The Natural Occurrence of Pyrithione (PT) Antimicrobials

World's Most Popular Anti-microbial agent

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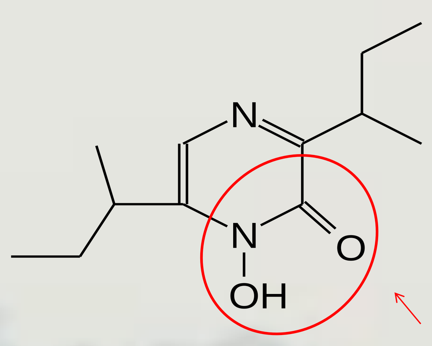
Pyrithione (PT)[1] molecule was first synthesized in 1947 by OLIN-Squibb chemists as a promising anti-biotic drug candidate. To-day pyrithione compounds (sodium, zinc and copper) are used globally in preservation of fluids; as the "gold-standard" in anti-dandruff shampoos; and as the preferred TBTO replacement in marine antifouling paints; as well as mildewcides in wallboards, in-can and dry-film preservatives in architectural paints; and for odor control in textiles etc. because of their broad spectrum of efficacy and proven ability to prevent the growth of microorganisms. A recent literature search showed 6082 references (patents and publications: 671 in hair care, 162 in bio-fouling, and many other applications) for PT molecules. Industrially produced PT antimicrobials have been successfully used for over 50 years. The most well known pyrithione, ZnPT, is a safe and effective OTC anti-dandruff agent (recognized by USFDA as Category I, GRAS and GRAE). Many other unexploited applications like control of malaria parasite (*Plasmodium*)[2], treatment of nail fungus[3], hand-sanitization etc. can only increase the potential of this molecule to protect and benefit mankind. Several scientific studies[4] have shown that pyrithione compounds are non-persistent and degrade rapidly in the environment through biotic and abiotic pathways to non-toxic terminal metabolites. In the past decade, there have been isolated reports[5] from China that a certain plant that grows wildly in Hainan and Guangdong province (*Polyalthia nemoralis*) and used extensively as a herbal remedy for many human afflictions contains significant amounts of pyrithione compounds. This poster presents unequivocal evidence for pyrithione compounds as active principles in the extracts from the roots of *Polyalthia nemoralis.* Pyrithione compounds have also been reported as minor constituents in extracts of other plant species such as *Allium stipitatum* Regel[6] - an ornamental plant in EU and in a New Zealand *Basidomycete* (Mushroom) – *Cortinarius*[7] species, thereby providing additional corroboration for the "Natural" occurrence of PT antimicrobials. The industrially produced and commercially sold PT compounds can therefore be considered "Nature identical".

Aspergillic acid (a hydroxamic acid)

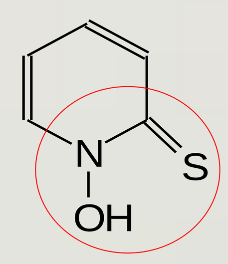
-an antibiotic substance produced by *Apergillus flavus*



Hydroxamic acid moiety

Discovery by OLIN-Squibb, 1947[1]

Pyrithione (a thiohydroxamic acid)

