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Synthesis and Binding Affinities of 2β-(3-Iodoallyloxycarbonyl)-3β-(4-substituted-aryl)tropane Analogues as Ligands for the Dopamine Transporter Studies

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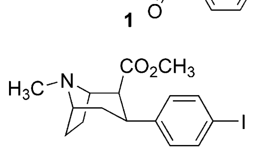
Abstract—Tropane analogues from cocaine, which is known to be one of the most reinforcing and addictive compounds, were designed, synthesized, and characterized for inhibition of presynaptic uptake of dopamine (DA) in brain. Eight new derivatives of 3β-aryl-2β-(3-iodoallyloxycarbonyl)tropanes were synthesized and tested for their potential abilities to displace [^{3}H]2β-carbomethoxy-3β-(4-fluorophenyl)tropane (WIN 35,428) binding to the rat striatal membranes. © 2001 Elsevier Science Ltd. All rights reserved.

R-Cocaine (**1**), well known as an addictive drug,[1] is a plant alkaloid purified from the leaves of *Erythroxylon coca*. It is known that many cocaine analogues have high binding affinity for the dopamine transporter (DAT).[2] In addition, the fact that the density of DAT decreases with the progress of Parkinson's disease (PD) calls for the development of PD diagnostic radiopharmaceuticals. Noninvasive imaging of the loss of DAT using a series of cocaine analogues such as [methyl-^{11}C]CFT (**2**, [methyl-^{11}C]2β-carbomethoxy-3β-(4-fluorophenyl)tropane, WIN 35,428),[3] [^{123}I]β-CIT (**3**, [^{123}I]2β-carbomethoxy-3β-(4-iodophenyl)tropane, RTI-55),[4] [^{123}I]IPT (**4**, [^{123}I]*N*-((*E*)-3-iodopropen-1-yl)-2β-carbomethyoxy-3β-(4-chlorophenyl)nortropane),[5] and TRODAT[6] has recently been achieved by the use of positron emission tomography (PET) and single photon emission computed tomography (SPECT).

Indeed, considerable research efforts have been made to understand the chemistry and the pharmacology of this cocaine. From the structure–activity relationship (SAR) of the several hundred cocaine derivatives, the knowledge of the mode of action of cocaine has improved dramatically. Among them, I-123 labeled β-CIT and IPT are used in clinical diagnosis for Parkinson's disease patients. Many structure–activity data concerning the substituents at the C2 position of cocaine have already been disclosed in previous publications.[7]

Iodoallyl group of IPT has been used as a bioisoster of methyl group for the introduction of radionucleus iodine. The goals of the present investigation were to synthesize *E*- and *Z*-iodoallyl ester instead of 2β-carbomethoxy substituent and to find out the SAR of *E*- and *Z*-isomers with the modification of *para* position of 3β-phenyl group.



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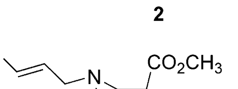

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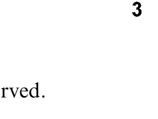

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0960-894X/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
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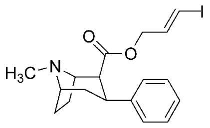
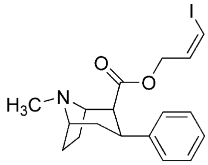
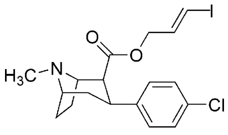
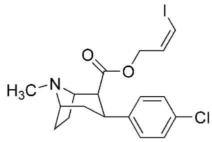
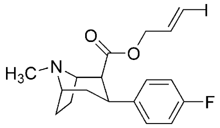
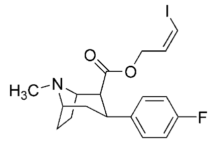
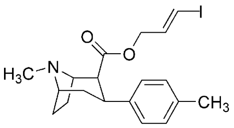
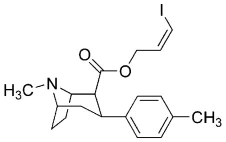
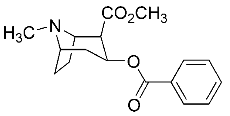
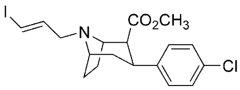
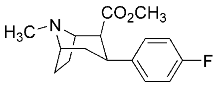
Table 1. Structures and binding affinities of the 3β-aryl-2β-(3-iodoallyl ester)tropanes for the dopamine transporter[a]

