Development of fragment-based workflows that enable rapid and cost-effective discovery of drug-like protein-protein interaction modulators targeting the Neuronal Calcium Sensor 1

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Neuronal Calcium Sensor 1 (NCS-1) plays a crucial role in regulating protein targets involved in G-protein signaling pathways, including the dopamine D2 and cannabinoid CB1 receptors, both of which are associated with neuronal disorders. Previous research has identified the interaction interface between NCS-1 and the G_{α} chaperone and guanine nucleotide exchange factor Ric-8A as a promising therapeutic target, with potential applications in neurodegenerative and neurodevelopmental diseases [1,2,3].

Building on insights from crystallographic fragment screening, streamlined and cost-efficient drug discovery workflows have been developed. By integrating semi-automated procedures and robotic systems for chemical synthesis, fragment-based compounds have been systematically designed, synthesized, and analyzed using X-ray crystallography and grating-coupled interferometry, directly from crude reaction mixtures. This approach has facilitated an extensive exploration of the chemical space at the NCS-1 protein-protein interaction (PPI) interface, leading to the identification of structurally diverse molecules with PPI modulatory activity. These compounds serve as a strong foundation for the development of selective hit-to-lead candidates with drug-like properties, tailored to different pharmacological targets.

[1] Mansilla, A. *et al. (*2017) *PNAS*, **114**, E999–E1008.

[2] Canal-Martín, A. *et al.* (2019) *Nat. Comms.* **10**, *Art. No. 2798.*

[3] Muñoz-Reyes D. *et al.* (2023) *eLife Journal* **12**, *e86151.*