EXPERT OPINION ON EMERGING DRUGS
https://doi.org/10.1080/14728214.2026.2696872

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EDITORIAL

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σ_1 receptor agonists: the new trend or an emerging therapeutic option?

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ARTICLE HISTORY Received 28 May 2026; Accepted 26 June 2026

KEYWORDS σ_1 receptor agonists; pharmacologic chaperone; neuroprotection; therapy; drug discovery

1. Introduction

Since its identification in the late 1970s as a putative subtype of opioid receptor, the sigma-1 (σ_1) receptor has emerged as a highly distinctive pharmacological target. Initially reclassified as 'non-opioid,' it was later defined as a ligand-operated intracellular chaperone [1]. Unlike classical membrane receptors coupled to second messenger systems, the σ_1 receptor is an intracellular membrane-associated protein mainly located in the endoplasmic reticulum (ER), especially within mitochondria-associated ER membranes (MAMs) [1]. Nevertheless, it can be selectively targeted by small exogenous molecules acting as agonists, antagonists, or positive modulators. Activation of the σ_1 receptor, that occurs by physiological signals such as cellular stress, or by agonists, primarily alters protein–protein interactions rather than directly triggering classical signaling cascades. This activity leads to modulation of ion conductance, intracellular signaling pathways, structural rearrangements, and intracellular translocation of the receptor itself. These unusual properties make the σ_1 receptor a unique pharmacological entity and an attractive therapeutic target. Interest in σ_1 receptor agonists has expanded considerably in recent years, with more than twenty clinical trials involving σ_1 agonists conducted during the past decade and two recent introductions in the market (Fintepla® by Zogenix and Auvelity® by Axsome).

The σ_1 receptor is a 25 KDa protein encoded by the SIGMAR1 gene. It is widely expressed throughout the body and broadly distributed in the central nervous system, including neurons, astrocytes, oligodendrocytes, and microglia. The receptor is particularly enriched in MAMs, where it interacts with lipid rafts and numerous client proteins such as the chaperone BiP. Its pharmacophore requirements are relatively simple, enabling the development of many selective ligands. Although endogenous ligands such as neurosteroids, trace amines, and choline have been proposed, their precise physiological roles remain unclear. Upon activation, the σ_1 receptor associates and dissociates from client proteins, thereby modulating multiple signaling pathways [2]. Agonists promote monomeric and dimeric receptor states, whereas antagonists favor higher-order oligomers [3]. Positive modulators have also been identified, being devoid of effect in simple cellular models but boosting agonist-mediated effects and being effective in vivo. Sustained activation can also induce receptor translocation along the ER network toward the nuclear envelope and neuritic terminals. Through these mechanisms, the σ_1 receptor exerts broad but finely tuned modulation of cellular homeostasis.

These unique features make the σ_1 receptor an appealing yet challenging therapeutic target. This editorial proposes some insights on the recent therapeutic developments of σ_1 receptor agonists.

2. Mechanisms of action of σ_1 receptor agonists

The σ_1 receptor is distributed across several intracellular compartments, including the ER, nuclear membrane, plasma membrane, and especially MAMs. Numerous client proteins have been identified in these regions, including ER stress proteins such as BiP and IRE1, RanGTP, Pom121, ion channels, NMDA receptors, GABA-B receptors, G protein-coupled receptors, and the TrkB receptor. Consequently, σ_1 receptor activity influences a broad range of cellular pathways involved in inflammation, pain, neurodegeneration, synaptic dysfunction, and metabolic stress.

At MAMs, the σ_1 receptor plays a central role in maintaining cellular homeostasis, particularly through regulation of ER–mitochondria calcium exchanges. Through these effects, σ_1 receptor activation modulates mitochondrial physiology, oxidative phosphorylation, and cellular energy metabolism while reducing oxidative stress and reactive oxygen species (ROS) accumulation. A clear demonstration of this protective role was provided in Wolfram syndrome models, where mutations in the wolframin protein disrupt calcium transfer from the ER to mitochondria [4]. In these models, σ_1 receptor overexpression or treatment with the agonist PRE-084 restored calcium flux and improved mitochondrial function [4]. The σ_1 receptor also contributes to antioxidant defense mechanisms through activation of the Nrf2/HO1 pathway, thereby limiting oxidative stress, ferroptosis, and mitochondrial dysfunction [5]. Similar protective effects have been observed in several pathological contexts, including Alzheimer's disease, amyotrophic lateral sclerosis (ALS), cardiac injury, and diabetic nephropathy. Overall, these findings support a major cytoprotective role for σ_1 receptor agonists in disorders involving mitochondrial impairment.

