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Preparation, Characterization, and Screening of a High Affinity Organometallic Probe for α-Adrenergic Receptors

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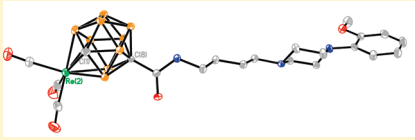
Supporting Information

ABSTRACT: An organometallic rhenium complex having high and selective affinity for α-adrenergic receptors is reported. A series of methoxyphenylpiperazinecarborane ligands complexed to the $[Re(CO)_3]^+$ core were prepared and the resulting organometallic compounds screened for binding to serotonin, σ, and adrenergic receptors as well as dopamine, serotonin, and norepinephrine transporters. An amide linked derivative, for which a single crystal X-ray structure was obtained, showed high and selective affinity toward α_{1A}, α_{1D}, and α_{2C} adrenergic receptors with K_i values of 17, 21, and 39 nM, respectively. A method to prepare the corresponding ^{99m}Tc complex was also developed where the resulting metallocarborane was shown to be stable and is therefore suitable for in vivo molecular imaging studies.



K_i values (nM) for α-Adrenergic Receptors:
$\alpha_{1A} = 17 \pm 1$
$\alpha_{1B} = 435 \pm 39$
$\alpha_{1D} = 21 \pm 1$
$\alpha_{2C} = 39 \pm 2$

INTRODUCTION

There has been growing interest in using organometallic chemistry to create high affinity molecular imaging probes (MIPs).[1−5] While most bioorganometallic probes are derived from cyclopentadiene (Cp), the strategy employed here utilized metallocarboranes which resulted in the discovery of the first organometallic MIP having high affinity for α-adrenergic receptors.

MIPs can be used to noninvasively monitor changes in protein expression associated with disease onset and progression, to determine optimal dosing levels and schedules, and to predict how patients and preclinical models will respond to therapies.[6] In central nervous system (CNS) imaging, for example, the appropriate MIP can be used with positron emission tomography (PET) or single photon emission computed tomography (SPECT) to identify changes in levels of active neuroreceptors and to visualize accumulation of β-amyloid or microglia as a means to help with the diagnosis of neurological diseases or disorders.

Gmeiner and co-workers demonstrated that it is possible to prepare high affinity organometallic probes for key proteins in the CNS. In their study, an arylpiperazine was linked to ferrocene where the complex showed exceptionally high binding to both the dopamine D_4 receptors (K_i = 0.52 nM) and serotonin 5-HT_{1A} (K_i = 0.50 nM) (Figure 1a).[7] When Alberto et al. linked the same vector to $CpRe(CO)_3$ (Figure 1b) through a different spacer group, the compound exhibited high affinity (IC_{50} = 6 nM) for 5-HT_{1A}.[8] Beyond these Cp-derived compounds, there are to our knowledge no other high affinity organometallic probes for the CNS that have been reported to date.

Carboranes are attractive ligands for bioorganometallic chemistry because they are stable in water, the cluster can be labeled with a range of different radionuclides, and they can be readily derivatized using a number of different strategies. These characteristics provide advantages over Cp which is challenging to radiolabel and derivatize because it frequently undergoes unwanted side reactions including dimerization.[9−11] These issues complicate the creation of libraries of candidates and development of adequate structure−activity relationship (SAR) studies when searching for new MIPs. Building on the advantages offered by carboranes, a family of novel carborane-1-(2-methoxyphenyl) piperazine (WAY) conjugates was synthesized and the corresponding rhenium complexes were isolated and screened against a panel of CNS targets. The compounds are designed to be used to image targets located in the brain if the anionic metal complexes can cross the blood−brain barrier, or alternatively they will be used for imaging targets in the periphery if they cannot. For the highest affinity compound a method to produce the radioactive analogue (^{99m}Tc) was also developed.

RESULTS AND DISCUSSION

A series of arylpiperazinecarborane derivatives were prepared having different tether lengths and linkages between the cluster and the targeting vector. These variations have been shown to result in significant changes in binding affinities and target selectivity

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profiles.[12] Attempts to convert 1-(2-methoxyphenyl)-4-(2-propynyl)piperazine (**1**) and 1-(2-methoxyphenyl)-4-(4-pentynyl)piperazine (**2**), which were prepared by simple alkylation with the appropriate haloalkyne,[13] to the corresponding clusters were unsuccessful using conventional methods. Success in isolating **3** and **4** was achieved using decaborane ($B_{10}H_{14}$) and a catalytic amount of ionic liquid (1-butyl-3-methylimidazolium chloride) in boiling toluene (Scheme 1a).[14,15]

Preparation of the amide linked cluster **5**, which can be considered a carborane analogue of the compound reported by Gmeiner and coworkers,[7] was achieved by combining the acid chloride **6** with amine **7** (Scheme 1b). Forceful reaction conditions were needed, which is likely due to the proximity of the acid to the extremely bulky cluster. Coupling also resulted in the formation of the *nido*-carborane with the protonated salt of the excess amine as the counterion. To ensure that the counterion would not interfere with the in vitro binding assays, a simple salt exchange using sodium hydroxide was performed.

