NOVEL SYNTHETIC ISOFLAVANOID FOR THE TREATMENT OF ALCOHOL AND NICOTINE CO-USE

15a

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Recent estimates suggest that as many as 70-90% of individuals who are alcohol dependent are also nicotine dependent. However, biochemical and behavioral factors contributing to this comorbidity, as well as the consequences of this co-dependence, are not understood. Our ongoing research program encompasses a multi-tiered screening of novel and synthetic product libraries and validation process to provide novel information about mechanisms underlying this co-morbidity and to identify novel chemical scaffolds to be exploited in the development of pharmacological treatments for this co-use disorder. In collaborating with scientists at the University of Kentucky Center for Pharmaceutical Research and Innovation (CPRI), our group has screened more than 40 synthetic compounds from the CPRI synthetic products repository for their ability to attenuate ethanol (100 mM)-induced cytotoxicity in a rodent organotypic hippocampal slice culture model.

CS86, a novel isoflavonoid, demonstrated potent cytoprotective effects in this assay. Trolox (100 µM), a potent antioxidant, was also found to reduce ethanol (100mM)-induced cytotoxicity. In a model of co-dependence, preliminary in vivo studies have demonstrated CS86 dose-dependently decreases ethanol consumption in a 2-bottle choice drinking paradigm, while having no effect on water, saccharin, or quinine fluid intake. In a standard two-lever choice procedure, CS86 was also found to decrease lever pressing for nicotine, however, only at doses that also decreased food intake. For comparison, the nicotinic receptor partial agonist and tobacco cessation drug, varenicline, was found to reduce nicotine intake, but not alcohol intake.

Discovery of vesicular monoamine transporter-2 inhibitors as potential treatment for methamphetamine abuse: N-Butyl(1-methyl-2-phenylethyl)amine isome

15b

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Background: Methamphetamine (METH) use continues to increase. Currently, there are no Food and Drug Administration approved pharmacological treatments for METH abuse. METH interacts with dopaminergic terminals, among others. METH increases dopamine (DA) concentrations in the cytosol and extracellular space by inhibiting monoamine oxidase-induced DA metabolism, inhibiting DA uptake into synaptic vesicles, promoting DA release from vesicles into the cytosol via the vesicular monoamine transpoter-2 (VMAT2), and promoting DA release into the extracellular space via the DA transporter (DAT).

Purpose: GZ-888 (racemic) was found previously to selectively inhibit VMAT2 function and attenuate METH-evoked locomotor activity. In this study, we synthesized its two isomers and determined its affinity and selectivity at VMAT2 over DAT, serotonin transporter (SERT), and hERG channel interaction.

Methods: We measured [3H]DA uptake via VMAT2 using rat striatal synaptic vesicular fraction, [3H]DA uptake via DAT and [3H]serotonin uptake via SERT using rat striatal synaptic fraction, and [3H]dofetilide binding on hERG channel using HEK cell membrane fraction.

Results: GZ-11610 (R-isomer) exhibited the highest affinity (Ki = 8.71 ± 3.65 nM) and selectivity at VMAT2 over DAT (288-fold), SERT (637-fold), and hERG channel (1091-fold).

Conclusion: The effect of R-isomer on METH induced locomotor activity and METH self- administration in rats is being evaluated (Supported by NIH 5U01DA013519-12).