application in the production of various drugs.

ISBN 978-5-00058-198-8

Introduction

Microbial conversions of organic compounds has applications in many fields. Chemical, pharmaceutical and biotechnology industries draw on microbiological methods for synthesis of compounds that are difficult to obtain by the methods of organic chemistry alone (Petersen and Kiener 1999; Parshikov et al. 2012; Parshikov et al. 2014; Silva et al. 2014). Nitrogen-containing heterocyclic rings serve as key moieties of many drugs. In the last 15 years, several reviews of the microbial transformation of nitrogen-containing heterocyclic compounds, such as azaarenes and quinolones, have been published (Hüttel and Hoffmeister 2010; Petersen and Kiener 1999; Sukul and Spiteller 2007; Vickers and Polsky 2000).

In this monography, data from the literature on nitrogen-containing heterocyclic compounds have been compiled. For example, mitomycin C shows antibiotic and antitumor activities that have been related to the aziridine ring (Fürmeier and Metzger 2003), and aziridine derivatives are used in the synthesis of anti-malarial drugs (D'hooghe et al. 2011; Ghorai et al. 2007; Fattorusso and Taglialatela-Scafati 2009; Wright et al. 2002; Pacorel et al. 2010; Seebacher and Weis 2011; Richardson and Wyso 1960; Faber 2004; Baker 1987; Duran et al. 2000).

Pyridine rings are found in the bisphosphonate drugs risedronate and zoledronate, used to treat bone diseases (Gatti and Adami 1999), the antimycobacterial prodrugs isoniazid, ethionamide, and prothionamide (Deretic et al. 1996; Wang et al. 2007), and other antibacterial, anticancer, and antimalarial compounds (Kumar et al. 2008; Prachayasittikul et al. 2009; Ge et al. 2010; Duran et al. 2000; Ahmad et al. 2001; Petersen and Kiener, 1999; Rui et al. 2005; Hüttel and Hoffmeister 2010; Faber 2011; Rajini et al. 2011; Takayama et al. 2010; Saliba and Kirk 1998; Kaur et al. 2010; Rocco 2003; Achan et al. 2011; Baird 2011; Vale et al. 2009; Peters 1999; Vale et al. 2009; Brocks and Mehvar 2003).

Hybrid antimalarial drugs, such as those combining the structure of quinine with artemisinin (Walsh et al. 2007) or those combining derivatives of 4-aminoquinoline with a 1,2,4-trioxane or a 1,2,4-trioxolane (Coslédan et al. 2008; Araújo et al. 2009; Chauhan et al. 2010; Muregi and Ishih 2010), may have more antimalarial activity than their components. Other derivatives of quinoline have been used for the treatment of tuberculosis (Andries et al. 2005) and for pain relief (Gomtsyan et al. 2005). The isoquinoline alkaloids include morphine and many other drugs (Petersen and Kiener 1999; Banasik et al. 1992; Waring et al. 1975; Refaie et al. 2005; Gomtsyan et al. 2005; Taggart et al. 1948; Guetzoyana et al. 2009; Araújo et al. 2009; Jones et al.

2009; Kalkanidis et al. 2002; Boibessot et al. 2002; Boibessot et al. 2002; Agarwal et al. 2005; Kontnik and Clardy 2008; Kaur et al. 2009; Resnick et al. 1993; Zefirov et al. 1993; Parshikov et al. 1994b; Kaiser et al. 1996; Fetzner 1998; Petersen and Kiener 1999; Willumsen et al. 2005; Rajini et al. 2011).

Bacterial enzymes involved in azaarene hydroxylation include naphthalene 1,2-dioxygenase (Ensley et al. 1983; Resnick et al. 1993), quinaldine 4-oxidase (Stephan et al. 1996), carbazole 1,9a-dioxygenase (Inoue et al. 2006), biphenyl 2,3-dioxygenase (Resnick et al. 1993), and toluene dioxygenase (Boyd et al. 2002). Bacterial aldehyde oxidases (Yasuhara et al. 2002) and cytochromes P450 (Kelly et al. 2003) may transform azaarenes to the corresponding lactams (Vickers and Polsky 2000). Fungi may also produce cytochromes P450 that transform azaarenes to lactams; some fungi, such as *Beauveria bassiana*, *Aspergillus* spp., and *Cunninghamella* spp., are especially useful for drug biotransformations because of the regio- and stereospecificity of their enzymes (Grogan and Holland 2000; Lehman and Stewart 2001).

The quinolones are a large group of synthetic compounds that have been developed as antimicrobial agents (Ball, 2000b). They are used extensively in human clinical and veterinary medicine for treating diseases caused by Gram-negative and Gram-positive bacteria (Oliphant and Green, 2002; Andersson and

MacGowan, 2003; Dalhoff and Schmitz, 2003). Their antibacterial effectiveness is due to their inhibition of DNA gyrase (topoisomerase II) activity in Gram-negative bacteria and topoisomerase IV activity in Gram-positive bacteria (Drlica and Zhao, 1997; Brighty and Gootz, 2000; Cattoir and Nordmann, 2009). Some quinolones also have antitumor, antiviral (against hepatitis B and C, HIV and herpes viruses), antiallergic, anti-tubercular, immunomodulatory, and antidiabetic activity (Boteva and Krasnykh, 2009; Mugnaini et al., 2009; Kloskowski et al., 2010). Quinolones may even be effective against different types of malaria parasites (Mahmoudi et al., 2003).

The differences in molecular structure and in activities of quinolones in vitro are the basis for their classification (Ball, 2000; King et al., 2000; Schellhorn, 1998; Oliphant and Green, 2002). Antimicrobial activities of first-generation quinolones (i.e., nalidixic acid, oxolinic acid, cinoxacin, piromidic acid, pipemidic acid, and flumequine) are excellent against aerobic Gram-negative bacteria, but not against aerobic Gram-positive bacteria and anaerobic bacteria. In 1980 came the second generation of quinolones, when norfloxacin was synthesized by introducing a fluorine atom at position 6 of the 4-quinolone molecule and a diamine, piperazine, in position 7 (Brighty and Gootz, 2000). These modifications make possible the antimicrobial activity of quinolones against aerobic Gram-positive bacteria, as well as to

increase their activity against Gram-negative bacteria. Second-generation quinolones include ciprofloxacin, ofloxacin, enoxacin, fleroxacin, lomefloxacin, pefloxacin and rufloxacin (Andersson and MacGowan, 2003; Andriole, 2000). However, the second generation of quinolones still did not have activity against anaerobic bacteria. Subsequently, quinolones of the third generation, such as grepafloxacin, gatifloxacin, sparfloxacin, enrofloxacin, danofloxacin, and pradofloxacin, effective against Gram-positive bacteria, particularly pneumococci, were developed and had high activity against anaerobic bacteria (Andriole, 2000). The fourth-generation quinolones (e.g., trovafloxacin, clinafloxacin, sitafloxacin, moxifloxacin, and gemifloxacin) have high activity against anaerobes and pneumococci (Andriole, 2000; Andersson and MacGowan, 2003).

Involvement of microbial technologies in the modification of quinolones will provide chemists and pharmacologists with unique derivatives. These may have novel therapeutic properties for the treatment of many bacterial diseases and even parasitic diseases, such as malaria (Mahmoudi et al., 2003). Most of the biotransformation processes that have been developed for quinolones use fungi [Wetzstein et al., 2010], but a few of them use bacteria (Kieslich et al., 1973; Chen et al., 1997; Adjei et al., 2006). In addition to the microbial transformations of the quinolones, those of some naphthyridones (including nalidixic

acid), pyranoacridones (including acronycine), and cinnolones (cinoxacin) will be considered.

Chapter 1. Microbial transformation of saturated nitrogen-containing heterocyclic compounds

Organic chemists and pharmacologists have a great interest in the stereochemistry and regiochemistry of synthetic processes (Hassner 2009), such as the molecular stereochemistry of aziridines (Keifer et al. 1988) and the hydroxylation of azetidine, pyrrolidine, and their derivatives (Romanova et al. 1995; Feula al. 2010).

Some mono- and bi-cyclic polyhydroxylated alkaloids are known as potent glycosidase inhibitors; for instance, castanospermine and deoxynorjirimycin are promising anti-cancer and anti-HIV compounds, respectively. Some stereoisomers of 2-(hydroxymethyl)pyrrolidine-3,4-diols also have been reported as glycosidase inhibitors (Ahn and Shin 1997). The 3-hydroxypyrrolidine moiety is found in a range of naturally occurring bioactive alkaloids and many synthetic approaches to produce 3-hydroxypyrrolidines also have been developed (Aurrecoechea et al. 2009; Hodgson et al. 2006; Rios et al. 2007).

Many hydroxylated piperidine alkaloids are potent inhibitors of glycosidases and related enzymes (Grishina et al. 2011). 4-Hydroxypiperidines are present in many drugs, such as the antidiarrhoeal loperamide and the schizophrenia medications haloperidol and benztropine (McKay et al. 2010). Polyhydroxypiperidines and polyhydroxyazepanes have attracted

attention of researchers due to their biological importance in the development of glycosidase inhibitors (Shih et al. 2007; Shih et al. 2011).

Azocanes used in the asymmetric synthesis of α-alkylated α-amino acids also demonstrate potential biological activities as potent inhibitors of some enzymes (Georg and Guan 1992).

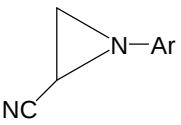
Microbial technologies for hydroxylation in different positions of molecules may help in creating a series of new drugs; for instance, hydroxylated derivatives of saturated nitrogen-containing heterocycles may be obtained using microbial technologies and used to create hybrid molecules of artemisinin, quinine, or chloroquine (Walsh et al. 2007).

1.1. Microbial transformation of aziridine derivatives

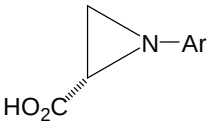
Aziridine groups are three-membered ring structural elements, found in a wide variety of natural products that have antibiotic and antitumor properties (Thibodeaux et al. 2012). The aziridines have been targets of investigation for synthetic chemists, both as useful intermediates and as final products (Chawla et al. 2013). Compounds having a 5-(aziridin-1-yl)-2,4-dinitrobenzyl structure were shown to have significant growth-inhibitory properties against *Trypanosoma brucei* and *Trypanosoma cruzi* (Bot et al. 2010). Clean reactions of the aziridine compounds that

have exceptionally good regioselectivity and/or stereoselectivity are desirable (Chawla et al. 2013).

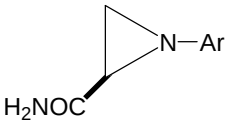
Racemic aziridine-containing carbonitriles (**I**, Ar – substituted aryl) are separated into the corresponding carboxylic acids (**II**) and enantiopure isomers (**Ia**) by *Rhodococcus erythropolis* AJ270 with yields of 45-50% (Dexian and Meixiang 2010):



I



II



Ia

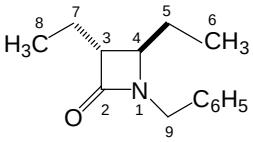
1.2. Microbial transformation of azetidine derivatives

The azetidines are saturated nitrogen heterocycles containing a four-membered ring. Derivatives of azetidines have been used in traditional Asian medicine for over a thousand years (Diethelm and Carreira, 2013). The skeleton of 2-azetidinone is the pharmacophore of a widely employed class of antibiotics, the β-lactam antibiotics (penicillins, cephalosporins, carbapenems, monobactams, and penems) (Sharma et al. 2011). The metabolism of nitrogen heterocyclics may lead to lactam formation.

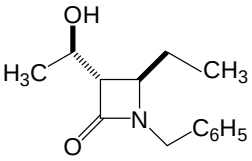
Among the saturated nitrogen heterocycles, there is great interest in the transformation of monocyclic β-lactams, since they

often have antimicrobial activity. Furthermore, 3-azido-, 3-amino- and 3-(1,2,3-triazol-1-yl)-β-lactams have been synthesized and studied as drugs against *Plasmodium falciparum* (Singh et al. 2011). A bifunctional hybrid structure based on 7-chloroquinoline and a β-lactam recently was synthesized as a potential antimalarial agent (Singh et al. 2012).

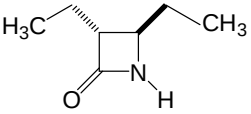
Transformation of a monocyclic β-lactam (**III**) by a growing culture of the fungus *Beauveria bassiana* ATCC 7159 produces a hydroxy derivative (**IV**) with a yield of 10%; a second product (**V**) with a yield of 20% is formed by elimination of the benzyl radical (Archelas et al. 1988):



III

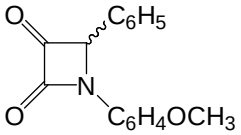


IV

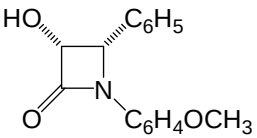


V

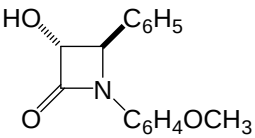
Biotransformation of an α-keto-β-lactam (**VI**) with growing cells of *Saccharomyces cerevisiae* for five days produces both the *cis*-hydroxy derivative (**VII**, 62% yield) and the *trans*-hydroxy derivative (**VIII**, 38% yield) (Mihovilovic et al. 2005):



VI

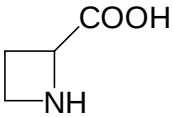


VII

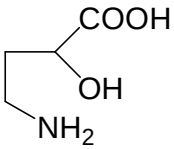


VIII

The conversion of azetidine-2-carboxylic acid (**IX**) by a hydrolase from *Pseudomonas* sp. A2C forms 2-hydroxy-4-aminobutyric acid (**X**) (Gross et al. 2008):

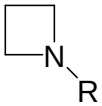


IX

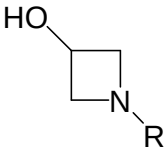


X

Hydroxylation of *N*-substituted azetidines (**XI**, R= $CO_2C_6H_5$; CO_2t-Bu) by cells of the bacterium *Sphingomonas sp.* HXN-200 leads to the formation of hydroxy derivatives (**XII**, R= $CO_2C_6H_5$; CO_2t-Bu) in position 3 of the heterocyclic ring with yields of 91-98% (Chang et al. 2002):

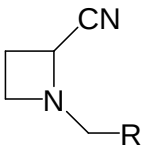


XI

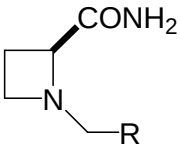


XII

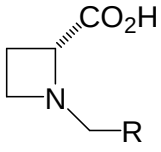
Later, it was shown that the resolution of racemic 1-benzylazetidine-2-carbonitriles (**XIII**, R= C_6H_5; 4-Me- C_6H_4; 4-MeO-C_6H_4; 4-Br-C_6H_4; 3-Br-C_6H_4; 2-Br-C_6H_4) in phosphate buffer by *R. erythropolis* AJ270 produces isomers **XIV** and **XV** with yields up to 46% (Leng et al. 2009):



XIII



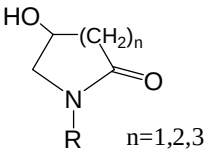
XIV



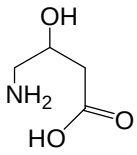
XV

1.3. Microbial transformation of pyrrolidine and its derivatives

Pyrrolidine forms a part of the molecule of an antibiotic, clindamycin, which has antimalarial properties (Bertrand and Kremsner 2002). Furthermore, pyrrolidine derivatives inhibit the growth of chloroquine-resistant strains of *P. falciparum* (Mendoza et al. 2011). There are several pharmacologically interesting compounds with the general formula (**XVI**) (Archelas et al. 1986):



XVI

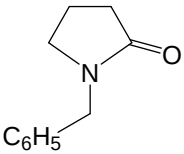


XVII

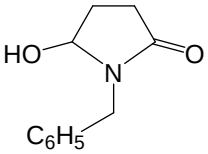
They can also be regarded as analogs of γ-amino-β-hydroxybutyric acid (**XVII**), which has great medical importance (Archelas et al. 1986).

