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Isolation and Characterization of Biologically Active Components from *Streptomyces milbemycinus*

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I. INTRODUCTION

Among the natural products, polypropionates represent an important class which can be found as common products of metabolism in plants, bacteria, insects, fungi and marine organisms. The group includes plant flavonoids, fungal aflatoxins, as well as many compounds that can inhibit the growth of bacteria, viruses, fungi, parasites or human tumor cells [1]. Indeed, at least hundred compounds from approximately 10000 known polypropionate natural products possess drug activity [2].

II. RESULTS AND DISCUSSION

A strain of *Streptomyces milbemycinus* NRRL 5739 is known for production of several antibacterial and antiparasitic substances or their precursors. We have isolated from the aforementioned strain milbemycins A4 and A3. The latter are active substances of well known miticide *Milbeknock* and the key starting materials for the semi-synthesis of milbemycin oxime, a prominent antihelminthic drug. For the first time these important natural products are fully characterized by X-ray diffraction analysis.

In accordance of X-ray crystallographic data the crystals represent a solid solution of milbemycins A3 and A4. In the crystal structure the occupation g-factor of molecule A3 is 0.28, all other positions are occupied by molecules A4. Figure 1 shows a perspective view of the molecular structure. In spite of the two hydroxy groups intermolecular hydrogen bonds are not observed in the structure. These groups form intramolecular hydrogen bonds (1 and 2 in Fig. 1) with lengths of 2.630(4) and 2.746(4) Å. By means of these bonds the additional five- and six-membered cycles are formed in the molecules.

The structure of pure milbemycin A4 is isomorphous to the solid solution. The parameters of the trigonal lattice of milbemycin A4 are only on 3% greater than these in the solid solution.

On the other hand, we have unexpectedly isolated natural product dianemycin from the strain of *Streptomyces milbemycinus* NRRL 5739. It is known since 1970-ties; however, its previous X-ray studies were not based on crystals with excellent quality. In our case the X-ray quality crystals of the product were isolated in the form of methanol solvate (methanolsodium dianemycin — methanol (1:2)) with the final *R*-factor 0.058 (Fig. 2) [3].

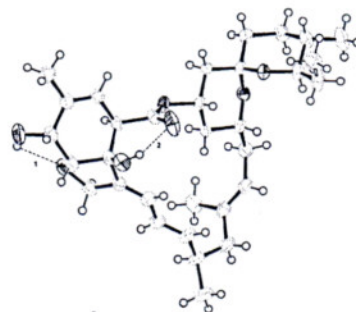


Fig.1. ORTEP molecular structure of the solid solution of milbemycins A3 and A4 showing formation of hydrogen bonds.

Dianemycin belongs to the class of carboxyl ionophores that complex the first row metal cations and therefore affect the transport of these latter in mitochondria. This property results in outstanding activity against chloroquine-resistant forms of malaria.

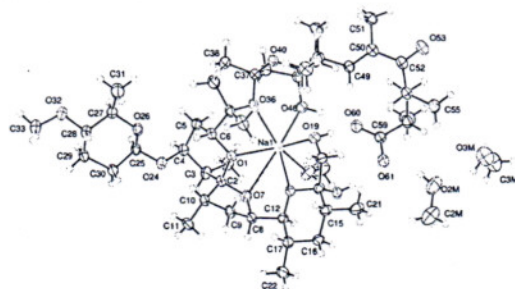


Fig.2. ORTEP molecular structure of methanolsodium dianemycin — methanol (1:2) [3].

III. REFERENCES

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