three times daily at 6 hourly intervals for 3 days. At the end of the incubation period, cells were counted with either a hemocytometer or a Coulter Counter, Model ZM, after detachment of cells from the dish by short incubation with a solution of trypsin (0.1%) in versene. The IC_{50} values shown in Table II are the concentrations of test compounds which inhibited cell growth by 50%.

Cytotoxicity Assay. Cells (1×10^5/well) were incubated for 24 h with the test compound and with medium supplemented with only 1% fetal calf serum, as larger serum concentrations interfered with the LDH assay. Diacylglycerols were added 3 times at 6 hourly intervals. The supernatant was removed and briefly centrifuged at 1000 rpm at the end of the incubation or when it was replaced with fresh medium and agent. The supernatant was kept on ice until assayed. The activity of LDH in the cell supernatant was measured spectrophotometrically as described by Leathwood and Plummer[28] with a Beckman DU-7 spectrophotometer. The amount of maximally releasable LDH was measured in the supernatant of control cells lysed by 1% Triton X-100 immediately before the assay. The LC_{50} values shown in Table II are the concentrations of test compounds which caused 50% of the maximal LDH leakage.

Computer-Assisted Modeling. Molecular modeling was performed on a DEC8650 processor using the CHEM-X graphics package developed and distributed by Chemical Design Ltd., Oxford, U.K. The coordinates for phorbol were obtained from the published crystal structure;[29] the acetyl group coordinates and those for cyclohexane were obtained from the CHEM-X fragments database. Structural modification and conformational analysis was performed by using the supplied routines. Briefly, the energy of each molecule as a function of rotations about each carbon–oxygen single bond of the diester moiety was calculated and minima in this (4-dimensional) conformational space were located. Each was then subjected to a full molecular mechanics minimization, subject to interatom distance restraints if required, in order to determine the lowest energy conformation. For the cyclohexanetriol diesters, both chair conformations of the ring were considered separately as start points.

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Registry No. **3a**, 117918-47-5; **3b**, 117918-48-6; **3c**, 117918-52-2; **3d**, 117918-53-3; **4**, 72137-22-5; **5**, 117918-43-1; **6a**, 117918-44-2; **6b**, 118013-64-2; **7a**, 117918-45-3; **7b**, 117918-46-4; **7c**, 117918-50-0; **7d**, 117918-51-1; **8**, 117918-49-7; $CH_3(CH_2)_6COCl$, 111-64-8; phorbol, 17673-25-5.

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New Brain Perfusion Imaging Agents Based on ^{99m}Tc-Bis(aminoethanethiol) Complexes: Stereoisomers and Biodistribution

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In developing new brain perfusion imaging agents, we prepared ^{99m}Tc complexes of racemic mixtures of bis(aminoethanethiol) (BAT) derivatives containing an *N'*-benzylpiperazinyl (BPA) side chain. Due to the presence of a chiral center, a mixture of diastereomers (syn and anti) following chelation with the ^{99m}Tc (no-carrier-added) was obtained. The neutral and lipid-soluble ^{99m}Tc–BPA-BAT (^{99m}Tc, $T_{1/2}$ = 6 h) isomers were separated. The syn and anti isomers of carrier-added ^{99}Tc–BPA-BAT (^{99}Tc, $T_{1/2} = 2 \times 10^5$ years) were also synthesized, separated, and crystallized. The X-ray crystallography of ^{99}Tc–BPA-BAT showed the syn and anti conformations (in relationship with the central TC(=O)N_2S_2 core). Despite a similarity in the partition coefficients for the two isomers, the syn isomer showed a higher in vivo brain uptake and longer brain retention in rats (2.77 and 1.08% dose/organ at 2 and 15 min) than that of the corresponding anti isomer (0.57 and 0.27% dose/organ at 2 and 15 min). This information is important and should be taken into consideration when new ^{99m}Tc-labeled brain perfusion imaging agents are being designed.

