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Discovery of a Novel PDE10A Inhibitor as Highly Effective for Schizophrenia

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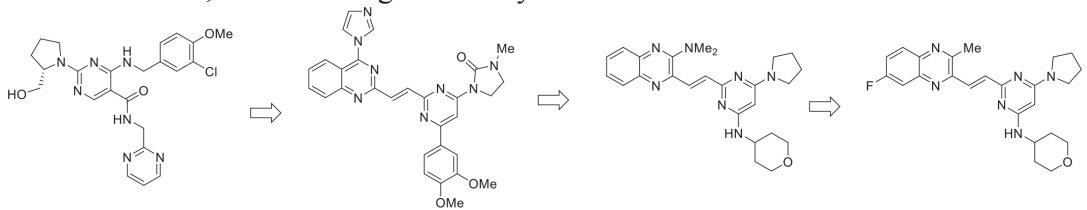
Phosphodiesterase10A (PDE10A), a dual hydrolase of cAMP and cGMP, is highly expressed in striatal medium spiny neurons (MSN). Inhibition of PDE10A modulates the activity of MSN via the regulation of cAMP. Therefore PDE10A inhibitor is expected as a therapeutic method for schizophrenia. We transformed Avanafil **1** (PDE5 inhibitor) derivatives, and discovered compound **2** that had weak inhibitory activity against PDE10A. More conversion of compound **2** improved the metabolic stability and brain penetration, and dimethylaminoquinoxaline substituted compound **3** that attenuated conditioned avoidance responses (CAR) in rats was produced. We performed in-depth optimization, and successfully obtained stilbene compound **4.** The compound was substituted with 3-methyl-7-fluoro quinoxaline substituents, and reduced genotoxicity and CYP inhibition.



1
Avanafil (treatment for ED)
PDE5 IC_{50} 5.2 nM

2
PDE10A IC_{50} 8.6 nM
PDE5 IC_{50} >10000 nM

3
PDE10A IC_{50} 0.10 nM
Other PDEs selectiviety >1000
rat CAR ED_{50} 1.6 mg/kg, po

4
PDE10A IC_{50} 0.14 nM
Other PDEs selectiviety >1000
rat CAR ED_{50} 0.63 mg/kg, po