Review



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# Oral Small-Molecule GLP-1 Receptor Agonists: Mechanistic Insights and Emerging Therapeutic Strategies

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**Abstract:** Small-molecule glucagon-like peptide-1 receptor agonists (GLP-1RAs) represent an innovative advancement in oral therapeutics, addressing key limitations associated with injectable peptide-based incretin therapies. These nonpeptidic agents exert their actions primarily through non-canonical orthosteric sites within the GLP-1 receptor transmembrane domain, enabling selective G protein (Gs)-biased signaling with reduced β-arrestin–mediated adverse effects. Orforglipron has notably advanced through phase 3 clinical development, demonstrating significant reductions in hemoglobin A1c and body weight (up to 7.9%) with favorable tolerability. Conversely, promising candidates such as danuglipron and lotiglipron were discontinued due to hepatotoxicity, underscoring critical safety concerns intrinsic to small-molecule GLP-1RA development. Current clinical candidates, including GSBR-1290, CT-996, and ECC5004, continue to offer substantial potential due to their oral bioavailability, simplified dosing regimens, and favorable gastrointestinal tolerability. Nevertheless, challenges persist regarding hepatic safety, pharmacodynamic variability, and limited long-term outcome data. This review integrates current structural, pharmacological, and clinical evidence, highlights key mechanistic innovations—including biased agonism, covalent binding strategies, and allosteric modulation—and discusses future directions for this rapidly evolving therapeutic class in metabolic disease management.

**Keywords:** GLP-1 receptor agonists; small-molecule therapeutics; biased agonism; orforglipron; danuglipron; aleniglipron; CT-996; AZD5004; type 2 diabetes mellitus; obesity pharmacotherapy

## 1. Introduction

Type 2 diabetes mellitus (T2DM) affects more than 530 million adults worldwide as of 2025, and its global prevalence is projected to surpass 800 million by 2050, positioning it as one of the most rapidly escalating threats to public health and longevity [1]. Its increasing burden, often linked to rising obesity rates and aging populations, has driven the need for more effective, accessible, and sustainable therapeutic strategies [2].

Over the past two decades, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as a cornerstone in the treatment of T2DM and obesity [3]. These agents improve glycemic control by enhancing glucose-stimulated insulin secretion and suppressing glucagon release, while also

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delaying gastric emptying, reducing appetite, and promoting weight loss [4]. Furthermore, multiple large-scale trials have shown that injectable GLP-1RAs reduce cardiovascular events and slow the progression of diabetic kidney disease [5].

However, their clinical use has traditionally been limited by their peptide nature, which requires subcutaneous injection and cold-chain storage—factors that negatively affect adherence and global scalability [6]. The development of oral semaglutide (Rybelsus®®, Novo Nordisk, Bagsværd, Denmark) marked a pharmacological milestone by enabling the first non-injectable GLP-1RA. Nevertheless, its peptide structure still requires co-formulation with the absorption enhancer sodium N-[8-(2-hydroxybenzoyl)amino] caprylate (SNAC) under fasting conditions, and the doses required for weight management, as show in the OASIS trials, thereby increasing cost and limiting scalability [7,8].

Against this backdrop, small-molecule, nonpeptidic GLP-1RAs represent a transformative innovation. These nonpeptidic compounds are chemically stable, amenable to large-scale synthesis, and suitable for oral delivery without permeation enhancers [9]. Their pharmacological profile supports food-independent dosing and incorporation into fixed-dose combinations. As such, they have the potential to overcome key limitations of current GLP-1RA therapies and broaden access, particularly in low-resource settings [10].

The emergence of this new class has catalyzed a competitive wave of pharmaceutical innovation. Several companies have initiated the development of orally bioavailable, nonpeptidic compounds aiming to replicate or even surpass the metabolic benefits of injectable incretin therapies [9,10]. This unprecedented effort has led to a growing pipeline of investigational agents, many of which are progressing through early- and mid-phase clinical trials. While their oral formulation offers clear advantages in terms of patient adherence, manufacturing, and distribution, questions remain regarding their long-term safety, efficacy, and regulatory positioning. These developments mark a pivotal shift in the trajectory of incretin-based therapies and warrant comprehensive scientific evaluation.

From a mechanistic standpoint, small-molecule GLP-1RAs are designed to mimic the beneficial signaling pathways of their peptide counterparts through novel receptor engagement strategies [11]. These include the selective activation of G protein–mediated signaling cascades and the exploration of allosteric binding within the GLP-1 receptor. Such approaches aim to enhance tolerability, oral bioavailability, and pharmacodynamic precision, distinguishing these agents from traditional peptide-based incretin therapies [12].

Despite their promise, these agents have yet to achieve the magnitude of metabolic benefit observed with dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, such as tirzepatide (Eli Lilly and Company, Indianapolis, IN, USA), which has demonstrated superior glycemic and weight-reducing effects in multiple head-to-head clinical trials (e.g., SURPASS-2, SURMOUNT-1) [13–15]. Nevertheless, small-molecule GLP-1RAs offer distinct advantages in terms of manufacturing, cost, and oral administration. As of 2025, neither the American Diabetes Association (ADA) nor the European Association for the Study of Diabetes (EASD) recognizes them as a distinct therapeutic class due to their investigational status [16,17]. However, their rapid development may soon position them as viable oral alternatives to peptide-based incretin therapies.

This review presents an updated synthesis of the molecular mechanisms, clinical development, and translational potential of small-molecule GLP-1RAs. It situates their emergence within the historical evolution of incretin-based pharmacotherapy—from exenatide to the recent completion of orforglipron's phase 3 trials—highlighting key pharmacological and developmental milestones (Figure 1). This framework sets the stage for a critical examination of the design principles, efficacy data, and safety considerations that will shape the future of this emerging therapeutic class. Although small-molecule GLP-1RAs have not yet matched the efficacy of dual GLP-1/GIP agonists, ongoing innovations in dual-target molecules and blood–brain barrier for central nervous system (CNS) designs may further close this therapeutic gap.

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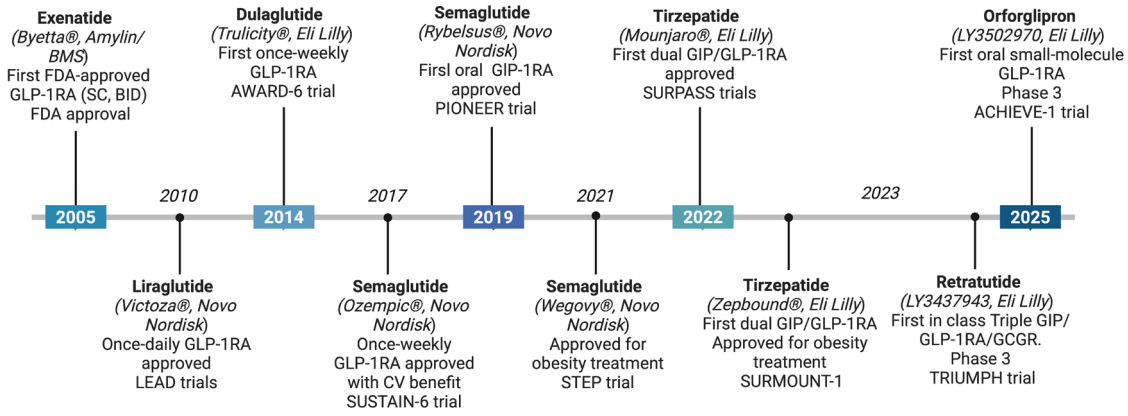


**Figure 1.** Timeline of Key Milestones in the Development of GLP-1RAs, 2005–2025. This timeline summarizes pivotal clinical and regulatory events in the evolution of GLP-1RAs over the last two decades. Exenatide (Byetta®®) became the first FDA-approved GLP-1RA in 2005, followed by the approval of once-daily and once-weekly peptide-based agents such as liraglutide (Victoza®®), dulaglutide (Trulicity®®), and semaglutide in various formulations (Ozempic®®, Rybelsus®®, Wegovy®®). The approval of tirzepatide (Mounjaro®®, Zepbound®®), a dual GLP-1/GIPRA, marked a new pharmacological class in 2022–2023. In parallel, nonpeptidic, orally bioavailable small-molecule GLP-1RAs have emerged, led by orforglipron (LY3502970), which completed its first Phase 3 trial in 2025 (ACHIEVE-1). Retratutide (LY3437943), a first-in-class triple GIP/GLP-1/glucagon receptor agonist (GCGR), remains under Phase 3 clinical evaluation (TRIUMPH program) for obesity. The figure illustrates both approved therapies and late-stage investigational agents, highlighting structural diversification and expansion of incretin-based metabolic treatments [14,18–28].

