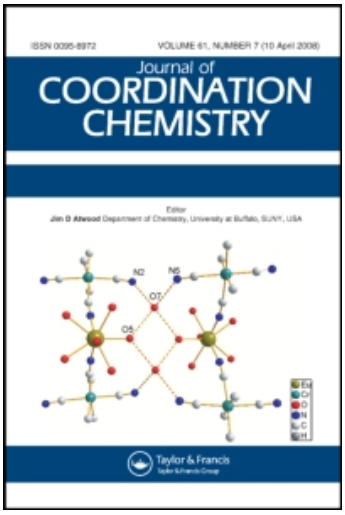


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# Recent advances on technetium complexes: coordination chemistry and medical applications¶

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# Recent advances on technetium complexes: coordination chemistry and medical applications¶

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Current literature (1990–2005) on methods for synthesizing technetium (Tc) complexes is presented. The development and design of Tc complexes for imaging of different organic tissues, of special interest for their medical applications, are also reviewed.

*Keywords:* Technetium; Imaging; Radiopharmaceuticals; Nuclear medicine



## 1. Introduction

Technetium (Tc) and its derivatives are of considerable interest in modern chemistry and technology. Its coordination compounds have been extensively covered in a series of recent monographs and reviews [1–17]. Among these publications, an excellent recent comprehensive review of Tc metal-complex chemistry deserves special emphasis [5]. It covers the main physical, chemical and radiochemical properties of this metal, its systematic chemistry as a function of oxidation state, selected topics in Tc chemistry and its radiopharmaceutical chemistry. Another comprehensive source, a specialized book on Tc radiopharmaceuticals has been recently published [3], whose Chapter 12 summarizes the many $^{99}$Tc coordination and organometallic compounds in oxidation states from +VII to −I. Additionally, several reviews on molecular mechanics applied to Tc(V) imaging agents [18, 19], structural characteristics of Tc complexes [20], polynuclear halide clusters [21], separation techniques of $^{99m}$Tc radiopharmaceuticals [22–25] are available at present.

The chemistry of Tc has become very important, especially in relation to the use of the isotope $^{99m}$Tc as a diagnostic agent [6] in nuclear medicine. It has been used

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¶Dedicated to Professor Alexander D. Garnovskii (Rostov State University, Russia) on the occasion of his 73rd birthday (30 August 2005).

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for many years in bone scanning and more recently in studying different diseases of the heart, brain, kidneys, liver, and other organs as well as tumor tissue. Tc complexes are of great interest for the radiopharmaceutical industry [26, 27]. $^{99m}$Tc is the radioisotope of choice for imaging in diagnostic nuclear medicine due to its ideal energy $E_\gamma = 140\,\text{keV}$, lack of particulate radiation dose, half-life of 6 h, and wide availability [28, 29]. The status of positron emission tomography and its applications using radionuclides has been reviewed recently [30].

Some other applications of technetium are the following [31]: use of some of its alloys as superconductors with high critical temperature, use of $^{99}$Tc in high-temperature thermocouples, construction of basic anticorrosive covers for nuclear reactors, etc. Recovering Tc from contaminated soils and studies of solubility of Tc ions in several media have been also reported [32–37]. The use of Tc ($TcO_2$ and $TcS_2$) as a catalyst for dehydrogenation of alcohols and cyclic hydrocarbons, dehydrocyclization of *n*-hexane and *n*-heptane, hydrogenation of benzene and carbon oxides, and hydrazine decomposition, has been reviewed before, indicating that Tc is a promising catalyst for hydrogenation–dehydrogenation, even compared to its Re and Mn analogs [38].

Taking all the earlier accounts into consideration, in this review the most recent results in the area of Tc coordination compounds are discussed. The systematization is made according to the character of donor atoms in the coordination sphere and metal oxidation number. Among the earlier mentioned numerous aspects of practical application of technetium compounds [8], special attention is paid to their uses in nuclear medicine [6, 9] which are being rapidly developed at present. Due to the diversity of ligands employed in the design of Tc complexes, in this article they have been grouped in a way that will facilitate their discussion although sometimes, because of the complex nature of the coordinating core, it will be as arbitrary as any grouping scheme.



## 2. Fundamental chemistry of Tc coordination compounds

### 2.1. *Oxidation states*

Tc oxidation numbers range from −1 to +7 (see table 1) and their coordination compounds can have diverse ligand environments (C-, N-, O-, S-, Se-, P-donor centers and their combinations) [5–7]. This situation requires selection of appropriate synthetic techniques for obtaining specific Tc coordination compounds [7, 11] and determines their stereochemistry [5] and physical and chemical properties [2].

The very rich and diverse redox chemistry of technetium makes it difficult to control the oxidation state and the lability of the formed Tc complexes. At the same time, it provides more opportunities to modify the structure and properties of Tc complexes by the choice of an appropriate chelating system [6].

The mostly used peptide complexes of technetium cannot be obtained using pertechnetate anion without its reduction. When Tc(VII) in $^{99m}TcO_4^-$ is reduced, the oxidation state of the metal depends on the nature of the reducing agent, the chelator, and the reaction conditions [6]. Table 2 illustrates some of these and other synthetic possibilities [39–47].

Another facet of technetium compounds is their isomerism, including geometric isomers, epimers, enantiomers, and diastereomers, mostly frequently found for oxotechnetium complexes. The isomers often have different lipophilicities and biodistributions in biological systems. The formation of isomers for a technetium chelate can have a significant impact on the biological properties of a radiopharmaceutical [6].

