# PH-Domain focused screening by DNA display of lipidic small molecules library identifies novel mTORC2 inhibitor

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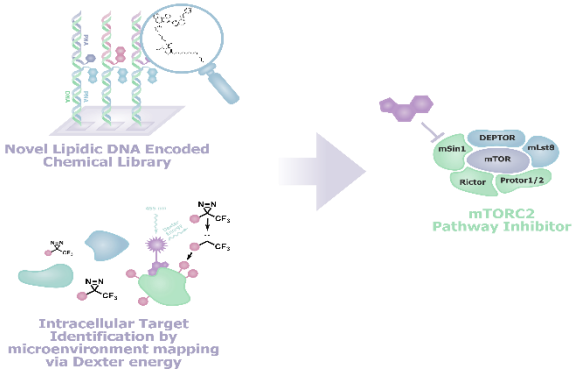
The PH domains represent the largest family of proteins that interact with phosphoinositide. Protein-lipid interactions are essential in many cellular processes. However, designing small molecules that can effectively target these PH domains remains a challenging task due to their structural similarities, the positively charged binding pocket, and the hydrophobic binding environment of the membrane.[1] Our study focuses on mTORC2, a protein complex that plays a crucial role in regulating cell growth, proliferation and autophagy. Within this complex, the AKT and mSin1 domains are responsible for mediating phosphorylation cascade.[2] In order to identify selective binders for these PH domains, we conducted a screening campaign using encoded PNA/DNA libraries of small molecules.[3] To enhance our chances of success, we created a unique library of PNA-encoded lipid-mimetic small molecules using standard SPPS methods, which allowed us to explore a vast chemical space. Through a two-step combinatorial screening approach, involving the combination of 500 x 450 (250,000) fragments followed by the generation of 625-membered focus libraries by covalently paring the best fragments, we found several potential selective binders. One of these compounds exhibited *in cellulo* activity on the AKT phosphorylation pathway. To further investigate the target engagement of the hit compound, we leveraged on Dexter energy transfer and found that mSin1 was the primary target enriched in the mass spectrometry data.[4]

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