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Review article

A comprehensive review of salinomycin derivatives as potent anticancer and anti-CSCs agents

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ABSTRACT

Polyether ionophore antibiotics (ionophores) represent a large group of more than 120 lipid-soluble compounds that are widely used in veterinary medicine because of their significant antimicrobial activity. In addition to the industrial use of ionophores, some of them effectively and selectively inhibit properties of different cancer cells and enhance the antitumor effects of chemo- and/or radiotherapy. Salinomycin (**SAL**) is particularly interesting in this regard as it shows potent activity against various types of cancer cells, including those that display multi-drug resistance, and cancer stem cells. Therefore, a very interesting direction of research is chemical modification of **SAL** which may lead to obtaining analogs that are characterized by better biological activity and lower toxicity than those of the starting compound. This review article is focused on the possible role of both **SAL**-based drug delivery systems and **SAL** derivatives in future cancer therapy.

Contents

1. Introduction

Although substantial progress has been made toward reducing cancer mortality and extending life expectancy throughout the

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world over the past few decades, invasive cancers are still the second leading cause of death in economically developed countries after cardiovascular diseases, and one of the most leading cause of death in developing countries [1]. According to the World Health Organization, over eight million people die because of cancers each year; it is about 13% of the total number of deaths worldwide. At the same time, it is estimated that the number of people diagnosed with cancer will systematically increase in the next few decades. Indeed, about 10 million new cancer patients were diagnosed in 2000, and this number is unfortunately expected to double in 2020 [2]. In 2015, the five most common types of cancer that kill men (in order of frequency) were lung, liver, stomach, colorectal and prostate cancers, while breast, lung, colorectal, cervical and stomach cancers were the most deadly among women [2]. On the other hand, the most frequent types of childhood cancers are leukemia, lymphomas and tumors of the central nervous system [2].

Oncology has already had some crucial moments in the fight against cancers, but despite considerable progress we are still waiting to find novel and effective ways to combat this group of diseases. Chemotherapy, whose usefulness is based on inhibiting of cell division, is effective in many types of cancers but in many others it is completely ineffective. In response to the systematically growing number of people diagnosed with cancers, many research groups around the world are engaged in finding new and highly effective anticancer agents. The history of discoveries of novel chemotherapeutics clearly indicates that one of the most rational ways to invent such drugs is to chemically modify the natural products with proven high biological activity. The ionophore antibiotics (ionophores) should undoubtedly be included in such compounds, among which salinomycin and its semi-synthetic derivatives deserve special attention in particular in the light of the recently published reports.

2. Ionophore antibiotics

Polyether ionophore antibiotics are a large group of natural bioactive compounds that are isolated from *Streptomyces* spp [3]. The first isolation and the discovery of biological properties of the compound belonging to this group took place in 1942, when Georgyi Gause and Maria Brazhnikova during the research conducted on bacteria of the *Bacillus brevis* genus noticed that after mixing them with a colony of *Staphylococcus*, a strong inhibition of growth of the latter occurred. Gramicidin S responsible for this phenomenon became the first known ionophore antibiotic [4,5].

In 1964, Pressman et al. described a new class of antibiotics which transport alkali metal cations from aqueous solutions to the hydrophobic phase [6]. The high biological activity of these compounds may be strictly connected with their natural ability to bind cations and transport them through biological membranes; for this reason, they are called ionophores (ion carriers) [7–9]. Till now, more than 120 ionophore antibiotics have been identified. Among them, six have been widely used in veterinary medicine as coccidiostatic agents and non-hormonal growth promoters (Fig. 1), *i.e.* lasalocid acid (Avatec®, Bovatec®), maduramycin (Cygro®), monensin A (Coban®, Coxidin®, Elancoban®, Rumensin®), narasin (Maxiban®, Monteban®), salinomycin (Biocox®, Sacox®, Salinomax®) and semduramycin (Aviax®) [3,7].

Although more than 70 years have passed since the discovery of gramicidin S, there is no universally accepted system of classification of ionophore antibiotics. The most precise system seems to be the division of this group of compounds into natural and synthetic ionophores. Natural ionophores may be distinguished by cyclic ionophores and non-cyclic neutral or carboxylic ionophores, complexing mono- and/or divalent cations. In the group of natural cyclic ionophores, cyclopeptides (composed of amino acids only), cyclodepsides (composed of hydroxyacids only) and cyclodepsipeptides (composed of amino acids and hydroxyacids) may be found (Fig. 2A) [3].

2.1. Properties and mode of action of ionophore antibiotics

All polyether ionophores have common structural features. Their inner part is the hydrophilic cavity (pocket) formed by the oxygen atoms that belong to a variety of functional groups (ether, carbonyl, hydroxyl). The polar pocket with strictly defined size is able to coordinate only the cations whose size (radius) closely matches the size of this polar pocket; it simultaneously ensures high selectivity of the complexation process of both mono- and divalent cations. On the other hand, the outer part of their molecules is non-polar because it consists mainly of hydrophobic hydrocarbon skeletons. The presence of such hydrophobic surface guarantees high lipophilicity and facilitates diffusion through cell membranes from the extracellular environment into the cell [10,11].

Ionophore antibiotics may act in two different ways – as cation carriers or as elements that form channels within the cell membranes (Fig. 2B). In the first case, the ionophore molecule forms with the cation a complex of unique structure, inside which the cation remains isolated from the external environment; the adoption of such structure allows the cation to be easily transported through the lipid bilayers. In contrast, channel-forming ionophores make a continuous pore within the biological membranes that is filled with water molecules, through which the flow of the respective cations is possible to conform to a concentration gradient. The studies on membrane transport have shown that more than 10^7 cations are transported through such a channel over a single second, while a single carrier-type ionophore may transport no more than 10^3 cations per second [3,11].

2.2. Mechanism of cation transport

The non-cyclic carboxylic ionophores, such as lasalocid acid, monensin A and salinomycin (Fig. 1), make a large class of naturally-occurring products from the group of carrier-type ionophore antibiotics. All carboxylic ionophores contain both tetrahydrofuran and tetrahydropyran rings. Importantly, these compounds may exist in the pseudocyclic crown ether-like form. Such a structure is stabilized by intramolecular hydrogen bonds that connect the two ends of the molecule; at one end there is a carboxyl group and at the opposite one there are one or two hydroxyl groups.

The broad spectrum of bioactivity of ionophore antibiotics is related to their natural ability to complex cations, mainly sodium and potassium, and a great ease in transferring the resulting electrically inert or charged complex across biological membranes. Inside the cell, the cation is released thus disturbing the natural Na^+/K^+ concentration gradient and changing the intracellular pH, which in turn leads to cell death [11].

Knowledge of the mechanism of cation transport realized by carboxylic ionophores is essential for fully understanding of the functioning of this group of compounds as well as for explaining the broad spectrum of their biological properties (Fig. 3A). At present, three different mechanisms of cation transfer across biological membranes by carrier-type ionophores are known: (i) electroneutral transport - if the transmembrane potential does not change, (ii) electrogenic transport - if the transmembrane potential is changed, and (iii) biomimetic transport, which is carried out by ionophores with a chemically modified carboxyl group [12,13].

The electroneutral transport is carried out in an inert or basic environment, because only in such conditions the carboxyl group

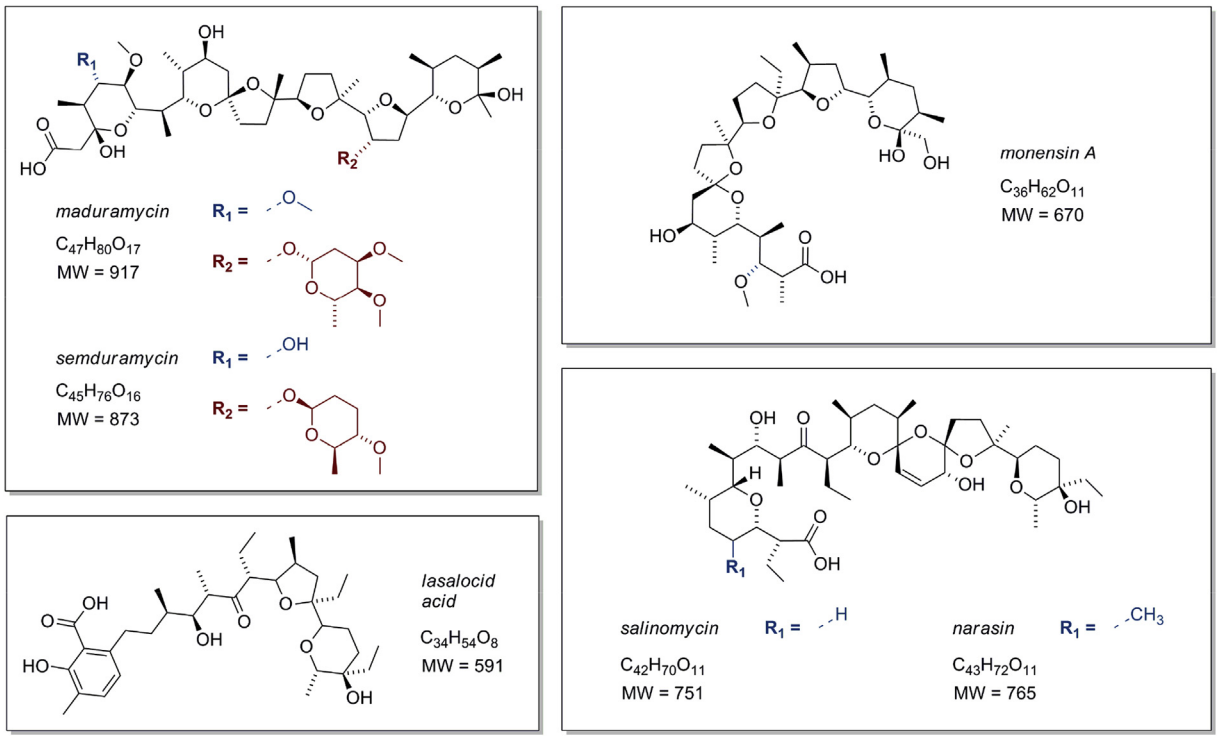


Fig. 1. Structure of selected carboxylic ionophore antibiotics.

