EUROPEAN ACADEMIC RESEARCH
Vol. III, Issue 10/ January 2016

ISSN 2286-4822
www.euacademic.org

Impact Factor: 3.4546 (UIF)
DRJI Value: 5.9 (B+)

# A Review on Biotransformational Studies of β-Artemether

AZIZUDDIN[1]
MUHAMMAD IQBAL
Department of Chemistry
Federal Urdu University of Arts, Science & Technology
Gulshan-e-Iqbal Campus, Karachi
Pakistan

**Abstract:**

*β-Artemether (**1**) is used more effectively for the treatment of malaria. As a result of biotransformation of β-artemether (**1**) variety of metabolites, **2-10** were identified by fermentation with Fusarium lini, Macrophomina phaseolina, Cunninghamella elegans and Streptomyces lavendulae, and from plant suspension cultures of Glycyrrhiza glabra, Lavandula officinalis and Azadirachta indica. This present review will discuss metabolites **2-10**, obtained from β-artemether (**1**) up to 2012.*

**Key words**: Biotransformation, ß-artemether, *Fusarium lini, Macrophomina phaseolina, Cunninghamella elegans, Streptomyces lavendulae, Glycyrrhiza glabra, Lavandula officinalis, Azadirachta indica*

## INTRODUCTION

Biotransformation has been employed as a powerful synthetic tool for introducing the biological active functionalities in the molecules for new analogs of natural and synthetic organic compounds. Thousands of biotransformation involving various

[1] Corresponding author: azizpobox1@yahoo.com

types of reactions with natural products and synthetic organic compounds has been reported. Many of them are very useful in synthetic organic chemistry. In the last decade, biotransformation of various classes of organic compounds including steroids, alkaloids and terpenes on commercial scale have been used as an interesting alternative approach to produce new and novel biological active compounds (Bhatti and Khera, 2012; Rathbone and Bruce, 20012; Parshikov et al, 2012). The tool box of biotransformation need to be filled with more efficient strains and novel enzymes for the structural modification of specific classes of organic compounds to increase the structural diversity of compounds. The field of biotransformation is being developed day by day by employing new biotechnological methods.

ß-Artemether (**1**) is a semisynthetic and polyoxygenated amorphene, consists of three substituted rings; a cyclohexane ring, a tetrahydropyrane ring and a oxacycloheptane ring (contained an endoperoxide bridge), which are fused together (Figure 1) (Butcher et al, 2007). It is the *O*-methyl ether derivative of dihydroartemisinin, a reduced product of artemisinin (Qinghaosu). Artemisinin was isolated from Chinese herbal plant *Artemisia annua* (Linn.) in 1972 by Chinese researchers (Klayman, 1985). ß-Artemether (**1**) is active against the erythrocytic phase of the *Plasmodium* (Blum et al, 1998). The antimalarial action of ß-artemether (**1**) is unique and totally different from the conventional antimalarial drugs. The antimalarial action of ß-artemether (**1**) appears like artemisinin, when an endoperoxide bridge of **1** is converted into free radical by free iron, and killed the *Plasmodium* species (Klayman, 1985; Brossi et al, 1988; Cumming et al, 1997). ß-Artemether (**1**) also kills water-born parasitic *Platyhelminthes*, which belong to schistosomes order trematoda (Xiao et al, 2000).

## Transformed products from biotransformation of β-artemether (1)

Biotransformation of β-artemether (**1**) are reported in literature by using various fungal, bacterial and plant cell suspension cultures, which resulted isomeric, rearranged, hydroxylated and reduced products **2-10** up to 2012 (Table 1, Figure 2).

## Biotransformation of β-artemether (1) by *Glycyrrhiza glabra*

Biotransformation of β-artemether (**1**) with the plant cell suspension culture of *Glycyrrhiza glabra* (Linn.) yielded a rearranged transformed product β-artemether furano acetate (**2**) (Patel et al, 2011).

