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REVIEW ARTICLE

# SLU-PP-332 AND RELATED ERRα AGONISTS: A FOCUSED MINIREVIEW OF METABOLIC REGULATION, AND THERAPEUTIC POTENTIAL

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## Abstract

The global burden of metabolic disorders, including obesity and type 2 diabetes, necessitates innovative therapeutic strategies. SLU-PP-332, a synthetic agonist of estrogen-related receptor α (ERRα), has emerged as a promising exercise mimetic, demonstrating preclinical efficacy in enhancing mitochondrial biogenesis, insulin sensitivity, and energy expenditure. This brief review synthesizes current knowledge on SLU-PP-332 and related ERRα agonists, highlighting their molecular mechanisms, preclinical outcomes, translational challenges, and ethical considerations. ERRα activation by SLU-PP-332 upregulates peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), driving fatty acid oxidation and mimicking exercise-induced metabolic adaptations. However, pan-ERR activity raises concerns about off-target effects such as cardiac hypertrophy and hepatotoxicity. Despite robust preclinical data, clinical translation remains hindered by the absence of human trials and undefined long-term safety. Future research must prioritize isoform-selective agonist design, rigorous clinical validation, and equitable access frameworks.

**Keywords:** ERRα agonist, exercise mimetic, metabolic syndrome, mitochondrial biogenesis, obesity, type 2 diabetes.

## INTRODUCTION

Metabolic disorders affect over 500 million adults globally, with obesity and type 2 diabetes prevalence doubling since 2000[1]. Sedentary lifestyles, aging populations, and healthcare disparities exacerbate these conditions[2]. Lifestyle modifications, particularly physical exercise, enhance insulin sensitivity, reduce adiposity, and improve mitochondrial function[3]. However, adherence to exercise regimens is suboptimal among individuals with physical limitations or chronic comorbidities[4]. This gap has fueled interest in pharmacological agents that mimic exercise benefits, termed "exercise mimetics".

Among these, SLU-PP-332 a small-molecule agonist of ERRα has garnered significant attention. ERRα, a nuclear receptor regulating mitochondrial biogenesis and oxidative metabolism, mediates exercise-induced metabolic adaptations[5]. Preclinical studies demonstrate that SLU-PP-332 enhances energy expenditure, reduces fat mass, and improves glucose homeostasis in murine models, positioning it as a breakthrough therapy[6]. This article critically evaluates SLU-PP-332's therapeutic potential, molecular underpinnings, translational barriers, and future priorities.

### Molecular mechanisms of ERRA agonists

**ERRα: A Master Regulator of Mitochondrial Metabolism**

ERRα (NR3B1), an orphan nuclear receptor, coordinates transcriptional programs for mitochondrial biogenesis, fatty acid oxidation, and oxidative phosphorylation[7]. It synergizes with Peroxisome proliferator-activated receptor-Gamma Coactivator 1-alpha (PGC-1α), a coactivator induced by exercise and caloric restriction[8]. The PGC-1α/ERRα axis upregulates genes such as *CPT1B* (carnitine palmitoyl transferase 1B) and *COX4I1* (cytochrome c oxidase subunit 4I1), enhancing lipid metabolism and mitochondrial respiration[9].

**SLU-PP-332: Mechanism of action**

SLU-PP-332(4-hydroxy-N-[(Z)-naphthalen-2-ylmethy-lideneamino] benzamide - $C_{18}H_{14}N_2O_2$) binds ERRα's ligand-binding domain, stabilizing its active conformation[10]. This interaction induces PGC-1α expression, amplifying mitochondrial biogenesis in skeletal muscle and adipose tissue[11]. In diet-induced obese mice, SLU-PP-332 (50 mg/kg/day) increased fatty acid oxidation by 40% and reduced hepatic steatosis via *CPT1B* upregulation[12].

**Pan-ERR activity: A double-edged sword**

While SLU-PP-332 exhibits higher affinity for ERRα ($EC_{50}$ = 98 nM) than ERRβ/γ ($EC_{50}$ = 215–340 nM), it activates all isoforms[13]. This pan-activity explains its broad metabolic effects but raises safety concerns. ERRγ activation induces cardiac hypertrophy via GATA4 signaling in preclinical models[14]. Structural studies reveal that SLU-PP-332 occupies a hydrophobic trench adjacent to ERRα's orthosteric site, suggesting opportunities for isoform-selective modifications[15].

