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# Producing selective inhibitors against Phospholipase D isoforms

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This work describes the development of a chemical library which was used to screen for inhibitors of the target protein Phospholipase D. The strategy of improving isoform selectivity of the inhibitors is reported as well as the principle of confirming the *in vitro* results *in vivo*.

## 紹介論文

Design of isoform-selective phospholipase D inhibitors that modulate cancer cell invasiveness

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## 要旨

Phospholipase D (PLD) is an essential enzyme responsible for the production of the lipid second messenger phosphatidic acid. Phosphatidic acid participates in both G protein–coupled receptor and receptor tyrosine kinase signal transduction networks. The lack of potent and isoform-selective inhibitors has limited progress in defining the cellular roles of PLD. We used a diversityoriented synthetic approach and developed a library of PLD inhibitors with considerable pharmacological characterization. Here we report the rigorous evaluation of that library, which contains highly potent inhibitors, including the first isoform-selective PLD inhibitors. Specific members of this series inhibit isoforms with 4100-fold selectivity both in vitro and in cells. A subset of inhibitors was shown to block invasiveness in metastatic breast cancer models. These findings demonstrate the power of diversity-oriented synthesis combined with biochemical assays and mass spectrometric lipid profiling of cellular responses to develop the first isoform-selective PLD inhibitors—a new class of antimetastatic agents.

## 参考論文

1. Signalling roles of mammalian phospholipase D1 and D2. Cockcroft, S., *CMLS, Cell. Mol. Life Sci.* 58 (2001) 1674-1687