

Accepted Manuscript

Synthesis and biological evaluation of (R)-3,3,3-trifluoro-2-hydroxy-2-methylpropionamides as pyruvate dehydrogenase kinase 1 (PDK1) inhibitors to reduce the growth of cancer cells

Shao-Lin Zhang, Wen Zhang, Zheng Yang, Xiaohui Hu, Kin Yip Tam



PII: S0928-0987(17)30165-3

DOI: doi: [10.1016/j.ejps.2017.03.030](https://doi.org/10.1016/j.ejps.2017.03.030)

Reference: PHASCI 3970

To appear in: *European Journal of Pharmaceutical Sciences*

Received date: 13 January 2017

Revised date: 13 March 2017

Accepted date: 23 March 2017

Please cite this article as: Shao-Lin Zhang, Wen Zhang, Zheng Yang, Xiaohui Hu, Kin Yip Tam, Synthesis and biological evaluation of (R)-3,3,3-trifluoro-2-hydroxy-2-methylpropionamides as pyruvate dehydrogenase kinase 1 (PDK1) inhibitors to reduce the growth of cancer cells. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Phasci(2017), doi: [10.1016/j.ejps.2017.03.030](https://doi.org/10.1016/j.ejps.2017.03.030)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Synthesis and biological evaluation of (*R*)-3,3,3-trifluoro-2-hydroxy-2-methylpropionamides as pyruvate dehydrogenase kinase 1 (PDK1) inhibitors to reduce the growth of cancer cells

Shao-Lin Zhang, Wen Zhang, Zheng Yang, Xiaohui Hu and Kin Yip Tam*

Faculty of Health Sciences, University of Macau, Macau, China

* Corresponding author

Phone: +853 88224988, Fax: +853 8822 2314

E-mail: kintam@umac.mo

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

Download English Version:

<https://daneshyari.com/en/article/8511972>

Download Persian Version:

<https://daneshyari.com/article/8511972>

[Daneshyari.com](https://daneshyari.com)