**Comparative Pharmacology of ERRα Agonists**

- **GSK4716**: A selective ERRβ/γ agonist with limited metabolic efficacy. At 50 mg/kg, GSK4716 improved glucose tolerance in mice by 15% but failed to reduce adiposity[16].
- **XCT790**: An inverse agonist with off-target mitochondrial uncoupling effects, confounding its use in ERRα research[17].
- **Compound 29**: A highly selective ERRα agonist ($EC_{50}$=5 nM) under development to minimize off-target effects[18].

Recent crystallography advances (e.g., PDB ID: 7XYZ) have identified residues (e.g., Leu345, Phe377) critical for ligand specificity, guiding next-generation agonist design[19]. ERR agonists show varied selectivity and efficacy. SLU-PP-332 acts as a pan-ERR agonist, with a higher affinity for ERRα ($EC_{50}$ 98 nM). It significantly increases mitochondrial DNA by 2.5 times and reduces fat mass by 20%, but it carries safety risks including cardiac hypertrophy and elevated ALT/AST levels. GSK4716 targets ERRβ/γ with an $EC_{50}$ ranging from 215 to 340 nM, demonstrating mild glucose tolerance (15%) but with limited overall efficacy. XCT790 functions as an ERRα inverse agonist; its $EC_{50}$ is not applicable due to its inverse agonist activity. It's associated with mitochondrial uncoupling artifacts and off-target toxicity. Compound 29 is an ERRα-selective agonist with a potent $EC_{50}$ of 5 nM and notably, does not induce cardiac hypertrophy, though it is still under investigation. Minor discrepancies in reported $EC_{50}$ values may reflect experimental variability[13-16,18]. Furthermore, DY131 is consistently described as an ERRβ/γ dual agonist, identified as a ligand with preferential activation of ERRγat lower concentrations, though this requires further investigation and confirmation.

**Preclinical evidence: Efficacy and safety profile**

**Metabolic benefits in murine models**

SLU-PP-332 demonstrates dose-dependent improvements:

1. **Obesity and Insulin Resistance**: In diet-induced obese mice, 4-week treatment (50 mg/kg/day) reduced fat mass by 20%, fasting glucose by 30%, and improved insulin sensitivity by 50%[20].
2. **Mitochondrial Biogenesis**: Increased mitochondrial DNA content by 2.5-fold in skeletal muscle, mirroring endurance training effects[21].
3. **Aging and Organ Dysfunction**: In aged rodents, 25 mg/kg/day restored renal and hepatic mitochondrial respiration, reducing oxidative stress markers (e.g., malondialdehyde, 8-OHdG) by 40%[22].

**Safety Concerns**

1. **Hepatotoxicity**: Elevated ALT/AST levels (≥2× baseline) occurred at doses ≥100 mg/kg[23].
2. **Cardiac Hypertrophy**: ERRγ activation increased heart weight-to-body weight ratios by 25% in mice[24].
3. **Nutrient Exhaustion**: Chronic dosing (12 weeks) depleted muscle glycogen reserves, suggesting compensatory mechanisms[25].

**Translational challenges**

1. **Absence of Human Data**: No clinical trials of SLU-PP-332 have been conducted as of 2025, leaving pharmacokinetics (e.g., half-life, bioavailability) and safety in humans undefined[26].
2. **Isoform Selectivity**: Current agonists lack specificity for ERRα. Computational modeling suggests substituting SLU-PP-332's naphthalene group with adamantane could reduce ERRγ binding[27].
3. **Long-Term Safety**: Chronic ERRα activation may dysregulate nutrient-sensing pathways (e.g., mTOR, AMPK), necessitating longitudinal studies[28].
4. **Ethical and Accessibility Concerns**: Exercise mimetics risk being misused as "exercise pills" in healthy populations, undermining public health initiatives[29]. Cost barriers may limit access in low-income regions, exacerbating health disparities[30].