## 2. Mechanistic Innovations in Small-Molecule GLP-1RA

The emergence of small-molecule GLP-1RAs has redefined the pharmacological landscape of incretin-based therapies. Unlike peptide analogs that interact with the extracellular domain, these nonpeptidic compounds utilize novel receptor engagement strategies—including biased agonism, allosteric modulation, and covalent binding—to achieve selective signaling with enhanced oral bioavailability [29,30]. The molecular basis for these innovations has been clarified through high-resolution structural studies, particularly the cryo-EM structure of GLP-1R in complex with a peptide agonist and Gs protein reported by Zhao et al. (2020), which revealed an active-like receptor conformation characterized by outward movement of transmembrane helix 6 (TM6) and reorganization of TM7, facilitating ligand entry into deep transmembrane pockets and defining new allosteric binding topologies [31].

### *2.1. Gs-Biased Agonism: Preferential G Protein Signaling and Therapeutic Relevance*

Biased agonism refers to the ability of a ligand to preferentially activate one intracellular signaling pathway over others. For GLP-1R, this often entails selective stimulation of Gαs-mediated cAMP production while minimizing recruitment of β-arrestin—a pathway linked to receptor internalization and adverse gastrointestinal effects [32]. The pharmacodynamic relevance of this signaling selectivity has garnered increasing attention in early-phase clinical trials, where differential tolerability profiles are beginning to emerge.

Among small-molecule GLP-1RAs, GSBR-1290 (Structure Therapeutics) has demonstrated a near-complete Gs-biased profile with negligible β-arrestin engagement, whereas orforglipron (Eli Lilly) exhibits partial bias, indicating mechanistic heterogeneity even within this subclass. ECC5004

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(AstraZeneca/Eccogene) also displays attenuated arrestin recruitment in preclinical studies, further supporting its tolerability profile [31–34].

This signaling bias carries not only mechanistic but also clinically relevant implications. Gs-biased agonists may reduce nausea and vomiting, prolong receptor responsiveness, and attenuate tachyphylaxis [32]. Downstream, sustained cAMP signaling activates effectors such as protein kinase A (PKA), exchange protein directly activated by cAMP 2 (Epac2), and MAP kinase pathways, which together mediate enhanced insulin secretion, β-cell survival, and reduced inflammation [11]. Whether this biased signaling confers long-term metabolic or cardiovascular advantages remains under investigation [35]. Figure 2 illustrates representative GLP-1R agonists across structural classes, highlighting their receptor engagement, signaling bias, and downstream effects. Native GLP-1 and its peptide analogues engage both G protein (Gs) and β-arrestin pathways, resulting in balanced agonism, whereas small-molecule agonists preferentially activate Gs signaling with minimal β-arrestin recruitment.

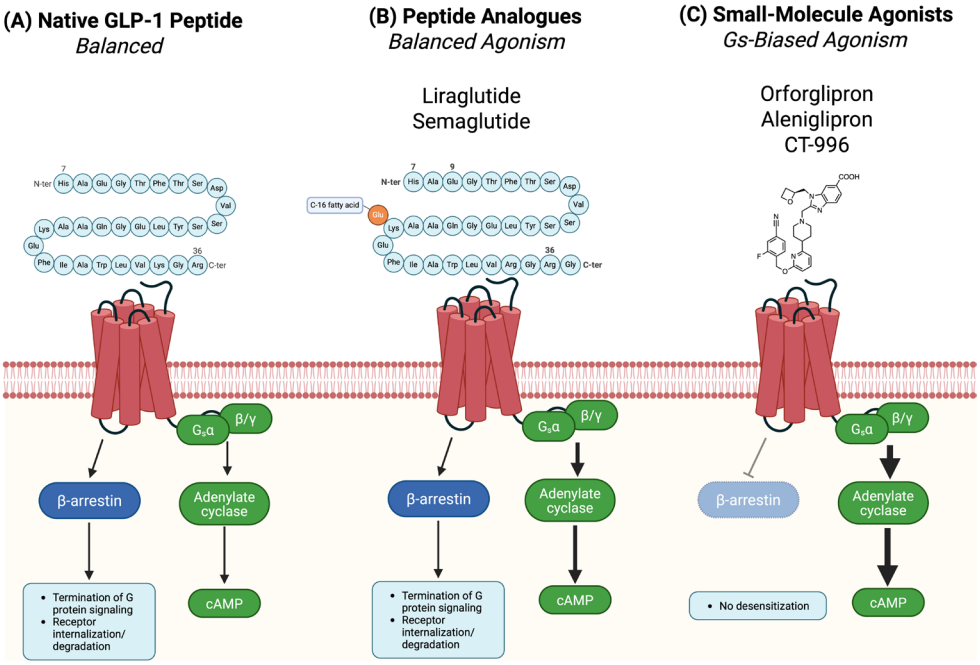


**Figure 2.** Structural classes, receptor engagement, and signaling outcomes of GLP-1R agonists. (A) Native GLP-1 peptide (balanced agonism): The amino acid sequence of native GLP-1 is shown, with full-length linear structure (residues 7–36). GLP-1 engages both Gs (green arrows) and β-arrestin (solid blue arrow), promoting cyclic AMP (cAMP) production via adenylate cyclase and triggering receptor internalization and desensitization. (B) Peptide analogues (balanced agonism): Liraglutide and semaglutide, shown with the C-16 fatty acid side chain (orange circle), mimic GLP-1 structure but include modifications for increased half-life. Their signaling profile mirrors that of native GLP-1, with balanced G protein and β-arrestin engagement. The visual layout emphasizes the preservation of dual signaling (Gs and β-arrestin) despite structural modifications. (C) Small-molecule agonists (Gs-biased agonism): Representative small molecules (orforglipron, aleniglipron, CT-996) bind within non-canonical transmembrane (TM) pockets. Their chemical structure is shown above the receptor. These agents selectively activate Gs without significant β-arrestin recruitment, as depicted by a dashed light-blue arrow, indicating minimal β-arrestin engagement and reduced receptor desensitization (blue box: "No desensitization"). All GLP-1Rs are embedded within a stylized plasma membrane (bilayer with red dots), and the directionality of intracellular signaling cascades is indicated with black solid arrows for active signaling, dashed lines for attenuated pathways, and lighter opacity for minimal interactions. Gαs and Gβγ subunits are shown as green ovals, with adenylate cyclase downstream. The consistent receptor structure (seven-

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transmembrane helices in dark red) emphasizes conserved topology across ligand classes. This figure was created using BioRender.Created in BioRender. Saldivar Ceron, H. (2025). https://BioRender.com/wacjpfq [9,32].

*2.2. Non-Canonical Binding and Allosteric Modulation in Small-Molecule GLP-1R Agonism*

A hallmark of small-molecule GLP-1R agonists is their engagement with non-canonical transmembrane pockets, distinct from the extracellular binding site utilized by endogenous peptides and their analogues [36]. Structural studies of compounds such as danuglipron (LY3502970) (Pfizer Inc., New York, NY, USA) have revealed binding within a cleft formed by transmembrane helices and extracellular loop regions, where residues like Trp33—a primate-specific anchor—contribute to ligand stabilization, although the compounds remain functionally orthosteric in nature [37]. Similar Trp33-dependent engagement has been proposed for ECC5004/AZD5004 (Eccogene (Shangai, China) and AstraZeneca (Cambridge, UK) and GSBR-1290 by Structure Therapeutics, Inc. (San Francisco, CA, USA) highlighting the translational limitations of rodent models and reinforcing the need for primate or humanized systems [38].

