# AN UPDATE ON BIOTRANSFORMATIONAL STUDIES OF EPLERENONE

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**Abstract**

Biotransformation indicates the various chemical modifications, which undergo drugs in the body to give metabolites as new molecules having their own features, generally different from those of drug. Eplerenone (1) is an effective antihypertensive agent, and improve the morbidity and mortality of heart failure. Various transformed products 2-11 up to 2009 were obtained from the biotransformation of eplerenone (1) using human volunteers, dogs and rats. This review may be of general interest, and helpful in the comparative studies among transformed products 2-11, obtained by different ways.

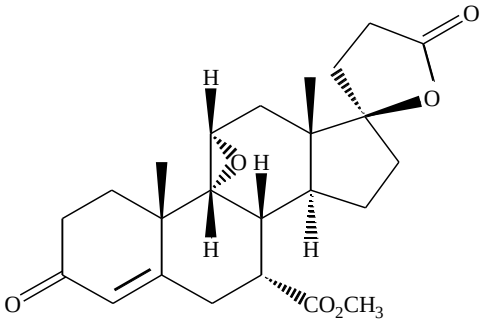
## Introduction

Biotransformation are chemical reactions that are catalyzed by microorganisms or isolated enzymes. Biotransformation is sometime more better than traditional chemical synthesis. The reactions including reduction, oxidation, dehydrogenation, hydroxylation, epoxidation, glycosylation, hydrolysis, alkylation, double bond formation and isomerization are now routinely performed in the industry using biotransformation. Biotransformation takes place under mild conditions. Therefore, chemicals can be converted into desirable products without decomposition. With mild reaction conditions, bioprocesses save not only operational energy, but also capital investment. So it is not false that biotransformation is "environmentally friendly" methodology. Biotransformation technology led to the development of scientifically novel and commercially successful processes using novel enzyme systems for the manufacture of molecules of high biological activity (Cheetham, 1993).

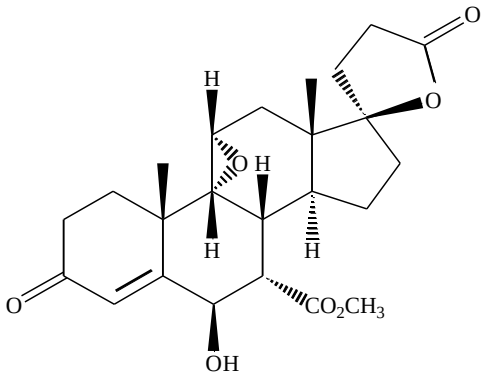
Eplerenone (pregn-4-ene-7$\alpha$,21-dicarboxylic acid-9,11$\alpha$-epoxy-17$\alpha$-hydroxy-3-oxo,$\gamma$-lactone, methyl ester) (**1**) blocks the action of aldosterone (a natural substance that raises blood pressure in the body), so eplerenone (**1**) is known as highly selective aldosterone (mineralocorticoid) receptor antagonist (Ahn *et al*., 2012; Zhang *et al*., 2003). Aldosterone is an important mediator in the pathogenesis of heart failure, and increased plasma aldosterone levels are associated with a poor prognosis (Kalidindi *et al*., 2007). Aldosterone exerts major effects on all the principal mechanisms, which produce hypertension (Zhang *et al*., 2003), ventricular hypertrophy, cardiac fibrosis, malignant, nephrosclerosis, stroke, myocardial necrosis (Delyani *et al*., 2001), cardiac death (Zillich and Carter, 2002), coronary endothelial dysfunction, LV fibrosis, autonomic imbalance (Struthers, 2000) and also effects on renal function. Eplerenone (1) has ability to block both the epithelial and non-epithelial actions of aldosterone (Sica, 2005). It is also a useful drug in proteinuric patients with chronic kidney disease. Eplerenon (1) reduces progestational and antiandrogenic side effects compared with spironolactone, while maintaining aldosterone blocking activity by its 9,11-epoxide group (Cook *et al*., 2003a).