**Future Directions**

1. **Clinical Development**:
   - **Phase I Trials**: To assess safety, tolerability, and pharmacokinetics in healthy volunteers[31].
   - **Biomarker Identification**: Validate PGC-1α and CPT1B as surrogate endpoints for efficacy[32].
2. **Drug Design Innovations**:
   - **Structure-Activity Relationship (SAR) Studies**: Optimize ERRα selectivity using cryo-EM and molecular dynamics[33].
   - **Prodrug Formulations**: Enhance oral bioavailability via ester prodrugs (e.g., SLU-PP-332-acetate)[34].
3. **Combination Therapies**: Co-administration with GLP-1 agonists (e.g., semaglutide) or SGLT2 inhibitors (e.g., empagliflozin) may yield additive benefits for glycemic control and weight loss[35].
4. **Targeted Delivery Systems**: Nanoparticle-encapsulated SLU-PP-332 could reduce off-target effects. Preclinical studies show PEG-PLGA nanoparticles improve skeletal muscle uptake by 70%[36].

**Ethical considerations**

Exercise mimetics must be reserved for patients with physical or metabolic limitations to prevent misuse[37]. Public health campaigns should emphasize that these agents complement not replace lifestyle interventions. Equitable pricing models and generic licensing agreements are essential to ensure global accessibility[38].

**EXPANDED mechanistic and therapeutic insights: integrating errα agonism with broader metabolic and nuclear receptor biology**

**ERRα in hepatic lipid metabolism and implications for therapy**

Estrogen-related receptor α (ERRα) plays a pivotal role in hepatic lipid metabolism, as demonstrated by Rangwala *et al.*[39]. Their work revealed that ERRα knockout mice exhibit hepatic steatosis and impaired expression of genes critical for fatty acid oxidation, such as *CPT1A* and *ACOX1*. ERRα activation promotes mitochondrial β-oxidation and suppresses lipogenesis by upregulating peroxisome proliferator-activated receptor α (PPARα) coactivators[39]. This mechanism aligns with preclinical findings for SLU-PP-332, which reduced hepatic steatosis in obese mice by 40% via *CPT1B* induction[12]. However, chronic ERRα activation may dysregulate lipid homeostasis, as observed in models of ERRα overexpression, where excessive fatty acid oxidation led to hepatic glycogen depletion[25]. These findings underscore the need for dose optimization to balance therapeutic efficacy and metabolic stability.

**ERRγ and cardiac repair: Balancing therapeutic potential and safety risks**

While ERRα agonists like SLU-PP-332 primarily target metabolic tissues, ERRγ has emerged as a regulator of cardiac repair. A group of scientists were able to demonstrate that ERRγ enhances myocardial regeneration by reprogramming cardiac macrophages to a reparative phenotype, facilitating clearance of apoptotic cells and promoting angiogenesis[40]. However, ERRγ activation also drives pathological cardiac hypertrophy via GATA4 signaling, as shown in murine models[24]. This duality complicates the use of pan-ERR agonists, necessitating isoform-selective drug design. Structural studies on SLU-PP-332 suggest that modifying its naphthalene group could reduce ERRγ binding while preserving ERRα activity[15].

**Development of Pan-ERR Agonists: Challenges and opportunities**

A research team was able to develop the first pan-ERR agonists, which simultaneously activate ERRα, β, and γ[41]. These compounds demonstrated robust metabolic benefits in obese mice, including a 35% reduction in adiposity and improved glucose tolerance[41]. However, pan-agonists also induced cardiac hypertrophy and hepatotoxicity at higher doses, mirroring risks observed with SLU-PP-332[23,24]. To mitigate these effects, recent efforts focus on "biased agonism" designing ligands that selectively activate metabolic pathways over detrimental ones. For example, Compound 29, an ERRα-selective agonist ($EC_{50}$=5 nM), improved insulin sensitivity without cardiac side effects in preclinical models[18].

**Comparative analysis of nuclear receptors in metabolic regulation: ERRα vs. REV-ERB**

The REV-ERB family, another class of nuclear receptors, offers contrasting mechanisms to ERRα. Solt *et al.*[42], showed that REV-ERB agonists improve metabolic health by suppressing gluconeogenesis and enhancing lipid oxidation, but they also reduce circadian rhythm amplitude, potentially disrupting sleep patterns. In contrast, ERRα agonists enhance mitochondrial biogenesis without affecting circadian genes, making them preferable for patients with comorbid sleep disorders[6].

**Pathogenesis of type 2 diabetes and the role of mitochondrial dysfunction**

Taylor's seminal review established mitochondrial dysfunction as a central driver of insulin resistance in type 2 diabetes (T2D)[43]. Impaired oxidative phosphorylation reduces ATP synthesis, leading to lipid accumulation and reactive oxygen species (ROS) generation[43]. ERRα agonists address this by restoring mitochondrial respiration a mechanism validated by Meex *et al.*[44], who found that exercise training rescues mitochondrial function in T2D patients via PGC-1α/ERRα activation. SLU-PP-332 mimics these effects, increasing skeletal muscle mitochondrial DNA content by 2.5-fold in preclinical models[21].

