Discovery of Aminoquinolines as a New Class of Potent Inhibitors of Heat Shock Protein 90 (Hsp90)

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Technology description

Technical Summary

We have identified a known anti-malarial agent quinocide-dihydrochloride through high-throughput screening, as having inhibitory activity at the n-terminal ATP binding site of Hsp90. This compound has a novel chemical scaffold when compared to known Hsp90 inhibitors. This compound is interesting as it has shown activities in the low micromolar range in both fluorescent polarization and western blot assays and many analogs of this scaffold (aminoquinolines) are available for SAR from the National Cancer Institute (NCI) compound collection. We identified thirty-five compounds from the NCI collection and tested these in both our FP and WB assays as the starting point for the development of novel Hsp90 small molecule inhibitors.

We have generated a number of novel aminoquinoline molecules based on the SAR data from the NCI compounds and in silico structural analysis of active compounds and the ATP binding site on Hsp90. Additional chemistry follow up is planned in order to further evaluate this family of molecules forin vivoefficacy and toxicity.

Hsp90 has emerged as an important biological target that modulates a variety of cellular processes including cell maturation, stability, and conformational maintenance of signature cancer proteins. Reports indicate that Hsp90 from stress-induced cells exhibits a higher affinity for small molecule inhibitors relative to normal cells as a result of increased refolding requirements of its mutated or altered clients. Thus, identification of selective tumor-specific Hsp90 inhibitors could lead to the specific targeting of cancer cells and circumvent systemic toxicities.

Application area

Compositions and methods for inhibiting Hsp90 activity.

Advantages

Ongoing drug development project in the Emory Institute for Drug Discovery.

Several series of molecules identified by HTS having Hsp90 inhibitory activit.

Novel family of small molecules having significant Hsp90 inhibitory activity (Ganesh, T. et al., Bioorg. Med. Chem. (2008).

Selectivity and potency enhancement under exploration with multiple third-party assay panels and additional chemistry work.

Institution

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