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Novel amides and esters prodrugs of olmesartan: Synthesis, bioconversion, and pharmacokinetic evaluation

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ABSTRACT

Synthesis of novel amides and esters prodrugs of olmesartan is described. Their in vitro stability in rat plasma was tested. The results showed that the ester derivative **IIa** with *n*-octyl substituted dioxolone moiety was rapidly converted into olmesartan within 30 min. The pharmacokinetic parameters of **IIa** were studied and compared with those of olmesartan medoxomil. Compound **IIa** is proposed to be a promising prodrug of olmesartan.

Hypertension is a disease which affects an estimated one billion people worldwide.[1] It 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, and cerebral vascular disease are the main objectives for the treatment of hypertension.[2]

The renin–angiotensin aldosterone system (RAAS) is a very complex system that plays an important 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 blocking of vasoconstriction, reduction of sodium and water retention, and decrease of cellular proliferation and hypertrophy.[6] Besides AT_1-R blockade, olmesartan is assumed to exhibit an angiotensin-converting enzyme (ACE) inhibitory action, 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 which showed potent and long-lasting antihypertensive activity by oral administration.[8] Olmesartan medoxomil is rapidly de-esterified by an enzyme, arylesterase, which is located in both the intestine and plasma.[6] Figure 1 illustrates the enzymatic hydrolysis of olmesartan medoxomil into the active metabolite, olmesartan.[9]

In the present investigation, we report the design, synthesis, and biological evaluation of novel amides and esters prodrugs of olmesartan. The medoxomil moiety of olmesartan medoxomil was modified in different ways. Substitution of the dioxolone ring with a lipophilic *n*-octyl group instead of methyl group (compound **IIa**), ring expansion and isosteric substitution of the methyl-substituted

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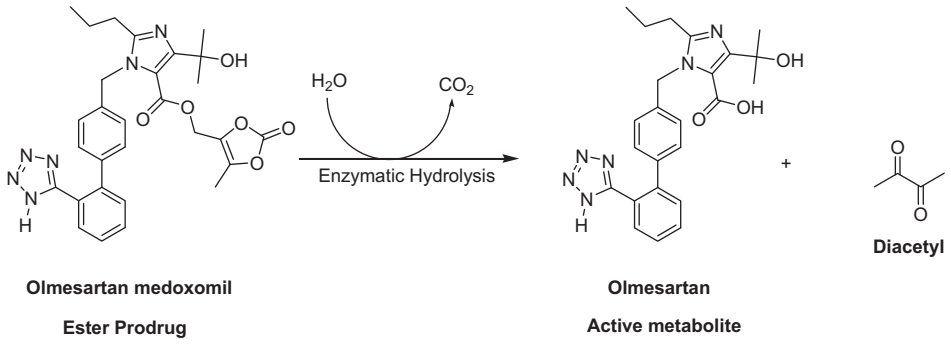
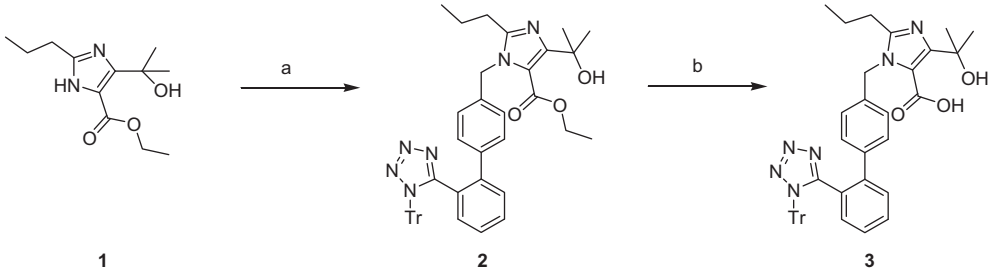


Figure 1. Hydrolysis of olmesartan medoxomil to olmesartan.

