Small Molecule Allosteric Agonists of Glucagon-like Peptide 1 Receptor for Type 2 Diabetes & Obesity

Lead Inventors

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Unmet Need

The prevalence of obesity globally has increased six-fold over the past four decades, with this trend projected to continue unabated. Obesity significantly increases the risk of serious health conditions, including cardiovascular disease and type-2 diabetes, which accounts for approximately 90-95% of all diabetes cases[1].

Current therapies targeting the Glucagon-Like Peptide 1 Receptor (GLP-1R), a Class B GPCR family member, have demonstrated substantial efficacy in managing type-2 diabetes and obesity. GLP-1R agonists have rapidly expanded in popularity due to their impressive weight-loss capabilities and their potential therapeutic benefits in cardiovascular, renal, hepatic, neurological, and addictive disorders[2].

However, current peptide-based GLP-1R agonists have critical limitations:

- High manufacturing costs.
- Side effects, notably nausea and vomiting.
- Limited availability of orally bioavailable formulations optimized for obesity treatment.

For instance, the injectable semaglutide (Wegovy™) is approved for obesity management, while its oral counterpart (Rybelsus™) currently lacks approval at effective obesity treatment dosages. Therefore, there remains significant market demand for potent, orally bioavailable small molecule GLP-1R agonists.

Opportunity

- Allosteric targeting of GPCRs represents an innovative and promising strategy in drug discovery. Unlike traditional orthosteric ligands, allosteric agonists offer several key advantages:
- Enhanced potency and oral bioavailability.
- Ability to amplify endogenous GLP-1 signaling without relying on peptide stability or bioavailability.
- Potential for reduced adverse side effects due to receptor specificity and modulation.

Building on prior GLP-1R research, investigators have optimized previous lead compounds, developing novel small molecule GLP-1R positive allosteric modulators (PAMs). These optimized compounds show superior pharmacokinetic properties, efficacy, and drug-like profiles, making them promising candidates for oral administration.

Specifically, the investigators have developed Compound 7, a uniquely potent GLP-1R PAM[3]:

- Low molecular weight (299 Da), significantly smaller than other known PAMs.
- Features a pharmacologically versatile 2-aminothiophene (2-AT) scaffold with proven anti-cancer, anti-viral, anti-microbial, and anti-tubercular properties.
- Meets Lipinski's rule of five and Veber's criteria, ensuring optimal drug-like properties.
- Demonstrated efficacy in lowering glucose levels by enhancing endogenous GLP-1 signaling (validated in vitro and in vivo).

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[1] Bulik CM, Hardaway JA. Turning the tide on obesity? *Science*. 2023;381(6657):463.
[2] Couzin-Frankel J. Obesity meets its match. *Science* 2023;382(6676):1227.
[3] Redij T, McKee JA, Do P, et al. 2-Aminothiophene derivatives as a new class of positive allosteric modulators of glucagon-like peptide 1 receptor. *Chem Biol Drug Des*. 2022;99(6):857-867.

- Capable of crossing the blood-brain barrier.
- Simultaneously modulates GLP-1R, glucagon receptor, and GIPR, aligning with current industry interest in multi-target therapeutics.
- Consequently, the global GLP-1 market is projected to surpass $100 billion by 2030[4].

Compound 7's favorable profile and demonstrated effectiveness position it as an exceptional candidate for oral GLP-1R therapeutic development. Furthermore, the methodology used to develop Compound 7 provides a scalable platform for creating novel small molecule allosteric modulators targeting additional GPCRs implicated in cardiovascular and immune diseases.

Unique Attributes

- The invention is based, in part, on a novel synthesis methodology that can produce high molecular weight gelatin-DOX conjugates.
- In one aspect, the invention provides a high molecular weight compound comprising gelatin and DOX (i.e., a high molecular weight gelatin-DOX conjugate), where the gelatin is covalently linked to DOX through a cleavable linker.

Clinical Applications

- Type-2 Diabetes
- Obesity
- Substance abuse / addiction

Stage of Development

Preclinical stage. Lead compounds have demonstrated efficacy in vitro and in vivo. Chemical samples of optimized top-ranked compounds are available for demonstration purposes.

Intellectual Property

Provisional Patent application filed May 2024.
US Patent application published as US 2022/0193080 A1, June 2022.
PCT application published as WO2020/210582 A1, October 2020.

Collaboration or Licensing Opportunity

Actively seeking licensee for commercialization or collaboration to complete preclinical studies.

References and Publications

Campbell JA, Do P, Li Z, Malik F, Mead C, Miller N, Pisiechko C, Powers K, Li Z. Synthesis and biological studies of 2-aminothiophene derivatives as positive allosteric modulators of glucagon-like peptide 1 receptor. Bioorg Med Chem. 2024; 111:117864.

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[4] The increase in appetite for obesity drugs", J.P. Morgan, November 2023