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LETTER TO THE EDITOR

NATURAL PHOSPHOR ESTER CHOLINESTERASE INHIBITORS

It was with great interest and pleasure that I read the contribution of Patocka et al. in the MMSL reviewing the literature on anatoxin-A(s) an Organophosphorus Cholinesterase Inhibitor (OP) of natural origin produced by cyanobacteria (formerly identified as algae). Anatoxin-A(s), a phosphate ester of imidazole (Figure 1), is a very interesting substance that lacking the ability to cross the blood-brain-barrier selectively and irreversibly inhibits the cholinesterases in the periphery.

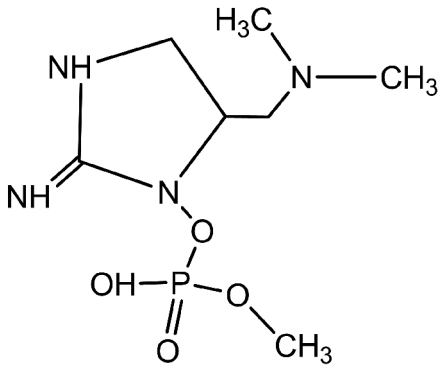

Figure 1. Anatoxin-A(s) an Organophosphorus Cholinesterase Inhibitor (OP) of natural origin produced by cyanobacteria.

The authors conclude their review with the statement that "*anatoxin-A(s) is the only known natural OP*" [Patocka et al, 2011].

On this particular detail the authors err: while anatoxin-A(s) ability to inhibit cholinesterase was first suggested 1986 by Mahmood & Carmichael and confirmed by the same authors one year later [Mahmood & Carmichael, 1986; 1987], there are (at least) two other natural OPs identified: cyclophostin and ulosantoin.

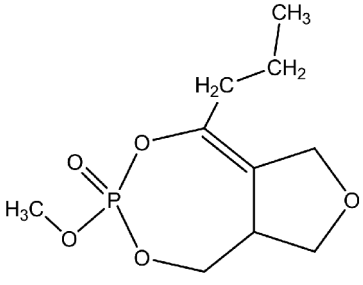

Figure 2a. CGA 134-735: propyl substituted furo-dioxa-phosphepin with an IC_{50} for AChE of ≈500 nM

Cyclophostin:

Neumann & Peter working for (what was then known as Ciba-Geigy) in Switzerland isolated from cultures of Streptomyces antibioticus two related furo-dioxa-phosphepin organo-phosphorus cholinesterase inhibitors (dubbed CGA 134-735 & 134-736) (Figure 2) [Neumann & Peter, 1987].

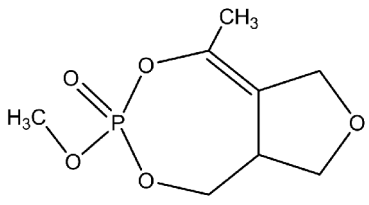

Figure 2b. CGA 134-736: methyl substituted furo-dioxa-phosphepin with an IC_{50} for AChE of ≈100 nM

Kurokawa and others later isolated related compounds from Streptomyces lavendulae and they named the methyl substituted compound cyclophostin [Kurokawa et al, 1993]. The mechanism of cholinesterase inhibition by cyclophostin and related compounds and the difficulties in enzyme reactivation when using pyridinium oximes have been recently described in detail [Dutta et al, 2010].

Uloasantoin:

More recently Van Wagenen et al. isolated from the marine sponge Ulosa ruetzleri a phosphor ester hydantoin derivative which they named ulosantoin (Figure 3). The compound has, according to the authors an AChE inhibitory potency comparable to that of paraoxon [Van Wagenen et al, 1993].

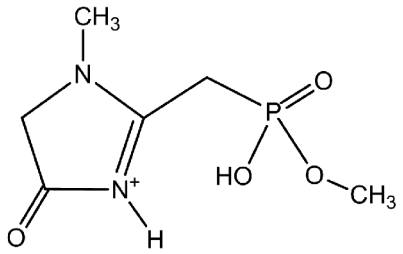

Figure 3. Ulosantoin, (*ulo*sa hyd*antoin*) isolated from the marine sponge Ulosa ruetzleri

While men made organophospahtes were synthesized by the middle of the XIXth century (Voegeli, Moschnine and de Clermont) Nature created them much earlier [Petroianu 2008, 2009].

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