
IGOR A. PARSHIKOV
Features of Antitumor and Antimalarial Artemisinins Biotransformations

Igor A. Parshikov

Features of Antitumor and Antimalarial Artemisinins Biotransformations

Primedia E-launch LLC

Dallas, 2018

Reviewers:
Kaluzhin O.V., 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. Features of Antitumor and Antimalarial Artemisinins Biotransformations. – Dallas: Primedia E-launch LLC, 2018. – 30 p.

This book describes examples of the use of microbial technologies for the preparation of artemisinins derivatives. Some examples of the formation of various metabolites depending on the composition of the nutrient medium are considered. The production of new artemisinins derivatives with increased antimalarial and antitumor activity is an important research task in the field of microbial biotechnology and medical chemistry.

ISBN: 978-1-64440-369-3
e-ISBN: 978-1-5323-8697-8
DOI: 10.18411/9781644403693

Introduction

The transformation of organic compounds by microbial cultures has long been of interest to the pharmaceutical, chemical and food industries because of numerous advantages compared to chemical synthesis (Pandey et al., 2000; Parshikov, 2015; Parshikov, 2016a,b).

Artemisinin (qinghaosu) is a natural product derived from the medicinal herb *Artemisia annua*, which has long been used in traditional Chinese medicine for the treatment of fevers. A series of powerful antimalarial drugs have been obtained from artemisinin (Ho et al., 2014). However, recent reports show that artemisinin also has effective anticancer activity (Ho et al., 2014; Das, 2015). Artemisinin and its derivatives show high anticancer activity with both drug-sensitive and drug-resistant lines of cancer cells (Das, 2015). However, despite the effectiveness of artemisinin, there remain problems with its low water solubility, which makes the creation of an effective oral dosage form difficult (Balducci et al., 2013), and with side effects associated with lesions in the brainstem at high doses in experimental animals (Genovese and Newman, 2008). These problems

force us to search for new and effective artemisinin derivatives.

Artemisinin and its derivatives are useful and effective drugs against most chloroquine-resistant strains of *P. falciparum* (Klayman, 1985). However, problems associated with artemisinin, including low solubility in water and even in oil (Luo and Shen, 1987; Hien and White, 1993; Vroman et al., 1999), have prompted scientists to seek new artemisinin derivatives. Some of these artemisinin-derived drugs have been reported to be neurotoxic to animals when injected (Vroman et al., 1999; Gordi and Lepist, 2004; Liao, 2009; Medhi et al., 2009; Mannan et al., 2010). There is also evidence of reproductive toxicity of artemisinin derivatives at high doses in animals (Medhi et al., 2009; Clark, 2012). Increasing resistance of malaria parasites to currently used drugs, including *P. vivax* resistance to chloroquine and primaquine in parts of New Guinea, Asia, and Africa (Price et al., 2011) and *P. falciparum* resistance to artemisinin in western Cambodia, eastern Thailand, and some nearby areas (Noedl et al., 2008; Wongsrichanalai and Meshnick, 2008; Dondorp et al., 2010; O'Brien et al., 2011), is another important reason for developing new antimalarial drugs.

Some artemisinin analogs may be obtained by semisynthetic processes; for example, artemisinin can be easily reduced chemically to the more effective, but neurotoxic, dihydroartemisinin (Klayman, 1985; Vroman et al., 1999; Avery et al., 2002). Other structural changes in artemisinin remain a challenge for chemists because of the difficulty of introducing specific functional groups by conventional synthetic methods.

Many microorganisms, especially certain fungi, have the ability to transform terpenoids regioselectively and stereoselectively (Sutherland, 2004; Parshikov, 2016). In this book to outline some of the variety of modifications, that can be expected from the use of microorganisms for the transformation of artemisinins. The biochemical mechanisms have scarcely been investigated, but it seems likely that cytochromes P450 and perhaps dioxygenases will be found to be involved in many of the transformations (Martin et al., 2008; Krings et al., 2009). It is our hope that further developments in microbial biotechnology, including the discovery of new strains with unique enzyme systems for the transformation of artemisinins, may make it possible to

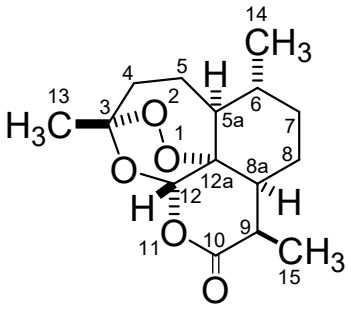
derive a variety of newer and more useful drugs from those now available.