**Biotransformed products of eplerenone (1):**
Various transformed products 2-11 were obtained by different pathways of biotransformation of eplerenone (**1**) up to 2009 (Fig. 1). This review may help in comparative studies among transformed products 2-11, obtained by different pathways. The detail of these compounds 2-11 is also mentioned in Table-1.

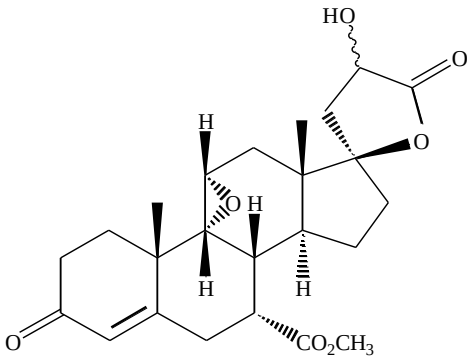
**Biotransformed products of eplerenone (1) from urine of male and female rats:**
Cook and co-workers in 2003a investigated eplerenone (1) in male and female rats, where it was extensively metabolized. They were also observed that eplerenone (1) was more metabolized in male than female rats. 6β-hydroxyeplerenone (2) was the major metabolite in the male and female rats. The studies indicated that metabolism of eplerenone (1) to 6β-hydroxyeplerenone (**2**) was mediated primarily by CYP3A in the rat. The dose-dependent manner of eplerenone (1) in both male and female rats indicating that eplerenone (1) was a CYP3A inducer in the rat.



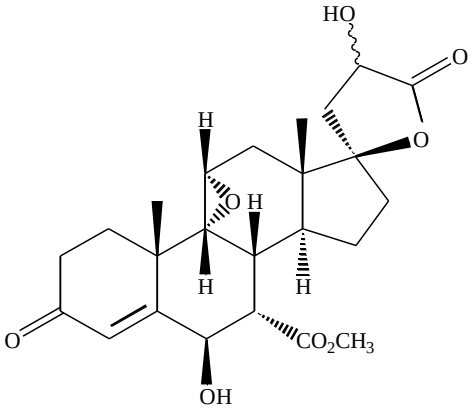
Eplerenone (**1**)



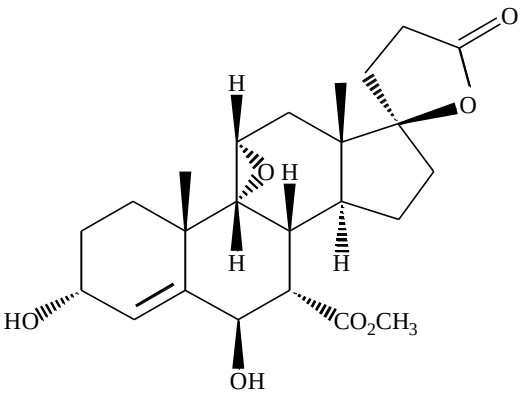
6β-Hydroxyeplerenone (**2**)



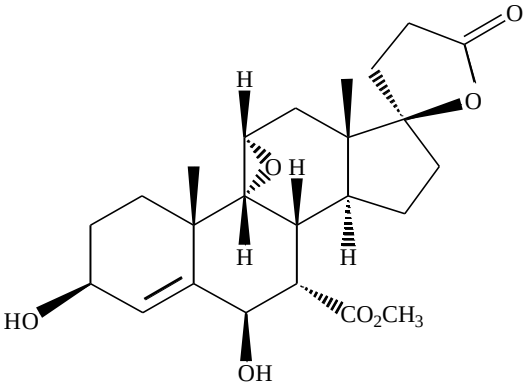
21-Hydroxyeplerenone (**3**)



6β,21-Dihydroxyeplerenone (**4**)

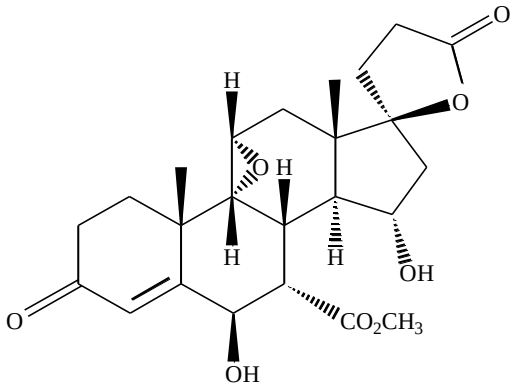


3α,6β-Dihydroxyeplerenone (**5**)

