Chinese Chemical Letters Vol. 16, No. 8, pp 1004-1006, 2005
http://www.imm.ac.cn/journal/ccl.html

Synthesis Hexadecyl 3-{4-[2-Hydroxy-3(isopropylamino)propoxy] phenyl}propionate as Potential Ligand for Liposome Targeting to Ischemic Myocardium

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Abstract: Novel hexadecyl 3-{4-[2-hydroxy-3(isopropylamino)propoxy]phenyl}propionate (HPP) was synthesized and its effect on delivery of liposomes into cultured cardiomyocytes was examined. The structure of HPP was characterized by ^{1}H NMR, IR and MS. The amount of cardiomyocytes uptake of HPP-liposome was 3.9-fold higher than plain-liposome, and the increase was 6.2-fold when hypoxia happens. It indicated that HPP was a potential ligand for liposome targeting to ischemic myocardium.

Keywords: Hexadecyl 3-{4-[2-hydroxy-3(isopropylamino)propoxy]phenyl}propionate, liposome, targeting, ischemic myocardium.

Liposomes have been suggested as efficient carriers for delivery of drugs into ischemic myocardium and enhance the therapeutic effects by increasing drug association. It was reported that β_1-adrenoreceptor (1-AR) predominates in mammalian ventricular cardiomyocytes and its levels will significantly increase when hypoxia happens[1]. To improve the efficiency of liposomal drug delivery into the ischemic myocardium, the novel hexadecyl 3-{4-[2-hydroxy-3(isopropylamino)propoxy]phenyl}propionate(HPP) was synthesized, which had similar structure with esmolol (a selective β_1-adrenoreceptor blocker), and its effect as surface modification on delivery of liposomes into cultured cardiomyocytes was examined.

Experimental

The synthetic route of hexadecyl 3-{4-[2-hydroxy-3(isopropylamino)propoxy]phenyl}-propionate(HPP) was shown in **Scheme 1**.

HPP was synthesized according to the reference[2] with a little modification. Compound **II** was obtained by reacting compound **I** with methyl iodine (4.0 eq.) and potassium carbonate (3.3 eq.) in well-stirred acetone solution (150 mL). Cetyl alcohol (2.5 g) was dissolved in THF (50 mL) under nitrogen atmosphere, then cooled to -78℃,

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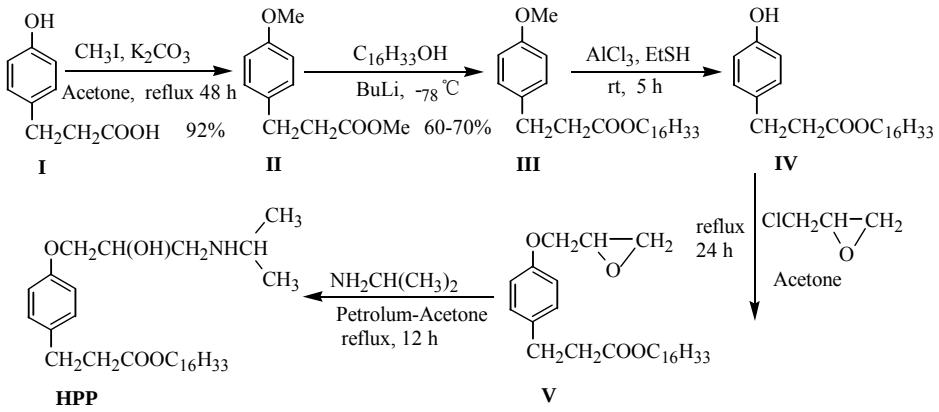
Scheme 1 The synthetic route of HPP



butyl lithium (7.7 mL) and compound **II** (2.0 g in 10 mL THF) were dropped into the solution, after 4 h compound **III** was obtained. A mixture of compound **III** (1.4 g), aluminium chloride (1.3 g) and thioglycol (30 mL) were stirred at room temperature for 5 h to give the compound **IV** which was added to 30 mL acetone together with epoxy choropropane (4-5 eq.) and potassium carbonate (3.0 eq.), then refluxed with stirring for 24 h, to give the compound **V**. Finally, compound **V** was treated with cetyl alcohol (0.1 eq.) and excessive isopropylamine to give the target compound HPP.

