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论文

新的核苷类化合物*β*-*L*-D4A的化学合成及体外抗HBV作用

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摘要：

目的以*D*型谷氨酸为原料，通过一系列化学转化，合成了新的核苷类化合物*β*-*L*-D4A，并初步探索其体外抗HBV作用。方法合成*β*-*L*-D4A，用红外光谱、核磁共振氢谱和质谱确证目标化合物的结构，以2.2.15细胞(HepG2细胞进行HBV基因组转染后所得)培养为基础，Southern印迹法检测不同浓度化合物体外抑制HNV DNA复制作用，并求出50%抑制的药物浓度，即EC_{50}。以四噻唑蓝(MTT)比色分析法检测不同浓度药物的细胞毒性，求出IC_{50}。结果化合物*β*-*L*-D4A经红外光谱、核磁共振氢谱和质谱确证；2.2.15细胞培养上清液病毒DNA的Southern印迹、自显影结果显示病毒的抑制呈明显的浓度依赖性，计算出EC_{50}为0.2 μmol·L^{-1}，胞内DNA的Southern印迹、自显影显示类似的结果；细胞毒性实验显示IC_{50}为200 μmol·L^{-1}。结论体外实验显示*β*-*L*-D4A具有明显的抑制病毒DNA复制作用，且无明显的细胞毒性，TI值为1 000，高于临床用Lamivudine (750)，有望开发为临床抗HBV用药。

关键词： 核苷类化合物 *β*-*L*-D4A 化学合成 乙肝病毒

Synthesis of a novel ***L***-nucleoside , ***β*-*L***-D4A and its inhibition on the replication of hepatitis B virus ***in vitro***

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Abstract:

AimNucleoside analogues have become the most promising candidates of anti-HBV drugs. In this study, *β*-*L*-D4A was synthesized and explored its inhibitiory action against hepatitis B virus (HBV) in 2.2.15 cells derived from HepG2 cells transfected with HBV genome. Methods*β*-*L*-D4A was stereo-controlled synthesized from *D*-glutamic acid, and the structure was identified by IR, ^{1}H NMR and MS. 2.2.15 Cells were placed at a density of 5×10^{4} per well in 12-well tissue culture plates, and treated with various concentrations of *β*-*L*-D4A for 6 days. At the end, medium was processed to obtain virions by a polyethlene glycol precipitation method. At the same time, intracellular DNA was also extracted and digested with Hind III. Both of the above DNA were subjected to Southern blot, hybridized with a ^{32}P-labeled HBV probe and autoradiographed. The intensity of the autoradiographic bands was quantitated by densitometric scans of computer and EC_{50} was calculated. 2.2.15 cells were also seeded in 24-well tissue culture plates, and cytotoxicity with different concentrations was examined by MTT method. IC_{50} was calculated. ResultsThe synthesized compound structure conformed with *β*-*L*-D4A; Autoradiographic bands showed similar for supernatant and intracellular HBV DNA. Episomal HBV DNA was inhibited in a dose-dependent manner. EC_{50} 0.2 μmol·L^{-1}. The experiment of cytotoxicity gained IC_{50} 200 μmol·L^{-1}. Conclusion*β*-*L*-D4A has been synthesized successfully. *β*-*L*-D4A possessed potent inhibitory effect on replication of HBV *in vitro* with low cytotoxicity, TI value was 1 000. It is expected to be developed clinically into a new anti-HBV drug.

Keywords: *β*-*L*-D4A chemical synthesis hepatitis B virus Nucleoside analogue

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