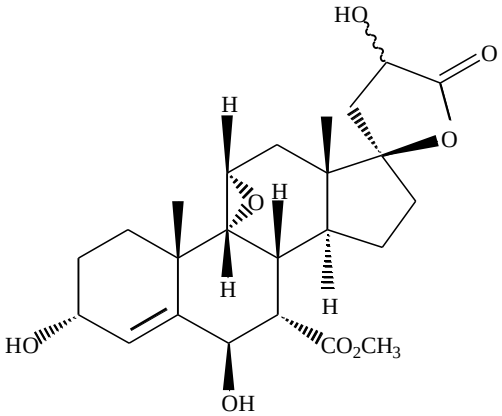


3β,6β-Dihydroxyeplerenone (**6**)

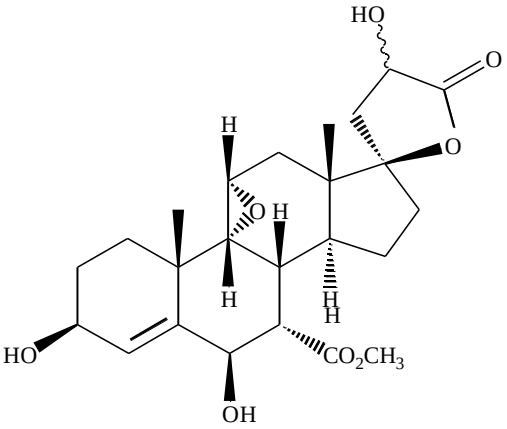
**Fig. 1. Structures of eplerenone (1) and its biotransformed products 2-11.**



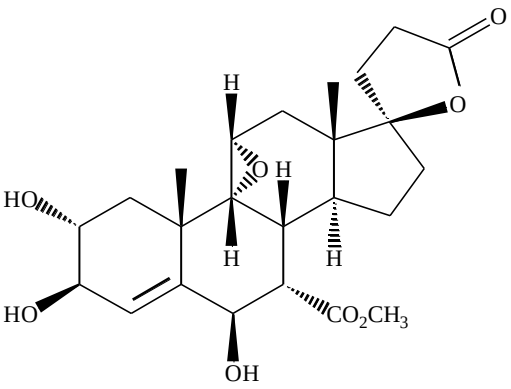
6β,15α-Dihydroxyeplerenone (**7**)



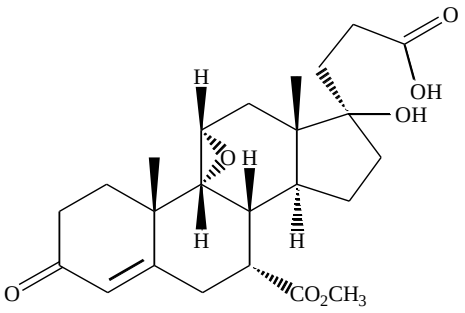
3α,6β,21-Trihydroxyeplerenone (**8**)



3β,6β,21-Trihydroxyeplerenone (**9**)



2α,3β,6β,-Trihydroxyeplerenone (**10**)



Hydrolyzed eplerenone (**11**)