Neutral and lipid-soluble compounds labeled with γ-emitting isotopes are potentially useful as brain perfusion imaging agents in nuclear medicine.[1-9] Due to the superior physical characteristics of ^{99m}Tc ($T_{1/2}$ = 6 h, 140 keV) for nuclear medicine imaging, there is a growing interest in the development of ^{99m}Tc-labeled brain perfusion imaging agents. Two types of ^{99m}Tc ligands have been studied extensively, namely, propylenediamine oxime (PnAO)[10-14] and bis(aminoethanethiol) (BAT).[15-22] Both ligands are known to form a neutral $Tc^{III}O$ complex with a pyramidal center core. Introduction of any single substituent on the ligand will generally produce epimers with relationship to the pyramidal center core. One of the derivatives of PnAO, ^{99m}Tc–HMPAO, is currently used in nuclear medicine clinics as a regional brain perfusion imaging agent.

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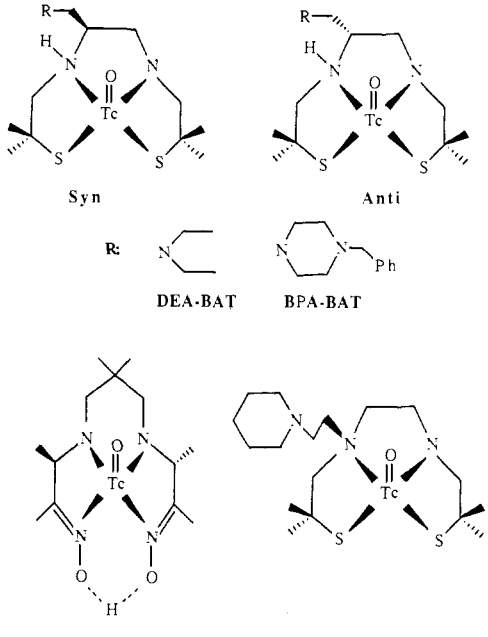
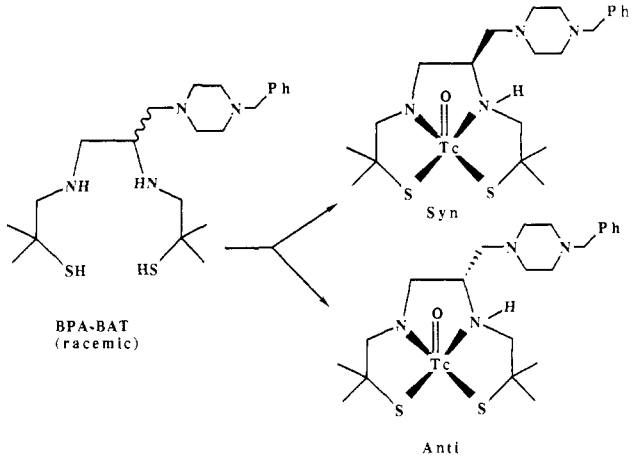
Scheme I. Chemical Structures of ^{99m}Tc Complexes



Scheme II. Formation of Syn and Anti Isomers of ^{99m}Tc- and ^{99}Tc-BPA-BAT Complexes



Derivatives containing a monoamine side chain of the ^{99m}Tc-BAT have been reported earlier by us (DEA-BAT)[21]

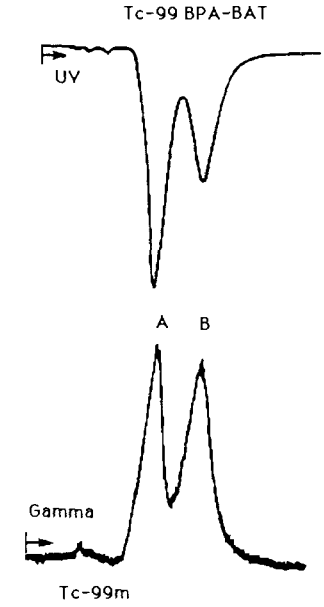


Figure 1. High-pressure liquid chromatography tracing of ^{99}Tc-BPA (UV) and ^{99m}Tc-BPA-BAT (gamma): peak A, syn; peak B, anti.

