Pergamon

Bioorganic & Medicinal Chemistry 6 (1998) 1663–1672

BIOORGANIC & MEDICINAL CHEMISTRY

Novel Rhenium Complexes Derived from α-Tropanol as Potential Ligands for the Dopamine Transporter

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Received 13 January 1998; accepted 23 March 1998

Abstract—A series of rhenium complexes was synthesized as model compounds for the corresponding radioactive technetium-99m complexes for preliminary biological investigations. In a '3 + 1' mixed-ligand approach the tropanol molecule was linked with the metal core through a ω-mercaptoester group as monodentate ligand. Bis(thioethyl)sulphide was used as the tridentate dithiol ligand to block the remaining free coordination sites. The ω-mercaptoesters were synthesized via the trityl-protected precursors. Binding tests on the cloned human dopamine transporter revealed moderate binding affinities for some of the prepared compounds. The complexes were characterised by X-ray and the lipophilicity as well as pK_a values were determined.

Introduction

Since the readily available radionuclide technetium-99m is the preferred radionuclide for nuclear medical diagnosis, there is great interest in the development of novel imaging agents based on this nuclide. Currently over 85% of clinical nuclear medicine procedures use technetium-99m because of its ideal gamma emission of 140 keV and its good availability by the Mo-99/Tc-99m generator. Since the both most common nuclides of technetium, technetium-99m and technetium-99 are radioactive the handling affords great care and is subjected to some restrictions. The chemistry of the third-row congener rhenium is well investigated and offers the advantage of work with 'cold' isotopes. The chemical behaviour of rhenium and technetium is nearly identical. In particular both elements form complexes with the same coordination geometry. This results in similar parameters like size and lipophilicity. Therefore, rhenium compounds serve as ideal model compounds for the analogous technetium-99m complexes.

Our investigations aimed at the development of new technetium compounds that specifically bind to the dopamine transporter and we spend our effort on rhenium complexes as predecessors in investigations that will finally be extended to technetium.

Dopaminergic neurotransmission, among other mechanisms, depends on the efficient removal of the transmitter from the synaptic cleft by a re-uptake mechanism into the dopaminergic neuron. There is considerable interest in this uptake system because of profound effects of drugs such as cocaine that inhibit this process. Moreover, protection against the action of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which elicits syndromes similar to Parkinson's disease (PD), can be achieved with selective dopamine uptake inhibitors.[1] This fact contributed to the development of current hypotheses regarding the aetiology of PD, which are focused on the potential contributions of environmental toxins.[2]

Key words: Dopamine transporter; rhenium; technetium; SPECT ; α-tropanol.
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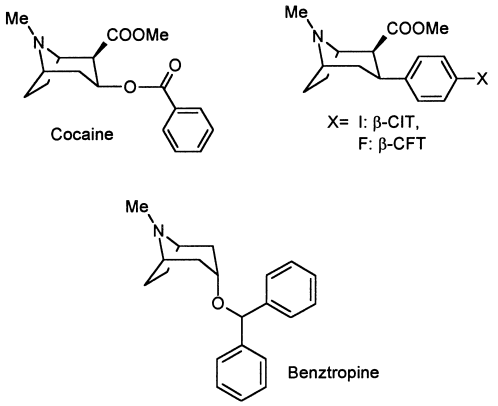
0968-0896/98/$—see front matter
PII: S0968-0896(98)00144-8

In the past 10 years, emission tomography has considerably contributed to the understanding of parkinsonism.[3] Several cocaine analogues have been recently synthesized as potent dopamine transporter (DAT) ligands for positron emission tomography (PET)[4–10] and single photon emission computed tomography (SPECT).[11–14] [^{123}I]β-CIT [*N*-methyl-2β-carbomethoxy-3β-(4-iodophenyl) tropane] has been successfully used for SPECT imaging of DAT in the living human brain.[15] However the ligand also displays considerable affinity towards the serotonin transporter (5-HTT).[16] β-CFT [*N*-methyl-2β-carbomethoxy-3β-(4-fluorophenyl)-tropane] (or WIN 35,428) has a higher selectivity and was recently labeled with ^{99m}Tc.[14] Specific accumulation in the striatum as the target tissue was shown. Even though substituents in 2-position seem to be necessary for high affinity, there are also ligands without substituents in 2-position such as benztropine analogues.[17]

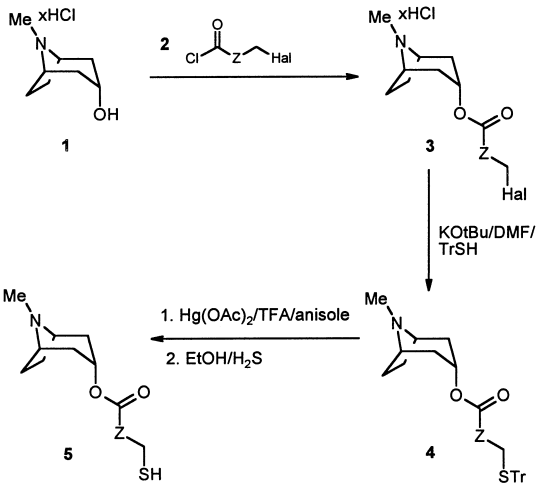


The most striking advantage of the benztropines is their selectivity towards the DAT against 5-HTT and the norepinephrine transporter. On the other hand, they show a very high affinity to the muscarinic m_1 receptor. It has also been suggested that the benztropines may interact on the DAT at a different binding site than cocaine.[17] Further examples show the possibility of accommodating bulky π-electron-rich substituents in 3-position without a decrease in affinity.[18] Therefore, we decided to mimic one or both of the phenyl rings in the benztropines with the π-electron-rich chelate moiety.[19]

Results and Discussion

Chemistry

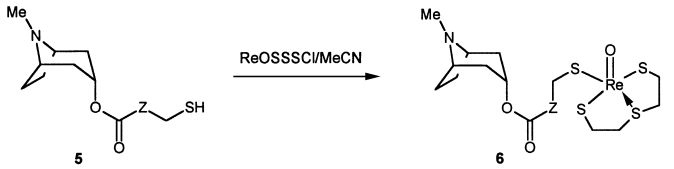
The '3 + 1' mixed-ligand concept[20,21] is a very convenient way to prepare a large number of compounds for a primary screening. '3 + 1' mixed-ligand complexes are easily accessible by combining appropriate tridentate and monodentate ligands. '3 + 1' complexes, especially, formed by use of bis(thioethyl)sulphide as the tridentate ligand are very stable. Accordingly, the complexes were obtained by reaction of the tridentate dithiol ligand with tetrachlorooxorhenate, providing a preformed metal unit[22] with a remaining chloro atom, which is substituted by the monothiol bearing the tropane ring. An intriguing advantage is the lack of stereoisomers in relation to the chelate unit, which obviates the need for lengthy purifcation procedures. This would make potential high affinity compounds particularly useful for clinical use.



Scheme 1. Synthesis of ω-mercaptoesters of tropane. Z: **a** = 0, **b** = CH_2, **c** = C_2H_4, **d** = C_3H_6, **e** = C_4H_8, **f** = 1,3-phenyl, **g** = 1,4-phenyl.

As we linked the tropane molecule with the metal core by an ester chain the required thiol group was introduced into the ω-position of the acid moiety (Scheme 1).