Table 1. Oxidation states and stereochemistry of Tc compounds [with permission from Shuang Liu and D. Scott Edwards, *Chem. Rev.*, **99**, 2235–2268 (1999)].

| Oxidation state | Example | Coordination geometry | Coordination number |
|---|---|---|---|
| +7 ($d^0$) | $[TcH_9]^{2-}$ | Trigonal prism | 9 |
| | $TcO_4^-$ | Tetrahedron | 4 |
| +6 ($d^1$) | $TcO_4^{2-}$ | Tetrahedron | 4 |
| +5 ($d^2$) | $[Tc(NCS)_6]^-$ | Octahedron | 6 |
| | $[Tc(Diars)_2Cl_4]^+$ | Dodecahedron | 8 |
| | $TcOCl_4^-$ | Square pyramid | 5 |
| +4 ($d^3$) | $[TcCl_6]^{2-}$ | Octahedron | 6 |
| +3 ($d^4$) | $[Tc(Diars)_2Cl_2]^+$ | Octahedron | 6 |
| +2 ($d^5$) | $[TcCl_2(PhP(OEt)_2)_4]$ | Octahedron | 6 |
| +1 ($d^6$) | $[Tc(CNC(CH_3)_3)_6]^+$ | Octahedron | 6 |
| 0 ($d^7$) | $[Tc_2(CO)_{10}]$ | Octahedron | 6 |
| −1 ($d^8$) | $[Tc(CO)_5]^-$ | Trigonal bipyramid | 5 |

Diars, *o*-phenylenebis(dimethylarsine).



## 2.2. *Technetium cores*

Tc cores [6] are depicted in **1**–**6**; the corresponding compounds can be used for $^{99m}$Tc-labeling of biomolecules, such as antibodies, antibody fragments, peptides, peptidomimetics, etc. The cores below are as follows: a ''naked'' Tc atom (**1**) (oxidation state +3 or +4, the coordination geometry can be an octahedron or a trigonal prism); $[Tc{=}O]^{3+}$ core (**2**) (very stable square pyramidal oxotechnetium complexes; the most frequently used for labeling of biomolecules); $[O{=}Tc{=}O]^+$ core (**3**) (octahedral Tc complexes); rarely used Tc(V)-containing $[Tc{\equiv}N]^{2+}$ core (**4**) (it is isoelectronic with the $[Tc{=}O]^{3+}$ core); $[Tc(CO)_3]^+$ core (**5**) and [Tc]HYNIC core (**6**) [with permission from Shuang Liu and D. Scott Edwards, *Chem. Rev.*, **99**, 2235–2268 (1999)].

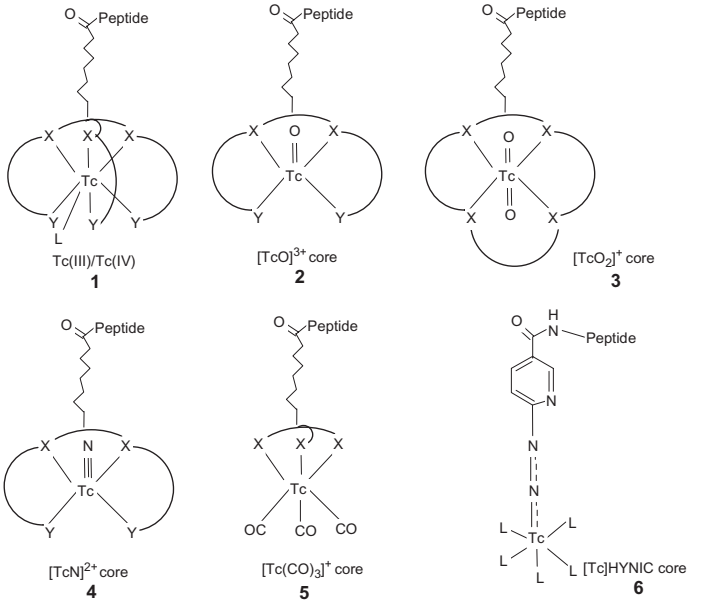
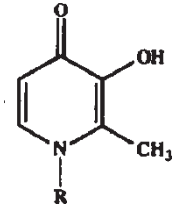
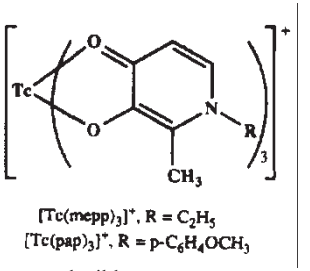
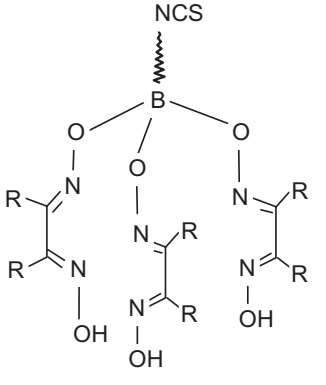


Table 2. Reduction of $TcO_4^-$ with various reductants.

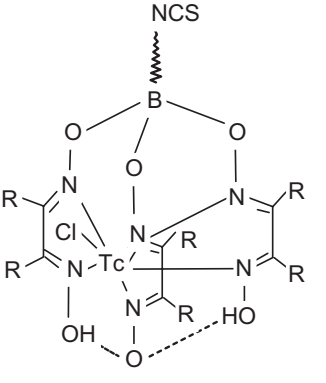
| Precursor(s) (Ligand/complex), conditions | Reductant | Remarks | Product | Reference |
|---|---|---|---|---|
| $TcO_4^-$, pH 11–13 | Sodium dithionite, hypophosphorous acid, formamidine sulfinic acid, dithiothreitol, hydrazine, and hydroxylamine. | Only sodium dithionite in the pH range 11–13 was found to give quantitative yields of the required Tc complex. | Tetraphenylarsonium oxotechnetiumbis-(ethane-dithiolate) $[^{99}TcO(SCH_2CH_2S)_2]^-$ | [39] |
| $TcO_4^-$, $PhCOS(CH_2)_nCONH)_2X$ ($n=1$, $X=(CH_2)_2$, $(CH_2)_3$, and $o$-$C_6H_4$; $n=2$, $X=(CH_2)_2$ and $(CH_2)_3$), 70°C. | Sodium dithionite | The reduction of pertechnetate in basic ethanol solution by sodium dithionite in the presence of an excess of the benzoyl esters gave good yields of the oxotechnetate(5+) anions, isolated as their tetraphenyl arsonium salts. The complexes are readily soluble in polar non-aqueous solvents. | $[TcO(S(CH_2)_nCONXNCO(CH_2)_nS)]^-$ ($n=1$, $X=(CH_2)_2$, $(CH_2)_3$, and $o$-$C_6H_4$; $n=2$, $X=(CH_2)_2$) | [40] |
| $TcO_4^-$, pentane-2,4-dione, reflux | Sodium dithionite | The reaction of $Tc(acac)_3$ and ferricenium tetrafluoroborate in acetonitrile yields the Tc(IV) species, $[Tc(acac)_3]BF_4$ in 60% yield. | Tc(III) complex $[Tc(acac)_3]$ | [41] |