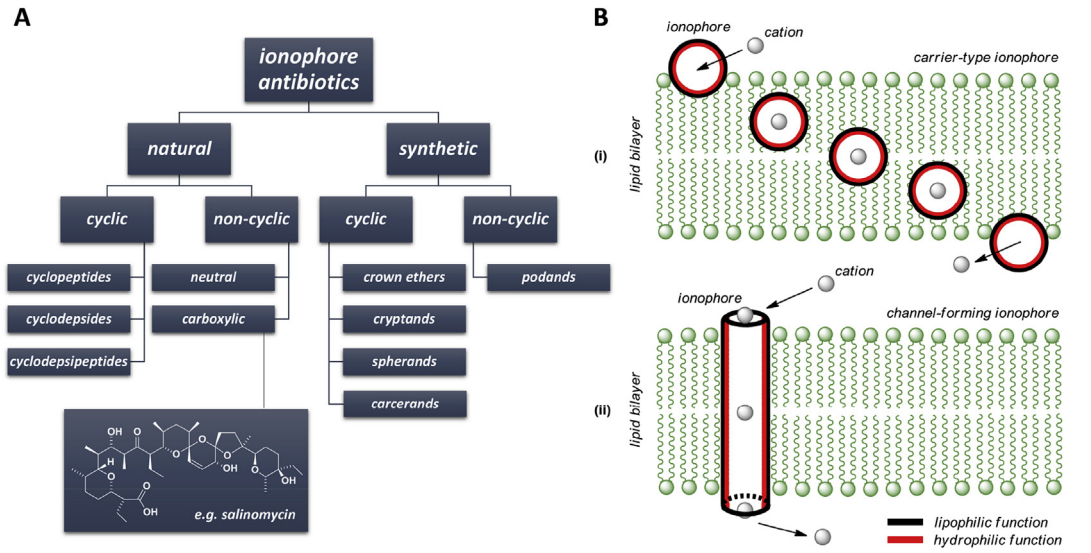


Fig. 2. (**A**) Classification of ionophore antibiotics, and (**B**) methods of cation transport realized by ionophores. Principle of action: (i) a carrier-type ionophore, (ii) a channel-forming ionophore.

may be deprotonated to form the carboxylate group [12,13]. In the cancer cells and their immediate environment often acidification takes place. This phenomenon related to the process of anaerobic glucose metabolism is called the Warburg effect [14]. Due to the fact that also under such conditions ionophore antibiotics are highly active against cancer cells, in recent years an alternative mode of transport (electrogenic) was proposed; it may be effectively carried out by ionophores with a protonated carboxylic group [12,13]. The biomimetic transport, being a type of electrogenic transport mode, may be also found in the scientific literature; it is carried out by ionophore antibiotics with a chemically modified carboxyl group, *e.g.* by their amides or esters [12,13].

3. Salinomycin – a new cancer drug candidate

Salinomycin (**SAL**, **1**, Fig. 1) was isolated for the first time from *Streptomyces albus* in 1974 during screening tests in the search for new antibiotics [15]. The first derivative of this natural monocarboxylic ionophore (*para*-iodophenacyl ester) was obtained one year later; it was also the first crystalline derivative of **SAL**, whose structure was successfully solved [16]. The first total synthesis of **SAL** was proposed by Kishi et al. in 1981 [17] and developed in

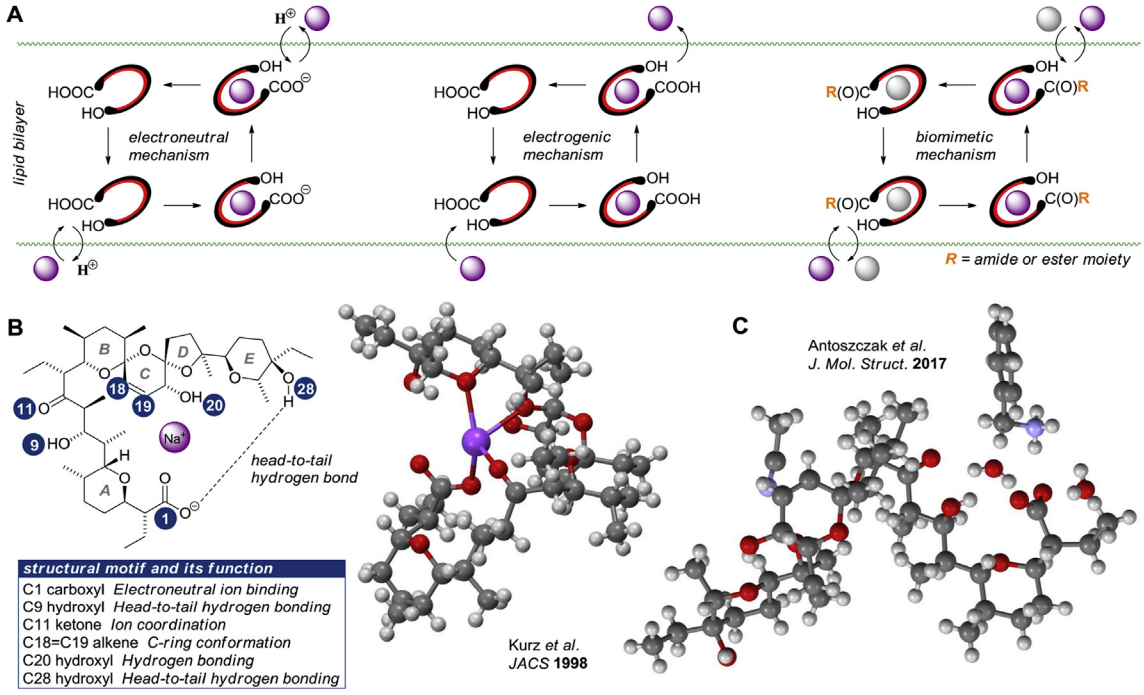


Fig. 3. (**A**) Mechanisms of cation transport realized by carboxylic ionophores; (**B**) structure and mode of complex formation of salinomycin with sodium cation, and (**C**) with benzylamine molecule.

subsequent years by other chemists (Brimble, Kocieński, Urpi, Yadav) [18–23]. Furthermore, the biosynthesis of **SAL** was presented in 2012 [24].

SAL molecule has in its structure 11 oxygen atoms included in various functional groups, such as carboxylic, hydroxyl, ether or ketone; its molecule also includes four tetrahydropyran and one tetrahydrofuran rings. Moreover, the 6-6-5 spiro-ketal ring system characteristic of **SAL** structure and observed relatively rarely in other natural products, stiffens of entire molecule [25–27]. Importantly, **SAL** molecule exists in the open-chain structure, as shown in Fig. 1. Because of the presence of carboxylic group on the one end of its molecule and hydroxyl group on the opposite end, there is however the possibility to create the intramolecular 'head-to-tail' hydrogen bonds. This process leads to formation of the pseudocyclic structure in which the oxygen atoms extend towards the interior of the molecule, so that **SAL** may easily complex cations, especially sodium and potassium (Fig. 3B). On the other hand, the external part is hydrophobic which allows an easy transfer of created complex across the biological membranes [10]. It has been found that **SAL** transports monovalent cations more efficiently than divalent ones [28]. It has also been proved very recently that **SAL** is able to form complexes with organic amines (Fig. 3C) [29].

SAL shows significant bioactivity against Gram-positive bacteria, mycobacteria, *Staphylococcus aureus*, and parasites. **SAL** has also been found to be an effective agent against some fungi, including *Candida albicans*, *Colletotrichum gloeosporioides*, *Fusarium oxysporum* f.sp. *albedinis*, *Fusarium solani* and *Saccharomyces cerevisiae*. Additionally, it has been established that **SAL** shows interesting antiviral properties, for example, activity against human immunodeficiency virus (HIV). **SAL** has been reported to be a potent anticoccidial agent that is active towards *Eimeria acervulina*, *Eimeria brunetti*, *Eimeria maxima*, *Eimeria necatrix* and *Eimeria tenella*, and this activity is greater than that exhibited by commonly used coccidiostatic agents. As a result, **SAL** has been used in veterinary medicine as an additive to feed, a coccidiostatic agent and non-hormonal stimulator of poultry and cattle growth [11]. **SAL** proved to be ineffective against Gram-negative bacteria, which is related to the presence of an additional, outer cell membrane in their cells impermeable by this type of hydrophobic compounds [30].

In addition to the industrial use of **SAL**, it has been also shown that **SAL** effectively and selectively inhibits properties associated with different human cancer cells, including those that display multi-drug resistance (MDR). *In vitro* and *in vivo* activity of **SAL** against cholangiocarcinoma, colorectal, gastric, hepatocellular, leukemic, lung, nasopharyngeal, osteoblastoma, prostate and many other cancer cells has been demonstrated in the last 10 years [31–44]. The sensitizing effects of **SAL** in combination with radiotherapy or with different chemotherapeutic agents, including colchicine, gemcitabine, imatinib, tamoxifen and vinblastine, have been proven as well [45–59].

One of the reasons why tumors are so difficult to control is the presence of a small sub-population (2–5% of the tumor mass) of cancer cells inside a cancerous tumor. These cells, known as cancer stem cells (CSCs) or cancer initiating cells, are a sub-population of cancer cells with many clinical implications in most cancer types, including their ability to asymmetrically divide, differentiate and self-renew, to having increased intrinsic resistance to therapy, and their role in cancer metastases as reflected by their ability to initiate and drive micro- and macro-metastases [60,61]. Evidence from preclinical and clinical studies has demonstrated that most of the currently used chemotherapeutics effectively destroy the highly proliferating and relatively differentiated cells making the bulk of the tumor rather than the more quiescent CSCs. Paradoxically, the elimination of non-CSCs by such a treatment may provide more space for CSCs to expand and evolve into a more aggressive malignancy with higher self-renewal potential [62]. Targeted therapy is designed to destroy CSCs, thus leading to tumor shrinkage and slow regression of the disease, while the concept of combination therapy includes the features of both previously described therapies, resulting in complete eradication of the tumor [63].

In the light of the above reports, the search for effective ways to

destroy CSCs has become an extremely timely and important task to be solved by contemporary and future cancer therapy. The breakthrough in the perception of **SAL** as a novel CSC-selective chemotherapeutic drug candidate took place in 2009 when the screening studies performed on ~16,000 biologically active substances proved that only 32 tested compounds destroyed breast CSCs, and among of them the most active was **SAL**. This ionophore destroyed breast CSCs *in vitro* and inhibited mammary tumor growth *in vivo* with 100-fold improved selectivity when compared to the cytostatic drug taxol (paclitaxel), which is commonly used in the fight against this type of cancer [64]. What is worth noting, in 2012 the influence of **SAL** on cancer patients with invasive carcinoma of the head, neck, breast and ovary was confirmed. Therapy with the use of 200–250 $\mu g\ kg^{-1}$ of **SAL** administered intravenously every second day for three weeks resulted in inhibition of disease progress for months without any serious long-term adverse side effects often encountered after the use of standard chemotherapeutic drugs, such as alopecia, nausea or emesis [65].

