Total biosynthesis and structural diversification of fungal indole diterpene lolitrems

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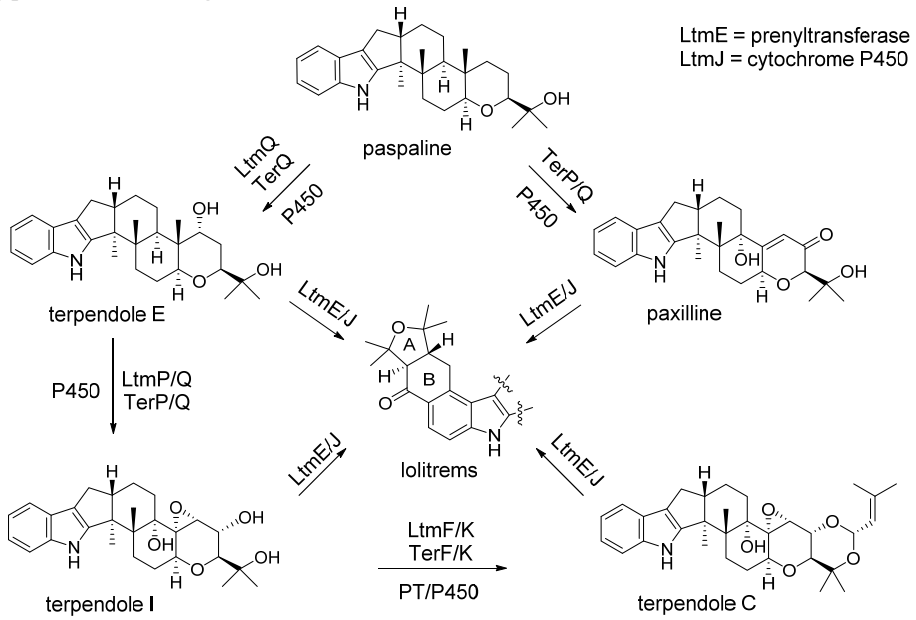
Indole-diterpenes (IDTs) with paspaline scaffold are one of important class of fungal secondary metabolites with various biological activities. Among them, lolitrem B is a potent tremorgenic mycotoxin[1] that isolated from *Epichloë festucae var. lolii* infected perennial ryegrass *Lolium perenne*.[2] The unique 5/6 bicyclic system (AB rings) of lolitrem B is predicted to be constructed by prenyltransferase LtmE and cytochrome P450 LtmJ,[3] but the detailed mechanism have not been elucidated yet. In addition, A/B rings are found to be a common feature in the lolitrem family with different indole diterpene cores, indicating a broad substrate specificity of LtmEJ.

By employing a combination of *Aspergillus oryzae* expression system and CRISPR/Cas9-mediated genome editing techniques[4], we successfully reconstituted the biosynthetic pathway for terpendoles and lolitrems. Moreover, *in vivo* biotransformation experiments revealed a three-step oxidative cyclization catalyzed by P450 LtmJ via an epoxyalcohol intermediate.[5] Further bioconversion experiments with several substrates confirmed the high substrate tolerance of LtmEJ and suggested the potential for the semi-synthesis of unnatural type lolitrem analogues.



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