Table I. Chromatography Data for the Syn and Anti Isomers of ^{99}Tc-BPA-BAT

	TLC-I[a]	TLC-II[b]	HPLC retention,[c] min
syn	0.85	0.62	9.5
anti	0.85	0.42	6.9

[a] Silica gel–acetone. [b] Silica gel–acetone:dichloromethane (1:2). [c] Column: reverse-phase Hamilton PRP-1. Solvent: acetonitrile–3,3-dimethylglutarate buffer pH 7.0, 0.1 mM (85:15). Flow rate: 1 mL/min.

and others (NEP-DADT)[17,22] (Scheme I). Both types of the carbon- and nitrogen-substituted BAT derivatives form diastereomers after complexation with $Tc^{III}O$. The biodistribution data in rats (% dose/organ uptake in brain) showed a distinctive disparity between the isomers; the syn isomer showed higher uptake and retention in rats and monkeys. In a continuous effort to develop new ^{99m}Tc-labeled brain perfusion imaging agents, neutral and lipid-soluble ^{99m}Tc complexes of BAT containing an *N'*-benzylpiperazinyl (BPA) side chain were prepared. Due to the presence of a chiral center, the BPA-BAT ligand (racemic mixture) is also expected to show two types of ^{99m}Tc and ^{99}Tc complexes, syn and anti isomers. In this paper, the preparation and structural identification of the ^{99}Tc-BPA-BAT complexes and the in vivo biodistribution in rats are reported.

Chemistry

The ligand synthesis is achieved by a procedure reported earlier for the corresponding monoamine derivatives of BAT.[21,22] Based on these steps, a racemic ligand BPA-BAT is produced. The no-carrier added ^{99m}Tc-BPA-BAT complexes were prepared by an exchange reaction between the racemic ligand and ^{99m}Tc-Sn^{II}-glucoheptonate (Scheme II). The syn and anti isomers (approximately 1:1 ratio) were

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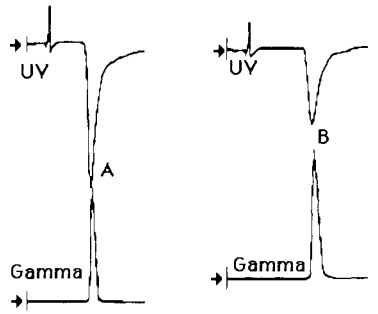


Figure 2. High-pressure liquid chromatography tracing of ^{99}Tc-BPA (UV) and ^{99m}Tc-BPA-BAT (gamma): peak A, syn; peak B, anti; after separation.

obtained and can be separated by HPLC (Figure 1). The no-carrier-added ^{99m}Tc preparation showing the same elution profiles and retention time of the ^{99m}Tc complexes (syn and anti) was used for the in vivo biodistribution study.

Since ^{99m}Tc is a short-lived isotope ($T_{1/2}$ = 6 h), it is impractical and infeasible to synthesize enough to perform chemical analysis. In order to ellucidate the chemical structures, we prepared the carrier-added ^{99}Tc ($T_{1/2}$ = 2 × 10^5 years) complexes by heating the racemic ligand, ammonium [^{99}Tc]pertechnetate, and sodium dithionite (reducing the pertechnetate from +7 to +5 state) under basic conditions (Scheme II). The diastereomeric mixture (approximately 1:1 ratio) was separated from other material by column chromatography (silica gel–acetone). A second column eluted with acetone–dichloromethane (1:2) successfully separated the syn from the anti isomer. The isomers were recrystallized from a mixture of acetonitrile and water (2:1). Prolonged standing of the ^{99}Tc complex in the acetonitrile and water mixture gave the desired crystals for X-ray crystallography analysis. Since the starting ligand (BPA-BAT) is a racemic mixture, a *d* and *l* pair of each of the syn and anti complexes was obtained. No attempt was made to separate the *d* from the *l* isomer. The chromatographic data is presented in Table I. Coinjection of the carrier-added and no-carrier-added complexes showed identical HPLC chromatography profiles, suggesting that the same chemical species was formed in each case (Figure 2). A distinct $Tc^{III}O$ IR absorption at 900 cm^{-1} for both isomers was observed. The UV spectra exhibited a peak at 428 μm (ε = 2142) and 423 μm (ε = 1622) for the syn and anti isomers, respectively. The elemental analysis was also consistent with the proposed structure. Partition coefficients of the isomers showed a relatively high value, with the syn slightly higher than the anti isomer (Table II).

