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Spectroscopic, semiempirical studies and antibacterial activity of new urethane derivatives of natural polyether antibiotic – Monensin A

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HIGHLIGHTS

- Two molecules of ionophore antibiotic – Monensin A are connected by different diurethane linkers.
- Structure of new compounds was determined using spectroscopic and semiempirical methods.
- Antimicrobial activity of Monensin derivatives were tested.
- Compounds show activity against Gram-positive bacteria and methicillin-resistant *Staphylococcus aureus*.

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ABSTRACT

A series of new Monensin A dimers linked by diurethane moiety were synthesised and their molecular structures were studied using ESI-MS, FT-IR, ^{1}H and ^{13}C NMR and PM5 methods. The results showed that the compounds form a pseudo-cyclic structure stabilized by three intramolecular hydrogen bonds and the sodium cation was coordinated by five oxygen atoms of polyether skeleton of Monensin moiety. The NMR and FT-IR data of complexes of Monensin urethane sodium salts demonstrated that within the pseudo-cyclic structure the carbonyl oxygen atom of the urethane group did not coordinate the sodium cation. Monensin urethanes were tested *in vitro* for the activity against Gram-positive and Gram-negative bacteria and fungi as well as against a series of clinical isolates of *Staphylococcus*: methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA). The most active compound against MRSA and MSSA was 1,4-phenylene diurethane of Monensin with MIC 10.4–41.4 μmol/L).

1. Introduction

The rapid appearance of multidrug resistant pathogenic microorganisms has become a serious health threat worldwide [1,2]. It has been postulated that the development of resistance to known antibiotics could be overcome by identifying new drug targets *via* improving existing antibiotics by their chemical modification. The chemical modifications of well-known antibiotics often led to new antibacterial agents with novel structures, superior properties and modes of action [3–6].

Monensin A (Scheme 1) isolated from *Streptomyces cinnamonensis* is a well-known representative of natural polyether ionophore antibiotics. It is able to form pseudo-macrocyclic complexes with monovalent cations (especially with Na^+ cation) and transport them across cell membranes [6]. The pharmacological and biological activity of Monensin is based on its ability to disrupt the Na^+/K^+ ion balance across cell membranes, which finally leads to the cell's death. Monensin is used commercially as a coccidiostat for poultry and as a growth promoter for ruminants [7,8]. Up to now it has been also shown that some Monensin A urethanes act as growth agents in ruminants, have antihypertensive and also antimalarial activity and have been used in the treatment of swine dysentery [9–14]. Also in our earlier paper the synthesis, detailed structural and spectroscopic characterization and antimicrobial activity of phenyl urethane of Monensin A has been reported [15]. We have provided evidence that this compound has higher antibacterial activity against human pathogenic bacteria, including antibiotic-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis*, than the parent unmodified Monensin [15]. Therefore, an attempt to synthesise and evaluate the antibacterial activity of Monensin A diurethane dimers appears to be very attractive.

These findings motivated us to study in details the possible modes of antibacterial action together with the structure activity relationship (SAR) of Monensin urethanes. Inspired by all above mentioned results, in this contribution we present the synthesis