## Biotransformation of β-artemether (1) by *Lavandula officinalis*

Biotransformation of β-artemether (**1**) by using the plant cell suspension culture of *Lavandula officinalis* (L.) afforded the same transformed product, β-artemether furano acetate (**2**), which was obtained by using plant cell suspension of *Glycyrrhiza glabra* (Linn.) (Patel et al, 2011).

## Biotransformation of β-artemether (1) by *Azadirachta indica*

Musharraf and co-workers in 2012 were obtained two transformed products β-artemether furano acetate (**2**) and 3α-hydroxydeoxy-β-artemether (**3**) by the biotransformation of β-artemether (**1**) with the help of plant cell suspension culture of *Azadirachta indica*. Both transformed products **2** and **3** did not exhibit antimalarial activity due to the absence of endoperoxide bridge, which is responsible for antimalarial activity (Musharraf et al, 2012).

**Biotransformation of β-artemether (1) by *Streptomyces lavendulae***

The bacterial culture of *Streptomyces lavendulae* transformed β-artemether (**1**) into three different transformed products, which were 9β-hydroxy-β-artemether (**4**), 9α-hydroxy-β-artemether (**5**) and 14-hydroxy-β-artemether (**6**) (Musharraf et al, 2012).

**Biotransformation of β-artemether (1) by *Cunninghamella elegans***

Abourasheed and Hufford in 1996 reported three different transformed products, 3α-hydroxydeoxy-β-artemether (**3**), 9β-hydroxy-β-artemether (**4**) and 9β-hydroxy-β-artemether furano acetate (**7**) by biotransformation of β-artemether (**1**) using the whole cell culture of fungi, *Cunninghamella elegans* (Abourasheed and Hufford, 1996).

**Biotransformation of β-artemether (1) by *Fusarium lini***

Musharraf and co-workers in 2012 reported biotransformation of β-artemether (**1**) by using whole cell culture of *Fusarium lini*. They obtained three transformed products, β-artemether furano acetate (**2**), 9α-hydroxyartemethin-II (**8**) and 10β-hydroxyartemethin-I (**9)**. All of them did not show antimalarial activity against *Plasmodium falciparum* (Musharraf et al, 2012).

**Biotransformation of β-artemether (1) by *Macrophomina phaseolina***

The whole cell culture of fungus, *Macrophomina phaseolina* transformed β-artemether (**1**) into three transformed products, which were β-artemether furano acetate (**2**), 3α-hydroxydeoxy-β-artemether (**3**) and 3α-hydroxydeoxy-β-dihydroartemisinin (**10**). All of them again did not show antimalarial activity against *Plasmodium falciparum* (Musharraf et al, 2012).

## CONCLUSION

This review aimed to highlight the biotransformed metabolites **2-10** of β-artemether (**1**). Regarding this detailed survey, it is assumed that it will assist in comparative studies among transformed products obtained by different ways of biotransformation.

## REFERENCES

Abourasheed, E.A. and Hufford, C.D. (1996). Microbial transformation of artemether. J. Nat. Prod. 59: 251-253.

Bhatti, H.N. and Khera, R.A. (2012). Biological transformation of steroidal compounds: a review. Steroids 77: 1267-1290.

Blum, W., Pfaar, U. and Kühnöl, J. (1998). Rapid characterization of artemether and its in vitro metabolites on incubation with bovine hemoglobin, rat blood and dog blood by capillary gas chromatography-chemical ionization mass spectrometry. J. Chromatogr. B 710: 101-113.

Brossi, A., Venugopalan, B., Gerpe, L.D., Yeh, H.J.C., Flippen-Anderson, J.L., Buchs, P., Luo, X.D., Milhous, W. and Peters, W. (1988). Arteether, a new antimalarial drug: synthesis and antimalarial properties. J. Med. Chem. 31: 645-650.

Butcher, R., Jasinsky, J.P., Yathirajan, H.S., Bindya, S. and Narayana, B. (2007). α-Artemether. Acta Crystallogr. E63: o3291-o3292.