Table II. Partition Coefficients for the Syn and Anti Isomers[a]

	pH 7.0	pH 7.4
syn	924 ± 45	1014 ± 125
anti	797 ± 50	921 ± 45

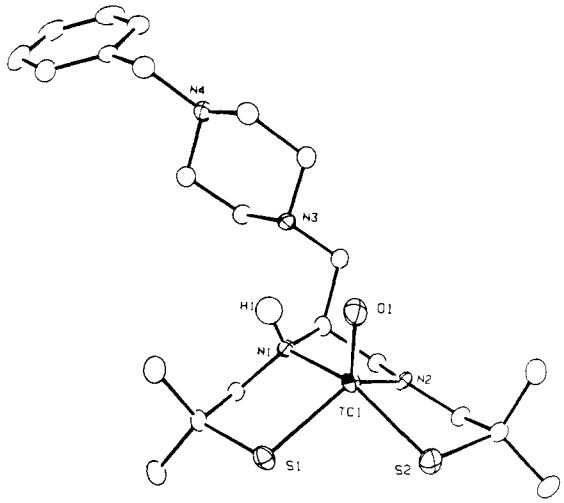
[a] Average of five measurements, 1-octanol–buffer.

Table III. X-ray Crystallography Data of ^{99}Tc-BPA-BAT Syn and Anti Isomers

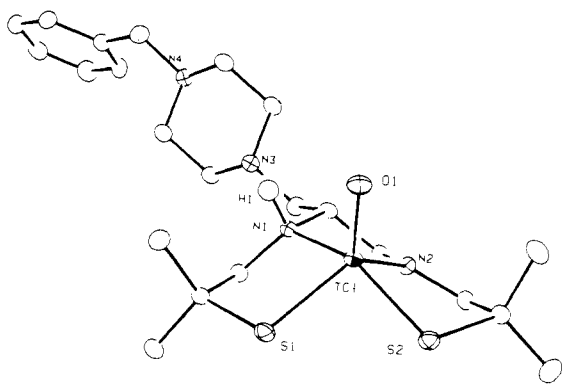
	^{99}Tc-BPA-BAT (syn)	^{99}Tc-BPA-BAT (anti)
formula	$TcS_2ON_4C_{22}H_{37}$	$TcS_2ON_4C_{22}H_{37}$
fw	536.69	536.69
space group	$P2_1/n$	$P2_1/c$
a, Å	15.241 (5)	12.243 (7)
b, Å	15.658 (7)	11.022 (2)
c, Å	11.385 (3)	19.180 (5)
α, deg	90	90
β, deg	109.91 (2)	102.19 (3)
γ, deg	90	90
V, Å^3	2554.6	2529.8
Z	4	4
D_{calcd}, cm^3	1.395	1.409
cryst size, mm	~0.20 × 0.50 × 0.40	~0.30 × 0.40 × 0.35
μ, cm^{-1}	7.26	7.33
abs cor	DIFABS	none
range	0.77–1.05	
scan method	ω	ω
scan range, deg	1.20–1.80	1.80–2.00
scan speed, deg/min	1.80–20.1	2.20–4.00
no. of reflctns measd	6607	5141
no. of indep reflctns used in refinement	2077	3360
no. of variables	275	271
R(*F*)	0.027	0.035
R_w(*F*)	0.027	0.038
max shift error on last cycle	0.58	0.04

