Health Canada
Santé Canada

STATUS DECISION OF CONTROLLED AND NON-CONTROLLED SUBSTANCE(S)

Substance: I- RTI-51 HCl
II- RTI-55 HCl
III- RTI-112
IV- RTI-113
V- RTI-177
VI- RTI-336

Based on the current information available to the Office of Controlled Substances, it appears that the above substance is:

Controlled ☐

Not Controlled ✓

under the schedules of the *Controlled Drugs and Substances Act* (CDSA) for the following reason(s):

- The substances are analogues of cocaine but cannot be included under Item 2 of Schedule I to the CDSA.

Prepared by: _____ Date: _____
Vincent Marleau

Verified by: _____ Date: _____
Mark Kozlowski

Approved by: _____ Date: _____
DIRECTOR, OFFICE OF CONTROLLED SUBSTANCES

This status was requested by: "third party information removed as per agreement with applicant"

Drug Status Report

Drug: I- RTI-51 HCl
II- RTI-55 HCl
III- RTI-112
IV- RTI-113
V- RTI-177
VI- RTI-336 (See Table 1 for chemical information).

Pharmacological class / Application: Cocaine analogues

International status:

US: RTI-51 HCl, RTI-55 HCl, RTI-112, RTI-113, RTI-177 and RTI-336 are not listed specifically in the Schedules to the US *Controlled Substances Act* and are not mentioned anywhere on the DEA website.

United Nations: The substances are not listed on the Yellow List - List of Narcotic Drugs under International Control, the Green List - List of Psychotropic Substances under International Control, nor the Red List - List of Precursors and Chemicals Frequently Used in the Illicit Manufacture of Narcotic Drugs and Psychotropic Substances under International Control.

Canadian Status: RTI-51 HCl, RTI-55 HCl, RTI-112, RTI-113, RTI-177 and RTI-336 are not currently listed in the CDSA. The substances are analogues of cocaine and some have been reported in the scientific literature to display potent binding affinities to transporters either selectively or non-selectively to dopamine, serotonin and/or norepinephrine.[1,2,3] Cocaine (benzoylmethylecgonine) is currently listed as sub-item 2(2) in Schedule I to the CDSA under the heading "Coca (Erythroxylon), its preparations, derivatives, alkaloids and salts including". Given that RTI-51 HCl, RTI-55 HCl, RTI-112, RTI-113, RTI-177 and RTI-336 are not synthesized from cocaine and the analogues of cocaine are not captured under the Item heading, these substances cannot be included under Item 2 of Schedule I to the CDSA. It is noteworthy that a structurally similar substance, RI-111, was previously reviewed and also not included in the schedules to the CDSA.

Recommendation: RTI-51 HCl, RTI-55 HCl, RTI-112, RTI-113, RTI-177 and RTI-336 are not included in the Schedules to the CDSA and are not controlled substances.

Date: March 22nd, 2012.

Table 1: Chemical information

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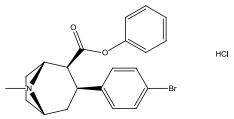
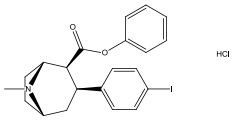
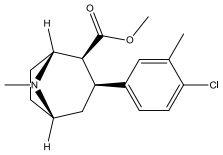
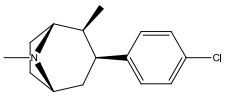
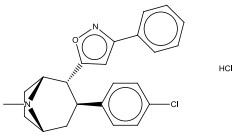
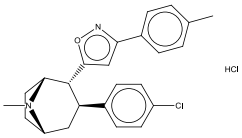
[1] Negus, S.S. *et al*. (2009) Effects of the monoamine uptake inhibitors RTI-112 and RTI-113 on cocaine- and food-maintained responding in rhesus monkeys. *Pharmacol Biochem behav*. **91(3)**:333-8.
[2] Howell, Leonard L. *et al*. (2004) Effects of Dopamine Transporter Inhibitors on Cocaine Self-Administration in Rhesus Monkeys: Relationship to Transporter Occupancy Determined by Positron Emission Tomography Neuroimaging. *The American Society for Pharmacology and Experimental Therapeutics*. **309(3)**: 959-969.
[3] Stathis, M., Scheffel, U., Lever, S. Z., Boja, J. W., Carroll, F. I., & Kuhar, M. J. (1995). Rate of binding of various inhibitors at the dopamine transporter in vivo. *Psychopharmacology*, **119(4)**: 376-384.

Name of substance	Synonyms	CAS-RN	Chemical Structure	Chemical formula
RTI-51 HCl	(1R,2S,3S,5S)-phenyl 3-(4-bromophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate hydrochloride.	N/A		$C_{21}H_{23}BrClNO_2$
RTI-55 HCl	(1R,2S,3S,5S)-phenyl 3-(4-iodophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate hydrochloride.	141899-24-3		$C_{21}H_{23}ClINO_2$
RTI-112	methyl(1R,2S,3S,5S)-3-(4-chloro-3-methylphenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate; 2β-carbomethoxy-3β-(3-methyl-4-chlorophenyl)tropane.	150653-92-2		$C_{17}H_{22}ClNO_2$
RTI-113	(1R,2S,3S,5S)-3-(4-chlorophenyl)-2,8-dimethyl-8-azabicyclo[3.2.1]octane; 2β-carbophenoxy-3β-(4-chlorophenyl)tropane.	141807-57-0		$C_{15}H_{20}ClN$
RTI-177	RTI 4229-177; 3β-(4-chlorophenyl)tropane-2β-(3-phenylisoxazol-5-yl)] HCl; 5-((1R,2R,3S,5S)-3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octan-2-yl)-3-phenylisoxazole hydrochloride.	170939-95-4		$C_{23}H_{24}Cl_2N_2O$
RTI-336	8-Azabicyclo(3.2.1)octane, 3-(4-chlorophenyl)-8-methyl-2-(3-(4-methylphenyl)-5-isoxazolyl)-, monohydrochloride, (1R,2S,3S,5S)-; RTI 4229-336; 3beta-(4-chlorophenyl) tropane-2beta-(3-(4'-methylphenyl) isoxazol-5-yl) hydrochloride.	204069-50-1		$C_{24}H_{26}Cl_2NO_2$