The synthesis of tropane esters is the key step in the whole reaction sequence. The best results were attained by mixing equimolar amounts of tropanol hydrochloride and the appropriate ω-halogen-substituted acid chloride at elevated temperatures.[23] The yields are very high and no epimerisation could be observed, as established by ^{1}H NMR spectra. The pseudo-triplett found around 5 ppm is typical for the β-orientation of the proton in 3-position in contrast to a multiplett usually found for its α-orientation.[24] Also in the following steps no additional peak for this proton suggesting an epimerisation could be found. Finally, the X-ray structure prove this results to have been correct. However, we observed an unexpected effect: the partial exchange of the ω-bromo atom of the haloester by chlorine. This was found by the chemical shifts in the ^{1}H NMR spectra. Thus, we observed four triplets in the ^{1}H NMR spectra of 3-halopropionic acid trop-3-yl ester. Two of the triplets have an intensity of about 66% each and the other two 33% each. By separate preparation of the 3-chloro



Scheme 2. Synthesis of the complexes.

propionic acid trop-3-yl ester according to the same procedure the two triplets with the higher intensity were assigned to this compound. That means that the amount of the bromo compound was approximately 33%. This fact was observed with all aliphatic bromoesters. Elemental analyses indicate a 1/1 ratio of the two halogens, so the salts are mainly hydrobromides (66%). The halogen exchange is probably caused by elimination of HBr and subsequent addition of HCl in an anti-Markovnikov manner or by a simple S_N2 reaction. Separation of the two compounds by simple recrystallization proved impossible but was actually unnecessary because further reactions are not affected by this fact. Therefore, no attempts were made to study the mechanism of the halogen exchange. In the further reaction steps a mixture of the bromo and chloro esters was used.

The introduction of the mercapto group was achieved by reacting the ω-halogen substituted tropane esters with triphenyl methane thiol and potassium *tert*-butoxide in DMF at temperatures between 50 and 60 °C. Flash chromatography gave the *S*-protected tropane mercapto esters in yields up to 80% as waxy or glassy solids which were difficult to purify. The deprotection of the mercapto group worked best with mercury acetate in trifluoroacetic acid and subsequent reaction with hydrogen sulphide. The mercaptans were purified by column chromatography and the purity determined by Elmann's test.

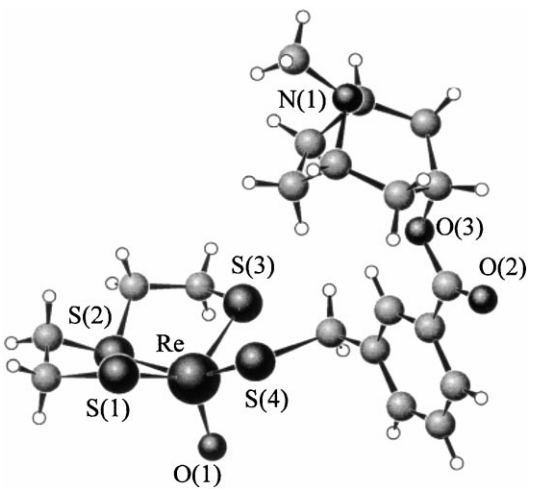


Figure 1. Powdercell plot of complex **6f**.

Complexation was performed according to a typical '3 + 1' procedure by reacting the mercaptane with 3-thiapentane-1,5-dithiolato-oxorhenium (V) [ReOSSSCl] in acetonitrile until a red colour appeared[22] (Scheme 2).

Flash chromatography yields the pure complexes which were crystallized after being allowed to stand by slow evaporation of the solvent. Some of the complexes were crystallized as oxalates or hydrochlorides. Complex **6f** crystallized in such a manner yielding suitable crystals for X-ray analysis (Fig. 1). X-ray crystallography displays the expected square pyramidal structure of the complex unit and the 3α-orientation of the ester group at the tropane ring.

An important aspect for all CNS-imaging agents is the brain uptake. In the case of passive transport brain uptake is influenced by such parameters as lipophilicity or pK_a values. In order to find correlations between structure and brain uptake for all new complexes developed by our working group the D_{HPLC}, P_{HPLC} and $pK_{a(c)}$ values were routinously estimated by HPLC methods. These values were derived from the retention times according to the equation $\log P = a \log k' + b$, where $k' = (t_R - t_0)/t_0$ represents the capacity factor, t_R is the retention time of the sample and t_0 the retention time of methanol as an unretained solute. With a given ionizable compound a sigmoidal D_{HPLC}/pH curve results. From the turning point of this curve the apparent pK_a value (pK_{HPLC}) was derived. A detailed

Table 1. Selected bond length and angles of complex **6f**

Bond length (Å)		Bond angles (°)	
Re-O (1)	1.684	O (1)-Re-S (3)	115.69
Re-S (3)	2.2825	O (1)-Re-S (1)	115.42
Re-S (1)	2.2905	S (3)-Re-S (1)	128.82
Re-S (4)	2.310	O (1)-Re-S (4)	104.85
Re-S (2)	2.383	S (3)-Re-S (4)	87.87
		S (1)-Re-S (4)	81.74
		O (1)-Re-S (2)	101.06
		S (3)-Re-S (2)	84.35
		S (1)-Re-S (2)	83.8
		S (4)-Re-S (2)	153.81

Table 2. P_{HPLC}, D_{HPLC} and $pK_{a(c)}$ values of the rhenium complexes

Compl	Z	P_{HPLC}	D_{HPLC} at pH 7.4	$pK_{a(c)}$
6a	0	34	2	9.34
6b	CH_2	36	2	9.51
6c	C_2H_4	94	6	9.44
6d	C_3H_6	163	7	9.48
6e	C_4H_7	330	9	9.85
6f	1.3-phenyl	398	25	9.04
6g	1.4-phenyl	478	18	9.45

description of the procedure is given in the experimental part. Some complexes were used in the HPLC-investigations in the form of their salts. Since the complexes are dissolved in an excess of buffer, they show identical behaviour on the HPLC column as free bases.

Whereas the $pK_{a(c)}$ values are more or less in the same order at about 9 (Cocaine: 8.5[25]), the P_{HPLC} and concomitantly the D_{HPLC} values at pH 7.4 increased with the number of carbon atoms in the ester chain. Hence the compounds **6f** and **6g** should have a lipophilicity high enough to penetrate the blood–brain barrier in reasonable amounts. For all other compounds the lipophilicity is too low and the basicity is too high as expressed by the distribution coefficient D_{HPLC}.

Receptor binding affinity

The affinity constants of the binding of compounds **6a–6g** to cloned human dopamine transporters are shown in Table 3 in terms of the IC_{50} values. For the binding of [^{3}H]WIN35,428 to cloned human dopamine transporters, a one-site model was assumed as suggested by Reith et al.[26] Under other circumstances the same authors have also reported a second low-affinity component of the [^{3}H]WIN35,428 binding[27] with a K_d between 3 and 8 μM. In our binding assay we did not find any evidence for a second binding component which may be due to the use of 1 μM GBR12909 for definition of non-specific binding.

Table 3. IC_{50} values for inhibition of [^{3}H]WIN35,428 binding on cloned human dopamine transporters

Ligand	IC_{50}
GBR12909	2.35 ± 0.35 nM
Cocaine	306 ± 48 nM
6a	> 10 μM
6b	> 10 μM
6c	> 10 μM
6d	17 ± 11 μM
6e	5.3 ± 4.5 μM
6f	2.4 ± 1.6 μM
6g	> 10 μM

In Table 3 the IC_{50} values of compounds **6a–6g** are compared with GBR12909, a drug which is known to bind to dopamine transporters with a high affinity.[27–29] Also the IC_{50} value of cocaine is given for comparison. As also found by others it has a much lower affinity in the binding assay.[26–29] Re complexes **6d–6f** exhibited an affinity to the DA transporter which is about 1000 times lower of that observed for GBR12909. For complexes **6a–c** and **6e** no affinities were estimated below to 10 μM. Inclusion of a phenyl moiety in the chain did not significantly improve the affinity of the complexes to the DAT.