N-Substituted pyrrolidines and their analogs may be hydroxylated by growing cultures of *B. bassiana* ATCC 7159. As

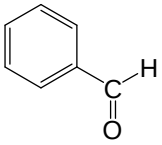
a result of the transformation of 1-benzylpyrrolidone-2 (**XVIII**), optically active 1-benzyl-5-hydroxypyrrolidone-2 (**XIX**, 12% yield) and benzaldehyde (**XX**, 2% yield) are formed (Srairi and Maurey 1987):



XVIII

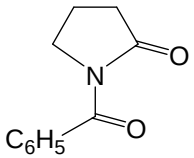


XIX

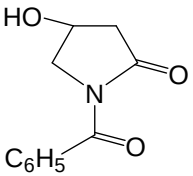


XX

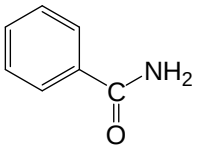
During the transformation of 1-benzoylpyrrolidone-2 (**XXI**), the optically active 1-benzoyl-4-hydroxypyrrolidone-2 (**XXII**, 21% yield) has been detected in a mixture with benzamide (**XXIII**) (Srairi and Maurey 1987):



XXI

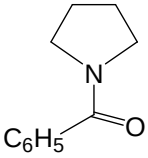


XXII

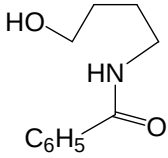


XXIII

In the transformation of 1-benzoylpyrrolidine (**XXIV**) by *B. bassiana*, however, a carbon atom at position 2 is hydroxylated with ring opening and formation of *N*-(4-hydroxybutyl)benzamide (**XXV**, 8% yield) (Archelas et al. 1986):

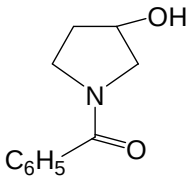


XXIV



XXV

During the transformation of 1-benzoylpyrrolidine (**XXIV**) or 1-benzoylpyrrolidone-2 (**XXI**) in growing cultures of the fungus *Cunninghamella verticillata* VKPM F-430, the optically active (-)-1-benzoyl-3-hydroxypyrrolidine (**XXVI**, 38% yield) or benzamide (**XXIII**), respectively, is produced (Parshikov et al. 1992; Parshikov et al. 2010a,b):

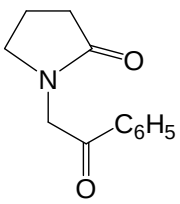


XXVI

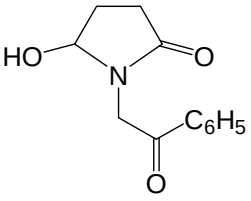
3-Hydroxy derivatives in yields of 66.4-93.5% also are formed in the transformation of *N*-substituted pyrrolidines by cells of the bacterium *Sphingomonas sp*. HXN-200; the substituent on the nitrogen atom may be $CH_2C_6H_5$, COC_6H_5, $CO_2CH_2C_6H_5$, $CO_2C_6H_5$, or CO_2*t*-Bu *(*Li et al. 2001).

During hydroxylation of 1-phenacylpyrrolidone-2 (**XXVII**) by *B. bassiana* ATCC 7159, an intermediate compound, 1-phenacyl-5-hydroxypyrrolidone-2 (**XXVIII**), and the final

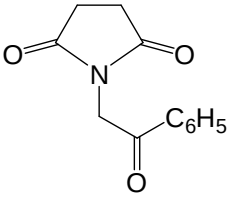
product, 1-phenacylpyrrolidinedione (**XXIX**), are formed with a yield of 23% (Srairi and Maurey 1987):



XXVII

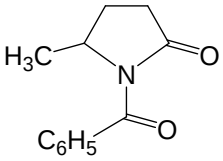


XXVIII

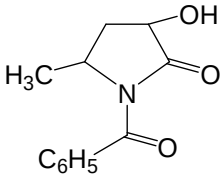


XXIX

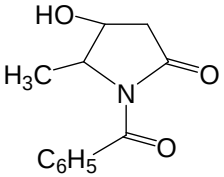
Further study of the biotransformation of substituted pyrrolidones in growing cultures shows that *B. bassiana* ATCC 7159 hydroxylates 5-methyl-1-benzoylpyrrolidone-2 (**XXX**) in either position 3 (**XXXI**, 11% yield) or position 4 of the hetero ring (**XXXII**, 12% yield), in a process accompanied by the formation of benzamide (**XXIII) (**Srairi and Maurey 1987):



XXX

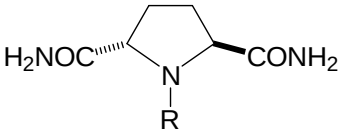


XXXI

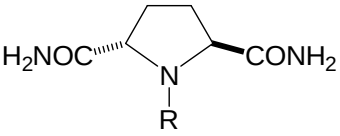


XXXII

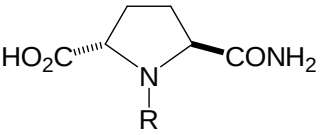
Separation of racemic *trans*-pyrrolidine-2,5-dicarboxamides (**XXXIII**, R= Bn; allyl; H), using the amidase of *R. erythropolis* AJ270, produces (2*S*,5*S*)-pyrrolidine-2,5-dicarboxamides (**XXXIV**) and (2*R*,5*R*)-5-carbamoylpyrrolidine-2-carboxylic acids (**XXXV**) in high yields (up to 52%) with excellent enantioselectivity (Chen et al. 2012):



XXXIII



XXXIV



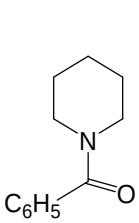
XXXV

1.4. Microbial transformation of piperidine and its derivatives

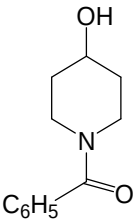
Some substituted piperidine rings are found in natural and synthetic compounds that have biological activity (Sun et al. 2000). Over the past 20 years, thousands of piperidine derivatives have been tested in pre-clinical and clinical studies (Weintraub et al. 2003), and some piperidine derivatives, such as febrifugine, are antimalarial drugs (Taniguchi and Ogasawara 2000).

In recent decades, the microbial chemistry of piperidines has flourished. Studies of the transformation of 1-benzoylpiperidine (**XXXVI**) by various research groups under different experimental conditions have resulted in the isolation of 1-benzoyl-4-hydroxypiperidine (**XXXVII**) with a yield of 18% after transformation with *B. bassiana* ATCC 7159 (Johnson et al. 1968a); 7% after transformation with *B. bassiana* ATCC 7159

(Archelas et al. 1986); 80% after transformation with *Aspergillus niger* VKM F-1119 (Parshikov et al. 1992); and 91−98% after transformation with *Sphingomonas sp*. HXN-200 (Chang et al. 2002):

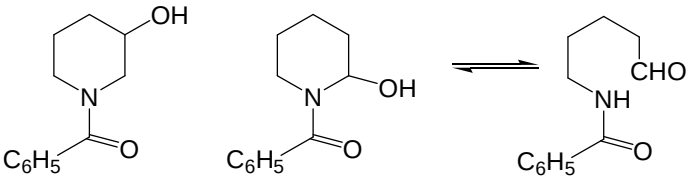


XXXVI



XXXVII

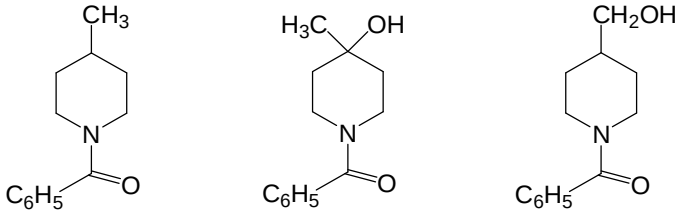
After the transformation of 1-benzoylpiperidine (**XXXVI**) by growing cultures of *B. bassiana* VKM F-3111D and *Penicillium simplicissimum* KM-16, 1-benzoyl-4-hydroxypiperidine (**XXXVII)** was isolated with yields of 60% and 3%, respectively, and the optically active (+)-3-hydroxy-1-benzoylpiperidine (**XXXVIII**) with yields of 1% and 3%, respectively (Parshikov et al. 1992). Furthermore, among the biotransformation products of 1-benzoylpiperidine (**XXXVI**) produced by *P. simplicissimum* KM-16, 2-hydroxy-1-benzoylpiperidine (**XXXIX**) was detected with a yield of 12% (Parshikov et al. 1992):



XXXVIII **XXXIX**

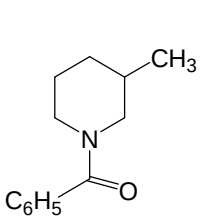
Transformation of 1-(4-acetylphenyl)piperidine by *B. bassiana* ATCC 7159 was similarly accompanied by the formation of 4-hydroxy-1-(4-acetylphenyl)piperidine with a yield of 20% (Johnson et al. 1992). Later, this result was confirmed by others (Osorio-Lozada et al. 2008).

With the introduction of a methyl substituent on the heterocyclic ring, the transformation process is different. In the transformation of 1-benzoyl-4-methylpiperidine (**XL**) in growing cultures of *B. bassiana* ATCC 7159, a 4-hydroxy compound (**XLI**, 13% yield) is obtained with 1-benzoyl-4-hydroxymethylpiperidine (**XLII**, yield 23%) (Johnson et al. 1969):

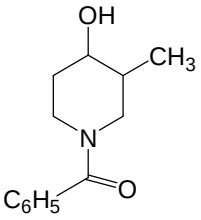


XL **XLI** **XLII**

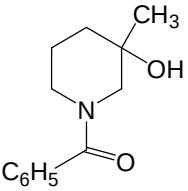
At the same time, 1-benzoyl-3-methylpiperidine (**XLIII**) is hydroxylated in position 4 (**XLIV**, yield 6%) and position 3 of the heterocyclic ring (**XLV**, 7% yield) (Johnson et al. 1969):



XLIII

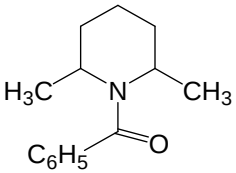


XLIV

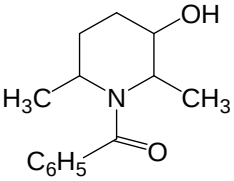


XLV

For a compound with two methyl substituents on the heterocyclic ring, 1-benzoyl-2,5-dimethylpiperidine (**XLVI**), the hydroxylation by *B. bassiana* ATCC 7159 occurs in position 3 of the ring (**XLVII**, 49% yield) (Johnson et al. 1969):

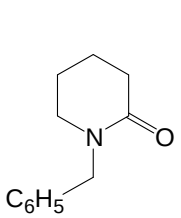


XLVI

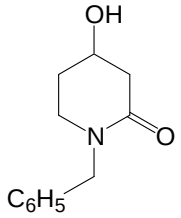


XLVII

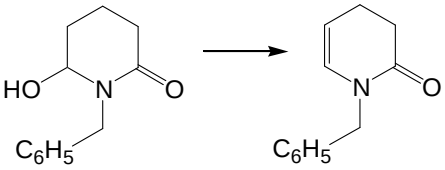
The introduction of a ketone group to the heterocyclic ring partially changes the site of hydroxylation. During growth of *B. bassiana* ATCC 7159 in the presence of 1-benzylpiperidone (**XLVIII**), in addition to 1-benzyl-4-hydroxypiperidone-2 (**XLIX**, 10% yield), the unstable 1-benzyl-6-hydroxypiperidone-2 (**L**, 5% yield) was detected but then was spontaneously converted to its dehydration product (1-benzyl-2-oxo-1,2,3,4-tetrahydropyridine) (**LI**) (Archelas et al. 1986):



XLVIII

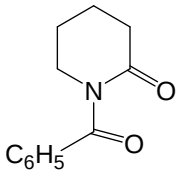


XLIX

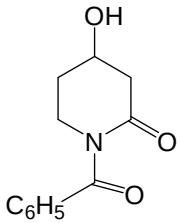


L **LI**

During 1-benzoylpiperidone-2 (**LII**) hydroxylation in growing cultures of *B. bassiana* ATCC 7159, along with benzamide (**XXIII**), the optically active 1-benzoyl-4-hydroxypiperidone-2 (**LIII**) was isolated with a yield of 27% (Archelas et al. 1986):

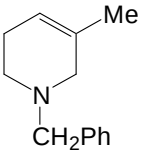


LII

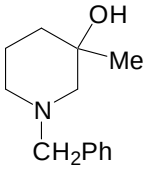


LIII

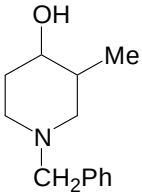
During the transformation of 1-benzyl-3-methyl-Δ^3-piperidine (**LIV**) by growing mycelia of *C. verticillata* VKPM F-430, three products were observed in a ratio of **LV**: **LVI**: **LVII** = 1:2:16 (Terent'ev et al. 1997):



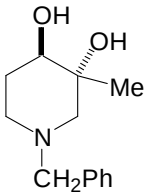
LIV



LV

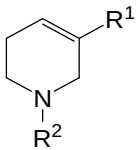


LVI

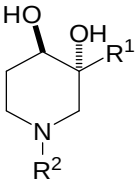


LVII

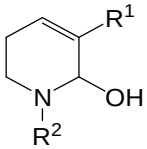
Other analogs of 1-benzyl-3-methyl-Δ^3-piperidine (**LIV**), 1,2,5,6-tetrahydropyridines (**LVIII a** = R^1=Bn; R^2=H; **b** = R^1=Bn, R^2=H; **c** = R^1=Pr, R^2=Me), were also converted by *C. verticillata* VKPM F-430 with formation of the isomers **LIX a** (97.6% yield), **LIX b** (100% yield), **LIX c** (19.0% yield), and **LX c** (59.0% yield) (Terent'ev et al. 2003):



LVIII a, b, c



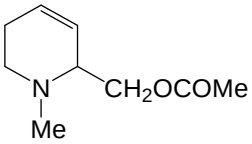
LIX a, b, c



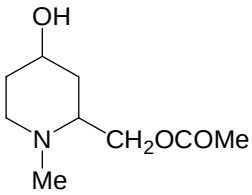
LX c

Also, in growing cultures of *C. verticillata* VKPM F-430, 2-acetoxymethyl-l-methyl-l,2,5,6-tetrahydropyridine (**LXI**) was

transformed into a 4-hydroxy derivative (**LXII**) with a low yield (Modyanova et al. 1999; Modyanova et al. 2010):



LXI



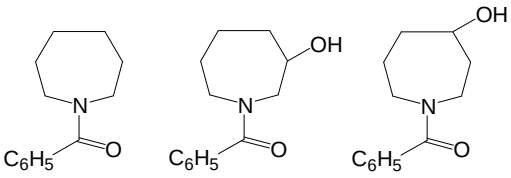
LXII

1.5. Microbial transformation of azepane, azocane and their derivatives

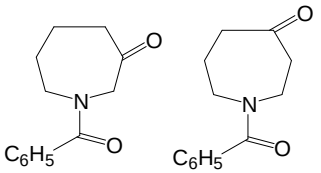
Azepane

Over the past 50 years, transformations of azepane (hexamethyleneimine) derivatives have been studied by several groups of researchers (Seebacher and Weis 2011).

