LISOFYLLINE AS A PRODUCT OF *IN VITRO* BIOTRANSFORMATION OF PENTOXIFYLLINE

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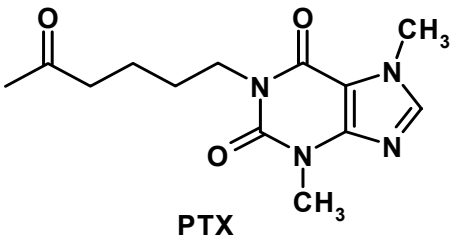
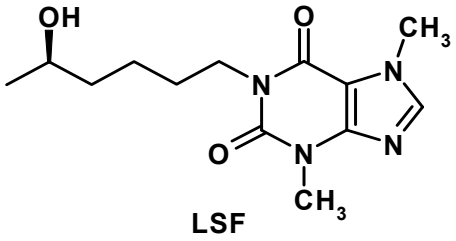
Lisofylline, 1-(5-R-hydroxyhexyl)-3,5-dimethylxanthine (LSF) is a novel methylxanthine with anti-inflammatory properties, that was originally developed to reduce cellular damage due to ischemic reperfusion, hypoxia, or autoimmune diseases. LSF is several hundred-fold more effective than its parent compound, pentoxifylline (PTX), at inhibiting responses to treatment with inflammatory cytokines. LSF inhibits stress-activated lipid metabolism, suppresses the production of inflammatory cytokines, such as interleukin (IL)-12,which exerts these effects through a common lipid intracellular signaling pathway, reduces toxicity and improves patient responses to cancer chemotherapy and radiation therapy. LSF can decrease dysfunction caused by IL-1ß in pancreatic islets, so may have therapeutic value in prevention of autoimmune disorders, including Type 1 diabetes, and autoimmune recurrence following islet transplantation, and in preservation of ß cell functional mass during isolation.



PTX



LSF

LSF can be synthesized in different ways (using chemical or microbial methods) [1-3]. As this agent is not commercially available in Poland we had to obtain it for the pharmacokinetic studies by new methods. One of them was biotransformation of PTX by enantioselective enzymatic reduction using alcohol dehydrogenase from *Lactobacillus kefi*r (LKADH-Fluka or Zyme) with ee = 100% [4].

In another type of experiments LSF was obtained under *Saccharomyces cerevisiae* – mediated reduction of PTX with different yield and enantiomeric excess. Five strains of yeast were used to the microbial conversion of PTX. Reductions were carried in water and in a few organic solvents. The yields of transformations and amounts of each enantiomer formation were examined by means of chiral HPLC.

[1]. Bianco J. A., Woodson P., Porubek D., Singer J. (Cell Therapeut. Inc.) JP 94509584, JP 96259565,
[2]. Klein J.P., Leigh A. J., Michnick J., Kumar A.M., Underiner G.E. (Cell Therapeut. Inc.) WO 9531450
[3]. Aretz W., Furrer H., Gebert U., Hinze H.J. (Hoechst AG) DE 3942872
[4]. Kieć-Kononowicz K., Pękala E. (CMUJ) P-369904, 2004

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