The precise anticancer mechanism of **SAL** needs still further investigation, but its high biological activity might be related to the natural ability of **SAL** to complex cations and transport them across the lipid membranes, which changes the Na^+/K^+ concentration gradient and intracellular pH. Consequently, these changes lead to mitochondrial injury, cell swelling, vacuolization and programmed cell death (apoptosis) [11]. Using an active fluorescent **SAL** conjugate, it has been also shown very recently that the molecular initiating event leading to selective reduction the proportion of CSCs after **SAL** treatment is strictly connected with a net outflux of the Ca^{2+} cations from the endoplasmic reticulum (ER) as a result of **SAL**-mediated alkali-metal ion transport across the ER membrane [66].

The effects on several signal transduction pathways were also invoked to explain the change in phenotype composition after **SAL** treatment [67]. Of note is that **SAL** was found to inhibit Wnt signaling pathway involved in tumorigenesis and embryogenesis through more than one mechanism [68]; the other ones include KRas [69] and modulation of Hedgehog signaling [70–72]. Mechanistically, the demonstrated effects of the treatment of different types of human cancers with **SAL** include decreased mitochondrial membrane potential, decreased ATP levels, increased reactive oxygen species (ROS) production that caused DNA damage and cell death as well as interference with ABC drug transporters [40,73–79]. In addition, **SAL** induced apoptosis in human cancer cells not only by interacting with such transporters, but also by overexpression of Bcl-2 or 26S proteasomes with enhanced proteolytic activity [80]. In contrast, it has been documented that **SAL** is able to decrease the expression of Bcl-2 and simultaneously to increase the expression of Bax, and to cleave caspase-3 and caspase-9 as well [74].

A massive autophagic response to **SAL** in prostate and breast cancer cells has been also noted, and this response has been substantially stronger than that to the commonly used autophagic inducer – rapamycin [77]. On the other hand, it has been found recently that **SAL** exerts antiangiogenic and antitumorigenic activities by inhibiting vascular endothelial growth factor receptor 2-mediated angiogenesis [81] and by suppressing the VEGF-VEGFR2-Akt/FAK signaling axis [82].

Due to the broad spectrum of interesting biological and pharmacological properties exhibited by **SAL**, the natural direction of research is synthesis of rationally designed **SAL**-based drug delivery systems and chemical modification of **SAL** structure, which can lead to obtaining unique systems/derivatives with significantly better biological activity and lower toxicity than those of the unmodified antibiotic. Such studies have been carried out for several years in different research groups around the world.

4. Drug delivery systems based on salinomycin

As mentioned above, targeting CSCs is an essential strategy for developing novel and effective cancer therapies to prevent disease progression, recurrence and emergence of MDR. Tumors display plasticity, so the targeting of CSCs without killing non-CSCs may therefore not result in the complete cancer elimination. For this reason, successful cancer therapy must eliminate both the bulk tumor cells as well as CSCs that are hidden inside the tumor [83,84]. **SAL** holds a great promise in this regard as it showed high potency in killing both cancer cells and CSCs of different origin, including those that are characterized by MDR phenotype [31–44]. **SAL** displayed however poor aqueous solubility (**SAL** was administered by intraperitoneal injection *in vivo* with the aid of ethanol only) [64,85], and some neural and muscular toxicity [79] when used in high concentrations. Several constructed **SAL**-based carriers may therefore hold great potential for tackling all these limitations (Fig. 4).

The unique physicochemical properties of nanomaterials provide the opportunities for multifunctional cancer therapy, imaging and diagnosis by improvement of the treatment efficacy while reducing detrimental side effects to normal tissues [86,87]. Nanocarrier-based therapeutics have been used to achieve improved bioavailability and stability, longer circulation times and higher drug loading efficiency over currently used drugs [88–90]. Recently, the scientists from many research groups around the world have successfully applied **SAL**-based nanomedicines to target not only non-CSCs, but also cancer cells with stem cell-like properties, leading to the elimination of tumor and to the prevention of cancer relapse.

For instance, **SAL** was conjugated to a hyaluronic acid-based nanogel to target $CD44^+$ MDR cells (Fig. 4) [91]. CD44 receptor is expressed at the surface of many cancer cells that bind hyaluronic acid [92–94], allowing selective targeting of such nanogels to CSCs. This approach enhanced the bioavailability, delivery and cytotoxic activity of **SAL** in both MDR cell cultures (human breast and pancreatic adenocarcinoma cells) and multicellular spheroids relative to those of free drugs [91]. In 2014, **SAL** was loaded on polyelectrolyte-conjugated gold nanorods and proved to lead to inhibition in mammosphere-forming efficiency of treated human breast cancer cells and to a decrease in $ALDH^+$ cell sub-population (Fig. 4) [95]. One year later, Zhang et al. established a gastric CSCs-specifically targeting drug delivery system, having **SAL** and chitosan coated single-walled carbon nanotubes (SWCNTs) conjugated with hyaluronic acid (Fig. 4). The treatment of gastric cancer cells with this complex, selectively eradicated gastric CSCs and decreased both mammosphere- and colony-forming abilities of such cancer cells. The migration and invasion of gastric CSCs were significantly blocked as well [96]. Very recently, **SAL** nanoparticles have been shown to interfere with tumor cell growth and with the tumor microenvironment in an orthotopic model of pancreatic cancer [97].

In another approach, combinations of **SAL** with other chemotherapeutic drugs through nanocarrier systems that show synergistic effects to target both cancer cells and CSCs, have been designed. For example, therapeutic efficacy of combining **SAL** and paclitaxel after conjugation with biocompatible CD44 antibody conjugated SWCNTs *via* hydrazone linker allowing pH-responsive release mechanism, has been proposed (Fig. 4). The enhanced therapeutic effect of the combined therapy was confirmed both *in vitro* and *in vivo* compared to the treatment with individual drug-conjugated nanocarriers or free drug suspensions [98]. An immunotolerant elastin-like polypeptide-based nanoparticles that released modified **SAL** under acidic conditions were also developed. Although no metastasis was detected in any of the mice, they

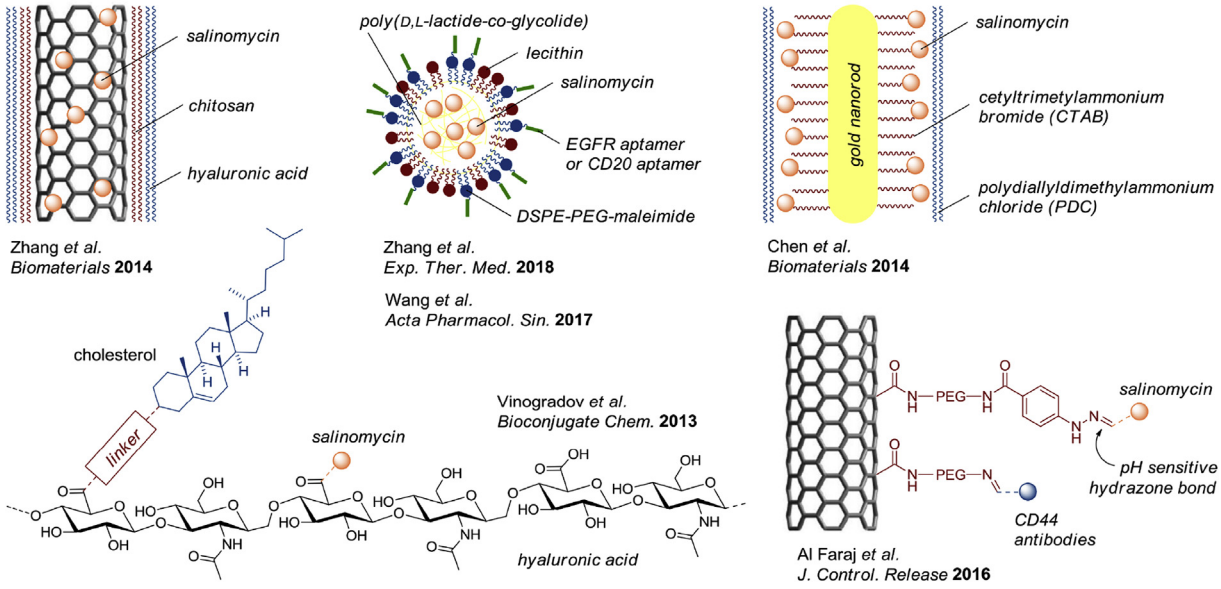


Fig. 4. Selected salinomycin-based drug delivery systems.

all died of primary tumor burdens. To overcome these limitations and improve the overall survival, the authors adopted a strategy similar to that mentioned above and applied a combination therapy of **SAL**-based nanoparticles and paclitaxel-based ones. Such a therapy effectively retarded primary orthotopic breast tumor growth and improved the overall mice survival [99,100]. Potent anticancer activity against different types of cancer and prominently reduced toxicity has been observed using other **SAL**-loaded nanoparticles as well [101–110].

Micelles and liposomes are the most extensively studied and understood pharmaceutical nanocarriers. These systems provide easier control, composition, size and *in vivo* stability in comparison with other drug delivery systems. Therapeutic agents in conjunction with such nanocarriers result in better pharmacokinetic properties of the drugs loaded on carriers thereby improving therapeutic activity [111]. In this context, in order to enhance the effect of eliminating breast cancer cells and reducing side effects, Zhang et al. have developed octreotide-modified **SAL**-loaded PEGylated polymeric micelles and paclitaxel-loaded PEGylated polymeric micelles. Thanks to the activity of paclitaxel against bulk cancer cells and the activity of **SAL** against CSCs, the proposed combination therapy with a targeted delivery system mounted a stronger anticancer response *in vitro* and *in vivo via* receptor-mediated endocytosis. The combination therapy was more effective than that with **SAL** alone *in vivo* [112]. Moreover, a type of dual-functional **SAL** plus chloroquine liposomes have been proposed for treatment of liver cancer through the differentiation strategy [113]. Very interesting anticancer activity both *in vitro* and *in vivo* of **SAL**-loaded micelles, nanoliposomes, PLGA nanofibers, and lipoprotein particles against various cancer cells and CSCs, including MDR cancer cells, was also proved by other authors [114–120].

5. Chemical modification of salinomycin

Due to the wide spectrum of interesting biological and pharmacological properties exhibited by **SAL**, the natural direction of research is its chemical modification leading to the creation of unique derivatives characterized by a higher therapeutic index and lower toxicity than the parent compound. However, chemical modification of **SAL** is not trivial; **SAL** undergoes irreversible decomposition in the presence of mineral acids/bases and as a result of excessive heating [22]. For this reason, it is necessary to choose such methods of chemical modification that will not degrade the starting compound and will result in the expected reaction products with satisfactory yields.

Work related to the chemical modification of **SAL** is currently successfully carried out in many research groups (Huczyński, Jiang, Rodriguez, Strand, Tian, Wu) [121–150]. In the following sections the synthesis procedures and results of biological activity studies of the most interesting derivatives of **SAL** are presented.

