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. Pironetin covalently binds α-tubulin, whereas all microtubule targeting agents currently approved by the FDA target β-tubulin. It has recently been shown that the gene encoding an isoform of α-tubulin (TUBA3C) is overexpressed in ovarian cancers and is associated with increased resistance to first line chemotherapeutics and shorter survival time, supporting α-tubulin as an attractive alternative 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 at high doses in mice and resulted in severe weight loss, indicating poor pharmacokinetic/pharmacodynamic (PK/PD) properties as well as off target toxicities. In an effort to address these concerns, we found that pironetin has a short half-life (< 7 minutes) in liver microsomes, identified pironetin’s major sites of metabolism, and confirmed the identity of the major metabolite through semi-synthesis. We are now engaged in the total synthesis of analogs which demonstrate improved PK/PD properties, highlighting the potential of metabolically stabilized pironetin analogs as novel anti-tubulin agents for resistant ovarian cancers.