Very often the quantity of transformation products and their chemical structure depends on the composition of the medium for the cultivation of microorganisms. Some examples we will consider in this book.

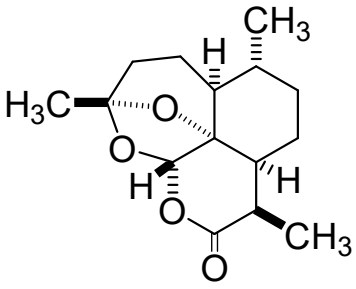
1. Transformation of artemisinin

Artemisinin (**I**) is the most important antimalarial sesquiterpenoid obtained from plants (Klayman, 1985; Luo and Shen, 1987; Liao, 2009), although several others have been described (Elmarakby et al., 1987; Chaturvedi et al., 2010; Rustaiyan et al., 2011). Biotransformation of artemisin has been aided by studies of QSAR (quantitative structure-activity relationships), which suggest modifications of artemisinin that are likely to increase antimalarial activity (Avery et al., 2002). Although many terpenoid biotransformations produce metabolites with less antimalarial activity, the products nevertheless may be useful for further modification (Liu et al., 2006). Occasionally, inactive compounds may be transformed to active metabolites by microbial processes (Musharraf et al., 2010).

The bacterium *Nocardia corallina* ATCC 19070 on dextrose-peptone-yeast extract medium transformed artemisinin to deoxyartemisinin (**II**, yield 24%), which lacks antimalarial activity, in 14 days (Lee et al., 1989). Cultures of *Aspergillus flavus* on Sabouraud dextrose broth in 48 h transformed artemisinin to deoxyartemisinin (**II**) with a yield of 30.5% (Srivastava et al., 2009):

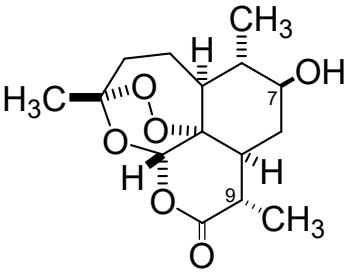


I

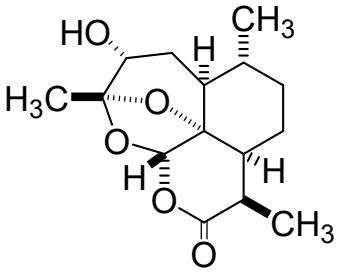


II

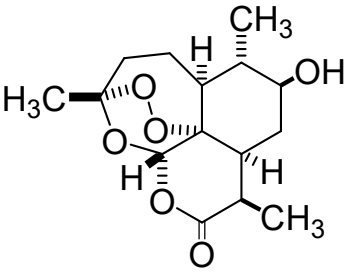
The fungus *Cunninghamella elegans* ATCC 9245 on malt extract-sucrose-peptone medium (true medium see by reference Parshikov et al., 2006) transformed artemisinin to four different hydroxylated derivatives, 7β-hydroxy-9α-artemisinin (**III**, yield 6.0%), 4α-hydroxydeoxyartemisinin (**IV**, yield 5.4%), 7β-hydroxyartemisinin (**V**, yield 21.0%) and 6β-hydroxyartemisinin (**VI**, yield 6.5%). The 7β-hydroxyartemisinin product (**V**), which cannot be produced chemically, is valuable for further synthesis of candidate antimalarial compounds (Parshikov et al., 2004a):



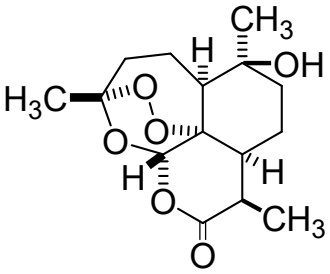
III



IV



V

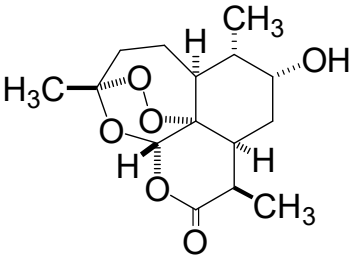


VI

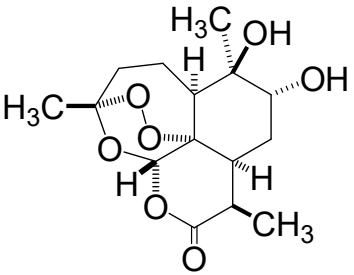
In publication Parshikov et al., 2004a accidently was described Sabouraud dextrose medium and as result high scale experiment in fermenter was not successful.