| | | | | |
|---|---|---|---|---|
| N-substituted pyridinone ligands, reflux.  | $Na_2S_2O_5$ or $Na_2S_2O_4$ | The $[Tc(L)_3]^+$ complexes formed with N-substituted-3-hydroxy-2-methyl-4-pyridinonate ligands with both $^{99m}Tc$ and $^{99}Tc$ have been unambiguously demonstrated to be chemically identical. | Tc(IV) complexes $[TcL_3]^+$ (L=N-substituted pyridinonate)  $[Tc(mepp)_3]^+$, R = $C_2H_5$ $[Tc(pap)_3]^+$, R = p-$C_6H_4OCH_3$ | [42] |
| ($^{99m}Tc$) intermediate $[^{99m}TcL(O)]^+$, L = one of the two tetradentate Schiff base ligands *N*,*N*′-ethylenebis(acetylacetone iminato), (en), or *N*,*N*′-propylene-1,2-bis(acetylacetone iminato), (pn) | Y = a monodentate phosphine, phosphite or isonitrile ligand as exemplified by $P(CH_3)_3$, $P(OCH_3)_3$ and $CN–C(CH_3)_3$, sodium dithionite, etc. | Strong support for the hypothesis that myocardial washout occurs only for those $^{99m}Tc(III)$ cations that undergo *in vivo* reduction to the neutral $^{99m}Tc(II)$ form. | 15 non-reducible technetium-99m(III) complexes of formula *tr*-$[^{99m}TcL(Y)_2]^+$; $[^{99m}Tc(DMPE)_2X_2]^+$ (X = Cl, Br) X = Cl, Br, DMPE = 1,2-bis(dimethylphosphino)ethane; $[Tc(DMPE)_3]CF_3SO_3$ | [43–45] |
| $TcO_4^-$, isonitrile ligands, reflux. | Sodium dithionite | As a reducing agent, $Na_2S_2O_4$ has proven to be quite versatile. Even Tc(I), a relatively unexplored oxidation state, is accessible from pertechnetate in aqueous solution. | Tc(I) complexes $[Tc(CNR)_6]^+PF_6$ (R = *ter*-butyl, methyl, cyclohexyl, and phenyl) | [46] |
| $^{99m}TcO_4^-$, pH 11, 0.9% NaCl/$H_2O$, 1 atm CO, 30–75°C | CO, $NaBH_4$ | First synthesis of the water and air stable organometallic aqua complex $[^{99m}Tc(OH_2)_3(CO)_3]^+$ directly from $[^{99m}TcO_4]^-$ in saline under 1 atm of CO. | Tc(I) complex $[Tc(H_2O)_3(CO)_3]^+$ | [47] |

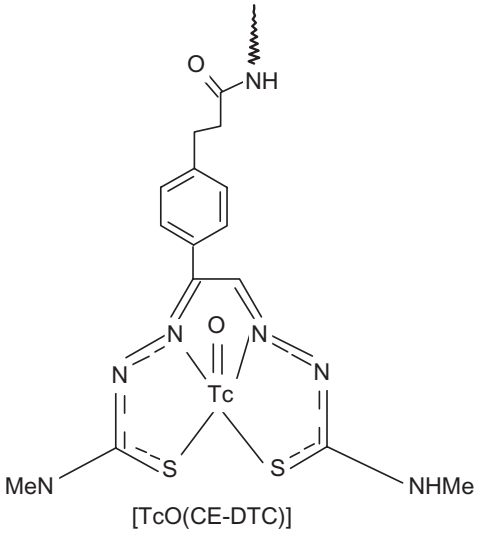
Some examples of these types of technetium complexes are shown as follows (**7**–**19**): BATO-NCS ligand **7** and its complex **8** [Tc(BATO-NCS)Cl] [with permission from Shuang Liu and D. Scott Edwards, *Chem. Rev.*, **99**, 2235–2268 (1999)], moiety $N_6Cl$, "naked" Tc atom; technetium complex **9** of the ligand *p*-carboxyethylphenylglyoxal-di(*N*-methylthiosemicarbazone) (CE-DTS), $[Tc{=}O]^{3+}$ core, $N_2S_2$ moiety; diaminetetrathiol (**10**) and its complex **11** $[TcO(N_2S_3)]$, $[Tc{=}O]^{3+}$ core, moiety $N_2S_4$; [TcN(dithiocarbamato)] (**12**), [TcN(dithiophosphinato)] **13**, and $[TcN(N_2S_2\text{-Schiff base})]$ (**14**) complexes, $[Tc{\equiv}N]^{2+}$ core; tetramine ligand **15** and its $[TcO_2(\text{tetramine})]$ complex **16**, $[O{=}Tc{=}O]^{2+}$ core, $N_4$ moiety; $[Tc(S_3)(CO)_3]$ complex **17**, $[Tc(CO)_3]^{+}$ core, $S_3$ moiety; ligand HYNIC **18** and its complex $[Tc(HYNIC)(tricine)_2]$ (**19**) (tricine = *N*-[tris(hydroxymethyl)methyl]glycine), [Tc]HYNIC core, $N_2O_3$ moiety.



