Chemical modification of macrolide antibiotic Oligomycin A and determination of structure-activity relationship

Abstract

Natural compounds are used to consider in drug discovery as “privileged structures” due to their high affinity to biomolecules which were evolutionarily selected by the nature. Oligomycin A is a macrolide antibiotic, produced by *Streptomyces*, with potent antiproliferative and antifungal activity. Its mode of action is connected with F_1Fo ATP-synthase inhibition, which is regarded as a molecular target for new drugs in the treatment of tumors and infections. In micromolar concentrations, Oligomycin A binds to F_O c-subunit and blocks proton translocation, resulting in disruption of the bioenergetic metabolism. According to the literature, Oligomycin A is a promising scaffold for the development of new antitumor agents. Thus, it possesses high selective activity against several cancer cell lines including the myeloid leukemia cell line K-562, breast cancer cell line MCF-7, and lung carcinoma cell line A-549. Also, Oligomycin A can overcome the p-gp-mediated multidrug resistance of cancers by inhibiting the p-glycoprotein activity and can inhibit the plasma membrane localization of KRas oncogene. This antibiotic and other mitochondrial inhibitors are promising agents for striking cancer stem cells, in addition, mitochondrial inhibition restores the sensitivity of cancer cells with the GLI1-inducible multidrug resistance to chemotherapy. However, high toxicity of oligomycin A for mammalian cells confines its clinical application. So, a chemical modification of oligomycin A with the aim to improve its pharmacological properties is a promising task.

The main goals of the present work were to develop new methods of selective chemical modification of oligomycin A and to investigate structure-activity relationships (SAR). In order to achieve these goals, **the following objectives have been proposed**:

- Modification of C-C and C-O double bonds of the lactone core of oligomycin A;
- Modification of the hydroxypropyl side chain of oligomycin A;

- Acylation of the hydroxyl groups of oligomycin A;
- Purification and structure determination of new semi-synthetic oligomycin A derivatives;
- SAR analysis, based on the comparison of the antiproliferative and antifungal activities of new oligomycin A derivatives to those of parent antibiotic.

Scientific novelty

A series of new methods of selective chemical modification of oligomycin A were performed: regioselective catalytic hydrogenation of double C-C bonds, regio- and stereoselective reduction of carbonyl groups, epoxidation of C16-C17 double bond followed by acid-catalyzed ring opening of epoxide, [4+2] cycloaddition to diene system, as well as regioselective oxidation, epimerization and acylation of C33-OH group and acylation of C9-OH group without using protecting groups. New semi synthetic oligomycin A derivatives were synthesized and purified, their structures were unambiguously determined as well as their biological activities were investigated. Comparative analysis of biological properties of oligomycin A and its derivatives allows to obtain new valuable information about structure-activity relationships. Several oligomycin A derivatives with high activity and lower toxicity *in vitro* (in comparison with parent antibiotic) were found for the first time.

Practical significance

As a result of this work, a promising way for improvement of oligomycin's A pharmacological properties was found (transformation of C33-OH and C9-OH groups), and less toxic derivatives with potent activity proposed as candidates for future in-depth biological investigations. Developed methods of chemical modification of oligomycin A might be useful for application to other antibiotics with complex structure, related to oligomycin A (other oligomycins, maclafungin, neomaclafungines, ossamycin etc). Furthermore, semi-synthetic oligomycin A derivatives are demanded for molecular genetic studies of mechanisms of antimicrobial resistance emergence.

Theses to be sustained

1. Chemical modification of antibiotic Oligomycin A is a promising way to optimize its biological properties (toxicity decreasing along with retaining high antitumor and antifungal activity).

2. For SAR investigations it is need to develop the methods of selective oligomycin's A structure modification in three directions: (I) transformation of the macrolactone double C-C and C-O bonds, (II) modification of the hydroxypropyl side-chain (III) acylation of the hydroxyl groups.

3. Modification of oligomycin A can be realized in one or two steps using commercially available reagents and avoiding protecting groups. Selectivity of this process can be achieved owing to different reactivity of functional groups, sterical hindrance, chiral surrounding and by variation of reagents, catalysts and other reaction conditions.

4. Transformation of the hydrohypropyl side-chain and acylation of the C-9 OH group are proved to be the most promising ways for oligomycin's structure optimization. Several new oligomycin A derivatives, modified at C33 and C9 positions, possess *in vitro* high activity and lower toxicity in comparison with parent antibiotic.