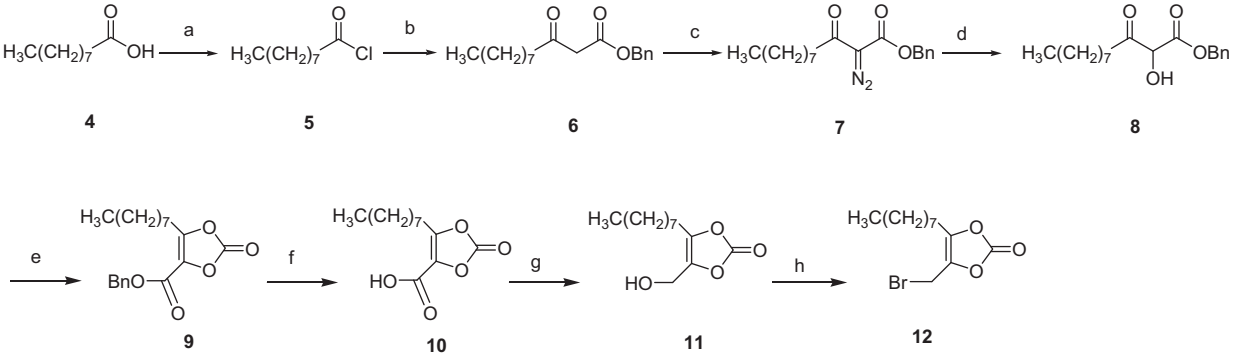
five-membered dioxolone moiety with a six-membered uracil ring (compound **IIb**), replacement with *n*-octyl group (compound **IIc**), or ring opening and insertion of some isosteres (compounds **Ia–c** and **IId–f**) were performed. Moreover, the ester moiety of olmesartan medoxomil was retained in compounds **IIa–f** but replaced with an isosteric amide moiety in compounds **Ia–c**. Our target is to improve the pharmacokinetic properties of olmesartan, and hence, the antihypertensive outcomes. The synthetic and screening protocols are illustrated in details.

For the synthesis of the target compounds **Ia–c** and **IIa–f**, it was important at the beginning to prepare the key carboxylic acid compound, trityl olmesartan **3**, as illustrated in Scheme 1. N-alkylation of ethyl 4-(1-hydroxy-1-methylethyl)-2-propylimidazole-5-carboxylate (**1**) with 5-(4′-bromomethyl-biphenyl-2-yl)-1-trityl-1*H*-tetrazole afforded the ethyl ester of trityl olmesartan **2**. Alkaline hydrolysis of the ethyl ester moiety of **2** followed by acidification of the formed potassium salt furnished trityl olmesartan **3**.[10]

For the synthesis of the target ester compound **IIa**, it was essential to prepare the corresponding alkyl halide, 4-(bromomethyl)-5-octyl-1,3-dioxol-2-one (**12**). Compound **12** was successfully prepared according to the sequence of reactions illustrated in Scheme 2. Nonanoic acid (**4**) was converted into the corresponding acid chloride **5** by refluxing in thionyl chloride.[11] Acylation of Meldrum's acid with the acid chloride **5** in the presence of pyridine gave the corresponding acyl Meldrum's acid, which underwent alcoholysis with benzyl alcohol to give the corresponding β-keto ester **6**.[12] Diazotization of **6** with TsN_3 in the presence of TEA gave the corresponding azo compound **7**, which was treated with rhodium acetate dimer to produce the corresponding α-hydroxy-β-keto ester **8**. Cyclization of **8** with carbonyldiimidazole afforded benzyl 5-octyl-2-oxo-1,3-dioxole-4-carboxylate (**9**), which upon hydrogenolysis in the presence of $Pd(OH)_2$ gave the corresponding carboxylic acid derivative **10**. Reduction of the carboxylic acid group of **10** to produce the corresponding primary alcohol **11**



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%.



Scheme 2. Reagents and conditions: (a) $SOCl_2$, reflux, 4 h, 99%; (b) (i) Meldrum's acid, C_5H_5N, CH_2Cl_2, 0 °C, 2 h; (ii) BnOH, CH_3CN, reflux, 9 h; (c) TsN_3, TEA, CH_3CN, 0 °C, 8 h, 99%; (d) $Rh_2(OAc)_4$, THF/H_2O, reflux, 2 h, 50%; (e) CDI, DIPEA, THF, 0 °C, 8 h, 60%; (f) $Pd(OH)_2$, H_2, EtOH, 1 h, 94%; (g) (i) oxalyl chloride, DMF, CH_2Cl_2, 0 °C, 1.5 h (ii) $(n\text{-}Bu)_4NBH_4$, CH_2Cl_2, −78 °C, 1 h, 60%; (h) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 0.5 h, 79%.

was carried out by using oxalyl chloride in the presence of DMF in CH_2Cl_2 at 0 °C. Bromination of **11** with CBr_4/PPh_3 in CH_2Cl_2 gave the target bromomethyl reagent **12**.

