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Discovery and synthetic optimization of a novel scaffold for hydrophobic tunnel-targeted autotaxin inhibition

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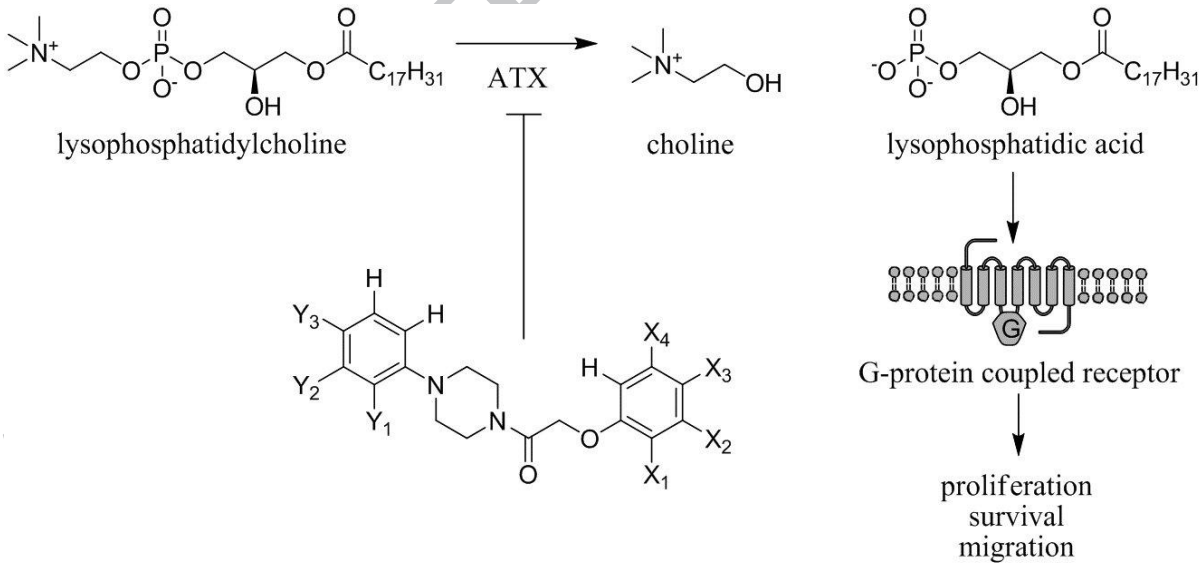
Abstract

Autotaxin (ATX) is a ubiquitous ectoenzyme that hydrolyzes lysophosphatidylcholine (LPC) to form the bioactive lipid mediator lysophosphatidic acid (LPA). LPA activates specific G-protein coupled receptors to elicit downstream effects leading to cellular motility, survival, and invasion. Through these pathways, upregulation of ATX is linked to diseases such as cancer and cardiovascular disease. Recent crystal structures confirm that the catalytic domain of ATX contains multiple binding regions including a polar active site, hydrophobic tunnel, and a hydrophobic pocket. This finding is consistent with the promiscuous nature of ATX hydrolysis of multiple and diverse substrates and prior investigations of inhibitor impacts on ATX enzyme kinetics. The current study used virtual screening methods to guide experimental identification and characterization of inhibitors targeting the hydrophobic region of ATX. An initially discovered inhibitor, GRI392104 (IC_{50} 4 μM) was used as a lead for synthetic optimization. In total twelve newly synthesized inhibitors of ATX were more potent than GRI392104 and were selective for ATX as they had no effect on other LPC-specific NPP family members or on LPA_{1-5} GPCR.



Keywords: autotaxin; structure-activity relationship; pharmacophore