Cumming, J.N., Ploypradith, P. and Posner, G.H. (1997). Antimalarial activity of artemisinin (qinghaosu) and related trioxanes: mechanism(s) of action. Adv. in Pharm. 37: 253-297.

Klayman, D.L. (1985). Qinghaosu (artemisinin): an antimalarial drug from china. Science 228: 1049-1055.

Musharraf, S.G., Uddin, J., Akhter, M., Parvez, M., Saifullah, Khan, S., Yousuf, S., Khan, S. and Choudhary, M.I. (2012). Biotransformation of an antimalarial drug, artemether by plant and fungal cell cultures. J. Mol. Catal. B: Enzymatic 82: 80-85.

Parshikov, I.A., Netrusov, A.I. and Sutherland, J.B. (2012). Microbial transformation of antimalarial terpenoids. Biotechnol. Adv. 30: 1516-1523.

Patel, S., Gaur, R., Upadhyaya, M., Mathur, A., Mathur, A.K. and Bhakuni, R.S. (2011). *Glycyrrhiza glabra* (Linn.) and *Lavandula officinalis* (L.) cell suspension cultures-based biotransformation of β-artemether. J. Nat. Med. 65: 646-650.

Rathbone, D.A. and Bruce, N.C. (2002). Microbial transformation of alkaloids. Curr. Opin. Microbiol. 5: 274-281.

Xiao, S.H., Hotez, P.J. and Tanner, M. (2000). Artemether, an effective new agent for chemoprophylaxis against schistosomiasis in China: its in vivo effect on the biochemical metabolism of the Asian schistosome. Southeast Asian J. Trop. Med. Public Health 31: 724-732.

**Table 1: List of reported biotransformed products 2-10 of β-artemether (1)**

| S. No. | Biotransformed products | Biological system | References |
|---|---|---|---|
| 1 | β-Artemether furano acetate (**2**) | *Fusarium lini*<br>*Macrophomina phaseolina*<br>*Glycyrrhiza glabra*<br>*Lavandula officinalis*<br>*Azadirachta indica* | Patel et al, 2011; Musharraf et al, 2012 |
| 2 | 3α-Hydroxydeoxy-β-artemether (**3**) | *Cunninghamella elegans*<br>*Macrophomina phaseolina*<br>*Azadirachta indica* | Patel et al, 2011; Musharraf et al, 2012 |
| 3 | 9β-Hydroxy-β-artemether (**4**) | *Cunninghamella elegans*<br>*Streptomyces lavendulae* | Musharraf et al, 2012 |
| 4 | 9α-Hydroxy-β-aremether (**5**) | *Streptomyces lavendulae* | Musharraf et al, 2012 |
| 5 | 14-Hydroxy-β-artemether (**6**) | *Streptomyces lavendulae* | Musharraf et al, 2012 |
| 6 | 9β-Hydroxy-β-artemether furano acetate (**7**) | *Cunninghamella elegans* | Musharraf et al, 2012 |
| 7 | 9α-Hydroxy artemethin-II (**8**) | *Fusarium lini* | Patel et al, 2011 |
| 8 | 10β-Hydroxy artemethin-I (**9**) | *Fusarium lini* | Patel et al, 2011 |
| 9 | 3α-Hydroxydeoxy-β-dihydroartemisinin (**10**) | *Macrophomina phaseolina* | Patel et al, 2011 |