5.1. Modification of salinomycin carboxyl group

The most numerous group of **SAL** derivatives includes its esters and amides obtained by the chemical modification of C1 carboxyl group. To date, Huczyński et al. have synthesized several dozen analogs of this type, among which various aliphatic, aliphatic-aromatic and aromatic derivatives were found (Fig. 5) [121–129]. All **SAL** C1 esters and amides were more or less anticancer active depending on the cancer cell line studied. The tests were carried out on cancer cells of different origin, *i.e.* on vincristine-sensitive and vincristine-resistant leukemia (HL-60 and HL-60/vinc, respectively), and doxorubicin-sensitive and doxorubicin-resistant colon adenocarcinoma (LoVo and LoVo/DX, respectively). In addition, to determine the toxicity and selectivity, the effects of C1 esters and amides on normal mice embryonic fibroblasts (BALB/3T3) were determined. Antiproliferative activity was estimated by determining the IC_{50} values, *i.e.* the concentration of the compound (expressed in μM) inhibiting in 50% the biological and biochemical functions of the cells (Fig. 5) [123–126].

According to the results obtained, the majority of **SAL** C1 derivatives are anticancer active at micromolar range of IC_{50} (Fig. 5, analogs **2**–**13**), and overcome (strongly or moderately) simultaneously MDR of tumor cells, especially LoVo/DX cells, which suggests preferential activity of **SAL** analogs against this type of cancer. Most of the derivatives obtained were characterized by stronger MDR overcoming than **SAL** and two commonly used cytostatic drugs – cisplatin and doxorubicin [123–126]. Importantly, very recently **SAL** C1 derivatives have been shown to exhibit higher activity than the starting structure against primary acute

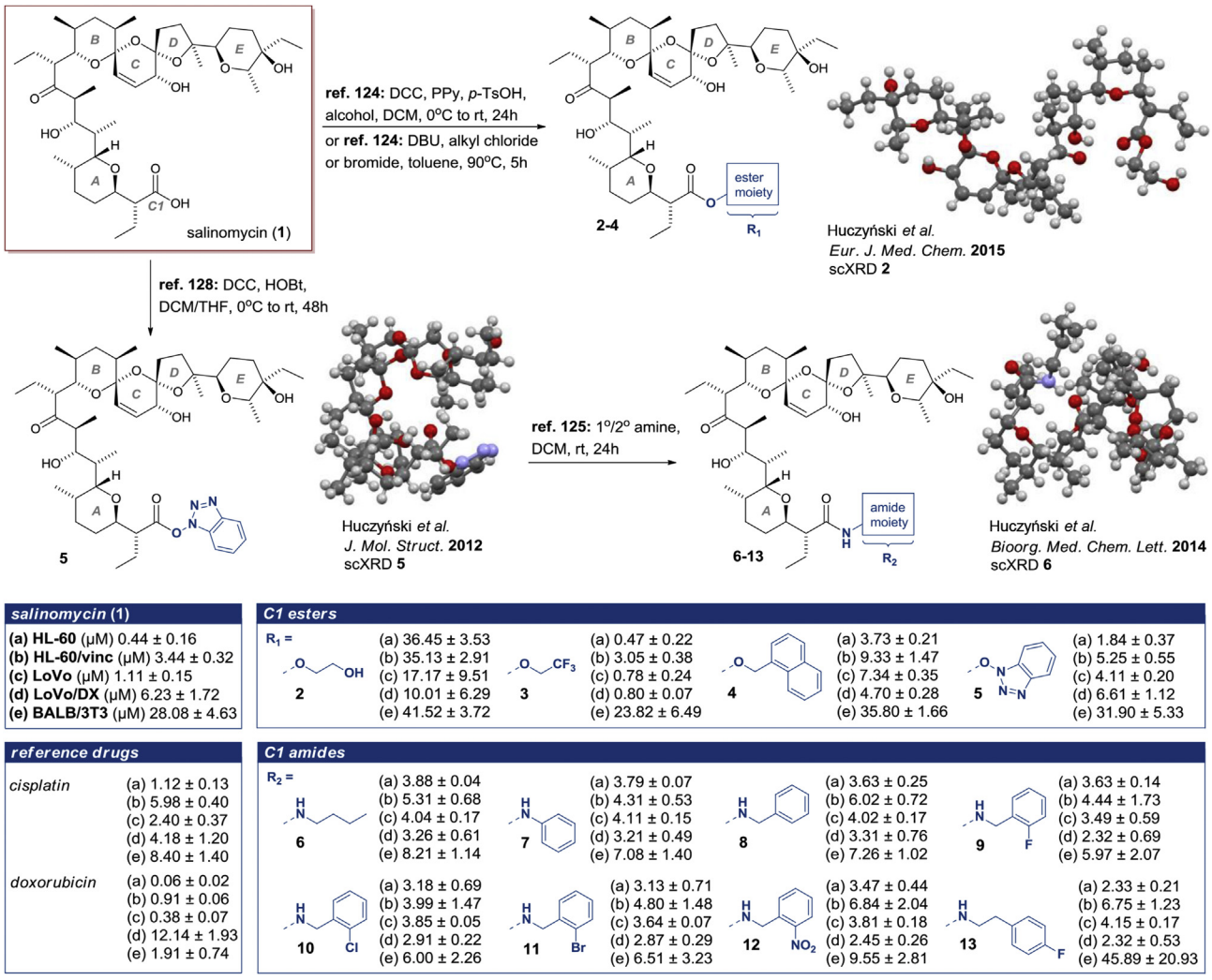


Fig. 5. Synthesis and anticancer activity of selected salinomycin C1 esters and amides.

lymphoblastic leukemia cells *in vitro* [129]. It has also been proved that the majority of C1 **SAL** esters and amides are less toxic to normal cells than cisplatin and doxorubicin, which pointed out their high therapeutic potential (Fig. 5) [123–126]. **SAL** derivatives have been tested for their antimicrobial activity as well. The studies clearly demonstrated that selected **SAL** analogs show antibacterial, antitubercular, and trypanocidal activity [122–125,127,128].

Huczyński et al. have also conducted the synthesis of a series of C1 **SAL** bioconjugates with *Cinchona* alkaloids (quinine, quinidine, cinchonine, cinchonidine), selected nucleosides (floxuridine, AZT), flavonoids (silybin) and blocked amino acids [130–134]. In this group, particularly interesting were the hybrids with floxuridine **25** [132], and methyl esters of L-phenylalanine **26**, L-histidine **27**, and L-glycine **28** because of their high antitumor activity (Fig. 6) [134]. Their activity against cancer cells was significantly higher than that of cisplatin and doxorubicin, including activity against biphenotypic myeloid leukemia (MV4-11), colorectal (HT-29, LS-180, SW707), and LoVo/DX cancer cells with MDR phenotype. It was an important observation because cancer cells may acquire resistance to cytostatic agents during long-term monochemotherapy and it may result in the recurrence of cancer and poor prognosis for cancer patients [132,134].

In 2017, Wu et al. obtained a series of 10 conjugates of **SAL** with hydroxamic acids linked by ester bonds [135]. Most of them, particularly analogs **14**–**21**, showed several times higher activity than **SAL** against colon (HT-29) and stomach (HGC-27) cancer cells, and especially against triple negative breast (MDA-MB-231) cancer cells (Fig. 6). This observation was explained by the ability of such conjugates to hydrolyze within tumor cells to produce **SAL** and the corresponding hydroxamic acid that results in the synergistic anticancer effects [135]. At the same time, it might explain much lower cytostatic activity of other **SAL** hybrids with hydroxamic acids obtained in the Strand group [136], linked by the amide bonds rather than the ester ones (Fig. 6, analogs **22**–**24**). According to Wu et al., these types of conjugates had no possibility of hydrolysis to the starting components inside tumor cells due to the enzymatic stability of the amide bonds [135], which resulted in much lower biological activity of such hybrids [136]. Although the authors have suggested that the better membrane permeability and hydrolysis rate of the conjugates may lead to the activity improvements [135], it should be mentioned here that there is no evidence of the synergistic anticancer effects of **SAL** and the corresponding hydroxamic acid.

5.2. Modification of salinomycin hydroxyl groups

Another large group of **SAL** derivatives are the compounds obtained as a result of chemical modification of its hydroxyl groups.

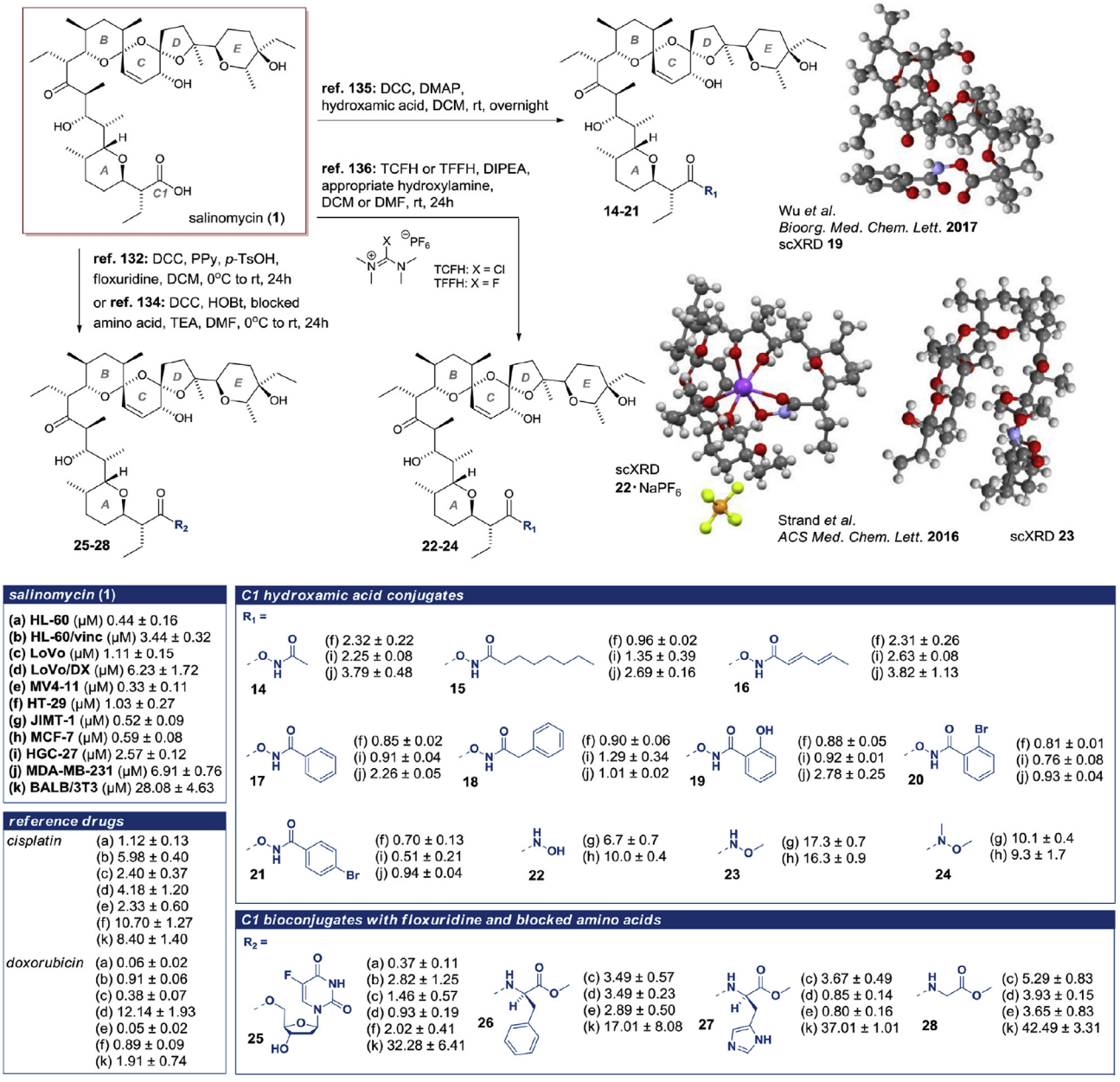


Fig. 6. Synthesis and anticancer activity of selected salinomycin C1 conjugates.