The same strain *Cunninghamella elegans* ATCC 9245 (Zhan et al., 2017) on Sabouraud dextrose brothin 14 days transform artemisinin (**I**) in four products which were identified as 6β-hydroxyartemisinin (**VI**), 7α-hydroxyartemisinin (**VII**), 7β-hydroxyartemisinin (**V**), and 6β,7α-dihydroxyartemisinin (**VIII**). Product (**VIII**) is a novel

compound and was reported there for the first time (Zhan et al., 2017):

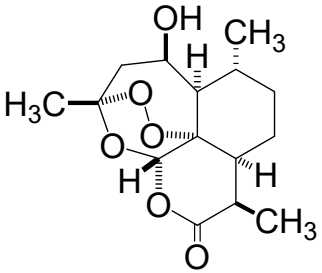


VII



VIII

Fungus *Aspergillus niger* VKM F-1119 on malt extract-sucrose-peptone medium hydroxylated artemisinin to 5β-hydroxyartemisinin (**IX**, yield 80%) and 7β-hydroxyartemisinin (**V**, yield 19%) (Parshikov et al., 2006):



IX

Later, were reported about others metabolites of artemisinin (I) obtained with same strain *Aspergillus niger* VKM F-1119 (Zhan et al., 2015) on malt extract-sucrose-peptone medium that seems impossible. Probably, strain

Aspergillus niger VKM F-1119 long time was keeped in Olemiss (USA) laboratory (dried slants in work table from 2006 to 2015) and as result was infected (Zhan et al., 2015). Qualified microbiologists should take part in that job also.

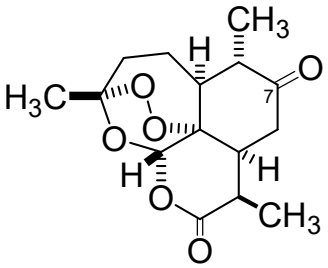
Three strains of *Umbelopsis ramanniana* (*Mucor ramannianus*) on malt extract-sucrose-peptone medium hydroxylated artemisinin in 14 days to 7β-hydroxyartemisinin (**V**, yield 51–88%), 6β-hydroxyartemisinin (**VI**, yield 1–51%), and two other isomers (Parshikov et al., 2005).

White-rot basidiomycetes *Pycnoporus sanguineus* and *Funalia trogii*. on malt extract-sucrose-peptone medium hydroxylated artemisinin in 14 days to 5β-hydroxyartemisinin (**IX**, yield 92.1%) and 7β-hydroxyartemisinin (**V**, yield 89.7%) (Parshikov et al., 2018)

Penicillium chrysogenum ATCC 9480 on dextrose-peptone-yeast extract medium transformed artemisinin to two inactive compounds, deoxyartemisinin (**II**, yield 1.0%) and 4α-hydroxydeoxyartemisinin (**IV**, yield 3.6%) in 13 days (Lee et al., 1989). *Cunninghamella echinulata* AS 3.3400 and *Aspergillus niger* AS 3.795 on potato medium in four days transformed artemisinin to 6β-hydroxyartemisinin (**VI**,

yield 50%) and 4α-hydroxydeoxyartemisinin (**IV**, yield 15%), respectively (Zhan et al., 2002a), and *Mucor polymorphosporus* AS 3.3443 on potato medium produced 7β-hydroxyartemisinin (**V**) and two other hydroxylated products (Zhan et al., 2002b).

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

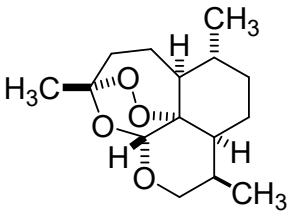


X

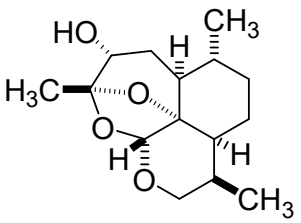
2. Transformation of 10-deoxoartemisinin

Semisynthetic derivatives of artemisinin also have interested researchers seeking possible microbiological modifications. For example, *U. ramanniana* 1839 on

