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论文

多羟基芳香族化合物对HIV-1整合酶的抑制作用

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摘要:

目的研究HIV-1整合酶抑制剂,为艾滋病的治疗提供新作用靶位的抗HIV药物。方法用HIV-1整合酶ELISA法检测3种萘醌类化合物,10种白藜芦醇及其衍生物和7种吡喃香豆素类化合物对整合酶的抑制作用。结果双羟基-1,4-萘醌(NQ-2)对HIV-1整合酶有抑制活性,IC_{50}为78.5 μmol·L^{-1},发现萘醌类新化合物NQ-3对HIV-1整合酶的抑制作用优于NQ-2,IC_{50}为37.2 μmol·L^{-1}。用分步测定法发现NQ-2主要抑制HIV-1整合酶的链转移活性,而NQ-3则对装配和链转移都有较强的抑制。结论萘醌类化合物(NQ-2,3)对HIV-1整合酶有抑制作用,NQ-3为新化合物值得进一步研究。

关键词: HIV-1整合酶 抑制剂 多羟基芳香族化合物

STUDIES ON THE INHIBITION OF POLYHYDROXYLATED AROMATIC COMPOUNDS AGAINST HIV-1 INTEGRASE

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Abstract:

AIMThree major enzymes of HIV-1, reverse transcriptase (RT), protease (PR), and integrase (IN), are important targets for anti-HIV drugs. Nine RT and five PR inhibitors have been effectively used in treatment of AIDS patients. In order to find active integrase inhibitors, twenty polyhydroxylated aromatic compounds were tested. METHODSELISA method was used to test the integrase activity. The synthesized donor substrate oligonucleotide representing the HIV-1 U5LTR was immobilized onto Covalink polystyrene microtiter plates, and a synthesized biotinlated 20 bp oligonucleotide was used as the target substrate. The products were detected and quantified by a colorimetric avidin-linked alkaline phosphatase reporter system. RESULTSCompound NQ-2 was found to inhibit HIV-1 integrase with the IC_{50} of 78.5 μmol·L^{-1} by ELISA method. Its novel analogue NQ-3 was found to be 2 fold more potent on HIV intrgrase than NQ-2, IC_{50} was 37.2 μmol·L^{-1}. The IC_{50}s of NQ-2 and NQ-3 to inhibit the 3′-pro+assembly activity of integrase were 96.94 μmol·L^{-1} and 8.48 μmol·L^{-1}; to inhibit assembly activity were 168 and 6.9 μmol·L^{-1} and to inhibit strand-transfer activity were 49.8 and 1.1 μmol·L^{-1}, respectively. Compound NQ-2 mostly inhibited the strand transfer activity of HIV-1 integrase. Compound NQ-3 inhibited both the assembly and strand-transfer with high activities. CONCLUSIONNaphthoquinone compound NQ-3 was found to be a novel HIV integrase inhibitor which warrants further study. Uncoupled ELISA HIV integrase assay is shown to be useful to screen HIV-1 integrase inhibitors.

Keywords: inhibitor polyhydroxylated aromatic compound HIV-1 integrase

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