In contrast, other compounds such as DA-15864 (Dong-A ST, Seoul, South Korea) exhibit covalent allosteric mechanisms, selectively targeting intracellular residues like Cys347 to prolong receptor activation and modulate pharmacokinetics [29,39]. This mechanism represents a departure from traditional orthosteric paradigms, potentially enabling sustained signaling through irreversible binding.

Furthermore, positive allosteric modulators (PAMs)—including BETP (4-(3-(benzyloxy)phenyl)-2-ethylsulfinyl-6-(trifluoromethyl)pyrimidine) and its analogues—have demonstrated the ability to enhance the efficacy of endogenous GLP-1 by stabilizing favorable receptor conformations [29,40,41]. These PAMs do not activate the receptor alone but potentiate GLP-1–mediated responses, offering a rationale for combination therapies that preserve physiological tone while enhancing therapeutic effects. Together, Gs-biased signaling and alternative binding strategies—including allosteric and covalent mechanisms—form the mechanistic backbone of modern small-molecule GLP-1RA design. Table 1 summarizes representative GLP-1R ligands, detailing their class, binding site, receptor domains engaged, signaling bias, and pharmacological notes.

These properties not only differentiate small-molecule GLP-1RAs from injectable peptide-based agonists but also lay the groundwork for next-generation therapeutics. Notably, several candidates are being engineered as dual GLP-1/GIP or GLP-1/glucagon co-agonists or designed to cross the blood–brain barrier for CNS indications, including obesity and neurodegenerative disorders. [30,42–44]. Such mechanistic precision represents a paradigm shift in GLP-1R targeting, expanding therapeutic possibilities beyond glycemic control into the realms of neurohormonal regulation and personalized metabolic medicine.

**Table 1.** Structural Class, Binding Characteristics, and Signaling Bias of Representative GLP-1 Receptor Ligands. This table summarizes representative glucagon-like peptide-1 receptor (GLP-1R) ligands across distinct structural classes, including native peptides, peptide analogues, small-molecule agonists, covalent activators, and positive allosteric modulators. Ligands are characterized by their molecular class, receptor binding site, engaged GLP-1R domains, signaling bias (Gs versus β-arrestin), and relevant pharmacological properties. Canonical peptide agonists interact with both the extracellular domain (ECD) and transmembrane (TM) bundle to promote balanced G protein and β-arrestin signaling. In contrast, small-molecule agonists bind within non-canonical orthosteric pockets located deep in the TM domain and often exhibit Gs-biased signaling. Covalent compounds such as DA-15864 prolong receptor activation by targeting intracellular residues, while PAMs like BETP modulate receptor conformation to potentiate endogenous GLP-1 effects without intrinsic agonism. Functional heterogeneity among these ligands has implications for efficacy, tolerability, pharmacokinetics, and translational applicability.

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| Ligand (Representative Compound) | Molecular Class | Binding Site Location | GLP-1R Domains Engaged | Signaling Bias | Pharmacological Notes |
|---|---|---|---|---|---|
| GLP-1 (native peptide) | Endogenous peptide | Canonical orthosteric (dual-site model) | Extracellular domain (ECD) + TM1, TM2, TM7 | Balanced (Gs + β-arrestin) | Reference ligand; activates both Gs and β-arrestin pathways [18] |
| Liraglutide | Peptide analogue | Canonical orthosteric | ECD + TM core bundle | Balanced | Long-acting; maintains native GLP-1 signaling profile [20] |
| Semaglutide | Peptide analogue | Canonical orthosteric | ECD + TM core bundle | Balanced | High GLP-1R affinity; acylated for prolonged action [7] |
| Orforglipron (LY3502970) | Small molecule | Non-canonical orthosteric (deep TM pocket) | TM1, TM2, TM3, TM5, TM7 | Gs-biased | Strong Gs activation; negligible β-arrestin recruitment [45] |
| Danuglipron (PF-06882961) | Small molecule | Non-canonical orthosteric (TM cavity) | TM1, TM2, TM7 | Gs-biased | Robust cAMP signaling; limited β-arrestin activity [46] |
| Lotiglipron | Small molecule | Non-canonical orthosteric | TM domain | Gs-biased | Designed for potent cAMP activation; discontinued due to liver toxicity [47] |
| GSBR-1290 (Aleniglipron) | Small molecule | Non-canonical orthosteric | TM1, TM2, TM7 | Gs-biased | Selective Gs activator; minimal receptor internalization [38] |
| CT-996 | Small molecule | Non-canonical orthosteric | TM core (specific residues not fully disclosed) | Gs-biased | Avoids β-arrestin recruitment; long pharmacokinetic half-life [48] |
| ECC5004 (AZD5004) | Small molecule | Non-canonical orthosteric | TM domain | Gs-biased | Enhances cAMP; minimal β-arrestin coupling [49] |
| TERN-601 | Small molecule | Non-canonical orthosteric | TM domain | Gs-biased | Preclinical candidate; strong cAMP response [50] |
| GS-4571 | Small molecule | Non-canonical orthosteric | TM domain | Gs-biased | Stimulates insulinotropic cAMP pathway in β-cells [51] |
| DA-15864 | Small molecule | Non-canonical orthosteric | TM domain | Gs-biased | Investigated for metabolic and neurological applications [52] |
| MLX-7505 | Small molecule | Non-canonical orthosteric | TM domain | Gs-biased | Early-stage development; bias profile under investigation [53] |

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|---|---|---|---|---|---|
| RGT-075 | Small molecule | Non-canonical orthosteric | TM domain | Balanced | Full agonist; dual activation of Gs and β-arrestin pathways [54] |
| BETP *(PAM)* | Positive allosteric modulator | Allosteric (extracellular TM cleft) | TM domain, near ECL2 | Modulates Gs (not an agonist) | Enhances endogenous GLP-1 response; no intrinsic activity; explored in combination therapy [41] |

## 3. Clinical Development and Leading Candidates of Small-Molecule GLP-1RAs

The development of orally active small-molecule GLP-1RAs marks a significant innovation in the pharmacologic management of T2DM and obesity. While peptide-based GLP-1RAs have demonstrated robust efficacy, their subcutaneous administration and cold chain requirements have limited widespread adoption, with discontinuation rates exceeding 30% in real-world use during the first year [55]. In contrast, orally bioavailable small molecules offer greater convenience, do not require refrigeration, and may be better suited for fixed-dose oral combination therapies [56].

In recent years, more than a dozen small-molecule GLP-1RA programs have progressed into Phase 1 through Phase 3 clinical trials [57]. These agents differ not only in chemical structure but also in pharmacodynamic properties, including but not limited to biased agonism, allosteric modulation, receptor residence time, and hepatic metabolism. Several compounds have demonstrated clinically meaningful reductions in HbA1c and body weight, while others have raised safety concerns—particularly hepatotoxicity—underscoring the pharmacologic heterogeneity and the need for compound-specific assessment [56,58,59].

This section provides a comprehensive overview of the clinical development landscape for small-molecule GLP-1RAs. It synthesizes efficacy outcomes, safety profiles, and mechanistic attributes of leading compounds, aiming to inform both therapeutic positioning and the future design of next-generation agents in the management of metabolic diseases.

### *3.1. Orforglipron (Eli Lilly): A Clinically Advanced Oral G Protein–Biased GLP-1RA in Phase 3 Trials*

Orforglipron (LY3502970) is an orally administered, nonpeptidic GLP-1RA developed by Eli Lilly [58]. It represents one of the most clinically advanced small-molecule agents in this emerging therapeutic class. Mechanistically, orforglipron exhibits partial G protein–biased agonism at the GLP-1 receptor, robustly activating cAMP signaling while limiting β-arrestin recruitment and receptor internalization [36]. This selective signaling profile has been proposed to prolong receptor responsiveness, attenuate tachyphylaxis, and reduce gastrointestinal intolerance compared with balanced peptide-based GLP-1RAs. Although its full pharmacological differentiation remains under investigation, early-phase studies have supported its tolerability and glycemic efficacy in both T2DM and obesity [28,58,60–64].