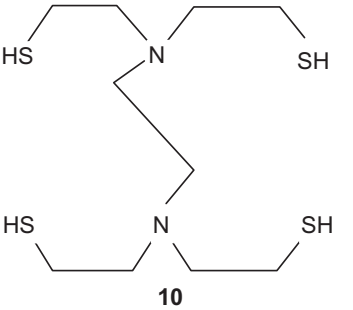

BATO-NCS
**7**



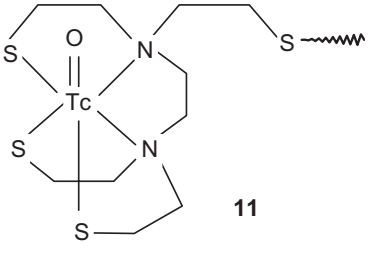

[Tc(BATO-NCS)Cl]
**8**



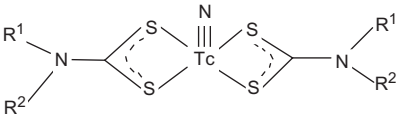

[TcO(CE-DTC)]
**9**



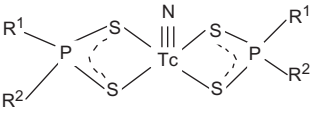

**10**



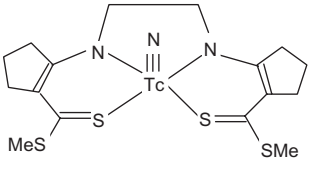

**11**



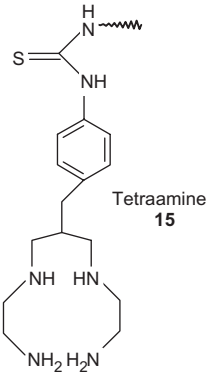
[TcN(dithiocarbamato)]
**12**



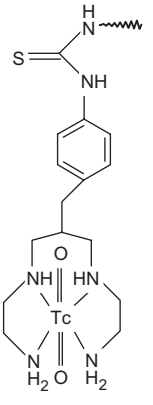
[TcN(dithiophosphinato)]
**13**



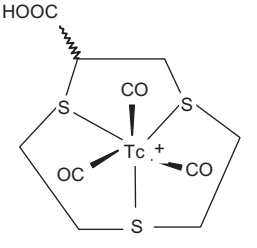
[TcN($N_2S_2$-Schiff base)]
**14**



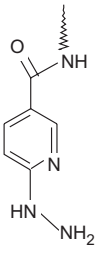
Tetraamine
**15**



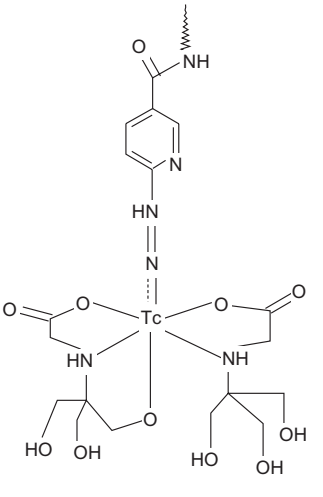
[$TcO_2$(Tetraamine)]
**16**



[$Tc(S_3)(CO)_3$]
**17**



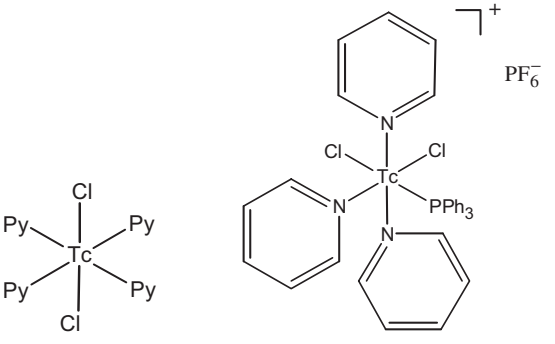
6-HYNIC
**18**



[Tc(HYNIC)(tricine)$_2$]
**19**

### 2.3. *Complexes with N-containing ligands*

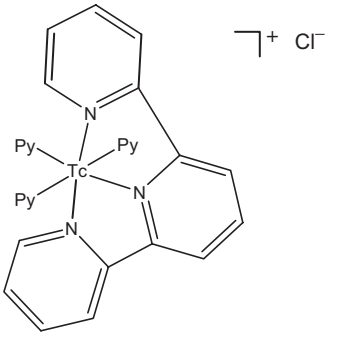
Among the complexes with an $N_x$-core, a series of Tc(III), Tc(II), and Tc(I) complexes with pyridine ligands was reported [48]. The interest of the authors was "to develop a coordinatively unsaturated, low-valent, electron-rich, Tc metal center dominated by a very weak $\pi$-acid ligand environment". The Tc complexes **20**–**22** were prepared *via* substitution chemistry of $TcCl_3(PPh_3)_2(MeCN)$, and the Tc(II) and Tc(I) complexes were obtained by their subsequent reduction by zinc dust. The formed products {some of them are $TcCl_2(py)_4$ (**20**), $TcCl_3(PPh_3)_2$(tmeda), $TcCl_3$(*t*-butyl$_3$tpy), [Tc(tpy)(py)$_3$]Cl (**22**) (tmeda = tetramethylethylenediamine, tpy = terpyridine)} were characterized by electrochemical, X-ray and spectrophotometric methods.




**20**




**21**

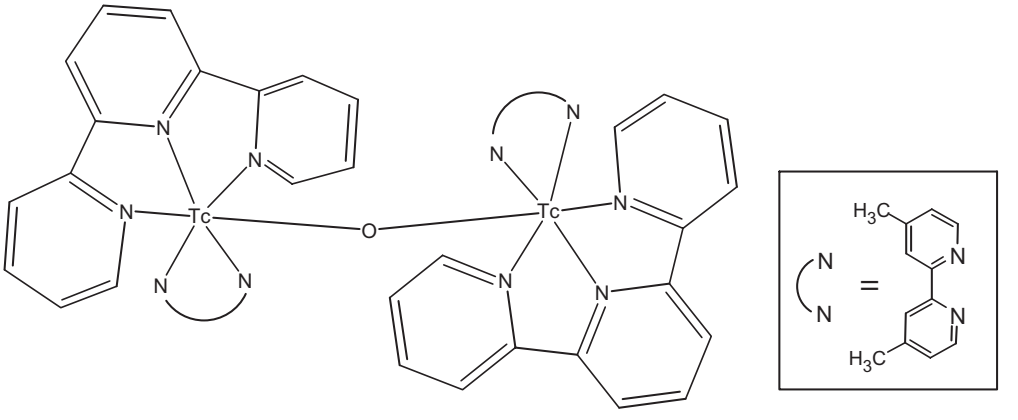



**22**

According to the data obtained, significant $\pi$-back-bonding interactions exist in the cases of Tc(II) and Tc(I) complexes relative to Tc(III). Thus, the decrease of 0.04–0.06 Å in Tc–N bond lengths between Tc(III) and Tc(II) pyridine complexes and the decrease of 0.09 Å in Tc–N(internal) bond lengths between Tc(III) and Tc(I) terpyridine complexes take place [48]. These effects support a stabilization of the low oxidation states of the metal. The Tc(III) pyridine complexes exhibit Knight-shifted $^1$H NMR spectra, transitions in the visible spectra that are tentatively assigned as charge transfer from the halide to metal, and multiple reversible electrochemical redox couples.

