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SYNTHESIS OF β-CIT-BAT, A POTENTIAL TECHNETIUM-99m IMAGING LIGAND FOR DOPAMINE TRANSPORTER

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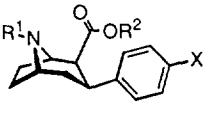
Summary: The synthesis of an N_2S_2 conjugated BAT phenyltropane ligand is described. This agent can be further used to incorporate technetium-99m to form a neutral complex for SPECT imaging of the dopamine transporter.

The primary clinical interest in single photon emission computed tomography (SPECT) agents specific for dopamine transporters (DA_T) is in the diagnosis and staging of Parkinson's disease (PD), which is characterized by a loss of dopaminergic neurons in stratial regions of the brain.[1] It has been demonstrated by us and others with ^{123}I, ^{11}C, ^{18}F-labeled phenyltropanes (Figure 1), a class of ligands with high affinity to the dopamine transporter, that the loss of dopamine transporters can be correlated with the severity of PD.[2,3] Unlike technetium-99m (^{99m}Tc), the most commonly used radionuclide for diagnostic nuclear medicine, [^{123}I], [^{11}C] and [^{18}F], however, are cyclotron produced radionuclides which are expensive and not readily available.



$R^1 = {}^{11}CH_3$	$R^2 = CH_3$	[^{11}C]-β-CIT
$R^1 = {}^{18}FCH_2CH_2CH_2$	$R^2 = CH_3$	[^{18}F]-FP-β-CIT
$R^1 = CH_3$	$R^2 = {}^{11}CH_3$	[^{11}C]-β-CIT
$R^1 = R^2 = CH_3$	$X = {}^{123}I$	[^{123}I]-β-CIT

Figure 1. [^{123}I], [^{11}C], [^{18}F]-labeled phenyltropanes

As the preferred radionuclide for use in the SPECT imaging study is ^{99m}Tc, the development of a technetium labeled phenyltropane derivative would be a useful tool for routine clinical diagnosis of Parkinson's disease[4]. To obtain such an analog, the target molecules must contain structural features capable of coordinating with the Tc atom. One of the stable ligand chelating systems is the bis(aminoethanethiol) (BAT) which contains four hetero atoms (two N and two S).[5] This moiety tends to form stable neutral oxo-Tc(V) chelates with good brain penetration.[5] However, the synthesis of such ^{99m}Tc-labeled molecules presents formidable challenges.

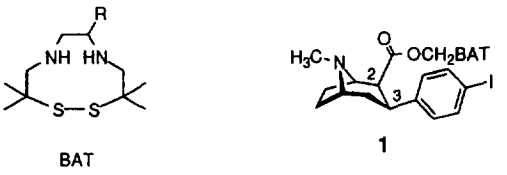
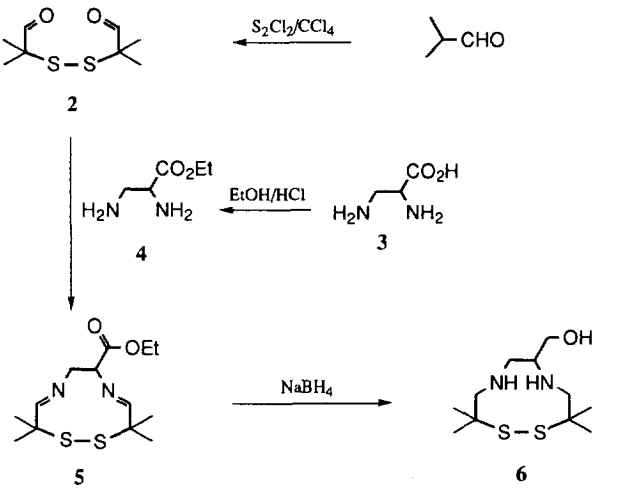


Figure 2

In recent years, only a few examples of ^{99m}Tc chelates attached to biologically active molecules have been described.[6] Meegalla[4] has recently described a related tropane analog incorporating ^{99m}Tc complex as a dopamine transporter imaging agent. In the course of developing a Tc-based receptor binding agent for DA transporters, we present the synthesis of phenyltropane-BAT **1** which could permit subsequent specific chelation with ^{99m}Tc.

