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Florida International University
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Abstract

Design and Synthesis of Novel Nucleoside Analogues. Oxidative and Reductive Approaches toward Synthesis of 2'-Fluoro Pyrimidine Nucleosides

by

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Fluorinated nucleosides are known to exert potent biological activities. In the first part of this dissertation, *oxidative* and *reductive* methodologies toward the synthesis of 2'-fluoro pyrimidine nucleosides from the corresponding 2'-arylthiopyrimidine precursors were designed. Also, novel *oxidative* desulfurization-difluorination methodology was developed for the synthesis of α,α-difluorinted esters from the corresponding α-arylthio esters, wherein the arylthio group is present on a secondary internal carbon. Reductive desulfonylation of 2'-arylsulfonyl uridine derivatives by organic electron donors was also studied.

In the second part of this research work, a novel bromination protocol for the C5-bromination of pyrimidines and C8-bromination of purines using 1,3-dibormo-5,5,-dimethylhydantoin (DBH) was designed. The effect of Lewis acids, solvents, and temperature on the efficiency of bromination was studied. A convenient methodology for the synthesis of 8-bromotoyocamycin and 8-bromosangivamycin using *N*-bromosuccinimide (NBS) or DBH was also discovered.

The 6-*N*-benzylated derivatives of 7-deazapurine nucleoside antibiotics, such as tubercidin, sangivamycin and toyocamycin, were synthesized by two methods: (i) Dimroth rearrangement; (ii) fluoro-diazotization followed by S_NAr displacement of the 6-fluoro group by a benzylamine. The 6-*N*-benzylated 7-deazapurine nucleosides showed type-specific inhibition of cancer cell proliferation at micromolar concentrations and weak inhibition of human equilibrative nucleoside transport protein (hENT1).

In the fourth part of this dissertation, novel synthesis of 8-azidotoyocamycin and subsequent strain promoted click chemistry with cyclooctynes to give the corresponding 8-triazolyl derivatives was presented. In addition, iodine catalyzed CH activation of tubercidin with benzotriazole was also discussed.

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