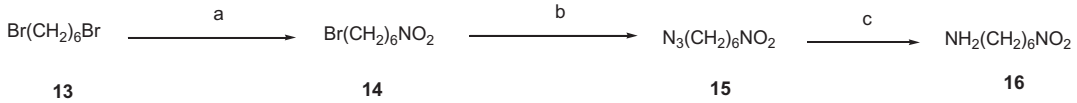
Interaction of the commercially available 1,6-dibromohexane (**13**) with $NaNO_2$ (0.86 equiv) in DMSO afforded 1-bromo-6-nitrohexane (**14**), which was purified by fractional distillation.[13] The bromo group of **14** was substituted with azido group using sodium azide to give **15**. Treatment of the azido compound **15** with PPh_3/H_2O in THF produced 6-nitrohexan-1-amine (**16**) (Scheme 3). Compounds **14** and **16** were utilized for the synthesis of the target compounds **IId** and **Ia**, respectively.

Synthesis of ethyl 7-aminoheptanoate (**19**) was carried out by the same procedure as described for the preparation of **16** starting with ethyl 7-bromoheptanoate (**17**) (Scheme 4). Compounds **19** was utilized for the synthesis of the target compound **Ib**.

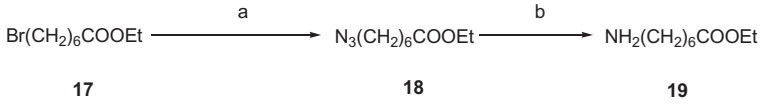
Condensation of trityl olmesartan **3** with amine derivative **16** or **19** in the presence of HOBt, EDCI, and TEA in anhydrous DMF afforded the corresponding trityl olmesartan amide derivatives **20a,b**. Detritylation of **20a,b** with concd HCl gave the target amide derivatives **Ia,b**. Upon detritylation of **20b**, the ethyl ester moiety was simultaneously hydrolyzed to give the corresponding carboxylic acid **Ib** (Scheme 5).

We tried to synthesize the (2-(2-hydroxyethylamino)ethyl) amide derivative **Ic** by the same procedure utilized for synthesis of **Ia,b** but these trials failed. Compound **Ic** was successfully synthesized by another procedure as illustrated in Scheme 6. The lactone derivative **21** was prepared by heating **3** with 2-(2-aminoethylamino)ethanol in the presence of HOBt, EDCI, and TEA in anhydrous DMF. Detritylation and amide formation were achieved in one step by refluxing **21** with 2-(2-aminoethylamino)ethanol in dry acetonitrile.

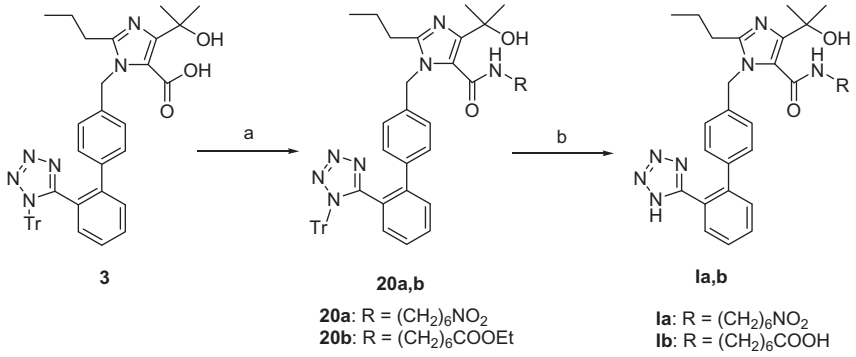
The target ester compounds **IIa–f** were synthesized by esterification of the carboxylic acid group of **3** with the appropriate alkyl halide, and subsequent detritylation using concd HCl. Detritylation of **22e** lead to simultaneous hydrolysis of the terminal ester group to give a mixture of terminal ester **IIe** and terminal acid **IIf**



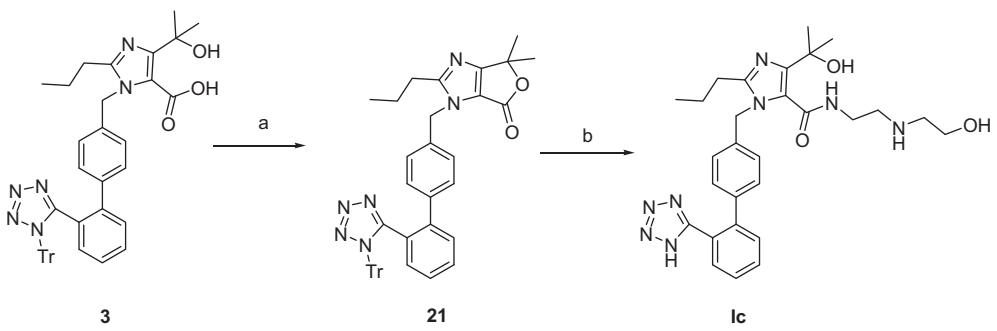
Scheme 3. Reagents and conditions: (a) $NaNO_2$, DMSO, rt, 1 h, 30%; (b) NaN_3, DMF, rt, 12 h, 95%; (c) PPh_3, H_2O, THF, rt, 3 days, 85%.