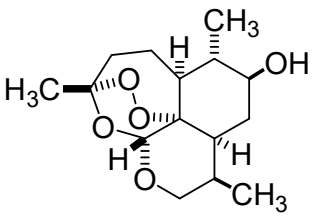
dextrose-peptone-yeast extract medium transformed the semisynthetic antimalarial drug 10-deoxoartemisinin (**XI**) to the inactive 4α-hydroxydeoxy-10-deoxoartemisinin (**XII**, yield 7.0%) and the partially active 7β-hydroxy-10-deoxoartemisinin (**XIII**, yield 10.9%) in 14 days (Khalifa et al., 1995). *Cunninghamella elegans* ATCC 9245 on malt extract-sucrose-peptone medium transformed 10-deoxoartemisinin (**XI**) to three hydroxylated derivatives, 5β-hydroxy-10-deoxoartemisinin (**XIV**, yield 8.8%), 4α-hydroxydeoxy-10-deoxoartemisinin (**XII**, yield 4.6%) and 7β-hydroxy-10-deoxoartemisinin (**XIII**, yield 83.9%) (Parshikov et al., 2004b):



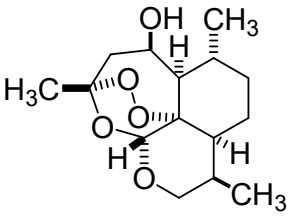
XI



XII

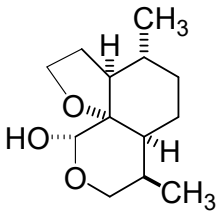


XIII

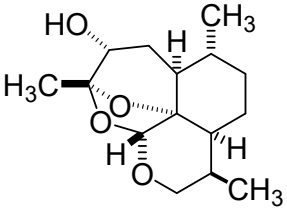


XIV

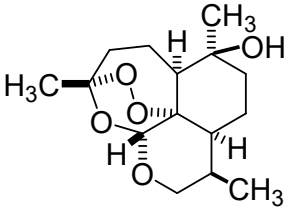
Medeiros et al. (2002) optimized the conditions for transformation of **XI** and obtained on potato/dextrose broth a 45% yield of **XIII**, which despite its lower antimalarial activity may be useful for further transformations, in 14 days. Formation of compound **XIII** was accompanied by formation of products **XV**, **XVI** and **XVII** (Medeiros et al., 2002):



XV

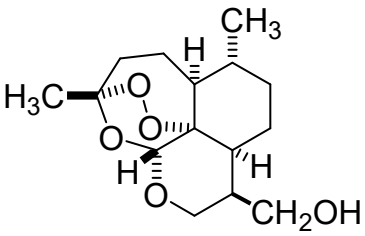


XVI



XVII

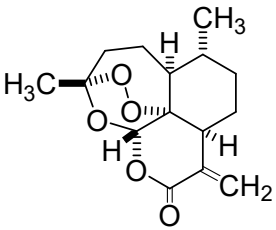
Aspergillus niger on malt extract-sucrose-peptone medium (true medium see by reference Parshikov et al., 2006) hydroxylated 10-deoxoartemisinin (**XI**) to 7β-hydroxy-10-deoxoartemisinin (**XIII**, yield 69%) and 15-hydroxy-10-deoxoartemisinin (**XVIII**, yield 26%) (Parshikov et al., 2004c).



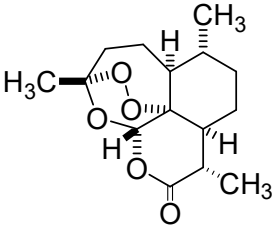
XVIII

3. Transformation of artemisitene

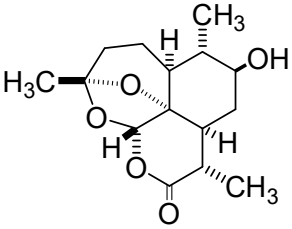
A minor sesquiterpene of *Artemisia annua*, artemisitene (**XIX**), can also be produced chemically from artemisinin (Chaturvedi et al., 2010). Artemisitene was transformed by *A. niger* NRRL 599 on dextrose-glycerol-yeast extract-peptone medium to 9α-artemisinin (**XX**), 7β-hydroxydeoxy-9α-artemisinin (**XXI**) and 7β-hydroxy-9α-artemisinin (**III**), which has antimalarial activity (Orabi et al., 1999):



XIX



XX



XXI

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

Conclusion

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

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

Arteether can be converted to several metabolites, not only by mammalian systems but also by fungi and bacteria

