Synthesis and biological evaluation of Ko143 derivatives

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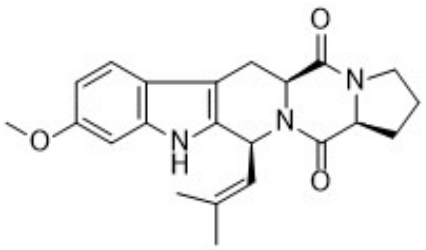
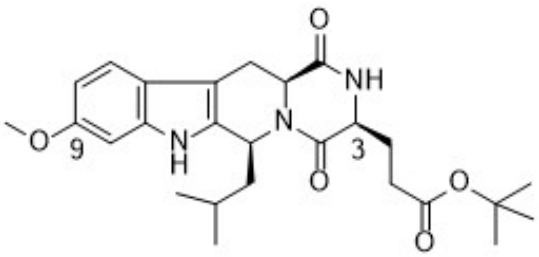
Fumitremorgin C (FTC) is a natural product produced by the fungus *Aspergillus fumigatus* that was first isolated in 1977 by Clardy. The compound is a potent and partly selective inhibitor of the ABCG2 transporter, but it also exhibits profound neurotoxicity. Ko143 is a synthetic analog of FTC, which is not neurotoxic, but retains the ABCG2-inhibitory capacity of the naturalproduct.[1] Over the course of this project, several analogues of Ko143 with modifications at positions 3 and 9 of the tricyclic scaffold as well as a ring expanded analogue were synthesized. Moreover, a new and more efficient synthesis of Ko143 and fumitremorgin C was developed. This involves an improved route to the 6-methoxytryprophan building block, a stereoselective reduction of an imine-intermediate and a more efficient approach to amide bond formation.

The biological activity of the Ko143 analogs was evaluated in an ATPase assay in proteoliposomes incorporating recombinant ABCG2. Several analogs with potencies similar to or potentially better than that of Ko143 have been identified. More recently the compounds have also been assessed in a proliferation assay in PC-9 cells in combination with the EGFR kinase inhibitor gefitinib.



Fumitremorgin C



Ko143

[1] Li Yuexian, Hayman Eric, Plesescu Mihaela, Prakash Shimoga, *Tetrahedron Letters* **2008**, *49,* 1480-83.