Phase 1a and 1b studies provided foundational evidence for the safety, pharmacokinetics, and preliminary efficacy of orforglipron (NCT04426474). In a single- and multiple-ascending-dose trial involving healthy adults, orforglipron exhibited favorable oral bioavailability, a terminal half-life of approximately 30 hours, and no requirement for co-formulation with absorption enhancers such as SNAC [45,64]. These properties enabled once-daily dosing under fed conditions and supported its advancement to Phase 2.

In Phase 2 studies, orforglipron demonstrated robust metabolic efficacy in both T2DM and obesity. In individuals with T2DM (NCT04426474), it achieved placebo-adjusted $HbA_1c$ reductions of –1.2% to –1.7% over 26 weeks, with body weight loss of up to 8.6 kg and >80% of participants reaching $HbA_1c$ <7.0% [45,63–65]. These results were comparable to those observed with injectable

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GLP-1RAs and reinforced the viability of oral delivery without compromising metabolic efficacy. In adults with obesity without diabetes (NCT04881760), orforglipron induced dose-dependent weight reductions ranging from 8.6% to 14.7% over 36 weeks, with 75% of those on the highest dose achieving ≥10% weight loss [58,61]. These results, observed in both T2DM and obesity trials, are comparable to those achieved with injectable GLP-1RAs and support the potential of oral small-molecule agonists to match their metabolic efficacy, particularly when adherence and tolerability are optimized [25,58]. To date, no data have been reported on cardiometabolic or hepatic endpoints beyond weight and glycemia, including effects on blood pressure, lipid profiles, or liver enzymes. These outcomes suggest that orally delivered small-molecule GLP-1RAs may match the metabolic efficacy of injectable incretins, provided that tolerability and adherence profiles are favorable. However, direct head-to-head comparisons and longer-term outcome studies are necessary to establish therapeutic equivalence.

Unlike oral semaglutide, orforglipron does not require co-formulation with absorption enhancers and maintains food-independent bioavailability [63]. This allows flexible administration, potentially improving adherence in real-world settings. The safety profile is consistent with peptide-based GLP-1RAs, with gastrointestinal adverse events—nausea (up to 40%), diarrhea (20–25%), and vomiting—being dose-dependent and most prevalent during dose escalation. These events were typically transient and subsided with continued treatment, especially after reaching maintenance doses. Discontinuation rates ranged from 5% to 17%. No serious hepatotoxicity, hypoglycemia, or major cardiovascular events were reported [28,58,61–63,65].

Orforglipron is the first oral small-molecule GLP-1RA to enter Phase 3 development for both obesity and T2DM [66]. In April 2025, Eli Lilly announced that orforglipron met the primary endpoints of the ACHIEVE-1 and 3 trial, showing $HbA_1c$ reductions of 1.3–1.6% and average weight loss of 7.9% at the highest dose, along with a tolerability profile similar to that of injectable GLP-1RAs [66,67]. These results will be presented at the 85th Scientific Sessions of the ADA 2025 and are expected to be published in a peer-reviewed journal [68].

If confirmed in ongoing Phase 3 trials, orforglipron's profile may establish a benchmark for future compounds in this class. Its combination of potent efficacy, oral pharmacokinetics, and selective signaling positions it as a promising candidate in next-generation metabolic therapies. Nonetheless, its long-term cardiovascular outcomes, durability of glycemic control, and comparative cost-effectiveness remain to be established through dedicated outcome trials.

### *3.2. Danuglipron and Lotiglipron (Pfizer): The Collapse of a Promising Class*

Pfizer's parallel development of danuglipron (PF-06882961) and lotiglipron (PF-07081532) once stood as a leading example of innovation in oral small-molecule GLP-1RA [46,47]. Both compounds were designed to be nonpeptidic, orally bioavailable agents capable of delivering glycemic and weight loss benefits without absorption enhancers. However, despite promising early-phase data, the discontinuation of both programs—most recently danuglipron in April 2025 due to hepatotoxicity—has raised profound questions about the viability of this approach and the predictive power of preclinical safety models [46,56,62,69–71].

Danuglipron had initially emerged as a frontrunner. It engaged the GLP-1 receptor via allosteric binding and exhibited G protein–biased agonism, favoring cAMP signaling while minimizing β-arrestin recruitment [56,69]. In a 16-week Phase 2b trial (NCT03985293), danuglipron induced $HbA_1c$ reductions of up to –1.16% and weight losses between 4 and 5.5 kg, with over 65% of participants reaching $HbA_1c$ <7.0% [56]. Administered twice daily without dietary restrictions, it was positioned as a metabolically potent and patient-friendly alternative to peptide-based injectables.

Its safety profile appeared consistent with other GLP-1RAs, marked by dose-dependent gastrointestinal adverse events and no significant elevations in hepatic transaminases across over 1,400 treated individuals [46,70]. This distinction was especially notable when compared to

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lotiglipron, whose development was terminated in 2023 following asymptomatic but sustained elevations in liver enzymes during Phase 1 and 2 studies [47,72].

However, in April 2025, Pfizer abruptly halted all danuglipron clinical programs following a confirmed case of drug-induced liver injury (DILI), as reported by Science magazine [70,71]. Although the liver toxicity resolved upon discontinuation and appeared isolated, the company opted to terminate development after a full clinical and regulatory review. This decision underscores the unpredictable nature of hepatotoxicity in this pharmacologic space and erodes prior confidence in danuglipron's hepatic safety profile.

The failure of both agents—despite sharing biased Gs signaling, oral bioavailability, and preclinical tolerability—challenges foundational assumptions about safety prediction in small-molecule GLP-1RA design. While biased agonism remains a compelling strategy to reduce receptor desensitization and gastrointestinal symptoms, it does not confer protection against off-target hepatic effects. Preclinical studies had suggested that danuglipron had a more favorable metabolic profile and hepatic clearance than lotiglipron, including reduced formation of reactive metabolites [73]. Nonetheless, these findings ultimately proved insufficient to safeguard its clinical trajectory.

Pfizer has since discontinued its oral GLP-1RA program entirely, marking a major setback in the pursuit of non-injectable incretin-based therapies. The collapse of both danuglipron and lotiglipron highlights a critical need for earlier, more predictive hepatic toxicity assays and a deeper understanding of how structural modifications influence metabolic liabilities. Recent medicinal chemistry studies have explored alternative scaffolds designed to mitigate hERG inhibition and liver-related off-target effects [74], signaling a potential future path for safer development.

These failures serve as a cautionary tale. Rational design and biased signaling, while necessary, are not sufficient. Future efforts must integrate receptor pharmacology, metabolic profiling, and systems toxicology to anticipate and mitigate class-related risks. The case of Pfizer's GLP-1 small-molecule portfolio illustrates that even highly promising candidates can fail late—reminding us that innovation in metabolic therapeutics must be matched by equally rigorous safety foresight.

### *3.3. GSBR-1290/Aleniglipron (Structure Therapeutics): Allosteric Gs-Biased Agonist with Hepatic Safety*

GSBR-1290 (also known as aleniglipron) is an orally bioavailable, nonpeptidic GLP-1RA developed by Structure Therapeutics, Inc. Among next-generation candidates, it has gained attention for combining meaningful metabolic efficacy with a favorable safety profile in early clinical studies. Mechanistically, GSBR-1290 binds to a deep orthosteric cavity within the transmembrane domain (TM1, TM2, TM7), without engaging the extracellular domain. Although spatially distinct from the canonical peptide binding site, this interaction remains functionally orthosteric and directly activates the receptor, contributing to its Gs-biased pharmacology [38].

In a 12-week, double-blind, placebo-controlled Phase 2a trial (NCT05762471), GSBR-1290 administered once daily at 60 mg and 120 mg achieved placebo-adjusted weight reductions of 4.7% and 6.2%, respectively, in adults with overweight or obesity [38,75]. At the higher dose, 67% of participants achieved ≥6% weight loss [38]. These changes were accompanied by improvements in insulin sensitivity (evidenced by reductions in fasting insulin and HOMA-IR), despite the absence of intensive lifestyle interventions—highlighting intrinsic pharmacologic efficacy [33].

