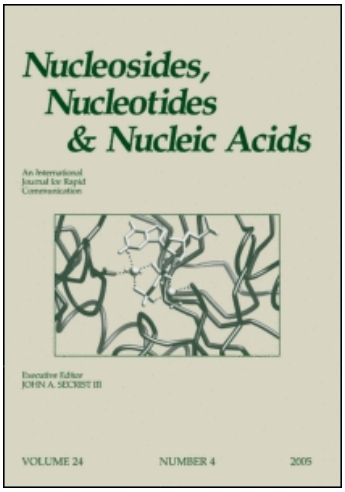

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Optimization of Antiviral Prodrug Properties Using Combinatorial Methods

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Optimization of Antiviral Prodrug Properties Using Combinatorial Methods

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ABSTRACT

Some diacid biodegradable synthesis of aziduthymidine (AZT) were synthesized and applied to production of about 60 different derivatives.

Key Words: Azidothymidine (zidovudine); Drug delivery.

Various esters of bifunctional acids of zidovudine (AZT) and stavudine (d4T),[1,2] were synthesized to optimize the pro-drug properties. The free functional groups of the spacer are suitable for combinatorial synthesis application, which could be exemplified by the acrylic ester of d4T and some dicarboxylic aliphatic- and aromatic esters of AZT.

Various ester derivatives of antiviral nucleosides with modified solubility, penetrating ability and other properties in the same reaction conditions or anti-HIV double-drugs conjugates could be obtained. The synthetic restriction in the final parallel synthesis conditions is lability of the anti-HIV moiety.

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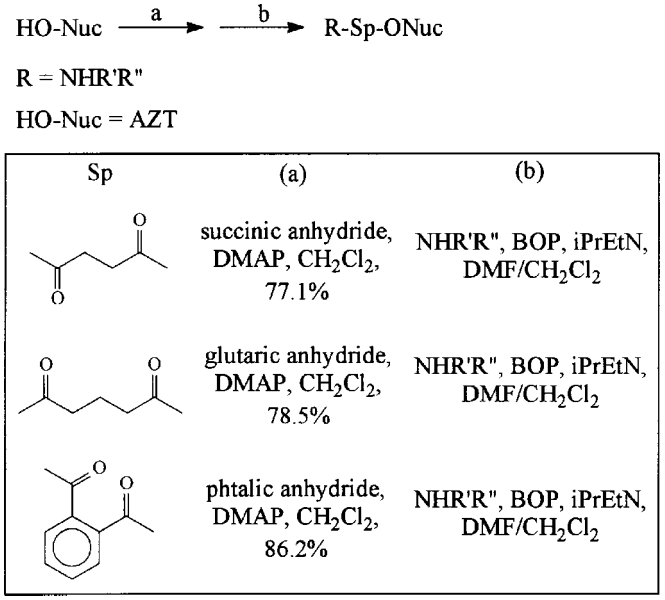
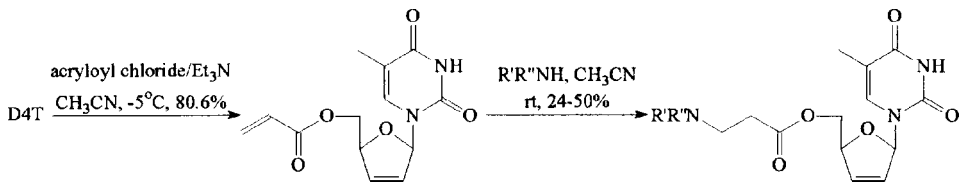


Scheme 1.

By using synthones such as dicarboxylic esters, a number of nucleoside. 5′-esters by original parallel synthesis technology of "ChemBridge Corp." were obtained (Sch. 1). About 60 compounds with 37 various secondary aliphatic and alicyclic amines carrying different functional groups, such as tertiary amino group (substituted *N*-alkyl- and *N*-aryl-piperazines); aryl- or heteroaryl group (1,2,3,4-tetrahydroisoquinoline; 1-(2-pyrazinyl)-piperazine, etc.), and ester group (ethyl isonipecotate, etc.) were synthesized. These derivatives were obtained in 10–100 mg quantities. According to ^{1}H-NMR data the percentage of impurities ranged between 5–10%.

Also the acrylic ester of d4T, used as another synthon, showed principal ability for applying parallel synthesis (Sch. 2). A range of derivatives were obtained with primary and secondary (aliphatic, alicyclic and aromatic) amines, but their application required development of a suitable parallel synthesis technology.

Anti-HIV activity of final compounds is under investigation. For instance, alkylaminopropionic esters of d4T (Sch. 2) were degraded according to *pseudo*-first-order



Scheme 2.

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kinetics to yield d4T in fetal bovine serum media. The half-lives were found to be in the range from 15 min to 3 h for all derivatives investigated.

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REFERENCES

1. Berezovskaya, Y.V.; Chudinov, M.V.; Kirillova, Y.G.; Shastina, N.S.; Shvets, V.I.; Yurkevich, A.M. Design of the new molecular transport systems for the nucleosides-pharmacophores carrying. Nucleosides & Nucleotides **1998**, *17* (9–11), 2127–2133.
2. Berezovskaya, Y.V.; Chudinov, M.V.; Yurkevich, A.M. Goryzonty Fiziko-Khimicheskoy Biologii. Pushino, May 28, 2000–June 2, 2000.

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