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TITLE

LC-MS Method Development for the DPP-IV Inhibitor Screening

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Dipeptidyl peptidase IV (DPP-IV) is an enzyme of considerable biomedical interest. It plays an important role in glucose homeostasis through proteolytic inactivation of incretin hormones, primarily glucagon like peptide-1 (GLP-1) which is critical in sugar balance. Traditionally, the DPP-IV inhibitors were evaluated using fluorogenic or chromogenic methods. However, it is limited by the selection of substrates since the cleavage product of the substrates must be fluorogenic or chromogenic. In addition, it requires that the candidate inhibitors should be of no fluorescence or chromophorous.

Herein, we reported an LC-MS method for the DPP-IV inhibitors screening by monitoring the decrease of the substrate and the increase of proteolytic product. This LC-MS method was further utilized to determine the IC_{50} values of two positive control compounds (Sitagliptin and Vildagliptin), and validated by comparing the results with those obtained by the fluorogenic method (shown below).

Compounds	IC_{50} Value (nM)		
	LC-MS method	Fluorogenic method	Reported
Sitagliptin	63.07	20.49	18
Vildagliptin	20.82	11.45	3.5

We also prepared two unique tripeptide substrates, Gly-Pro-LeuOMe and Gly-Pro-AspOMe, for this LC/MS method. They are water-soluble and stable in aqueous solution with low backgrounds in biological samples, and can be quickly proteolyzed. The Gly-Pro-LeuOMe has low K_m value (311nM) compared with Gly-Pro-Pna (691.9nM), and Gly-Pro-AspOMe can be completely proteolyzed in 15 min. compared with Gly-Pro-Pna in 60 min.

Biography

Professor Lei Fu received his Ph.D. degree in Chemistry from Stanford University. After a one-year postdoctoral research at Stanford, he joined Pharmacyclics Inc., California in 1998, conducting drug discovery and development research on anti-cancer and anti-cardiovascular diseases. Dr. Fu has been a Professor of Medicinal Chemistry at Shanghai Jiao Tong University since 2006. His principal research interests are 1) drug discovery and development; 2) traditional Chinese Medicines as botanical cosmeceuticals; 3) medical devices as targeted drug delivery systems and 4) chemical induction of hypothermia. He was a visiting scholar in the Department of Chemistry, Stanford University in 2009.