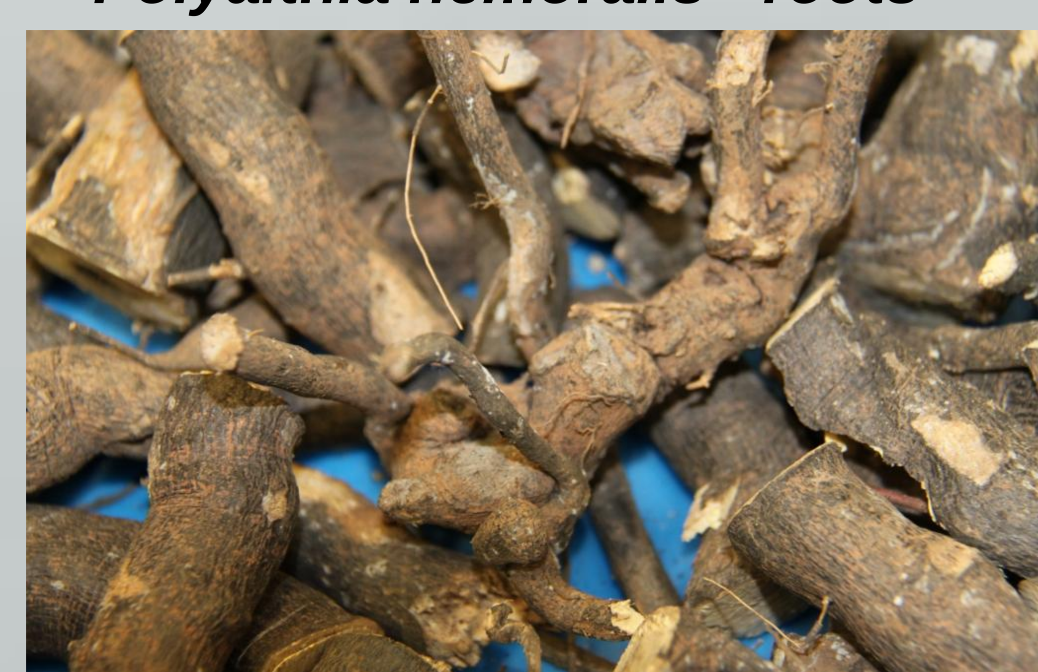


Thiohydroxamic acid moiety

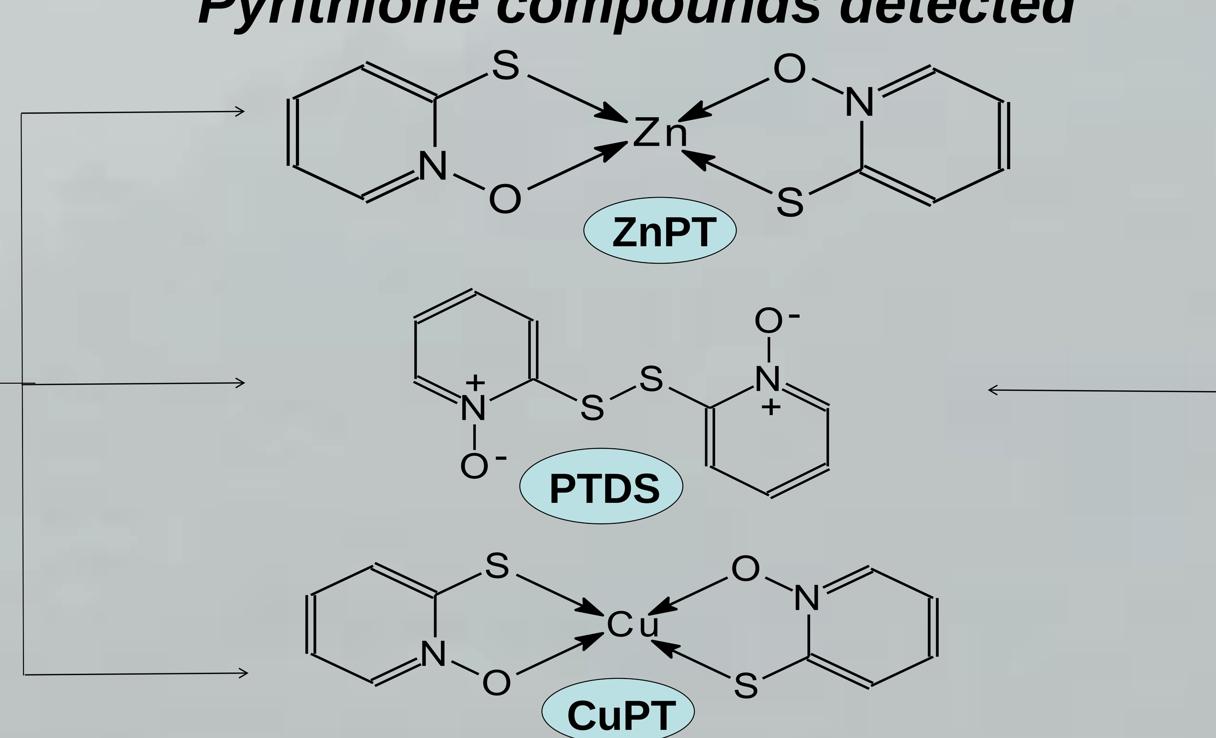
The antibiotic potential of aspergillic acid prompted the Squibb researchers to synthesize a thiohydroxamic acid compound (parent compound – Pyrithione). While it did not show enhanced anti-biotic properties, it exhibited broad spectrum anti-microbial activity vs. bacteria, fungi and yeasts