The preparation of the *nido*-forms of **3** and **4** was accomplished using sodium fluoride[16] immediately prior to complexation with the $[Re(CO)_3]^+$ core. Repeated microwave heating in the presence of excess $[Re(CO)_3(H_2O)_3]Br$ was used to generate the rhenacarborane complexes **8**, **9**, and **10** in 82%, 95%, and 10% yields, respectively (Scheme 1c).[17] The rhenium complexes were isolated by column chromatography where LC−MS showed a single peak in the UV spectrum and the expected mass and isotope pattern in the mass spectrum, which for Re−B_9 clusters is distinct. ^{1}H NOE experiments indicated that compounds **8** and **10** were 2, 1, 8 clusters while compound

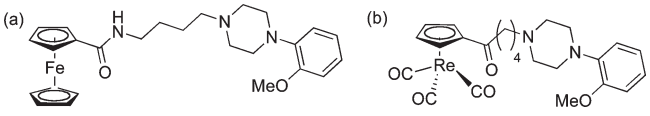


Figure 1. Organometallic derivatives of 1-(2-methoxyphenyl)piperazine (WAY): (a) WAY ferrocenylcarboxamide[7] and (b) WAY $CpRe(CO)_3$ derivatives.[8]

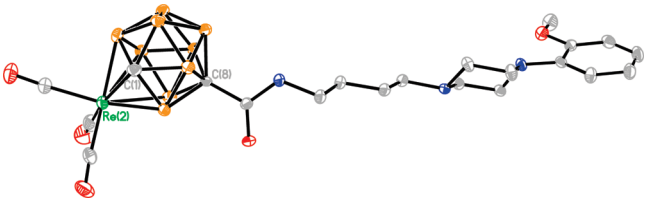
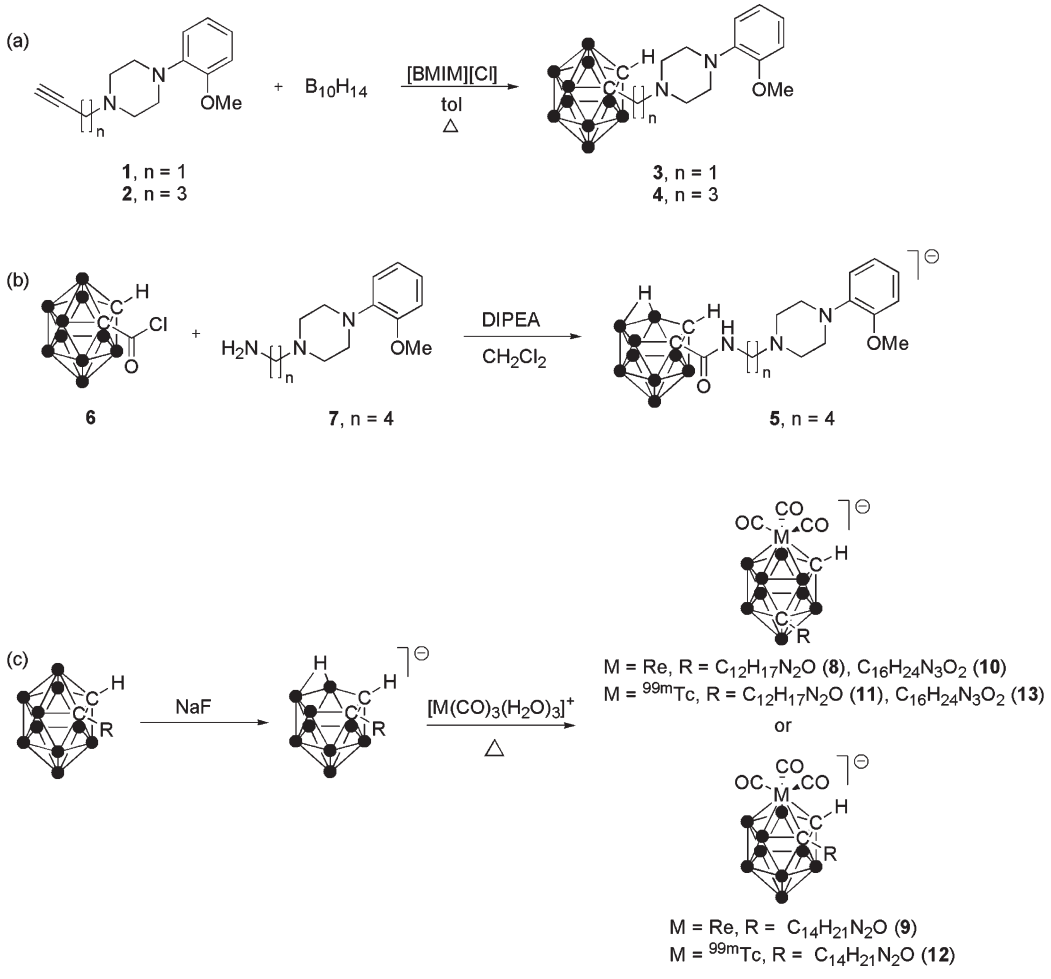


Figure 2. Thermal ellipsoid plot of **10** (50% probability ellipsoids). Hydrogen atoms have been omitted for clarity.

Scheme 1. Preparation of Compounds 3−13 (Solid Black Spheres = BH)[a]



[a] Full structures for all compounds can be found in the Supporting Information.