Unlike peptide-based GLP-1RAs, GSBR-1290 does not require co-formulation with a permeation enhancer and maintains bioavailability regardless of fed or fasted states, supporting once-daily, food-independent oral administration. Pharmacokinetic data suggest a terminal half-life of 25–28 hours, enabling sustained receptor engagement and potentially stable therapeutic effects over time [38].

Importantly, GSBR-1290 has shown a favorable tolerability profile. In the Phase 2a trial, the most common adverse events were mild nausea (18%) and reduced appetite (15%), primarily during dose escalation. No serious adverse events, treatment discontinuations, or liver enzyme elevations were reported [75]. In contrast to the hepatotoxicity observed with compounds such as danuglipron and lotiglipron, GSBR-1290's clean hepatic profile is notable. According to preclinical data and Phase 2a

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results presented at scientific meetings, the sponsor reports that GSBR-1290 exhibits stable hepatic metabolism with no evidence of mitochondrial dysfunction or hepatocellular stress [38].

A 12-week, randomized, placebo-controlled Phase 2b study (NCT06693843) is currently underway, enrolling ~300 participants to evaluate dose-response relationships, glycemic outcomes, and long-term safety [76]. While initial data are promising, the magnitude of weight loss remains moderate compared to injectable GLP-1RAs over longer durations. Nonetheless, GSBR-1290 exemplifies a new generation of oral small-molecule agonists that combine oral convenience, signaling selectivity, and hepatic safety—features that may position it as a viable noninjectable option for obesity and early T2DM management, particularly in populations seeking alternatives to peptides or at risk of hepatic complications. However, whether this signaling bias translates into clinically superior tolerability or long-term durability remains to be demonstrated in larger, active-controlled trials

### *3.4. CT-996 (Roche/Carmot Therapeutics): Fast-Onset Candidate with Food-Independent Absorption*

CT-996 is an orally active, small-molecule GLP-1RA initially developed by Carmot Therapeutics, Inc. (Berkeley, CA, USA) and currently co-developed by F. Hoffmann-La Roche Ltd. (Basel, Switzerland). It has shown rapid-onset, clinically meaningful weight loss in short-duration trials, distinguishing it from other compounds in this class. CT-996 also offers practical advantages, including food-independent absorption and once-daily oral dosing, which may enhance patient adherence [77,78] .

In a 4-week, multiple ascending dose Phase 1 study (NCT05814107), 72 adults with overweight or obesity were randomized to receive CT-996 or placebo. At the highest tested dose (500 mg once daily), CT-996 produced a placebo-adjusted mean weight loss of 6.1%—a magnitude comparable to that of injectable semaglutide at similar timepoints. Weight reduction followed a dose-dependent pattern, with significant effects observed as early as week 2, highlighting rapid pharmacodynamic activity [78,79].

Mechanistically, CT-996 functions as a G protein–biased GLP-1RA, with minimal β-arrestin engagement or receptor internalization in preclinical models. In vitro and animal studies have demonstrated sustained cAMP signaling, enhanced glucose tolerance, and maintenance of receptor responsiveness with chronic exposure [79]. Structural modeling suggests CT-996 occupies a deep, non-canonical orthosteric pocket within the transmembrane domain, avoiding extracellular domain interaction. This configuration supports Gs-biased signaling without receptor internalization [79].

Pharmacokinetic analyses indicate a terminal half-life of approximately 22–26 hours and show no significant impact of food intake on drug absorption. This food independence eliminates the need for fasting windows or co-formulation with permeation enhancers, offering a practical advantage over oral semaglutide, which requires co-formulation in fasting state with SNAC to achieve optimal bioavailability [48,78].

To date, CT-996 has demonstrated a favorable safety profile. The most common adverse events were mild to moderate nausea (12%) and transient appetite suppression (10%), primarily during dose escalation. No serious adverse events, liver enzyme elevations, cardiovascular events, or treatment discontinuations were reported [48]. Tolerability was consistent across all dose cohorts.

A Phase 2 randomized controlled trial has been initiated by Roche to evaluate the long-term efficacy, weight loss durability, and glycemic outcomes of CT-996 in individuals with obesity and early-stage T2DM [80]. If early efficacy and tolerability are confirmed, CT-996 may become a competitive oral GLP-1RA, particularly attractive to patients seeking flexible dosing and rapid therapeutic onset.

CT-996 exemplifies a new generation of orally available, structurally distinct GLP-1RAs that combine rapid-onset metabolic efficacy with simplified administration. Its food-independent pharmacokinetics, Gs-biased signaling profile, and promising early results support its potential for broader clinical adoption. Nonetheless, whether these pharmacologic advantages will translate into

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sustained efficacy and tolerability over longer durations remains to be demonstrated in larger, active-controlled trials.

*3.5. ECC5004/AZD5004 (Eccogene/AstraZeneca): Primate-Selective Molecule with Simplified Dosing*

ECC5004 (also known as AZD5004) is an orally bioavailable, nonpeptidic GLP-1 receptor agonist initially developed by Eccogene (Shanghai, China) and subsequently licensed to AstraZeneca (Cambridge, UK). It belongs to a new generation of G protein–biased agonists that selectively stimulate cAMP production while minimizing β-arrestin recruitment and receptor internalization. This intracellular signaling bias is designed to preserve receptor responsiveness, mitigate gastrointestinal intolerance, and enable food-independent oral dosing without the need for permeation enhancers such as SNAC [34]. AZD5004 is not yet approved for clinical use and remains under investigation.

In a 28-day, randomized, double-blind, placebo-controlled Phase 1 trial (NCT05654831) involving adults with T2DM, ECC5004 was administered once daily at doses ranging from 5 mg to 50 mg. At the highest dose, ECC5004 led to a mean reduction of 2.2 mmol/L in fasting plasma glucose and a placebo-adjusted body weight loss of approximately 2.5–3.0 kg. These changes emerged within the first two weeks of treatment and followed a dose-dependent trajectory, consistent with the expected pharmacodynamic profile of GLP-1RAs. However, statistical significance and interindividual variability have not yet been fully disclosed, and long-term outcomes remain unconfirmed [49,81].

Mechanistically, ECC5004 demonstrates high affinity for the human GLP-1 receptor and preferentially activates Gs signaling with minimal engagement of β-arrestin pathways. ECC5004 binds within a non-canonical orthosteric region, exhibiting Trp33-dependent engagement in primates. This profile has been linked to reduced receptor desensitization and potentially improved tolerability in vivo. Of particular note, ECC5004 exhibits species-selective pharmacology, with robust activation in primates but minimal functional effect in rodents, necessitating the use of non-human primate models for translational evaluation—a factor that enhances its clinical predictability while limiting traditional preclinical toxicology strategies [34]. Structural modeling suggests that ECC5004 binds to a transmembrane domain conformation of GLP-1R that favors Gs over β-arrestin coupling. This mechanism is consistent with cryo-EM data showing that biased agonists stabilize distinct active conformations of the receptor's helical bundle, particularly around transmembrane helices 5–7 [82].

Pharmacokinetic analyses indicate a terminal half-life of 22–26 hours, with no significant effect of food intake on absorption. This food-independent bioavailability supports flexible oral administration and avoids the fasting restrictions and co-formulation requirements of oral semaglutide, which depends on SNAC for optimal absorption [34].

ECC5004 has demonstrated a favorable safety and tolerability profile across all evaluated dose cohorts. The most common adverse events were mild nausea (≤15%) and reduced appetite (≤12%), occurring primarily during early dose escalation. No treatment discontinuations, serious adverse events, or elevations in hepatic enzymes were reported—distinguishing ECC5004 from other small-molecule GLP-1RAs that have been discontinued due to hepatotoxicity [34]. Nonetheless, further evaluation is required to confirm this favorable profile in larger and longer trials.

