Synthesis and Structure-Activity Relationship of Griseofulvin Analogues as Inhibitors of Centrosomal Clustering in Cancer Cells - DTU Orbit (15/06/2017)

Synthesis and Structure-Activity Relationship of Griseofulvin Analogues as Inhibitors of Centrosomal Clustering in Cancer Cells

Griseofulvin was identified as an inhibitor of centrosomal clustering in a recently developed assay. Centrosomal clustering is an important cellular event that enables bipolar mitosis for cancer cell lines harboring supernumerary centrosomes. We report herein the synthesis and SAR of 34 griseofulvin analogues as inhibitors of centrosomal clustering. The variations in the griseofulvin structure cover five positions, namely the 4, 5, 2', 3', and 4' positions. Modification of the 4 and 5 positions affords inactive molecules. The enol ether must be at the 2' position, and the 4' position needs to be Sp2 hybridized. The most active analogues were the 2'-benzyloxy and 2'-(4-methylbenzyloxy) analogues as well as the oxide of the former with a 25-fold increase of activity compared to griscofulvin. Comparison of the results obtained in this work with prior reported growth inhibition data for dermatophytic fungi showed both similarities and differences.

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