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Table 1. Binding Affinities of Rhenacarborane Complexes 8−10 to Serotonin, Adrenergic and σ Receptors

	K_i (nM)										
	serotonin					adrenergic				σ	
compd	5-HT$_{1A}$	5-HT$_{1D}$	5-HT$_{2B}$	5-HT$_6$	5-HT$_7$	α_{1A}	α_{1B}	α_{1D}	α_{2C}	σ_1	σ_2
8	834 ± 54	>1000	>1000	>1000	*a*	>1000	*a*	270 ± 15	575 ± 25	*a*	>1000
9	118 ± 8	>1000	211 ± 16	>1000	*a*	115 ± 6	122 ± 7	174 ± 9	244 ± 10	*a*	>1000
10	*a*	>1000	128 ± 7	692 ± 77	40 ± 5	17 ± 1	435 ± 39	21 ± 1	39 ± 2	*a*	201 ± 9
WAY100635	0.5 ± 0.04	661 ± 82	302 ± 11	*a*	248 ± 23	62 ± 4	162 ± 9	36 ± 1	562 ± 28	*a*	*a*

[a] In the primary binding assay <50% inhibition of specific binding was measured.

9 remained 3, 1, 2. These configurations are consistent with our previous reports where *nido*-carboranes isomerize upon complexation with Re(I) when sterically demanding or electron withdrawing groups are located immediately adjacent to the cluster.[18] An X-ray quality crystal of **10** (Figure 2) was obtained from slow evaporation of methanol, confirming that the isomer is in fact 2, 1, 8 which is consistent with the NMR data.

To assess the affinity and selectivity of the metallocarboranes for several CNS targets, a series of in vitro binding assays were performed. All screens were run in duplicate and in parallel with the 5-HT$_{1A}$ receptor antagonist *N*-{2-[4-(2-methoxyphenyl)-1-piperazinyl] ethyl}-*N*-(2-pyridyl)cyclohexanecarboxamide (WAY100635) as a positive control which showed affinities that are consistent with literature values for 5-HT$_{1A}$ binding.[19] Compounds **8**−**10** were screened for binding to both serotonin (5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1E}$, 5-HT$_{2A}$, 5-HT$_{2B}$, 5-HT$_{2C}$, 5-HT$_3$, 5-HT$_{5A}$, 5-HT$_6$, 5-HT$_7$) and adrenergic receptors (α_{1A}, α_{1B}, α_{1D}, α_{2A}, α_{2B} α_{2C}, β_1, β_2, and β_3), as well as dopamine, serotonin, and norepinephrine transporters (DAT, SERT, and NET, respectively) and σ_1 and σ_2 receptors; findings are summarized in Table 1. The complete binding assay results of all the receptors are available in the Supporting Information. Derivatives **8**−**10** showed either less than 50% of specific binding in the primary assay or >1000 nM binding for 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1E}$, 5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_3$, and 5-HT$_{5A}$ serotonergic receptors, adrenergic receptors (α_{2A}, α_{2B}, β_1, β_2, and β_3), σ_1-receptor, and DAT, NET, and SERT transporters.

Moderate to poor binding was observed for complexes **8**−**10** for the serotonin 5-HT$_{1A}$, 5-HT$_{2B}$, and 5-HT$_6$ receptors and for the α_{1B} adrenergic receptor. Interestingly, the amide linked cluster **10** showed high affinity toward 5-HT$_7$ serotonergic receptor (40 nM), adrenoceptors α_{1A} (17 nM), α_{1D} (21 nM), and α_{2C} (39 nM) with modest affinity for the σ_2 receptor (201 nM). While there are a number of reported PET probes derived primarily from carbon-11 or fluorine-18 for imaging adrenergic receptors[20,21] and SPECT probes using ^{99m}Tc,[22] there are no examples of organometallic agents which in the case of technetium is extremely desirable because of the isotope's widespread use in nuclear medicine and low cost.

Compound **10** is a unique example of a technetium probe with high affinity for three α-adrenergic subtypes (1A, 1D, and 2C). An additional attractive feature of these compounds is the low to negligible affinity toward σ receptors, which are abundant in several CNS regions and can therefore affect target to nontarget ratios. The selectivity of the compound must be influenced by the cluster, since arylpiperazine derivatives have often been shown to bind to both serotonin and adrenergic receptors, which is due to the high degree of homology between the receptors (approximately 45%).[23]

Given the positive screening results, a method to prepare the technetium-99m analogue of **10** was developed. *nido*-Carborane **5** as the sodium salt was combined with $[^{99m}Tc(CO)_3(H_2O)_3]^+$, which was prepared using a standard kit method (Scheme 1c). After microwave heating for 15 min at 195 °C, the desired product formed as the major radioactive product. HPLC purification, which is not absolutely necessary given the formation of a single radiolabeled compound, can be used to remove residual ligand but it reduces the radiochemical yield (14%). By use of either approach, sufficient quantities of **13** can be prepared for preclinical imaging studies. Analytical HPLC analysis showed that the retention time of the radioactive product matched that for the analogous rhenacarborane complex (observed using UV−HPLC). For comparison, the *nido*-carboranes of **3** and **4** were also labeled under similar conditions and the radiochemical yields were comparable. The stabilities of the ^{99m}Tc complexes (**11**−**13**) were tested by resuspending the products in ethanol/saline and checking the purity by HPLC under different elution solvents and gradients. There were no signs of degradation in any case for up to 6 h, which is consistent with our previous stability data on radiometallocarborane complexes.[24]

α-Adrenergic receptors are of particular interest for molecular imaging applications because of their involvement in contraction and growth of smooth and cardiac muscle, regulation of arterial blood pressure,[25] cognitive function such as attention and memory,[26] and motor activity.[27] Studies have also indicated the involvement of α-adrenergic receptors in pain[28] and Alzheimer's disease[26] through abnormalities in neurotransmission. The exact role of this system in normal and disease physiology has been difficult to study because of a lack of a suitable molecular imaging probe.[29] While a high affinity metallocarborane for the α-class of adrenoceptors is a major step toward addressing this issue, the carborane complexes have a negative charge which will likely render these probes useful for studying peripheral α-adrenergic receptors only. We are therefore currently using **13** as a platform for making neutral analogues to facilitate crossing of the blood−brain barrier and as the basis for identifying even higher affinity analogues by exploiting the versatile chemistry of carboranes.[30,31]