Polyalthia nemoralis

Polyalthia nemoralis - roots



Pyrithione compounds detected



From Bulbs

Allium stipitatum Regel

From fruiting bodies

Cortinarius spp. Mushroom

P. nemoralis extracts: LC/MS comparison vs. PT std.

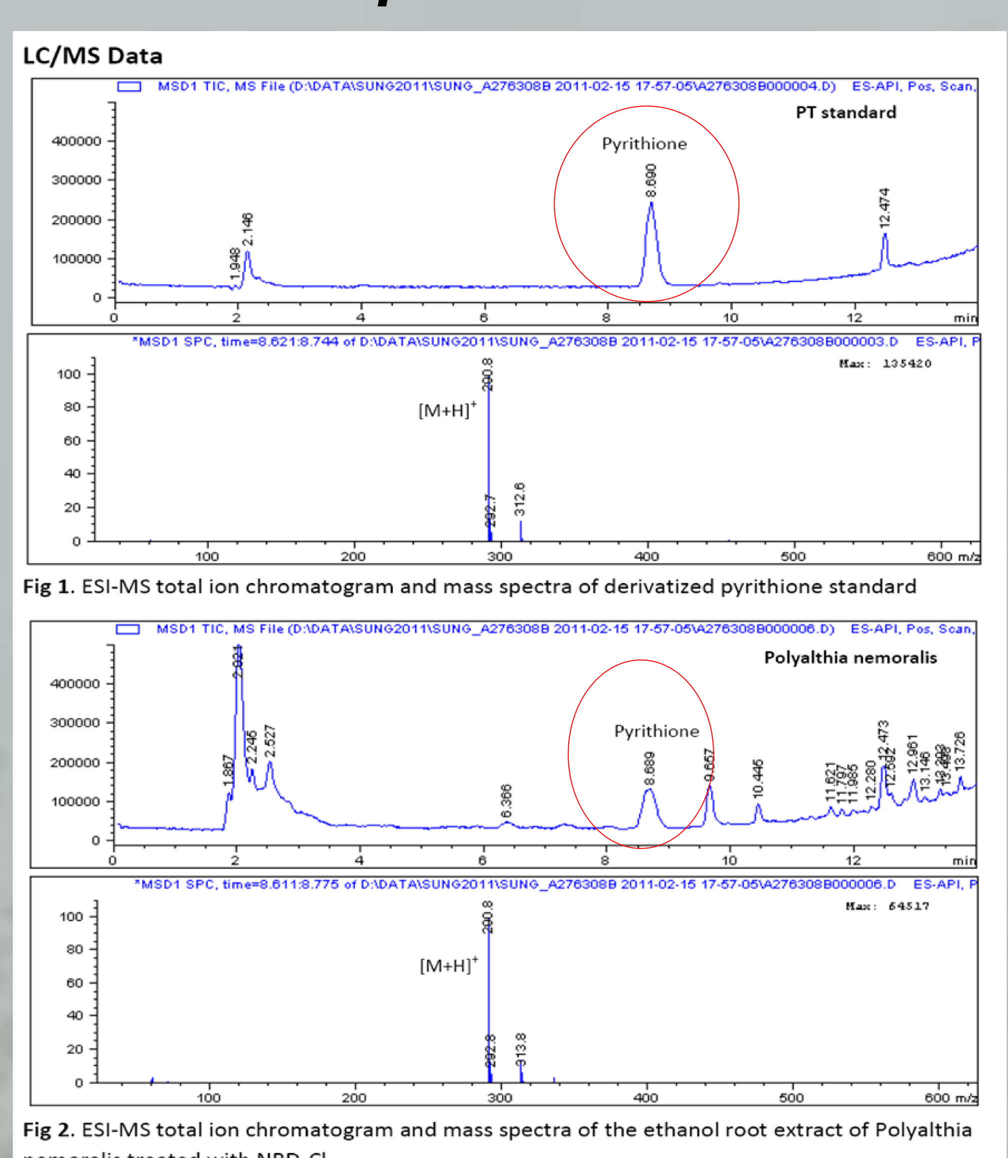


Fig 1. ESI-MS total ion chromatogram and mass spectra of derivatized pyrithione standard

Fig 2. ESI-MS total ion chromatogram and mass spectra of the ethanol root extract of Polyalthia nemoralis treated with NBD-Cl

P. nemoralis extract: Microbiology – MIC vs. ZnPT

Micro-organism	*P. nemoralis* extract	ZnPT
Staphylococcus aureus (6538)	39.1 (**1.13**)*	**2.44**
Klebsiella pneumoniae (4352)	78.1 (**2.26**)	**2.44**
Pseudomonas aeruginosa (9027)	625 (**18.06**)	**39.1**
Pseudomonas aeruginosa (15442)	1250 (**36.13**)	**39.1**
Escherichia coli (10536)	78.1 (**2.26**)	**2.44**
Enterobacter gergoviae (33028)	78.1 (**2.26**)	**2.44**
Bacillus subtilus (6633)	19.5 (**0.56**)	**1.22**
Aureobasidium pullulans (9348)	78.1 (**2.26**)	**1.22**
Gliocladium virens (9645)	313 (**9.03**)	**19.5**
Penicillium pinophilium (11797)	< 4.88 (**0.14**)	**< 0.31**
Paecilomyces sp.	156 (**4.52**)	**9.77**
Candida albicans (10231)	78.1 (**2.26**)	**4.88**
LB penecillium sp.	< 4.88 (**0.14**)	**< 0.31**
Aspergillus niger	313 (**9.03**)	**4.88**

