# Developement of Metalloproteinase Inhibitors from a Fungal Metabolite, Gelastatin

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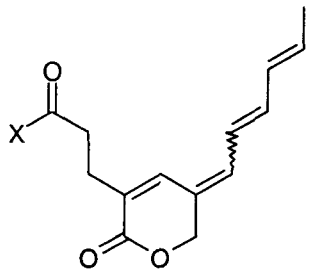
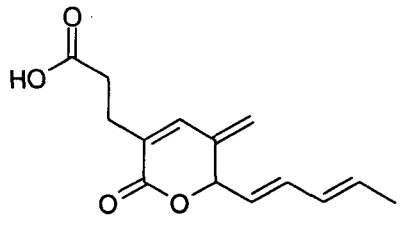
Gelastatins (1) were isolated in 1997 as a mixture of two olefinic stereoisomers from the culture broth of *Westerdykella multispora* F50733 found in Korean soil sample[1] and later found to be attainable from more abundant related natural product Dykellic acid[1] through acid catalyzed rearrangement during isolation. Stereo-isomers of gelastatins (gelastatin A and gelastatin B) were separable by LC but readily isomerized back to the same mixture of isomers and slowly decomposed in the air at room temperature. Gelastatins were found to exhibit impressive biological activities, including inhibition of gelatinase A (MMP-2) and inhibition of tumor necrosis factor-α converting enzyme (TACE)[2] that plays important roles in a number of inflammatory and degenerative diseases including rheumatoid arthritis, stroke, multiple sclerosis, tumor invasion, and metastasis.[3]



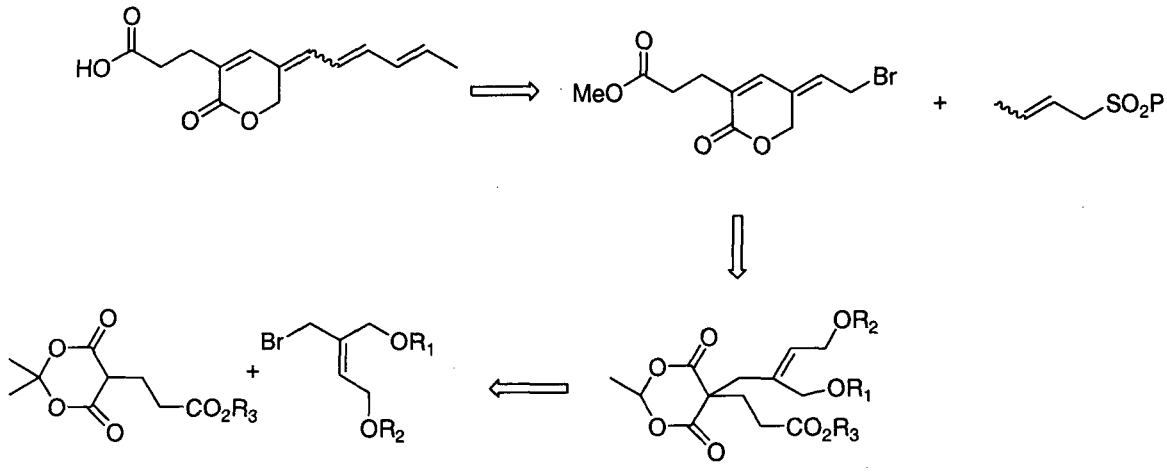

Gelastatin X=OH (**1**)
Gelastatin Hydroxamate X=NHOH (**2**)




Dykellic acid (**3**)

To study the biological activities of gelastatins and their hydroxamate analogs in detail, gram quantity of gelastatins were required and the natural source could not provide enough quantity of gelastatins. Furthermore, gelastatins and their hydroxamate analogs were not good inhibitors of TACE. Then we started the research on the practical synthesis of gelastatins and the design of compounds with better stability and better activity against TACE.

We were able to devise a total synthesis of gelastatins[4] practical enough to provide gram quantities of the material after exploring five different synthetic routes.



At the same time, we were able to find compounds with the improved activity and selectivity for TACE through extensive modification of the core structure of gelastatins. In this seminar, the design, synthesis and the biological activity of gelastatin analogs for TACE will be presented and a molecular modeling approach to the binding mode of the newly synthesized compounds will be discussed.

**References and notes**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