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## Exploring Vanadium Chemical Transferrin Mimetic Compounds for Insulin Enhancement

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# Exploring Vanadium Chemical Transferrin Mimetic Compounds for Insulin Enhancement\*

Amanda Feliciano; Arthur D. Tinoco, Ph.D.; and Sergio A. Loza

## Abstract

*Diabetes Mellitus* (DM) is caused by a lack of insulin production (Type 1) or the body's cells' inability to properly receive it, also known as insulin resistance (Type 2), resulting in greatly elevated levels of blood glucose. Vanadium(IV) and vanadium(V) ions are believed to enhance insulin activity by inhibition of protein tyrosine phosphatase 1B (PTP1B). PTP1B is normally responsible for downregulating the insulin signaling, but in DM type 2, PTP1B activity is overexpressed leading to the insulin signaling blocking. The most promising V(IV) compounds are designed for oral delivery: they are absorbed into the gut and delivered into the bloodstream where they are bound by the iron transporting protein serum transferrin (sTf). STf delivers the compound into cells via endocytosis, where vanadium can bind PTP1B. A limitation of these compounds is their poor stability at the stomach acidic conditions in which they undergo a significant amount of dissociation, resulting in a very inefficient gut absorption. This study explores the use of a chemical transferrin mimetic (cTfm) ligand to create V(IV) and V(V) compounds featuring excellent acidic pH stability for improved gut absorption. The cTfm-V(IV,V) compounds are expected to be labile in the pH of the bloodstream and thus the vanadium species can be quickly ligand exchanged with sTF. The cTfm ligand N,N'-di(o-hydroxybenzyl)ethylenediamine-N,N'-diacetic acid (HBED) was used to synthesize VO(IV)HBED and VO(V)HBED which demonstrated great aqueous stability in the 1-4 pH range. The role of citrate as a vehicle for delivering vanadium to sTf to regulate the transport of vanadium is also examined.

**KEYWORDS:** Diabetes; insulin vanadium; transferrin mimetic; aqueous stability

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### **ABSTRACT**

*Diabetes Mellitus* (DM) is caused by a lack of insulin production (Type 1) or the body's cells' inability to properly receive it, also known as insulin resistance (Type 2), resulting in greatly elevated levels of blood glucose. Vanadium(IV) and vanadium(V) ions are believed to enhance insulin activity by inhibition of protein tyrosine phosphatase 1B (PTP1B). PTP1B is normally responsible for downregulating the insulin signaling, but in DM type 2, PTP1B activity is overexpressed leading to the insulin signaling blocking. The most promising V(IV) compounds are designed for oral delivery: they are absorbed into the gut and delivered into the bloodstream where they are bound by the iron transporting protein serum transferrin (sTf). sTf delivers the compound into cells via endocytosis, where vanadium can bind PTP1B. A limitation of these compounds is their poor stability at the stomach acidic conditions in which they undergo a significant amount of dissociation, resulting in a very inefficient gut absorption. This study explores the use of a chemical transferrin mimetic (cTfm) ligand to create V(IV) and V(V) compounds featuring excellent acidic pH stability for improved gut absorption. The cTfm-V(IV,V) compounds are expected to be labile in the pH of the bloodstream and thus the vanadium species can be quickly ligand exchanged with sTF. The cTfm ligand N,N'-di(o-hydroxybenzyl)ethylenediamine-N,N'-diacetic acid (HBED) was used to synthesize VO(IV)HBED and VO(V)HBED which demonstrated great aqueous stability in the 1-4 pH range. The role of citrate as a vehicle for delivering vanadium to sTf to regulate the transport of vanadium is also examined.

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### **ACKNOWLEDGMENTS**

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