EXPERIMENTAL SECTION

Reagents and General Procedures. Unless otherwise stated, all chemicals and reagents were purchased and used as received from Sigma-Aldrich without further purification. Decaborane and *o*-carborane were obtained and used as received from Katchem Ltd., and 1-butyl-3-methylimidazolium chloride ([BMIM][Cl]) was purchased from Strem Chemicals. Compounds prepared according to literature procedures were 1-(2-methoxyphenyl)-4-(prop-2-ynyl)piperazine (**1**),[13]

1,2-dicarba-*closo*-dodecaborane-1-carboxylic acid,[32] $[Re(CO)_3(H_2O)_3][Br]$,[33] and $[^{99m}Tc(CO)_3(H_2O)_3]^+$.[34]

Reactions were performed under an inert atmosphere unless otherwise stated. All solvents were obtained from Caledon and either dried by a Pure-Solv solvent purification system (Innovative Technology Inc.) or dried over calcium hydride (acetonitrile, dichloromethane, and toluene), sodium/benzophenone (diethyl ether and tetrahydrofuran), or sodium iodide (acetone) and distilled prior to use. Deuterated solvents for NMR samples were purchased from Cambridge Isotope Laboratories. Technetium-99m complexes were prepared from pertechnetate $[^{99m}TcO_4]^-$ which was obtained from a $^{99}Mo-^{99m}Tc$ generator (Lantheus Medical Imaging) in saline (0.9% NaCl).

Reactions were monitored using Alugram Sil G/UV_{254} thin-layer chromatography (TLC) plates. Carborane-containing species were visualized with 0.2% $PdCl_2$ in hydrochloric acid (3.0 M), which upon heating gave dark brown spots. Amines were visualized with ninhydrin spray. Silica gel 60PF_{254} containing gypsum (EM Science) was used for making preparative TLC plates and plates for the Chromatotron model 7924T (Harrison Research). Column chromatography was accomplished with silica gel 60 (EMD Chemical Inc.) or Ultra Pure silica gel 60 (Silicycle). Automated normal and reverse-phase (C18) silica gel chromatography was performed on a Biotage SP1 purification system operated at ambient temperature using solvent gradients as specified. Solid phase extraction cartridges (C18) obtained from Waters were used following pretreatment with water (10 mL), methanol, or ethanol (10 mL) and a second wash with water (10 mL) and HCl (10 mM, 10 mL).

Instrumentation. Nuclear magnetic resonance spectra (^1H, $^{13}C\{^1H\}$, $^{11}B\{^1H\}$) were recorded on either a Bruker 500 or 600 MHz spectrometer at ambient temperature. The chemical resonances (δ) are reported in parts per million (ppm), with the ^1H NMR shifts referenced to the residual proton signal of the deuterated solvent and the ^{13}C shifts referenced to the carbon signal of the solvent. The chemical shifts (δ) for $^{11}B\{^1H\}$ NMR spectra were reported relative to an external reference of $BF_3 \cdot Et_2O$. Infrared spectra were acquired on a Bio-Rad FTS-40, Nicolet 510, or 6700 Fourier transform IR spectrometer at ambient temperature. Samples were run on a KBr plate or as KBr pellets. A Gallenkamp melting point apparatus was used to determine melting points. Reactions involving microwave heating were performed on a Biotage Initiator 60 or Initiator 8 microwave reactor using crimped-sealed vials. Mass spectra were obtained from the McMaster Regional Centre for Mass Spectrometry on a Micromass Quattro Ultima (LC-ESI/APCI triple quadrupole) mass spectrometer for electrospray ionization (ES) mass spectrometry, a Micromass GC-EI/CI time of flight mass spectrometer instrument for chemical ionization (CI) and electron ionization (EI) spectra, and a Micromass Global Ultima (MALDI/CapLC-ESI quadrupole time of flight) mass spectrometer for high resolution mass spectra. A Capintec dose calibrator was used to determine the activity of samples containing technetium-99m (>300 kBq).

Tested compounds were purified to >95% as determined by high performance liquid chromatography (HPLC), which was performed on a Varian ProStar model 230 or 230I solvent delivery system fitted with a Varian ProStar model 230 or 335 PDA detector and an in-line radioactivity detector (IN/US γ-RAM). The wavelength for detection was set at 250 or 254 nm, and the dwell time in the γ detector was 0.5 s with a 10 μL loop. A Varian Nucleosil C18 100-5 (250 mm × 4.6 mm) column was used with a sample volume of either 100 or 500 μL. The following solvent gradients were employed: method A (solvent A = acetonitrile (0.1% formic acid), solvent B = 20 mM ammonium acetate, 1 mL/min) 0−15 min 65−100% A, 15−20 min 100% A; method B (solvent A = aqueous tetraethylammonium phosphate, pH 2.0−2.5, solvent B = methanol, 1 mL/min) 0−3 min 100% A, 3−6 min 100−75% A, 6−9 min 75−67% A, 9−20 min 67−0% A, 20−22 min 0% A, 22−25 min 0−100% A, 25−30 min 100% A; method C (solvent A = acetonitrile, solvent B = water, 1 mL/min) 70:30 A/B isocratic for 15 min; method D (solvent A = acetonitrile (0.1% formic acid), solvent B = water (0.1% formic acid), 1 mL/min) 70:30 A/B isocratic for 15 min; method E (solvent A = acetonitrile (0.1% formic acid), solvent B = 20 mM ammonium acetate, 1 mL/min) 70:30 A/B isocratic for 15 min; method F (solvent A = acetonitrile, solvent B = 0.1 M ammonium formate, 1 mL/min) 70:30 A/B isocratic for 15 min; method G (solvent A = methanol, solvent B = water, 1 mL/min) 70:30 A/B isocratic for 15 min.