ECC5004 is currently under evaluation within AstraZeneca's metabolic portfolio. According to a company announcement from October 2024, a global Phase 2b clinical trial is already in progress to assess the efficacy, safety, and dose-response characteristics of ECC5004/AZD5004 in individuals with obesity and T2DM [83]. Although this trial is not yet registered in public databases, it is ongoing per sponsor statement. The translation of early efficacy and safety signals into durable, clinically meaningful outcomes remains to be established through larger, head-to-head and outcome-driven trials.

*3.6. TERN-601 (Terns Pharmaceuticals): Low-Burden Oral Option for Weight-Centric Therapy*

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TERN-601 is an orally bioavailable, small-molecule GLP-1RA developed by Terns Pharmaceuticals, Inc. (Foster City, CA, USA). It is designed for once-daily administration without peptide-based formulations or permeation enhancers. TERN-601 is not yet approved for clinical use and remains under investigation [50].

In a 28-day, randomized, placebo-controlled Phase 1 trial in 36 adults with overweight or obesity, TERN-601 achieved a placebo-adjusted mean weight loss of 4.9% at the highest dose (740 mg), with 67% of participants attaining ≥5% weight reduction. These effects were observed without lifestyle interventions and followed a dose-dependent pattern [50,84,85]. Exploratory trends also suggested improvements in fasting glucose and insulin sensitivity, though glycemic endpoints were not the study's primary focus.

Preclinical data indicate that TERN-601 acts as a G protein–biased GLP-1R agonist, favoring cAMP signaling with minimal β-arrestin recruitment. Pharmacokinetic analysis showed a terminal half-life of 20–26 hours and consistent bioavailability under fed and fasted conditions. The compound was generally well tolerated; the most common adverse events were mild nausea and appetite suppression, mostly during early dose escalation. No serious adverse events or hepatic abnormalities were reported [84].

A Phase 2 trial is currently being planned to assess long-term weight loss and metabolic outcomes [86]. While early signals are encouraging, the durability, comparative efficacy, and safety of TERN-601 remain to be confirmed in larger trials.

### *3.7. GS-4571 (Gilead Sciences) and Emerging Preclinical Candidates: Expanding the Oral GLP-1RA Pipeline*

GS-4571 is an orally active, nonpeptidic small-molecule GLP-1 receptor agonist under development by Gilead Sciences, Inc. (Foster City, CA, USA). As of 2025, it is being evaluated in a Phase 1 clinical trial (NCT06562907) to assess safety, tolerability, pharmacokinetics, and exploratory biomarker responses in healthy volunteers, individuals with obesity, and patients with T2DM [51,87]. Although no human efficacy data have been published to date, GS-4571 has emerged as a promising candidate within Gilead's metabolic pipeline of oral incretin-based agents [88].

Preclinical studies have shown that GS-4571 selectively activates the human GLP-1 receptor, eliciting glucose-lowering effects and weight reduction in rodent and primate models. In cynomolgus monkeys, 36 days of once-daily oral dosing led to approximately 6.5% weight loss and a 50% reduction in food intake [88]. The compound reportedly crosses the blood–brain barrier, suggesting potential central effects on appetite regulation, although these remain to be confirmed in humans. Its molecular structure has not been publicly disclosed, but patent filings describe nonpeptidic heterocyclic scaffolds with high GLP-1 receptor affinity [89].

Several additional small-molecule GLP-1RAs remain in early-stage development. DA-15864, developed by Dong-A ST Several additional small-molecule GLP-1RAs remain in early-stage development. DA-15864, developed by Dong-A ST,, is a G protein–biased agonist that activates cAMP signaling with minimal β-arrestin recruitment and enhances insulin secretion while improving glucose tolerance in animal models [89]. Similarly, Compound S6, from the University of Toronto (Toronto, Canada), binds covalently to the GLP-1 receptor in human pancreatic islets, supporting prolonged receptor activation and modulating β-cell ion channel activity [90].

Other investigational compounds include MLX-7005, from Mabwell Therapeutics (Shanghai, China), which stimulates insulin secretion in β-cell models without measurable β-arrestin recruitment [53]; ID110521156, developed by Ildong Pharmaceutical (Seoul, South Korea), a receptor-binding molecule that increases cAMP and improves glucose and weight outcomes in diabetic monkeys [91]; and RGT075, from Rgenix Inc. (New York, USA), a rationally designed agent that enhances glucose tolerance and reduces food intake in prediabetic primates through Gs-biased signaling with minimal receptor internalization [54,92].

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Collectively, these candidates reflect a growing effort to diversify the chemical space of GLP-1RAs beyond injectable peptides. Although they remain in preclinical or early clinical stages, their design strategies aim to replicate the efficacy of peptide-based therapies with simplified oral administration, scalable synthesis, and potentially improved tolerability. The structural diversity of these agents is illustrated in Figure 3, underscoring the relevance of scaffold design for receptor engagement and pharmacokinetics.

Nonetheless, it remains uncertain whether these pharmacologic attributes will translate into sustained efficacy and safety in human populations. Most supporting data derive from in vitro systems or animal studies. Accordingly, translational validation and rigorous early-phase trials are essential to determine their therapeutic viability and to distinguish candidates with genuine clinical potential from those with promising but untested mechanisms [34,61]. The chemical structures of the most clinically advanced small-molecule GLP-1RAs are illustrated in Figure 3, highlighting key differences in scaffold design and potential implications for receptor binding and pharmacokinetics.

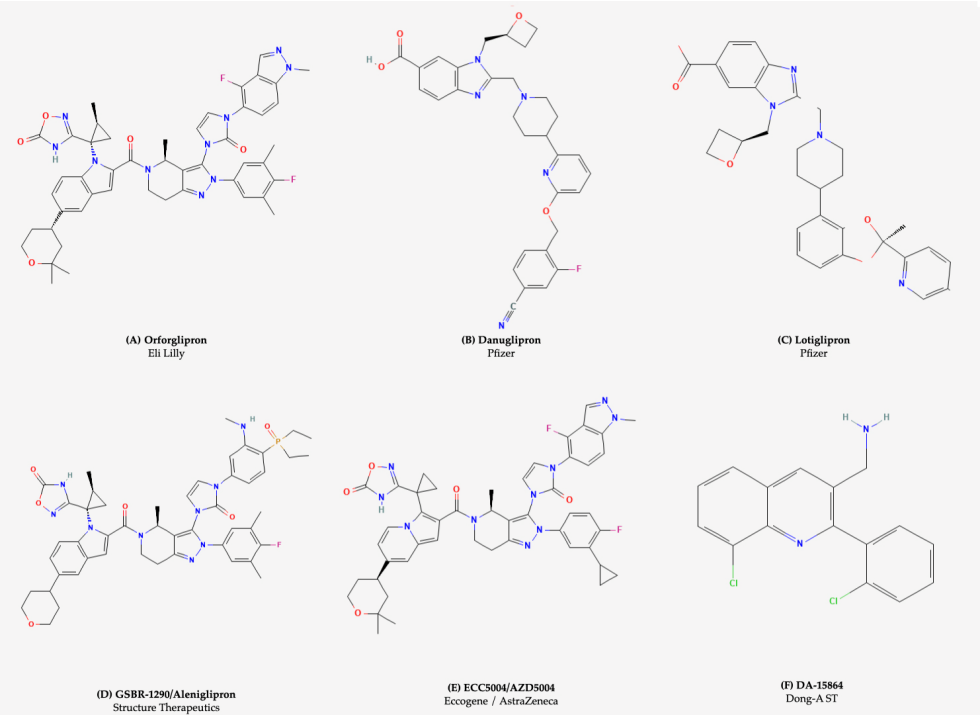


**Figure 3.** Chemical structures of selected orally active small-molecule GLP-1RAs under clinical investigation. (A) Orforglipron (Eli Lilly, PubChem CID: 137319706); (B) Danuglipron (Pfizer, CID: 134611040); (C) Lotiglipron (Pfizer, CID: 146609022; development discontinued); (D) Aleniglipron / GSBR-1290 (Structure Therapeutics, CID: 164809721); (E) ECC5004/AZD5004 (Eccogene / AstraZeneca, CID: 167350327); (F) DA-15864 (Dong-A ST, CID: 59264634). Molecular structures were retrieved directly from PubChem using the official export tool and rendered without manual redrawing. Atom coloring follows IUPAC conventions as used by PubChem: red denotes oxygen, blue indicates nitrogen, green represents halogens (Cl, F), and black lines represent carbon bonds. These candidate agents are designed to activate the GLP-1 receptor via G protein–biased or allosteric mechanisms. Structural variation may affect receptor binding dynamics, intracellular signaling, pharmacokinetics, and tolerability. Structures for compounds such as CT-996 and TERN-601 are not shown due to the absence of publicly available, validated chemical data [93–98].

