

## Development of CatSper Blockers as Potential Male Contraceptives.

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The cation channel of sperm (CatSper) is the principal mode of entry for calcium in mature human sperm and mediates several important processes including hyperactivation and capacitation, both critical to successful fertilization. Mutations within CatSper, as confirmed by mouse knockout studies, led to complete infertility of males with no other observable phenotypes. Given these observations, compounds that can block the function of this channel would be promising reversible, non-hormonal contraceptives.

A FLIPR assay using human sperm was used to conduct a 35,000 compound HTS campaign. Screening hits showing both good potency for blocking calcium influx and well-behaved FLIPR traces were selected as initial hit compounds. Six hit compounds were selected for SAR by commerce and evaluation by patch clamp electrophysiology. Due to their promising activity in electrophysiology experiments, GPHR-00032750 and GPHR-00213869 were chosen for additional SAR studies. The elaboration of GPHR-00213869 by a substructure-based approach is described herein, as well as further evaluation of hits by sperm patch clamp electrophysiology.