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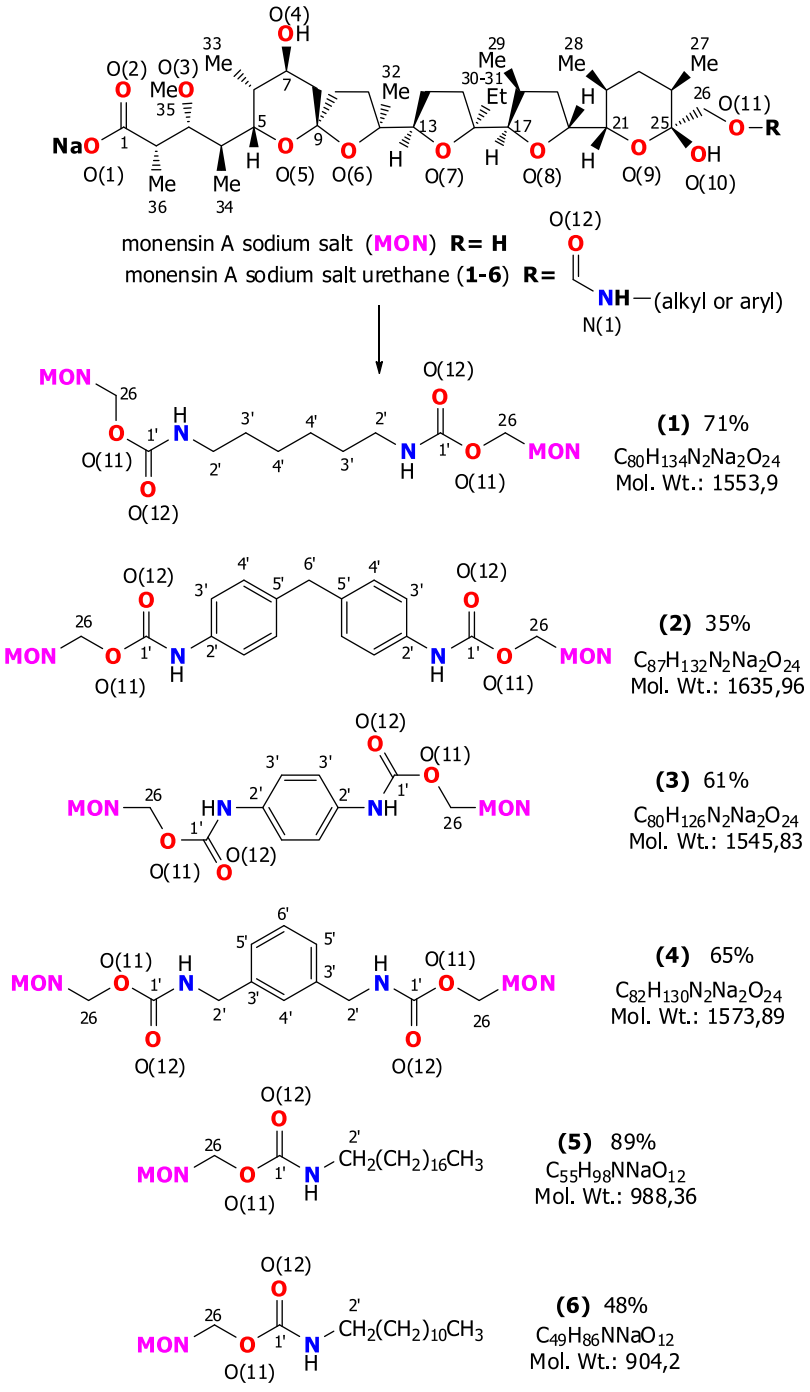

Scheme 1. The formula of MON and its urethane derivatives (**1–6**) with yield of respective reactions.

and antimicrobial activity of six new urethane derivatives of Monensin (Scheme 1). It is generally believed that dimers of biologically active compounds such as antibiotics show enhanced biological activity relative to the single ligand [16–19]. Hence, we can understand the great interest in making such dimeric compounds. The dimeric Monensin ligands, in which two identical antibiotic groups are linked by a spacer unit, can have exceptionally high binding affinity toward the sodium cation, and consequently can be useful modulators of biological function of ionophore antibiotics. However, the optimization of linkers between the ionophore binding groups can be challenging, and yet it is crucial in both fragment-based ligand's (and ionophore antibiotic) design and in the discovery of bi-ionophore antibiotics. In this paper, we describe a batch of symmetrical dimers of Monensin that was prepared to extend our understanding of the effects of linker length and flexibility on the compounds' biological activity.

In this paper series of six new C(26—O-urethane of Monensin A sodium salt (**1–6**) was synthesised and their structure studied in the in dichloromethane solution using ^{1}H NMR, ^{13}C NMR and FT-IR spectroscopic methods. The structures of monensin urethanes were also visualized by the PM5 calculations.

The antibacterial activity of Monensin urethanes determined on a series of clinical isolates of *Staphylococcus*: methicillin-susceptible *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA) and methicillin-resistant S. *epidermidis* (MRSE) was compared with the activity of pure monensin.