Phosphonoxins: Novel Phosphonate Analogs of Antifungal Polyoxins

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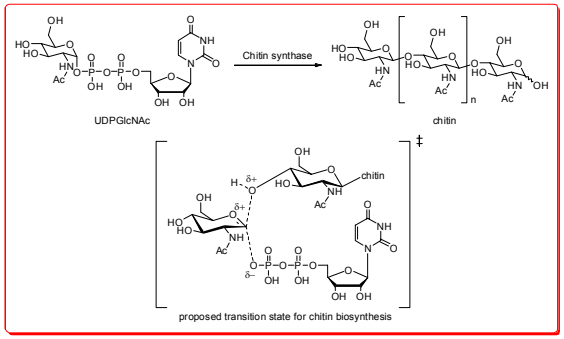
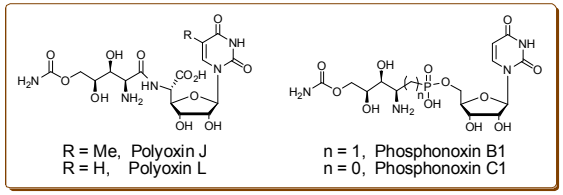
Background: Chitin

- Chitin is an essential component of the cell walls of nearly all zoopathogenic and phytopathogenic fungi.
- Chitin or a chitin-like polysaccharide is also essential for arthropods, ascarids and many protozoans.[1]
- Biosynthesis of this polysaccharide is catalyzed by chitin synthase using uridine diphosphoryl-N-acetylglucosamine (UDP-GlcNAc) as the glycosyl donor.[2]
- The protozoal parasite *Giardia lambila*, a common cause of diarrhea, manufactures a chitin-like polysaccharide, β-1-3-linked poly(N-acetylgalactosamine), for its cyst wall via a mechanism analogous to chitin biosynthesis.[3]
- **Inhibitors of chitin synthase are likely to be broad spectrum antifungal and antiparasitic agents.**

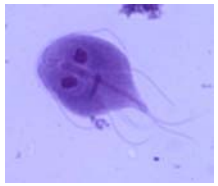


Polyoxins and Phosphonoxins

- Polyoxins are a class of natural product peptidyl nucleosides isolated from *Streptomyces cacoi*.[4]
- Polyoxins are known to have high antifungal activity due to their inhibition of chitin synthase, but the clinical utility of these compounds is compromised by their poor bioavailability and metabolic instability.[5]
- We have recently synthesized new class of compounds, called phosphonxins, which resemble the polyoxins but substitute the peptide linkage with a phosphonate linkage to the nucleoside.
- The phosphonate moiety of the phosphonoxins is designed to mimic the transition state of chitin biosynthesis and is chemically and metabolically stable.

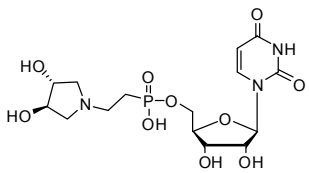


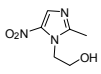
Giardia Lamblia Trophozoite



Giardia Lamblia Cyst

Phosphonoxin A: A simplified polyoxin analog with anti-Giardia activity[6]



Compound	Giardia MIC (μM)	MDBK Cell tox IC50 (μM)	Therapeutic index	*Giardia* cyst formation percent of control
Phosphonoxin A	**0.48**	**>250**	**>520**	**5.73**
 Metronidazole	5			13.7

- Phosphonoxin A displayed greater activity at inhibiting *Giardia* growth and cyst wall formation than the standard drug, Metronidazole, *in vitro*.[6]
- Biological activity studies of phosphonoxins B1, B2, B3 and C1 will be performed in due course.

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Synthesis of Phosphonoxins B1, B2, B3[7] and C1