During the transformation of 1-benzoylhexamethyleneimine (**LXIII**) by growing cultures of *B. bassiana* ATCC 7159, two optically active 3- and 4-hydroxy derivatives (**LXIV**, 3% yield; **LXV**, 11% yield) and a ketone (**LXVI**, 10% yield), with a carbonyl group at position 3 of the heterocyclic ring, are obtained (Archelas et al. 1986):



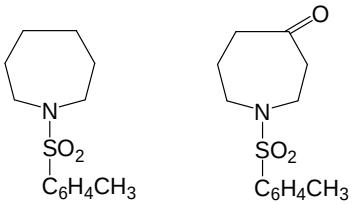
LXIII **LXIV** **LXV**



LXVI **LXVII**

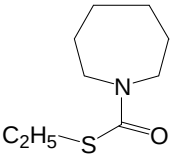
Other authors (Johnson et al. 1968a) reported that *B. bassiana* ATCC 7159 oxidizes 1-benzoylhexamethyleneimine (**LXIII**) to a mixture of 3- and 4-oxo-1-benzoylhexamethyleneimines (**LXVI** and **LXVII**) and the 4-hydroxy derivative (**LXV**).

Transformation of 1-(4-tolylsulfonyl)-hexamethyleneimine (**LXVIII**) by *B. bassiana* ATCC 7159 was accompanied by formation of only the 4-oxo derivative (**LXIX**) (Johnson et al. 1968a):

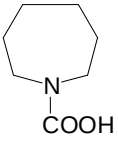


LXVIII **LXIX**

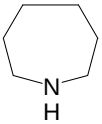
The bacterium *Gulosibacter molinativorax* ON4 oxidizes molinate (**LXX**) in several stages: azepane-1-carboxylic acid (**LXXI**), hexamethyleneimine (**LXXII**), and caprolactam (**LXXIII**), followed by the opening of the hetero ring (Barreiros et al. 2008):



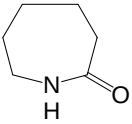
LXX



LXXI

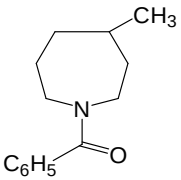


LXXII

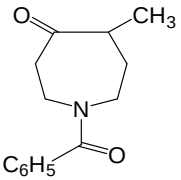


LXXIII

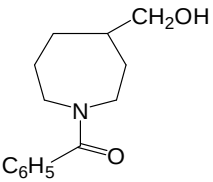
Transformation of 4-methyl-1-benzoylhexamethyleneimine (**LXXIV**) in growing cultures of *B. bassiana* ATCC 7159 produces an oxo derivative (**LXXV**, 11% yield) and a second product of oxidation (**LXXVI**, 29% yield) that has a hydroxymethyl group (Johnson et al. 1968a):



LXXIV

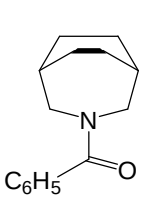


LXXV

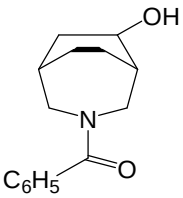


LXXVI

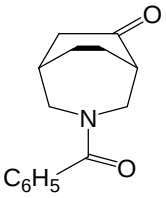
Increasing the complexity of the molecular structure of hexamethyleneimine may still lead to similar results. For example, transformation of 3-benzoyl-3-azabicyclo[3.2.2]nonane (**LXXVII**) by *B. bassiana* ATCC 7159 also produces hydroxy and oxo derivatives (**LXXVIII**, 50% yield and **LXXIX**, 22% yield) (Johnson et al., 1968b):



LXXVII

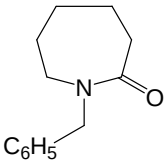


LXXVIII

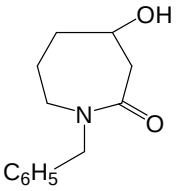


LXXIX

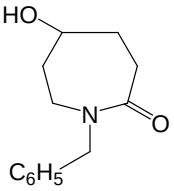
1-Benzylcaprolactam (**LXXX**) hydroxylation in cultures of *B. bassiana* ATCC 7159 produces two optically active isomeric hydroxy derivatives (**LXXXI** and **LXXXII**) (Archelas et al. 1986):



LXXX



LXXXI

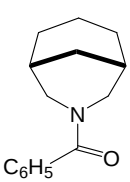


LXXXII

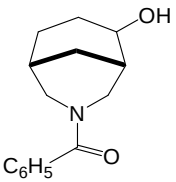
Azocane

Despite the fact that azocanes (and their derivatives) include drugs with antiviral and antimalarial properties (Hocart et al. 2011), such as reactivators of phosphorylated cholinesterases

(Radic et al. 2012), their microbiological transformations have rarely been investigated. During the transformation of 3-benzoyl-3-azabicyclo[3.2.2]nonane (**LXXXIII**) in growing cultures of *B. bassiana* ATCC 7159, only one product (**LXXXIV**, 60-70% yield) is detected (Johnson et al. 1968b):



LXXXIII



LXXXIV

Chapter 2. Microbial transformation of azaarenes

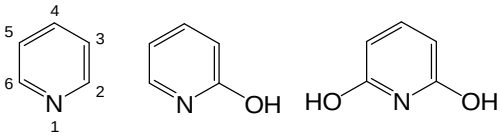
Many pharmaceutical drugs that contain azaarene structures, especially pyridine, quinoline, acridine, and indole, have been isolated from nature or synthesized (Khasaeva et al. 2014). Among the microbial transformation processes reviewed here, those that are perhaps of greatest interest produce regiospecifically and stereospecifically hydroxylated derivatives of azaarenes that may be useful in development of candidate drugs (Zefirov et al. 1993; 1995; Boyd et al. 2002). Carboxylated derivatives of azaarenes may also be valuable for the same purpose (Kiener 1992). It is likely that microbial technology will be used in the future to produce new derivatives of heterocyclic

compounds with novel and completely unexpected therapeutic properties.

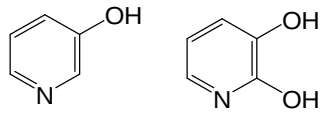
2.1. Transformation of single-ring azaarenes

Pyridine

The transformation of pyridine (**LXXXV**) and its derivatives has been investigated with bacteria isolated mostly from soils (Kost and Modyanova 1979; Shukla 1984; Fetzner 1998). *Rhodococcus opacus* hydroxylates pyridine to 2-hydroxypyridine (**LXXXVI**) and 2,6-dihydroxypyridine (**LXXXVII**); and *Arthrobacter crystallopoietes* hydroxylates pyridine to 3-hydroxypyridine (**LXXXVIII**) and 2,3-dihydroxypyridine (**LXXXIX**) (Zefirov et al. 1993; 1994):



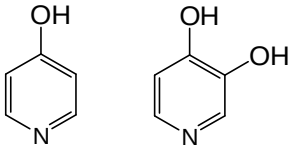
LXXXV **LXXXVI** **LXXXVII**



LXXXVIII **LXXXIX**

Further biotransformation of pyridine after hydroxylation by *A. crystallopoietes* and *R. opacus* may also include opening of

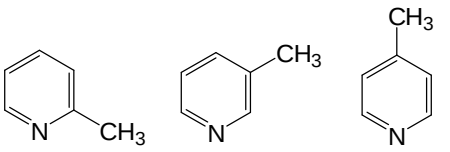
the ring (Zefirov et al. 1993; 1994). *Agrobacterium* sp. transforms 4-hydroxypyridine (**XC**) to 3,4-dihydroxypyridine (**XCI**) (Watson et al. 1974):



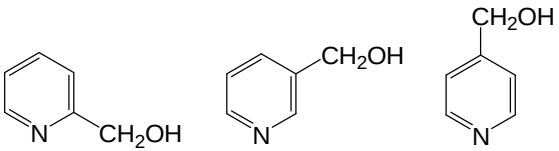
XC **XCI**

Alkylpyridines

Some fungi, including the insect pathogen *Beauveria bassiana*, oxidize α-, β-, and γ-picolines [2-methyl- (**XCII**), 3-methyl- (**XCIII**), and 4-methylpyridine (**XCIV**)] to the corresponding hydroxymethylpyridines (**XCV, XCVI,** and **XCVII**). The products are not further metabolized (Modyanova et al. 1990; Zefirov et al. 1993):

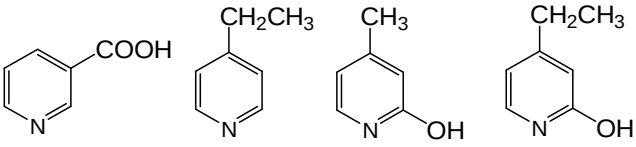


XCII **XCIII** **XCIV**



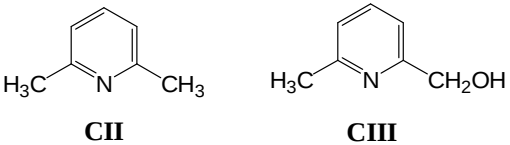
XCV **XCVI** **XCVII**

The methyl group of 3-methylpyridine can be oxidized by the bacterium *Pseudomonas putida*; the product is pyridine-3-carboxylic acid (**XCVIII**) (Kiener 1992). 4-Methylpyridine and 4-ethylpyridine (**XCIX**) are both hydroxylated at carbon 2 by another bacterium, *Pseudonocardia* sp., to produce 2-hydroxy-4-methylpyridine (C) and 2-hydroxy-4-ethylpyridine (**CI**), respectively (Lee et al. 2006):

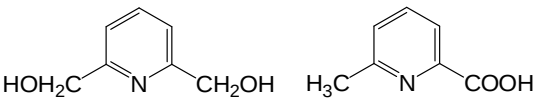


XCVIII **XCIX** **C** **CI**

Several fungi and bacteria are able to transform not only monoalkyl-, but also dialkylpyridines (Kost and Modyanova 1979; Kiener 1992). For example, *B. bassiana* cultures hydroxylate 2,6-lutidine (2,6-dimethylpyridine, **CII**) to 2-hydroxymethyl-6-methylpyridine (**CIII**), with a yield of 88%, and trace amounts of 2,6-dihydroxymethylpyridine (**CIV**) (Modyanova et al. 1990):



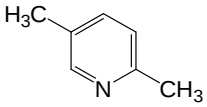
CII **CIII**



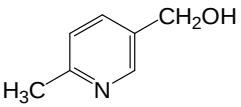
CIV **CV**

Another fungus, *Exophiala dermatitidis*, converts 2,6-lutidine to 6-methylpicolinic acid (6-methylpyridine-2-carboxylic acid, **CV**) (Yoshida et al. 2010).

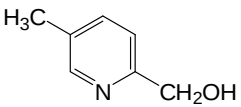
The hydroxylation of 2,5-lutidine (2,5-dimethylpyridine, **CVI**) by *B. bassiana* leads to a mixture of 3-hydroxymethyl-6-methylpyridine (**CVII**) and 2-hydroxymethyl-5-methylpyridine (**CVIII**) (Modyanova et al. 1990):



CVI

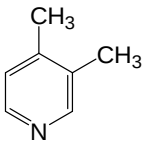


CVII

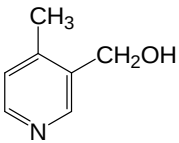


CVIII

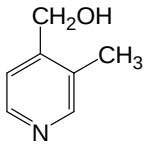
During the oxidation of 3,4-lutidine (3,4-dimethylpyridine, **CIX**) by *B. bassiana*, two isomers are formed; the yield of 3-hydroxymethyl-4-methylpyridine (**CX**) is significantly higher than that of 4-hydroxymethyl-3-methylpyridine (**CXI**) (Modyanova et al. 1990):



CIX



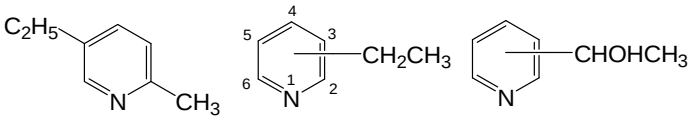
CX



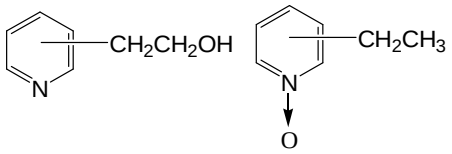
CXI

The transformation of 5-ethyl-2-methylpyridine (**CXII**) and either 2-ethyl- or 4-ethylpyridine (**CXIII**) by *B. bassiana* produces an α-hydroxyethyl derivative (**CXIV**), a β-hydroxyethyl

derivative (**CXV**), and an *N*-oxide (**CXVI**) in each case (Vorobyeva et al. 1990):



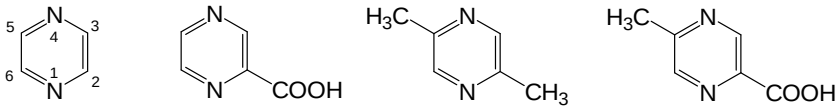
CXII **CXIII** **CXIV**



CXV **CXVI**

Pyrazine and alkylpyrazines

Pyrazine (**CXVII**) is carboxylated by the bacterium *Rhodopseudomonas palustris* to produce pyrazinoic acid (**CXVIII**) (Sasikala et al. 1994); and 2,5-dimethylpyrazine (**CXIX**) is oxidized by *P. putida* to produce 5-methylpyrazine-2-carboxylic acid (C**XX**) (Kiener 1992):



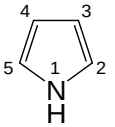
CXVII **CXVIII** **CXIX** **CXX**

2,3,6-Trimethylpyrazine can also be oxidized by *P. putida* (Kiener 1992); the bacterial transformation of alkylpyrazines and

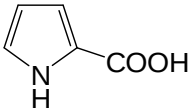
other substituted pyrazines has been reviewed recently (Müller and Rappert 2010; Rajini et al. 2011).