X-ray Crystallography

The X-ray crystallographic analysis confirmed the syn and anti conformations (in relationship to the Tc(=O)N_2S_2 core) for the two isomers of ^{99}Tc-BPA-BAT (Table III). The Tc(=O)N_2S_2 core is square pyramidal, and the N_2S_2 plane is highly puckered with a maximum deviation of 0.22



syn



anti

Figure 3. X-ray crystallograph of syn and anti isomers of ^{99}Tc-BPA-BAT.

Table IV. Biodistribution of Isomers of ^{99m}Tc-BPA-BAT in Rats[a]

	syn		anti	
	2 min	15 min	2 min	15 min
blood	5.37 (4.91–6.23)	2.04 (1.97–2.17)	3.42 (3.36–3.52)	1.21 (1.12–1.36)
muscle	8.43 (7.15–10.2)	18.1 (16.0–20.1)	17.2 (9.34–24.6)	20.6 (15.6–30.1)
heart	2.46 (1.85–2.78)	0.43 (0.39–0.47)	1.86 (1.45–2.20)	0.39 (0.36–0.43)
lungs	18.5 (16.2–21.0)	3.38 (3.19–3.49)	5.47 (4.76–6.53)	1.46 (1.27–1.62)
spleen	0.70 (0.51–0.81)	0.79 (0.87–0.97)	0.59 (0.46–0.66)	0.61 (0.52–0.70)
kidneys	7.80 (6.08–9.06)	2.22 (1.98–2.34)	6.21 (5.82–6.71)	2.07 (1.94–2.29)
stomach	1.85 (1.32–2.61)	4.51 (3.88–5.09)	1.76 (1.17–2.80)	3.33 (2.23–4.60)
liver	14.0 (11.7–17.5)	18.6 (17.2–20.9)	12.2 (9.72–14.0)	14.4 (13.0–15.7)
skin	9.18 (6.53–10.6)	15.7 (13.4–19.7)	7.50 (6.97–8.46)	6.62 (5.35–7.70)
thyroid	0.22 (0.20–0.25)	0.07 (0.07–0.08)	0.17 (0.17–0.18)	0.08 (0.07–0.11)
brain	2.77 (2.56–3.11)	1.08 (0.54–1.58)	0.57 (0.45–0.69)	0.27 (0.24–0.30)
brain[b]				
blood	5.33	5.82	1.84	2.50

[a] Average of three rats, % dose/organ. [b] Percent dose/gram ratio.

Å and 0.24 Å at the N_2 atom for the N_2S_2 plane of syn and anti isomers, respectively. Apparently for both isomers the hydrogen atom on the N_2 atom was ionized during the chelation, while the hydrogen atom on N_1 remained (Figure 3). As a consequence, the total net charge of the Tc(=O)N_2S_2 core is 0. It should be pointed out that a racemic mixture, *d* and *l*, of the syn and anti isomers was observed, but only one of the two isomers is shown in Figure 3. It is conceivable that hydrogen bonding between the N_1 and N_3 atoms may contribute to the compacting of the syn isomer, making this molecule more readily penetrable through the intact blood–brain barrier by a simple diffusion mechanism.

Biodistribution

After an iv injection, both isomers showed uptake in the brain; however, the uptake at 2 min for the syn isomer (2.77% dose/organ) is higher than that for the anti (0.57% dose/organ) (Table IV). A similar disparative result was observed for the 15-min study. The syn isomer clearly showed a superior brain uptake value as well as a better brain-to-blood ratio. Since the partition coefficients of the two isomers is very similar, the difference in brain uptake is probably due to the structural differences between the two stereoisomers. The syn isomer is more compact than the anti, and the rotational energy barrier may be smaller for the syn conformer to pass through the blood–brain barrier via a simple diffusion mechanism. One may also speculate that there may be a specific transport mechanism for this molecule which is sensitive to the conformation. However, a preliminary biodistribution study using an additional carrier-added ^{99}Tc complex did not change the brain uptake in rats (data not shown), suggesting that the uptake and retention process is not saturable and may not be due to a specific mechanism.