Conclusions

The preferred radioligands for the DA transporter are based on the 4-fluorophenyl derivative (WIN 35,428)[29] and the 4-iodophenyl derivative (RTI-55) of cocaine.[30] Based on these compounds, potential SPECT imaging agents like [^{99m}Tc]Technepine[14] and [^{99m}Tc]TRODAT[31] have been developed showing the possibility to incorporate a metal as a radioactive label preserving the biological activity. However, with cocaine as the usual starting material, synthetic flexibility is naturally restricted and alternative synthesis strategies have already been considered.[32,33] The rationale of the present study was the synthesis of DA transporter affine rhenium complexes starting from the tropanol molecule in order to avoid stereochemical problems and to check whether substitution in 3α-position is a suitable strategy for the design of Tc complexes with affinity to the DA transporter. Newmann[17] and Meltzer[34] already showed that with different substituents in the 3α position in the benztropine series the affinity differs by 3 orders of magnitude. Therefore structural variations should be promising at this site. We recently showed that aromatic moieties in the ketanserine molecule may be replaced by Re or Tc chelates with preservation of the receptor affinity.[35] Similar features of the complexes are expected in our study. QSAR models for the phenyl-tropane series suggest that distribution properties such as hydrophobicity are important contributors to binding at the DAT.[36] On the other hand, Davies et al.[32] concluded from their studies that the DAT has a relatively strict requirement as regards size around the 3-position. It is also known that excessive bulk leads to reduced potency.[36] A certain spacer length may, therefore, be required for hydrophobic interactions. Complexes (**6d,e**) with a longer spacer length displayed better affinities than complexes with a short spacer length (**6a–c**). Inclusion of the Re chelate in 4-position of the phenyl

ring **6g** instead of in 3-position as in compound **6f** reduces the affinity to the DAT. To explain this fact further investigations have to be carried out.

In conclusion, our data obtained show that it is possible to obtain Re complexes with DA transporter affinity by substitution at the 3-position of the tropanol molecule even if the affinity is to low to permit radiopharmaceutical drug development. On the other hand our data show that a lack of a substituent in 2-position of the tropan ring seems not to be tolerated by the DAT. However, the results are considered a good starting point for further optimization of the substituents at the 3-position of the tropane ring at derivatives obtained from naturally occuring cocaine. In this case, additional substitutions between the 2- and 4-positions of the phenyl ring could provide further information about what it takes to obtain high-affinity compounds.

Experimental

General

All reagents were of commercial grade unless otherwise stated. DMF was dried over molecular sieves. Flash chromatography was performed on silica gel (E. Merck) 70–230 mesh. IR spectra were recorded on an M 80 (Carl Zeiss Jena). NMR spectra were recorded on a Bruker MSL 300 and a Bruker DRX 500 in chloroform or methanol (hydrochlorides and oxalates) as solvent. ^{1}H spectra were obtained at 500.13 MHz unless otherwise noted and ^{13}C spectra were obtained at 125.77 MHz. Coupling constants are given in Hz. Mass spectra were recorded on a MAT 95 spectrometer from Finnigan by the FAB method with positive ions in glycerol as matrix. Elemental analyses were carried out on a LECO Elemental Analyzer CHNS-932 and are within a range of 0.4%. For thiols and tritylthioethers, no elemental analyses were carried out.

Esters of tropanol

Preparation of the ω-halide esters;[23] general procedure: 30 mmol tropanole hydrochloride and 30 mmol of the appropriate acid chloride were mixed in an autoclave bottle and heated in an oven for 3 h at 140 °C. The ester halogenides were then recrystallised from ethanol/ether.

2-Chloroacetic acid trop-3α-yl ester hydrochloride 3a. Yield: 5.8 g (76%); mp: 215–220 °C; IR: ν-CO: 1732 cm^{-1}; ^{1}H NMR δ 2.2 (d, J = 16.68, 2H), 2.3–2.63 (m, 6H), 2.9 (s, 3H), 3.97 (bs, 2H), 4.33 (s, 2H), 5.21 (t, J = 4.94). Anal. calcd for $C_{10}H_{17}NO_2Cl$: C, 47.26; H, 6.74; N, 5.51. Found C, 46.92; H, 6.84; N 5.46.

3-Halopropionic acid trop-3α-yl ester 3b (mixture of compounds)[1†]: 1/3 3-bromopropionic acid trop-3α-yl ester x HCl. 2/3 3-Chloropropionic acid trop-3α-yl ester x HBr. Yield: 8.3 g (88%); ^{1}H NMR δ 2.23 (d, J = 16.33, 2H), 2.4–2.52 (m, 4H), 2.58 (dt, J_1 = 16.24, J_2 = 3.96, 2H), 2.9 (s, 3H), 2.95 (t, J = 6.24, 2H, int. 66%), 3.09 (d, J = 6.34, 2H, int. 33%), 3.74 (d, J = 6.34, 2H, int. 33%), 3,9 (d, J = 6.24, 2H, int. 66%), 4.02 (bs, 2H), 5.18 (t, J = 5, 1H). Anal. calcd for $C_{11}H_{19}NO_2BrCl$: C, 42.26; H, 6.13; N, 4.48. Found C, 42.07; H, 6.31; N 4.45.

4-Halobutyric acid trop-3α-yl ester 3c (mixture of compounds)[1†]: 1/3 4-bromobutyric acid trop-3α-yl ester x HCl. 2/3 4-Chlorobutyric acid trop-3α-yl ester x HBr. Yield: 7.9 g (80%); ^{1}H NMR δ 2.1–2.52 (m, 10H), 2.64 (t, J = 7.31, 2H), 2.9 (s, 3H), 3.61 (t, J = 6.51, 2H int. 33%), 3.72 (t, J = 6.4, 2H, int. 66%), 4.0 (bs, 2H), 5.18 (t, J = 4.88, 1H). Anal. calcd for $C_{12}H_{21}NO_2BrCl$: C, 44.12; H, 6.48; N, 4.29; Found C, 43.64; H, 6.56; N, 4.25.

5-Halopentanoic acid trop-3α-yl ester 3d (mixture of compounds)[1†]: 1/3 5-bromopentanoic acid trop-3α-yl ester x HCl. 2/3 5-Chloropentanoic acid trop-3α-yl ester x HBr. Yield: 9.36 g (92%); ^{1}H NMR δ 1.88 (m, 4H), 1.98 (m, 2H, int. 33%), 2,2 (d, J = 16,17, 2H), 2,37–2.56 (m, 8H), 2.88 (s, 3H), 3.55 (t, J = 6.35, 2H int. 33%), 3.67 (t, J = 5.78, 2H), 3,99 (bs, 2H), 5.13 (t, J = 4,81, 1H). Anal. calcd for $C_{13}H_{23}NO_2BrCl$: C, 46.01; H, 6.23; N, 4.13. Found C, 45.2; H, 6.84; N, 4.13.