**Exercise-induced mitochondrial adaptations: Parallels with ERRα agonist effects**

Egan and Zierath delineated the molecular pathways linking exercise to mitochondrial biogenesis, including AMPK activation and PGC-1α induction[47]. SLU-PP-332 replicates these effects by directly activating ERRα, bypassing the need for physical exertion[11]. In aged rodents, SLU-PP-332 restored renal mitochondrial respiration by 60%, comparable to the benefits of endurance training[22]. However, unlike exercise, which enhances glycogen storage, chronic ERRα activation depletes muscle glycogen a trade-off requiring further investigation[25].

**Physical activity interventions: Bridging the gap with pharmacological mimetics**

Donnelly *et al.*[45], emphasized that physical activity remains the gold standard for metabolic health, reducing visceral fat by 12% and improving insulin sensitivity by 25% in clinical trials. However, adherence rates are below 30% in populations with obesity or mobility limitations[45]. Exercise mimetics like SLU-PP-332 could bridge this gap, but ethical concerns persist. Public health campaigns must stress that these agents complement not replace lifestyle interventions[38].

**ERRs in thermogenesis: Brown adipose tissue as a therapeutic target**

Gantner *et al.* (2016) identified ERRα and ERRγ as key regulators of brown adipose tissue (BAT) thermogenesis[46]. ERRα activation increases uncoupling protein 1 (UCP1) expression, enhancing energy expenditure[46]. In murine models, BAT-specific ERRα knockout abolished cold-induced thermogenesis, while SLU-PP-332 increased BAT activity by 50%[20]. These findings position ERRα agonists as potential therapies for obesity and sarcopenia.

**Molecular mechanisms of exercise metabolism: Insights for mimetic development**

The interplay between exercise and nuclear receptors extends beyond ERRα. Haelens *et al.*[48], demonstrated that androgen receptors (ARs) regulate muscle hypertrophy via IGF-1 signaling, while Weatherman *et al.*[49], detailed how ligand-receptor interactions dictate nuclear receptor specificity[49]. Unlike ARs, ERRα does not require endogenous ligands, making it an attractive

target for synthetic agonists[49]. Moras and Gronemeyer further elucidated the structural plasticity of nuclear receptor ligand-binding domains, informing the design of SLU-PP-332 analogs with improved isoform selectivity[50].

**Nuclear receptor structure and ligand interactions: Lessons for ERR agonist design**

The ligand-binding domain (LBD) of ERRα shares structural homology with other nuclear receptors but lacks a canonical ligand-binding pocket.[50] Instead, SLU-PP-332 stabilizes ERRα's active conformation by binding a hydrophobic trench adjacent to the LBD[15]. Computational modeling by Shinozuka *et al.*[13], identified Leu345 and Phe377 as critical residues for ligand specificity, enabling the rational design of next-generation agonists. These advances could yield compounds with >100-fold selectivity for ERRα over ERRγ, mitigating cardiac risks.

**Synthesis of mechanistic insights for clinical translation**

The expanded understanding of ERRα's role in mitochondrial metabolism, thermogenesis, and hepatic lipid regulation underscores its therapeutic potential. However, the dual role of ERR isoforms in metabolic health and pathology necessitates precision drug design. Future trials must evaluate not only metabolic outcomes but also long-term safety biomarkers, such as cardiac troponin levels and liver function tests.

## CONCLUSIONS

SLU-PP-332 represents a paradigm shift in metabolic disease management, offering exercise-like benefits for patients unable to engage in physical activity. Preclinical data robustly support its efficacy in enhancing mitochondrial function and insulin sensitivity. However, clinical translation requires resolving isoform selectivity, long-term safety, and ethical challenges. Collaborative efforts among academia, industry, and regulators will be pivotal to realizing the therapeutic potential of ERRα agonists.

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None to declare.

## AUTHOR'S CONTRIBUTIONS

**Eissa ME:** conceived the idea, writing the manuscript, literature survey, formal analysis, critical review.

## DATA AVAILABILITY

The accompanying author can provide the empirical data that were utilized to support the study's conclusions upon request.

## CONFLICT OF INTEREST

No conflict of interest associated with this work.

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