1-(2-Methoxyphenyl)-4-(pent-4-ynyl)piperazine (2). The synthesis was adapted from a procedure reported by Khatuya and coworkers.[13] Sodium iodide (1.2 g, 8.0 mmol) was added to a solution of 5-chloro-1-pentyne (0.83 mL, 7.8 mmol) in acetonitrile (20 mL), and the resulting mixture was stirred at 25 °C for 1 h. A solution of 1-(2-methoxyphenyl)piperazine (1.0 g, 5.2 mmol) in acetonitrile (15 mL) was added dropwise to the reaction mixture followed by a single addition of potassium carbonate (9.4 g, 68 mmol). The mixture was heated at reflux (82 °C) for 48 h. The mixture was cooled to room temperature, and distilled water (50 mL) was added. The product was extracted with ethyl acetate (3 × 30 mL); the combined organic fractions were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The product was purified by either flash or automated (40+M) silica column chromatography using a gradient of 6−50% ethyl acetate/hexanes. The product was isolated as a pale yellow solid (1.0 g, 74%). TLC R_f(50% ethyl acetate/hexanes) = 0.38. Mp = 62 °C. ^1H NMR (600 MHz, $CDCl_3$) δ: 6.98 (m, 1 H, Ar−H), 6.92 (m, 2 H, Ar−H), 6.85 (m, 1 H, Ar−H), 3.85 (s, 3 H, OCH_3), 3.09 (s, 4 H, NCH_2), 2.64 (s, 4 H, NCH_2), 2.50 (t, 2 H, CH_2, J = 4.0 Hz), 2.25 (td, 2 H, CH_2, J = 7.0 Hz, J = 2.3 Hz), 1.95 (t, 1 H, CH, J = 2.6 Hz), 1.75 (m, 2 H, CH_2). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ: 152.3, 141.5, 122.9, 121.1, 118.3, 111.3, 84.3, 68.5, 57.5, 55.4, 53.5, 50.7, 25.9, 16.5. IR (KBr, cm^{-1}): ν 3295, 2149, 1501. HRMS (CI+) m/z for $C_{16}H_{22}N_2O$: calculated, 259.1810; observed, 259.1812 $[M + H]^+$.

1-[(4-(2-Methoxyphenyl)piperazin-1-yl)methyl]-1,2-dicarba-*closo*-dodecaborane (3). A solution of compound **1** (0.33 g, 1.4 mmol) in toluene (1.5 mL) was added to a suspension of 1-butyl-3-methylimidazolium chloride (0.050 g, 0.29 mmol) and decaborane (0.071 g, 0.58 mmol) in toluene (1 mL). The heterogeneous mixture was heated at reflux (110 °C) for 2 h. The mixture was concentrated to a viscous yellow liquid using a rotary evaporator. The product was purified by preparative TLC and an eluent of 100% dichloromethane. The product was obtained following extraction of the silica with 10% methanol/dichloromethane and evaporation under reduced pressure to yield a white solid (0.07 g, 35%). TLC R_f(100% dichloromethane) = 0.79. Mp = 133−135 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.02 (m, 1 H, Ar−H), 6.92 (m, 2 H, Ar−H), 6.86 (m, 1 H, Ar−H), 4.02 (s, 1 H, CH), 3.85 (s, 3 H, OCH_3), 3.12 (s, 6 H, NCH_2, CH_2), 2.80 (s, 4 H, NCH_2). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ: 152.2, 140.8, 123.2, 120.9, 118.2, 111.3, 74.9, 62.1, 58.2, 55.4, 54.9, 50.7. $^{11}B\{^1H\}$ NMR (160 MHz, $CDCl_3$) δ: −4.1, −6.5, −10.1, −12.5, −13.6, −14.3. IR (KBr, cm^{-1}): ν 2576, 1500. HRMS (CI+) m/z for $C_{14}H_{28}N_2OB_{10}$: calculated, 350.3132; observed, 350.3109 $[M^+]$.

1-[(4-(2-Methoxyphenyl)piperazin-1-yl)propyl]-1,2-dicarba-*closo*-dodecaborane (4). A solution of decaborane (0.082 g, 0.67 mmol) in toluene (5 mL) was added to a suspension of 1-butyl-3-methylimidazolium chloride (0.041 g, 0.24 mmol) in toluene (5 mL). A solution of compound **2** (0.23 g, 0.89 mmol) in toluene (5 mL) was added to the reaction mixture. The heterogeneous mixture was heated at reflux (110 °C) for 7 days, then concentrated to a viscous yellow liquid using a rotary evaporator. The product was purified by using automated silica gel chromatography (12+M) employing a gradient of 0−2% methanol/dichloromethane, giving a beige solid following evaporation of the solvent (0.033 g, 13%). TLC R_f(1% methanol/dichloromethane) = 0.12. Mp = 138 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.00 (m, 1 H, Ar−H), 6.93 (m, 2 H, Ar−H), 6.86 (m, 1 H, Ar−H), 3.85 (s, 3 H, OCH_3), 3.60 (s, 1 H, CH), 3.08 (s, 4 H, NCH_2), 2.61 (s, 4 H, NCH_2),

