Autotaxin (ATX) is a secreted glycoprotein with lysophospholipase D (LPLD) activity that generates the bioactive lipid lysophosphatidic acid (LPA) from lysophosphatidylcholine (LPC). Both ATX and LPA have been linked to the promotion and progression of cancer, as well as cardiovascular disease, neuropathic pain, and obesity. Despite the fact that ATX inhibitors have the potential to be useful chemotherapeutics for multiple indications, few examples of potent, drug-like ATX inhibitors are described in the current literature. Structure-based screening against a comparative model produced the first published non-lipid ATX inhibitors. These allowed the development of a binary QSAR model to rapidly prioritize additional candidate inhibitor selection. ATX inhibitors identified using these early computational tools fueled database mining using pharmacophore models. These methods together have successfully contributed to the identification of small, drug-like, and structurally diverse ATX inhibitors with sub-micromolar Ki values.