Among similar complexes with pyridine-type ligands, the oxo-bridged Tc(III) polypyridyl [(tpy)($Me_2$bipy)Tc-O-Tc(tpy)($Me_2$bipy)](OTf)$_4$ (**23**) (bipy = bipyridine,

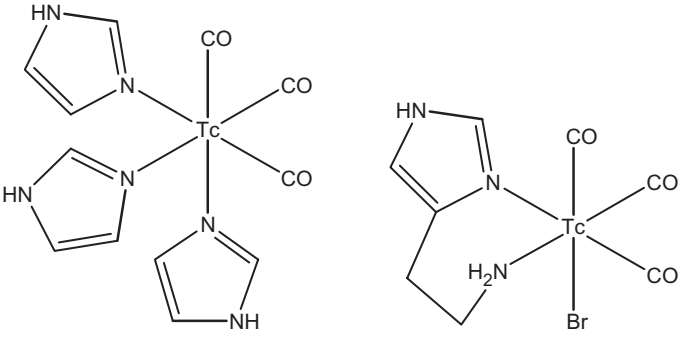
Otf = trifluoromethanesulfonate), complex was prepared from the reaction of $TcCl_3$(tpy), TlOTf and adventitious water [49]. Cyclic voltammetry analyses suggest a relatively weak metal–metal interaction, and spectrophotometric and magnetic data indicate an interesting delocalized molecular orbital description of the system.




**23**



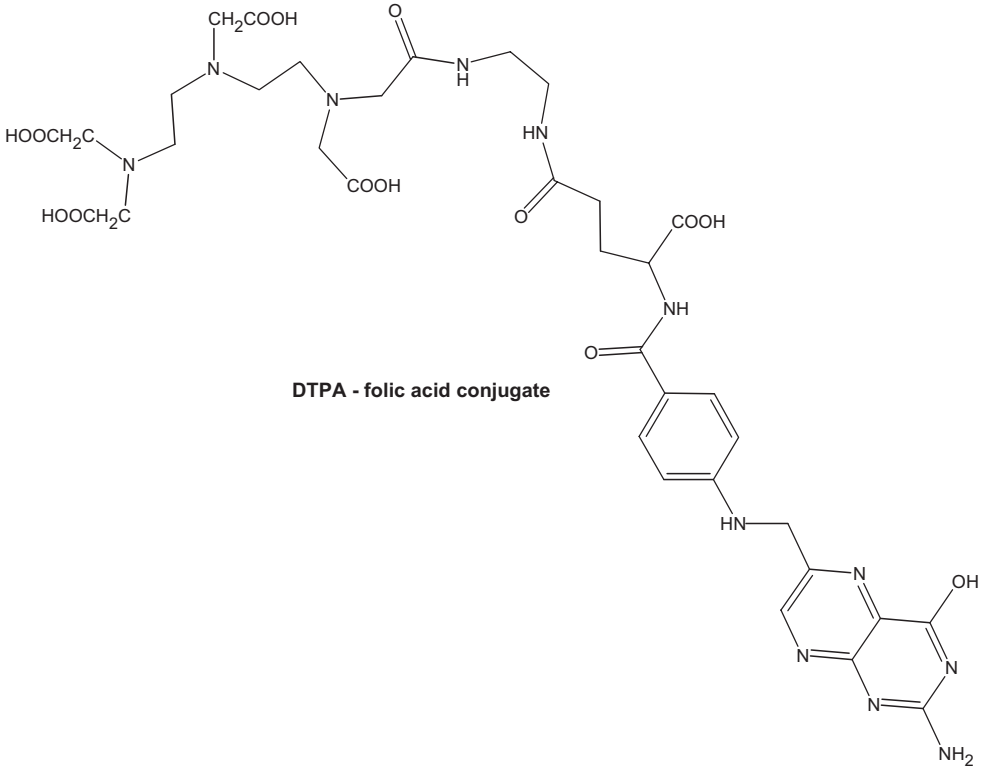
Stable, novel, carbonyl–Tc(I) complexes with structures such as **24** and **25**, were obtained by a one-step labeling procedure from $[^{99m}Tc(H_2O)_3(CO)_3]^+$ (this very important precursor for Tc complexes will be discussed later) and three short His-tagged recombinant peptides: (1) His-Gly-Gly-Ala-Ala-Leu, (2) Ala-Gly-His-Gly-Ala-Leu, and (3) Leu-Ala-Ala-Gly-Gly-His [50]. $[^{99m}Tc(H_2O)_3(CO)_3]^+$ was obtained by treating $Na[^{99m}TcO_4]$ in 0.9% saline media ($NaCl/Na_2CO_3$), at 1 atm of CO, pH 11, at 75°C during 30 min.




**24** **25**

Similar studies for a folate-receptor-targeted $^{99m}$Tc-radiopharmaceutical, $[Tc(CO)_3$DTPA-folate] with the diethylenetriaminepentaacetate (DTPA)-folic acid ligand **26**, have been reported [51]. It is not clear from this article what the coordination sphere around the Tc center is, but it is suggested that coordination occurs through the terminal amine nitrogen and the two associated acetate carboxyl oxygen atoms, analogous to the coordination of $[fac\text{-}Tc(CO)_3]^+$ by iminodiacetic acid, or *via* the three amine

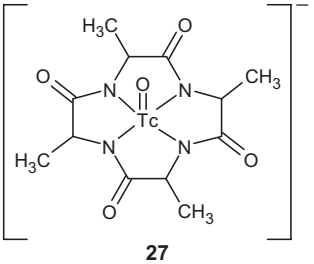
*N* atoms of the DTPA backbone, as well as by using two amine *N* atoms and one carboxyl O donor to satisfy the requirements of the Tc(I) center.