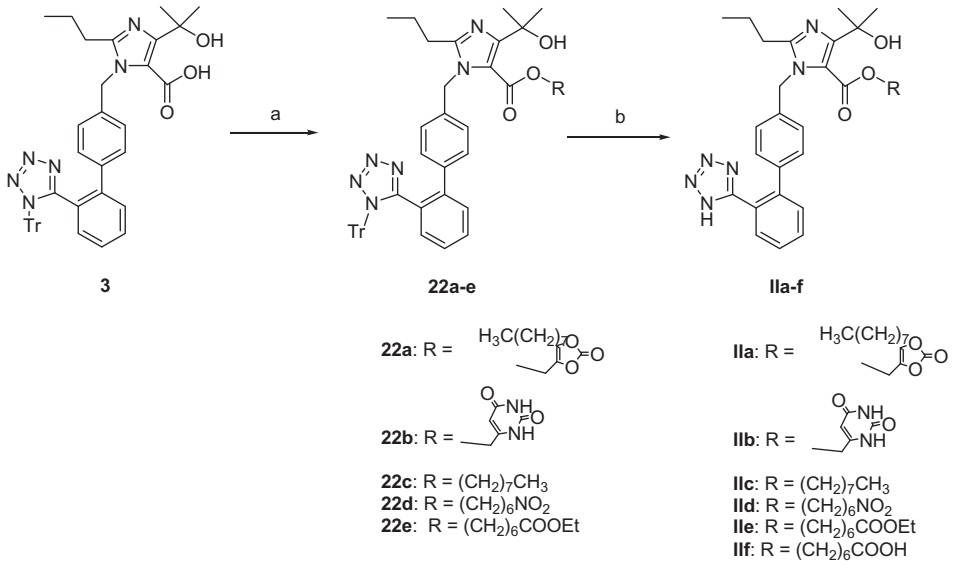
Scheme 4. Reagents and conditions: (a) NaN_3, DMF, rt, 12 h, 95%; (b) PPh_3, H_2O, THF, rt, 7 h, 90%.



Scheme 5. Reagents and conditions: (a) appropriate amine, HOBt, EDCI, TEA, DMF, rt, 6 h, (**20a**: 60%, **20b**: 55%); (b) concd HCl, acetone, H_2O, rt, 2 h, (**Ia**: 80.1%, **Ib**: 82%).



Scheme 6. Reagents and conditions: (a) $NH_2(CH_2)_2NH(CH_2)_2OH$, HOBt, EDCI, TEA, DMF, 60 °C, 5 h, 75%; (b) $NH_2(CH_2)_2NH(CH_2)_2OH$, CH_3CN, reflux, 24 h, 53.7%.



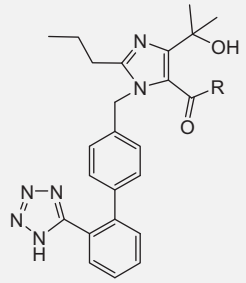
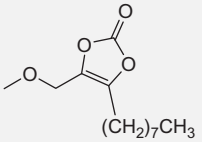
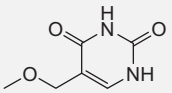
Scheme 7. Reagents and conditions: (a) R-X, K_2CO_3, KI, DMAc, 70 °C, 2 h, (**22a**: 76%, **22b**: 68.3%, **22c**: 72%, **22d**: 64%, **22e**: 75%); (b) concd HCl, acetone, H_2O, rt, 2 h, (**IIa**: 68%, **IIb**: 93.7%, **IIc**: 91%, **IId**: 93%, **IIe**: 26.6%, **IIf**: 30%).

derivatives which were separated by column chromatography (Scheme 7).

