Galoflavina um novo inibidor da dehidrogenase láctica, eficaz na DHL A e B: nova arma no câncer

Galloflavin (CAS 568-80-9): A Novel Inhibitor of Lactate Dehydrogenase.

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ChemMedChem. 2011 Nov 4. doi: 10.1002/cmdc.201100471.

Source

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Abstract

One of the most prominent alterations in cancer cells is their strict dependence on the glycolytic pathway for ATP generation. This observation led to the evaluation of glycolysis inhibitors as potential anticancer agents. The inhibition of lactate dehydrogenase (LDH) is a promising way to inhibit tumor cell glucose metabolism without affecting the energetic balance of normal tissues. However, the success of this approach depends chiefly on the availability of inhibitors that display good selectivity. We identified a compound (galloflavin, CAS 568-80-9) which, in contrast to other inhibitors of human LDH, hinders both the A and B isoforms of the enzyme. To determine the mechanism of action, we collected LDH-A and -B inhibition data in competition reactions with pyruvate or NADH and evaluated the results using software for enzyme kinetics analysis. We found that galloflavin inhibits both human LDH isoforms by preferentially binding the free enzyme, without competing with the substrate or cofactor. The calculated K(i) values for pyruvate were 5.46 μM (LDH-A) and 15.06 μM (LDH-B). In cultured tumor cells, galloflavin blocked aerobic glycolysis at micromolar concentrations, did not interfere with cell respiration, and induced cell death by triggering apoptosis. To our knowledge, the inhibition of LDH is, to date, the only biochemical effect described for galloflavin. Because galloflavin is not commercially available, we also describe herein a procedure for its synthesis and report its first full chemical characterization.

PMID: 22052811