# The Novel *N*-Substituted Benztropine Analog GA2-50 Possesses Pharmacokinetic and Pharmacodynamic Profiles Favorable for a Candidate Substitute Medication for Cocaine Abuse

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**ABSTRACT:** GA2-50 is a novel *N*-substituted benztropine analog with improved potency and selectivity for the dopamine transporter. The pharmacokinetic and pharmacodynamic properties of GA2-50 were characterized as a part of its preclinical evaluation as a substitute medication for cocaine abuse. *In vitro* transport and metabolism studies as well as pharmacokinetic studies in rats were conducted. Effect of GA2-50 on the extracelluar nucleus accumbens (NAc) dopamine levels and on cocaine's induced dopamine elevation was evaluated using intracerebral microdialysis. GA2-50 showed high transcellular permeability despite being a P-glycoprotein substrate. GA2-50 was a substrate of human CYP2D6, CYP2C19, CYP2E1, rat CYP2C11, CYP2D1, CYP3A1, and CYP1A2; with low intrinsic clearance values. *In vivo*, GA2-50 showed high brain uptake ($R_i \sim 10$), large volume of distribution ($V_{ss} = 37$ L/kg), and long elimination half-life ($t_{½} = 19$ h). GA2-50 resulted in 1.6- and 2.7-fold dopamine elevation at the 5 and 10 mg/kg i.v. doses. Dopamine elevation induced by GA2-50 was significantly reduced, slower and longer lasting than previously observed for cocaine. GA2-50 had no significant effect on cocaine's induced dopamine elevation upon simultaneous administration. Results from the present study indicate that GA2-50 possesses several attributes sought after for a substitute medication for cocaine abuse.  J Pharm Sci 97:5453–5470, 2008

**Keywords:** cocaine abuse; substitution therapy; pharmacokinetics; pharmacodynamics; microdialysis

Abbreviations: DA, dopamine; DAT, dopamine transporter; BZT, benztropine; GA2-50, *N*-((*R*)-2″-amino-3″-methyl-*n*-butyl)-3α-[(bis-4′-fluorophenyl)methoxy]tropane; JHW 025, *N*-(dimethyl)-3α-[(bis-4′-fluorophenyl)methoxy]tropane; JHW 007, *N*-(*n*-butyl)-3α-[(bis-4′-fluorophenyl)methoxy]tropane; NAc, nucleus accumbens; aCSF, artificial cerebrospinal fluid; AUC, area under the curve; $R_i$, brain-to-plasma partition coefficient; CL, clearance; $V_c$, volume of the central compartment; $V_p$, volume of the peripheral compartment; $Q$, intercompartmental clearance; IAV, interanimal variability; $V_{ss}$, steady-state volume of distribution.

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## INTRODUCTION

Cocaine abuse continues to represent a serious health problem in the United States. Recent estimates (2005) indicated that 2.4 million Americans aged 12 or older were current cocaine users. In addition, approximately 2,400 Americans initiated cocaine use daily.[1] Currently, there are no approved pharmacotherapies for treatment of cocaine abuse[2] which further aggravates the problem.

The substitute approach for treatment of drug abuse is based on replacing the illicit drug with a safer legal maintenance medication, that shares mechanisms of action and produces some effects in common with the illicit drug, in order to stabilize the patient.[3] This approach has shown success for treatment of opioid and nicotine dependence.[4,5] In addition, several preclinical and clinical reports[6–8] emphasize the validity and signal the possible successful outcomes of pursuing the substitute approach for treatment of cocaine abuse.

Cocaine inhibits the reuptake of dopamine (DA), serotonin, and norepinephrine via blocking their corresponding transporters.[9,10] However, the addictive and euphorogenic effects of cocaine are attributed mainly to the blockade of the DA transporter (DAT) and the resultant potentiation of dopaminergic neurotransmission.[11–13] Therefore, much research has focused on the DA uptake inhibitors as candidate substitute medications for cocaine abuse.[2,14] However, in order to be considered as a promising candidate, the DA uptake inhibitor should have high selectivity for DAT; so as to minimize the side effects that may result from actions at other sites. More importantly, it should result in a slow onset and significantly reduced magnitude of DA elevation in comparison with cocaine. In addition, the DA uptake inhibitor should be eliminated slowly from the body and possess long duration of action. These characteristics are believed to reduce the abuse potential[15–18] which is a considerable safety concern for a medication targeted to such a vulnerable patient population.

The analogs of benztropine (BZT) are potent DA uptake inhibitors that have been synthesized as potential substitute therapeutics for cocaine abuse. The design of these analogs included several structural modifications in order to improve the affinity and selectivity to DAT (for review, see[19,20]). When tested in animal models of drug abuse, many BZT analogs demonstrated reduced cocaine-like behavioral effects and low preclinical abuse potential.[21,22] In addition, recent studies have indicated that certain compounds from this series may even block the stimulant effects of cocaine *in vivo*.[23] These attributes suggest that a successful cocaine medication may come from this class of compounds. Pharmacokinetic and pharmacodynamic evaluation of several BZT analogs in our laboratory have indicated that these compounds have slower clearance and result in slower and prolonged DA elevation in comparison with cocaine.[24,25] However, recent studies indicated that the pharmacokinetics and pharmacodynamics of the BZT analogs were highly sensitive to structural modifications, resulting in significant differences in the rate of elimination, apparent distribution characteristics, as well as in onset, extent and duration of the extracellular DA elevation induced by these compounds in experimental rats.[26,27]

GA2-50 is a novel BZT analog with high affinity and selectivity to the DAT as well as high potency as a DA uptake inhibitor (Tab. 1). The structural modifications in the design of GA2-50 included *para*-substitution of a fluoro-group on each of the pendant phenyl rings of BZT. In addition, the *N*-methyl group of BZT was replaced with an (*R*)-2″-amino-3″-methyl-*n*-butyl group (Fig. 1). It has been previously shown that the di-fluoro substitution enhanced the affinity and selectivity of the BZT analogs to DAT versus the serotonin and norepinephrine transporters (NET). In addition, a bulky *N*-substitution significantly reduced the affinity to the muscarinic $M_1$ receptors.[19,28] Stereoselectivity was originally reported for DAT binding with GA2-50,[28] however, subsequent testing showed no stereoselectivity at DAT and only a twofold difference in affinity at muscarinic M1 receptors.[19] Preliminary behavioral evaluation of GA2-50[29] suggested that this dopamine uptake inhibitor does not demonstrate a cocaine-like behavioral profile and may have potential for development as a cocaine abuse medication.

The present study was designed to evaluate the impact of the structural modifications of GA2-50 on its *in vitro* transport, *P*-glycoprotein mediated efflux, metabolism, as well as on its *in vivo* pharmacokinetics, and effect on extracellular brain DA levels in Sprague–Dawley rats. In addition, the study was designed to determine whether GA2-50 will competitively block the effect of cocaine on the brain DA levels upon simultaneous administration. The results from this study are essential to further explore the potential of this compound as a candidate medication for