**Fig. 1. Continue.**

**Table 1. Biotransformed products 2-11 of eplerenone (1).**

| S. No. | Biotransformed products | Biotransformation pathways | References |
|---|---|---|---|
| 1 | 6β-Hydroxyeplerenone (2) | from urine of male and female rats; blood, saliva, breath, urine and fecal of human volunteers, and dogs | Cook *et al*., 2002; Cook *et al*., 2003a; Cook *et al*., 2003b |
| 2 | 21-Hydroxyeplerenone (3) | from blood, saliva, breath, urine and fecal of human volunteers, and dogs | Cook *et al*., 2002; Cook *et al*., 2003b |
| 3 | 6β,21-Dihydroxyeplerenone (4) | from blood, saliva, breath, urine and fecal of human volunteers | Cook *et al*., 2003b |
| 4 | 3α,6β-Dihydroxyeplerenone (5) | from blood, saliva, breath, urine and fecal of human volunteers | Cook *et al*., 2003b |
| 5 | 3β,6β-Dihydroxyeplerenone (6) | from blood, saliva, breath, urine and fecal of human volunteers | Cook *et al*., 2003b |
| 6 | 6β,15α-Dihydroxyeplerenone (7) | from blood, saliva, breath, urine and fecal of human volunteers | Cook *et al*., 2003b |
| 7 | 3α,6β,21-Trihydroxyeplerenone (8) | from blood, saliva, breath, urine and fecal of human volunteers | Cook *et al*., 2003b |
| 8 | 3β,6β,21-Trihydroxyeplerenone (9) | from blood, saliva, breath, urine and fecal of human volunteers | Cook *et al*., 2003b |
| 9 | 2α,3β,6β-Trihydroxyeplerenone (10) | from blood, saliva, breath, urine and fecal of human volunteers | Cook *et al*., 2003b |
| 10 | Hydrolyzed eplerenone (11) | from urine of human volunteers | Zhang *et al*., 2003 |

**Biotransformed products of eplerenone (1) from human volunteers:**

Cook and co-workers in 2003b investigated metabolism of eplerenone (1) in humans after its oral administration. They were collected fecal, breath, urine, blood and saliva samples at specific intervals, which were analyzed. Nine metabolites; 6β-hydroxyeplerenone (2), 21-hydroxyeplerenone (3), 6β,21-dihydroxyeplerenone (4), 3α,6β-dihydroxyeplerenone (5), 3β,6β-dihydroxyeplerenone (6), 6β,15α-dihydroxyeplerenone (7), 3α,6β,21-trihydroxyeplerenone (8), 3β,6β,21-trihydroxyeplerenone (9) and 2α,3β,6β-trihydroxyeplerenone (10) were identified. Metabolite 2 was the major metabolite in plasma whereas 3, 4 and 5 were also isolated as minor metabolites. Metabolites 2 and 4 were major metabolites in urine whereas 3, 5, 7 and 8 were identified as minor metabolites. Greater number of metabolites was excreted in feces than that in urine. The major metabolic pathways were 6β- or 21-hydroxylation and 3-keto reduction. In this study, it was investigated that no any change or alteration occur on the epoxide ring and methyl ester due to steric hindrance of these molecules and that is very important for the selectivity of eplerenone (1) as compared with spironolactone. It was also observed that eplerenone (1) was more stable in human plasma than in the dog and rat plasma.

Cook and co-workers in 2002 isolated two metabolites of eplerenone (1) formed in human liver microsomes by *in vitro* study. The major *in vitro* metabolite was 6β-hydroxyeplerenone (2) and minor metabolite was 21-hydroxyeplerenone (3).

Zhang and co-workers in 2003 identified the hydrolyzed eplerenone (11) metabolite of eplerenone (1) in human urine.

**Biotransformed products of eplerenone (1) from dogs:**

Cook and co-workers in 2002 demonstrated the two isolated metabolites 6β-hydroxyeplerenone (2) and 21-hydroxyeplerenone (3) of eplerenone (1) with dog liver microsomes after oral administration. The studies indicated that formation of 6β-hydroxyeplerenone (2) and 21-hydroxyeplerenone (3) was mediated by CYP3A12 in the dog. Therefore, proportion of these two metabolites 2 and 3 in dog was substantially different as compare with human. The formation of metabolite 3 was relatively higher than 2.

**Conclusion**

The review highlighted the biotransformed metabolites 2-11 of eplerenone (1). Regarding this detailed survey, it is assumed that it will assist in comparative studies among transformed products obtained by different pathways of biotransformation.

**Acknowledgement**

Dr. Azizuddin acknowledges his BS student, Ms. Zobia Naz for her cooperation in the preparation of this review.

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