Strand et al. performed regioselective *O*-acylation of all three hydroxyl groups of **SAL** in 2013 [137]. The results of the antiproliferative activity tests on human breast cancer cells (JIMT-1 and MCF-7) proved that regioselective modification of the allylic C20 hydroxyl of **SAL** opened the access to synthetic analogs that display increased cytotoxic activity relative to that of the native structure. Their IC_{50} values were reduced by up to 20% compared to those of chemically unmodified **SAL** (Fig. 7, analogs **29**–**40**) [137]. At the same time, it was shown that the most active derivatives in this series effectively destroy breast CSCs at nanomolar concentrations at which **SAL** remained inactive [138]. Moreover, the treatment with each of the three C20 *O*-acylated analogs **29**, **37** and **39** (Fig. 7) has reduced colony forming efficiency and cell migration, and has increased the expression of the epithelial markers E-cadherin and β-catenin at the cell surface [138]. Importantly, exposure of human colorectal cancer cells (SW480 and SW620) to the selected C20 *O*-acylated analogs of **SAL** resulted in reduced tumor cell number and impaired tumor cell migration at lower concentrations than **SAL**. When used at micromolar concentrations, these effects were accompanied by induction of apoptotic cell death. **SAL** C20 acetate **29** and C20 ethyl carbonate **37** (Fig. 7) further exposed the improved activity against CSCs compared to that of the starting material [139].

On the other hand, Wu et al. have synthesized C20-*epi*-salinomycin where the stereochemical configuration at C20 position is inversed [140]. It was clearly proven that the inversion of configuration at C20 position was possible after blocking of C1 carboxyl group only, and using a substituted benzoic acid with a suitable acidity as an acylating agent. The Mitsunobu reaction proposed by these authors was effective using *para*-nitrobenzoic acid (pKa 3.43), while the intermediate **41** (Fig. 7) was not observed when benzoic acid (pKa 4.20) or *para*-bromobenzoic acid were used (pKa 3.97).

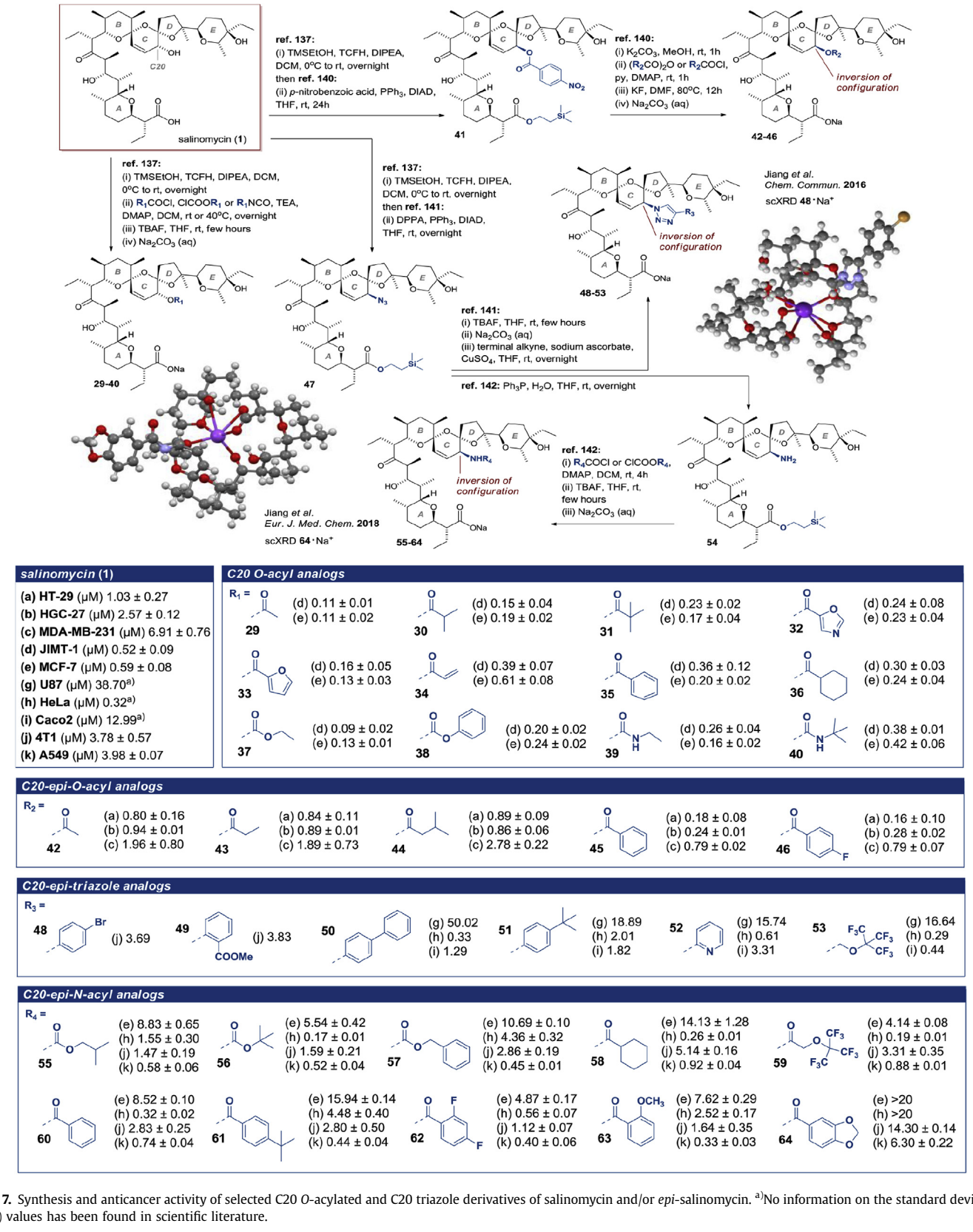


Fig. 7. Synthesis and anticancer activity of selected C20 *O*-acylated and C20 triazole derivatives of salinomycin and/or *epi*-salinomycin. [a)]No information on the standard deviation (SD) values has been found in scientific literature.

With access to the targeted C20-*epi*-salinomycin, Wu et al. have obtained a series of its *O*-acylated analogs (Fig. 7, analogs **42**–**46**) [140]. The results of anticancer activity tests carried out on colon (HT-29), stomach (HGC-27) and triple negative breast (MDA-MB-231) cancer cells reveal that C20-*epi*-salinomycin shows a similar activity to that of **SAL**, whereas the activity of respective C20 *O*-

acylated analogs is even 2–10 times higher than that of **SAL**. In addition, derivatives **45** and **46** were characterized by a significantly higher selectivity as compared to that of the starting structure (Fig. 7) [140]. Mechanistically, the spatial configuration of C20 hydroxyl of **SAL** had little influence on the anticancer properties, but the *O*-acyl groups caused an obvious difference by producing possible effects on the stability and/or permeability of the **SAL**–alkali metal cation complexes [140].

Introduction of an azide group to **SAL** molecule was possible in the Mitsunobu reaction as well, using DPPA as a nucleophile. In this context, Jiang et al. have proved for the first time that the inversion of the configuration at C20 position creates a convenient site for the chemical modification of **SAL**, particularly by sterically volatile reagents. C20 azide **47** was then used to obtain several tens of **SAL** derivatives with a variety of aliphatic, aliphatic-aromatic and aromatic terminal alkynes using Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition reaction (Huisgen 'click' chemistry) (Fig. 7, analogs **48**–**53**) [141]. The synthesized C20 triazole derivatives were tested for their activity against glioma (U87), cervical (Hela), breast (MCF-7) and colorectal (Caco2) cancer cells as well as normal human liver cells to check their toxicity (selectivity of action). The four analogs **50**–**53** were characterized by the cytostatic activity several and even a few dozen times higher than **SAL** (Fig. 7); C20 triazole derivatives were simultaneously less toxic to normal cells than the starting compound [141].

To improve the druggability of **SAL**, a library of C20-*epi*-amino-C20-deoxysalinomycin derivatives was synthesized (Fig. 7, analogs **55**–**64**) from which a few novel **SAL** analogs with high potency and selectivity were identified through a comprehensive *in vitro* cytotoxicity study. The cytotoxicity of the obtained compounds was evaluated against a series of cancerous cells, including murine breast cancer cells (4T1), human promyelocytic leukemia cells (HL-60), adenocarcinomic human alveolar basal epithelial cells (A549), human cervical cancer cells (HeLa), human breast cancer cells (MCF-7), human colon adenocarcinoma cells (SW480), and human hepatocarcinoma cells (SMMC-7721); some of these derivatives were found to be over 80-fold more potent against selected cancer cells than **SAL** and simultaneously exhibited a similar toxicity [142]. Using a doxycycline-inducible K-ras^{G12V} expression cellular model, the authors have found that **SAL** and its C20-*epi*-amino-C20-deoxy derivatives may eliminate cancerous cells through pathways other than inhibition of oxidative phosphorylation in mitochondria [142].