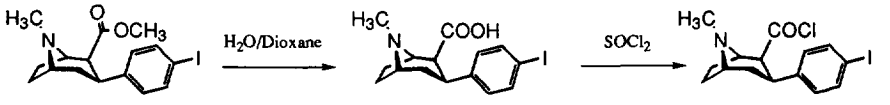
The design of the compound **1** is based on the structural modification of 2β-carbomethoxy-3β-(4-iodophenyltropane) (β-CIT, **7**), a highly potent DAT inhibitor.[7] The 2-position on the phenyltropane system was selected to attach the BAT chelating group on the basis of an SAR study of a series of cocaine analogs which indicated that bulky substituents can be tolerated by the cocaine receptor at this position.[8] The synthesis of the 10-membered bis(aminoethanethiol) derivative **6** was explored initially (Scheme 1). The 2,2-dithio-bis(2-methylpropanal) **2** was prepared by addition of sulfur monochloride to a solution of isobutyraldehyde in carbon tetrachloride. The bis(imine) **5** was assembled by condensation of 2,2-dithio-bis(2-methylpropanal) **2** with ethyl 2,3-diaminopropionate **4** which was prepared by esterification of its readily commercially available acid precursor **3**.



Scheme 1

The key transformation of bis(imine) **5** to BAT **6** is controled by the reaction temperature. The reported procedure[5] for reduction of **5** with $NaBH_4$ could not be repeated. As known before[9] that bicyclic by-product can be the predominant product when the reaction is carried out at 0°C [5] we conducted the reduction at 50°C to obtain BAT **6** in 56% yield and reach the levels required for our study.

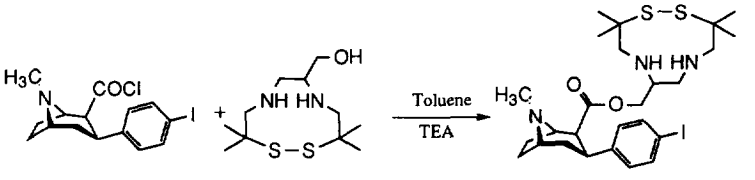
The preparation of β-CIT **7** was accomplished in 4 steps in 15% yield as previously reported by our laboratory.[10] Conversion of **7** to **9** is shown in Scheme 2. Complete hydrolysis of **7** in water at 80°C gave the desired acid **8** which was conveniently isolated in quantitative yield. The treatment of acid **8** with thionyl chloride at 0°C provided the acyl chloride **9** which can be used directly in the next step.



7 **8** **9**

Scheme 2

The acyl chloride **9** was esterified with hydroxyl BAT **6** in toluene in the presence of triethylamine to afford the final compound **1** isolated as a tritartrate salt.[11] The ^{1}H-NMR (300 MHz), MS and elemental analysis were consistent with the assigned structure. In preliminary labeling experiments, reaction of disulfide ligand **1** with Na[^{99m}Tc] TcO_4 in presence of $SnCl_2$ in aqueous ethanol at 90ºC afforded 17% [^{99m}Tc]-**1**, extractable into EtOAc, suggesting a neutral, lipophilic complex.



9 **6** **1**

Scheme 3

In summary, we have presented the first applicable synthetic pathway to attach the BAT chelating system to a ligand selective for the dopamine transporter. This BAT tagged compound should be useful to form complexes with Tc radionuclide for further evaluation as a SPECT imaging agent.

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11) analytical data for **1** ^{1}H NMR free base ($CDCl_3$, 250MHz) : δ 7.57 (d, J=8.4 Hz, 2H); 7.02 (d, J=8.4 Hz, 2H); 3.95 (m, 2H); 3.59 (m, 2H); 3.43 (m, 2H); 3.28 (m, 4H); 2.90 (m, 2H); 2.55 (m, 2H); 2.29 (m, 6H); 1.96 (m, 1H); 1.74 (m, 3H); 1.35 (m, 12H);

C,H,N Cal C : 42.74, H : 5.47, N : 3.93. found ; 42.69, H : 5.65, N : 3.98

$[\alpha]_D^{20}$: -66.3 (c=0.25, MeOH), MP=174-176°C

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