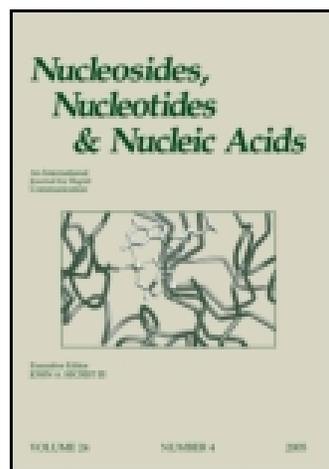


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SYNTHESIS AND BIOLOGICAL EVALUATION OF CONFORMATIONALLY RESTRICTED AND NUCLEOBASE-MODIFIED ANALOGS OF THE ANTICANCER COMPOUND 3'-C-ETHYNYLCYTIDINE (ECYD)

Patrick J. Hrdlicka^a, Jan S. Jepsen^b & Jesper Wengel^a

^a Nucleic Acid Center, Department of Chemistry, University of Southern Denmark, Odense M, Denmark

^b Department of Tumor Endocrinology, Danish Cancer Society, Institute of Cancer Biology, Copenhagen, Denmark

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SYNTHESIS AND BIOLOGICAL EVALUATION OF CONFORMATIONALLY RESTRICTED AND NUCLEOBASE-MODIFIED ANALOGS OF THE ANTICANCER COMPOUND 3'-C-ETHYNYLCYTIDINE (ECYD)

Patrick J. Hrdlicka □ *Nucleic Acid Center, Department of Chemistry, University of Southern Denmark, Odense M, Denmark*

Jan S. Jepsen □ *Department of Tumor Endocrinology, Danish Cancer Society, Institute of Cancer Biology, Copenhagen, Denmark*

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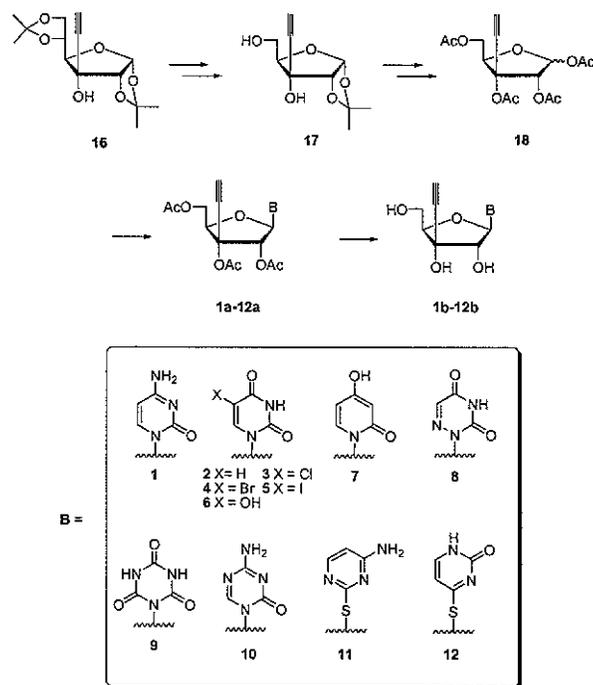
□ *A series of conformationally restricted and nucleobase-modified analogs of the anticancer compound 3'-C-ethynylcytidine (ECyd) and its uracil analog (EUrd) have been synthesized. While none of the conformationally restricted analogs displayed anticancer activity, 5-iodo-EUrd and 5-bromo-EUrd displayed potent anticancer activity with IC_{50} values of 35 nM and 0.73 μ M.*

INTRODUCTION

The clinically evaluated 3'-C-ethynylcytidine (ECyd, **1b**) and its uracil congener (EUrd, **2b**) (Scheme 1) display highly potent antitumor activity against a variety of massive tumors in vitro as well as in animal models with excellent selectivity.^[1] To generate EUrd/ECyd analogs that can potentially overcome the crucial uridine-cytidine kinase (UCK) catalyzed phosphorylation step,^[2] we synthesized EUrd/ECyd analogs **3b–12b** (Scheme 1) containing modified nucleobase moieties that are known to be tolerated by UCK in non-modified ribonucleosides.^[3] Furthermore, since conformational restriction of the otherwise flexible furanose ring has been a successful strategy to probe for conformational preferences of enzymes involved in nucleoside metabolism and nucleotide polymerization,^[4] we synthesized

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Address correspondence to Patrick J. Hrdlicka, Nucleic Acid Center, Department of Chemistry, University of Southern Denmark, Odense M DK-5230, Denmark; Fax: +45-66158780; E-mail: pjh@chem.sdu.dk