The σ_1 receptor is highly expressed in immune cells such as leukocytes, macrophages, lymphocytes, and microglia.

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Through its interaction with ER stress pathways and chaperone proteins including BiP and IRE1, the receptor contributes to regulation of inflammatory responses [6]. Activation of the σ_1 receptor has been shown to restrain excessive inflammation in sepsis models and to modulate cytokine and chemokine production in neurodegenerative diseases. In particular, σ_1 receptor agonists influence microglial activation in models of autoimmune encephalomyelitis, retinopathy, and Alzheimer's disease. These anti-inflammatory effects are increasingly recognized as important contributors to the therapeutic potential of σ_1 receptor agonists.

An emerging area of σ_1 receptor research concerns its involvement in autophagy. Loss of σ_1 receptor function leads to ER abnormalities and defective autophagic processes, whereas activation of the receptor stimulates autophagy and improves proteostasis [7,8]. Studies indicate that σ_1 receptor activity is involved in autophagosome maturation and autophagosome–lysosome fusion. Recent findings also suggest a direct role in autophagosome biogenesis through interaction with LC3 mRNA. The receptor appears to bind LC3 mRNA and ribosomes, promoting localized LC3 translation necessary for autophagosome formation [9]. The σ_1 receptor may additionally facilitate nuclear transport of transcription factor EB (TFEB), a master regulator of autophagy and lysosomal biogenesis [10]. Through these combined mechanisms, σ_1 receptor activation enhances cellular clearance pathways that are critical in neurodegenerative diseases characterized by protein aggregation and impaired proteostasis.

The σ_1 receptor also regulates neuronal signaling and synaptic plasticity. Beyond ion channel regulation, the σ_1 receptor influences several intracellular signaling pathways, including CREB, c-fos, and NF-κB. These effects contribute to long-term potentiation and synaptic efficacy. Particular attention has focused on the receptor's interaction with brain-derived neurotrophic factor (BDNF) and its receptor TrkB. σ_1 Receptor agonists regulate BDNF expression and enhance BDNF/TrkB signaling. In Huntington's disease models, the agonist pridopidine restored trafficking of BDNF and TrkB and improved synaptic neurotrophin signaling [11]. The receptor also plays important roles in oligodendrocytes and myelination. σ_1 Receptor activation promotes oligodendrocyte differentiation and may contribute to white matter repair following ischemic injury or demyelinating disorders.

Taken together, these findings establish the σ_1 receptor as a multifunctional intracellular chaperone capable of modulating diverse cellular pathways involved in survival, neuroprotection, inflammation, and cellular homeostasis.

3. Clinical indications and preclinical pipeline

The first generation of σ_1 receptor agonists developed for clinical use includes compounds such as igmesine, fenfluramine, edonerpic maleate, blarcamesine, pridopidine, cutamesine, panamesine, and dextromethorphan+bupropion combination. These agents have been investigated for a wide range of neurological and psychiatric conditions, including depression, cognitive disorders, Rett syndrome, schizophrenia, Alzheimer's disease, Huntington's disease, Parkinson's disease, and ALS. Among these compounds, the most advanced clinical programs involve blarcamesine in Alzheimer's disease and Rett syndrome [12], and pridopidine in Huntington's disease and ALS [13]. These phase 2 and phase 3 trials have played a major role in increasing acceptance of σ_1 receptor-targeting therapies among clinicians and regulatory agencies.

Several clinically used drugs with partial σ_1 receptor activity are also being reconsidered for repurposing strategies. Examples include fluvoxamine, hydroxybupropion, and fenfluramine, which are being explored for depression, anxiety, fibrosis, and Dravet syndrome. Although some first-generation compounds were initially thought to act primarily through other targets, recent receptor occupancy and pharmacological studies suggest that σ_1 receptor engagement may represent a major component of their therapeutic activity.

Current medicinal chemistry efforts increasingly focus on second-generation compounds, some of them designed as hybrids or acting as multi-target directed ligands (MTDLs). These molecules intentionally combine σ_1 receptor agonism with additional neuroprotective mechanisms in order to achieve additive or synergistic therapeutic effects. Recent hybrid compounds have been designed to target σ_1 receptors together with σ_2 receptors, cholinesterases, serotonergic receptors, dopaminergic receptors, NMDA receptors, muscarinic receptors, histone deacetylases (HDACs), and other targets relevant to neurodegenerative disorders. One recent example is Amylovis-201, a σ_1 receptor agonist that also promotes amyloid-β disaggregation through its naphthalene moiety [14]. Such MTDL approaches are particularly attractive for complex neurodegenerative diseases involving multiple pathological pathways simultaneously.