5-Chlorohexanoic acid trop-3α-yl ester 3e. Yield: 6.6 g (71%), mp: 158–161 °C, IR: ν-CO: 1736; ^{1}H NMR δ 1.58 (m, 2H), 1.76 (qui, 2H), 2,2 (d, J = 16,17, 2H), 2.37–2.56 (m, 8H), 2.88 (s, 3H), 3.55 (t, J = 6.35, 2H), 3.67 (t, J = 5.78, 2H), 3,99 (bs, 2H), 5.13 (t, J = 4,81, 1H); Anal. calcd for $C_{14}H_{25}NO_2Cl_2$: C, 54.20; H, 8.12; N, 4.51. Found C, 53.98; H, 8.17; N, 4.62.

3-(Chloromethyl)benzoic acid trop-3α-yl ester 3f. Yield: 9.6 g (97%); mp: 195–197 °C; IR: ν-CO: 1712 cm^{-1}; ^{1}H NMR δ 2.38 (d, J = 16.29, 2H), 2.46–2.58 (m, 4H), 2.64 (dt, J_1 = 16.32, J_2 = 4.09, 2H), 2.92 (s, 3H), 4.05 (bs, 2H), 4.81 (s, 2H), 5.38 (t, J = 4.84, 1H), 7.61 (t, J = 7.7, 1H), 7.77 (d, J = 7.73, 1H), 8.06, (d, J = 7.9, 1H). Anal. calcd for $C_{16}H_{21}NO_2Cl_2$: C, 58.19; H, 6.41; N, 4.24. Found C, 58.01; H, 6.17; N, 4.04.

4-(Chloromethyl)benzoic acid trop-3α-yl ester 3g. Yield: 8.8 g (88%); mp: 232–235 °C; IR: ν-CO: 1716 cm^{-1}; ^{1}H NMR δ 2.36 (d, J = 16.34, 2H), 2.46–2.65 (m, 6H), 2.92 (s, 3H), 4.04 (bs, 2H), 4.79 (s, 2H), 5.38 (t, J = 4.89, 1H),

[†]due to halogen exchange

7.65 (d, $J=8,3$, 2H), 8.1, (d, $J=8.3$, 1H). Anal. calcd for $C_{16}H_{21}NO_2Cl_2$: C, 58.19; H, 6.41; N, 4.24. Found C, 58.21; H, 6.33; N, 4.16.

Preparation of the ω-thiotritylated esters. Sixteen millimoles triphenyl methane thiol and 30 mmol potassium *tert*-butoxide were dissolved in 50 mL DMF and stirred for 15 min. Then 15 mmol of the tropane ester hydrohalide were added portionwise over 15 min and the resulting mixture was stirred for 2 h at room temperature and an additional hour at 50–60 °C. After cooling to room temperature, 50 mL of dichloromethane were added and the whole mixture was poured into a cold saturated solution of ammonium chloride. The aqueous layer was extracted three times with 20 mL of dichloromethane. The organic layer was washed twice with brine and dried over sodium sulphate. After removing the solvent the residue was chromatographed on silica gel by gradient elution, employing first ethyl acetate and then methanol/dichloromethane/triethyl amine 80/20/0.1 to give thick yellow oils, which became glassy upon standing.

2-Triphenylmethylmercaptoacetic acid trop-3α-yl ester 4a. Yield: 1.3 g (19%); $R_f=0.16$; ^{1}H NMR δ 1.8 (d, $J=15.77$, 2H), 1.95–2.1 (m, 4H), 2.57 (s, 3H), 2.7 (m, 2H), 2.9 (s, 2H), 3.49 (bs, 2H), 4.91 (t, $J=4.77$, 1H), 7.15–7.35 (m, 15H); ^{13}C NMR δ 24.38, 33.97, 34.7, 38.7, 61.42, 65.82, 67.27, 126.97, 128.02, 129.33, 143.7, 168.03.

3-Triphenylmethylmercaptopropionic acid trop-3α-yl ester 4b. Yield: 6.1 g (81%); $R_f=0.2$; ^{1}H NMR δ 1.62 (d, $J=14.85$, 2H), 1.76 (m, 2H), 1.94 (m, 2H), 2.07 (dt, $J_1=14.85$, $J_2=4.38$, 2H), 2.19 (t, $J=7.55$ 2H), 2.24 (s 3H), 2.45 (t, $J=7.55$ 2H), 3.05 (bs, 2H), 4.92 (t, $J=5.28$, 1H), 7.18–7.43 (m, 15H); ^{13}C NMR δ 25.48, 26.93, 34.1, 36.28, 40.23, 59.73, 66.75, 67.57, 126.64, 127.68, 129.48, 144.54, 170.62.

4-Triphenylmethylmercaptobutyric acid trop-3α-yl ester 4c. Yield: 4.0 g (52%); $R_f=0.19$; ^{1}H NMR (200.13 MHz) δ 1.45–2.1 (m, 14H), 2.2 (s, 3H), 2.95 (bs, 2H), 4.85 (t, $J=5.28$, 1H), 7.0–7.4 (m, 15H); ^{13}C NMR δ 23.76, 25.54, 31.22, 33.92, 36.52, 40.39, 59.65, 66.48, 67.32, 126.53, 127.76, 129.44, 144.70, 171.65.

5-Triphenylmethylmercaptopentanoic acid trop-3α-yl ester 4d. Yield: 5.7 g (72%); $R_f=0.3$; ^{1}H NMR (300.13 MHz) δ 1.35 (m, 2H), 1.5 (m, 2H), 1.9 (s, 2H), 2.05 (m, 8H), 2.45 (s, 3H), 3.38 (bs, 2H), 4.93 (t, $J=5.03$, 1H), 7.1–7.5 (m, 15H); ^{13}C NMR δ 23.12, 23.95, 24.93, 27.90, 31.29, 34.07, 34.69, 38.72, 60.38, 65.42, 66.39, 126.47, 127.71, 129.41, 144.73, 171.90.

6-Triphenylmethylmercaptohexanoic acid trop-3α-yl ester 4e. Yield: 6.1 g (79%); $R_f=0.41$(methanol 1/chloroform 4); ^{1}H NMR δ 1.25 (m, 2H), 1.38 (m, 2H), 1.48 (qui, $J=7.62$, 2H), 1.83 (d, $J=15.52$, 2H), 2.12 (m, 6H), 2.18 (t, $J=7.54$, 2H), 2.56 (s, 3H), 2.68 (d, $J=14.82$, 2H), 3.47 (bs, 2H), 5.04 (t, $J=4.77$, 1H), 7.1–7.45 (m, 15H); ^{13}C NMR δ 24.23, 24.35, 24.88, 28.18, 28.37, 31.70, 34.43, 34.88, 39.14, 61.11, 65.22, 66.42, 126.53, 127.78, 129.52, 144.90, 172.15.

3-(Triphenylmethylmercaptomethyl)benzoic acid trop-3α-yl ester 4f. Yield: 7.3 g (86%); $R_f=0.33$; ^{1}H NMR δ 2.12 (d, $J=16.81$, 2H), 2.28 (m, 2H), 2.45 (d, $J=8.52$, 2H), 2.79 (d, $J=3.34$, 3H), 3.18 (d, $J=14.23$, 2H), 3.36 (s, 2H), 3.82 (bs, 2H), 5.37 (bs, 1H), 7.2–7.8 (m, 19H); ^{13}C NMR 24.61, 34.66, 36.58, 39.37 62.27, 65.29, 67.61, 126.82, 127.73, 127.91, 128.75, 129.52, 130.01, 130.15, 134.11, 138.09, 144.44, 164.97.