Compd		IC_{50} (nM) Mean ± SEM[a]	Compd		IC_{50} (nM) Mean ± SEM[b]	IC_{50} (*E*)/ IC_{50} (*Z*)
12Ea		875.9 ± 73.9	**12Za**		308.1 ± 97.9	2.84
12Eb		46.6 ± 18.6	**12Zb**		24.9 ± 9.0	1.87
12Ec		566.6 ± 164.6	**12Zc**		356.3 ± 97.1	1.59
12Ed		189.9 ± 105.8	**12Zd**		39.2 ± 17.3	4.84
1		510.6 ± 108.0	4		6.1 ± 2.1	
2		149.4 ± 1.4				

[a]The inhibition of [^{3}H]WIN 35,428 binding to rat striatal synaptic membranes was measured using 3 nM [^{3}H]WIN 35,428 and 13 concentrations of the test compounds between 10^{-12} and 10^{-4} M. Nonspecific binding was defined as that determined in the presence of 100 μM (−)-cocaine.

[b]The values represent mean ± standard error of three separate experiments done in duplicate.

Chemistry

The structures of compounds selected for the synthesis and binding data on the dopamine transporter are shown in Table 1. All compounds described herein were prepared from natural (*R*)-cocaine, and therefore they have the same absolute configuration as (*R*)-cocaine. Compound **5** were prepared from cocaine based on the previous reports.[8] According with Carroll's modification[9] of the original procedure of Clarke et al.,[10] the 3β-intermediate WIN analogues **6a–d** were synthesized in 52% yield with 3α-isomers (26%) as shown in Scheme 1. Transesterification from methyl to tributylstannylallyl group was conducted step-by-step by sponification, formation of acid chloride using oxalyl chloride, and esterification with (*E*)- and (*Z*)-allyl alcohol **9** and **10**. (*E*)- and (*Z*)-3-(tri-*n*-butylstannyl)allyl alcohols (**9** and **10**) were prepared from propargyl alcohol (**8**) in 56% yield with 3:1 ratio of *E*/*Z* from by the method by Jung[11] (Scheme 2).

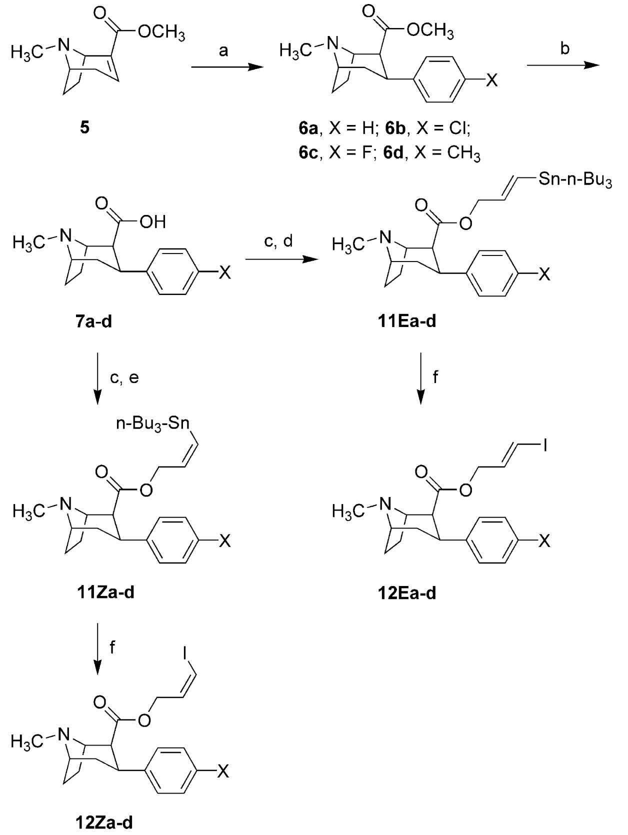
In vitro dopamine transporter binding studies

Binding of [^{3}H]WIN 35,428 to the dopamine transporter was measured according to the method of Madras et al.[12] with slight modifications using crude synaptic membranes prepared from the rat striatum.[13] Competition binding assays were performed to measure the concentrations of test compounds which inhibited the specific binding by 50% (IC_{50} values) using 3 nM [^{3}H]WIN 35,428 and 13 concentrations of the unlabelled compounds between 10^{-12} and 10^{-4} M. Nonspecific binding was defined as that determined in the presence of 100 μM (−)-cocaine. IC_{50} values were determined from the competition binding data using computer-assisted curve fitting with GraphPad Prism 3.0 program.