4. Expert opinion

4.1. Clinical development of σ_1 receptor agonists as a new trend

Historically, σ_1 receptor research was largely confined to molecular neuropharmacology and medicinal chemistry. During the first decades of investigation, extensive binding studies and pharmacological analyses led to the development of highly selective ligands such as PRE-084, igmesine, cutamesine, and the BD series. These compounds remain valuable experimental tools.

However, progress toward clinical application was initially slowed by incomplete understanding of the receptor's biology and mechanisms of action. The identification of the σ_1 receptor as a ligand-operated intracellular chaperone by Hayashi and Su [1] represented a turning point that significantly accelerated the field. Today, improved molecular tools, fluorescent probes, antibodies, and pharmacological methods allow much more precise characterization of σ_1 receptor function and ligand activity. As confidence in the biological relevance of the receptor has increased, so too has interest in therapeutic development.

A selective σ_1 receptor agonist may effectively function as a polypharmacological agent because it simultaneously modulates processes occurring in the ER, mitochondria, nucleus,

and plasma membrane. Through regulation of calcium signaling, receptor activity, stress responses, and cellular survival pathways, σ_1 receptor agonists can broadly restore cellular homeostasis. Importantly, favorable safety profiles observed in previous clinical studies have further stimulated drug development efforts. In parallel, hybrid compounds and MTDLs have emerged as promising strategies for treating multifactorial disorders. By targeting multiple disease mechanisms with a single molecule, these compounds may improve efficacy while minimizing side effects associated with combination therapies. Recent examples include dual σ_1 receptor agonist/HDAC inhibitors capable of reducing tau aggregation and promoting tau solubility [15], as well as σ_1 receptor agonist/butyrylcholinesterase inhibitors designed to simultaneously enhance intracellular neuroprotection and reduce extracellular amyloid toxicity [16].

Overall, medicinal chemistry programs focused on σ_1 receptor agonists remain highly active, and the steady increase in new chemical series reported over the last decade suggests sustained momentum in the field.

4.2. Clinical development of σ_1 receptor agonists as an emerging therapeutic option

Positive data from ongoing phase 2 and phase 3 clinical trials in Alzheimer's disease, Huntington's disease, and ALS have substantially strengthened the therapeutic credibility of σ_1 receptor agonists [12,13]. Regulatory discussions are ongoing, and growing clinical experience is helping refine treatment protocols and biomarker selection.

The range of potential indications for σ_1 receptor agonists continues to expand. Beyond neurodegenerative diseases, these compounds may prove useful in cognitive disorders, anxiety disorders, psychiatric illnesses, autism spectrum disorders, motor neuropathies, autoimmune diseases, and various tauopathies such as frontotemporal dementia and progressive supranuclear palsy. Some of these conditions are associated with SIGMAR1 mutations, emphasizing the direct pathophysiological relevance of the receptor. Nevertheless, many of these indications remain insufficiently explored. For instance, aging-related alterations in σ_1 receptor expression and regulation, by endogenous neuroteroids for instance, in the different organs and structures involved in the pathologies must be fully understood.

Because of the receptor's unusual intracellular biology, successful therapeutic development requires detailed understanding of pharmacokinetic and pharmacodynamic properties. Future preclinical and clinical studies will therefore need to optimize dosing strategies, target engagement measurements, and biomarker identification.

One of the greatest advantages of targeting the σ_1 receptor lies in its ability to induce broad but moderate activation of endogenous cellular survival mechanisms. Rather than acting through a single pathway, σ_1 receptor agonists restore cellular homeostasis through coordinated modulation of multiple intracellular processes.

Accumulated data now support beneficial effects ranging from the cellular level to organ and systemic physiology. Consequently, the clinical development of σ_1 receptor agonists is likely to accelerate in the coming years, offering a potentially transformative therapeutic approach for complex diseases that currently lack effective treatments.

Funding

This paper was not funded.

Declaration of interest

The author holds patents on drugs and is a co-founder and shareholder of Sitera Pharmaceuticals, developing σ_1 receptor agonists in rare genetic diseases. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The author declares that no generative AI tools were used in the preparation of this manuscript.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgments

The author thanks the COST action CA23156, SIGMA-1 EUROPE, for support and helpful discussions.

Author contributions

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