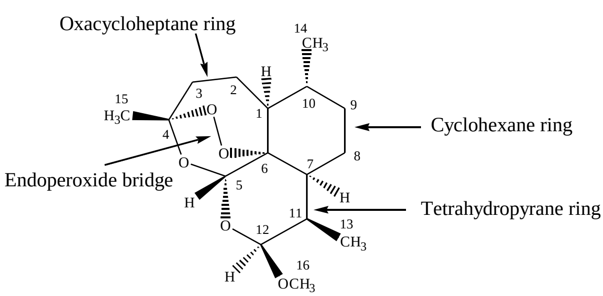
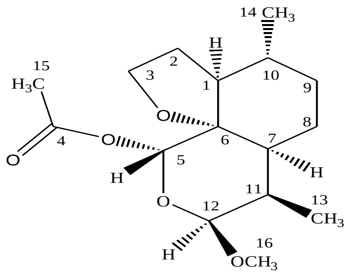
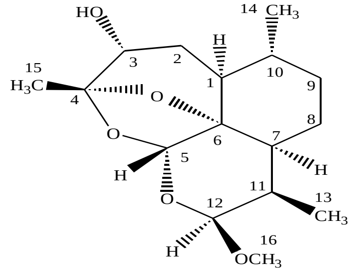


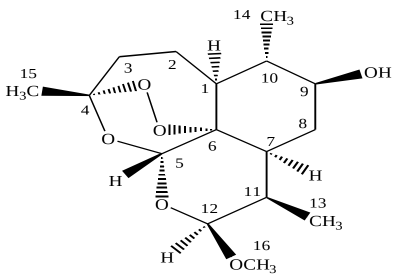

**Figure 1:** Structure of β-artemether (**1**)



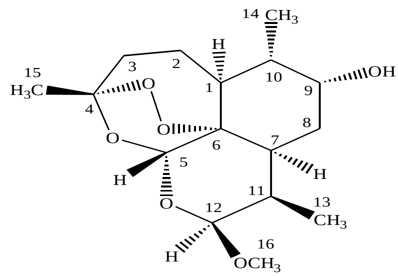
β-Artemether furano acetate (**2**)



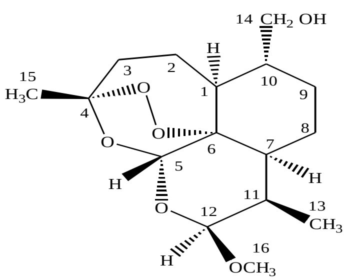
3α–Hydroxydeoxy-β-artemether (**3**)



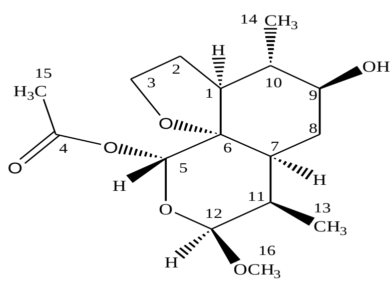
9β-Hydroxy-β-artemether (**4**)



9α-Hydroxy-β-artemether (**5**)

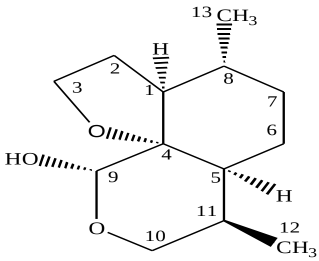


14-Hydroxy-β-artemether (**6**)

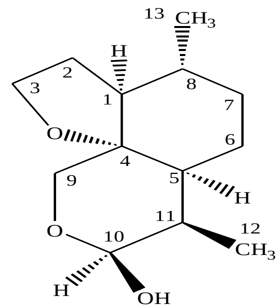


9β-Hydroxy-β-artemether furano acetate (**7**)

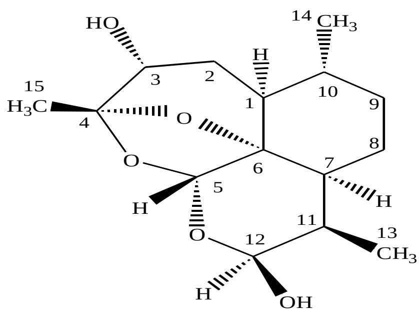
**Figure 2:** Biotransformed products of β-artemether (**1**)



9α-Hydroxy artemethin-II (**8**)



10β-Hydroxy artemethin-I (**9**)



3α–Hydroxydeoxy-β-dihydroartemisinin (**10**)

**Figure 2:** Continue