Molecule of the Month

Maitotoxin - Holder of Two World Records

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The structure of a large and extremely toxic natural product is described.

Nature is an excellent synthetic organic chemist. Using mild reaction conditions and a few elemental combinations, a large variety of complex molecules are made in and around us. The atoms are put together in precise arrangements to enable the molecules to carry out different tasks with remarkable specificity. The treasure house of natural chemicals contains delicate perfumes, spectacularly coloured substances, medicines for numerous ailments and also the deadliest of poisons. It is a stimulating and challenging exercise to determine the molecular structures of various substances and to relate them to their properties. From a chemical point of view, even poisonous compounds are interesting.

The most venomous substances associated with snakes, scorpions, and even some bacteria and plants have a common structural feature. These compounds are in fact proteins. However, many non-peptide toxins are also known. Palytoxin was considered the most toxic of such compounds till recently. It is one of several poisonous marine natural products. A compound named tetrodotoxin, found in puffer fish, is another well known example. It was shown to be the culprit in numerous cases of food poisoning associated with consumption of sea food. The molecule which should perhaps head the list of deadly natural toxins is maitotoxin, named after the Tahitian fish maito.

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Maitotoxin was first discovered in 1976 from the surgeon fish *Ctenochaetus striatus*. It has also been isolated from cultured cells of *Gambierdiscus toxicus* and has been purified using HPLC.[1] Toxicological investigations and physicochemical studies to determine the molecular structure have been carried out on purified samples. Maitotoxin turns out to be remarkable both for its structure and its biological activity.

[1] High performance liquid chromatography is an excellent procedure to separate components from a mixture. It is an essential tool in natural products research.

Maitotoxin is lethal. In the units normally used to specify toxicity, the LD_{50} value (lethal dose to kill 50% of subjects) is 50 nanogram (10^{-9}g) per kilogram of mice. Since a mouse usually weighs no more than 20 g, one can state the result of the experiment in a macabre fashion: a gram of maitotoxin can kill approximately half a billion mice! No non-peptide natural product has such lethal potency.

Even to the chemists who abhor violence, maitotoxin is appealing for a different reason. It is the largest molecule made by nature, leaving aside bio-polymers like polypeptides and polysaccharides. The molecular weight of maitotoxin is 3422 Daltons.[2] Thus, the molecule currently holds two world records: it is the largest non-biopolymeric natural product and the most lethal non-peptide natural product.

[2] One atomic unit of mass is called a Dalton.

The full 3-dimensional structure of maitotoxin has not yet been solved using X-ray crystallography. But the basic molecular skeleton as well as the complete stereochemistry (relative disposition of atoms at chiral centres) have been fully worked out. Using infrared, ultraviolet and mass spectra, many key features of the structure were determined. More details of the structure could be obtained only through nuclear magnetic resonance spectroscopy, especially through extensive two-dimensional (2D) NMR techniques. Molecular mechanics calculations were also imaginatively used to interpret the coupling constant patterns as well as Nuclear Overhauser Effect data.[3] It is truly a triumph of modern spectroscopic methods that the stereo-structure of a molecule with such complexity can be solved.

[3] Vicinal coupling constants are related to H-C-C-H dihedral angles through a simple expression called Karplus equation. NOE data provide information about distances between non-bonded hydrogen atoms.

The gross structure of maitotoxin is shown in *Figure* 1. The molecule contains numerous fused saturated rings. To keep track of different portions of structures of polycyclic molecules, organic chemists usually label the rings A, B, C, etc. The rings in maitotoxin exhaust the English alphabets and so the labelling has to go beyond Z to A', B' and so on up to F'. Note the presence of numerous oxygen atoms. There are 32 ether linkages and 28 hydroxyl groups. These are evidently involved in the interactions of the molecule with cations. It is not a coincidence that the biological activity of maitotoxin is linked to its ability to elevate intracellular Ca^{2+} concentration. The molecule is likely to be an excellent model for probing cellular events associated with Ca^{2+} flux.

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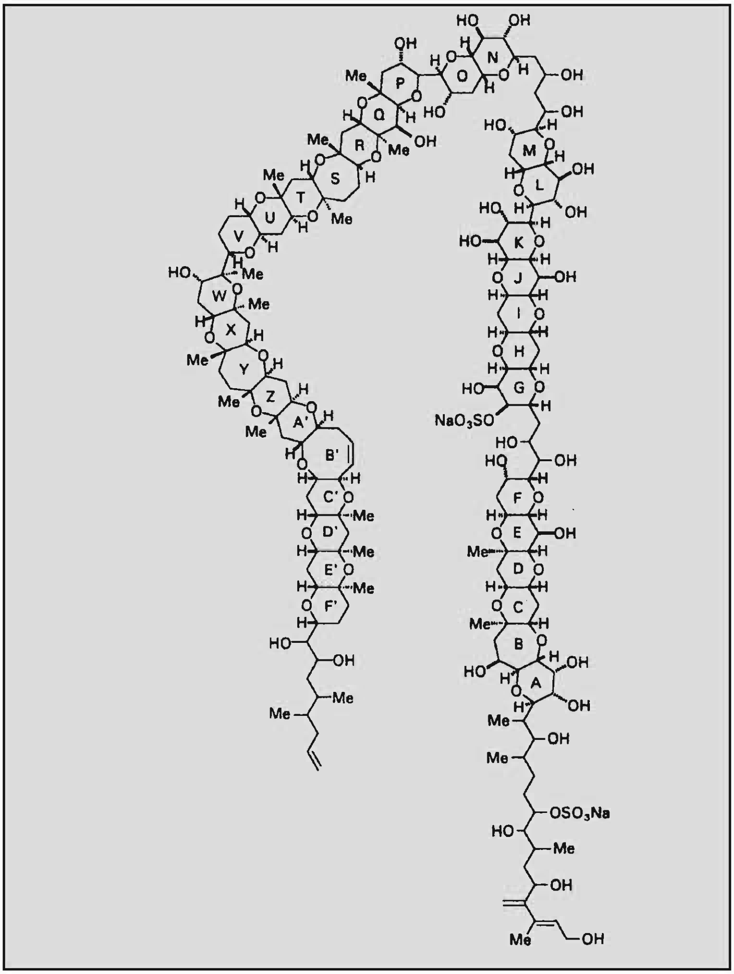

Figure 1. Molecular structure of maitotoxin. Not all stereochemical relationships are shown.

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