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Discovery of olmesartan hexetil: A new potential prodrug of olmesartan

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ABSTRACT

Synthesis of a new ester prodrug of olmesartan, olmesartan hexetil (**1**), is described. It is in vitro stabilities and in vivo pharmacokinetics (PK) were evaluated. It showed high stability in simulated gastric juice, and was rapidly hydrolyzed to olmesartan in rat liver microsomes and rat plasma in vitro. C_{max} and AUC_{last} for olmesartan were significantly increased in case of hexetil prodrug, compared with olmesartan medoxomil. Olmesartan hexetil is proposed to be an efficient prodrug of olmesartan with markedly increased oral bioavailability.

In the current era of globalization; which is characterized by so much stress, worry, and hurry; the incidence of cardiovascular disorders has dramatically increased. Hypertension is a disease which affects an estimated one billion people worldwide.[1] The American Heart Association estimates high blood pressure affects approximately one in three adults in the United States. Hypertension is a serious disease with a momentous impact on health and life expectancy. Controlling blood pressure and prevention of its complications such as coronary heart disease, renal failure, eye damage, and brain damage (stroke) are the main objectives for the treatment of hypertension.[2]

The renin–angiotensin–aldosterone system (RAAS) is a very complex system that plays a pivotal role in the regulation of blood pressure. Angiotensin II, the primary effector hormone of RAAS, affects the cardiovascular system by influencing the vascular tone, fluid volume, and electrolyte balance.[3,4]

There are many antihypertensive drugs available, many of which act on the RAAS system. Angiotensin receptor blockers (ARBs) are a class of antihypertensive agents that are growing in popularity due to their excellent blood pressure control potential, low adverse event profile, and high patient tolerability.[5] Olmesartan is an example of ARBs which acts by blocking type 1 angiotensin II receptors (AT_1-R), leading to prevention of vasoconstriction, reduction of sodium and water retention, and decrease of cellular proliferation and hypertrophy.[6] In addition to AT_1-R blockade, olmesartan is assumed to exhibit an angiotensin-converting enzyme (ACE) inhibitory effect, prevent an increase in angiotensin II level, and protect cardiovascular remodeling through an increase in cardiac nitric oxide production and endogenous angiotensin-(1–7) via over-expression of ACE2.[7]

The once daily dosing interval of most ARBs helps enhance patient compliance which may lead to better patient outcomes.[5] Olmesartan medoxomil is an ester prodrug of olmesartan that has shown potent and long-lasting antihypertensive activity after oral administration.[8] Olmesartan medoxomil is rapidly de-esterified by enzymatic hydrolysis in the intestine, liver, and plasma. After oral administration of the prodrug, first-pass bioactivation occurs in the intestine, followed by the portal blood and liver, before the prodrug reaches the systemic circulation. It was reported that multiple enzymes are capable of bioactivating olmesartan medoxomil in human, including plasma albumin,[9] and an intestinal and liver hydrolase carboxymethylenebutenolidase homolog (CMBL).[10] High metabolic clearance of intestinal CMBL suggests that the intestinal bioactivation firstly and predominantly contributes to the quick onset of drug action after oral administration of

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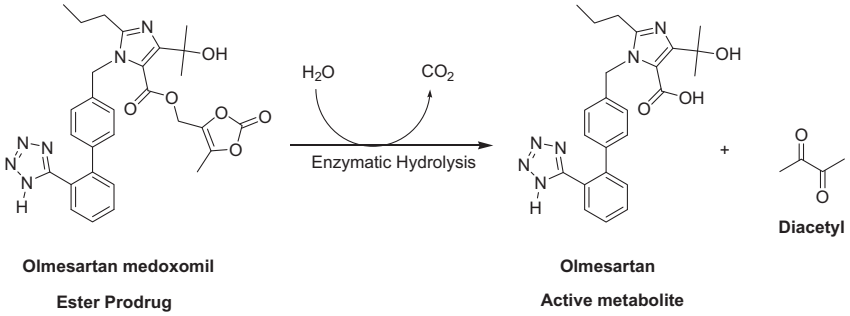
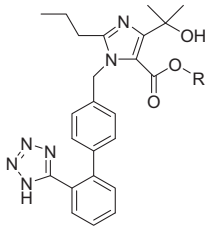
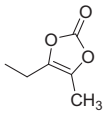
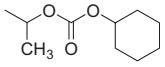


Figure 1. Hydrolysis of olmesartan medoxomil to olmesartan.

