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Abstract:

Most cancer cells exhibit a high rate of glycolysis and reduced capacity in mitochondrial oxidative phosphorylation. The expression of pyruvate dehydrogenase kinases (PDKs) was found to be increased in many cancer cells. Inhibition of PDKs increases the oxidative phosphorylation of glucose, which may disrupt the balance between the demand and supply of oxygen in cancer cell, thus leading to cell death. Several reports suggested that compounds containing (*R*)-3,3,3-trifluoro-2-hydroxy-2-methylpropionamide group could inhibit PDKs in pyruvate dehydrogenase primary enzymatic assay. However, none of them were capable of reducing the growth of cancer cells. Herein, we report the synthesis and biological evaluation of some novel PDK1 inhibitors containing the (*R*)-3,3,3-trifluoro-2-hydroxy-2-methylpropionamide warhead. Excitingly, these novel PDK1 inhibitors exhibited good potency to reduce the growth of cancer cells. We have demonstrated that these compounds could physically associate with PDK1 and activate pyruvate dehydrogenase in low micromolar levels.

***Keywords*:** Pyruvate dehydrogenase kinase; pyruvate dehydrogenase complex; anti-proliferation; binding affinity