

Study of chemical stability, plasma and microsomal metabolism of LASSBio-1772: A novel anti-diabetes prototype

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Abstract

LASSBio-1772 is a new anti-diabetes prototype that showed great chemical and plasma stability and a slow metabolism rate in rat liver microsomes.

Introduction

Diabetes mellitus is a chronic and prevalent disease related to various complications when poorly controlled ^[1]. Recently, LASSBio-1772 was discovered as a novel partial agonist of PPAR- γ , showing hypoglycemic effect and analgesic activity in a murine model of diabetic neuropathy ^[2].

In order to establish the real therapeutic potential of LASSBio-1772, its pharmacokinetic profile should be disclosure. In this context, we report the evaluation of chemical stability, the plasma and microsomal metabolism profile of LASSBio-1772 and its permeation in PAMPA assays.

Results and Discussion

The anti-diabetes prototype LASSBio-1772 was evaluated for chemical stability in buffered ambience of pH 2 and pH 7,4, in order to predict its stability in biological environments, considering the stomach and plasma pH.

LASSBio-1772 is stable in the two ambiances, according to analysis by HPLC-PDA. In addition, the recovery rate of more than 95% of this prototype proves its stability in these environments, indicating its preservation in biophase.

The study of plasma and microsomal metabolism *in vitro* was performed with plasma and liver microsome from male Wistar rats, in order to assess the formation of oxidative metabolites against the enzymes present in the microsomal fraction (e.g. CYP450, CES and FMO) and in plasma (e.g. hydrolases).

LASSBio-1772 showed stability against the action of plasma esterases, according to the analyzes by HPLC-PDA. The absence of classic metabolically labile sites to the action of these enzymes, in the molecular structure of LASSBio-

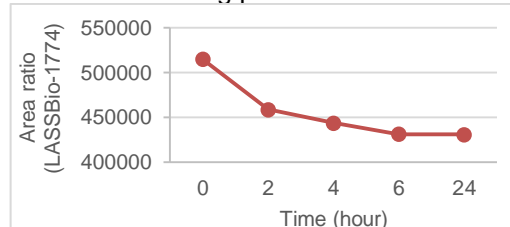
1772, shows a strong indicator of the plasma stability of this compound.

The prototype LASSBio-1772 was little metabolized in the microsomal fraction in the presence of cofactor, indicating oxidative action of CYP450 and/or FMO.

Two metabolites were identified with close retention time and the same ultraviolet spectrum. The characterization of these metabolites was made by HPLC/MS, identifying two isomers of position generated from a demethylation metabolism.

As demonstrated in Chart 1, LASSBio-1772 has a slow metabolism rate, with a slow decline of area ratio *versus* the incubation time, indicating its high half-life.

Chart 1. Metabolizing profile of LASSBio-1772



Conclusion

We demonstrated that LASSBio-1772, previously identified as new prototype to treat diabetes and its chronic complications, has great chemical and plasma stability and showed slow metabolism in the presence of rat liver microsomes. LASSBio-1772 half-life and its permeation profile are been studied.

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