## 4. Redefining Metabolic Therapy: Clinical Promise of Small-Molecule GLP-1RAs

The emergence of orally available small-molecule GLP-1RA carries significant clinical implications that go beyond pharmacologic innovation. These agents address longstanding barriers in the management of T2DM and obesity, particularly those related to treatment accessibility, patient

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adherence, and preferences. While peptide-based GLP-1RAs have transformed the therapeutic landscape, real-world data reveal high discontinuation rates—often attributed to injection burden, gastrointestinal intolerance, and cold-chain storage requirements. In contrast, small-molecule GLP-1RAs eliminate the need for subcutaneous administration, offer greater convenience, and facilitate integration into fixed-dose oral combinations—factors that may enhance long-term adherence and broaden therapeutic reach [9,55–57,99]. None of the small-molecule GLP-1RAs discussed are currently approved for clinical use and remain under investigation.

In the context of obesity, the clinical potential of oral GLP-1RAs is particularly compelling. Agents such as orforglipron and CT-996 have demonstrated rapid and clinically meaningful weight loss, approaching the efficacy observed with first-generation injectable incretin therapies, particularly in early-phase studies. Their use in non-diabetic individuals, coupled with favorable tolerability, supports their positioning as primary pharmacologic interventions for weight loss rather than adjunctive metabolic therapies. The ability to induce substantial weight reduction within 4 to 8 weeks in some cases also opens the possibility of short-term, indication-specific use, such as preoperative optimization or early-stage metabolic syndrome management [48,58,61,64].

In T2DM, oral GLP-1RAs may shift therapeutic algorithms by offering a potent, non-injectable alternative capable of achieving HbA1c reductions exceeding 1.5%. This is particularly relevant in newly diagnosed individuals or in patients unwilling or unable to initiate injectable regimens. Moreover, in resource-limited settings where cold-chain logistics and injection infrastructure are challenging, orally bioavailable agents may expand access to incretin-based therapies [47,56,61].

Beyond T2DM and obesity, therapeutic applications for oral GLP-1RAs are likely to expand. Preclinical and early clinical evidence supports their exploration in non-alcoholic steatohepatitis (NASH), cardiometabolic prevention, and potentially neuroprotection—especially for agents capable of crossing the blood–brain barrier. Oral administration also facilitates co-formulation with other drug classes such as sodium-glucose cotransporter-2 inhibitors (SGLT2i), dipeptidyl peptidase-4 (DPP-4) inhibitors, or dual incretin agonists, enabling synergistic modulation of metabolic pathways [32,34,57,99].

Despite these advantages, heterogeneity in receptor signaling, pharmacokinetics, and hepatic metabolism across compounds may translate into differences in clinical efficacy, tolerability, and safety. Agents like GSBR-1290 and ECC5004 may offer improved tolerability through selective pathway activation, while others such as orforglipron demonstrate greater efficacy at the cost of increased gastrointestinal side effects. As a result, therapeutic decisions may increasingly depend not only on potency, but also on mechanistic profiles and individualized risk–benefit considerations [31–34,65].

In summary, small-molecule GLP-1RAs are poised to expand and refine therapeutic strategies for metabolic disease—not as replacements for peptide-based agents, but as complementary options that improve accessibility and personalization. Their successful integration into clinical practice will require rigorous long-term safety monitoring, regulatory oversight, and adaptation by healthcare systems. To date, no outcome studies have demonstrated cardiovascular benefit or direct comparisons with injectable incretin therapies. Nonetheless, their potential to reshape the incretin therapy landscape is both substantial and imminent [34,56,57,59]. The oral formulation of these agents may reduce manufacturing and distribution costs compared to peptides, offering a scalable alternative in resource-limited settings where injectable infrastructure and cold-chain logistics are barriers to treatment. A comparative summary of pharmacodynamic properties, clinical outcomes, and tolerability profiles of leading oral small-molecule GLP-1RAs is presented in Table 2.

**Table 2.** Clinical profile of orally active small-molecule GLP-1RA under development. This table summarizes the pharmacodynamic characteristics, clinical efficacy, safety, and dosing advantages of leading small-molecule GLP-1RA in clinical development for the treatment of obesity and/or T2DM. HbA1c reduction and weight loss refer to maximal placebo-adjusted changes reported in the most advanced clinical trials available per compound. Mechanisms refer to receptor signaling bias (G protein vs. β-arrestin) and binding modality (orthosteric,

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allosteric, or transmembrane), as described in published preclinical or clinical studies. Tolerability profiles focus on the incidence of gastrointestinal adverse events, hepatotoxicity, and discontinuation rates. Dosing characteristics reflect formulation, frequency, food requirements, and titration regimens. Abbreviations: GI, gastrointestinal; AEs, adverse events; SAEs, serious adverse events; QD, once daily; MR, modified-release; T2DM, type 2 diabetes mellitus, FPG, Fasting plasmatic glucose.

| Agent | Developer | Clinical Stage | HbA1c Reduction | Weight Loss | Mechanism | Tolerability | Dosing / Notes |
|---|---|---|---|---|---|---|---|
| Orforglipron [28,58,64,66–68,108] | Eli Lilly | Phase 3 (T2DM, obesity) | ~1.2–1.7% | Up to 14.7% (36w) | G protein–biased; partial β-arrestin | GI AEs; 10–17% discontinuation | Once daily; food-independent |
| Danuglipron [56,71,109] | Pfizer | Discontinued (April 2025) | ~1.16% | 4–5.5 kg (16w) | G protein–biased; allosteric | GI AEs; hepatotoxicity (late) | BID; QD formulation abandoned |
| Lotiglipron [47,59,72] | Pfizer | Discontinued (2023) | ~1.0–1.6% | ~5.4% | G protein–biased | ALT/AST ↑; hepatotoxicity | Once daily; program halted |
| GSBR-1290 (Aleniglipron) [75,76] | Structure Therapeutics | Phase 2b (ongoing) | ~1.0% | Up to 6.2% (12w) | G protein–biased; allosteric | Mild GI AEs; no hepatotoxicity | Once daily; no permeation enhancer |
| CT-996 [48,77,79,110] | Roche / Carmot | Phase 2 (initiated) | Not reported | 6.1% (4w) | G protein–biased; transmembrane site | Well tolerated; no SAEs | QD; food-independent; rapid onset |
| ECC5004 (AZD5004) [34] | Eccogene / AstraZeneca | Phase 2b (per sponsor) | ~2.2 mmol/L (FPG) | ~2.5–3.0 kg (28d) | G protein–biased; primate-selective | Mild GI AEs; no hepatotoxicity | QD; food-independent; primate efficacy only |
| TERN-601 [84,86] | Terns Pharmaceuticals | Phase 1 completed | Trend only | Up to 5.5% (28d) | G protein–biased | No SAEs or discontinuations | QD; dose-escalation tested |
| GS-4571 [51] | Gilead Sciences | Phase 1 (ongoing) | Preclinical only | 6.5% (preclinical) | Presumed Gs-biased; CNS-penetrant | No human data | Structure unpublished |

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## 5. Challenges and Future Directions

Despite encouraging clinical outcomes and mechanistic innovations, several challenges must be addressed before small-molecule GLP-1RAs can be fully integrated into long-term clinical practice. These challenges encompass pharmacological development, safety surveillance, regulatory oversight, and healthcare system adaptation. Future progress will require not only robust evidence of efficacy and safety, but also strategic positioning within evolving metabolic care paradigms.

