



## Increasing absorption of hydrophilic drugs by phospholipase

### C inhibition



The preferred route of therapeutic drug administration is orally. However, hydrophilic drugs often have poor oral bioavailability due to their inability to cross the intestinal epithelium. The absorption of hydrophilic drugs can be improved by transiently disrupting tight junctions in the intestinal epithelium to increase paracellular flux. Currently available compounds that increase paracellular flux are toxic and therefore have not been able to be used clinically. Screening compounds that inhibit phospholipase C (PLC) should allow for the identification of compounds that have both high potency in increasing paracellular flux and are minimally toxic.

### Benefits

- PLC is a novel drug target for enhancers of paracellular drug flux.
- Inhibiting PLC would increase the oral bioavailability and therefore efficacy of many hydrophilic drugs.
- PLC inhibitors that increase the ability of therapeutic drugs to get through the blood-brain barrier would have significant clinical applications.



## For More Information

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## The Technology

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Poor absorption of hydrophilic drugs across the intestinal epithelium is a major clinical problem. Drugs are unable to cross the intestinal epithelium due to tight junctions which obstruct paracellular flux. Currently available compounds that improve paracellular flux by opening tight junctions are either not very potent or are toxic. PLC is involved in the regulation of tight junctions. Three classes of PLC inhibitors appear to increase the opening of tight junctions by inhibiting PLC. These compounds could have clinical relevance due to their ability to increase the absorption of hydrophilic drugs across the intestinal epithelium.

Three classes (alkylphosphocholines, 3-nitrocoumarines, and N-alkylsuccinimido steroid derivatives) of PLC inhibitors have been found to have the potential to increase paracellular flux of drugs by opening tight junctions. The potency of alkylphosphocholines as enhancers of tight junction permeability is strongly correlated with its ability to inhibit PLC. In studies of these compounds in *in vitro* models of the intestinal epithelium, PLC was found to regulate tight junctions by affecting actin filament organization. Inhibitors of PLC were found to increase tight junction permeability by causing actin filament disorganization.

Identification of inhibitors of PLC presents an ideal target for the production of drugs that increase intestinal absorption of hydrophilic drugs. Additionally, PLC inhibitors may be used to enhance the ability of neurological therapeutic drugs to cross the blood brain barrier.

## Opportunity

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