2.37 (m, 2 H, CH_2), 2.28 (m, 2H, CH_2), 1.70 (m, 2 H, CH_2). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ: 152.4, 141.4, 123.1, 121.2, 118.3, 111.5, 75.4, 61.5, 57.2, 55.5, 53.5, 50.7, 36.1, 26.7. $^{11}B\{^1H\}$ NMR (160 MHz, $CDCl_3$) δ: −2.7, −6.2, −9.7, −11.9, −12.5, −13.5. IR (KBr, cm^{-1}): ν 2589, 1501. HRMS (CI+) m/z for $C_{16}H_{32}B_{10}N_2O$: calculated, 378.3445, observed 378.3452 $[M^+]$.

Sodium *rac*-*N*-[7-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl]-7,8-dicarba-*nido*-undecaborate-1-carboxamide (5). To a solution of 1,2-dicarba-*closo*-dodecaborane-1-carboxylic acid (1.0 g, 5.3 mmol) in dichloromethane (50 mL) were added thionyl chloride (1.2 mL, 16 mmol) and *N*,*N*-dimethylformamide (0.30 mL, 3.9 mmol). The solution was heated at reflux for 3.5 h. The solvent was removed under reduced pressure to yield **6** (1.1 g, 5.3 mmol). Compound **6** was immediately dissolved in dichloromethane (30 mL) and cooled to 0 °C. Diisopropylethylamine (1.8 mL, 10 mmol) and compound **7** (2.8 g, 11 mmol) were dissolved in dichloromethane (35 mL) and added to the reaction vessel. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was washed with HCl (0.01 M, 3 × 30 mL) and brine (30 mL). The organic fraction was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The reaction mixture was purified by silica column chromatography using a gradient of 0−10% methanol/ethyl acetate. The product was stirred in an ethanolic solution of sodium hydroxide (5 equiv) overnight, then concentrated under reduced pressure. The residue was redissolved in ethyl acetate and washed with HCl (0.1 M), brine, and water. The organic fraction was concentrated and lyophilized to yield **5** as a white solid. Yield: 0.4 g, 17%. TLC R_f(10% methanol/dichloromethane) = 0.53. Mp ≥ 230 °C. ^1H NMR (500 MHz, $(CD_3)_2CO$): δ 7.04 (m, 1 H, Ar−H), 6.98 (m, 2 H, Ar−H), 6.91 (m, 1 H, Ar−H), 6.65 (s, 1 H, NH), 3.86 (s, 3 H, OCH_3), 3.45 (s, 6 H, NCH_2), 3.27 (m, 4 H, NCH_2, CH_2), 2.53 (s, 1 H, CH), 1.89 (m, 2 H, CH_2), 1.79 (m, 2 H, CH_2), 1.64 (m, 4 H, CH_2). $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$): δ 173.9, 152.7, 139.6, 123.9, 121.0, 118.8, 112.0, 56.3, 54.9, 54.0, 52.9, 47.7, 40.6, 37.1, 27.1, 20.0. $^{11}B\{^1H\}$ NMR (160 MHz, $(CD_3)_2CO$): δ −9.6, −10.6, 14.6, −17.1, −17.7, −21.4, −23.0, −32.8, −36.1. IR (KBr, cm^{-1}): ν 3419, 2916, 2523, 1593. HRMS (ES+): calculated for $C_{18}H_{35}B_9N_3O_2$, 424.3567; observed, 424.3593 $[M^+]$.

4-[4-(2-Methoxyphenyl)piperazin-1-yl]butan-1-amine (7). The synthesis was adapted from Chu and co-workers.[35] To a solution of compound **14** (4.1 g, 15.8 mmol) in dry diethyl ether (150 mL) at 0 °C, 25 mL of lithium aluminum hydride (1.0 M in Et_2O) was added dropwise with stirring. The reaction mixture was stirred at 0 °C for 10 min, then stirred at room temperature for 2 h and finally heated at reflux for 2 h. The mixture was cooled to 0 °C, and saturated aqueous $NaHCO_3$ (50 mL) was added slowly. The reaction mixture was stirred for 10 min at 0 °C and 10 min at room temperature. The mixture was filtered through Celite, and the filtrate was added to a separatory funnel. The layers were separated, and the aqueous fraction was further extracted with dichloromethane (3 × 20 mL). The combined organic fractions were dried with anhydrous Na_2SO_4, filtered and the solvent was removed to yield compound 7 as a yellow oil (3.8 g, 91%). Characterization data matched the data reported in the literature.[35]

General Preparation of Rhenacarboranes 8−10. The desired *nido*-carborane was generated by heating the corresponding *closo*-carborane derivative (**3** or **4**) with sodium fluoride (7 equiv) in aqueous ethanol (10−15%) in a microwave reactor (195 °C, 10−15 min), while *nido*-carborane **5** was used directly. Complexation was accomplished by heating the $[Re(CO)_3(H_2O)_3][Br]$ (1 equiv) with the *nido*-carboranes in a microwave reactor at 180−195 °C for 10 min. Two subsequent additions of $[Re(CO)_3(H_2O)_3][Br]$ (1.0 and 0.5 equiv) were performed where each addition was accompanied by heating the mixture at 180−195 °C for 10 min.

