European Journal of Medicinal Chemistry 76 (2014) 435–444

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis, cytotoxicity and antibacterial activity of new esters of polyether antibiotic – salinomycin

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ARTICLE INFO

Article history:
Received 12 December 2013
Received in revised form
10 February 2014
Accepted 13 February 2014
Available online 14 February 2014

Keywords:
Salinomycin
Anticancer activity
Antibacterial activity
MRSA
MRSE

ABSTRACT

A series of 12 novel ester derivatives of naturally occurring polyether antibiotic – salinomycin were synthesized, characterised by spectroscopic method and evaluated for their *in vitro* antibacterial activity and cytotoxicity. The new esters were demonstrated to form complexes with monovalent and divalent metal cation of 1:1 stoichiometry in contrast to the salinomycin which forms only complexes with monovalent cations. All the obtained compounds show potent antiproliferative activity against human cancer cell lines and a good selectivity index for cancer versus mammalian cells. Additionally, 3 compounds showed higher antiproliferative activity against the drug-resistant cancer cells and lower toxicity towards normal cells than those of unmodified salinomycin and standard anticancer drugs such as cisplatin and doxorubicin. Some of the synthesized compounds showed good inhibitory activity against *Staphylococcus* strains and clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis* (MRSE). These studies show that salinomycin esters are interesting scaffolds for the development of novel anticancer and Gram-positive antibacterial agents.

1. Introduction

Salinomycin (**1**) (Scheme 1), isolated from *Streptomyces albus*, is an antibiotic belonging to a large group of natural polyether ionophores [1]. Salinomycin and its salts, due to the presence of carboxyl group on one side of the molecule and two hydroxyl groups on the other side, are able to form "head to tail" type of intramolecular hydrogen bonds resulting in formation of a pseudo-cyclic structure. The polyether skeleton of this pseudo-cyclic structure is able to form complexes with metal cations and transport them across lipid cell membranes [2].

The mechanism of salinomycin activity is based on the transport of metal cations (especially Na^+ and K^+) from the extracellular environment through the biological membranes into a cell, where they are exchanged for protons. This leads to disturbance of intracellular pH and to increasing osmotic pressure inside the cell, leading finally to apoptosis [1]. For this reason, salinomycin shows antimicrobial activity against Gram-positive bacteria, including *Staphylococcus aureus* and mycobacteria, *Plasmodium falciparum* or *Eimeria* spp, parasites, and protozoa, which are responsible for coccidiosis in poultry [3]. Salinomycin sodium salt is commercially used in the veterinary medicine as a coccidiostatic and non-hormonal growth-promoting agent.

In addition to the well recognised antibacterial activity of **1**, in 2009 this compound was shown to be nearly 100-fold more effective against breast cancer stem cells than commonly used cytostatic drug – Taxol (Paclitaxel) [4].

Recent studies have proved that **1** is able to induce mass programmed death of human tumour cells of various tissues showing multidrug resistance (MDR), for example leukemic stem cells, by the expression of ATP-binding cassette (ABC) transporters [5]. Additionally, **1** inhibits Wnt signalling pathway and induces apoptosis of tumour cells in patients with chronic lymphocytic leukemia [6]. The ability of **1** to reduce the subpopulations of breast cancer stem cells, as well as colon carcinoma stem cells, has been also described [7]. Moreover, **1** blocks the growth and migration of chemoresistant prostate cancer cells [8]. *In vitro* tests have