(Vroman et al., 1999). Other chemical derivatives of artemisinin may be useful in the future for the microbial biosynthesis of new drugs with novel therapeutic properties. The combination of artemether with the unrelated drug lumefantrine is one of five artemisinin-based combinations currently recommended by the World Health Organization (WHO) for treatment of malaria (Omari et al., 2004; O'Brien et al., 2011). Various laboratories now are conducting research on hybrid trioxaquine molecules that have two different modes of action (Chauhan et al., 2010), such as a drug combining the structures of artemisinin and quinine that is highly effective against *P. falciparum* (Walsh et al., 2007). Also artemisinin-acridine hybrids have good antitumour and antimalarial activity (Jones et al., 2009).

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

proteins of the parasite to cause its death (Chaturvedi et al., 2010).

Some of the artemisinin derivatives, especially the trioxane dimers, are selectively cytotoxic; they have been shown not only to target cancer cells by inducing apoptosis but also to prevent tumor growth by antiangiogenesis (Beekman et al., 1998; Posner et al., 2006; Nakase et al., 2008). The endoperoxide moiety required for antimalarial activity also appears to be required for cytotoxicity toward tumor cell lines (Beekman et al., 1998; Meunier and Robert, 2010). Therefore, in the development of microbial biotransformation processes for the derivatization of artemisinin, the endoperoxide group should be preserved.

Among the microbial biotransformation processes described here, the ones of greatest interest are those for the regiospecific and stereospecific hydroxylation of artemisinins because they increase solubility and provide sites for further modification (Medeiros et al., 2002; Parshikov et al., 2006). Microbial biotransformation procedures can be used to obtain artemisinin derivatives hydroxylated in almost any position, including some not obtainable by organic synthesis, such as 7β-hydroxyartemisinin (Parshikov et al., 2004a; Khor and

Uzir, 2011). These metabolites may be used for further chemical or biological transformations that yield many potential candidate drugs from one compound. However, it should be remembered that the structure of metabolites often depends on the composition of the nutrient medium.

Future research on antimalarial artemisinins should include studies of the biochemistry of the most useful biotransformations and of the antiplasmodial efficacy and toxicity of each of the metabolites. The compounds that are most effective against drug-resistant strains of *P. falciparum* or *P. vivax* may be produced in higher yields by the use of biotechnology. New biotransformations of artemisinins, perhaps combined with chemical derivatization, may provide ways to overcome parasite resistance to currently used antimalarial drugs.

Hydroxylated derivatives of artemisinins obtained by microbial techniques may be used to create hybrid molecules based on molecules of other drugs.

References

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

Balducci A.G., Mogosso E., Colombo G., Sonvico F., Khan N.A.K., Yuen K.H., Bettini R., Colombo P., Rossi A. Agglomerated oral dosage forms of artemisinin/β-cyclodextrin spray-dried primary microparticles showing increased dissolution rate and bioavailability. AAPS PharmSciTech. 2013; 14: 911-918.

Beekman A.C., Wierenga P.K., Woerdenbag H.J., van Uden W., Pras N., Konings A.W.T., et al. Artemisinin-derived sesquiterpene lactones as potential antitumour compounds: cytotoxic action against bone marrow and tumour cells. Planta Med. 1998; 64:615–619.

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

Chaturvedi D., Goswami A., Saikia P.P., Barua N.C., Rao P.G. Artemisinin and its derivatives: a novel class of anti-malarial and anti-cancer agents. Chem Soc Rev. 2010; 39:435–454.

Chauhan S.S., Sharma M., Chauhan P.M.S. Trioxaquines: hybrid molecules for the treatment of malaria. Drug News Perspect. 2010; 23:632–646.

Clark R.L.. Effects of artemisinins on reticulocyte count and relationship to possible embryotoxicity in confirmed

and unconfirmed malarial patients. Birth Defects Res Part A. 2012; 94:61–75.

Das A.K. Anticancer effect of antimalarial artemisinin compounds. Ann. Med. Health Sci. Res. 1995; 5(2): 93–102.

Dondorp A.M., Yeung S., White L., Nguon C., Day N.P.J., Socheat D., et al. Artemisinin resistance: current status and scenarios for containment. Nature Rev Microbiol. 2010; 8:272–280.

Elmarakby S.A., el-Feraly F.S., Elsohly H.N., Croom E.M., Hufford C.D. Microbial transformation studies on arteannuin B. J Nat Prod. 1987; 50:903–909.

