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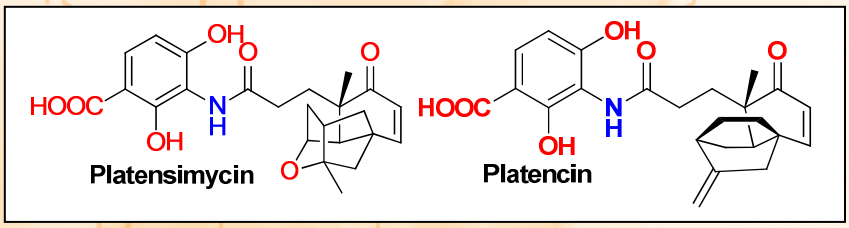
Platensimycins

Novel Structures

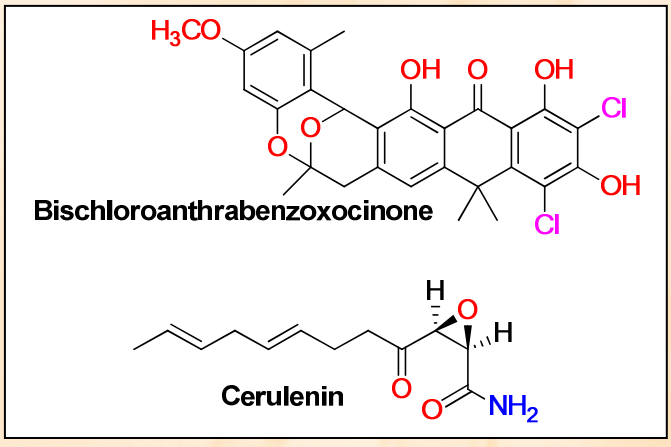
In 2006 Singh and colleagues at Merck published the *Streptomyces platensis* metabolite **platensimycin -** a novel antibiotic with a highly selective mode of action and activity against antibiotic resistant bacteria. The publication was heralded with considerable fanfare and commentary by the journal, Nature.



Platensimycin was the product of a screening program targeting bacterial fatty acid synthesis (FAS). The screening strategy was based on the differing pathways of FAS in mammals (type I) and bacteria (type II) providing an "absolute" selectivity between host and pathogen. **Platensimycin** was found to selectively target *β*-ketoacyl-(acyl-carrier-protein (ACP)) synthase I/II (FabF/B).

Platencin, a more hydrophobic analogue, was later published with a similar but broader mode of action, as it inhibited FabF/B and also, FabH, another enzyme in the pathway. Both metabolites were potent antibiotics against G+ve and G-ve bacteria and had activity against MRSA and vancomycin resistant enterococci (VRE).

Interestingly, **platensimycin** was not the first reported inhibitor of the FabF/B pathway. In 2005 Singh's group reported **bischloroanthrabenzoxocinone** (**BABX**) as a moderate inhibitor of the elongation phase, sharing the same biochemical profile as **cerulenin**, another inhibitor of FabF/B.



Like **platensimycin**, **BABX** was a broad spectrum antibiotic with potent G+ve and G-ve activity. Not long after, the same group demonstrated that **BABX** and related metabolites inhibited binding to the Liver X receptor, an integral component of cholesterol homeostasis, suggesting that these metabolites are designed by nature to regulate lipids via a multi-locus strategy.

Perhaps counter-intuitively, **platensimycin** has now been demonstrated to inhibit mammalian FASI, specifically hepatocyte fatty acid synthesis and oxidation. So in an interesting twist, this new generation antibiotic is now under consideration as a therapeutic lead for diabetes and metabolic disorders.

1. Platensimycin is a selective FabF inhibitor with potent antibiotic properties. Wang, J. et al., *Nature* **2006**, 441, 358.
2. Isolation, structure, and absolute stereochemistry of platensimycin, a broad spectrum antibiotic discovered using an antisense differential sensitivity strategy. Singh S. B. et al. *J. Am. Chem. Soc.* **2006**, 128, 11916.

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3. Isolation and structure of platencin: A FabH and FabF dual inhibitor with potent broad-spectrum antibiotic activity. Jayasuriya H. et al. *Angew. Chem. Int. Ed.* **2007**, 46, 4684.
4. Discovery of platencin, a dual FabF and FabH inhibitor with *in vivo* antibiotic properties. Wang J. et al. *PNAS* **2007**, 104, 7612.
5. Determination of selectivity and efficacy of fatty acid synthesis inhibitors. Kodali S. et al. *J. Biol. Chem.* **2005**, 280, 1669
6. Antidiabetic and antisteatotic effects of the selective fatty acid synthase (FAS) inhibitor platensimycin in mouse models of diabetes. Wu M. Et al. *PNAS* **2011**, 108, 5378.

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