Development of novel rhodacyanine-based heat shock protein 70 inhibitors

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In this study, we report a new series of rhodacyanine-based Hsp70 Inhibitors, represented by compounds 1 and 6, in which the cationic thiazol-3-ium or pyridin-1-ium rings of existing Hsp70 inhibitors were replaced by a benzo-fused N-heterocycle. We obtained several lines of evidence that these compounds act on Hsp70 to exert their antitumor activities. First, these inhibitors displayed differential antiproliferative efficacy against breast cancer cells (IC50 as low as 0.25 μM) versus nonmalignant MCF-10A breast epithelial cells (IC50 5 μM), which correlated with the relative expression levels of Hsp70 between these two types of cells. Second, using a protein-refolding assay, we demonstrated the ability of these agents to inhibit Hsp70’s chaperon activity. Third, these inhibitors effectively suppressed the expression of Hsp70’s oncogenic client proteins, including FoxM1, HuR, and Akt, with potency parallel to their antiproliferative efficacy. Fourth, consistent with the role of Hsp70 in regulating protein refolding, these Hsp70 inhibitors induced autophagy, as characterized by LC3B-II conversion. Furthermore, these Hsp70 inhibitors did not cause the compensatory elevation in Hsp90 expression, which contrasted the reported effect of Hsp90 inhibitors on Hsp70 upregulation. Together with the finding that compounds 1 and 6 showed improved microsomal stability, these data suggest the translational potential of these newly developed Hsp70 inhibitors to foster new strategies for cancer therapy.

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