

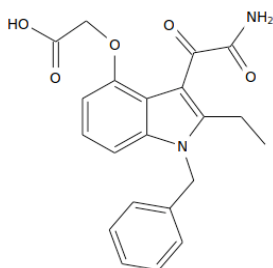
Secreted Phospholipase A₂ Inhibitors

*Nathan Cermak and Michael H. Gelb**

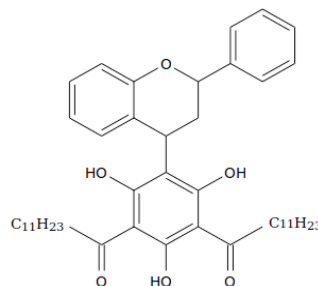
Department of Chemistry, University of Washington, Seattle, WA

Secreted phospholipases A₂ (sPLA₂s) are a family of enzymes which catalyze the hydrolysis of glycerophospholipids at the sn-2 position. Of primary interest is the release of arachidonic acid, a precursor to a wide variety of inflammatory mediators known as eicosanoids (including prostaglandins and leukotrienes).¹ Nine different sPLA₂s have been shown to be expressed in humans, but the biological functions of these enzymes are not well known. Several are suspected to be involved in a variety of diseases, including atherosclerosis, asthma and arthritis.^{1,2} For this reason there has been much interest on sPLA₂ inhibitors as drugs – Eli Lilly did a large amount of work on this in the 1980s, followed recently by Anthera Pharmaceuticals, which currently has an sPLA₂ inhibitor in phase III clinical trials for atherosclerosis.³

My work has focused on developing highly specific and potent inhibitors for sPLA₂ enzymes. I have worked on a series of indole-based inhibitors⁴ similar to **A**, and am currently working on a series of trihydroxytoluene compounds derived from the lower half of YM-26734, a potent sPLA₂ inhibitor shown below (**B**). After synthesis and purification, the derivatives will be tested in an *in vitro* fluorometric assay to determine potency, and then also tested in cells which naturally express various sPLA₂s. So far, this trihydroxytoluene-based class of inhibitors appear to be highly selective on one group of sPLA₂s (IIA), and preliminary results suggest they effectively inhibit sPLA₂ activity in rat areolar fibroblasts (L929 cells).



A



B

References:

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