IMS-P6

Identification, Synthesis of Novel and Potent Series of Pyrazolo[3,4-d]pyrimidine as GPR119 Agonist

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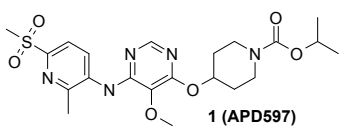
Type 2 diabetes (T2D) is a serious disease affecting hundreds of millions of patients worldwide, and its incidence is correlated with increasing levels of obesity. The consequences of diabetes include increased risk of stroke, heart disease, kidney damage, blindness, and amputation. In fact, diabetic retinopathy is the leading cause of blindness among the working-age population of the United States and diabetes is the leading cause of non-traumatic lower-extremity amputations. Although there are a number of treatments available for T2D, there remains a considerable degree of unmet medical need and novel methods of treatment are being sought.

We designed and synthesized a novel series of phenylamino- and phenoxy-substituted pyrazolo[3,4-d]pyrimidine derivatives as GPR119 agonists. SAR studies indicated that electron-withdrawing substituents on the phenyl ring are important for potency and full efficacy. Compound **21** combined good potency with a promising pharmacokinetic profile in mice, and lowered the glucose excursion in mice in an oral glucose-tolerance test.



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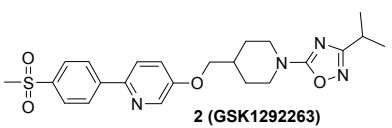

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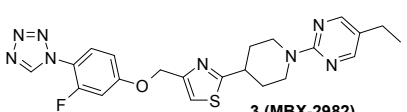

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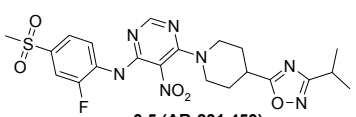

3.5 (AR-231,453)