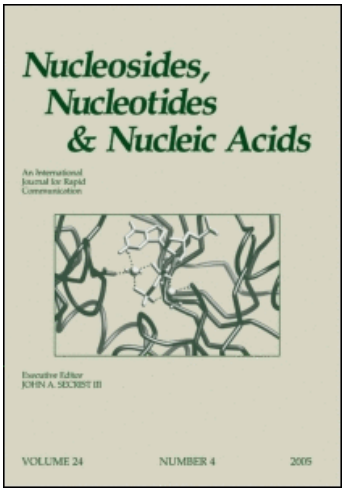

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Synthesis of L-Sangivamycin and Toyocamycin Analogues and Their Inhibitory Activities of SER/THR Protein Kinases

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SYNTHESIS OF L-SANGIVAMYCIN AND TOYOCAMYCIN ANALOGUES AND THEIR INHIBITORY ACTIVITIES OF SER/THR PROTEIN KINASES

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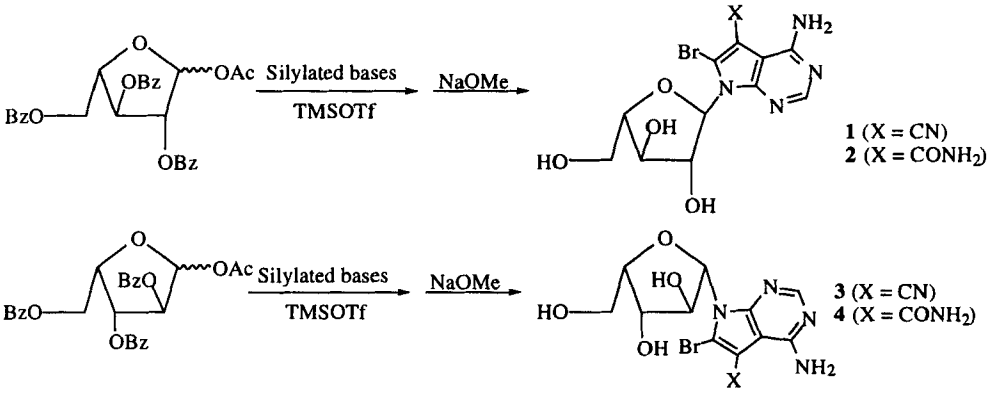
Abstract: Novel L-sangivamycin and toyocamycin analogues were synthesized and evaluated for Cdc2 protein kinase activity. Among the compounds tested, L-xylose derivative and L-arabinose derivative exhibited potent inhibitory activity against Cdc2 protein kinase with IC_{50} values of 3.7 and 1.6 μM, respectively.

Ser/Thr protein kinases play important roles in signal transduction pathways that control the proliferation and differentiation of eukaryotic cells.[1] It was reported that sangivamycin and toyokamycin isolated from soil microorganisms exhibited potent inhibitory activity against Cdc2 protein kinase, a cyclin-dependent and Ser/Thr protein kinase.[2] In an attempt to search for a specific inhibitor that inhibits the Cdc2 protein kinase with a minimum side effect on other Ser/Thr protein kinase activity, we synthesized L-derivatives of these second microbial metabolites and evaluated them for Cdc2 protein kinase inhibitory activity.

Synthesis of the target nucleosides **1-4** is shown in Scheme 1. L-Arabinofuranosyl acetate was first condensed with silylated pyrrolo[2,3-d]pyrimidine bases in the presence of TMSOTf as a Lewis acid to give the only α nucleosides which were deprotected with sodium methoxide to afford the final α nucleoside analogues **1** and **2**, respectively. For the synthesis of L-xylose derivatives, L-xylofuranosyl acetate was condensed with silylated pyrrolo[2,3-d]pyrimidine bases to afford the only β nucleosides which were deprotected with sodium methoxide to afford the final β nucleoside analogues **3** and **4**, respectively.[3]

Scheme 1



Among the synthesized compounds tested, it was found that compound **4** exhibited the potent Cdc2 protein kinase inhibitory activty with IC_{50} value of 1.6 μM, while compound **2** showed weaker activity (IC_{50} = 3.7 μM) than compound **4**. The inhibitory activities were similar to those of other reported Cdc2 kinase inhibitors such as olomoucin (IC_{50} = 7.0 μM) and butyrolactone-1 (IC_{50} = 0.6 μM). Compounds **2** and **4** also inhibited other Ser/Thr protein kinase activity such as cAMP-dependent protein kinase (PKA),[4] casein kinase II (CK II) and protein kinase C (PKC), but only with at two to three order magnitude higher concentrations than those inhibiting Cdc2 kinase activity (IC_{50} = 290 μM for PKA and IC_{50} = 70 μM for CK II). It is presumed that this selective activity may result from binding poorly to the ATP binding sites of other protein kinases since the synthesized L-derivatives **2** and **4** do not exist in nature. Other compounds **1** and **3** were found to show no inhibitory activity.

Acknowledgment

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