**26**

Tc–carbonyl complexes of tryptophan and histidine (His) were synthesized by a two-step method and their biodistribution in mice bearing the sarcoma 180 (S180) tumor demonstrated that the Tc–carbonyl complex of His has good stability *in vivo* and accumulates selectively at the tumor [52]. Mutant proteins annexin V-122 and annexin V-123 obtained from annexin V (a family of proteins with the ability of binding calcium and phospholipids) were constructed with *N*-terminal extensions containing either three or six His residues and labeled with carbonyl precursors, without altering its high affinity for cell membranes [53]. The application sequence of Tc–MIBI (MIBI = 2-methoxy-isobutyl-isonitrile), including other radionuclides as well as pertechnetate as radiopharmaceutical agents and radioimmunassay (RIA) methods, for thyroid cancer diagnosis has been explored, recommending the use of an algorithm for radionuclide application [54].

Complexation of Tc with tetraalanine yields [55] an unstable complex that converts to a monooxotechnetium(V) complex **27** of cyclic tetraalanine. The compound structure was determined by X-ray crystallography. Cyclization occurs on both no-carrier ($^{99m}$Tc) and carried ($^{99}$Tc) added scale. This procedure may provide a new synthetic methodology for cyclic tetrapeptides.



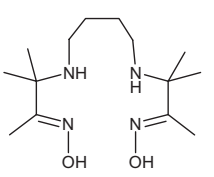
**27**

The reaction between $[^{99m}Tc(OH_2)_3(CO)_3]^+$ and a periodate activated SMS-Dx-His (SMS-Dx-His = histidine-tagged somastostatin dextran) conjugate, produced a $^{99m}Tc$ labeled somastostatin *via* a reductive amination under reducing conditions [56]. This labeling method may be useful for the labeling of peptides containing disulfide bonds for therapeutic applications. As an example of labeling of peptides using Tc as radiotracer, tityustoxin and venom from the scorpion Tityus serrulatus were labeled in the presence of stannous chloride and sodium borohydride with a yield of 60–70% for the venom and 75–85% for tityustoxin [57]. Although the coordination sphere of this compound can be variable, it is safe to assume that it is mostly by N-donor centers to the metal center from amino groups contained at the peptidic structure, besides some Cys (S-donor atom) binding possibilities.

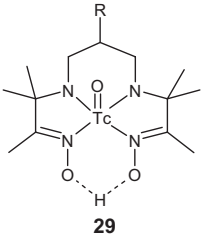
A synthetic octapeptide analog of somatostatin (lanreotide) was labeled with $^{99m}Tc$ by reduction of the cysteine bridge and transchelation through the sulfhydryl groups. Stannous chloride was used as reducing agent and tartrate as transchelating agent [58]. This direct method may be useful for preparation of freeze-dried kits. Another peptide derived complex, $^{99m}Tc$-Sulesomag, the Fab fragment of anti-NCA-90, is used as an *in vivo* granulocyte labeling agent for imaging inflammation [59]. A new somatostatin analog, $^{99m}Tc$-P829 was prepared and applied to 11 patients with Zollinger–Ellison syndrome, 16 patients with carcinoid tumors and 16 patients with endocrine tumors, in order to evaluate its scintigraphy compared with $^{111}In$-pentetreotide scintigraphy [60]. The detection rate was lower than that of $^{111}In$-pentetreotide scintigraphy, especially for liver metastases in patients with endocrine tumors.

A $^{99m}Tc$ labeled cyclam [*N*-2-methoxyethyl-2-(3′-nitro-1′-triazide)acetamide, AH 2123] was reported [61]. This complex may be useful as a hypoxic tumor-imaging agent as *in vivo* studies on Wistar strain rats indicated good biodistribution and stability. A water-soluble cyclam acid porphyrin (CAP), 5,10,15,20-tetrakis-[l4-{4′,8′,11′-tris-(carboxymethyl)-1′-(1′,4′,8′,11′-tetraazacyclotetradecane)amidomethyleneoxy}phenyl)-porphyrin], has been synthesized and labeled with $^{99m}Tc$ by the same authors [62] and its biodistribution studied in induced mammary tumor bearing rats in order to determine if they can be useful tumor imaging agents. Other hypoxic tissue imaging agents were prepared from the corresponding propylene diamine dioxime (PnAO)-glucoronide Tc-labeled molecules [synthesized from the reaction of 1-D-(2-nitroimidazolyl)glucuronic acid and 6-methyl-6-methylamino-HMPnAO (HMPnAO = hexamethyl propylene amine oxime) in the presence of benzotriazole-1-yl-oxy-tris (dimethylamino)phosphonium (BOP) reagent in anhydrous dimethylsulfoxide (DMSO)]. The compound was able to delineate tumors, as well as being useful as a large intestine and liver scintigraphic imaging agent [63]. $^{99m}Tc$-HL91, **28** (HL91 = 4,9-diaza-3,3,10,10-tetramethyldodecan-2,11-dione dioxime), was developed as a hypoxic marker. After administration on mice

bearing human tumors, tumor visualization was clear 4 h after injection. Oxygen concentration on the tissues affects the uptake of the marker, making it useful for evaluating oxygenation status of some tumors in non-abdominal regions [64].



**HL91**
**28**

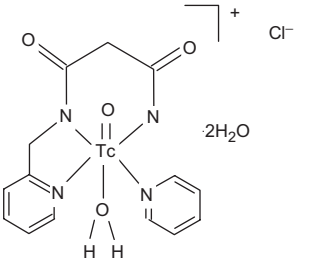


**29**

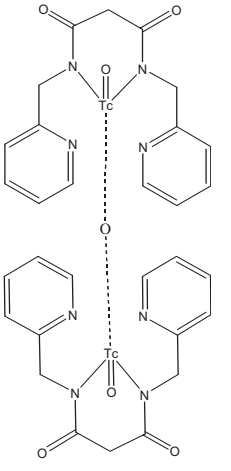
TcO(PnAO-6-R)
R = H, Me, $CH_2CHMe_2$, COOMe, OH, $OCH_3$, OEt, F, CN, NHCOMe

Similar complexes with a $[N_4]$ coordinating core, $^{99m}Tc$ and $^{99}Tc$ complexes of PnAO substituted in the 6-position (PnAO-6-R), **29**, were synthesized [65] by reacting $NH_4[TcO_4]$ with the corresponding PnAO-6-R ligand under reductive conditions at pH ~ 8.5. Only one isomer was obtained when R=H, $CH_2CH(CH_3)_2$. When $R = COOCH_3$, OH, $OCH_3$, $OCH_2CH_3$, F, CN, $NHCOCH_3$ and $NHCOCH_2CH_3$, the *anti* and *syn* species were obtained. An oxo inversion mechanism involving *trans* water attack was proposed for the interconversion process between the two isomers, with the *syn* isomer stabilized in water with respect to the *anti* isomer.

