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# Synthesis and biological activity of salinomycin-hydroxamic acid conjugates

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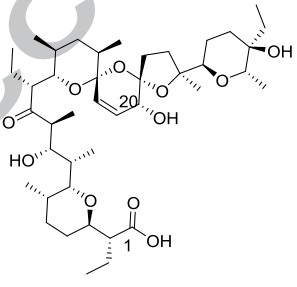
**ABSTRACT:** Several salinomycin-hydroxamic acid conjugates were designed and synthesized. Most conjugates showed better antiproliferative activities than salinomycin in HT-29 colon cancer, HGC-27 gastric cancer, and especially in MDA-MB-231 triple-negative human breast cancer cells. These conjugates are stable in cell culture media, and they showed much better biological activities than the 1:1 physical mixture with hydroxamic acids and salinomycin. The better membrane permeability and hydrolysis rate of the conjugates may lead to the activity improvements.

Salinomycin (**1**, Fig 1) is a kind of polyether antibiotics isolated from *Streptomyces albus*, which can transfer alkali metal ions such as $Na^+$ and $K^+$ through cytomembrane.[1] It has been used in broiler batteries and other livestock as an anticoccidial drug and growth promoters for many decades.[2] Recent studies proved salinomycin also effectively kills cancer stem cells (CSCs) and differentiated cancer cells that display efficient mechanisms of resistance to cytotoxic drugs and radiation, including leukemia, breast cancer, gastric cancer, lung adenocarcinoma, osteosarcoma, colorectal cancer, squamous cell carcinoma, prostate cancer *in vitro* and *in vivo*.[3] Several possible mechanisms of salinomycin were illuminated, such as induction of apoptosis and cell death, interference with ABC transporters, inhibition of oxidative phosphorylation and inhibition of the Wnt/β-catenin signaling pathway, but the exact mechanisms were still not fully elucidated.[4]

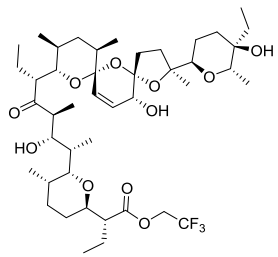



**Salinomycin (1)**

Figure 1. The structure of salinomycin

To study the structure–activity and structure–toxicity relationship of salinomycin, medicinal chemists have synthesized several C1 and C20-modified salinomycin derivatives, some of which showed better antitumor activities.[5-15] Daniel Strand's group synthesized several C20 hydroxyl acylated salinomycin analogs, which efficiently decreased the CSC population at a 50 nM concentration.[6,16] Their following study found the anti-cancer activity of C20-deoxy-saliomycin is reduced, which emphasizes the importance of substitution at C20 for the activity.[8] Our group synthesized several salinomycin diastereoisomers and their acylated derivatives, and we found the stereochemistry has important influences on the biological activities.[17-18] These results together suggest that the alkali metal ion transport ability of salinomycin is crucial to its biological activities.

Compared to C20-modified derivatives, which showed obviously higher pharmacological activities, the C1-ester, amide and conjugates with other active substances such as amino acid[11], floxuridine[12] and silybin[13] almost showed much lower antitumor activities. A possible explanation is that extra steric hindrance on the head (C1) affects the combination and transport of the sodium ions, because salinomycin need form "head to tail" type of intramolecular hydrogen bonds as a pseudo-cyclic structure.[19] Nevertheless, some C1-modified salinomycin derivatives which have a readily hydrolyzed connecting bond showed better antitumor activities such as compound **2**[9] and **3**[5] (Fig 2).

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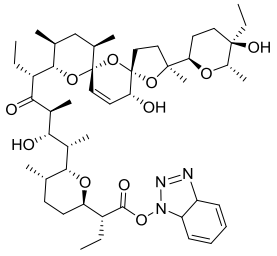


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Figure 2. The structure of salinomycin derivatives.