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Zinc(II) complexes with allixin-derivatives as oral therapeutics for type 2 diabetes

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Abstract:
During the investigation on the development of Zn(II) complexes with a blood glucose-lowering effect in experimental diabetic animals, we found a potent bis(maltolato)Zn(II) complex ($Zn(ma)_2$) which exhibited an excellent blood glucose lowering effects in a type 2 diabetic animal model by daily intraperitoneal (*i.p.*) injections. In order to find orally active Zn(II) complexes in treating type 2 diabetic mellitus, we examined the *in vitro* and *in vivo* structure-activity relationships of Zn(II) complexes by using bis(3-hydroxypyronato)Zn(II) complex ($Zn(3hp)_2$) as a leading compound. Zn(II) complex ($Zn(alx)_2$) with allixin (Halx) isolated from garlic, exhibited the relatively high *in vitro* insulin-mimetic activity, as determined by the inhibition of free fatty acid (FFA)-release in isolated rat adipocytes treated with epinephrine. The insulin-mimetic activity of Zn(II) complexes examined strongly correlated with the partition coefficient of the ligand, indicating that the activity of Zn(II) complexes depends on the lipophilicity of the ligand. In type 2 diabetic KKA^y mice, $Zn(alx)_2$ exhibited higher anti-diabetic activity than $Zn(ma)_2$ by daily *i.p.* injections for 2 weeks. In addition, daily oral administrations of $Zn(alx)_2$ lowered the high blood glucose levels in KKA^y mice, however the effect was not so high. In order to find more active Zn(II) complexes than $Zn(alx)_2$, three $Zn(alx)_2$-related complexes were newly prepared and a Zn

(II) complex ($Zn(tanm)_2$) with 1,6-dimethyl-3-hydroxy-5-methoxy-2-pentyl-1,4-dihydropyridine-4-thionato was found to have extremely high *in vitro* insulin-mimetic activity.

Key words: Zn(II) complex, allixin, *in vitro* insulin-mimetic effect, anti-diabetic effect, KKA^y mice

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