A similar steric effect for syn and anti isomers has been reported for ^{99m}Tc-NEP-DADT.[24] Two epimeric complexes were obtained, and one of the complexes (syn isomer) showed a superior brain uptake and retention. In addition, a similar disparative renal clearance of racemic isomers of a new renal imaging agent, ^{99m}Tc-2,3-bis(2-thioacetamido)propanoate, was reported.[25,26] Structural

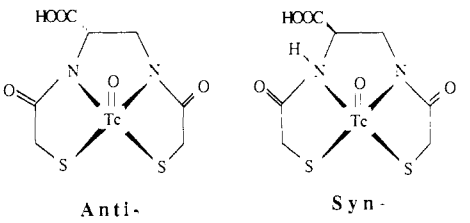


Figure 4. Syn and anti isomers of ^{99m}Tc-2,3-bis(2-thioacetamido)propanoate.

analysis confirmed the syn and anti conformation (Figure 4). In this case the syn isomer showed a better renal clearance and a lower liver uptake, desirable properties for a renal imaging agent.

The reports mentioned above and the data presented in this paper strongly suggest that the biodistribution of ^{99m}Tc imaging agents is very sensitive to minor steric changes, despite the fact that the brain uptake of the ^{99m}Tc imaging agents may not be a specific process, probably by a simple diffusion mechanism. However, the steric effect should be taken into consideration when additional substituents are introduced to the core structure for structure–activity relationship studies.

Experimental Section

Elemental analyses were performed commercially (Atlantic Microlab, Inc.). Infrared spectra were taken on a Matson polaris FT-IR and UV data on a Beckman DU-7. Spectral properties were consistent with the proposed structures. High-performance liquid chromatography (HPLC) was carried out on a Hamilton PRP-1 reverse-phase column eluted with acetonitrile–water (85:15); the radioactive eluent was detected by a sodium iodide detector and recorded on a multichannel analyzer, and also by a UV detector and recorded on a strip chart recorder.

^{99}Tc-BPA-BAT (syn): IR (KBr) 900 cm^{-1}; UV (ethanol) 428 μm (ϵ = 2142). Anal. ($C_{22}H_{37}N_4S_2OTc$) C, H, N, S.

^{99}Tc-BPA-BAT (anti): IR (KBr) 910 cm^{-1}; UV (ethanol) 423 μm (ϵ = 1622). Anal. ($C_{22}H_{37}N_4S_2OTc$) C, H, N, S.

Preparation of ^{99}Tc-BPA-BAT Complexes. Ammonium pertechnetate (1 mmol) and the BPA-BAT ligand (a racemic mixture), prepared by a method reported earlier[21] (1.2 mmol), were mixed in 60 mL of water–ethanol (9:1) and heated with stirring at 80 °C for 10 min. A solution of sodium thiosulfate ($Na_2S_2O_3$), 1.3 mmol in 3 mL of 2 N NaOH solution, was added dropwise. The reaction mixture was stirred at the same temperature for another 30 min. The solution was extracted with chloroform (3 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate. The desired product was purified by a silica gel column eluted with acetone. The product was recrystallized from acetonitrile–H_2O (2:1) (yield 50%).

Separation of optical isomers of ^{99m}Tc-BPA-BAT was achieved by silica gel column chromatography using acetone–dichloromethane (1:2) as the eluting solvent. Appropriate fractions were combined, and each isomer was recrystallized separately from an

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acetonitrile-H_2O (2:1) mixture.