Sodium *rac*-8-[(4-(2-Methoxyphenyl)piperazin-1-yl)methyl]-2,2,2-tricarbonyl-2-rhenium-2,1,8-dicarba-*closo*-dodecaborate (8). The procedure employed 0.093 g (0.26 mmol) of compound **3**. Following the final heating, the mixture was cooled to room temperature and diluted with water (10 mL). The product was then extracted with dichloromethane (3 × 10 mL). The organic fractions were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The product was isolated as an ivory solid (0.13 g, 82%) by either flash or automated (12+M) silica gel chromatography and a gradient of 12−100% ethyl acetate/hexanes or using a reverse phase automated purification system and a gradient of 20−100% acetonitrile/water. TLC R_f(50% ethyl acetate/hexanes) = 0.24. Mp = 110 °C. ^1H NMR (600 MHz, CD_2Cl_2) δ: 7.12 (m, 1 H, Ar−H), 6.93 (m, 3 H, Ar−H), 3.84 (s, 3 H, OCH_3), 3.79 (AB, 1 H, CH_2, J = −13.7 Hz), 3.61 (m, 4 H, NCH_2), 3.53 (AB, 1 H, CH_2, J = −13.7 Hz), 3.37 (m, 2 H, NCH_2), 3.12 (m, 2 H, NCH_2), 1.88 (s, 1 H, CH). $^{13}C\{^1H\}$ NMR (150 MHz, CD_2Cl_2) δ: 197.8, 153.1, 138.1, 125.7, 121.5, 119.8, 112.1, 66.8, 57.0, 56.9, 55.8, 48.4, 48.4, 44.1, 28.8. $^{11}B\{^1H\}$ NMR (160 MHz, CD_2Cl_2) δ: −5.8, −8.0, −11.4, −18.5, −20.3. IR (KBr, cm^{-1}): ν 2539, 2005, 1907, 1502. HRMS (ES−) m/z for $C_{17}H_{27}N_2O_4B_9Re$: calculated, 609.2353; observed, 609.2366 $[M^+]$. UV−HPLC: method A, t_R = 15.0 min; method B, t_R = 22.6 min.

Sodium *rac*-1-[(4-(2-Methoxyphenyl)piperazin-1-yl)propyl]-3,3,3-tricarbonyl-3-rhenium-3,1,2-dicarba-*closo*-dodecaborate (9). The procedure employed 0.032 g (0.086 mmol) of compound **4**. Following the final heating, the mixture was cooled to room temperature, diluted with water (10 mL), and extracted with dichloromethane (3 × 15 mL). The organic fractions were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The product was isolated as an ivory solid (0.052 g, 95%) by either flash or automated (12+M) silica gel chromatography and a gradient of 12−100% ethyl acetate/hexanes or using a reverse phase automated purification system and a gradient of 20−100% acetonitrile/water. TLC R_f(5% methanol/dichloromethane) = 0.52. Mp = 193 °C. ^1H NMR (600 MHz, $(CD_3)_2CO$) δ: 7.04 (m, 1 H, Ar−H), 6.99 (m, 2 H, Ar−H), 6.91 (m, 1 H, Ar−H), 3.86 (s, 3 H, OCH_3), 3.38 (m, 4 H, NCH_2), 2.81 (s, 4 H, NCH_2), 1.91 (m, 6 H, CH_2), 1.75 (s, 1 H, CH). $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2CO$) δ: 200.4, 153.5, 140.4, 124.8, 121.9, 119.5, 113.0, 79.2, 58.0, 55.9, 54.2, 53.2, 48.5, 37.7, 25.4. $^{11}B\{^1H\}$ NMR (160 MHz, $(CD_3)_2CO$) δ: −5.2, −7.8, −9.8, −11.2, −12.1, −18.0, −19.7. IR (KBr, cm^{-1}): ν 2542, 1995, 1897, 1500. HRMS (ES−) m/z for $C_{19}H_{31}N_2O_4B_9Re$: calculated, 637.2697; observed, 637.2679 $[M^+]$. UV−HPLC: method A, t_R = 14.8 min; method B, t_R = 23.4 min.

Sodium *rac*-8-[*N*-[7-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl]]-2,2,2-tricarbonyl-2-rhenium-2,1,8-dicarba-*closo*-dodecaborate-1-carboxamide (10). The procedure employed 0.30 g (0.67 mmol) of compound **5**. Following the final heating, the solvent was evaporated and the mixture was suspended in acetonitrile (15 mL) and filtered. The complex was isolated as a white solid following purification by reverse phase chromatography using a gradient of 20−100% acetonitrile/water followed by silica column chromatography or preparative TLC using a gradient of 10% methanol/dichloromethane (0.046 g, 10%). TLC R_f(5% methanol/dichloromethane) = 0.31. Mp ≥ 230 °C. ^1H NMR (600 MHz, CD_3CN) δ: 7.03 (m, 1 H, Ar−H), 6.94 (m, 3 H, Ar−H), 6.53 (s, 1 H, NH), 3.83 (s, 3H, OCH_3), 3.22 (m, 4 H, NCH_2), 3.12 (m, 6 H, NCH_2, CH_2), 2.89 (m, 2 H, CH_2), 1.86 (s, 1 H, CH), 1.58 (m, 2 H, CH_2), 1.47 (m, 2 H, CH_2). $^{13}C\{^1H\}$ NMR (125 MHz, CD_3CN) δ: 199.7, 168.5, 153.4, 141.1, 124.5, 122.0, 119.4, 112.9, 57.7, 56.1, 53.8, 49.2, 39.6, 28.6, 27.3, 22.2. $^{11}B\{^1H\}$ NMR (160 MHz, CD_3CN) δ: −5.8, −7.7, −8.9, −12.2, −18.8, −19.9. IR (KBr, CH_3CN, cm^{-1}): ν 2517, 2002, 1917, 1896. HRMS (ES−) m/z for $C_{21}H_{35}N_3O_5B_9Re$: calculated, 695.2972; observed, 695.2999 $[M^+]$. UV−HPLC: method A, t_R = 13.7 min.

