Replacement of a Quinone Moiety Diminishes Accidental Necrosis

Renieramycins are a group of bistetrahydroisoquinoline quinone marine alkaloids possessing potent cytotoxicity to several cancer cell lines. Renieramycin M (1) was the major alkaloid isolated from marine sponge, Xestospongia sp. This compound has been shown to possess potential anticancer effects in which it prevents metastasis and induces apoptosis in lung cancer cells through activation of p53-dependent pathway. Modes of cell death are divided into apoptosis and necrosis. Apoptosis is the major mechanism for human body to eliminate unwanted and damaged cells. Necrosis is classified into two types according to morphological and biochemical characteristics: regulated and accidental necrosis. Accidental necrosis is nonspecific and induces damages to surrounding cells and tissues. Thus, the accidental necrosis inducing effect of 1 has limited its further development due to undesired toxicity. In this study, the author tried to eliminate undesired accidental necrosis inducing effect of 1 by modification of its quinone moiety, which provides vision for future research on this concern.

J. Nat. Prod., 2013, 76, pp 1468-1474
Replacement of a Quinone by a 5-O-Acetylhydroquinone Abolishes the Accidental Necrosis Inducing Effect while Preserving the Apoptosis-Inducing Effect of Renieramycin M on Lung Cancer Cells
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Currently, novel drugs and strategies with high efficacy are gaining high interest in cancer research. Thus, most anticancer drugs are designed to eliminate cancer cells through apoptosis instead of accidental necrosis. Renieramycin M (1) which was isolated from Xestospongia sp. exhibited potential anticancer activities. However, its accidental necrosis inducing effect due to the presence of two quinone moieties has ceased its further development. In this research, one quinone moiety in 1 was modified to produce 5-O-acetylated hydroquinone (2), which was determined to reduce accidental necrosis significantly while preserving apoptosis-inducing effects of parent 1. The accidental necrosis inducing effects of 1 was ROS-dependent, which was due to its ability to generate intracellular superoxide anions. Interestingly, the remaining quinone in 2 was required for its cytotoxicity as 5,8,15,18-O-tetraacetylated bishydroquinone (3) exhibited weak cytotoxicity after removal of both quinone moieties. Thus, this study has demonstrated a simple way to eliminate undesired accidental necrosis inducing effect of substance which may be developed as improved anticancer drug candidates.