CHAPTER I

INTRODUCTION

Renieramycins are bistetrahydroisoquinoline marine natural products that are structurally related to other tetrahydroisoquinoline alkaloids including saframycins, naphthyridinomycins, bioxalomycins, quinocarcins, and ecteinascidins (Scott and Williams, 2002). These related compounds exhibited excellent cytotoxic activities especially ecteinascidin 743 which is currently being studied in phase II/III clinical trials for ovarian, breast, endometrial, prostate, and pediatric cancers (Henriquez *et al.*, 2005). Renieramycins were mainly isolated from the marine sponges belonging to genera *Reniera* (Frincke and Faulkner, 1982; He and Faulkner, 1989), *Xestospongia* (Davidson, 1992; Suwanborirux *et al.*, 2003; Amnuoypol *et al.*, 2004), *Haliclona* (Parameswaran *et al.*, 1998), *Cribrochalina* (Pettit *et al.*, 2000) and *Neopetrosia* (Oku *et al.*, 2003). Renieramycins exhibited potent biological activities for example, antimicrobial and cytotoxic activities (Frincke and Faulkner, 1982; Suwanborirux *et al.*, 2003; Amnuoypol *et al.*, 2004). Most renieramycins contain an unstable carbinolamine function at C-21 (eg. renieramycins E and F) that caused oxidative decomposition during isolation process and limited further chemical and biological studies of the compounds. Recently, Suwanborirux and co-workers have accomplished the isolation of stabilized renieramycin M in gram-scale together with other minor renieramycins from a Thai blue sponge *Xestospongia* sp. pretreated with KCN (Suwanborirux *et al.*, 2003). Another related compound, jorumycin containing an acetyl ester instead of an angelate ester, was isolated from the skin and the mucus of the Pacific nudibranch *Jorunna funebris*. This compound exhibited cytotoxicity at very low concentrations against NIH 3T3 fibroblast cells in primary assay and against some tumor cell lines, such as P388 mouse lymphoma, A549 human lung carcinoma, HT29 human colon carcinoma, and MEL28 human melanoma (Fontana *et al.*, 2000). Jorumycin was also available in minute quantity for further study because of its unstable carbinolamine functional group.

Both renieramycin E and jorumycin showed cytotoxic potency as described in a previous report (Saito *et al.*, 2004). This information suggests that the ester side chain at C-22 is required for potent cytotoxicity of the bistetrahydroisoquinolines. The

success in preparation of renieramycin M in high yield led the author to investigate a number of renieramycin analogs by varying the ester side chain at C-22 which might be important to their antitumor activity and structure cytotoxicity relationships. In this thesis, chemical transformations of renieramycin M to several acyclic, alicyclic and aromatic ester derivatives are prepared from the key intermediate deangeloylrenieramycin M and the cytotoxicity of these renieramycin analogs is comparatively evaluated. Moreover, DNA microarray analyses of renieramycins for transcriptional fingerprint profiles (gene expressions) are also presented.

In addition, the author found the Thai nudibranch *J. funebris* feeding on the blue sponge *Xestospongia* sp., growing around Sichang Island in the Gulf of Thailand. Based on our knowledge, the nudibranch *J. funebris* from Thai marine environment has never been chemically studied, thus this nudibranch has been chosen to be investigated for its chemical constituents. In this thesis, the author also reports isolation, structural elucidation, and evaluation cytotoxicity of renieramycin derivatives from this nudibranch.