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Guanyl hydrazone-based structures as BBB-compliant binders of the retromer complex for ALS treatment

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The Retromer complex plays a central role in endosomal protein sorting and retrograde trafficking to the Trans-Golgi Network (TGN), thereby preserving cellular homeostasis and proteostasis through the recycling of key membrane proteins. Its dysfunction is implicated in major Neurodegenerative Diseases (NDDs), including Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic Lateral Sclerosis (ALS), where impaired protein quality control and toxic misfolded protein aggregation represent shared pathogenic mechanisms. Consequently, the Retromer complex has emerged as a validated therapeutic target, and its stabilization—particularly through protection of core components such as Vps35 from degradation—has been proposed as a promising disease-modifying strategy to counteract proteotoxicity.1 In this context, a Structure-Based Drug Design (SBDD) approach was employed to target the Vps35–Vps29 interface, leveraging extensive structural information from NMR and Cryo-EM studies. The most advanced lead compound, DN48, was obtained through iterative structural refinement aimed at reducing undesirable polypharmacology, including off-target activity at 5HT1A receptors, although residual off-target interactions remain to be optimized. The selection of the aryl guanyl hydrazone (GH) moiety was guided by the need to ensure Blood-Brain Barrier (BBB) permeability, a critical requirement for central nervous system (CNS) therapeutics. Unlike highly basic or permanently charged functionalities found in early high-throughput screening hits (e.g., isothiourea groups in R55), aryl GHs display moderate basicity (pKa 6.5–9.2),2 allowing a substantial fraction to remain nonionized at physiological pH (7.4), thus favoring passive diffusion across the BBB. Moreover, the GH scaffold provides structural adaptability through tautomeric equilibrium between hydrazone and preferential azine forms, enabling flexible charge distribution within the binding site and supporting effective stabilization of the Retromer complex.

References:

[1] A. Hierro et al. Nature **2007**, 449,1063–1067.

[2] L. Muzio *et al*. *Nat. Commun*, **2020**, 11, 3848.