New diamido dipyridino $(N_4)$ water-soluble ligands $\{(2\text{-}C_5H_4NCH_2NHCO)_2CH_2$, $2\text{-}C_5H_4NNHNHCO)_2CH_2$ and $[2\text{-}C_5H_4N(O)CH_2NHCO]_2CH_2\}$ were synthesized and reacted with $^{99g}Tc$-pertechnetate. As a result, the structures $[^{99}TcO(L_1)(H_2O)]^+Cl^-$ (**30**), and $[TcO(L_1)]_2O$, (**31**) ($L_1H_2 = (2\text{-}C_5H_4NCH_2NHCO)_2CH_2$) are formed. Structure (**30**) showed a distorted octahedron with four nitrogen atoms in the equatorial plane and a double-bonded oxygen and a water molecule occupying the apical positions, ascertained by X-ray diffraction [66].

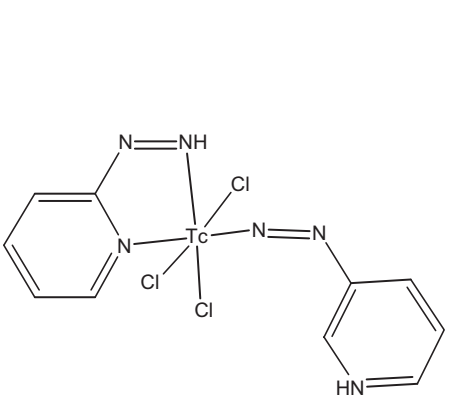


**30**

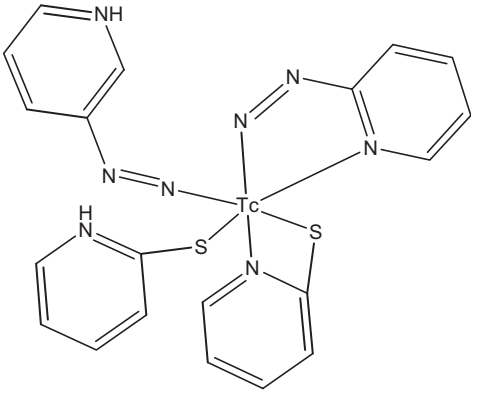


**31**

Reduction of pertechnate (as well as perrhenate and molybdate) with 2-hydrazinopyridine dihydrochloride in methanol led [67] to the preparation of a class of complexes represented by $[TcCl_3(NNC_5H_4NH)(HNNC_5H_4N)]$ (**32**). This compound was used to obtain $[Tc(C_5H_4NS)_2(NNC_5H_4N)(HNNC_5H_4N)]$ (**33**), which is a precursor of $^{99m}$Tc-peptide imaging agents. Such bifunctional hydrazine ligands, used in this work, are effective and versatile linkers for labeling antibodies and protein fragments [68–75].

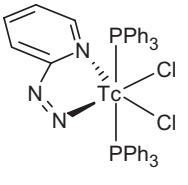



**32**

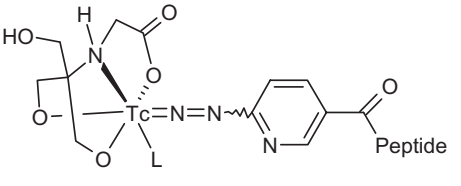



**33**

$[TcCl_2(C_8H_5N_4)(PPh_3)_2]\cdot 0.75C_6H_5CH_3$ and $[TcNCl_2(PPh_3)_2]\cdot 0.25CH_2Cl_2$ were prepared from the reaction of $[TcOCl_4]^-$ and hydralazine hydrochloride ($C_8H_5N_4$) in toluene at room temperature, in the presence of two equivalents of $PPh_3$, or by refluxing them in $CH_2Cl_2$, respectively [76]. A Tc(III) organo-hydrazine complex $[Tc(NNC_5H_4N)(PPh_3)_2Cl_2]$ (**34**), was obtained by reaction of $[Tc(MeCN)(PPh_3)_2Cl_3]$ with 2-hydrazinopyridene (HYPY). Compound **34** can also be obtained by reacting $NH_4[TcO_4]$ and organohydrazona-2-hydrazinopyridine [77].