Fernández I., Robert A. Peroxide bond strength of antimalarial drugs containing an endoperoxide cycle. Relation with biological activity. Org Biomol Chem. 2011; 9:4098–4107.

Genovese R.F., Newman D.B. Understanding artemisinin-induced brainstem neurotoxicity. Arch. Toxicol. 2008; 82: 379-385.

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

Goswami A., Saikia P.P., Barua N.C., Bordoloi M., Yadav A., Bora T.C., et al. Bio-transformation of artemisinin using soil microbe: direct C-acetoxylation of artemisinin at C-9 by *Penicillium simplicissimum*. Bioorg Med Chem Lett. 2010;.20:359–361.

Hien T.T., White N.J. Qinghaosu. Lancet. 1993;341:603–608.

Ho W.E., Peh H.Y., Chan T.K., Wong W.S. Artemisinins: Pharmacological actions beyond anti-malarial. Pharmacol. Ther. 2014; 142(1): 126–139.

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

Jones M., Mercer A.E., Stocks P.A., La Pensee L.J., Cosstick R., Park B.K., Kennedy M.E., Piantanida I., Ward S.A., Davies J., Bray P.G., Rawe S.L., Baird J., Charidza T., Janneh O., O'Neill P.M. Antitumour and antimalarial activity of artemisinin-acridine hybrids. // Bioorg. Med. Chem. Lett. 2009. V.19. N 7. P.2033-2037.

Khalifa S.I., Baker J.K., Jung M., McChesney J.D., Hufford C.D.. Microbial and mammalian metabolism studies on the semisynthetic antimalarial, deoxoartemisinin. Pharm Res. 1995; 12:1493–1498.

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

Klayman D.L. *Qinghaosu* (artemisinin): an antimalarial drug from China. Science. 1985;228:1049–1055.

Krings U., Lehnert N., Fraatz M.A., Hardebusch B., Zorn H., Berger R.G. Autoxidation versus biotransformation of α-pinene to flavors with *Pleurotus sapidus*: regioselective hydroperoxidation of α-pinene and stereoselective dehydrogenation of verbenol. J Agric Food Chem. 2009; 57:9944–9950.

Lee I-S., ElSohly H.N., Croom E.M., Hufford C.D. Microbial metabolism studies of the antimalarial sesquiterpene artemisinin. J Nat Prod. 1989; 52:337–741.

Li Q-G., Peggins J.O., Fleckenstein L.L., Masonic K., Heiffer M.H., Brewer T.G.. The pharmacokinetics and bioavailability of dihydroartemisin, arteether, artemether, artesunic acid and artelinic acid in rats. J Pharm Pharmacol. 1998; 50:173–182.

Liao F. Discovery of artemisinin (qinghaosu). Molecules. 2009; 14:5362–5366.

Liu J-H., Chen Y-G., Yu B-Y., Chen Y-J.. A novel ketone derivative of artemisinin biotransformed by *Streptomyces griseus* ATCC 13273. Bioorg Med Chem Lett. 2006; 16:1909–1912.

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

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

Martin G.D.A., Durrant M.C., Reese P.B.. A predictive cytochrome P450 monooxygenase functional model for generic hydroxylation by *Rhizopus oryzae* ATCC 11145. J Theor Comput Chem. 2008; 7:421–433.

Medeiros S.F., Avery M.A., Avery B., Leite S.G.F., Freitas A.C.C., Williamson J.S.. Biotransformation of 10-deoxoartemisinin to its 7β-hydroxy derivative by *Mucor ramannianus*. Biotechnol Lett. 2002; 24:937–941.

Medhi B., Patyar S., Rao R.S., Byrav P., Prakash A. Pharmacokinetic and toxicological profile of artemisinin compounds: an update. Pharmacology. 2009; 84:323–332.

Meunier B., Robert A. Heme and target for trioxane-containing antimalarial drugs. Accounts Chem Res 2010; 43:1.444–451.

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

Musharraf S.G., Najeeb A., Khan S., Pervez M., Ali R.A, Choudhary MI. Microbial transformation of 5α-hydroxycaryophylla-4(12),8(13)-diene with *Macrophomina phaseolina*. J Mol Catal B Enzym. 2010; 66:156–160.