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http://dx.doi.org/10.1016/j.ejmech.2014.02.031
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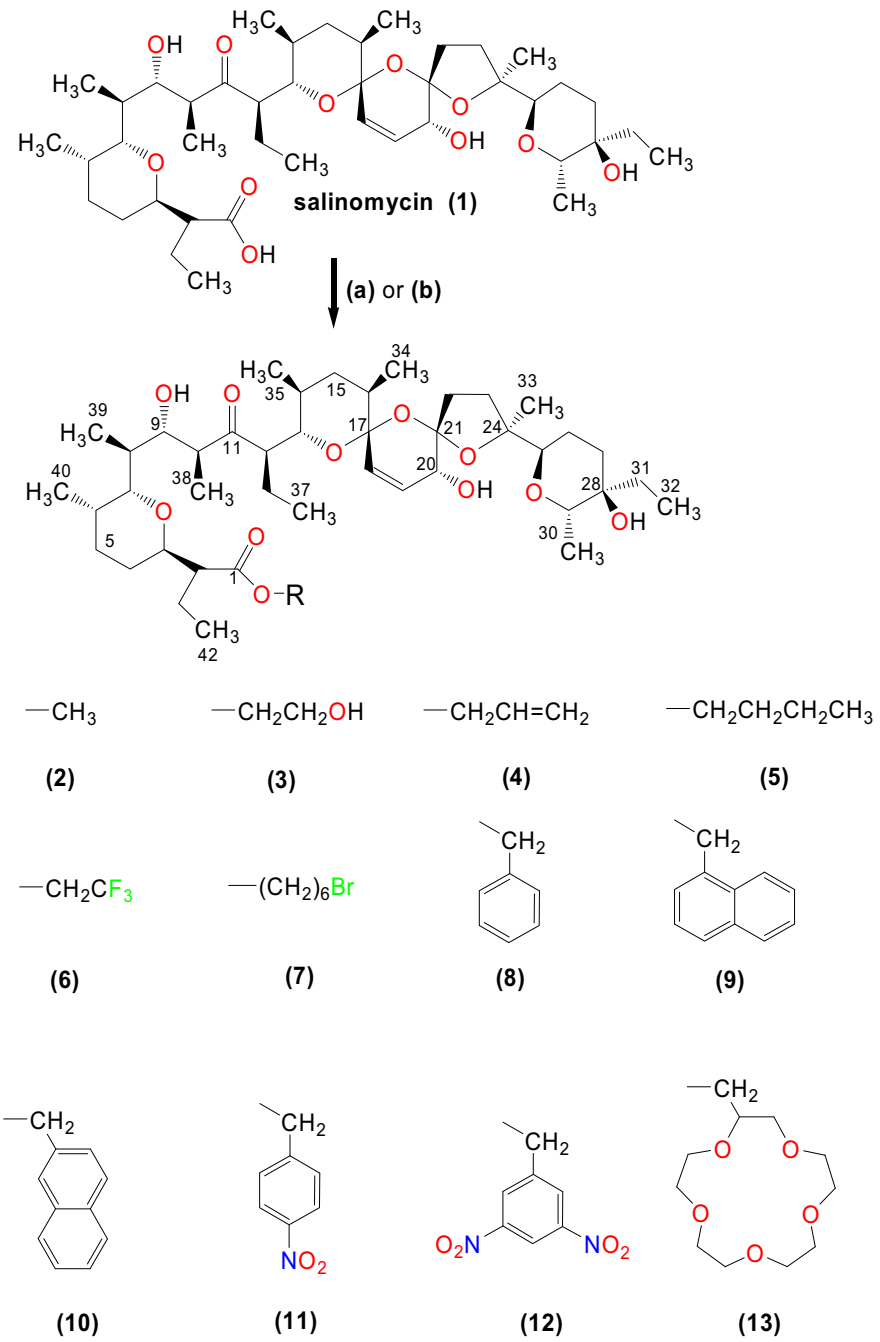

Scheme 1. Synthetic access to salinomycin ester derivatives. *Reagents and conditions*: (a) **1** (1 eq), R–OH (7.5 eq), DCC (1.5 eq), PPy (0.5 eq), *p*-TSA (0.23 eq), CH_2Cl_2, 0 °C to rt, 24 h; (b) **1** (1 eq), R-*X* (bromides or chlorides) (2.2 eq), DBU (1.75 eq), toluene, 90–100 °C, 5 h.

confirmed the strong antitumor activity of this compound against the lung cancer cell lines [9]. Furthermore, sensitizing effects of salinomycin during irradiation and treatment with cytostatic agents suggest that the sensitizing mechanism of action of the antibiotic is preserved both in the application of radiotherapy and chemotherapy [10,11]. Additionally, it has been showed that the sodium salt of **1** is able to selectively deplete breast cancer stem cells with efficiency comparable to that of **1** [12].

Chemical modifications of **1** yielded its various derivatives characterised by significantly lower toxicity and better biological activity than the unmodified antibiotic, and this discovery has opened an interesting direction of research. Until now the synthesis, structure and biological activity of the series of amides [13,16], *O*-acyl derivatives [15], as well as one ester of salinomycin with 1-hydroxybenzotriazole [14,16] have been described. Among the tested compounds, **1** and its several amide derivatives showed high activity against Gram-positive bacteria [13]. The antiproliferative activity tests of **1** and its amide derivatives have clearly shown that some of the amides possess high antiproliferative effect against normal and drug resistant cancer cells, and these compounds were less toxic against normal cells than commonly used cytostatic agents – cisplatin and doxorubicin [16].