Pyrrole and alkylpyrroles

Bacillus megaterium has been used to carboxylate pyrrole (C**XXI**) to pyrrole-2-carboxylate (C**XXII**) (Wieser et al. 1998):



CXXI

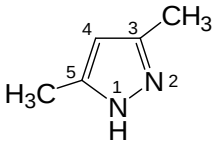


CXXII

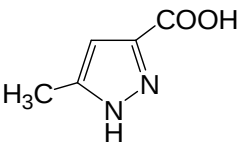
In addition, the 2-methyl group of 2,5-dimethylpyrrole can be oxidized by *P. putida* (Kiener 1992).

Alkylpyrazoles

3,5-Dimethylpyrazole (C**XXIII**) can be oxidized to 5-methylpyrazole 3-carboxylic acid (C**XXIV**) by *P. putida* (Kiener 1992):



CXXIII

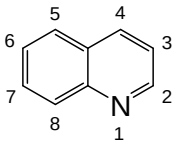


CXXIV

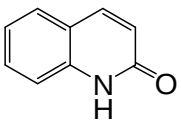
2.2. Transformation of quinoline, alkylquinolines, and isoquinoline

Quinoline

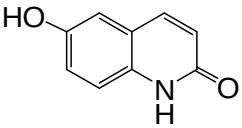
A variety of bacteria metabolize quinoline (C**XXV**) (Fetzner et al. 1998). *Moraxella* sp., *Nocardia* sp., *Pseudomonas diminuta*, and *Bacillus circulans* oxidize quinoline to 2-quinolinone (carbostyril, C**XXVI**) and 6-hydroxy-2-quinolinone (C**XXVII**) (Grant and Al-Najjar 1976; Shukla 1987; Bott and Lingens 1991). *Rhodococcus* sp. transforms quinoline not only to 2-quinolinone and 6-hydroxy-2-quinolinone but also to 5-hydroxy-6-(3-carboxy-3-oxopropenyl)-2-pyridone (C**XXVIII**) and pyrano-2-one-(3,2*b*)-6-pyridone (C**XXIX**) (Schwarz et al. 1989):



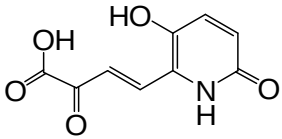
CXXV



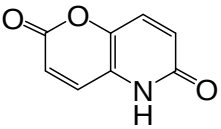
CXXVI



CXXVII



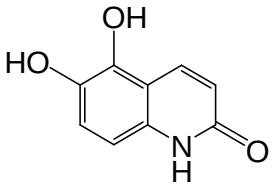
CXXVIII



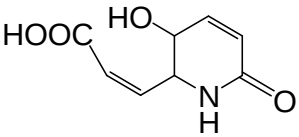
CXXIX

The aerobic conversion of quinoline by *Comamonas* sp. resulted in the formation of five metabolites in 30 h, including 2-quinolinone, 6-hydroxy-2-quinolinone, 5,6-dihydroxy-2-

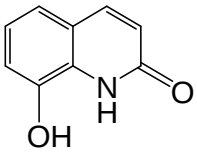
quinolinone (C**XXX**), 5-hydroxy-6-(2-carboxyethenyl)-2-pyridone (C**XXXI**), and 8-hydroxy-2-quinolinone (C**XXXII**) (Cui et al. 2004):



CXXX

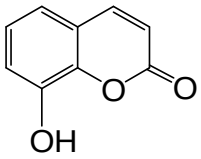


CXXXI

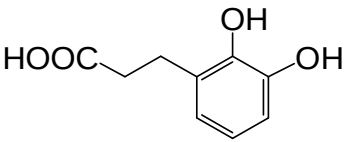


CXXXII

Several *Pseudomonas* spp. transform quinoline to 2-quinolinone, 8-hydroxy-2-quinolinone, 8-hydroxycoumarin (C**XXXIII**), and 2,3-dihydroxyphenylpropionic acid (C**XXXIV**) (Shukla 1986; 1987; Schwarz et al. 1989; Aislabie et al. 1990; Kilbane et al. 2000):

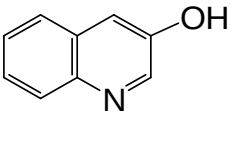


CXXXIII

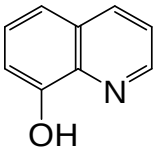


CXXXIV

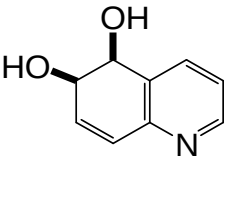
P. putida converts quinoline to 3-hydroxyquinoline (C**XXXV**) and 8-hydroxyquinoline (C**XXXVI**), the quinoline *cis*-5,6- (C**XXXVII**) and *cis*-7,8-dihydrodiols (C**XXXVIII**), and anthranilic acid (C**XXXIX**) (Boyd et al. 1987; 1993):



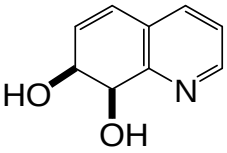
CXXXV



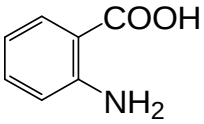
CXXXVI



CXXXVII

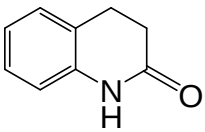


CXXXVIII

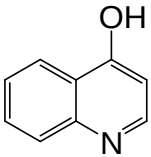


CXXXIX

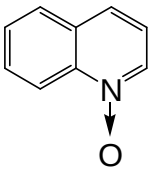
The same bacterium produces enantiopure quinoline *cis*-5,6- and 7,8-dihydrodiols using toluene dioxygenase (Boyd et al. 2002). *Desulfobacterium indolicum* hydroxylates quinoline to 2-quinolinone and then to 3,4-dihydro-2-quinolone (**CXL**) under anaerobic conditions (Johansen et al. 1997; Licht et al. 1997). Quinaldine 4-oxidase purified from an *Arthrobacter* sp. oxidizes quinoline to 4-hydroxyquinoline (**CXLI**) (Stephan et al. 1996):



CXL



CXLI

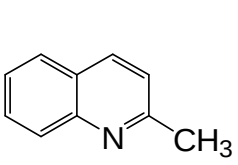


CXLII

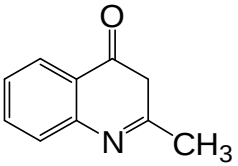
The fungus *Cunninghamella elegans* oxidized quinoline (**CXXV**) to quinoline *N*-oxide (**CXLII**) with a yield of 65% in 7 days (Sutherland et al. 1994a).

Alkylquinolines (including quinine)

The quinaldine 4-oxidase from *Arthrobacter* sp. oxidizes quinaldine (2-methylquinoline, **CXLIII**) to 2-methyl-4-quinolinone (**CXLIV**) (Stephan et al. 1996):

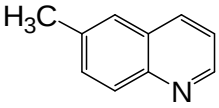


CXLIII

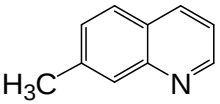


CXLIV

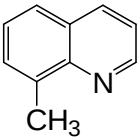
Pseudomonas sp. hydroxylates 6-, 7-, and 8-methylquinolines (**CXLV, CXLVI** and **CXLVII**) at unidentified positions (Aislabie et al. 1990) and *P. putida* hydroxylates 6-methylquinoline, probably at the 2-position (Rothenburger and Atlas 1993):



CXLV

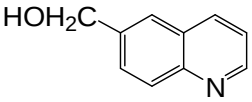


CXLVI

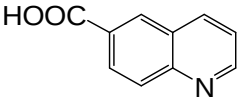


CXLVII

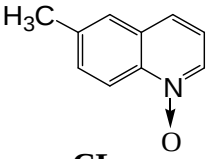
Cunninghamella elegans transforms 6-methylquinoline to 6-hydroxymethylquinoline (**CXLVIII**), quinoline-6-carboxylic acid (**CXLIX**), and 6-methylquinoline-*N*-oxide (**CL**) (Mountfield and Hopper 1998):



CXLVIII

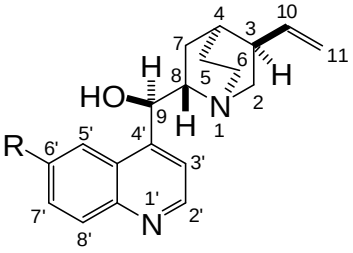


CXLIX

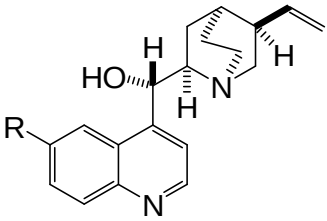


CL

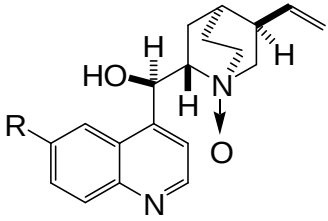
The 6'-methoxylated cinchona alkaloid quinine (**CLI**), its diastereomer quinidine (**CLII**), and its non-methoxylated analogs cinchonidine (**CLIII**) and cinchonine (**CLIV**) may be metabolized by fungi and bacteria (Siebers-Wolff et al. 1993; Shibuya et al. 2003). The fungus *Xylaria* sp. metabolizes quinine, quinidine, cinchonidine, and cinchonine to the corresponding 1-*N*-oxides (C**LV**, yield 90%, C**LVI**, yield 71%, C**LVII**, yield 82%, and C**LVIII**, yield 52%), respectively, in two weeks (Shibuya et al. 2003):



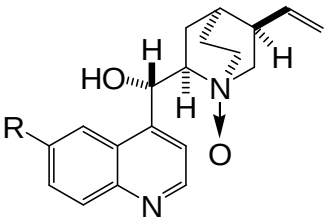
CLI R=OCH_3
CLIII R=H



CLII R=OCH_3
CLIV R=H

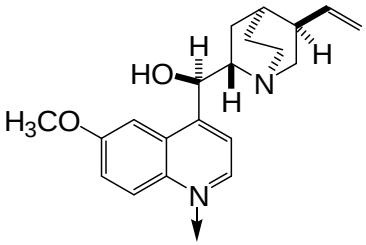


CLV R=OCH_3
CLVII R=H

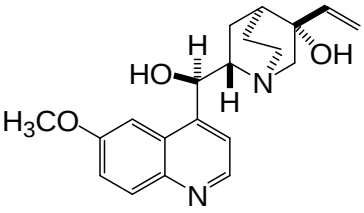


CLVI R=OCH_3
CLVIII R=H

Mycobacterium smegmatis produces quinidine 1-*N*-oxide from quinidine; and the fungus *Pellicularia filamentosa* produces cinchonidine 1-*N*-oxide from cinchonidine (Siebers-Wolff et al. 1993). The fungus *Microsporum gypseum* produces both of the possible *N*-oxides: quinine 1-*N*-oxide and quinine 1'-*N*-oxide (C**LIX**) from quinine, but *Cunninghamella echinulata* instead produces 3-hydroxyquinine (C**LX**) (Siebers-Wolff et al. 1993):

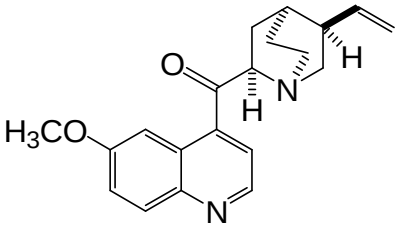


CLIX



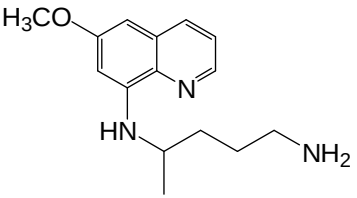
CLX

Quininone (C**LXI**) was reduced by the yeast *Hansenula anomala* var. *schneggii* to quinidine (yield 50%) in 7 days (Ray et al. 1983):

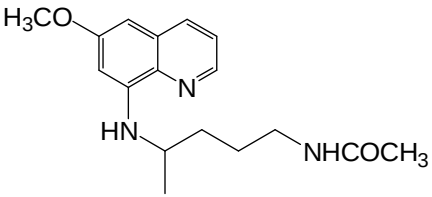


CLXI

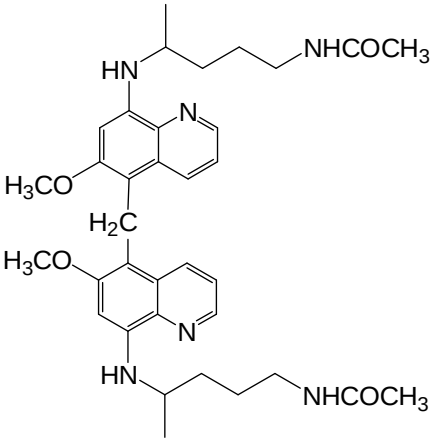
The transformation of the synthetic antimalarial primaquine (C**LXII**) by the yeast *Candida tropicalis* produced two metabolites, including primaquine *N*-acetate (C**LXIII**, yield 3.9%) and a small amount of a primaquine dimer with a methylene bridge (C**LXIV**, yield 0.4%), in 13 days (Clark et al. 1984a):



CLXII

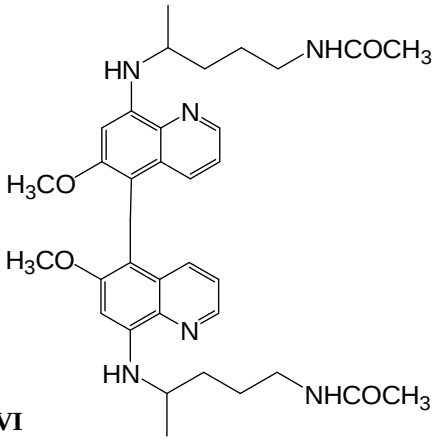


CLXIII



CLXIV

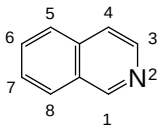
The bacterium *Streptomyces rimosus* also produces the acetylated derivative from primaquine, but the dimer it produces (C**LXV**) lacks the methylene bridge (Clark et al. 1984b):



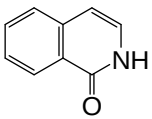
CLXVI

Isoquinoline

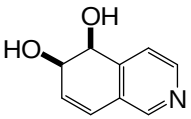
Several bacteria metabolize isoquinoline (C**LXVII**) (Fetzner 1998). *Pseudomonas putida* converts it to 1-isoquinolinone (isocarbostyril, C**LXVIII**), the *cis*-5,6- and 7,8-dihydrodiols (C**LXIX** and C**LXX**, respectively), and the 4-, 5-, and 8-hydroxyisoquinolines (C**LXXI**, C**LXXII,** and C**LXXIII**, respectively) (Boyd et al. 1987; 1993). Isoquinoline is also oxidized to 1-isoquinolinone by various other bacteria (Aislabie et al. 1989; Röger et al. 1990; Sutherland et al. 1998a) and by purified quinaldine 4-oxidase from *Arthrobacter* sp. (Stephan et al. 1996). *Cunninghamella elegans* oxidized isoquinoline to isoquinoline *N*-oxide (C**LXXIV**) with a yield of 3% in 7 days (Sutherland et al. 1994a).



