

Novel Dipeptidyl Peptidase IV Inhibitors

MARKET

Diabetes mellitus is a chronic, progressive disease affecting >180 million people worldwide; it is estimated that this disease will affect >360 million people by 2030.¹ According to Centers for Disease Control and Prevention estimates, the total costs attributable to diabetes in 2007 in the United States were \$174 billion.²

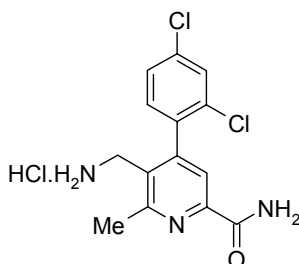
MECHANISM

Inhibition of DPP-IV is a promising therapeutic approach for the treatment of diabetes in which the endogenous incretin hormones are targeted. These agents improve glycemic control by preventing the rapid inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic peptide (GIP), leading to a longer stimulation of insulin release, inhibition of glucagon secretion, and potentially an improvement in pancreatic beta-cell function. In view of likely toxic side effects associated with the inhibition of other members of DPP family, it has become necessary to design more selective inhibitors targeting DPP-IV.

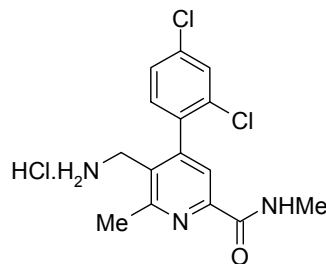
COMPOUNDS

At EMC, novel 4-aryl substituted pyridines were identified as selective and highly potent inhibitors of the dipeptidyl peptidase IV enzyme. These compounds are prepared in good yields and high purity in any scale.

Examples:



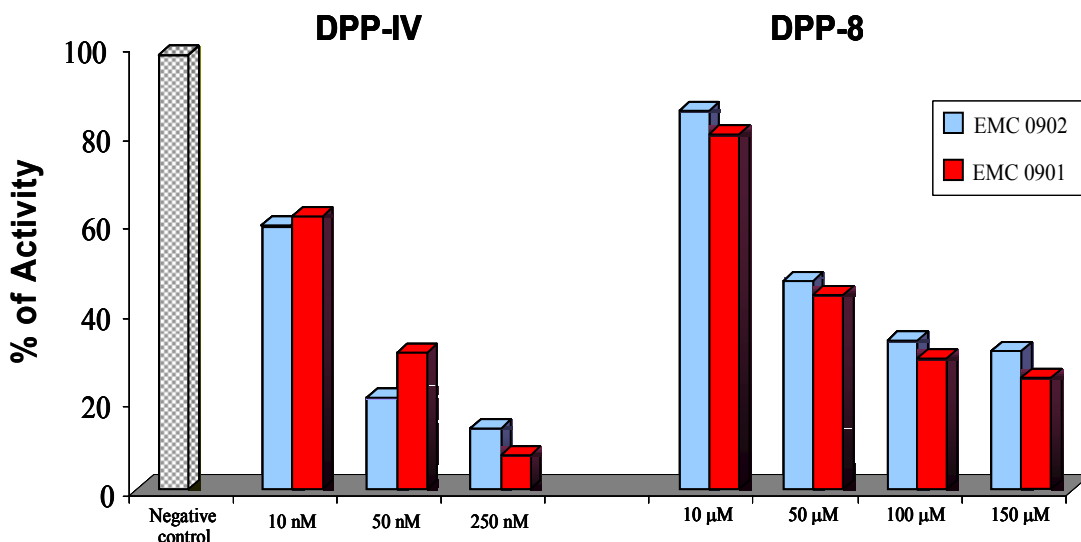
EMC 0901



EMC 0902

EFFICIENCY

Inhibitory activity of the new compounds was measured by the inhibition of human recombinant DPP-IV and DPP-8 activity by following the absorbance increase upon cleavage of the chromogenic substrate Gly-Pro-pNA.



SELECTIVITY

The new compounds show a very high selectivity. The IC₅₀ levels for the inhibition of DPP-IV are in the low nanomolar range. In contrast, for the inhibition of DPP-8, a 3000-fold bigger amount is necessary.

	EMC 0901	EMC 0902
IC₅₀ DPP-IV	16 nM	11 nM
IC₅₀ DPP-8	33 µM	39 µM

TOXICITY

No toxic effects were observed on HeLa cell line at compound concentrations up to 10 µM.

INTELLECTUAL PROPERTY

The new compounds are covered by an EP application filed in October 2009 (EP 09 01 2781).

REFERENCES

1. World Health Organization. The diabetes fact sheet (no. 312, Nov 2008). Available at: www.who.int/mediacentre/factsheets/fs312/en
2. Centers for Disease Control and Prevention. National diabetes fact sheet, 2007. Available at: www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf

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