The Vesicular Monoamine Transporter-2 (VMAT2): An Important Pharmacological Target for the Discovery of Novel Therapeutics to Treat Methamphetamine Abuse

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Purpose
Methamphetamine (METH) abuse is a serious concern in the United States, but no approved therapeutics are available to treat addicted individuals. Meth increases extracellular dopamine in reward-relevant dopamine pathways by interacting at the vesicular monoamine transporter-2 (VMAT2). Lobeline, the major alkaloid in *Lobelia inflata*, potently inhibited methamphetamine-evoked dopamine release from striatal slices and attenuated meth self-administration in rats. Improved water solubility and enhanced drug-likeness was afforded by the synthesis of GZ-793A, which similarly inhibited the neurochemical and behavioral effects of methamphetamine without the development of tolerance.

Methods
The mixture of p-hydroxybenzaldehyde and 2,6-lutidine was refluxed in acetic anhydride to get the meso-transdiene, which was hydrogenated by using H2-Pd/C to get saturated compound followed by treatment with (S)-glycidol in ethanol gave the appropriate compound, in which acetyl groups were deprotected by K2CO3/MeOH gave the tetrahydroxy derivative of GZ-793A. This was treated with 18F radio labeled ethyl flouro tosylate to get 18F radio labeled GZ-793A.

Results
GZ-793A was a potent competitive inhibitor of DA uptake at VMAT2, exhibiting a Ki value of 29 nM and Imax of 86%. GZ-793A, administered peripherally across a reasonable dose range (3-30 mg/kg), decreased methamphetamine self-administration in rats, without altering responding for food reinforcers. Importantly, tolerance did not develop to the GZ793A-induced decrease in responding for methamphetamine in the self-administration assay. GZ-793A was found to inhibit methamphetamine-evoked DA release from isolated striatal synaptic vesicles via a surmountable allosteric inhibition, and to interact with VMAT2 at several distinct sites on the protein, both extravesicular and intravesicular. These results from the neurochemical assays support VMAT2 as an important pharmacological target and GZ-793A as a lead compound for reducing the neurochemical effects of methamphetamine.

Conclusion
Various lobelane derivatives were synthesized and evaluated for VMAT2 binding studies. Among all these compounds GZ-793A was very potent and competitive inhibitor of dopamine uptake at VMAT2. We synthesized various radiolabeled GZ-793A analogs which will reveal the real time kinetic data from the PET studies.