The C20 hydroxyl group of **SAL** might be chemoselectively oxidized with high yields to the C20 ketone group using activated manganese(IV) oxide (Fig. 8, analog **65**) [143]. In 2017, Rodriguez et al. described a procedure for the synthesis of a series of amine derivatives of **SAL** obtained by stereoselective reductive amination of such a C20 ketone group (Fig. 8). Among these novel analogs, the most interesting derivative was C20-propargylaminosalinomycin **66** (Fig. 8) that showed almost 10-times higher antiproliferative activity against breast CSCs (HMLER CD24^{low}) than **SAL**, both *in vitro* and *in vivo*, with an IC_{50} value of about 100 nM whilst maintaining selectivity over control cells [144]. According to the authors, a more potent activity and selectivity of action of **66** (Fig. 8) against breast CSCs has resulted from accumulation and sequestration of iron in lysosomes. In response to the ensuing cytoplasmic depletion of iron, cancer cells have triggered the degradation of ferritin in lysosomes, leading to further iron loading in this organelle. Iron-mediated production of ROS has promoted lysosomal membrane permeabilization, activating finally a cell death pathway consistent with ferroptosis [144].

Interestingly, two conformationally restricted **SAL** derivatives by tethering hydroxyl groups at positions C1 and C20 through chains of different lengths were designed and synthesized (Fig. 9, analogs **72**–**73**). The cyclic derivatives showed better biological activities than C1/C20 double-modified analogs **70**–**71** (Fig. 9), indicating the importance of the compact conformation for the ion binding capacity. In addition, the length of the connective chain plays a critical role in biological activities, thus cyclic derivative **73** preserved some pharmacological activity but derivative **72** with two carbon atoms shorter chain showed significantly reduced anticancer activity [145].

5.3. Modification of salinomycin ketone group and ring C

C11 ketone group, next to C1 carboxyl group, is directly involved in the binding of cations. Therefore, an interesting direction of research is to study all chemical modifications of this group that could affect the complexing properties of the compounds obtained, and thus their bioactivity. In 2017, Strand et al. proposed a diastereoselective method to reduce C11 ketone group; in the presence of $LiBH_4$, highly *anti*-selective reduction was identified, while using the Luche reduction ($CeCl_3 \cdot 7H_2O$, $NaBH_4$), a highly *syn*-selective reduction was observed (with respect to the C10 methyl group) (Fig. 10, analogs **76** and **77** with absolute configuration *S* and *R* at C11 chiral center, respectively). It allowed the isolation of both novel derivatives in stereochemically pure form. However, the results of tests performed against breast cancer cells (JIMT-1 and MCF-7) demonstrated a significantly lower cytostatic activity of both C11 alcohols than that of the parent compound [143].

Characteristic of **SAL** is the presence of tricyclic 6-6-5 bis-spiroketal ring system with *cis* isomerism, stiffening its molecular structure. For this reason, all kinds of manipulations in the ring *C* of **SAL**, the central site of this system, are of interest. Previously, the chemoselective oxidation of C20 hydroxyl group to C20 ketone group using activated MnO_2 was described by Strand et al. (Fig. 8, analog **65**) [143]. The same research group (Strand) successfully hydrogenated the C18=C19 double bond using an Adams catalyst, and proposed then the chemoselective oxidation of compound **80**, using Dess-Martin periodinane, that resulted in the generation of a diketone **81** (Fig. 10). The antiproliferative activity tests on breast cancer cells (JIMT-1 and MCF-7) have proven a few times lower activity of both these derivatives compared to that of unmodified **SAL** [143].

Strand et al. have also developed an effective strategy for the synthesis of C20-deoxysalinomycin **78** and its saturated derivative – C18,C19-dihydro-C20-deoxysalinomycin **79** (Fig. 10) to compare the biological activity of such analogs to that of the native compound. The tests against breast cancer cells (JIMT-1 and HCC1937) clearly indicated that both derivatives had to be used at higher concentrations than **SAL** to induce similar cellular effects. On the other hand, analogs **78** and **79** caused a reduction in the ratio of breast CSCs ($CD44^+/CD24^-$) similar to **SAL** [146].

Rodriguez et al. have performed recently an effective functionalization of C18=C19 double bond of **SAL**; the authors performed the [π2s + π2s] photocycloaddition reaction which resulted in the generation of an apolar alkyn derivative **67** (Fig. 8). Unfortunately, this compound showed moderate anticancer activity but retained some selectivity compared to **SAL** [144]. Wu et al. have synthesized and then evaluated the antitumor activity of C17-*epi*-salinomycin **86**, C17,C21-di-*epi*-salinomycin **88** and their C20 benzoylated derivatives **85** and **87**, respectively (Fig. 11). It was shown that **86** and its analog **85** almost completely lost cytostatic activity, while **88** and its *O*-acylated derivative **87** showed significantly higher activity than **SAL** against colon (HT-29), stomach (HGC-27) and triple-negative breast (MDA-MB-231) cancer cells. Derivatives **87** and **88** (Fig. 11) were characterized simultaneously by high selectivity of action which proved that the configuration of C17 and C21-spiro atoms is of key importance for the bioactivity of derivatives of **SAL** [147].

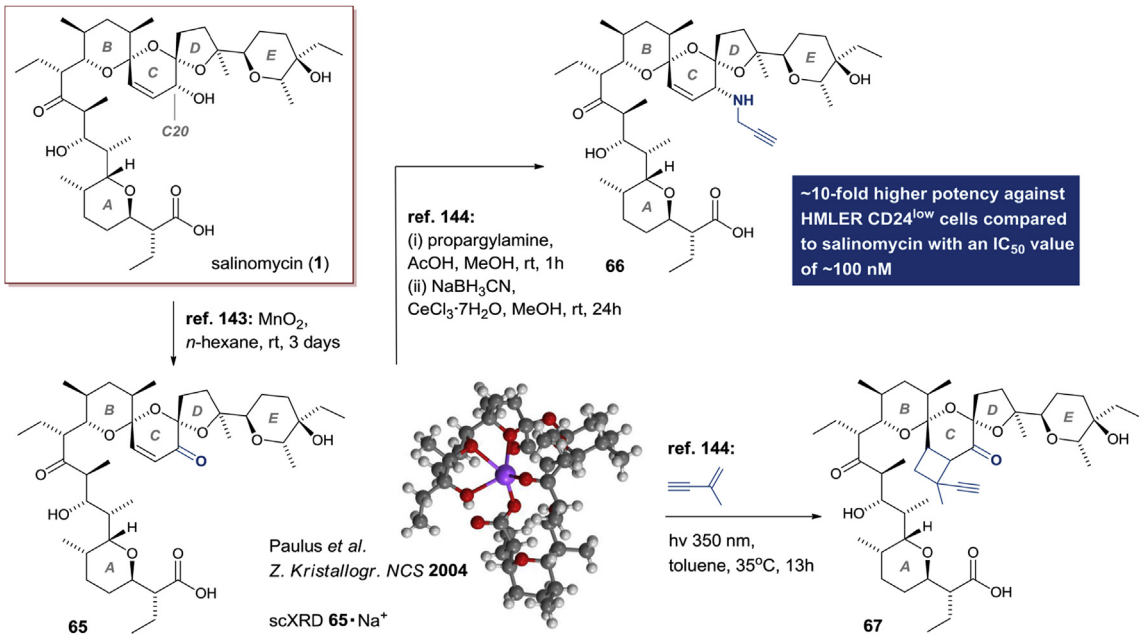


Fig. 8. Synthesis and anticancer activity of C20-propargyloaminosalinomycin, and functionalization of the C18=C19 double bond of salinomycin.

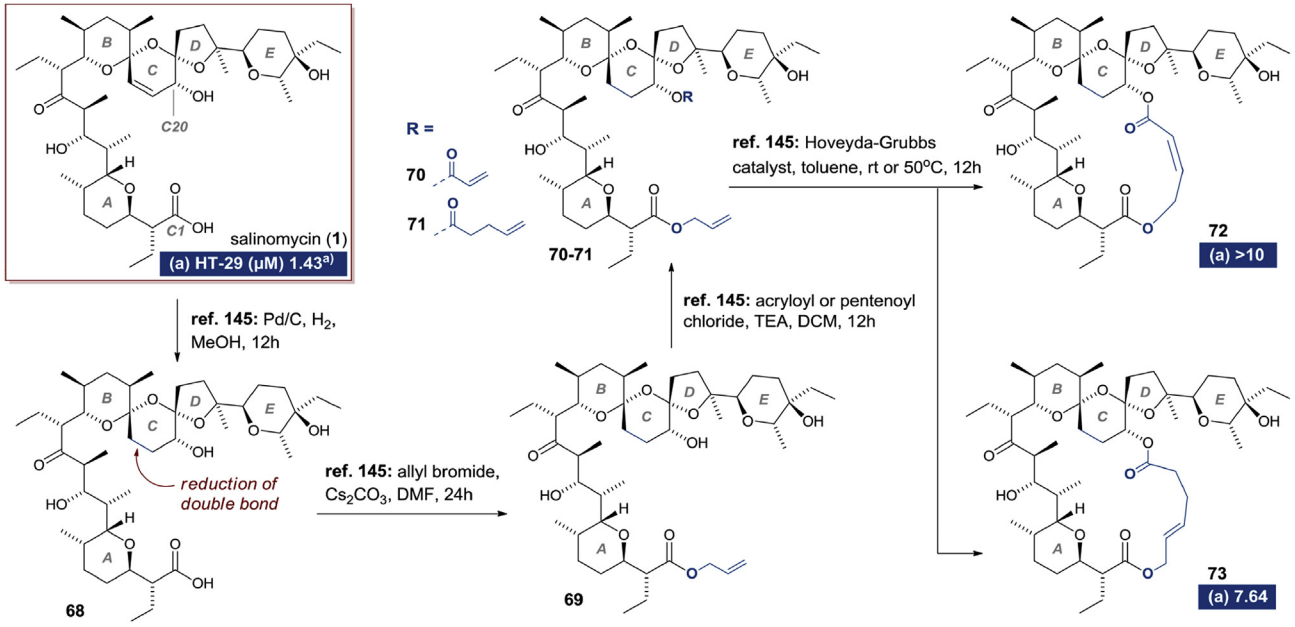


Fig. 9. Synthesis and anticancer activity of conformationally constrained salinomycin derivatives. [a)]No information on the standard deviation (SD) values has been found in scientific literature.

5.4. Dimerization of salinomycin

Until now, not much attention has been paid to ionophore antibiotics derivatives that are various types of their multivalent structures. Obtaining such structures is extremely interesting because of the potentially significant changes in the complex-forming properties and hence their biological activities.

In scientific literature, synthetic procedures and results of biological activity of 12 various **SAL** dimers have been described [125,148,149]. In 2014, Huczyński et al. described the synthesis of three dimers, in which **SAL** molecules were connected by amide bonds through *n*-butyl, phenyl and biphenyl linkers. However, such dimers did not show better antiproliferative activity than **SAL** against vincristine-sensitive and vincristine-resistant human leukemic cells (HL-60 and HL-60/vinc, respectively) as well as doxorubicin-sensitive and doxorubicin-resistant colon adenocarcinoma cells (LoVo and LoVo/DX, respectively) [125].