4-(Triphenylmethylmercaptomethyl)benzoic acid trop-3α-yl ester 4g. Yield: 6.83 g (80%); $R_f=0.19$; ^{1}H NMR δ 1.82 (m, 2H), 2.05 (m, 4H), 2.23 (dt, J*1* = 14.83, $J_2=4.23$, 2H), 2.31 (s, 3H), 3.15 (bs, 2H), 3.37 (s, 2H), 5.24 (t, $J=5.13$), 7.15–7.9 (m 19H); 25.59, 36.43, 36.58, 40.25, 59.69, 67.49, 67.75, 126.65, 127.76, 127.83, 129.02, 129.34, 129.99, 142.36, 144.31, 165.31.

Preparation of the mercaptans. Five millimoles of the compounds **4a–4g** were dissolved in 15 mL trifluoroacetic acid and cooled to 0 °C. Then 0.2 mL anisole and 5.5 mmol mercury acetate were added while stirring. The whole mixture was stirred for 2 h at room temperature. The solvent was removed in vacuo and ether was added to the residue. The white precipitate formed was stirred for 1 h at room temperature and then isolated by suction filtration. The mercury salt was dissolved in 30 mL ethanol and hydrogen sulphide was bubbled through the solution for 20 min. The black precipitate was filtered through a thick pad of Celite and the filtrate was evaporated in vacuo. The residue was dissolved in 20 mL dichloromethane and washed with saturated Na_2CO_3 solution and brine. The organic layer was separated, dried and the solvent was removed. The colourless oil obtained was purified by flash-chromatography on silica-gel employing methanol/chloroform = 1:4 as eluent. The purity of the compounds obtained by this procedure was in the most cases not sufficient to perform elemental analysis, but the quality was sufficient for the next reaction step.

2-Mercaptoethanoic acid trop-3α-yl ester 5a. Yield: ca. 500 mg impure product, only MS-spectra was recorded, MS: M = 215,31, $M^+ + 1$ (21), 216 (100), 217 (14), 218 (4).

3-Mercaptopropanoic acid trop-3α-yl ester 5b. Yield: 0.99 g (88%); $R_f=0.19$; ^{1}H NMR δ 1.64 (t, $J=8.15$, 1H), 2.0 (d, $J=15.74$, 2H), 2.2–2.4 (m, 4H), 2.62 (t,

$J=6.63$, 2H), 2.73–2.77 (m, 5H), 2.95 (d, $J=13.53$, 2H), 3.78 (bs, 2H), 5.13, (bs, 1H); ^{13}C δ 19.55, 24.28, 34.49, 38.49, 38.55, 39.27, 62.11, 64.85, 170.16.

4-Mercaptobutyric acid trop-3α-yl ester 5c. Yield: 0.83 g (68%); $R_f=0.2$; ^{1}H NMR δ 1.32 (t, $J=8.07$, 1H), 1.82 (d, $J=15.48$, 2H), 2.1 (qui, $J=7.05$, 2H) 2.15 (bs, 4H), 2.41 (t, $J=7.13$, 2H), 2.55–2.65 (m, 2H), 2.58 (s, 3H), 2.7 (t, $J=6.98$, 2H), 3.55 (bs, 2H), 5.05, (bs, 1H); ^{13}C NMR δ 23.9, 24.9, 32.84, 34.91, 37.57, 39.07, 60.77, 65.87, 171.68.

5-Mercaptopentanoic acid trop-3α-yl ester 5d. Yield: 1.09 g (85%); $R_f=0.28$; ^{1}H NMR δ 1.34 (t, $J=8.03$, 1H), 1.55–1.75 (m, 4H), 1.96 (d, $J=16.02$, 2H) 2.17–2.38 (m, 6H) 2.5 (q, $J=7.1$, 2H), 2.65 (m, 2H), 2.7 (s, 3H), 3.76 (bs, 2H), 5.05, (t, $J=4.58$, 1H); ^{13}C NMR δ 23.28, 24.02, 24.22, 33.07, 33.88, 34.69, 38.91, 61.99, 64.26, 171,83.

6-Mercaptohexanoic acid trop-3α-yl ester 5e. Yield: 0.7 g (52%); $R_f=0.19$; ^{1}H δ 1.3 (m, 2H), 1.4 (m, 2H), 1.57–1.7 (m, 6H), 1.85–2.05 (m, 4H), 2.13 (m, 2H), 2.27 (t, $J=7.7$, 2H), 2.28 (s, 3H), 3.1 (bs, 2H), 4.98, (t, $J=5.3$, 1H). ^{13}C NMR δ 24.34, 24.49, 27.82, 27.97, 33.55, 34.74, 36.49, 40.29, 59.83, 67.21, 172.63.

3-(Mercaptomethyl)benzoic acid trop-3α-yl ester 5f. Yield: 0.98 g (67%); $R_f=0.28$; ^{1}H NMR δ 1.78 (t, $J=7.73$, 1H), 2.14 (d, $J=15.88$, 2H), 2.33 (m, 2H), 2.44 (m, 2H), 2.77 (d, $J=4.76$, 3H), 3.73 (d, $J=7.72$, 2H), 3.85 (bs, 2H), 5.33 (t, $J=3.48$, 1H), 7.42 (t, $J=7.7$, 1H), 7,55 (d, $J=6.7$, 1H), 7,85 (d, $J=7.79$, 1H), 7.94 (s, 1H); ^{13}C NMR δ 24.44, 28.51, 34.73, 38.96, 61.92, 65.23, 127.84, 129.029, 120.07, 130.17, 133.09, 141.86, 165.02.

4-(Mercaptomethyl)benzoic acid trop-3α-yl ester 5g. Yield: 0.38 g (26%); $R_f=0.12$; ^{1}H NMR δ 1.75–1.85 (m, 3H), 2.0–2.12 (m, 4H), 2.22 (dt, $J_1=14.92$, $J_2=4.28$, 2H), 2.3 (s, 1H), 3.15 (s, 1H), 3.76 (s, 1H), 5.24 (t, $J=5.22$, 1H), 7.39 (d, $J=8.2$, 2H), 7.96 (d, $J=8.2$, 2H), ^{13}C NMR δ 25.79, 28.69, 36.67, 40.42, 59.81, 68.06, 128.13, 129.86, 142.43, 146.21, 165,49.

Preparation of the complexes[22]. ω-Mercapto acid trop-3α-yl-ester (150 μmol) was added while stirring to a boiling solution of 38.9 mg (100 μmol) chloro(3-tiapentane-1,5-dithiolato)oxorhenium (V) in 5 mL acetonitrile. The mixture was heated to reflux for 5 min. The solvent was removed in vacuo and the residue was purified by flash-chromatography using methanol/chloroform = 1:4 as eluent.

The dark red oils obtained were crystallised upon slow evaporation of the solvent or as oxalic acid salts or hydrochlorides.

(3-Thiapentane-1.5-dithiolato)(3-thiolato-ethanoic acid trop-3α-yl-ester) oxorhenium(V) 6a. Yield: 42 mg (73.9%) dark red crystals, mp: 186–188 °C (decomp), IR: ν-CO: 1704 cm^{-1}, ReO: 968 cm^{-1}; $R_f=0.07$; ^{1}H NMR δ 1.72 (d, $J=14.8$, 2H), 1.92–2.12 (m, 8H), 2.24 (s, 3H), 3.05 (bs, 2H), 3.1 (m,2H), 3.93 (m, 2H), 4.28 (dd, $J_1=13.14$, $J_2=4.61$, 2H), 4.03 (s, 2H), 5.02 (t, $J=4.32$, 1H); ^{13}C NMR δ 25.6, 36.48, 40.17, 40.36, 43.66, 46.76, 59.78, 68.32, 170.97; MS: M = 568.81, $M^+ + 1$: 568 (48.3); 569 (7.6); 570 (100); 571 (15.5); 572 (14.0); 573 (1.7). Anal. calcd for $C_{14}H_{24}NO_3S_4Re$: C, 29.56; H, 4.25; N, 2.46. Found C, 29.80; H, 4.33; N, 2.42.