4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyronitrile (14). The synthesis was adapted from a report by Chu and co-workers.[35] To a solution of 1-(2-methoxyphenyl)piperazine (5.1 g, 26.5 mmol) in acetonitrile (50 mL), sodium carbonate (5.6 g, 52.8 mmol) and bromobutyronitrile (2.0 mL, 20.1 mmol) were added with stirring. The reaction mixture was heated to reflux (82 °C) for 24 h. When the

Table 2. X-ray Crystal Data for Compound 10

parameter	
empirical formula	$C_{21}H_{35}B_9N_3O_5Re$
formula weight	693.01
crystal system	monoclinic
space group	$P2(1)/c$
unit cell parameters	
a (Å)	9.6837(5)
b (Å)	12.8205(7)
c (Å)	23.6507(13)
α (deg)	90
β (deg)	95.7870(10)
γ (deg)	90
temp of data collection (K)	173(2)
Z	4
R indices (all data)	
R1	0.0704
wR2	0.0752
goodness-of-fit	1.038

mixture was cooled, anhydrous Na_2SO_4 was added. The mixture was filtered and the solvent removed under reduced pressure to yield a yellow oil. The product was purified using silica column chromatography using a gradient of 75−100% ethyl acetate/hexanes (4.6 g, 88%). Characterization data matched the data reported in the literature.[35]

General Preparation of ^{99m}Tc Carborane Complexes. The *nido*-carborane were generated by heating the *closo*-carborane derivative **3** or **4** with sodium fluoride (7 equiv) in aqueous ethanol (10−15%) in a microwave reactor (195 °C for 10 min), while *nido*-carborane **5** was used directly. To a solution of the ligand (**3**, 6 mM; **4**, 5 mM; **5**, 4 mM), $[^{99m}Tc(CO)_3(H_2O)_3]^+$ (370−1850 MBq, 1 mL) was added to the reaction vessel. The mixture was heated in the microwave reactor at 195 °C for 10 min. The crude reaction mixture was passed through a C18 solid phase extraction cartridge where residual $[^{99m}Tc(CO)_3(H_2O)_3]^+$ was eluted with HCl (10 mM) and the product was eluted with acetonitrile. The excess ligand was removed by HPLC (method A). Decay corrected radiochemical yield: 36% (**11**), 19% (**12**), 14% (**13**). Radio-HPLC: method A, t_R = 15.7 min (**11**), 15.2 min (**12**), 14.0 min (**13**); method B, t_R = 22.9 min (**11**), 23.1 min (**12**).

Stability Studies. The ^{99m}Tc complexes **11**−**13** were dissolved in ethanol (0.5 mL) and transferred to a vial containing saline (0.9% NaCl, 4.5 mL). Analytical HPLC of the samples was performed every 30 min using a Varian Nucleosil C18 column (methods C−G). No decomposition was observed by radio-HPLC over 6 h under several different analytical HPLC conditions (mobile phase and pH).

In Vitro Assay. K_i determination was conducted by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract No. NO1MH32004. For experimental details refer to the PDSP Web site http://pdsp.med.unc.edu/. Compounds **8**−**10** were assayed against serotonin, α- and β-adrenergic, DAT, NET, SERT, and σ receptors.

X-ray Analysis. A colorless rod-shaped crystal of **10** was mounted on a MiTeGen polymer mount and placed in a cold stream of liquid nitrogen (77 K). Data (Table 2) were collected at 100 K on a Bruker APEX2 diffractometer equipped with CCD area detector using a graphite monochromator Mo Kα radiation and ϕ and ω scans. The APEX2 suite was used for data collection, and SAINT was used for data reduction; data were scaled using SADABS with both face-indexed absorption correction and a correction using redundant data.[36−38] The correct space group ($P2_1/c$) was chosen by examination of reciprocal space with the program MAX3D;[39] this indicated a *c*-glide that otherwise was not detected by APEX2. The structure was then solved by direct methods and refined by full matrix least-squares refinement on F^2 using the Bruker SHELXTL program library.[40] Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were located from the difference map. The hydrogen atoms that were well-behaved were allowed to refine; others were fixed at calculated positions and were refined as riding on the atom to which they were bonded. Protonation of one of the nitrogen atoms in the piperazine ring meant that there was no residual counterion in the complex. In the final stages of refinement, R = 3.89% and wR2 = 6.83%; CCDC No. 795365.

■ ASSOCIATED CONTENT

Supporting Information. Screening and characterization data for the ligands and metal complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

WAY, 1-(2-methoxyphenyl)piperazine; Cp, cyclopentadiene; MIP, molecular imaging probe; CNS, central nervous system; PET, positron emission tomography; SPECT, single photon emission computed tomography; SAR, structure−activity relationship; LC−MS, liquid chromatography−mass spectrometry; DAT, dopamine active transporter; SERT, serotonin transporter; NET, norepinephrine transporter; TLC, thin layer chromatography; ES, eletrospray; CI, chemical ionization; EI, electron impact; HPLC, high-performance liquid chromatography

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