Furthermore, Tian et al. obtained in 2017 a series of several triazole derivatives of **SAL**, including its four dimers connected at C20 position (Fig. 12, analogs **89**–**92**). It should be emphasized that in this group of compounds, the most active against breast cancer cells (MCF-7 and MDA-MB-231) turned out to be all dimer structures which showed several times higher activity than **SAL** on MCF-7 cells and comparable activity to the starting compound against

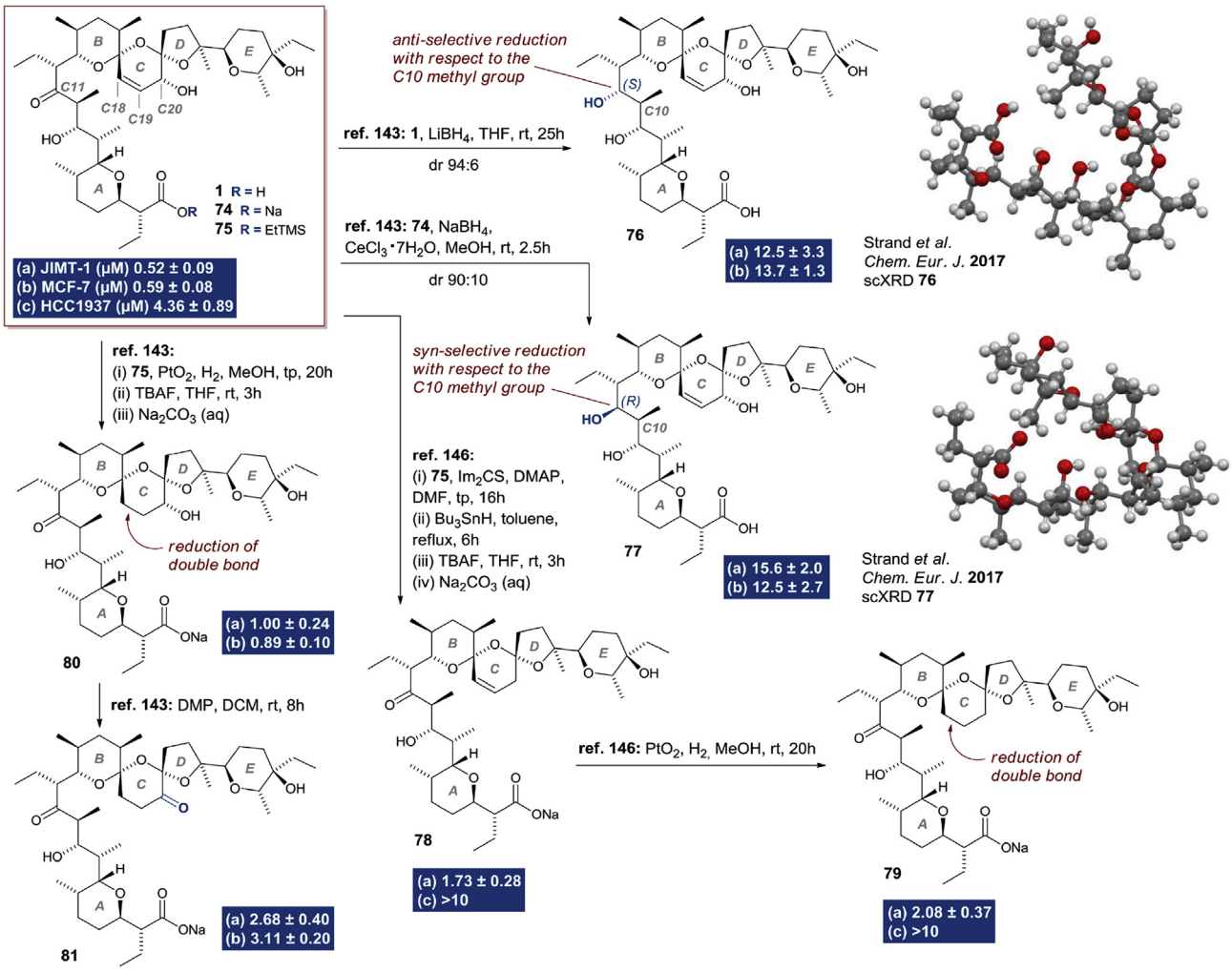


Fig. 10. Synthesis and anticancer activity of C11 alcohols and derivatives obtained by chemical modification of salinomycin C-ring.

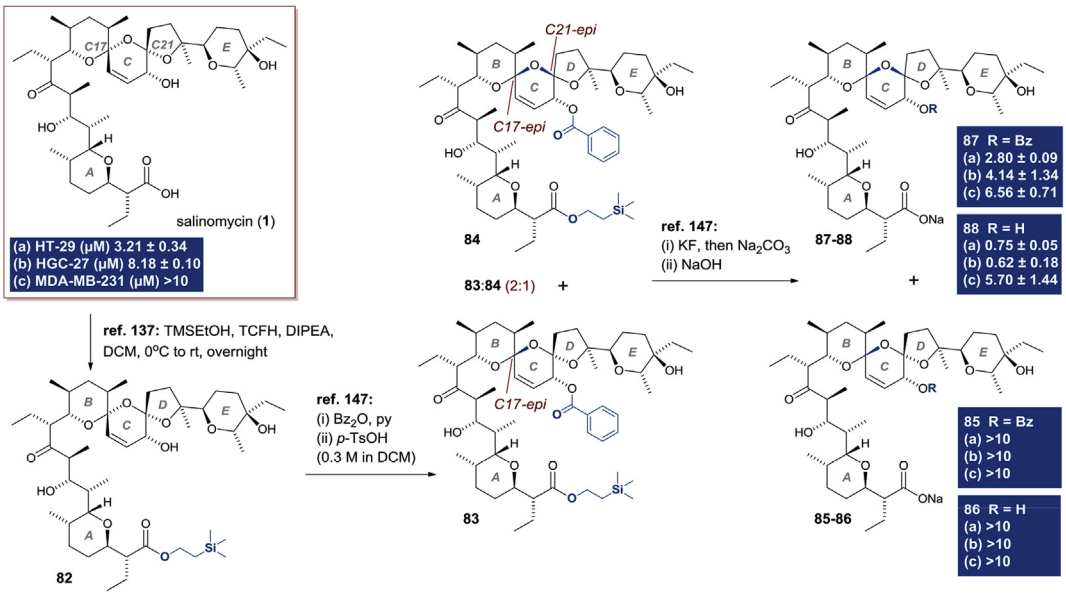


Fig. 11. Synthesis and anticancer activity of C17-*epi*-salinomycin, C17,C21-di-*epi*-salinomycin and their benzoylated derivatives.

MDA-MB-231 cells [148]. The activity of multivalent structures was also comparable to that demonstrated by the simple C20 *O*-acylated analogs described above (Fig. 7, analogs **29**–**40**) [137].

In the same year, Strand et al. presented the effective methods for the synthesis of **SAL** C1 and C20 dimers exhibiting C_2 symmetry, based on the Glaser coupling reaction. The tests carried out on colon adenocarcinoma cells sensitive and resistant to doxorubicin (LoVo and LoVo/DX, respectively) as well as breast cancer cells (JIMT-1, MCF-7, SKBR-3) showed that the C20-*O*-terephthalate dimer **93** is active in micromolar concentrations towards the used series of cancer cell lines, and this activity was comparable to that of **SAL** (Fig. 12). In addition, compound **93** was found to be less toxic to normal mammary gland cells (MCF-10A) than cisplatin and doxorubicin, proving a high therapeutic potential of this derivative. On the other hand, all novel **SAL** C1 dimers were practically inactive in these studies [149].

5.5. Double-modified salinomycin derivatives

Within the library of analogs investigated, **SAL** C1 esters/amides (Fig. 5, analogs **2**–**13**) and **SAL** C20 *O*-acyl derivatives (Fig. 7, analogs **29**–**40**) have shown noteworthy improvements in the biological activity profile [122–129,137–139]. In 2018, Strand et al. synthesized the first analogs combining such modifications (Fig. 13, analogs **94**–**105**) [150].

Evaluation of the anticancer activity against a series of cancer cell lines, including colon adenocarcinoma cell line (LoVo) and its doxorubicin-resistant subline (LoVo/DX) as well as breast cancer cell lines (JIMT-1, MCF-7, and SKBR-3), showed that acylation of the C20 hydroxyl group improved the activity of **SAL** C1 amides, but not of the corresponding C1 esters. With respect to the acyl groups, the analogs from the C20 carbamate series were consistently more active than those from the ester and carbonate series (Fig. 13) [150].

Importantly, the activity of several of the double-modified analogs surpasses that of commonly used cytostatic drugs cisplatin and doxorubicin in the LoVo/DX cell line (Fig. 13). In the light of the anticancer activity of the double-modified derivatives in the low μM concentration range, the low toxicity against the normal breast MCF-10A cell line is also noteworthy (Fig. 13). All analogs were tested against primary acute lymphoblastic leukemia ALL-5 cells in standard cell viability assays; three were more potent than **SAL** (Fig. 13, analogs **95**, **100** and **105**) [150].

Further studies revealed that selected analogs induced characteristics of apoptotic cell death and increased expression of p53. Additionally, using an *ex vivo* model of breast tumor, tumor cell viability significantly decreased after treatment with **SAL** or its double-modified derivative **100** (Fig. 13) in a time-dependent manner [150]. These findings support the double-modification of **SAL** as a useful strategy to generate promising lead compounds with interesting biological activity profiles for targeting various types of cancer.