(3-Thiapentane-1.5-dithiolato)(3-thiolato-propanoic acid trop-3α-yl-ester) oxorhenium(V) 6b. Yield: 28.6 mg (49%, free base), mp: 149–154 °C (oxalate), IR (KBr): ν-CO: 1724 cm^{-1}, ReO: 960 cm^{-1}; $R_f=0.23$; ^{1}H NMR (CD_3OD) δ 2.13–2.15 (m, 4H), 2.32–2.36 (m, 2H), 2.43–2.47 (m, 2H), 2.52–2.57 (m, 2H), 2.85 (s, 3H, CH_3), 2.98 (t, $J=6.85$, 2H, CH_2), 3.13 (td, $J_1=13.65$, $J_2=2.78$, 2H), 3.93 (bs, 2H), 4.06 (t, $J=6.85$, 2H, CH_2), 4.12 (dd, $J_1=10.74$, $J_2=3.37$, 2H), 4.37 (dd, $J_1=13$, $J_2=4.77$), 5.13 (t, $J=4.6$, 1H); ^{13}C NMR δ (CD_3OD): 24.89, 32.60, 36.03, 39.07, 39.46, 47.41, 48.49, 63.88, 65.63, 165.46, 172.97; MS: M = 583.03, $M^+ + 1$: 582 (54.3), 583 (10.5), 584 (100), 585 (19), 586 (17), 587 (3), 588 (1.4). Anal. calcd for $C_{17}H_{28}NO_7S_4Re$ (oxalate): C, 30.35; H, 4.19; N, 2.08. Found C, 30.41; H, 4.33; N, 2.20.

(3-Thiapentane-1.5-dithiolato)(4-thiolato-butyric acid trop-3(α-yl-ester) oxorhenium(V) 6c. Yield: 43.3 mg (72.6%); mp: 131–135 °C; IR: ν-CO: 1728 cm^{-1}; ReO: 960 cm^{-1}; $R_f=0.2$; ^{1}H δ 1.71 (d, $J=14.9$, 2H), 1.96 (m, 6H), 2.13 (dt, $J_1=14.84$, $J_2=3.91$, 2H), 2.22 (qui, $J=7.35$, 2H), 2.29 (s, 3H), 2.52 (t, $J=7.45$, 2H), 3.08 (m, 2H), 3.12 (bs, 2H), 3.84 (t, $J=7.1$, 2H), 3.91 (m, 2H), 4.27 (dd, $J_1=13.17$, $J_2=4.8$, 2H), 4.98 (t, $J=5.13$, 1H); ^{13}C NMR δ 25.51, 28.04, 33.86, 36.42, 36.7, 40.26, 43.70, 46.68, 59.93, 66.98, 172.52; MS: M = 597.058, $M^+ + 1$: 596 (42.6); 597 (4.1); 598 (100); 599 (7.5); 600 (12.2); 601 (1). Anal. calcd for $C_{16}H_{28}NO_3S_4Re$: C, 32.2.; H, 4.73; N, 2.35. Found C, 32.17; H, 4.97; N, 2.27.

(3-Thiapentane-1.5-dithiolato)(5-thiolato-pentanoic acid trop-3α-yl-ester) oxorhenium(V) 6d. Yield: 21 mg (34.4%) mp (oxalate): 172–74 °C, IR: ν-CO: 1724 cm^{-1}, ReO: 960 cm^{-1}; $R_f=0.25$; ^{1}H NMR δ 1.78–1.82 (m, 4H), 1.9 (d, $J=15.77$, 2H), 2.15–2.25 (m, 6H), 2.37 (m, 4H), 2.66 (s, 3H), 3.02 (dd, $J_1=14.13$, $J_2=4.13$, 2H), 3.66 (t, $J=6.87$, 2H), 3.78 (bs, 2H), 4.06 (dd, $J_1=10.6$, $J_2=3.46$, 2H), 4.28 (dd, $J_1=12.85$, $J_2=4.49$, 2H), 4.92 (bs, 1H); ^{13}C NMR δ ($CDCl_3$): 24.1, 24.45, 32.25, 34.54, 34.73, 36.76, 39.24, 43.72, 46.72, 62.40, 64.26, 172.06; MS: M = 610.89, $M^+ + 1$: 610 (50.1); 611 (5.7); 612 (100); 613 (10); 614 (12.6); 614 (0.9). Anal. calcd for

$C_{19}H_{32}NO_7S_4Re$ (oxalate): C, 32.56; H, 4.60; N, 2.00. Found C, 32.31; H, 4.55; N, 1.97.

(3-Thiapentane-1.5-dithiolato)(6-thiolato-hexanoic acid trop-3α-yl-ester) oxorhenium(V) 6e. Yield: 53.4 mg (81%) mp (hydrochloride): 193–195 °C; IR: ν-CO: 1726 cm^{-1}; ReO: 960 cm^{-1}; R_f = 0.29; 1H δ 1.46 (d, J = 6.92, 2H), 1.6 (d, J = 7.63, 2H), 1.76 (d, J = 7.3, 2H), 1.92 (bd, 2H), 2.1–3.3 (m, 6H), 2.34 (d, J = 7.37, 2H), 2.65 (bs, 3H), 3.02 (td, J_1 = 13.32, J_2 = 4.2, 2H), 3.32 (bs, 2H), 3.64 (t, J = 7.32), 3.81 (bs, 2H), 4.06 (dd, J_1 = 10.52, J_2 = 3.27, 2H), 4.28 (dd, J_1 = 12.91, J_2 = 4.58, 2H), 4.92 (t, J = 4.6, 1H); ^{13}C NMR δ 23.1, 23.95, 27.71, 32.18, 33.83, 34.02, 35.96, 37.8, 43.02, 45.52, 61.17, 63.91, 171.81. Anal. calcd for $C_{18}H_{33}ClNO_3S_4Re$ (hydrochloride): C, 32.67; H, 5.03; N, 2.12. Found C, 32.71; H, 5.02; N, 2.10.

(3-Thiapentane-1.5-dithiolato)(3-thiolatomethylbenzoic acid trop-3α-yl-ester) oxorhenium(V) 6f. Yield: 28.6 mg (44.3%) , mp: 206–208 °C; IR: ν-CO: 1712 cm^{-1}; ReO: 960 cm^{-1}; R_f = 0.15; ^{1}H NMR δ 1.83 (d, J = 14.63, 2H), 1.97 (m, 2H), 2.07 (m, 4H), 2.21 (dt, J_1 = 14.61, J_2 = 4.68, 2H), 2.29 (s, 3H), 3.1 (m, 2H), 3.14 (bs, 2H), 3.89 (m, 2H), 4.27 (dd, J_1 = 13.15, J_2 = 4.66, 2H), 5.05 (s, 2H), 5.23 (t, J = 5.3, 1H), 7.39 (t, J = 7.66, 1H), 7.66 (d, J = 7.67, 1H), 7.86 (d, J = 7.71, 1H), 8.09 (s, 1H); ^{13}C NMR δ 25.84, 36.56, 40.35, 42.32, 43.69, 46.72, 59.8, 67.94, 127.68, 128.55, 130.26 130.87, 133.77, 142.31, 165.87; MS: M = 645.05 $M^+ + 1$: 644 (44.5); 645 (8.4); 646 (100); 647 (6.77); 648 (6.5). Anal. calcd for $C_{20}H_{28}NO_3S_4Re$: C, 37.25; H, 4.38; N, 2.17. Found C, 36.97; H, 4.43; N, 1.99.