SCHEME 1

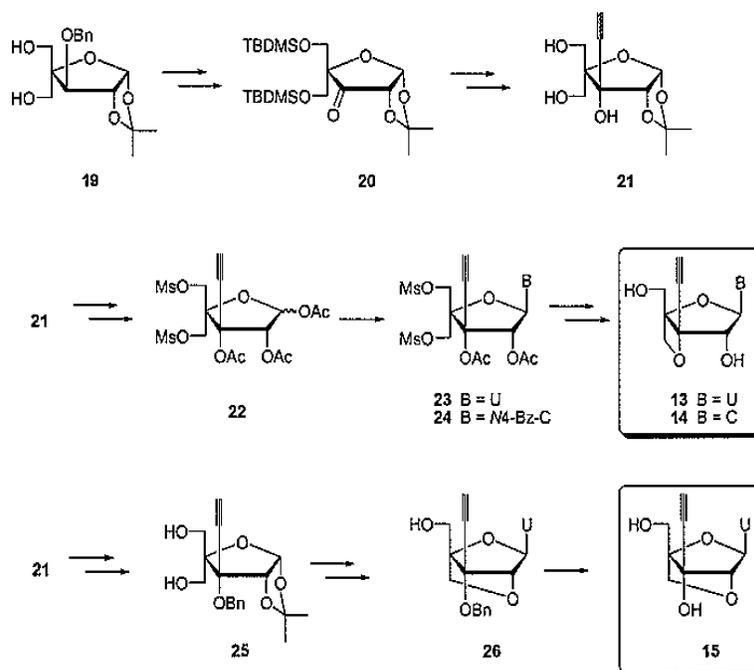
nucleosides **13–15**, which are chimeras of *S*-type 3'-*O*,4'-*C*-methylene ribonucleoside^[5] or *N*-type LNA nucleosides^[6] and EUrd/ECyd (Scheme 2).

RESULTS AND DISCUSSION

Synthesis of ECyd **1b**, EUrd **2b**, and nucleobase-modified analogs hereof **3b–12b** was initiated from furanose **16**,^[7] which was converted to diol **17** via a three-step sequence involving 5,6-*O*-isopropylidene cleavage, NaIO₄-mediated cleavage, and NaBH₄-reduction. Further conversion hereof using standard methods gave glycosyl donor **18** (Scheme 1). Subsequent glycosylation of **18** with a series of persilylated nucleobases according to the Vorbrüggen technique afforded nucleosides **1a–10a**, while reaction with persilylated 2-thiouracil or 4-thiouracil furnished *S*-linked ribosides **11a** and **12a**. Deacylation of **1a–12a** mmished nucleosides **1b–12b**.

Synthesis of the conformationally restricted EUrd/ECyd analogs **13–15** initiated from 4'-*C*-hydroxymethyl pentofuranose **19**,^[8] which, after protecting group manipulations and TEMPOIBAIB-mediated oxidation, afforded 3-ulose **20** (Scheme 2).

Subsequent nucleophilic addition of LiC \equiv CTMS and desilylation gave triol **21**, which, upon O5/O5'-mesylation, 1,2-*O*-isopropylidene cleavage, Lewis acid-catalyzed peracetylation (Ac₂O, TMSOTf, CH₂Cl₂, 0°C),^[9] and glycosylation of furanose **22** furnished nucleosides **23** and **24**. Treatment of nucleosides **23** and



SCHEME 2

24 resulted in tandem deacylation and selective 3'-O,4'-C ring closure (most likely due to preorganization of **23** and **24** in *S*-type conformations), which, after mesylate exchange with benzoate and debenzoylation, afforded the bicyclic nucleosides **13** and **14**.

The synthesis of EURd-LNA-type analog **15** was initiated from triol **21**, which was converted to furanose **25** via O5/O5'-DMT-protection, O3-benzylation, and detritylation (Scheme 2). Furanose **25** was then converted into nucleoside **26** in a sequence of steps similar to those described for bicyclic nucleosides **13** and **14**. Debenzoylation of nucleoside **26** with BCl₃ afforded the desired nucleoside **15**.

Although less active than the reference compounds ECyd **1b** and EURd **2b** (IC₅₀ = 2.2 nM and 2.5 nM, respectively), the 5-iodomidine derivative **5b** displayed very potent anticancer activity (IC₅₀ = 35 nM) against a human adenocarcinoma breast cancer (MCF-7) cell line. Decreasing the size of the 5-substituent as in nucleosides **3b** and **4b** resulted in a systematic drop in activity (IC₅₀ = 0.73 μM and >25 μM, respectively). 5-Azacytidine **10b** and 6-azauridine **8b** derivatives were only marginally active (IC₅₀ = 4.7 μM and 35 μM, respectively) and the remaining compounds inactive. We are currently investigating if the presented compounds are substrates of UCK.

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