### *5.1. Hepatic Safety and Structural Liability*

Hepatic safety remains a central concern in the development of small-molecule GLP-1RAs. Although agents such as orforglipron and GSBR-1290 have not shown hepatic safety concerns in early-phase studies, the discontinuation of lotiglipron due to asymptomatic transaminase elevations underscores the structural sensitivity and off-target liabilities inherent to this drug class. Given their hepatic metabolism—often via cytochrome P450 pathways—the risk of reactive metabolite formation, mitochondrial dysfunction, or hepatocellular injury must be closely monitored. Regulatory agencies are likely to demand comprehensive hepatic safety datasets, including extended follow-up and post-marketing pharmacovigilance, especially in populations with underlying liver disease or polypharmacy profiles [9,47,55,72].

### *5.2. Pharmacodynamic Variability and Clinical Differentiation*

Pharmacodynamic heterogeneity remains a significant challenge in the clinical development of small-molecule GLP-1RAs. Variations in receptor binding domains, signaling bias, receptor residence time, and central versus peripheral distribution can markedly influence both efficacy and tolerability. While G protein–biased agonism is hypothesized to mitigate receptor desensitization and gastrointestinal adverse events, its translation into cardiovascular or renal protection remains unproven. No compound in this class has yet demonstrated benefit in large-scale outcome trials. The lack of direct head-to-head comparisons further complicates therapeutic differentiation, highlighting the need for standardized endpoints, harmonized tolerability metrics, and validated biomarker panels. In this context, biomarkers such as plasma cAMP response, circulating incretin hormone profiles, and transcriptomic signatures may offer predictive value for therapeutic durability and help identify patient subgroups most likely to benefit [31,32,34,65].

### *5.3. Integration into Clinical Practice and Guidelines*

The introduction of oral GLP-1RAs may also challenge existing treatment algorithms. Their convenience and efficacy could support earlier use in the metabolic continuum, including prediabetes, metabolic syndrome, or even primary prevention. However, this expanded indication range raises unresolved questions regarding treatment duration, intermittent versus continuous use, and long-term cost-effectiveness in non-diabetic populations. Should these agents be positioned before or after SGLT2 inhibitors in patients with obesity but no diabetes? Updated clinical guidelines, payer frameworks, and clinician education will be essential to ensure rational and equitable adoption [56,57,59,99].

### *5.4. Market Competition and Therapeutic Positioning*

Finally, small-molecule GLP-1RAs face a competitive landscape dominated by peptide-based injectables. Agents such as semaglutide and tirzepatide have demonstrated robust efficacy, cardiovascular outcome benefit, and commercial leadership. Consequently, oral compounds must not only demonstrate comparable efficacy in glycemic and weight endpoints, but also offer meaningful advantages in terms of convenience, cost-effectiveness, or tolerability to justify widespread adoption and reimbursement. Clear therapeutic positioning, informed by real-world comparative data, will be crucial for market viability [56,61,64].

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## 6. Patent and Innovation Landscape

Over the past five years, the innovation landscape surrounding small-molecule GLP-1RAs has expanded rapidly. Driven by increased investment in structural diversification, signaling specificity, and oral pharmacologic optimization, major pharmaceutical companies—including Eli Lilly, Pfizer, Roche, AstraZeneca, and Gilead—have advanced proprietary scaffolds with distinct mechanisms of action. Many of the most clinically advanced compounds were first disclosed in international patent applications filed between 2018 and 2023, with broad claims encompassing allosteric binding pockets, biased G protein signaling, and novel oral formulations [47].

Three main domains of innovation dominate current development efforts. First, the design of allosteric modulators that avoid orthosteric competition with endogenous GLP-1 has enabled enhanced selectivity and reduced receptor desensitization. Second, selective Gs-biased agonists have emerged to minimize β-arrestin recruitment, potentially improving tolerability. Third, the synthesis of nonpeptidic macrocycles and heterocyclic scaffolds has enhanced membrane permeability and oral bioavailability. Early-stage discovery programs are also exploring irreversible GLP-1R ligands and dual GLP-1/GIP receptor agonists with differentiated binding kinetics and metabolic effects [37,59,100].

Patent families covering agents such as orforglipron, danuglipron, and GSBR-1290 are among the most frequently cited in the field, reflecting both strategic value and active commercial surveillance. In parallel, intellectual property related to fixed-dose oral combinations—particularly those pairing small-molecule GLP-1RAs with sodium-glucose cotransporter-2 inhibitors (SGLT2i), metformin, or dual incretin co-agonists—is expanding rapidly. These platforms seek to optimize polypharmacy in a single oral regimen, reducing treatment burden and improving adherence [33,41,47,58,59,64,76].

Despite the breadth of patent activity, relatively few molecules have advanced beyond Phase 2 trials, underscoring the translational gap between chemical innovation and clinical viability. Future development is likely to focus on combinatorial receptor targeting, improved CNS penetrance for appetite and reward modulation, and the integration of pharmacogenomic data to enable personalized metabolic therapy. In this increasingly competitive space, freedom-to-operate (FTO) evaluations, early differentiation based on structure–activity relationships, and formulation innovation will be key determinants of long-term clinical and commercial success [33,37,57].

## 7. Conclusions

Small-molecule GLP-1RAs represent a novel and potentially transformative class in the pharmacologic management of T2DM and obesity. Building on the metabolic efficacy of peptide-based incretin therapies, these orally bioavailable, nonpeptidic agents introduce key innovations: signaling selectivity via biased agonism, food-independent administration, and the potential for fixed-dose oral co-formulations. Recent patents have proposed combinations of small-molecule GLP-1RAs with oral SGLT2 inhibitors or metformin, aiming to enhance adherence and maximize glycemic and weight-loss outcomes through synergistic mechanisms. Collectively, these attributes may improve long-term adherence and expand therapeutic access across diverse clinical settings. Early clinical data from compounds such as orforglipron, GSBR-1290, and CT-996 suggest that small-molecule GLP-1RAs can achieve substantial reductions in HbA1c and body weight. In some cases, these effects approach those observed with injectable agents—particularly in short-term trials. However, long-term durability, cardiovascular protection, and renal outcomes remain unknown. Furthermore, variability in pharmacokinetics, receptor engagement, and hepatic metabolism may limit class generalization and necessitate agent-specific evaluation. To date, no dedicated cardiovascular outcomes trials (CVOTs) have been completed for small-molecule GLP-1RAs, limiting their comparability with agents such as liraglutide or semaglutide in cardiometabolic prevention.

As the field evolves, methodological rigor will be essential to move from proof-of-concept to clinical integration. Head-to-head comparative trials, long-term safety surveillance, and real-world

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evidence will be required to determine whether these agents can complement or even displace existing peptide-based therapies. Equally important will be regulatory clarity, equitable access models, and inclusion in clinical practice guidelines to ensure effective implementation.

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## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| ADA | American Diabetes Association |
| AEs | Adverse Events |
| cAMP | Cyclic Adenosine Monophosphate |
| CNS | Central Nervous System |
| CVOT | Cardiovascular Outcomes Trial |
| DPP-4 | Dipeptidyl Peptidase-4 |
| Epac2 | Exchange Protein Activated by cAMP 2 |
| ECL | Extracellular Loop |
| FDA | Food and Drug Administration |
| FPG | Fasting Plasma Glucose |
| GCGR | Glucagon Receptor |
| GI | Gastrointestinal |
| GI AEs | Gastrointestinal Adverse Events |
| GIP | Glucose-Dependent Insulinotropic Polypeptide |
| GLP-1 | Glucagon-Like Peptide 1 |
| GLP-1RA | Glucagon-Like Peptide 1 Receptor Agonist |
| HbA1c | Hemoglobin A1c |
| HOMA-IR | Homeostasis Model Assessment for Insulin Resistance |
| MR | Modified Release |
| PAM | Positive Allosteric Modulator |
| PK | Pharmacokinetics |
| PKA | Protein Kinase A |
| QD | Once Daily (quaque die) |
| SAEs | Serious Adverse Events |
| SNAC | Sodium N-[8-(2-hydroxybenzoyl)amino]caprylate |
| T2DM | Type 2 Diabetes Mellitus |
| TM | Transmembrane |

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