(3-Thiapentane-1.5-dithiolato)(4-thiolatomethylbenzoic acid trop-3α-yl-ester) oxorhenium(V) 6g. Yield: mp: 215–217 °C, IR: ν-CO: 1708 cm^{-1}, ReO: 960 cm^{-1}; R_f = 0.18; ^{1}H: 1.86 (d, J = 15.02; 2H), 1.98 (m, 2H), 2.11 (bs, 4H), 2.32 (bd, J = 15.06, 2H), 2.36 (s, 3H), 3.1 (m, 2H), 3.24 (bs, 2H), 3.9 (m, 2H), 4.28 (dd, J_1 = 13.24, J_2 = 4.73, 2H), 5.04 (s, 2H); 5.24 (t, J = 5.16, 1H), 7.53 (d, J = 8.2, 2H), 7.95 (d, J = 8.2, 2H); ^{13}C NRM δ 25.61, 36.31, 40.16, 42.26, 43.68, 46.76, 60.18, 67.35, 128.86, 129.33, 129.61, 147.26, 165.68; MS: M = 645.05, $M^+ + 1$: 644 (47.5); 645 (12.1); 646 (100); 647 (19.1); 648 (13.2); 649 (1.3). Anal. calcd for $C_{20}H_{28}NO_3S_4Re$: C, 37.25; H, 4.38; N, 2.17. Found C, 36.87; H, 4.22; N, 2.15.

X-ray crystal structure analysis of compound 6f. X-ray crystallographic data were obtained on a CAD4 diffractometer at 293 K using graphite-monochromatic Cu-K_α radiation of a wavelength of 0.71069 Å. Single crystals suitable for X-ray structure analysis were obtained by slow evaporation of a solution of **6f** in chloroform. Further details of the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen (Germany), on quoting the depository number CSD-40 70 92.

Crystallographic and refinement details:

Formula:	$C_{20}H_{28}NO_3ReS_4$
Formula weight	644.87
Space group	P 1 2_1/c 1
Lattice parameter	A = 11.374, b = 17.945, c = 12.068, β = 106.920
Crystal system	monoclinic
Volume of cell	2356.53 (2)Å^3
Z =	4
X-ray density (g/cm^3)	1.8177
Mass absorpt. coef. (cm^2/g)	72.19
Absorption coefficient	5.532 mm^{-1}
F (000)	1272
Crystal size	0.09×0.23×1.08 mm
Theta range for data collection	1.87 to 26.99 deg.
Index range	h: 0–14, k: 0–22, l:–15–14
Reflections collected	5382
Independent reflections	5128 [R(int) = 0.0205]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5128/0/266
Goodness-of-fit on F^2	1.045
Final R indices [I > 2sigma (I)]	R1 = o.0263, wR2 = 0.0585
Largest diff. peak and hole	1.017 and −0.666 e.Å^{-3}

Radioligand binding assays. Radioligand binding assays were performed on cloned human dopamine transporters (Receptor Biology, Inc., Baltimore, USA). Binding of [^{3}H]WIN35,428 (83.5 Ci/mmol, DuPont, Dreieich, Germany) to the transporters was performed according to published methods.[26,37] Briefly, about 2 µg of membrane, buffer (50 mM Tris–HCl, 100 mM NaCl, pH 7.4) and unlabeled ligands were incubated in a total volume of 1.0 mL for 2 h at 4 °C. Nonspecific binding was determined in the presence of 1 µM GBR-12909 (Research Biochemicals International, Natick, USA). The binding assays were terminated by rapid filtration over GF/B glass fibre filters (Whatman, Maidstone, UK) on the Brandel cell harvester. The filters were presoaked in 0.3% polyethylene imine. Following four washes with 4 mL portions of ice-cold buffer (see above) the filter paper containing the membrane-bound

[^{3}H]WIN35,428 was transferred into 10 mL of liquid scintillation cocktail (Ultima-Gold, Packard), and the radioactivity on each filter was counted in a Canberra-Packard liquid scintillation counter (TRI-CARB 2100TR). Aliquots of the incubation fluid were measured as well. Corrections were made for the binding of [^{3}H]WIN35,428 to the filters. Increasing concentrations (between 0.01 nM and 10 μM) of the unlabelled ligands, GBR 12909 (purchased from RBI) and cocaine (purchased from Th. Geyer, Rennningen, Germany) were competed against a fixed concentration of the radiolabeled ligand (total binding~1500 dpm). From the competition curves IC_{50} values were calculated using the program Fig. P (Biosoft).

Determination of lipophilicity and pK_a values. Reversed-phase HPLC was used to determine the lipophilicity of the rhenium complexes synthesized. Lipophilicity is expressed by the partition coefficient P (log P), which refers to the neutral state of the solute or the distribution coefficient D, which is obtained at a given pH and may thus result from the contributions of the cationic and neutral forms. Using HPLC various unknown factors caused and influenced by this system have to be taken into consideration.[38–40] Hence, only apparent partition and distribution coefficients designated in this work as P_{HPLC} and D_{HPLC} were obtained. These values were derived from the retention times according to the equation $\log P = a \log k' + b$, where $k' = (t_R - t_0)/t_0$ represents the capacity factor, t_R is the retention time of the sample and t_0 the retention time of methanol as an unretained solute. Aniline (0.9), benzene (2.13), and bromobenzene (2.99) served as log P references. With a given ionizable compound a sigmoidal D_{HPLC}/pH curve results. From the turning point of this curve the apparent pK_a value (pK_{HPLC}) was derived. Since measurements are performed in organic/aqueous solutions, values were corrected by comparing the experimental values with those obtained for amines. A plot of the pK_a values of these reference substances over the measured pK_{HPLC} gives a good correlation following the relationship $pK_a = 0.988\ pK_{HPLC} + 1.501$ ($R = 0.992$). Thus, a calibration curve is available for estimating the p$K_{a(c)}$ values from the measured pK_{HPLC} values of the complexes.

The above lipophilicity and ionization constants were determined by using the Perkin-Elmer HPLC Controller System Model 1022 equipped with a UV/VIS spectrometer detector at 254 nm and a Hamilton PRP-1 column (250×4.1 mm; 10 μm). As mobile phase an isocratic eluent (acetonitrile and 0.01 M phosphate or citrate buffer, 3:1, v/v) was applied with a flow rate of 1.5 mL/min. Before each application the certain pH values of the eluents were measured by using a glass electrode, which was calibrated with standard buffers daily.

