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masses called Lewy bodies form. Exosomes, membrane nanovesicles that are secreted by cells in the CNS, have been found to contain -Syn oligomers, which is interesting. Neurons from various brain regions, including the neocortex, hippocampus, substantia nigra, thalamus, and cerebellum, express -Syn at high levels in the central nervous system (CNS). In addition to other synucleinopathies, PD relies heavily on the aggregation of -Syn. Neuronal cell inclusions, axonal spheroids, and oligodendrocyte aggregates (glial cytoplasmic inclusions) that accumulate in MSA are the results of abnormal -Syn, making -Syn brils important therapeutic targets in PD and synucleinopathies that are related. With a global prevalence of over 6 million, PD is the second most common ND. Despite the fact that the exact cause of Parkinson's disease (PD) is still unknown, -Syn has emerged as the main molecule in PD pathogenesis. Lewy bodies, which are intracellular inclusions of aggregated -Syn, are a pathological hallmark of PD. e third most prevalent type of degenerative dementia is Lewy body dementia, or dementia with observable Lewy bodies. Visual hallucinations, movement disorders, cognitive issues, di culty sleeping, erratic attention, and depression are all symptoms of Lewy body dementia, which progresses over time and causes mental function to deteriorate [6].

Ubiquitination and phosphorylation of α-Syn

α -Syn is phosphorylated most frequently in serine and tyrosine residues. It is typically phosphorylated at S129 and S87 in Lewy bodies. Phosphorylation at S129 increases from 5% in healthy brains to about 90% in Lewy bodies, which are strongly linked to Parkinson's disease [7]. However, it is unclear why LBD pathologies like PD and DLB involve extensive phosphorylation. e impact of S129 on -Syn aggregation has been the subject of contradictory in vitro studies. It has been reported that mitochondrial impairment-induced increased Ca2+ in ux causes a change in the solubility of -Syn proteins from normally soluble to insoluble and causes Ser129 phosphorylation to produce a signal for proteasomal degradation [8]. -Syn aggregates may continue to undergo phosphorylation because Ser129 phosphorylation contributes to the process of removing excess -Syn. It also interacts with metal ions and various proteins, such as fatty acid-binding protein 3 and lipid membranes. e majority of S87-P-Syn was also found in the membrane fractions of brain homogenates from transgenic animals and diseased human brains. Within the NAC region, S87 is one of the few residues and phosphorylation sites. According to a previous study, S87 phosphorylation destabilizes the helical conformation of membrane-bound -Syn and decreases the protein's lipid-binding a nity around the phosphorylation site, altering its conformation and decreasing its a nity for lipid vesicles. It has been reported that the S87 cryo-TEM structure of -Syn brils faces the outside of the bril; As a result, it can still be used to modify -Syn brils in response to disease. e pathogenesis of a number of NDs has been linked to the ubiquitination of protein laments that have been aggregated or formed [9]. Ubiquitin-Syn is found in Lewy bodies; As a result, their immunoreactivity to anti-ubiquitin antibodies has been demonstrated. -Syn has eight lysine residues that are able to be ubiquitinated, and ubiquitin has multiple internal lysine residues that are able to form polyubiquitin chains. e presence of ubiquitin in synucleinopathies' intracellular inclusions suggests that, like tau in AD's neuro brillary tangles, abnormally aggregated or misfolded proteins are the target of ubiquitination in these inclusions [10].

e Brain and LPLs

rough the "Lands cycle," PLs and LPLs can join together to maintain lipid homeostasis. As a result of their neurotransmitter and/or neuromodulatory properties, some lipids, like LPLs, may be neuroprotective [11]. Long-chain polyunsaturated unsaturated fats have been found to signi cantly improve mouse mind phospholipids. According to recent research, LPC is the preferred carrier of polyunsaturated fatty acids into the brain across the BBB. Either the lecithin cholesterol acyltransferase (LCAT) reaction or the hydrolysis of PC by PLA2 (which involves removing a fatty acid group at the sn-2 position) are the processes that result in the production of LPC. According to a Drosophila model, PLA2G6 dysfunction, which causes PARK14-related familial Parkinson's disease, alters the binding a nity between -Syn and the synaptic membrane, causing damage to the phospholipid remodeling pathway and causing -Syn aggregation. e concentration of LPC in healthy individuals' blood plasma typically ranges between 200 and 300 M. Due to its rapid debasement, LPC is readily available and has a short half-life, preventing impairment of various vascular capabilities. Currently, it is thought that activated platelets release LPLs like LPC, LPE, and LPS, which the serum's lyso-PLD turns into LPA. LPC is said to have signi cant platelet-destroying e ects. Several NDs, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and prion diseases, all have impaired platelet function [12]. In NDs, platelet dysfunction is common. Secretory phospholipases' modi cation of lipoproteins slowed platelet activation and aggregation, according to a recent study. e researchers discovered that LPC is necessary for these e ects. LPC is increasingly being recognized as a key factor positively associated with NDs, as evidenced by lower plasma levels of LPC in AD patients [13]. It has been discovered that adult AD patients' blood plasma, cerebrospinal uid (CSF), and brain tissue contain lower LPC concentrations than healthy adults'. Phosphocholine makes up the headgroup of LPC, and glycerol makes up the backbone. Both of these groups are connected to a variable fatty acid group that can be bound at the sn-1 or sn-2 position. Polyunsaturated fatty acids (PUFAs) are typically bound in tissues and plasma at the sn-2 position, whereas saturated fatty acids (SFAs) are typically bound at the sn-1 position of LPC. e mind gets plasma unsaturated fats principally from two pools: plasma fatty acids without esteri cation and those with esteri cation as LPC. According to previous research, FAs bound to LPCs are more e ciently transported across the BBB into the brain than free fatty acids (FAs). containing MFSD2A, a member of the major facilitator superfamily An orphan transporter is a transporter that has been shown to act as a speci c LPC receptor, such as the human sodium carbonate electrogenic LPC symporter 1. LPCs carry long-chain PUFAs like DHA across the BBB [14]. According to other studies, the brain can only synthesize a few fatty acids; As a result, the BBB is necessary for the majority of blood-derived fatty acids to enter the brain. However, cholesterol and lipoproteins are unable to cross the BBB under normal physiological conditions. For a little molecule drug to cross the BBB in pharmacologically basic aggregates, the molecule ought to have twofold sub-nuclear characteristics, speci cally, a sub-nuclear mass of 400-500 Da and high lipid dissolvability. Accordingly, we conjecture that LPLs could be utilized to make an oral, little atom inhibitor of - Syn