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Discovery of novel scaffolds for p21-activated kinase 4 inhibitors targeting C- terminal

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P21-activated kinases (PAKs) are a family of serine/threonine kinases that act downstream of Rho GTPases, Rac and Cdc42. PAKs play a critical role in cytoskeletal organization, cell cycle progression, migration and invasion, and cell survival. PAK4, as the principal member of group II PAKs, mainly regulate its functions via a kinase domain in the C terminal, where all of the existing PAK4 inhibitors target. In this study, a series of novel 1-phenanthryl- tetrahydroisoquinoline analogues have been designed and synthesized as a novel class of small-molecule PAK4 inhibitors to fit into the cavity of PAK4. All of the target compounds were evaluated for their *in vitro* PAK4 inhibitory activities and antiproliferative activities. Its affinity to C-termini of PAK4 was confirmed by BSA (Biotin-Streptavidin assay). Furthermore, this compound inhibits the invasion and migration of A549 tumor cells by regulating PAK4-Lim domain kinase 1 (LIMK1)-Cofilin signaling pathways *in vitro*, and exhibits anti-tumor activity *in vivo* in the A549 tumor xenografts model.

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