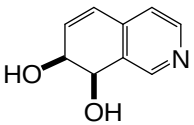
CLXVII



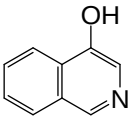
CLXVIII



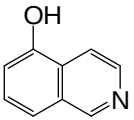
CLXIX



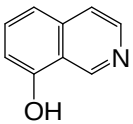
CLXX



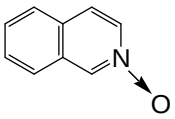
CLXXI



CLXXII



CLXXIII

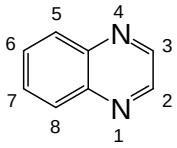


CLXXIV

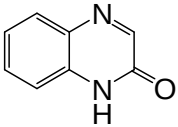
2.3. Transformation of benzodiazines and benzothiazines

Quinoxaline

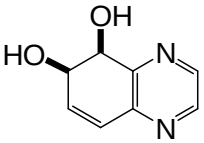
Quinoxaline (C**LXXV**) is converted to 2-quinoxalinone (C**LXXVI**), quinoxaline *cis*-5,6-dihydrodiol (C**LXXVII**), and 5-hydroxyquinoxaline (C**LXXVIII**) by *P. putida* (Boyd et al. 1987; 1993):



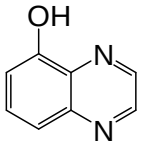
CLXXV



CLXXVI

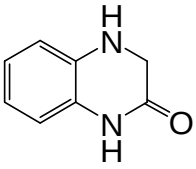


CLXXVII

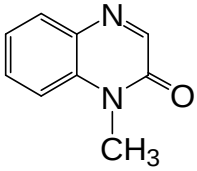


CLXXVIII

Streptomyces badius transforms quinoxaline to 3,4-dihydro-2-quinoxalinone (C**LXXIX**) and 2-quinoxalinone (Sutherland et al. 1996); and *S. viridosporus* transforms quinoxaline to 1-methyl-2-quinoxalinone (C**LXXX**, yield 12%) and 2-quinoxalinone (yield 8%) (Sutherland et al. 1998a):



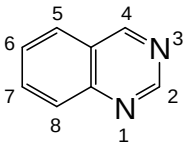
CLXXIX



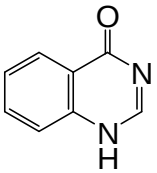
CLXXX

Quinazoline

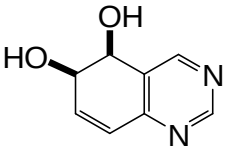
Quinazoline (C**LXXXI**) is converted by *Pseudomonas putida* to 4-quinazolinone (C**LXXXII**), quinazoline *cis*-5,6-dihydrodiol (C**LXXXIII**), and 5,6,7,8-tetrahydroquinazoline-*cis*-5,6-diol (C**LXXXIV**) (Boyd et al. 1987; 1993). It is oxidized to 4-quinazolinone by the quinaldine 4-oxidase from *Arthrobacter* sp. (Stephan et al. 1996) and further to 2,4-quinazolinedione (**C**, yield 4%) by *S. viridosporus* (Sutherland et al. 1998a). The fungus *Aspergillus niger* oxidizes quinazoline to both 4-quinazolinone and 2,4-quinazolinedione (Sutherland et al. 2011):



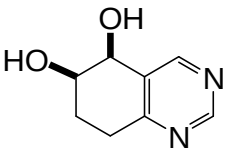
CLXXX



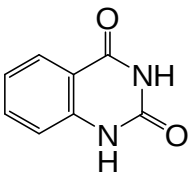
CLXXXI



CLXXXII



CLXXXIII

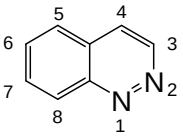


CLXXXIV

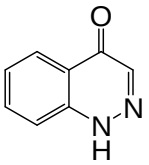
Cinnoline

Cinnoline (C**LXXXV**) is oxidized by the quinaldine 4-oxidase from *Arthrobacter* sp. to produce 4-cinnolinone (C**LXXXVI**) (Stephan et al. 1996). In contrast, *Cunninghamella*

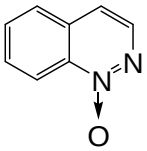
elegans and *Aspergillus niger* oxidize it to both of the possible *N*-oxides, the 1-oxide and the 2-oxide (C**LXXXVII** and C**LXXXVIII**) (Sutherland et al. 1998b):



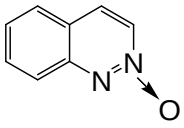
CLXXXV



CLXXXVI



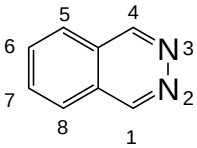
CLXXXVII



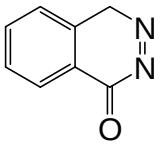
CLXXXVIII

Phthalazine

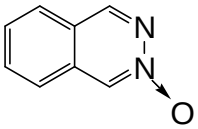
Phthalazine (C**LXXXIX**) is oxidized to 1-phthalazinone (**CXC**) by the quinaldine 4-oxidase from *Arthrobacter* sp. (Stephan et al. 1996) as well as by whole cells of *S. viridosporus* (Sutherland et al. 1998a). The fungi *Fusarium verticillioides* (= *F. moniliforme*) and *A. niger* also oxidize it to 1-phthalazinone (Sutherland et al. 1999; 2011), but *Cunninghamella elegans* oxidizes it instead to phthalazine *N*-oxide (**CXCI**) (Sutherland et al. 1999):



CLXXXIX



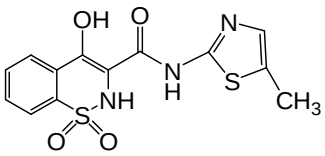
CXC



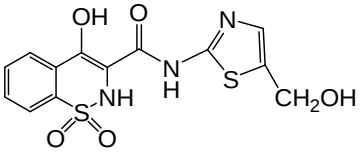
CXCI

Benzothiazines

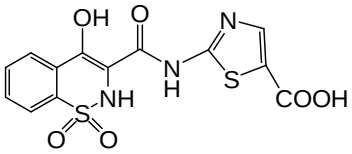
The microbial transformation of the anti-inflammatory drug meloxicam, a benzothiazine derivative (**CXCII**), by *Cunninghamella blakesleeana* produced three metabolites after 5 days: 5-hydroxymethylmeloxicam (**CXCIII**, 93% yield), 5-carboxy meloxicam (**CXCIV**, trace amounts), and an oxamic acid derivative of meloxicam (**CXCV**, yield 4%) (Prasad et al. 2009):



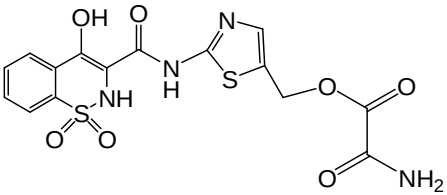
CXCII



CXCIII



CXCIV

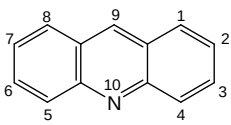


CXCV

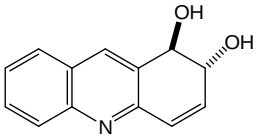
2.4. Transformation of benzoquinolines

Acridine

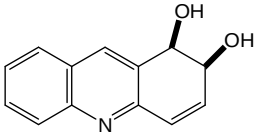
The transformation of acridine (benzo[*b*]quinoline, **CXCVI**) by *C. elegans* leads to the formation of acridine *trans*-1,2-dihydrodiol (**CXCVII**) with small amounts of 2-hydroxyacridine (**CXCVIII**) (Sutherland et al. 1994b):



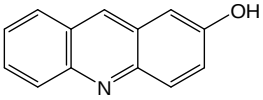
CXCVI



CXCVII

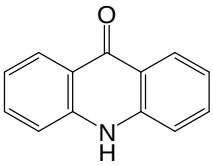


CXCVIII

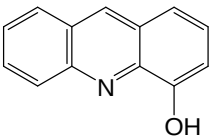


CXCIX

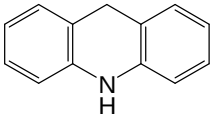
Acridine *cis*-1,2-dihydrodiol (**CXCIX**) is produced from acridine by a mutant strain of *Pseudomonas fluorescens* (Bianchi et al. 1997). *Sphingomonas* sp. metabolizes acridine to acridin-9-one (**CC**) (van Herwijnen et al. 2004). Acridine was transformed by growing cells of *Mycobacterium vanbaalenii*, however, to four metabolites: acridine *cis*-1,2-dihydrodiol (yield 1.1%), 4-hydroxyacridine (**CCI**, yield 5.4%), acridin-9-one (yield 1.1%), and 9,10-dihydroacridine (**CCII**, yield 55.2%) in 7 days (Sutherland et al. 2009):



CC



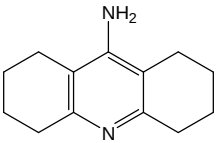
CCI



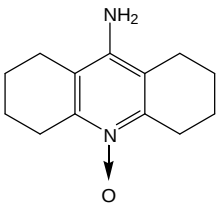
CCII

The partially hydrogenated 9-amino-1,2,3,4,5,6,7,8-octahydroacridine (**CCIII**) was transformed into an *N*-oxide

(**CCIV**) by a resting cell suspension of the fungus *Cunninghamella verticillata* VKPM F-430 with a yield of 90% (Parshikov et al. 1994a):



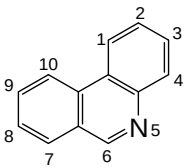
CCIII



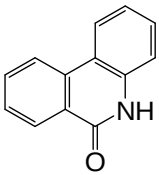
CCIV

Phenanthridine

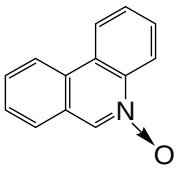
Phenanthridine (benzo[*c*]quinoline, **CCV**) is transformed by *Streptomyces viridosporus* to phenanthridin-6-one (**CCVI**, yield 25%) (Sutherland et al. 1998a). The fungus *Umbelopsis ramanniana* (*Mucor ramannianus*) transforms phenanthridine to phenanthridine *N*-oxide (**CCVII**) as well as phenanthridin-6-one (Sutherland et al. 2005):



CCV



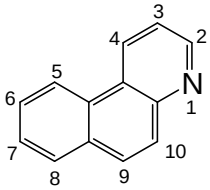
CCVI



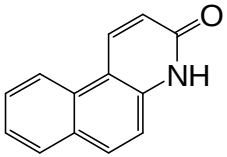
CCVII

Benzo[f]quinoline

Benzo[*f*]quinoline (**CCVIII**) is degraded, apparently via benzo[*f*]quinolin-2-one (**CCIX)**, by *Mycobacterium gilvum* (Willumsen et al. 2001):

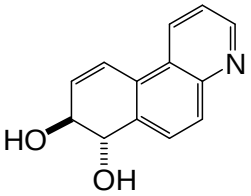


CCVIII

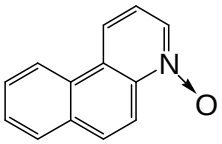


CCIX

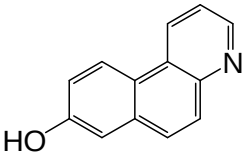
U. ramanniana transforms benzo[*f*]quinoline to the *trans*-7,8-dihydrodiol (**CCX**), the *N*-oxide (**CCXI**), and 7-hydroxybenzo[*f*]quinoline (**CCXII**) (Sutherland et al. 2005):



CCX



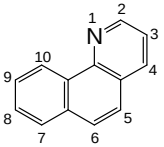
CCXI



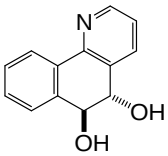
CCXII

Benzo[h]quinoline

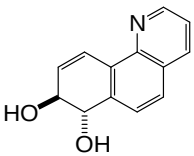
U. ramanniana also transforms benzo[*h*]quinoline (**CCXIII**) to the benzo[*h*]quinoline *trans*-5,6-dihydrodiol (**CCXIV**), benzo[*h*]quinoline *trans*-7,8-dihydrodiol (**CCXV**), and 7-hydroxybenzo[*h*]quinoline (**CCXVI**) (Sutherland et al. 2005):



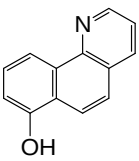
CCXIII



CCXIV



CCXV

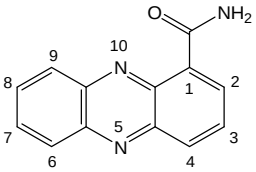


CCXVI

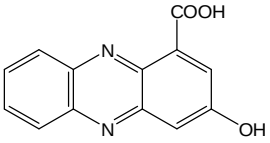
2.5. Transformation of phenazine and phenothiazine

Phenazine

Phenazine 1-carboxamide (**CCXVII**) is transformed by cultures of *Aspergillus sclerotiorum*, via phenazine 1-carboxylic acid, to 3-hydroxyphenazine 1-carboxylic acid (**CCXVIII**) (Hill and Johnson 1969):



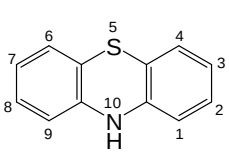
CCXVII



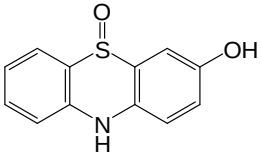
CCXVIII

Phenothiazine

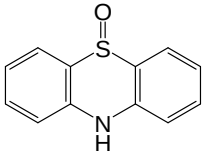
The transformation of phenothiazine (**CCXIX**) by cultures of *Cunninghamella elegans* forms two metabolites, 3-hydroxyphenothiazine sulfoxide (**CCXX**) and phenothiazine sulfoxide (**CCXXI**) (Sutherland et al. 2001):



CCXIX



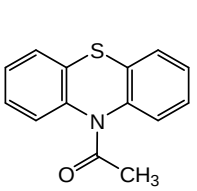
CCXX



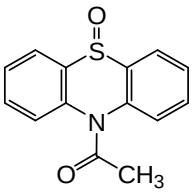
CCXXI

During the transformation of *N*-acetylphenothiazine (**CCXXII**) by *C. verticillata*, five metabolites were formed: the intermediate phenothiazine, phenothiazine sulfoxide (yield 5%),

