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Cyclopentadienyltricarbonylrheniumbenzazepines: Synthesis and Binding Affinity†

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Abstract—Analogues of the benzazepine dopamine D_1 receptor antagonist SCH-23390 incorporating the cyclo-pentadienyl-tricarbonyl-rhenium (CPTR) moiety were synthesized and evaluated pharmacologically. The CPTR derivatives retained affinity (0.3–2.9 nM) and D_1 selectivity of the parent compound, supporting their use as neuropharmacological surrogates for ^{99m}Tc-labeled SPECT radiopharmaceuticals.

Introduction

Single photon emission computed tomography (SPECT) is a cost-effective technique for functional imaging of the central nervous system. SPECT has been used to study interactions of specific radioligands and unlabeled drugs with brain receptor and transporter sites for clinical neuropharmacological studies.[1–3] Radioligands for this purpose are usually labeled with ^{99m}Tc or ^{123}I. Two Tc-labeled complexes, TRODAT-1 and technepine, have been reported to retain selective binding to the dopamine transporter, but their in vivo labeling of cerebral targets includes a high proportion of nonspecific labeling.[4,5] Moreover, ^{99m}Tc-labeled SPECT ligands that are highly selective for cerebral neurotransmitter receptor sites are still uncommon.

Limitations to developing ^{99m}Tc-labeled receptor ligands include the bulkiness or charge properties of relatively large chelation moieties required to complex technetium. In 1992, Wenzel and others reported treating a ligand to be labeled with [^{99m}Tc]-TcO_4 in the presence of a carbonyl donor to give the cyclopentadienyltricarbonyl-technetium analogue.[6–12] Such derivatives are likely to be less sterically hindered and less polar than other complexes traditionally used to bind ^{99m}Tc by chelation.[13] A problem for development of useful ^{99m}Tc-labeled compounds as imaging agents is the lack of compounds containing a comparable but stable isotope to serve as surrogates for pharmacological assessment. In general, the structural and biochemical properties of technetium correlate well with those of rhenium,[14,15] so that this represent a fruitful avenue of research.[16]

The benzazepine (+)-*N*-methyl-1-phenyl-2,3,4,5-tetrahydro-[1*H*-3]-7-chloro-8-hydroxybenzazepine (SCH-23390) is a highly selective antagonist for D_1-like ($D_{1/5}$) dopamine receptors. In radiolabeled form, [^{3}H]SCH-23390 is a standard laboratory radioligand for D_1 receptor labeling, and it has been labeled with ^{11}C for PET imaging.[17,18] TISCH, an iodinated analogue of SCH-23390, also has been synthesized, characterized, labeled with ^{123}I, and evaluated in vivo as a D_1-selective SPECT radioligand in non human primate.[19] We now report the preparation of rhenium containing cyclopentadienyl-tricarbonyl derivatives targeted to dopamine D_1 and assessments of their receptor binding properties.

Synthesis of benzazepine derivatives for D_1 receptor

A route to benzazepines of type **8a** was described that involved reacting the styrene oxide **3a** with the primary amine **2** to give **4a** (Scheme 1).[19] However, we found that the major product of this reaction was the dialkylated tertiary amine **5a** (60% yield), with a low yield

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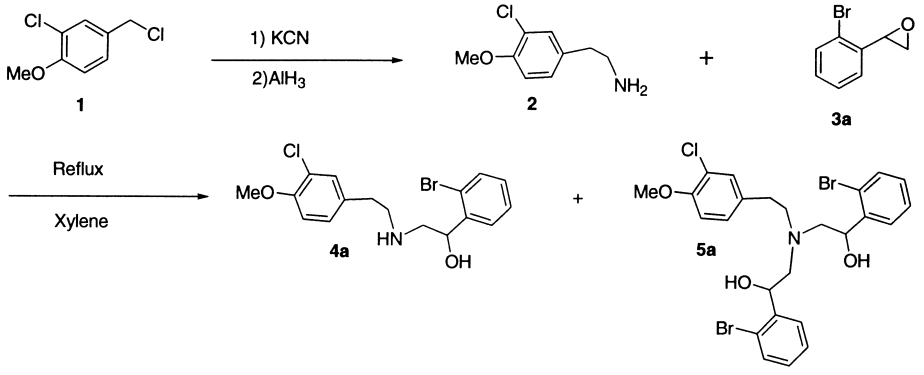


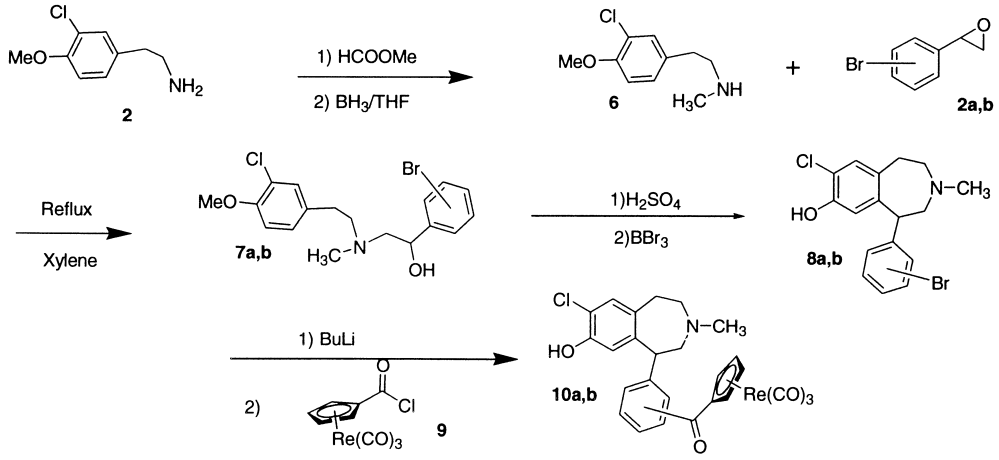
Scheme 1.