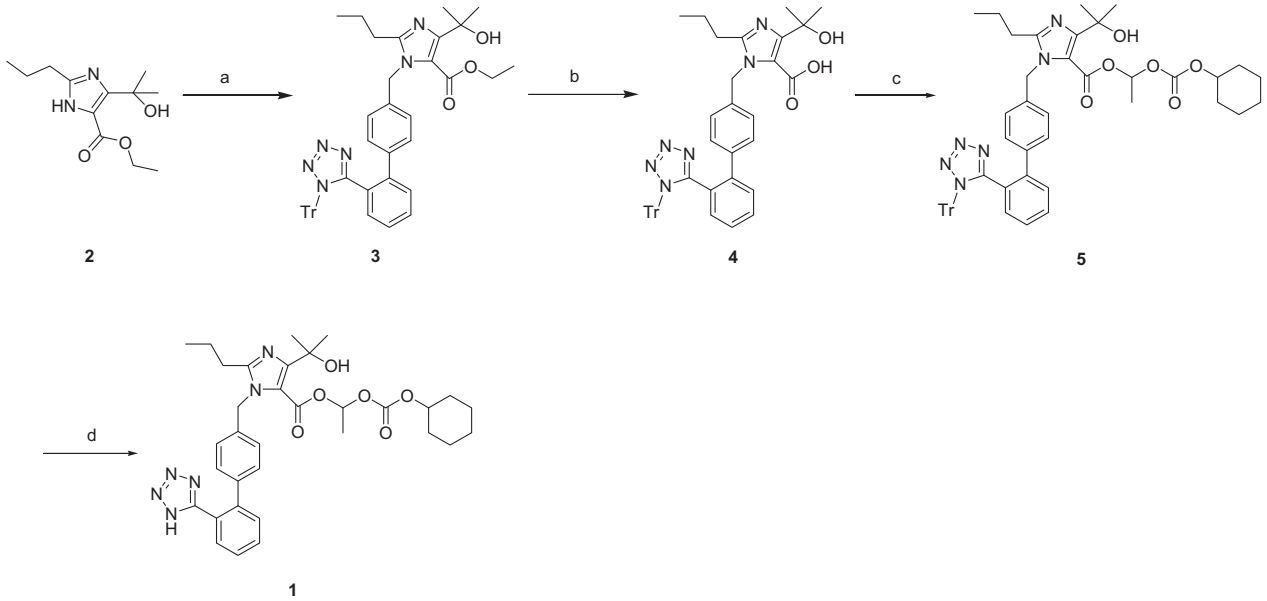
Table 1
c Log *P* and total polar surface area (TPSA) calculations for olmesartan medoxomil and olmesartan hexetil (**1**)

Structure	Compd no	R	*c*Log *P*	TPSA (A^2)
	Olmesartan medoxomil		3.49	162.18
	1		5.06	154.37

olmesartan medoxomil.[11] Figure 1 illustrates the enzymatic hydrolysis of olmesartan medoxomil into the active metabolite, olmesartan.[9]

We reported the synthesis, bioconversion, and PK evaluation of new prodrugs of olmesartan with higher lipophilicity than olmesartan medoxomil. The new ester prodrugs of olmesartan showed improved PK parameters for olmesartan, compared with olmesartan medoxomil.[12,13] These results showed that lipophilic ester prodrugs of olmesartan can improve the oral bioavailability and PK properties of olmesartan. In the present investigation, we report the synthesis, in vitro bioconversion, and in vivo PK evaluation of a new ester prodrug of olmesartan, olmesartan hexetil. The medoxomil moiety of olmesartan medoxomil was replaced by hexetil, a more lipophilic moiety, in order to increase the lipophilicity of olmesartan ester prodrug, and hence, olmesartan bioavailability. Hexetil promoiety has been reported to increase the oral bioavailability of candesartan.[14] The calculated *c*log *P*[15] and total polar surface area (TPSA)[16] values of olmesartan medoxomil and olmesartan hexetil prodrugs are illustrated in Table 1. Olmesartan hexetil (**1**) with higher *c*log *P* and lower TPSA values compared with olmesartan medoxomil (i.e., more lipophilic than olmesartan medoxomil) was synthesized and evaluated as a new potential prodrug of olmesartan. Our target is to improve the pharmacokinetic properties of olmesartan, and hence, the antihypertensive outcomes. The synthetic and screening protocols are illustrated in details.

Synthesis of the target compound **1** was carried out according to the sequence of reactions illustrated in Scheme 1. It was important at the beginning to prepare the key carboxylic acid compound, trityl olmesartan (**4**). N-alkylation of ethyl 4-(1-hydroxy-1-methyl-ethyl)-2-propylimidazole-5-carboxylate (**2**) with 5-(4′-bromomethyl-biphenyl-2-yl)-1-trityl-1*H*-tetrazole afforded the ethyl ester of trityl olmesartan (**3**). Alkaline hydrolysis of the ethyl ester moiety of **3** followed by acidification of the formed potassium salt gave trityl olmesartan (**4**).[17] The target hexetil ester **1** was obtained



Scheme 1. Reagents and conditions: (a) 5-(4′-bromomethyl-biphenyl-2-yl)-1-trityl-1*H*-tetrazole, K_2CO_3, acetone, DMAc, reflux, 10 h, 75%; (b) (i) KOH, isopropanol, 60 °C, 4 h; (ii) HCl, workup, 90%; (c) hexetil chloride, K_2CO_3, KI, DMAc, 70 °C, 2 h, 95%; (d) concd HCl, acetone, H_2O, rt, 2 h, 92%.