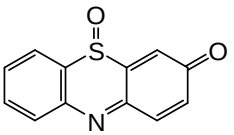
N-acetylphenothiazine sulfoxide (**CCXXIII**, yield 17%), phenothiazin-3-one (**CCXXIV**, yield 4%), and phenothiazine-*N*-glucoside (**CCXXV**, yield 4%) in 72 h (Parshikov et al. 1999):



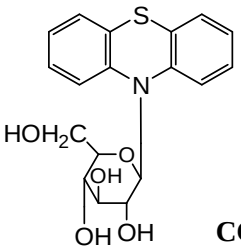
CCXXII



CCXXIII



CCXXIV

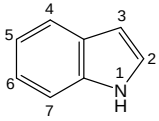


CCXXV

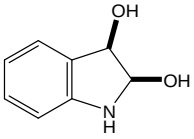
2.6. Transformation of indole, carbazole, and the carbolines

Indole

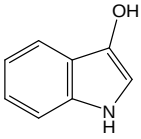
Many bacteria transform indole (**CCXXVI**) by different pathways (Oshima et al. 1965; Fetzner 1998). In one classic pathway, the naphthalene 1,2-dioxygenase from *Pseudomonas putida* oxidizes indole to indole *cis*-2,3-dihydrodiol (**CCXXVII**), which loses water spontaneously to produce indoxyl (3-hydroxyindole, **CCXXVIII**), which then is oxidized in air to indigo (**CCXXIX**) (Ensley et al. 1983):



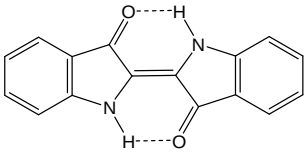
CCXXVI



CCXXVII

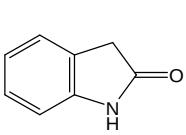


CCXXVIII

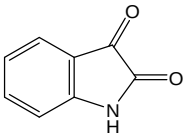


CCXXIX

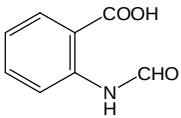
Other bacteria, including *Desulfobacterium indolicum* and some *P. putida* strains, transform indole to oxindole (2-indolinone, **CCXXX**), isatin (2,3-indolinedione, **CCXXXI**), and anthranilic acid (Johansen et al. 1997; Licht et al. 1997; Li et al. 2009):



CCXXX



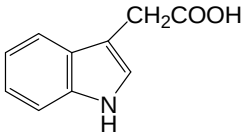
CCXXXI



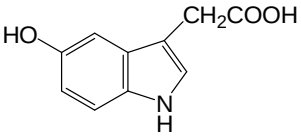
CCXXXII

Aspergillus niger converts indole to an indoxyl intermediate and then cleaves the heterocyclic ring to produce *N*-formylanthranilic acid (**CCXXXII**) (Kamath and Vaidyanathan 1990). The mushroom *Pleurotus ostreatus* degrades indole via isatin (Ren et al. 2006).

The ergot fungus *Claviceps purpurea* transforms indole-3-acetic acid (**CCXXXIII**); the major product is 5-hydroxyindole-3-acetic acid (**CCXXXIV**) (Teuscher and Teuscher 1965):

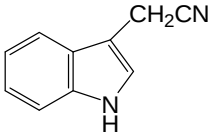


CCXXXIII

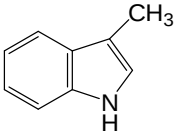


CCXXXIV

In the transformation of 3-indolylacetonitrile (**CCXXXV**) by *Beauveria bassiana*, the main product was 3-methylindole (**CCXXXVI**, yield 46%) in 13 days (Boaventura et al. 2004):

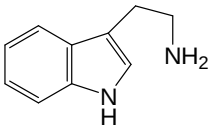


CCXXXV

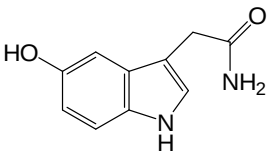


CCXXXVI

Tryptamine (**CCXXXVII**) was transformed by *A. niger* to 5-hydroxyindole-3-acetamide (**CCXXXVIII**, yield 24%) in 13 days (Boaventura et al. 2004):



CCXXXVII

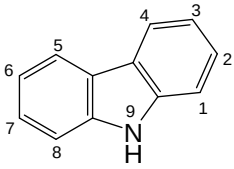


CCXXXVIII

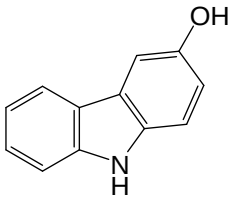
Carbazole

A great variety of bacteria metabolize carbazole (**CCXXXIX**), usually by a naphthalene-like oxidation of a ring carbon or by angular dioxygenation, to produce *cis*-dihydrodiols

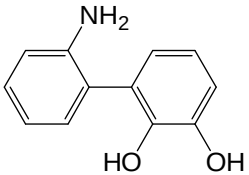
(Bressler and Fedorak 2000; Larentis et al. 2011). In the first method, carbazole is transformed by *Pseudomonas* sp. using naphthalene 1,2-dioxygenase and by *Sphingomonas yanoikuyae* B8/36 using biphenyl 2,3-dioxygenase, presumably via a transient *cis*-dihydrodiol in both bacteria, to produce 3-hydroxycarbazole (**CCXL**) (Resnick et al. 1993). In the second method, *Pseudomonas resinovorans*, *Pseudomonas* sp., and *Nocardioides aromaticivorans* transform carbazole by angular dioxygenation using carbazole 1,9*a*-dioxygenase, via 2'-amino-2,3-dihydroxybiphenyl (**CCXLI**), to anthranilic acid and 2-hydroxypenta-2,4-dienoic acid (**CCXLII**) (Ouchiyama et al. 1993; Nojiri et al. 2001; Inoue et al. 2006):



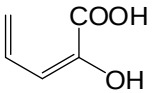
CCXXXIX



CCXL



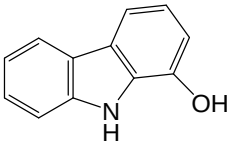
CCXLI



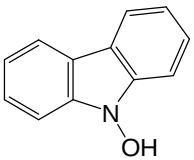
CCXLII

Pseudomonas sp. and *Flavobacterium* sp. transform carbazole via unknown pathways to indole-3-acetic acid and other

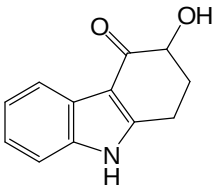
ring-cleavage products (Gieg et al. 1996; Obata et al. 1997). Using other pathways, *Ralstonia* sp. oxidizes carbazole to the 1-, 3-, and 9-hydroxycarbazoles (**CCXLIII**, **CCXL,** and **CCXLIV**, respectively) and to 3-hydroxy-1,2,3,9-tetrahydrocarbazol-4-one (**CCXLV**) (Waldau et al. 2009):



CCXLIII

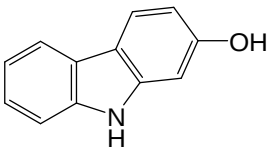


CCXLIV



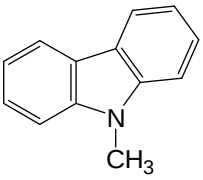
CCXLV

Aspergillus flavus transforms carbazole to 3-hydroxycarbazole, the main product, and small amounts of 1-hydroxycarbazole and 2-hydroxycarbazole (**CCXLVI**) in 2 days (Lobastova et al. 2004):

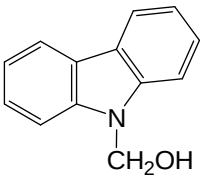


CCXLVI

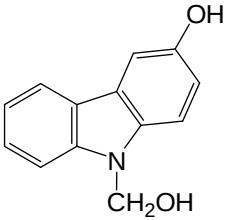
N-Methylcarbazole (**CCXLVII**) is biotransformed by *Cunninghamella echinulata* to carbazole, *N*-hydroxymethylcarbazole (**CCXLVIII**), 3-hydroxycarbazole, and 3-hydroxy-*N*-hydroxymethylcarbazole (**CCXLIX**) (Yang and Davis 1992):



CCXLVII

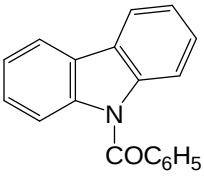


CCXLVIII

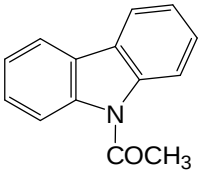


CCXLIX

The transformation of *N*-benzoylcarbazole (**CCL**) and *N*-acetylcarbazole (**CCLI**) by *A. flavus* forms carbazole as the main product and small quantities of 1-, 2-, and 3-hydroxycarbazoles (Lobastova et al. 2004):



CCL

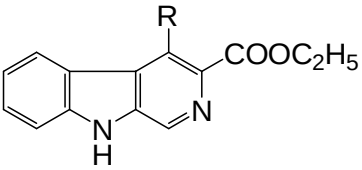


CCLI

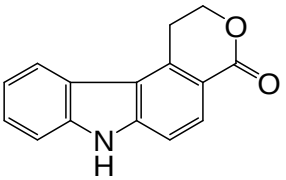
Beta-carbolines

The metabolism of ethyl-β-carboline-3-carboxylates (**CCLII**) by cultures of bacteria and fungi has been investigated (Neef et al. 1982). The bacteria *Streptomyces lavendulae* and *S. griseus* hydroxylated the 4-ethyl and 4-*n*-propyl derivatives of ethyl-β-carboline-3-carboxylate (**CCLII** with R = C_2H_5 or C_3H_7), producing the corresponding lactones (**CCLIII** and **CCLIV**) by

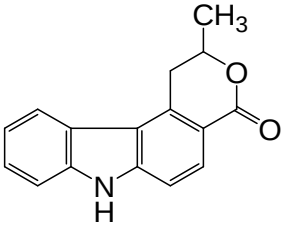
transesterification. The yields in these processes were 7-8% (Neef et al. 1982):



CCLII, R= C_2H_5; C_3H_7

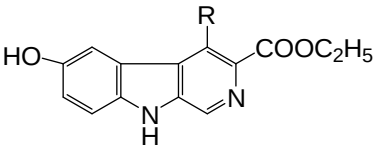


CCLIII

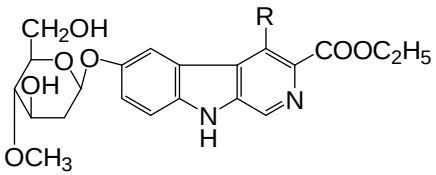


CCLIV

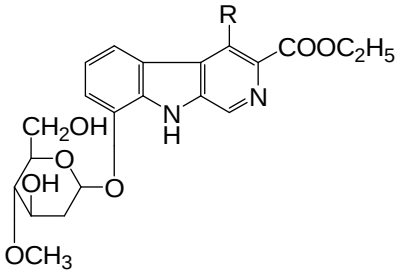
Beauveria bassiana hydroxylates the same compounds, usually forming a mixture of glucosides. Only in the case of 4-unsubstituted β-carboline-3-carboxylate (**CLXVIII**, R=H) has the non-glucosylated 6-hydroxy derivative (**CCLV**, yield 62%) been found. If there is an alkyl substituent in **CCLII** in position 4, then the 6- and 8-(4'-*O*-methyl)-β-glucosides (**CCLVI** and **CCLVII**, respectively), are produced. An increase in chain length of the alkyl substituent leads to an increase in the amount of the 8-glucoside (Neef et al. 1982):



CCLV, R=H



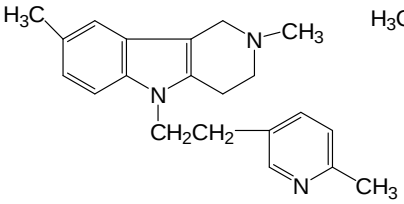
CCLVI, R=CH_3; C_2H_5; C_3H_7



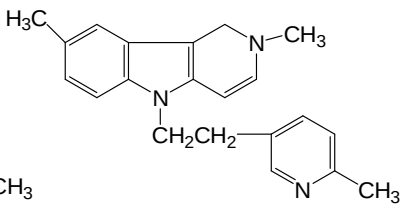
CCLVII, R=CH_3; C_2H_5; C_3H_7

Gamma-carbolines

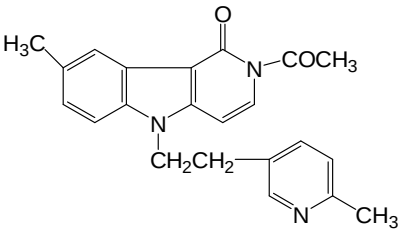
Penicillium simplicissimum transforms the antihistamine 2,3,4,5-tetrahydro-2,8-dimethyl-5-(2-(6-methyl-3-pyridyl)ethyl)-pyrido[4,3-*b*]indole (latrepirdine or Dimebon, **CCLVIII**) with the formation of a 2,3-dehydro derivative (**CCLIX**) and a 4-acetyl, 5-carbonyl, 2,3-dehydro derivative (**CCLX)** in 10.0% yields (Dovgilevich et al. 1991):



CCLVIII



CCLIX



CCLX

The 4-acetyl, 5-carbonyl, 2,3-dehydro derivative may be formed by 4*N*-demethylation and 5-position oxidation of the 2,3-dehydro derivative, followed by acetylation of the nitrogen at position 4 of the γ-carboline ring (Dovgilevich et al. 1991).

Chapter 3. Microbial transformations of quinolones and related drugs

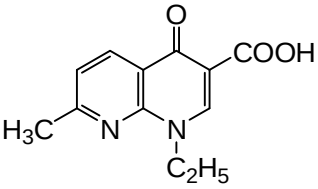
Because quinolones are widely used in medical and veterinary practices as well as in animal production and aquaculture in many countries (Martinsen and Horsberg, 1995; Andriole, 2000), and the problem of quinolone resistance among pathogenic bacteria remains serious (Cattoir and Nordmann, 2009), it will require the development of new antimicrobial agents.

It is likely that modification of the chemical structure of quinolones can help to solve these problems (Murphy et al., 2009). In addition, new quinolone derivatives obtained by the methods of regio- and stereospecific microbial biotransformation (Lehman and Stewart, 2001) combined with chemical synthesis may be useful in the synthesis of new generations of quinolones.

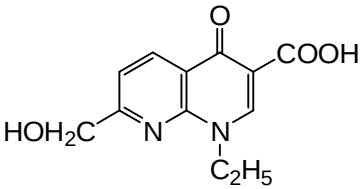
3.1. Transformations of first-generation quinolones and their analogs

Nalidixic acid (**CCLXI**), a derivative of 1,8-naphthyridine, inhibits DNA gyrase in bacteria (Sugino et al., 1977). It is usually considered the first of the quinolone-related compounds to be investigated as an antibacterial agent, even though it is, strictly speaking, not a quinolone (Lesher et al., 1962). Nalidixic acid has been used against urinary tract infections caused by Gram-negative bacteria (Sabbour et al., 1984) and it also has antimalarial properties (Divo et al., 1988; Mahmoudi et al., 2003).

