Obesity is an increasingly problematic medical, causing increased risk of developing type-2 diabetes, cardiovascular disease, hypertension, stroke, and cancer. Wide experimental evidence placed the melanin-concentrating hormone 1 GPCR receptor (MCH-1R) as a one of the most promising therapeutic targets in the treatment of obesity and appetite control, and its antagonists to become anti-obesity drugs. Despite many MCH-1R ligands being developed, none reached the clinic. A drop in new chemical matter for MCH-1R indicates that random methods, such as HTS, have run their course. Here we present a conceptually pioneering technology that integrates screening of 490 diverse pyranose compounds, combined with in-silico modelling that provided molecular-level insights into the MCH-1R structure, and followed up with a structure-based virtual screen. The high quality of the MCH-1R model was evaluated by SAR expansion, virtual screening enrichment factor and structure-based virtual screening yielded 15 novel MCH-1R ligands with hit rate of ~14%.