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Phenotypes of a novel series of 3-phosphoglycerate dehydrogenase inhibitors

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PHGDH (3-phosphoglycerate dehydrogenase) is the first enzyme branching from glycolysis into the serine synthetic pathway and it oxidizes 3-phosphoglycerate into phospho-hydroxypyruvate using nicotinamide adenine dinucleotide (NAD) as cofactor. Increase in PHGDH expression at both mRNA and protein levels have been observed in nearly 70% of estrogen receptor-negative breast cancers; in addition a fraction of malignant breast and melanoma cells are dependent on elevated expression of 3-phosphoglycerate dehydrogenase (PHGDH). Furthermore, serine starvation has been shown to have a dramatic effect on tumor growth during *in vivo* mouse xenograft experiments. PHGDH has been a target of interest in the pharma/biotech industry for several years since the initial reports in early 2012 of its relevance in cancer where PHGDH amplified and overexpressing cancer cell lines have been shown to possess unique sensitivity to PHGDH knockdown that cannot be rescued by nutritional serine. The mechanisms underlying these studies have been subjected to intense investigation but remain unclear. We have been able to successfully identify first in class small molecule inhibitors of this target with nanomolar cellular potency, high degree of selectivity and oral bioavailability. In several cancer cell lines, these compounds inhibited glucose derived serine flux with nanomolar median inhibitory concentrations without significantly affecting glucose derived lactate. These compounds also inhibited glucose derived serine in animal studies and have the potential to be highly useful tools for understanding the role of PHGDH in tumor progression. The data presented here will provide unexpected insights on the role of PHGDH in serine biosynthesis and the dependency of cancer cells on PHGDH catalytic function.

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Synthesis and anticancer activity of 6-aryl-2-naphthyl-imidazo[2,1 b][1,3,4]thiadiazole

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A number of imidazo[2,1-b][1,3,4]thiadiazole derivatives having aralkyl and aryl moieties attached to positions 2 and 6 of imidazo[2,1-b][1,3,4]thiadiazole nucleus, respectively, were prepared and characterized by IR, NMR and mass spectrometry. The cytotoxic activity of a new series of 2-naphthyl-imidazo[2,1-b][1,3,4]thiadiazoles against different human and murine cancer cell lines is reported. Among the tested compounds, five derivatives namely CH17, 24, 34, 37 and 39 emerged as the most potent against all the cell lines. To investigate the mechanism of action, we selected compounds CH34, 37 and 39. These compounds induced PARP and caspase-3 cleavages in HSC-2 cells, suggesting the apoptosis induction.

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