References and Notes

1. Horn, A. S. *Prog. Neurobiol.* **1990**, *34*, 387.
2. Jenner, P.; Shapira, A. H. V.; Marsden, C. D. *Neurology* **1992**, *42*, 2241.
3. Tedroff, J.; Aquilonius, S. M.; Hartvig, P. G.; Langstrom, B. In *Parkinson's Disease*; Battistin, L.; Scarlato, G.; Caraceni, T.; Ruggieri, S.; Eds; Lippincott-Raven Publ, 1996; Vol. 69, p 443.
4. Yu, D. W.; Gatley, S. J.; Wolf, A. P.; MacGregor, R. R.; Dewey, S. L.; Fowler, J. S.; Schlyer, D. J. *J. Med. Chem.* **1992**, *35*, 2178.
5. Müller, L.; Halldin, C.; Farde, L.; Karlsson, P.; Hall, H.; Swahn, C. G.; Neumeyer, J.; Gao, Y.; Milius, R. *Nucl. Med. Biol.* **1993**, *20*, 249.
6. Lundkvist, C.; Halldin, C.; Swahn C-G.; Hall, H.; Karlson, P.; Nakashima, Y.; Wang, S.; Milius, R. A.; Neumeyer, J. L.; Farde, L. *Nucl. Med. Biol.* **1995**, *22*, 905.
7. Halldin, C.; Farde, L.; Lundkvist, C.; Ginovart, N.; Nakashima, Y.; Karlson, P.; Swahn, C.-G. *Synapse* **1996**, *22*, 386.
8. Hume, S. P.; Luthra, S. K.; Brown, D. J.; Opacka-Juffry, J.; Osman, S.; Ashworth, S.; Myers, R.; Brady, F.; Kuhar, M. J.; Brooks, D. J. *Nucl. Med. Biol.* **1996**, *23*, 377.
9. Wilson, A. A.; DaSilva, J. N.; Houle, S. *Nucl. Med. Biol.* **1996**, *23*, 141.
10. Ametamey, S. M.; Halldin, C.; Swahn, C.-G.; Hall, H.; Schubiger, P. A.; Farde, L. *Nucl. Med. Biol.* **1995**, *22*, 959.
11. Metwally, S. A. M.; Gatley, S. J.; Wolf, A. P.; Yu, D. W. *J. Labelled Comp. Radiopharm.* **1992**, *31*, 219.
12. Shaya, E. K.; Scheffel, U.; Dannals, R. F.; Ricaurte, G. A.; Carrol, F. Y.; Wagner, H. N. Jr.,. Kuhar, M. J.; Wong, D. F. *Synapse* **1992**, *10*, 169.
13. Meegalla, S.; Ploessl, K.; Kung, M.-P.; Stevenson, D. A.; Liable-Sands, L. M.; Rheingold, A. L.; Kung, H. F. *J. Am. Chem. Soc.* **1995**, *117*, 11037.
14. Madras, B. K.; Jones, A. G.; Mahmood, A.; Zimmerman, R. E.; Garada, B.; Holman, B. L.; Davison, A.; Blundell, P.; Meltzer, P. C. *Synapse (N.Y.)* **1996**, *22*, 239.
15. Kuikka, J. T.; Tiihonen, J.; Bergström, K. A.; Karhu, J.; Hartikainen; P.; Vinamäki, H.; Länsimies, E.; Lehtonen, J.; Hakola, P. *J. Nucl. Med.* **1995**, *22*, 346.
16. Neumeyer, J. L.; Tamagnan, G.; Wang, S.; Gao, Y.; Milius, R. A.; Kula, N. S.; Baldessarini, R. J. *J. Med. Chem.* **1996**, *39(2)*, 543.
17. Newman, A. H.; Kline, R. H.; Allen, A. C.; Izenwasser, S.; George, C.; Katz, J. L. *J. Med. Chem.* **1995**, *38*, 3933.
18. Aronson, B.; Enmon, J. L.; Izenwasser, S.; Katz, J. L.; Kelkar, S. V.; Luo, L.; Nolan, S. P.; Trudell, M. L. *J. Med. Chem.* **1996**, *39*, 1560.
19. Hoepping, A.; Spies, H.; Johannsen, B. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2871.
20. Pietzsch, H. J.; Spies, H.; Hoffmann, S. *Inorg. Chim. Acta* **1989**, *161*, 15.
21. Spies, H.; Fietz, T.; Glaser, M.; Pietzsch, H. J.; Johannsen, B. In *Technetium and Rhenium in Chemistry and Nuclear Medicine*; Nicolini, N.; Bandoli, G.; Mazzi, U.; Eds; SG Editoriali: Padova, 1995; Vol. 4, p 243.

22. Fietz, T.; Spies, H.; Pietzsch, H.-J.; Leibnitz, P. *Inorg. Chim. Acta* **1995**, *231*, 233.

23. Wolfenstein, R.; Rolle, J. *Chem. Ber*. **1908**, *41*, 737.

24. Munoz, O.; Piovano, M.; Garbarino, J.; Hellwing, V.; Breitmaier, E. *Phytochem*. **1996**, *43*, 709.

25. Katzung, B. G. In *Basic and Clinical Pharmacology*; Katzung, B. G., Ed.; Appleton & Lange: Norwalk, 1995; pp 1–8.

26. Reith, M. E. A.; Xu, C. and Coffey, L. L. *Biochem. Pharmacol*. **1996**, *52*, 1435.

27. Reith, M. E. A.; Xu, C.; Zhang, L. A.; Coffey, L. L. *Naunyn-Schmiedebergs Archives of Pharmacology* **1996**, *354*, 295.

28. Madras, B. K.; Spealman, R. D.; Fahey, M. A.; Neumeyer, J. L.; Saha, J. K.; Milius, R. A. *Mol. Pharmacol*. **1989**, *36*, 518.

29. Gracz, L. M.; Madras, B. K. *J. Pharmacol. Exp. Ther*. **1995**, *273*, 1224.

30. Boja, J. W.; Patel, A.; Carroll, F. I.; Rahman, M. A.; Philip, A.; Lewin, A. H.; Kopajtic, T. A.; Kuhar, M. J. *Eur. J. Pharmacol*. **1991**, *194*, 133.

31. Kung, M. P.; Stevenson, D. A.; Plössl, K.; Meegalla, S. K.; Beckwith, A.; Essman, W. D.; Mu, M.; Lucki, I.; Kung, H. F. *Eur. J. Nucl. Med*. **1997**, **24**, 372.

32. Davies, H. M. L.; Saikali, E.; Huby, N. J. S.; Gilliatt, V. J.; Matasi, J. J.; Sexton, T.; Childers, S. R. *J. Med. Chem*. **1994**, *37*, 1262.

33. Kozikowski, A. P.; Araldi, G. L.; Ball, R. G. *J. Org. Chem*. **1997**, *62*, 503.

34. Meltzer, P. C.; Liang, A. Y.; Madras, B. K. *J. Med. Chem*. **1996**, *39*, 371.

35. Johannsen, B.; Scheunemann, M.; Spies, H.; Brust, P.; Wober, J.; Syhre, R.; Pietzsch, H. J. *Nucl. Med. Biol*. **1996**, *23*, 429.

36. Carroll, F. I.; Gao, Y.; Rahman, M. A.; Abraham, P.; Parham, K.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem*. **1991**, *34*, 2719.

37. Madras, B. K.; Spealman, R. D.; Fahey, M. A.; Neumeyer, J. L.; Saha, J. K. and Milius, R. A. *Mol. Pharmacol*. **1989**, *36*, 518.

38. Stylli, C.; Theobald, A. E. *Appl. Radiat. Isot., Int. J. Radiat. Appl. Instrum. Part A* **1987**, *38*, 701.

39. Thévenon-Emeric, G.; Tchapla, A.; Martin, M. *J. Chromatog*. **1991**, *550*, 267.

40. Pagliara, A.; Khamis, E.; Trinh, A.; Carrupt, P.-A.; Tsai, R.-S.; Testa, B. *J. Liquid Chromatog*. **1995**, *181*, 721.