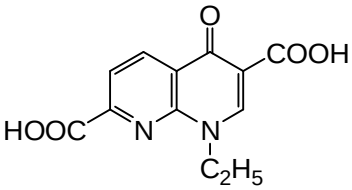
The transformation of nalidixic acid by the fungus *Penicillium adametzi* 737 has been studied (Hamilton et al., 1969). After 24 hours, the formation of a hydroxymethyl derivative (**CCLXII**) was observed with a yield reaching 60%. Its further oxidation led to the formation of a 3,7-dicarboxylic acid (**CCLXIII**) (Hamilton et al., 1969):



CCLXI

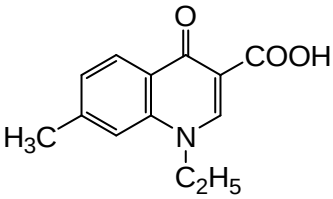


CCLXII

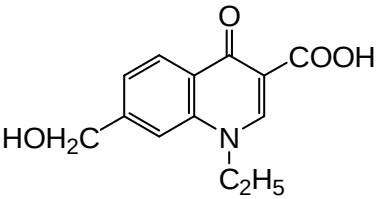


CCLXIII

The microbial transformation of analogues of nalidixic acid has also been of great interest. In a growing culture of *P. adametzi* ATCC 10407, oxidation of the methyl group of 3-carboxy-1-ethyl-7-methyl-4-quinolone (**CCLXIV**) to the alcohol, 3-carboxy-1-ethyl-7-hydroxymethyl-4-quinolone (**CCLXV**)**,** was observed; the aromatic carbon atoms were not involved in this process (Kieslich et al., 1973):



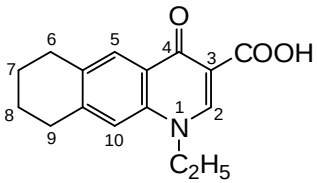
CCLXIV



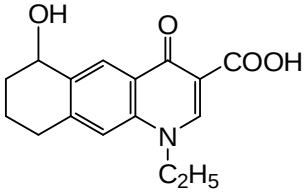
CCLXV

From the same substrate, the bacterium *Streptomyces surinam* formed an *O*-acetylated derivative at the carboxyl group instead. *P. adametzi* also metabolized a similar compound with a methoxyl group by demethylating it (Kieslich et al., 1973).

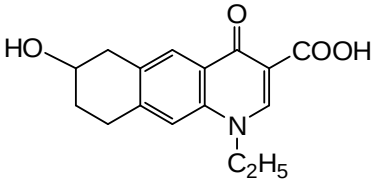
A similar pattern is observed in the oxidation of a more complicated quinolone with an additional saturated ring, 1-ethyl-4-oxo-1,4,6,7,8,9-hexahydrobenzo[*g*]quinoline-3-carboxylic acid (**CCLXVI**), by three different microorganisms (Kieslich et al., 1973). The fungus *Beauveria bassiana* ATCC 7159 introduced a hydroxyl group at position 6, forming the 6-hydroxy derivative (**CCLXVII**); *P. adametzi* formed the 7- and 8-hydroxy derivatives (**CCLXVIII** and **CCLXIX**); and *Streptomyces achromogenes* formed the 6-, 7-, and 8-hydroxy derivatives (**CCLXVII**, **CCLXVIII** and **CCLXIX**) (Kieslich et al., 1973):



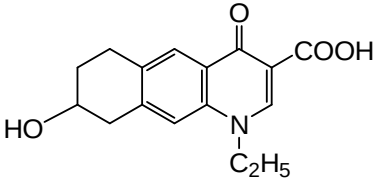
CCLXVI



CCLXVII

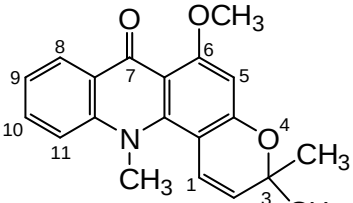


CCLXVIII

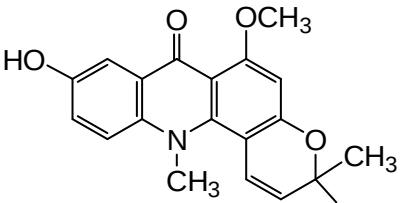


CCLXIX

Some analogs of acronycine (**CCLXX**), a pyranoacridone alkaloid, have antitumor activity (Nguyen et al., 2009) and antimalarial activity (Fujioka et al., 1989; 1990; Basco et al., 1994; Hari et al., 2010). The oxidation of acronycine by growing cultures of fungi in the genus *Cunninghamella* results in hydroxylation of the benzene ring (Betts et al., 1974). The most active strain, *C. echinulata* NRRL 3665, transformed the starting material into 9-hydroxyacronycine (**CCLXXI**) with a yield of 30% in 70 hours (Betts et al., 1974):

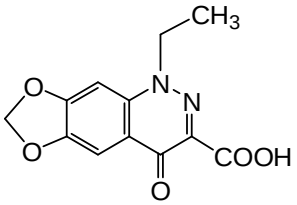


CCLXX

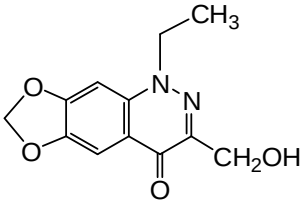


CCLXXI

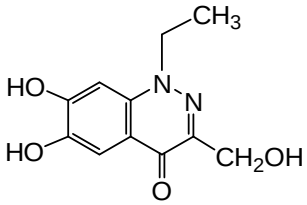
The transformation of cinoxacin (**CCLXXII**), a 4-cinnolone derivative that has been used for treating bacterial urinary tract infections [Sisca et al., 1983; Sabbour et al., 1984], was studied with *B. bassiana* ATCC 7159. Within 20 days, formation of two metabolites, 1-ethyl-1,4-dihydro-3-(hydroxymethyl)[1,3]dioxolo[4,5-*g*]cinnolin-4-one (**CCLXXIII**, yield 47.3%) and 1-ethyl-1,4-dihydro-6,7-dihydroxy-3-(hydroxymethyl)cinnolin-4-one (**CCLXXIV**, yield 5.6%), was observed (Parshikov et al., 2002a,b,c):



CCLXXII

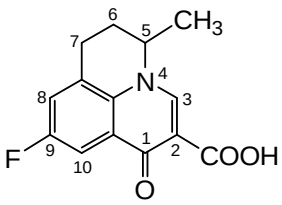


CCLXXIII

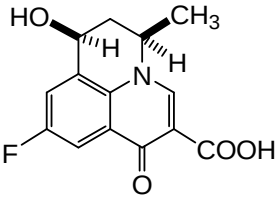


CCLXXIV

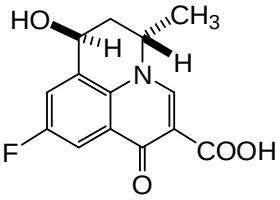
Flumequine (**CCLXXV**) is a quinolone derivative, produced as a racemic mixture, that is used in aquaculture in many countries as an antibacterial agent (Martinsen and Horsberg, 1995; Rigos and Troisi, 2005; Kim and Cerniglia, 2010). In the stereospecific transformation of the flumequine isomers by growing cultures of *Cunninghamella elegans*, the formation of two diastereomers, 7-hydroxyflumequine (**CCLXXVI**, yield 23%, and **CCLXXVII**, yield 43%) and also 7-oxoflumequine (**CCLXXVIII**, 11% yield) was observed within 7 days (Williams et al., 2007):



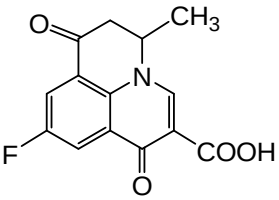
CCLXXV



CCLXXVI



CCLXXVII



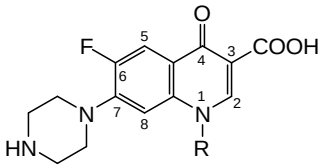
CCLXXVIII

3.2. Transformation of second-generation quinolones

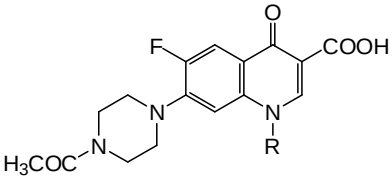
The emergence of norfloxacin (**CCLXXIX**) as an antibacterial agent marked the beginning of the second generation of quinolones (Appelbaum and Hunter, 2000; Brighty and Gootz, 2000). It is still used for treatment of urinary tract infections [Sabbour et al., 1984] and conjunctivitis (Miller et al., 1992); laboratory tests have shown that it also possesses antimalarial activity (Sarma, 1989; Mahmoudi et al., 2003).

During the transformation of norfloxacin by the fungus *Pestalotiopsis guepini* P-8, four metabolites, *N*-acetylnorfloxacin (**CCLXXX**, yield 55.4%), desethylene *N*-acetylnorfloxacin (**CCLXXXI**, yield 8.8%), *N*-formylnorfloxacin (**CCLXXXII**, yield 3.6 %) and 7-amino-1-ethyl-6-fluoro-4-oxo-1,4-

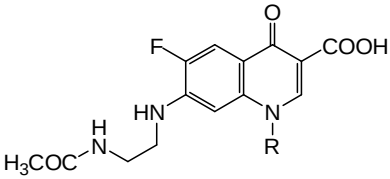
dihydroquinoline-3-carboxylic acid (**CCLXXXIII**, yield 2.1%), were obtained (Parshikov et al., 2001a; Williams et al., 2004), all of which are known from human and animal studies (Dalhoff and Bergan 1998; Pauliukonis et al., 1984):



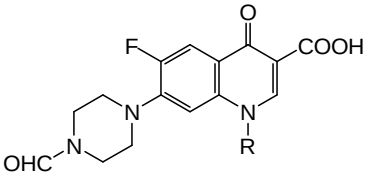
CCLXXIX, R=C_2H_5
CCLXXXV, R=C_3H_5



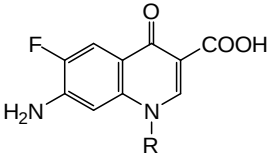
CCLXXX, R=C_2H_5
CCLXXXVI, R=C_3H_5



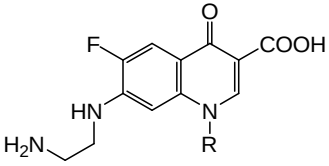
CCLXXXI, R=C_2H_5
CCLXXXVII, R=C_3H_5



CCLXXXII, R=C_2H_5
CCLXXXVIII, R=C_3H_5



CCLXXXIII, R=C_2H_5
CCLXXXIX, R=C_3H_5

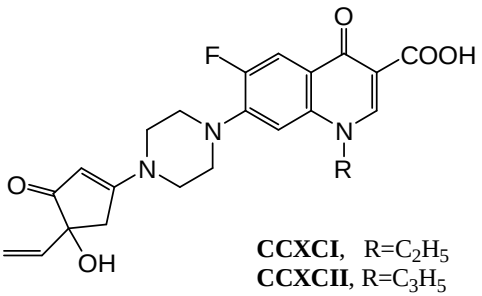


CCLXXXIV, R=C_2H_5
CCXC, R=C_3H_5

In an attempt to identify biotransformation products and the enzymes involved in their formation, a wood-decaying white-rot basidiomycete, *Trametes versicolor*, was grown in a medium containing norfloxacin (Prieto et al., 2011). It produced desethylene *N*-acetylnorfloxacin and 7-amino-1-ethyl-6-fluoro-4-

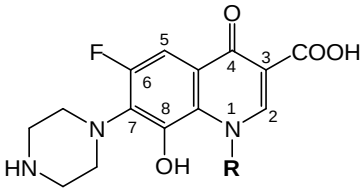
oxo-1,4-dihydroquinoline-3-carboxylic acid from norfloxacin, plus desethylene norfloxacin (**CCLXXXIV**) (Prieto et al., 2011). Although these products have not been specifically tested, they most likely have less antibacterial activity than norfloxacin or none at all (Dalhoff and Bergan 1998).

The fungus *Trichoderma viride*, when grown in the presence of norfloxacin and ciprofloxacin for 16 days, formed two conjugates (CC**XCI** and CC**XCII**) with yields of 42% and 31%. They were formed by the reaction of norfloxacin with a secondary metabolite of the fungus (Parshikov et al., 2000a; Parshikov et al., 2002):

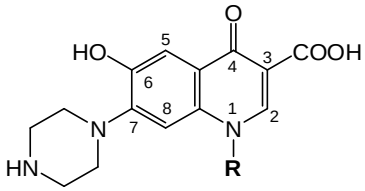


CCXCI, R=C_2H_5
CCXCII, R=C_3H_5

Norfloxacin was also transformed by growing cultures of *Microbacterium* sp. 4N2-2 within 14 days to four metabolites: *N*-acetylnorfloxacin, desethylene-*N*-acetylnorfloxacin, 8-hydroxynorfloxacin (CC**XCIII**), and 6-hydroxynorfloxacin (CC**XCV**) (Kim et al., 2011):

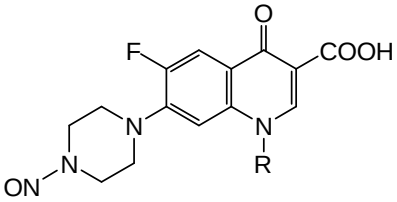


CCXCIII, R=C_2H_5
CCXCIV, R=C_3H_5



CCXCV, R=C_2H_5
CCXCVI, R=C_3H_5

Transformation of norfloxacin by growing cultures of an environmental isolate, *Mycobacterium gilvum* PYR-GCK, led to the formation not only of the inactive *N*-acetylnorfloxacin but also of *N*-nitrosonorfloxacin (**CCXCVII**) (Adjei et al., 2006):



CCXCVII, R=C_2H_5
CCXCVIII, R=C_3H_5

The *N*-acetylation of norfloxacin by cultures of an *Escherichia coli* strain from wastewater with the variant gene *aac(6')-Ib-cr* has also been observed (Jung et al., 2009).

The fluoroquinolone ciprofloxacin (**CCLXXXV**) has a broad spectrum of activity and is widely prescribed for diseases caused by many bacteria (Sharma et al., 2010). It shows antimalarial activity in vitro against chloroquine-sensitive strains of *Plasmodium falciparum*, but it was tested unsuccessfully for

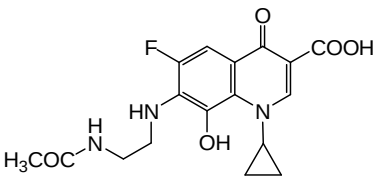
treating patients with chloroquine-resistant malaria (Divo et al., 1988; Watt et al., 1991). Ciprofloxacin is able to interrupt the cell cycle of tumor cell lines (Kloskowski et al., 2010).

