Available online at www.ujpronline.com
Universal Journal of Pharmaceutical Research
An International Peer Reviewed Journal
ISSN: 2831-5235 (Print); 2456-8058 (Electronic)

REVIEW ARTICLE

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

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Article Info:

Article History:
Received: 2 April 2025
Reviewed: 18 May 2025
Accepted: 23 June 2025
Published: 15 July 2025

Cite this article:
Mostafa Essam Eissa. SLU-PP-332 and related ERRα Agonists: A focused minireview of metabolic regulation, and therapeutic potential. Universal Journal of Pharmaceutical Research 2025; 10(3): 70-74.
http://doi.org/10.22270/ujpr.v10i3.1355

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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].