SUMMARY OF Ph.D. DISSERTATION

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Title

Synthetic studies of bioactive pyranonaphthoquinones

Abstract

1. Cdc25A Inhibitor

Novel pyranonaphthoquinone has a potential activity against Cdc25A phosphatase, which was isolated from *Streptomyces* sp. in 1999, and an attractive structure. Against such backgrounds, the author initiated a synthetic investigation of the pyranonaphthoquinones.

The synthesis commenced with conversion of vanillin by a known procedure into benzaldehyde, which on Horner-Wadsworth-Emmons coupling and cyclization gave a naphthalene derivative. Successfully regioselective bromination, Corey-Chaykovsky epoxidation, and Horner-Wadsworth-Emmons reaction gave an α,β-unsaturated ester. After several steps, bromine-lithium exchange reaction, followed by quenching with *n*-valeraldehyde and deprotection, provided a benzyl alcohol. Selective protection, oxidation into quinone, selective deprotection of C-6 position, and insertion of methylamino moiety gave a naphthoquinone. Oxidation and intramolecular Michael addition for construction of the pyran ring system gave natural compound.

Based on the synthetic route of natural pyranonaphthoquinone, a variety of derivatives were synthesized and evaluated the Cdc25A inhibitory activity. As a result, it was found that naphthoquinone-type compounds showed stronger activity of the Cdc25A inhibition than natural product.

2. Chloroquinocin

Chloroquinocin, isolated from the culture of *Streptomyces* sp. LL-A9227, has an attractive 3-chloro-1,4-naphthoquinone framework, and a moderate inhibitory activity against Gram-positive bacteria, including MRSA (MIC= 16 μg/ml). The synthetic approach to chloroquinocin was used the synthetic route of the Cdc25A inhibitor. The common intermediate was reacted with an acetylene unit, followed by deoxygenation and deprotection. Bromine-lithium exchange reaction, followed by quenching with *n*-propylaldehyde and oxidation, provided a naphthoquinone. After silyl-protection, novel chlorination steps, followed by deprotection afforded chlorinated naphthoquinone. Pd-induced cyclization reaction and deprotection gave chloroquinocin.