Preparation of No-Carrier-Added ^{99m}Tc Complexes of BPA-BAT. The no-carrier-added ^{99m}Tc-BPA-BAT was prepared by a ligand-exchange reaction. A solution of ^{99m}Tc-glucoheptonate (1-10 mCi, 0.1-1 mL), prepared by adding a desired amount of sodium [^{99m}Tc]pertechnetate into a freeze-dried kit (1 mg of glucoheptonate + 0.25 mg of stannous chloride), and 1 mg of ligand was heated at 100 °C for 30 min. The product was extracted with chloroform (3 × 2 mL), and the combined extracts were dried over anhydrous sodium sulfate. The solution was then condensed with a stream of air and redissolved in saline (radiochemical yield >80%). No decomposition of the ^{99m}Tc complex was observed on standing at room temperature for 18 h. For separating the syn and the anti isomers, the racemic mixture was injected into HPLC and appropriate fractions were collected (Table I). After condensing, reextraction with ethyl acetate (3 × 1 mL), and condensing with a stream of nitrogen, the products were redissolved in saline (total radiochemical yield >50%, radiochemical and isomeric purity >98%).

Partition Coefficients. The partition coefficient was measured by mixing the ^{99m}Tc-BAT compound with 3 g each of 1-octanol and buffer (pH 7.0 or 7.4, 0.1 M phosphate) in a test tube. This test tube was vortexed for 3 min at room temperature and then centrifuged for 5 min. Two weighed samples (0.5 g each) from the 1-octanol and buffer layers were counted in a well counter. The partition coefficient was determined by calculating the ratio of counts per minute/gram of octanol to that of buffer. Samples from the octanol layer were repartitioned until consistent partition coefficient values were obtained. The measurement was repeated three times.

Animal Distribution Studies. Male Sprague-Dawley rats (200-300 g) were injected intravenously (femural vein under ether anesthesia) with 0.2 mL of a saline solution containing the ^{99m}Tc-BAT complex (0.5-20 μCi). At selected intervals following the injection, blood samples (1 mL each) were collected by cardiac puncture, and the rats were sacrificed immediately thereafter by cardiectomy. The organs of interest were subsequently excised, weighed, and counted in a dual-channel automatic gamma counter (Beckman 5500). The % dose/organ values were determined by comparison of the tissue radioactivity with suitable dilutents of the injected dose. The % dose/gram values were computed from the % dose/organ values and the corresponding mean organ weights (mean organ weights: heart, 0.85 g; brain, 1.65 g; blood, 18 g; liver, 9 g; Kidneys, 1.9 g; lungs, 1.6 g). Finally, the brain:blood ratio was calculated from the corresponding % dose/gram values.

X-ray Crystallography. Crystal Data. ^{99}Tc-BPA-BAT (syn): $TcS_2ON_4C_{22}H_{37}$, dark brown, crystallized from 2:1 MeCN-water, monoclinic-b, $P2_1/n$ (no. 14), a = 15.241 (5) Å, b = 15.658 (7) Å, c = 11.385 (3) Å, β = 109.91 (2)°, from 24 reflections, T = -70 °C, V = 2554.6 Å^3, Z = 4, FW = 536.69, D_{calcd} = 1.395 g/cm^3, μ(Mo) = 7.26 cm^{-1}.

^{99}Tc-BPA-BAT (anti): $TcS_2ON_4C_{22}H_{37}$, red, block, -0.30 × 0.40 × 0.35 mm, crystallized from acetonitrile-water, monoclinic-b, $P2_1/c$ (no. 14), a = 12.243 (7) Å, b = 11.022 (2) Å, c = 19.180 (5) Å, β = 102.19 (3)°, from 20 reflections, T = -70 °C, V = 2529.8 Å^3, Z = 4, FW = 537.70, D_{calcd} = 1.411 g/cm^3, μ(Mo) = 7.33 cm^{-1}.