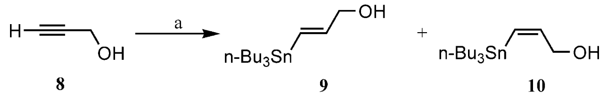
Table 1 illustrates the in vitro binding affinities of **12Ea–d** and **12Za–d** for the dopamine transporter of rat striatal membranes, including (−)-cocaine, β-CFT, and IPT.

Discussion

Recently, the goals of research and the summary of results regarding C2 modification of cocaine were well described.[2a] There are several reports that for the basic nitrogen and a hydrogen bond of 2β-carbomethoxy



Scheme 1. Reagents and conditions: (a) 4-X-aryl MgBr (X = H, Cl, F, CH_3), dried Et_2O under −20 °C, 3 h, 68% for **6a** (α:β = 19:49); 78% for **6b** (α:β = 26:52); 72.1% for **6c** (α:β = 22:50.1); 64% for **6d** (α:β = 16:48), (b) dioxane/H_2O (1:1), reflux, 2 h, 88% for **7a**; 92% for **7b**; 88% for **7c**; 90.2% for **7d**, (c) $(COCl)_2$, dried CH_2Cl_2, rt, 2 h; (d) **9**, DBU, dried CH_2Cl_2, overnight; 58% for **11Ea**; 63% for **11Eb**; 64% for **11Ec**; 62% for **11Ed**, (e) **10**, DBU, dried CH_2Cl_2, overnight, 55% for **11Za**; 45% for **11Zb**; 62% for **11Zc**; 58% for **11Zd**; (f) I_2, CH_2Cl_2, 0 °C, 30–60 min, 84% for **12Ea**; 86% for **12Eb**; 81% for **12Ec**; 80% for **12Ed**; 85% for **12Za**; 84% for **12Zb**; 73% for **12Zc**; 78% for **12Zd**.



Scheme 2. Reagents and conditions: (a) n-Bu_3SnH, AIPN (cat), toluene, 60 °C, overnight, 56% (E/Z = 3:1).

ester function of cocaine are not essential for potent activity. The major putative interaction of cocaine with DAT, however, would be (1) the ionic interaction of the protonated nitrogen and carboxylate of its receptor, (2) the hydrogen bond of 2β-carbomethoxy ester, and (3) lipophilic pocket of 3β-phenyl group. To explore the nature of interaction between the cocaine binding site and the high-affinity ligand and to find cocaine analogues with distinct selectivity as the monoamine transporters, a large number of C2 modified cocaine derivatives have been synthesized. Esters, carboxamides, isosteric heterocycles, and ketones are the functional groups remaining hydrogen-bonding pharmacophores.

Kozikowski et al. reported that in absence of H-bond acceptors in the ligand hydrophobic interaction are important in the region of the cocaine recognition site surrounding the C2 substituent.[7f] However the great lipophilicity of hydrophobic alkyl chain may dramatically drop a binding affinity; compound with C2 *n*-hexyl chain instead of carbomethoxy is about 128-fold less potent than the *n*-butyl analogue. Among 2β-allyloxycarbonyl-3β-phenyltropanes, 4′-azido-3′-iodophenethyl ester was used for photoaffinity labeling and 4′-isothiocyanophenethyl ester was used for conjugation to solid supporting materials. Thus, bulky ester group at C2 position were well tolerated without any significant loss in potency.

We synthesized eight 2β-allyloxycarbonyl-3β-phenyltropanes with *E*- and *Z*-3-iodoallyl group in accordance with the *para* position of phenyl group (Table 1). Four of the compounds showed binding affinities for the DAT better than parent methyl ester. While, in case of IPT, *E* isomer has a better activity than *Z* isomer, all *Z*-isomers of 12 have better binding activities for the DAT than corresponding *E* isomers. The ratios of $IC_{50}(E)/IC_{50}(Z)$ for the same substituents at *para* position of 3β-phenyl group are between 1.59 and 4.84.

In summary, when one attaches large group to tropane for photoaffinity labeling, conjugation to solid supporting materials, fluorescence labeling and even ligand for technetium, the introduction of large group at 3′-position of allyl group of 2β-allyloxycarbonyl-3β-phenyltropane as in *Z* form would be a useful method. More syntheses of C2 modified tropane derivatives are being currently pursued.

Acknowledgements

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