Results and Discussion

The structure of HPP (**Figure 1**) was confirmed by ^{1}H NMR, IR and MS. In ^{1}H NMR spectrum (DMSO -d_6, 600 MHz, δ ppm), the peaks of 7.10 (d, 2H, J=9.0 Hz, H_2 and H_6 of Ph-H), 6.83 (d, 2H, J=8.4 Hz, H_3 and H_5 of Ph-H), 4.05 (t, 2H, J=6.6 Hz, -CH_2-O-C=O), 4.03 (m, 1H, -CH-OH), 3.95 (m, 2H, -CH_2O-), 2.88 (t, 2H, J=6.5 Hz, -CH_2CH_2), 2.85 (d, 2H, J=6.6 Hz, -CH_2NH), 2.74 (m, 1H, -$CH(CH_3)_2$), 2.57 (t, 2H, J=7.8 Hz, -CH_2CH_2), 1.59 (t, 2H, J=6.6 Hz, -CH_2CH_2OC=O), 1.25 (s, 26H, -$(CH_2)_{13}$), 1.10 (d, 6H, J=6.6 Hz, 2×-CH_3CH), 0.88 (t, 3H, J=6.6 Hz, -CH_3CH_2). IR (KBr, cm^{-1}): 3224 (-OH), 1729 (-OC=O-), 1610, 1513, 1439, 1236, 1172, 1115, 889, 837. EI/MS (*m/z*): Calcd. for $C_{31}H_{55}NO_4$ 505.41, found 505.5(M).

The effect of HPP on delivery of liposomes into cultured cardiomyocytes was examined[3,4]. The liposome uptake was studied by incubating fluorescence labeled liposomes with cardiomyocytes *in vitro* and measuring the association of liposomes by a fluorescence spectrophotometer (Hitachi, 650-60). HPP-liposome and plain-liposome (without HPP) were added into the cultured cardiomyocytes and incubated 2 h under the normoxia or hypoxia conditions, respectively. The amount of cell uptake of HPP-liposome was 3.9-fold higher than plain-liposome, and the increase was 6.2-fold when hypoxia happened (**Figure 2**). We presumed that HPP had the abilities of recognizing and binding to the β_1-adrenoreceptor on the cardiomyocyte membrane. It indicated that HPP was a potential ligand for liposome targeting to ischemic myocardium.

Figure 1 The structure of HPP

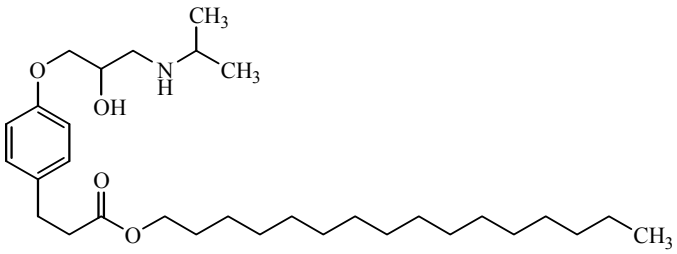
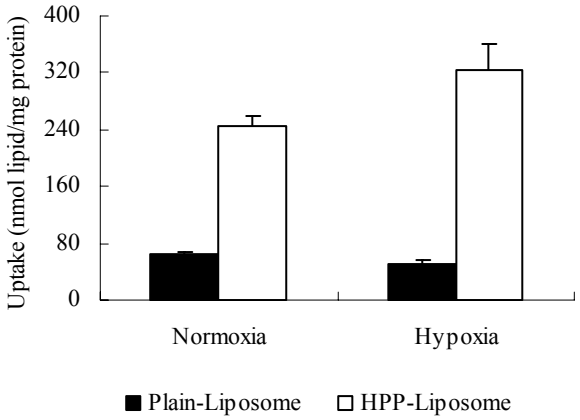


Figure 2 Uptake of plain-liposome and HPP-liposome by normoxia or hypoxia cardiomyocytes



Acknowledgments

The authors are thankful to Dr. Fu Chen BAI (Changchun Institute of Applied Chemistry, Jilin, China) for his friendly assistance. This project was supported by the National Natural Science Foundation of China (No.30271548).

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Received 23 September, 2004