During the oxidation of ciprofloxacin by the wood-decaying brown-rot fungus *Gloeophyllum striatum*, the metabolites 8-hydroxyciprofloxacin (**CCXCIV**) and 6-hydroxyciprofloxacin (**CCXCVI**) were detected [Wetzstein et al., 1999].

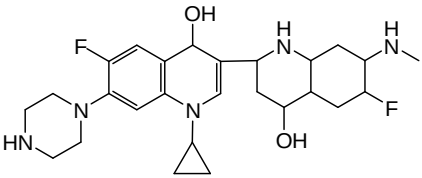
The transformation of ciprofloxacin by growing cultures of the fungus *Umbelopsis ramanniana* (= *Mucor ramannianus*) produces one inactive metabolite, *N*-acetylciprofloxacin (**CCLXXXV**), with a yield of 89.0% (Parshikov et al., 1999). The transformation of ciprofloxacin by *P. guepini* P-8 produces four metabolites: *N*-acetylciprofloxacin (**CCLXXXV**, yield 52.0%), desethylene-*N*-acetylciprofloxacin (**CCLXXXVI**, yield 9.2%), *N*-formylciprofloxacin (**CCLXXXVII**, yield 4.2%) and 7-amino-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**CCLXXXVIII**, yield 2.3%) (Parshikov et al., 2001a,c).

The *N*-acetylation of ciprofloxacin by growing cultures of *E. coli* that have *aac(6')-Ib-cr* has been observed [Robicsek et al., 2006; Jung et al., 2009]. Transformation of ciprofloxacin by growing cultures of *M. gilvum* leads to the formation not only of *N*-acetylciprofloxacin (**CCLXXXV**) but also of *N*-nitrosociprofloxacin (**CCXCVIII**) (Adjei et al., 2007).

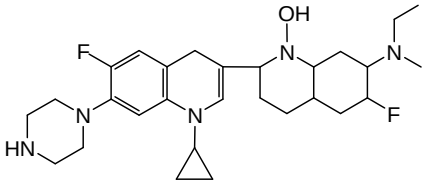
The basidiomycete *T. versicolor* transforms ciprofloxacin to 7-amino-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (**CCLXXXIX**), desethylene ciprofloxacin (**CCXC**) and 8-hydroxyciprofloxacin (**CCXCIV**),which are also produced by *G. striatum*; three novel metabolites of *T. versicolor* are desethylene *N*-acetyl-8-hydroxyciprofloxacin (**CCXCIX**) and two unusual conjugates (CC**C** and CC**CI**) (Prieto et al., 2011):



CCXCIX



CCC



CCCI

3.3. Transformation of third-generation quinolones

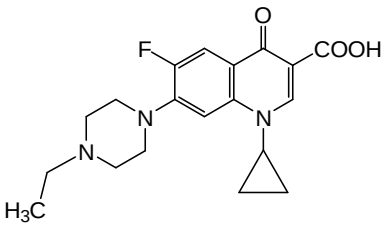
To date, the most-studied microbial transformations of third-generation quinolones are those of the veterinary antibiotics enrofloxacin (Sellyei et al., 2009), sarafloxacin (Edens et al., 1997; Amjad et al., 2006; Abd El-Ghany et al., 2011), danofloxacin (Sappal et al., 2009) and pradofloxacin (Wetzstein et al., 2005).

Enrofloxacin (CC**II**) is a veterinary antibacterial fluoroquinolone that is used for a great variety of purposes

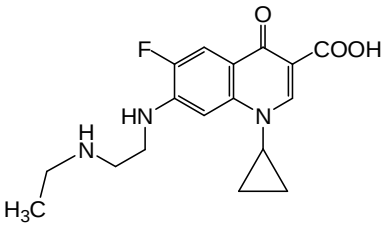
(Martinsen and Horsberg, 1995; Mitchell, 2006; Sellyei et al., 2009). It is degraded completely to CO_2 by brown-rot fungi from decaying wood and agricultural soils (Martens et al., 1996; Wetzstein, 2001; 2010). The brown-rot fungi produce hydroxyl radicals by nonenzymatic processes (Arantes et al., 2012), and these appear to be involved in the biotransformation. A total of 137 metabolites, including CO_2, produced by basidiomycetous fungi from enrofloxacin were identified in a series of brilliant investigations using high-performance liquid chromatography and high-resolution mass spectrometry (Wetzstein et al., 1997; 2006; Karl et al., 2006). During the transformation of enrofloxacin by *G. striatum* DSM 9592, 87 metabolites were detected and identified (Karl et al., 2006); additional metabolites were found in cultures of seven other fungi (Wetzstein et al., 2006). Some of the metabolites were *O*-acetylated or *N*-oxidized and others were produced by cleavage of the pyridone ring. Because of the abundance of metabolites produced from enrofloxacin alone, the reader is referred to the original papers (Karl et al., 2006; Wetzstein et al., 2006) for the structures.

As a result of transformation of enrofloxacin by *U. ramanniana*, a non-wood-decaying zygomycetous fungus, three products, desethylene enrofloxacin (CC**CIII**, yield 3.5%), enrofloxacin *N*-oxide (CC**CIV**, yield 62.0%) and *N*-

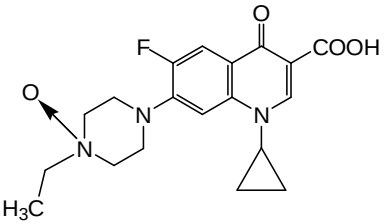
acetylciprofloxacin (**CCLXXXVI**, yield 8.0%), were produced within 21 days (Parshikov et al., 2000b,d):



CCCII

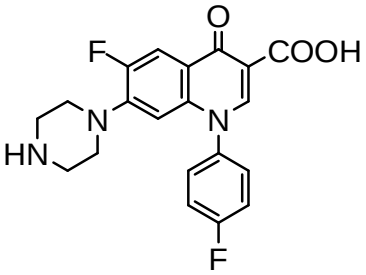


CCCIII

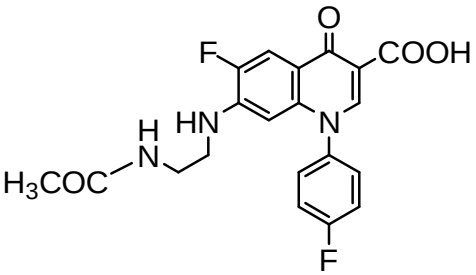


CCCIV

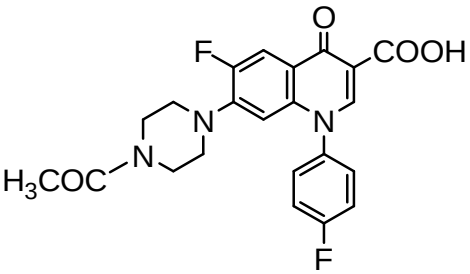
Sarafloxacin (CC**CV**) has been used as an antibacterial agent in poultry production (Jones et al., 1998; Abd El-Ghany et al., 2011) and in aquaculture (Martinsen and Horsberg, 1995; Kim and Cerniglia, 2010). The transformation of sarafloxacin was studied with growing cultures of *U. ramanniana*. Within 18 days, the formation of two metabolites, desethylene-*N*-acetylsarafloxacin (CC**CVI**, yield 26.0%) and *N*-acetylsarafloxacin (CC**CVII**, yield 15.0%), was observed (Parshikov et al., 2000c; Parshikov et al., 2001b):



CCCV

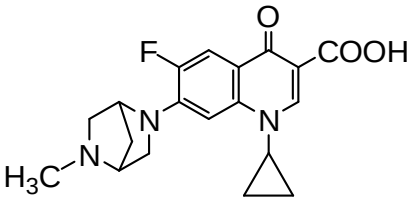


CCCVI

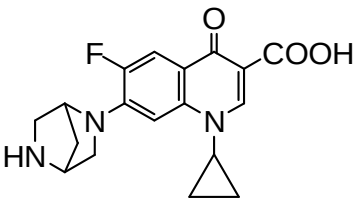


CCCVII

Danofloxacin (CC**CVIII**) is used for treating bacterial infections of cattle, pigs, and other livestock (McGuirk et al., 1992; Sappal et al., 2009). The transformation of danofloxacin by cultures of the bacteria *Mycobacterium smegmatis* UI AM-563 and *Pseudomonas fluorescens* UI AM-670 produces two metabolites, *N*-desmethyldanofloxacin (CC**CIX**) and a 7-amino derivative (CC**LXXXIX**) (Chen et al., 1997):

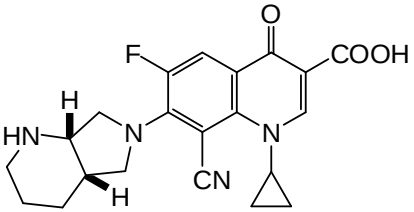


CCCVIII

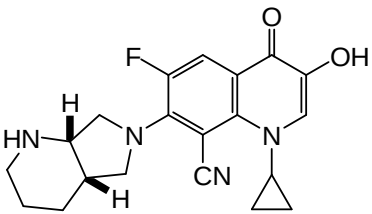


CCCIX

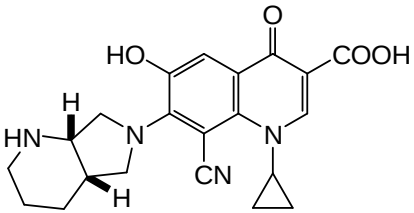
Pradofloxacin (CC**CX**) is a veterinary fluoroquinolone, with a cyano group on position 8, which was developed for treating bacterial infections in dogs and cats (Wetzstein, 2005). Transformation of pradofloxacin by *G. striatum* DSM 9592 produced six major metabolites, probably by hydroxyl radical reactions. The major metabolites were 2-hydroxy-8-cyanopradofloxacin (CC**CXI**, yield 3.0%), 6-hydroxy-8-cyanopradofloxacin (CC**CXII**, yield 9.0%), 5,6-dihydroxy-8-cyanopradofloxacin (CC**CXIII**, yield 3.0%), 8-hydroxypradofloxacin (CC**CXIV**, yield 1.0%), 8-cyano-7-amino pradofloxacin (CC**CXV**, 1.0% yield) and 6-[(E/Z)-1-cyano-2-hydroxyethenyl]-1-cyclopropyl-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid (CC**CXVI**, yield 1.0%) in 16 days (Wetzstein et al., 2012):



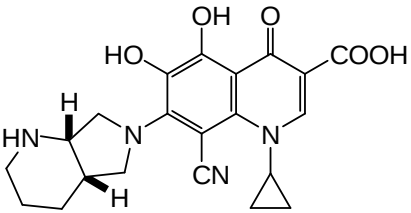
CCCX



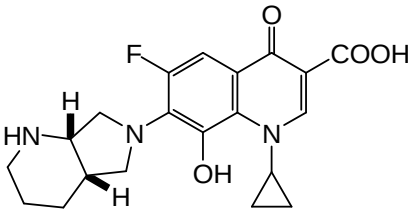
CCCXI



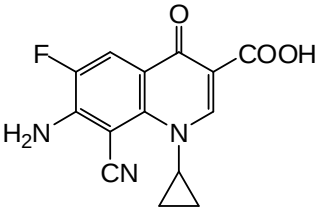
CCCXII



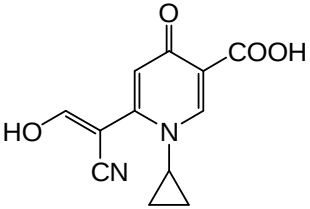
CCCXIII



CCCXIV



CCCXV

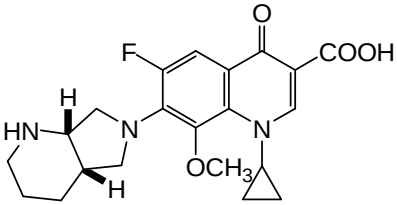


CCCXVI

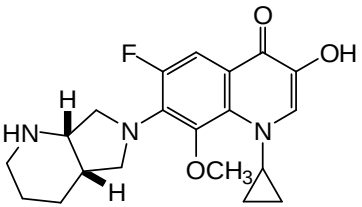
At least the 8-hydroxypradofloxacin metabolite lacks antimicrobial activity (Wetzstein and Hallenbach, 2011). The unique feature of this fungal biotransformation occurs after the pyrrolodinopiperidine group at position 7 is removed, when the carbocyclic ring is cleaved (Wetzstein et al., 2012). Cleavage of this aromatic ring has been suspected in the fungal transformation of other drugs but has previously not been confirmed.

3.4. Transformation of fourth-generation quinolones

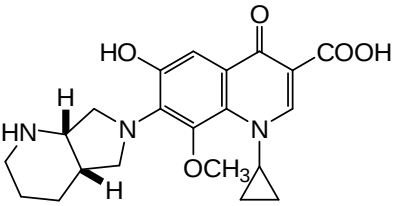
Therre is little information in the literature about the microbial transformations of fourth-generation quinolones except for moxifloxacin (CC**CXVII**), an 8-methoxyfluoroquinolone (BAY 12-8039) used for treating infections of the skin and respiratory tract (Keating and Scott, 2004). In the biotransformation of moxifloxacin by *G. striatum* DSM 9592, several metabolites, among them 3-hydroxymoxifloxacin (CC**CXVIII**), 6-hydroxymoxifloxacin (CC**CXIX**), and a demethylated derivative (8-hydroxymoxifloxacin) (CC**CXX**), were produced in 3 days (Wetzstein et al., 1997):



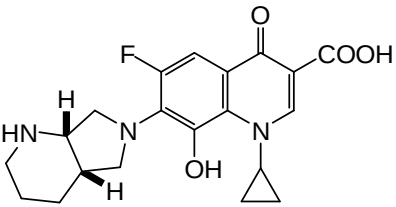
CCCXVII



CCCXVIII



CCCXIX



CCCXX

Conclusion

On the basis of compounds of a series azaarenes exist many types of medications. Derivatives of quinoline wide known among the most promising drugs. Primaquine has many side effects, so research is underway to develop an effective and safe antimalarial drug based on it (Vale et al., 2009).

Quinolones are widely used in medical practice. However, the problem of occurrence of antibiotic resistant strains of pathogenic microorganisms remains unchanged. Modification of the chemical structure of quinolones can solve these issues. Derivatives obtained by the methods of microbial chemistry may prove useful in the synthesis of a new generation of quinolones.

Hydroxylated derivatives of saturated nitrogen-containing heterocycles obtained by microbial techniques may be used to create hybrid molecules based, artemisinin (Parshikov et al., 2004a,b,c, 2005, 2006; Williamson et al., 2007), quinine and chloroquine.

References

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129515, г. Москва, ул. Академика Королева, 13
8 (800) 775-30-87
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Подписано в печать 24.03.15.
Формат 148x210. Гарнитура Таймс. Печ.л. 16,25.
Печать цифровая. Бумага офсетная.
Тираж 36 экз. Заказ № 123023

ISBN 978-5-00058-198-8

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


ISBN 978-5-00058-198-8
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9 785000 581988 >