The stabilities of all compounds were determined in rat plasma in vitro. The remaining percentages of the compounds in rat plasma after the incubation were summarized in Table 1. After the 30 min incubation period of **IIa**, the prodrug peak disappeared, and the olmesartan peak was increased. The results showed that compound **IIa** was rapidly hydrolyzed to olmesartan, active metabolite, in plasma. Based on stability testing results, pharmacokinetics study was conducted to determine whether **IIa** was converted into olmesartan in vivo. The prodrug **IIa** was administered orally using a feeding tube to male Sprague–Dawley rats at a dose of 20 mg/kg as olmesartan. The plasma concentrations of olmesartan were determined by a slight modification of the reported liquid chromatography-tandem mass spectrometric method.[14] The total area under the plasma concentration–time curve from time zero to the last measured time (AUC_{0-last}) was calculated by the linear trapezoidal rule method.[15] The mean arterial plasma concentration–time profiles of olmesartan after oral administration of **IIa** and olmesartan medoxomil in rats are shown in Figure 2, and some relevant pharmacokinetic parameters of olmesartan are summarized in Table 2. After oral administration, olmesartan was detected in plasma from the first blood sampling time, 30 min. Compound **IIa** was well absorbed from rat gastrointestinal tract and rapidly converted into the active form. After administration of prodrug **IIa**, both the C_{max} and AUC_{0-last} of olmesartan were significantly greater (128% and 95.1% increase, respectively) than those observed after administration of olmesartan medoxomil. The results indicated that introduction of long aliphatic chain enhanced the oral absorption and systemic exposure level of olmesartan. These effects are possibly due to a marked increase in lipophilicity of **IIa** induced by long aliphatic chain over olmesartan medoxomil.

In conclusion, we designed and synthesized a series of novel amides and esters prodrugs of olmesartan. We studied the in vitro metabolic stability of the newly synthesized compounds in comparison with olmesartan medoxomil. In addition, the

Table 1
In vitro stability of compounds **Ia–c** and **IIa–f** in rat plasma

Structure	Compound No.	R	Stability (% remaining)
	**Ia**	$-NH(CH_2)_6NO_2$	100.7
	Ib	$-NH(CH_2)_6COOH$	97.5
	Ic	$-NH(CH_2)_2NH(CH_2)_2OH$	98.9
	IIa		NA[a]
	IIb		96.3
	IIc	$-O(CH_2)_7CH_3$	90.2
	IId	$-O(CH_2)_6NO_2$	100.2
	IIe	$-O(CH_2)_6COOC_2H_5$	81.1
	IIf	$-O(CH_2)_6COOH$	98.8
	Olmesartan medoxomil		NA[a]

To determine the plasma stability, 50 μg/mL compound in rat plasma was incubated for 30 min at 37 °C.
[a] NA, not applicable.

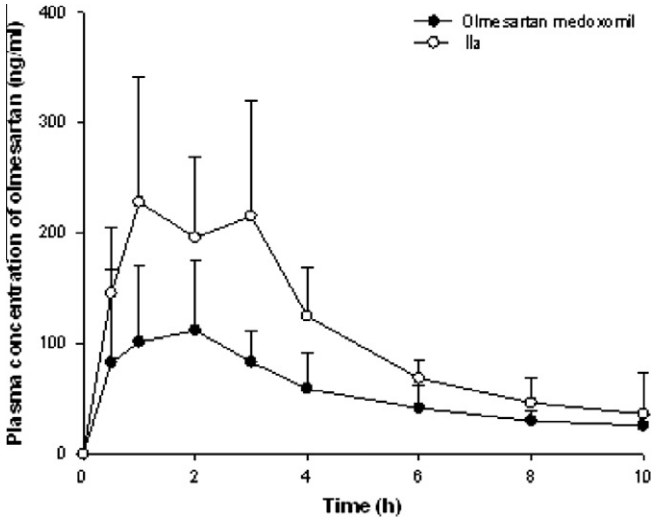


Figure 2. Mean arterial plasma concentration–time profiles of olmesartan after oral administration of olmesartan medoxomil (●; $n = 4$) and prodrug **IIa** (○; $n = 4$) at a dose of 20 mg/kg as olmesartan in rats. Bars represent SD.

Table 2
Pharmacokinetic parameters (mean ± SD) of olmesartan after oral administration of prodrugs (20 mg/kg as olmesartan) to male Sprague–Dawley rats C_{max}, peak plasma concentration; T_{max}, time to reach C_{max}; AUC_{0-last}, total area under the plasma concentration–time curve from time zero to last measured time

Parameter	Olmesartan medoxomil ($n = 4$)	**IIa** ($n = 4$)
C_{max} (ng/mL)	125 ± 72.5	285 ± 95.9
T_{max} (h)	0.5–3	1–3
AUC_{0-last} (ng h/mL)	569 ± 269	1110 ± 140

in vivo pharmacokinetic parameters of compound **IIa** were studied and compared with those of olmesartan medoxomil. The newly synthesized ester prodrug **IIa** with *n*-octyl substituted dioxolone ring is proposed to be an effective prodrug of olmesartan with improved oral bioavailability. Further modification of this compound in order to improve the pharmacokinetic properties and oral bioavailability of olmesartan is currently in progress. Our ultimate goal is to improve the antihypertensive impact of olmesartan.

Acknowledgments

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