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

Noedl H., Se Y., Schaecher K., Smith B.L., Socheat D., Fukuda M.M. Evidence of artemisinin-resistant malaria in western Cambodia. N Engl J Med. 2008; 359:2619–2620.

O'Brien C., Henrich P.P., Passi N., Fidock D.A. Recent clinical and molecular insights into emerging artemisinin resistance in *Plasmodium falciparum*. Curr Opin Infect Dis. 2011; 24:570–577.

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

Orabi K.Y., Galal A.M., Ibrahim A-R.S., El-Feraly F.S., Khalifa S.I., El-Sohly H.N.. Microbial metabolism of artemisitene. Phytochemistry. 1999; 51:257–261.

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

Parshikov I.A., Muraleedharan K,M., Avery M.A., Williamson J.S.. Transformation of artemisinin by *Cunninghamella elegans*. Appl Microbiol Biotechnol. 2004a; 64:782–786.

Parshikov I.A., Muraleedharan K.M., Miriyala B., Avery M.A., Williamson J.S. Hydroxylation of 10-deoxoartemisinin by *Cunninghamella elegans*. J Nat Prod. 2004b;.67:1595–1597.

Parshikov I.A., Miriyala B., Avery M.A., Williamson J.S. Hydroxylation of 10-deoxoartemisinin to 15-hydroxy-10-deoxoartemisinin by *Aspergillus niger*. Biotechnol Lett. 2004c; 26:607–610.

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

Parshikov I.A., Miriyala B., Muraleedharan K.M., Avery M.A., Williamson J.S. Microbial transformation of artemisinin to 5-hydroxyartemisinin by *Eurotium amstelodami* and *Aspergillus niger*. J. Ind. Microbiol. Biotechnol. 2006; 33(5): 349–352.

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

Parshikov I.A. Microbial Transformation of Nitrogen Containing Heterocycles. – Dallas: Primedia E-launch LLC, 2016a. − 130 p.

Parshikov I.A. Microorganisms in Chemistry of Terpenoids. – Dallas: Primedia E-launch LLC, 2016b. − 102 p.

Parshikov I.A., Hernandes-Luna C.E. Zaraisky E.I. Microbial transformation of the antimalarial and anticancer and anticancer drug artemisinin by white-rot basidiomycetes. Asian Journal of Microbiology, Biotechnology and Environmental Sciences. 2018; 20(4): in press.

Posner G.H., D'Angelo J., O'Neill P.M., Mercer A. Anticancer activity of artemisinin-derived trioxanes. Expert Opin Ther Patents. 2006; 16:1665–1672.

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

Rustaiyan A., Nahrevanian H., Kazemi M.. Isolation of artediffusin (tehranolide) as a new antimalarial agent. Asian J Chem. 2011;23:4810–4814.

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

Sutherland J.B. Degradation of hydrocarbons by yeasts and filamentous fungi. In: Arora DK, editor. Fungal Biotechnology in Agricultural, Food, and Environmental Applications. New York: Marcel Dekker; 2004. p. 443–455.

Vroman J.A., Alvim-Gaston M., Avery M.A. Current progress in the chemistry, medicinal chemistry and drug design of artemisinin based antimalarials. Curr Pharm Des. 1999; 5:101–138.

Walsh J.J., Coughlan D., Heneghan N., Gaynor C., Bell A. A novel artemisinin–quinine hybrid with potent

antimalarial activity. Bioorg Med Chem Lett. 2007; 17:3599–3602.

Wongsrichanalai C., Meshnick S.R. Declining artesunate-mefloquine efficacy against falciparum malaria on the Cambodia-Thailand border. Emerg Infect Dis. 2008; 14:716–719.

Zhan J., Guo H., Dai J., Zhang Y., Guo D. Microbial transformations of artemisinin by *Cunninghamella echinulata* and *Aspergillus niger*. Tetrahedron Lett. 2002a; 43:4519–4521.

Zhan J-X., Zhang Y-X., Guo H-Z., Han J., Ning L-L., Guo D-A. Microbial metabolism of artemisinin by *Mucor polymorphosporus* and *Aspergillus niger*. J Nat Prod 2002b; 65:1693–1695.

Zhan Y., Liu H., Wu Y., Wei P., Chen Z., Williamson J.S. Biotransformation of artemisinin by Aspergillus niger. Appl Microbiol Biotechnol. 2015; 99:3443-3446.

