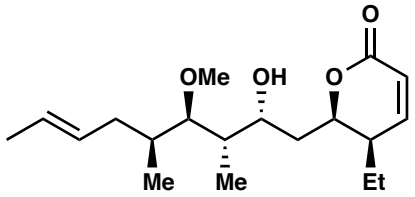
Strategies for the Development of Pironetin Chemotherapeutics

Sara K. Coulup, Henry L. Wong, and Gunda I. Georg
Department of Medicinal Chemistry, University of Minnesota, Minneapolis, MN, 55455

The natural product pironetin (**1**) displays potent cytotoxic activity against ovarian cancer cells both sensitive and resistant to first-line chemotherapeutics such as paclitaxel and cisplatin.[1] Pironetin covalently binds with α-tubulin, whereas all tubulin-binding agents currently approved by the FDA target β-tubulin.[2] α-Tubulin is therefore an attractive alternative drug target that would address the critical need for new treatments for drug-resistant ovarian cancers. Despite the potent *in vitro* activity, pironetin was only marginally effective in the single reported *in vivo* study, which resulted in severe weight loss in the mice, indicating poor pharmacokinetic/pharmacodynamic (PK/PD) properties as well as off target toxicities.[3] In order to address these concerns, we have identified pironetin's major sites of metabolism and are engaged in the total synthesis of analogs with predicted improved metabolic stability.



Pironetin (1)

1. Marco, J. A.; Garcia-Pla, J.; Carda, M.; Murga, J.; Falomir, E.; Trigili, C.; Notararigo, S.; Diaz, J. F.; Barasoain, I., *Eur. J. Med. Chem.* **2011,** *46* (5), 1630-1637.
2. Yang, J.; Wang, Y.; Wang, T.; Jiang; J.; Botting, C. H.; Liu, H.; Chen, Q.; Yang, J.; Naismith, J. H.; Zhu, X.; Chen, L., *Nat. Comm.* **2016,** *7*, 1-9.
3. Kondoh, M.; Usui, T.; Kobayashi, S.; Tsuchiya, K.; Nishikawa, K.; Nishikiori, T.; Mayumi, T.; Osada, H., *Cancer Lett.* **1998,** *126* (1), 29-32.