Data Collection and Treatment. For the syn isomer: Enraf-Nonius CAD4 diffractometer, graphite monochromator, Mo Kα radiation, 6607 data collected, 2.6° < 2θ <55.0°, maximum hkl = 19,20,14, data octants = +++, -++, -+-, ω scan method, scan width = 1.20-1.80° ω, scan speed = 1.80-20.10°/min, typical half-height peak width = 0.35° ω, two standards collected 30 times, adjusted for a 10% decrease in intensity, 1098 omitted, 10.2% variation in azimuthal scan, corrected for absorption (DIFABS), range of transmission factors = 0.77-1.05, 176 duplicates, 1.8% R-merge, 2077 unique reflections with $I > 3.0\sigma(I)$.

For the anti isomer: Enraf-Nonius CAD4 diffractometer, graphite monochromator, Mo Kα radiation, 6607 data collected, 2.2° < 2θ <55.0°, maximum hkl = 19,20,14, data octants = +++, -++, σ scan method, scan width = 1.80-2.00° ω, scan speed = 2.20-4.00°/min, typical half-height peak width = 0.28° ω, two standards collected 30 times, 7.3% variation in azimuthal scan, corrected for absorption (DIFABS), range of transmission factors = 0.77-1.05, 174 duplicates, 3.1% R-merge, 3360 unique reflections with $I \geq 3.0\sigma(I)$.

Solution and Refinement. For the syn isomer: The structure was solved by automated Patterson analysis (PHASE). The hydrogen atom on N1 was obtained from a difference map and refined. All other hydrogen atoms were idealized with C-H = 0.95 Å refinement by full-matrix least squares on F. Scattering factors include anomalous terms for Tc, S, weights $\alpha[\sigma^2(I) + 0.0009I^2]^{-1/2}$, 275 parameters, refined anisotropic, all non-hydrogen atoms; isotropic, H; fixed atoms, H; final R = 0.027, R_w = 0.028, error of fit = 1.11, max Δ/σ = 0.58 largest residual density = 0.26 e/Å^3, near S2. For the anti isomer: The structure was solved by automated Patterson analysis (PHASE). The hydrogen atom on N1 was obtained from a difference map and refined. All other hydrogen atoms were idealized with C-H = 0.95 Å refinement by full-matrix least squares on F. Scattering factors include anomalous terms for Tc, S, weights $\alpha [\sigma^2(I) + 0.0009I^2]^{-1/2}$, 271 parameters, refined anisotropic, all non-hydrogen atoms; isotropic, H; fixed atoms, H; final R = 0.035, R_w = 0.038, error of fit = 1.56, max Δ/σ = 0.04, largest residual density = 0.58 e/Å^3, near Tc.

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A Novel Class of "GABAergic" Agents: 1-Aryl-3-(aminoalkylidene)oxindoles

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Antagonism of mercaptopropionic acid (MPA) induced convulsions, reflecting a GABAergic mechanism, was observed in a series of 1-aryl-3-(aminoalkylidene)oxindoles. Optimal MPA antagonism was associated with 3-halo, 3-alkyl, and/or 4-alkoxy substituents in the pendant aryl ring and with (dimethylamino)methylene, 1-(dimethylamino)-ethylidene and N-methyl-2-pyrrolidinylidene side chains. The precise mechanism of action of these agents is unclear at this time; however, they are not GABA mimics and they do not affect GABA levels. Like other GABAergic agents, these compounds are potent enhancers of benzodiazepine binding and they antagonize cyclic GMP elevations induced by isoniazid. Compounds from this series may therefore have potential therapeutic utility as anticonvulsants or anxiolytics.

Safe GABAergic agents have been attractive targets for drug research in recent years because GABA serves as an important inhibitory neurotransmitter in the central nervous system and GABAergic agents have potential utility in the therapy of epilepsy, Huntington's chorea, schizophrenia, tardive dyskinesia, depression, and spas-

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