6. Conclusions

A new chapter has been opened in the chemical and biological studies of ionophore antibiotics. The results of previous studies encourage scientists from around the world to perform chemical modifications of salinomycin (**SAL**) aimed at obtaining derivatives with higher biological activity and lower toxicity, *i.e.* compounds with a higher therapeutic index, than that of the starting compound. In just a few years, promising anticancer activity of **SAL** and **SAL**-based drug delivery systems against a range of cancer types has been proven. The progress in structural modification of the **SAL** molecule as well as evaluation of biological properties of resulted

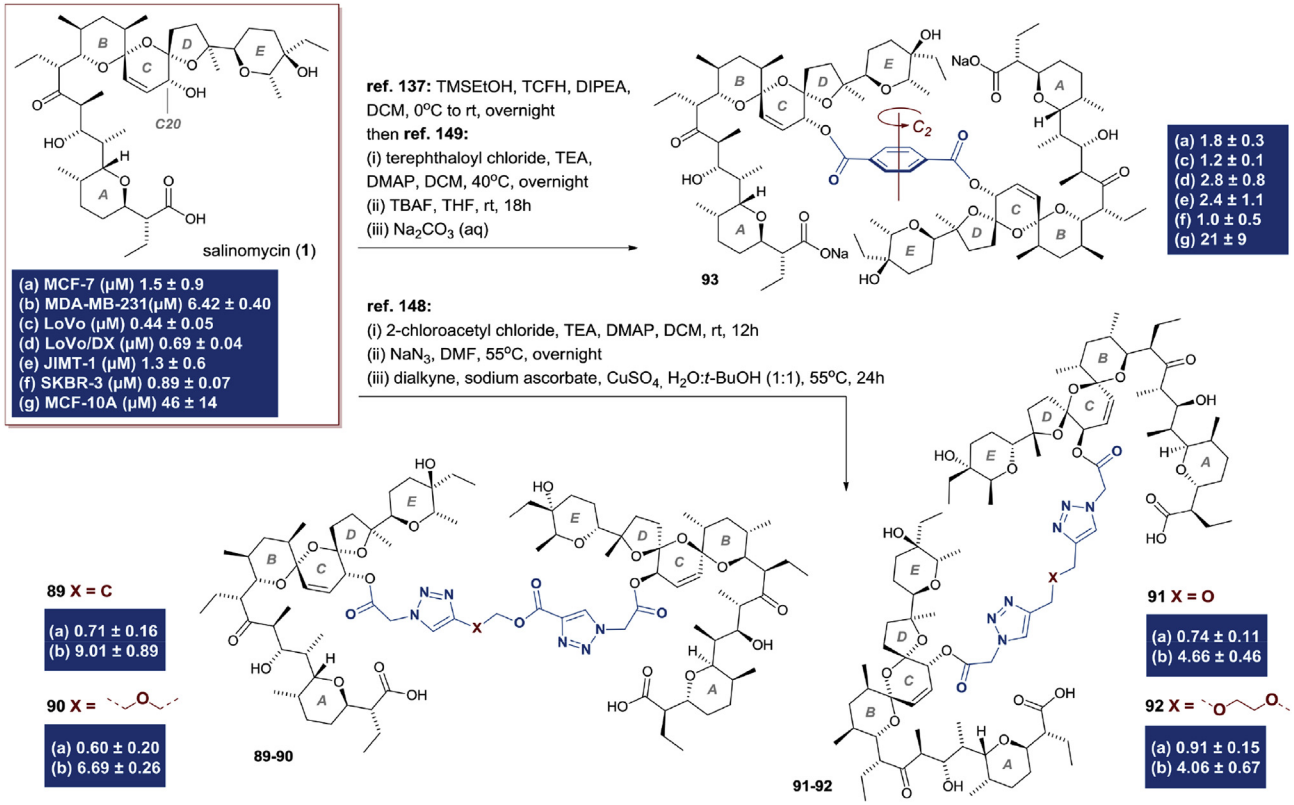
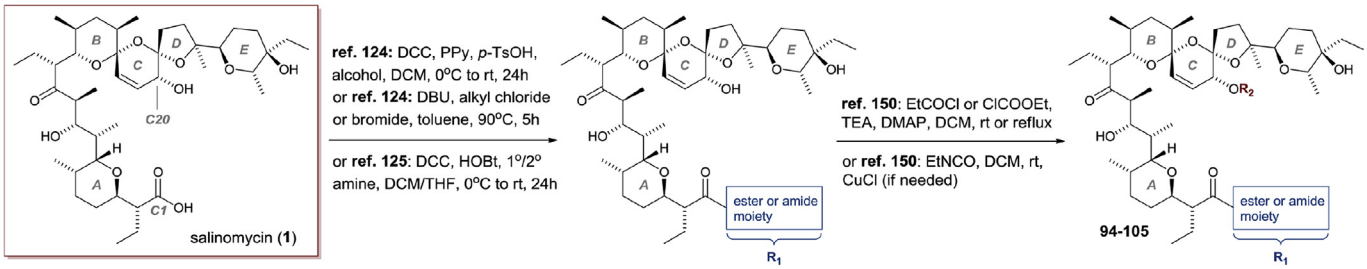


Fig. 12. Synthesis and anticancer activity of selected salinomycin dimers.



salinomycin (1)

(a) MCF-7 (μM) 1.5 ± 0.9
(b) ALL-5 (μM) 2.4 ± 0.7
(c) LoVo (μM) 0.44 ± 0.05
(d) LoVo/DX (μM) 0.69 ± 0.04
(e) JIMT-1 (μM) 1.3 ± 0.6
(f) SKBR-3 (μM) 0.89 ± 0.07
(g) MCF-10A (μM) 46 ± 14

reference drugs

cisplatin	(a) 7.7 ± 1.1 (c) 3.5 ± 0.6 (d) 3.5 ± 0.8 (e) 11 ± 2 (f) 8.2 ± 2.9 (g) 17 ± 5
doxorubicin	(a) 0.26 ± 0.09 (b) 0.04 ± 0.01 (c) 0.24 ± 0.09 (d) 10 ± 4 (e) 0.59 ± 0.09 (f) 0.37 ± 0.05 (g) 0.58 ± 0.09

Double-modified analogs

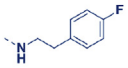
R_1 / R_2				
	**94** (a) 7.4 ± 1.7 (b) 2.6 ± 0.6 (c) 12 ± 8 (d) 5.2 ± 0.5 (e) 27 ± 4 (f) --- a) (g) --- a)	**97** (a) 5.8 ± 1.4 (b) 4.0 ± 0.3 (c) 4.4 ± 0.6 (d) 3.7 ± 0.3 (e) 17 ± 10 (f) 12 ± 1 (g) 92 ± 42	**100** (a) 3.7 ± 0.1 (b) 1.8 ± 0.1 (c) 4.0 ± 0.3 (d) 3.5 ± 0.4 (e) 3.7 ± 0.1 (f) 3.8 ± 0.2 (g) 43 ± 3	**103** (a) 12 ± 4 (b) --- b) (c) 8.7 ± 1.1 (d) 18 ± 11 (e) 39 ± 9 (f) --- a) (g) --- a)
	**95** (a) 38 ± 4 (b) 1.9 ± 1.2 (c) --- a) (d) 8.1 ± 1.7 (e) --- a) (f) --- a) (g) --- a)	**98** (a) 4.9 ± 0.4 (b) 17 ± 4 (c) 4.7 ± 0.3 (d) 3.8 ± 0.3 (e) 7.9 ± 1.3 (f) 16 ± 7 (g) --- a)	**101** (a) 3.9 ± 0.2 (b) 3.7 ± 1.4 (c) 4.7 ± 0.1 (d) 6.5 ± 1.3 (e) 7.0 ± 0.5 (f) 9.9 ± 2.4 (g) --- a)	**104** (a) 68 ± 26 (b) --- b) (c) --- a) (d) --- a) (e) --- a) (f) --- a) (g) --- a)
	**96** (a) 5.0 ± 0.9 (b) 6.9 ± 0.3 (c) 5.2 ± 0.5 (d) 3.4 ± 0.6 (e) 7.4 ± 1.1 (f) 25 ± 21 (g) --- a)	**99** (a) 4.7 ± 0.2 (b) 3.7 ± 1.6 (c) 4.2 ± 0.3 (d) 3.8 ± 0.1 (e) 5.9 ± 0.7 (f) 7.7 ± 1.0 (g) 82 ± 42	**102** (a) 3.8 ± 0.4 (b) 2.9 ± 0.1 (c) 3.5 ± 0.1 (d) 3.3 ± 0.3 (e) 4.4 ± 0.5 (f) 4.3 ± 0.2 (g) 58 ± 13	**105** (a) 6.1 ± 0.6 (b) 1.5 ± 0.1 (c) 5.3 ± 0.5 (d) 7.5 ± 1.4 (e) 11 ± 6 (f) 64 ± 14 (g) 60 ± 3

Fig. 13. Synthesis and anticancer activity of double-modified salinomycin derivatives. [a)]Inhibition of proliferation did not exceed 50% at the highest concentration tested of 100 μg mL^{-1}; [b)]inhibition of proliferation did not exceed 50% at the highest concentration tested of 10 μM.

derivatives has been also significant in the last decade.

Cancer is considered as one of the most serious health problems today. Over the past two decades, cancer stem cells (CSCs) have emerged as essential players in the pathogenesis of cancer, with the capacity to initiate, maintain and repopulate different tumors. Within the tumor bulk, CSCs represent a small sub-population, bestowed with the capacity to self-renew and yield heterogeneous lineages of cancer cells. In many scenarios, CSCs exhibit increased resistance toward irradiation and chemotherapy, and given their spectacular ability to replenish the tumor, they constitute a substantial therapeutic challenge.

In this context, the high efficacy of **SAL** and its analogs against tumors with multi-drug resistance seems to be of particular interest. Their unique and very selective mode of action by destroying CSCs may also provide a valuable potential for preventing cancer metastasis and recurrence. Also noteworthy is the ability of **SAL** to sensitize cancer cells treated with chemotherapy and/or radiotherapy. In my opinion, there will be many scientific articles about new discoveries in the field of cytostatic activity of **SAL** and its semi-synthetic derivatives in the next few years. There are also many indications that such compounds will become widely used and effective drugs in future cancer therapy, opening a new era in the cancer chemotherapy. Our research group is currently conducting intensive studies of further new derivatives of **SAL** and we expect that research inquisitiveness and persistence in pursuing the goal will lead to breakthroughs in this field.

Finally, I am convinced that the studies of the chemical modification strategies and structure-activity relationship of **SAL** could lead to finding more potent drug candidates and new drug delivery systems to achieve higher therapeutic efficacy. The results of the research presented in this review article clearly indicate that selected derivatives of **SAL** seem to be excellent candidates for novel chemotherapeutic drugs. However, several questions have to be answered in further studies. Firstly, analysis of the anticancer activity of the most promising analogs should be performed in animal models. Secondly, the potential toxic side effects of such derivatives have to be investigated in *in vivo* tests. Thirdly, although results of intensive studies have brought significant progress in this issue, the precise anticancer mechanism of **SAL** analogs is not fully understood and needs further investigation. Fourthly, the synergistic effects of the treatment with **SAL** derivatives in combination with other chemotherapeutic drugs or radiotherapy, that may significantly increase the effectiveness of the dual therapy applied, have to be evaluated. Although the increased activity of selected **SAL** analogs strongly suggest that similar effects as that of unmodified **SAL** can be induced at lower concentrations, which may be of great value towards their potential pre-clinical usage, only positive results of in-depth biological tests can open the door for their future therapeutic use.

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