* Numbers in parenthesis represent concentration of total pyrithione(s)

P. nemoralis extract: 1H –NMR

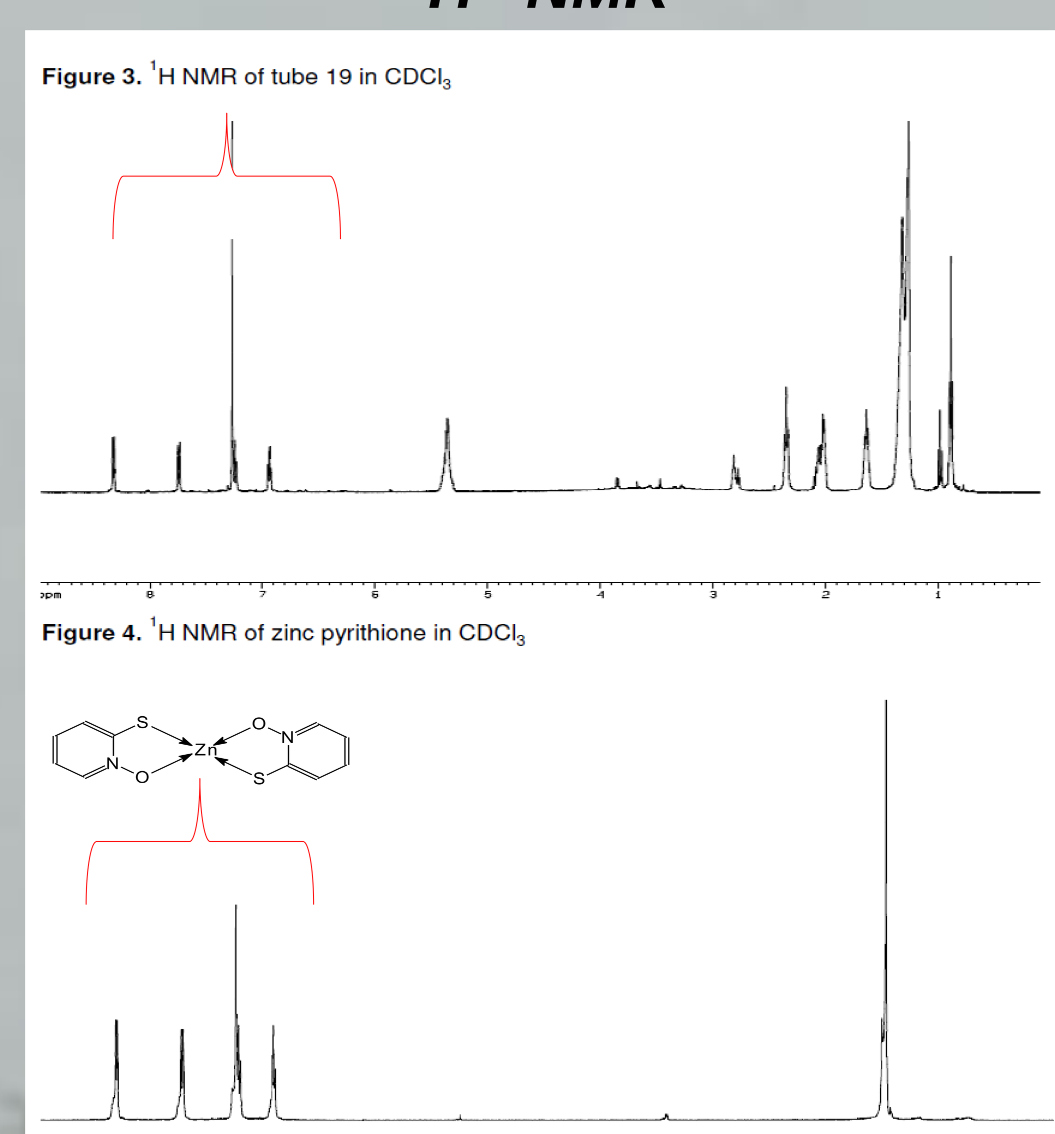


Figure 3. ^{1}H NMR of tube 19 in CDCl$_3$

Figure 4. ^{1}H NMR of zinc pyrithione in CDCl$_3$

21.4 mg of the enriched PT mixture can be obtained from 10 g of raw plant root material. The purity was estimated to be approximately 50%, therefore PT is present as 0.1% of the dried plant material.

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The background on this poster shows the Hainan-China forest where *Polyalthia nemoralis* plant was harvested – picture by J. Zhang.
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