26G-ISMS23 **Identification and Optimization of a Novel Series of Tetrahydroisoquinoline Derivatives as an Orally Active MGAT2 Inhibitor**

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MGAT2 (monoacylglycerol acyltransferase 2) is expected to be an attractive target for the drug treatment of obesity, diabetes, and other disease. We describe our exploration and structure-activity relationship (SAR) study of 2,3-dihydro-1*H*-isoindole-5-sulfonamide derivatives which was derived from a hit compound identified by our high throughput screening campaign. In this study, we identified an orally available MGAT2 inhibitor through optimization in terms of solubility. This compound exhibited moderate potency in the enzyme inhibitory assay (IC_{50} = 1522 nM) and an *in vivo* efficacy at an oral dose of 100 mg/kg in a mouse oral lipid tolerance test.

Further optimization of a novel series of 1,2,3,4-tetrahydroisoquinoline-6-sulfonamide derivatives to improve the intrinsic potency culminated in the identification of TP0455353, 2-[2-(4-*tert*-butylphenyl) ethyl]-*N*-[4-(3-cyclopentylpropyl)-2-fluorophenyl]-1,2,3,4-tetrahydroiso-quinoline-6-sulfonamide, which was the most potent MGAT2 inhibitor among this series with an IC_{50} value of 28 nM. Oral administration of TP0455353 at a dose of 3 mg/kg in the oral lipid tolerance test resulted in significant suppression of triglyceride synthesis.