(35%) of the desired secondary amine **4a**. Since this route (Scheme 1) gave a low yield, we investigated a new synthetic method to obtain **8a** or **8b** (Scheme 2).

A solution of the substituted benzyl chloride **1** in *N*,*N*-dimethylformamide was treated with aq KCN to give an intermediate phenylacetonitrile,[20] which was reduced directly to the corresponding phenethylamine **2** with AlH_3.[21] The primary amine **2** was then *N*-monomethylated with methyl formate, followed by reduction with borane/THF to give **6** in 95% yield. Condensation of the 2- or 3-bromostyrene oxide **3a** (2-) or **3b** (3-) with the amine **6** in refluxing xylene gave the tertiary amines **7a** or **7b** in 90% yield. Their cyclization with concentrated H_2SO_4 at 0 °C and *O*-demethylation with BBr_3 gave **8a** and **8b** in 40% yield. Addition of *n*-BuLi at −78 °C, followed by addition of the acyl chloride **9** led to the final desired CPTR-containing organometalic benzazepine derivatives **10a** and **10b**.

Pharmacological Activities

The synthesized CPTR analogues of the D_1-selective compound SCH-23390 (**10a** and **10b**) were evaluated for affinity (indicated by inhibitory potency, K_i) in competitive radioreceptor binding assays with tissue homogeates prepared from rat forebrain. Preliminary comparisons of SCH-23390 with its 2′- and 3′-Br derivatives indicated substantial retention of D_1 affinity and selectivity (Table 1). Moreover, the corresponding 2′- and 3′-CPTR derivatives **10a** and **10b** retained a high degree of selectivity (900- to 3,460-fold) for D_1-like over D_2-like receptors in homogenates of rat corpus striatum, with only moderate loss of D_1 affinity (Table 1). For comparison, SCH-23390 itself showed >10,000-fold D_1-over-D_2 selectivity (Table 1). Novel compounds **10a** and **10b** showed even lower affinity to cerebral 5-HT_{2A} and 5-HT_{2C} receptors than the parent compound SCH-23390.



Scheme 2.

Table 1. Potency (mean $K_i \pm$ SE, nM) of SCH-23390 and its CPTR derivatives at dopamine and serotonin receptors in homogenates of caudate-putamen tissue from rat brain

Test agent	D_1-like	D_2-like	5-HT_{2A}	5-HT_{2C}
(+)-SCH-23390	0.12 ± 0.02	1210 ± 100	10.8 ± 1.6	12.5 ± 0.63
(±)-2′-Br-SCH-23390	0.70 ± 0.08	583 ± 55	22.1 ± 3.0	11.8 ± 0.8
(±)-3′-Br-SCH-23390	0.26 ± 0.02	1120 ± 75	8.50 ± 0.95	2.08 ± 0.30
(±)-2′-CPTR-SCH-23390 (**8a**)	0.61 ± 0.07	549 ± 48	17.3 ± 1.2	28.5 ± 5.5
(±)-3′-CPTR-SCH-23390 (**8b**)	2.89 ± 0.32	>10,000	227 ± 17.7	106 ± 17.5

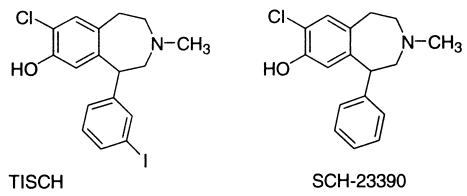


Figure 1.

These results indicate that compounds containing the relatively nonpolar and sterically unhindered cyclopentadienyl-tricarbonyl-rhenium (CPTR) moiety can be developed as nonradioactive surrogate analogues of potential ^{99m}Tc-labeled radioligands. The representative compounds reported here (**10a** and **10b**) largely retained the neuropharmacological properties of the parent ligand, including high affinity and selectivity for dopamine D_1 receptors. Compounds 2′-CPTR-SCH-23390 (**10a**) and 3′-CPTR-SCH-23390 (**10b**) showed little loss of affinity at dopamine D_1 receptors compared to the parent compound and retained high selectivity for D_1 over D_2 receptors in rat forebrain tissue, as well as over serotonin 2A and 2C receptors (Table 1). The relatively bulky rhenium group did not produce major loss of the neuropharmacological properties in the compounds tested as potential dopamine D_1 receptor ligands. These observations encourage further development and testing of the properties of rhenium-containing compounds as analogues that should predict the properties of ^{99m}Tc-labeled derivatives as potential radioligands for SPECT scanning of neurotransmitter receptors and other target sites of interest in human brain.

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