IMS-P20 **Discovery of TAK-063, a Highly Potent, Selective, and Orally Active Phosphodiesterase 10A (PDE10A) Inhibitor**

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We identified a pyridazin-4(1*H*)-one derivative as a potent PDE10A inhibitor by the high throughput screening. Our optimization efforts using structure-based drug design (SBDD) techniques on the basis of the X-ray crystal structure of PDE10A in complex with the hit compound (IC_{50} = 23 nM; 110-fold selectivity over other PDEs) led to the identification of 5-methoxypyridazin-4(1*H*)-one derivative TAK-063, which showed potent inhibitory activity (IC_{50} = 0.30 nM), excellent selectivity (>15000-fold selectivity over other PDEs), good oral absorption and excellent brain penetration. Furthermore, TAK-063 displayed a completely different binding mode to PDE10A compared to the previously reported PDE10A inhibitors. TAK-063 is currently under evaluation in Phase I clinical trials for the treatment of schizophrenia. The details of design, synthesis, biological activities, the binding mode and pharmacokinetic/pharmacological profiles of TAK-063 will be discussed.