Zhan Y.,Wu Y., Xu F, Bai Y., Guan Y., Williamson J.S., Liu B. A novel dihydroxylated derivative of artemisinin from microbial transformation. Fitoterapia. 2017; 120:93-97.

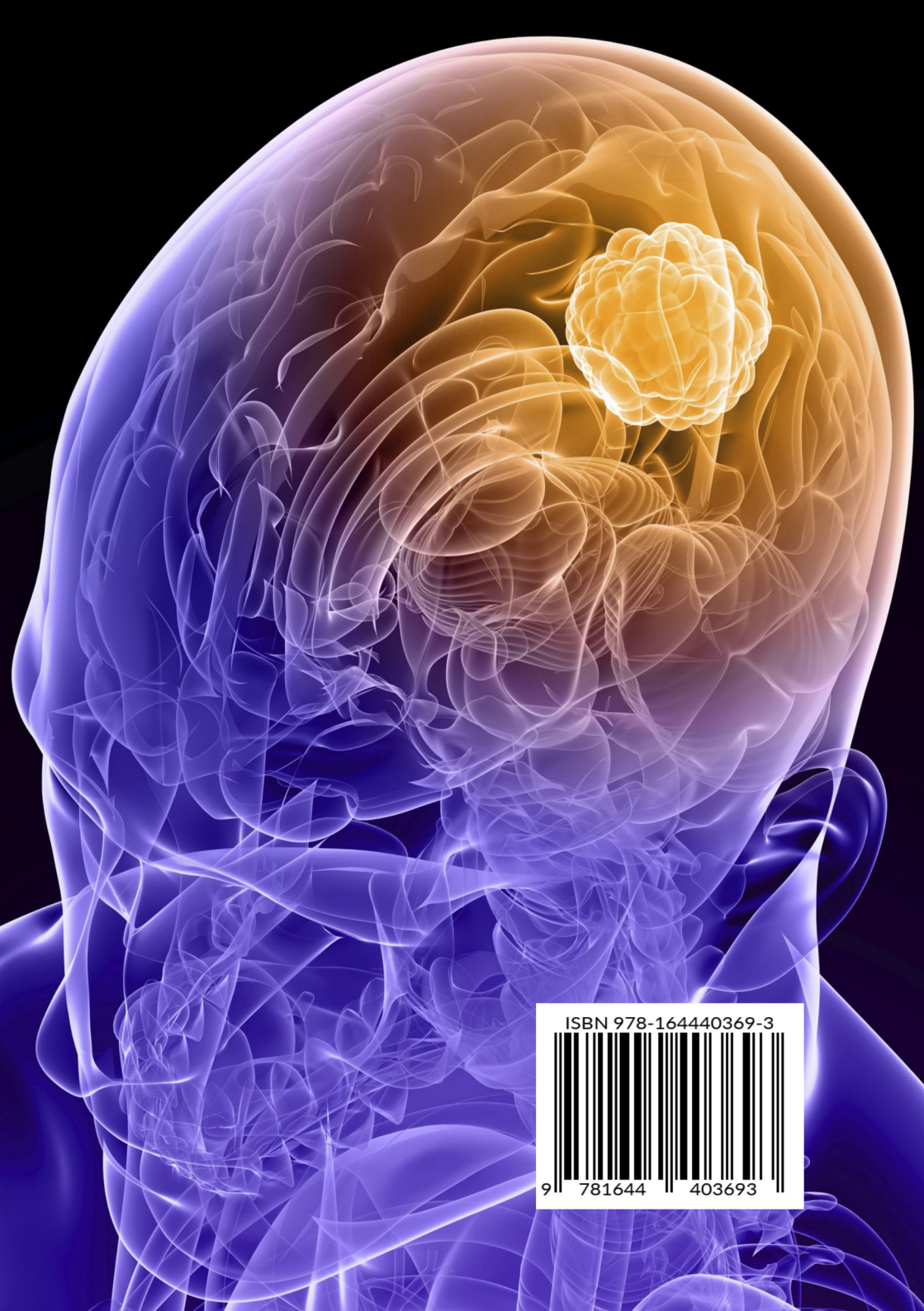
CONTENTS

Igor A. Parshikov

Features of Antitumor and Antimalarial Artemisinins Biotransformations

Primedia E-launch LLC
2137 Ash Grove Way Dallas, TX 75228
http://www.isbnservices.com/

Printed in the August 05, 2018
Offcet-print. Edition of 350 copies. Size: 15 x 21 cm



ISBN 978-164440369-3