In contrast to normal cells, malignant cells are frequently aneuploid and contain multiple centrosomes. To allow for bipolar mitotic division, supernumerary centrosomes are clustered into two functional spindle poles in many cancer cells. Recently, we have shown that griseofulvin forces tumor cells with supernumerary centrosomes to undergo multipolar mitoses resulting in apoptotic cell death. Here, we describe the characterization of the novel small molecule GF-15, a derivative of griseofulvin, as a potent inhibitor of centrosomal clustering in malignant cells. At concentrations where GF-15 had no significant impact on tubulin polymerization, spindle tension was markedly reduced in mitotic cells upon exposure to GF-15. Moreover, isogenic cells with conditional centrosome amplification were more sensitive to GF-15 than parental controls. In a wide array of tumor cell lines, mean inhibitory concentrations (IC50) for proliferation and survival were in the range of 1 to 5 μmol/L and were associated with apoptotic cell death. Importantly, treatment of mouse xenograft models of human colon cancer and multiple myeloma resulted in tumor growth inhibition and significantly prolonged survival. These results show the in vitro and in vivo antitumor efficacy of a prototype small molecule inhibitor of centrosomal clustering and strongly support the further evaluation of this new class of molecules. Cancer Res; 72(20); 5374–85. ©2012 AACR.