

## Synthesis of Novel Isoxazole-contained Analogues of Losartan

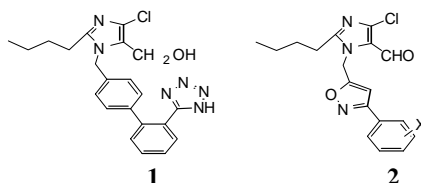
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**Abstract:** A series of novel isoxazole-contained analogues of Losartan were designed and synthesized with 1,3-DC reaction. The regioselectivity of the reaction was discussed and the compounds are potential antihypertensive.

**Keywords:** analogues of losartan, Synthesis, 1,3-DC, antihypertensin.

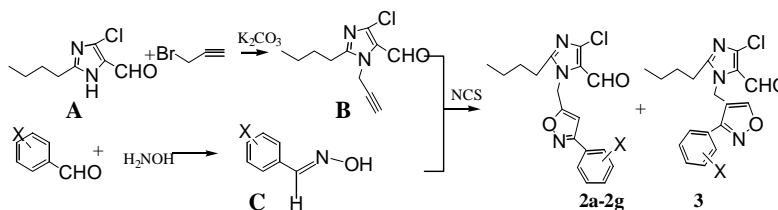
Losartan **1** (Dup-753) is a nonpeptide angiotensin II receptor (type AT<sub>1</sub>) antagonist discovered by Duncia, J.V. *et al.*<sup>1</sup> in 1990 and its potassium salt (**cozaar**) has been marketed as an antihypertensive since 1995<sup>2</sup>.



Starting from Dup-753, a great number of structural related compounds have been prepared by several laboratories and several antihypertensive drugs have been developed<sup>3</sup>.

In order to find new and more active compounds, a novel type of Losartan analogues **2** was designed and synthesized. In the molecule of compound **2**, isoxazole ring was introduced as the substituent of benzene ring in Losartan. For the free electron pairs in the isoxazole ring could make the molecule easier to bind with the receptor and may be more active than Losartan itself. 1,3-DC reaction of **B** and **C** can form two isomers (**2a-2g** and **3**). As shown in scheme, **2** is the favorable one.

**Scheme:** Seven new compounds were synthesized and their structures were confirmed by <sup>1</sup>HNMR and the <sup>13</sup>CNMR. The compounds are potential antihypertensive and the bio-analysis is undertaking.



## Experimental

**A** was synthesized by literature method<sup>6</sup>. Aryl aldehyde oximes **C** were easily obtained by the reaction of substituted aryl aldehydes with hydroxylamine. *o*-bromobenzaldehyde oxime 0.6g (3mmol) was put into 15 ml CH<sub>2</sub>Cl<sub>2</sub>. After it was dissolved, NCS 0.41g (3.3mmol) was added and the mixture was heated at 40–50 °C for 15 min. While the compound **B** was put into the mixture, triethylamine 0.33g (3mmol) was dropped into the reaction mixture and stirred for another 30 min. The solvent was removed under vacuum and the residue was separated by chromatography on silica-gel column using ethyl acetate/petroleum (1:4) as eluent. Removal of the solvent gave oily product **2e** and it was confirmed by the <sup>1</sup>HNMR and <sup>13</sup>CNMR taking by 200 MHz Varian NMR instrument. The oily product was solidified after standing.

**Table 1.** Analytical data on **2a–2g**

Product	X	m.p.(°C)	Yields(%)	<sup>1</sup> HNMR spectra(CDCl <sub>3</sub> , δ relative to TMS)		
				Ar-H	R-H	CHO
<b>2a</b>	H	77-78	55	7.4-7.8(m, 5H); 6.6(s,1H).	0.9(t,3H); 1.4(m,2H); 1.8(m,2H); 2.8(t,2H); 5.2(s,2H).	9.7( s, 1H).
<b>2b</b>	<i>p</i> -OMe	79-81	63	6.9-7.7(m,4H); 6.5(s,1H).	0.9(t,3H);1.4(m,2H); 1.8(m,2H); 2.8(t,2H); 3.8(s,3H); 5.7(s,2H).	9.7( s, 1H).
<b>2c</b>	<i>o</i> -OMe	71-72	65	7.0-7.8(m,4H); 6.8(s, 1H).	0.9(t,3H);1.4(m,2H); 1.8(m,2H); 2.8(t,2H); 3.9(s,3H); 5.6(s,2H).	9.7( s, 1H).
<b>2d</b>	<i>o</i> -Cl	oil	58	7.2-7.6(m,4H); 6.7(s,1H).	0.9(t,3H);1.4(m,2H); 1.8(m,2H); 2.8(t,2H); 5.6(s,2H).	9.7( s, 1H).
<b>2e</b>	<i>o</i> -Br	64-65	61	7.2-7.7(m,4H); 6.7(s,1H).	0.9(t,3H); 1.4(m,2H); 1.8(m,2H); 2.8(t,2H); 5.6( s, 2H).	9.7( s, 1H).
<b>2f</b>	<i>p</i> -CH <sub>3</sub>	82-84	67	7.2-7.7(m,4H); 6.6( s, 1H).	0.9(t,3H); 1.4(m,2H); 1.8(m,2H); 2.4(s,3H); 2.8(t,2H); 5.6( s, 2H).	9.7( s, 1H).
<b>2g</b>	11H	41	45	6.1( s, 1H).	0.9(t,3H);1.2-1.4(m,7H); 1.6-1.9(m,7H); 2.5-2.8(m,3H); 5.5( s, 2H).	9.7( s, 1H).

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