

Targeting the Hedgehog and Wnt Signaling Pathway with Small Molecules

Aberrant activation of Hedgehog (Hh) pathway has been associated with numerous malignancies including basal cell carcinoma, medulloblastoma, pancreatic, colorectal cancers. Several reports also suggest that positive regulators of Hh pathway could be used in the treatment of neurodegenerative diseases.

ChemDiv has been working on design and evaluation of compound libraries that are to modulate Hh and Wnt pathways. Considering “druggability” of specific targets in both pathways, we decided to focus our initial effort on identification of 7-TM (Smo, Fz) and S/T kinases (Fu, GSK3 β) and transcription factor (Gli's) specific inhibitors. A particular attention was paid to compounds acting downstream of Smo and Fz, a 7TM proteins. Initial set of 5,000 compounds was assayed to identify both Hh and Wnt modulators. For example, we identified compounds that affected Hh signaling in the Shh-N-producing HEK 293 cells with EC₅₀'s in 0.4-5 μ M range. Additional chemotypes with similar levels of activity were also detected in Wnt assay. Based on the success of the first phase of screening, we have assembled second generation libraries of Hh and Wnt pathway modulators (approx. **3,200 compounds each, no duplicates**). Particular attention has been paid to i) IP potential (estimated 60% of templates and respective compounds have Beilstein/SciFinder score “0”), ii) synthetic feasibility, iii) drug-like potential and iv) activity profile of the identified templates. We have also included several “universal” templates representing peptidomimetics (β , γ - turns) and Ro3 to enrich chemical diversity of these screening sets.