**34**



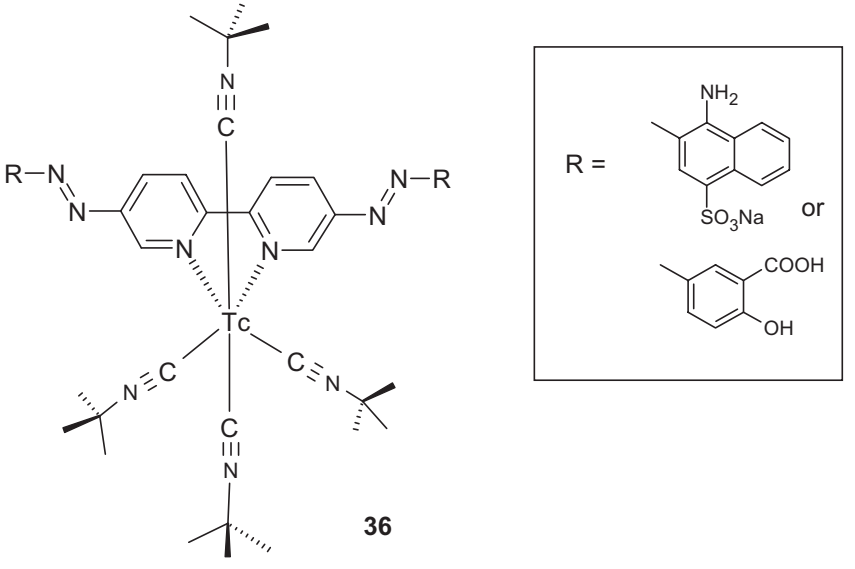

**35**

Compound **34** was also obtained as by-product (together with [Tc(HYPY)-($PPh_3$)(tricine)]) during the preparation of several Tc complexes with hydrazinonicotinamide-conjugated cyclic peptide [HYNICtide = cyclo-(D-Val-NmeArg-Gly-Asp-Mamb(5-(6-(6-hydrazinonicotinamido)hexanamide)))] and HYPY (**35**) (Mamb = *meta*-aminomethyl benzoic acid). The complexes were characterized by various spectroscopic methods. These complexes were developed as potential thrombosis imaging agents [78]. After preparation of a $^{99m}$Tc labeled 6-hydrazinonicotinic acid (HYNIC)-peptide using tricine as coligand, coligand exchange with acetonitrile and other nitriles at room temperature was observed [79]. From this study, it was concluded

than nitriles can act as coligands for HYNIC-conjugated peptides labeled with $^{99m}$Tc and tricine. It was applied for the synthesis of labeled interleukin-8, as an imaging agent for soft-tissue infection [80]. It can be also used for imaging infection and inflammation when conjugated to the leukotriene B4 (LTB4) receptor antagonist (SG380) [79]. The effects on physicochemical properties of the complexes when ternary co-ligands (3-benzoylpyridine, 3-acetylpyridine, 3-nicotinic acid, pyridine) are used, was studied [81]. They can be useful for controlling the pharmacokinetics of $^{99m}$Tc-labeled polypeptides. A $^{99m}$Tc-HYNIC-TNF (TNF = tumor necrosis factor) analog was prepared using ethylenediaminediacetic acid (EDDA) as coligand. The study strongly recommends further research on the potential uses of this analog for tumor (ovarian carcinoma) imaging [82].

Two $^{99}$Tc complexes **36** were synthesized using a bis-diazo ligand (obtained from 5,5′-diamino-2,2′-bipyridine, 4-amino-1-napthalenesulfonic acid and salicylic acid in 58% yield), which is structurally analogous to some reported biphenyl-linked aromatic azo dyes show to have high affinity for amyloid fibres [83]. The synthesized Tc complexes bind *in vitro* to amyloid fibrils, suggesting these compounds may be useful for diagnosis and monitoring of chemotherapeutic strategies related to Alzhheimer's disease (AD).



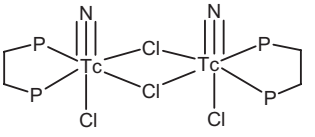



**36**

Similar $^{99m}$Tc complexes with cyclohexylisonitrile, 2-methylcyclohexylisonitrile, 2-methoxyisobutylisonitrile and 3,3,5-trimethylcyclohexyl isocyanide were prepared by ligand exchange reaction of a Cu(I)–cyclohexylisonitrile complex and an appropriate Tc precursor, and its heart and lung uptake were determined in mice. The compound may be suitable for cardiac blood pool imaging, although further studies need to be carried out [84–87].

Tc complexes with the $[Tc^{V}{=}N]^{2+}$ core are more stable in high oxidation states than the corresponding $[Tc{=}O]^{3+}$ (technetyl) complexes and their chemistry is similar to that for a technetyl core. The Tc(V) complex $[TcN(L')(H_2O)] \cdot 2H_2O$ has been synthesized [88] by a substitution reaction of $[TcNCl_2(dppe)_2]_2$ (**37**), with tetra-azamacrocycles L′. Another complex possessing the $[Tc{=}N]^{2+}$ core was obtained using ancillary ligands

such as multidentate ligands having phosphorus and nitrogen atoms. $[TcNBr_4]^-$ reacts with bipy in ethanol to yield a *cis*-octahedral $[TcNBr(bipy)_2]_2[TcBr_4]$ $[Tc{=}N]^{2+}$ core complex containing a tetrahedral tetrabromo technectate(II) dianion [89].

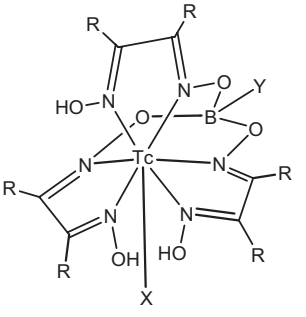



**37**

Binuclear Tc(VI) complexes were obtained by sodium reduction of $Tc(NAr')_3I$ ($Ar' = 2,6$-dimethylphenyl) or $Tc(NAr)_3I$ ($Ar = 2,6$-diisopropylphenyl), resulting in the $Tc_2(NAr')_4(\mu\text{-}NAr')_2$ and $Tc_2(NAr)_6$ complexes with edge-bridged tetrahedral and ''ethene-like'' conformation, respectively [90]. Other binuclear complexes involving Tc(VII) and Tc(V) with the bridging ligand 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (bptz) have been prepared by reacting the pertechnetate ion and the ligand bptz · 2HCl in the appropriate alcohol (X = OMe, OEt) yielding the respective product with general formula $(\mu\text{-bptz})[TcO_3X]_2$ (X = Cl, $OCH_3$, $OCH_2CH_3$). Mononuclear complexes of the ligand 4-phenyl-3,6,-bis(2′-pyridyl)pyridazine (pppz) were also prepared from pertechnetate and $TcOCl_4$ in ethanolic aqueous hydrochloride acid solutions [91].

Diazenido Tc-complexes were obtained by reacting $[TcCl(NNR)_2(PPh_3)_2]$ ($R = -C_6H_4\text{-}p\text{-}Cl$) with bidentate ligands ($L = S_2CNR_2$ and maltol), yielding $[Tc(NNR)L_2(PPh_3)]$ and $[TcCl(NNR)L(PPh_3)]$ in high yield or reacting $[TcO_4]^-$ with arylhydrazine hydrochlorides and $S_2CNR_2$ to give $[TcCl(NNR)_2(S_2CNR_2)_2]$ or with bipy to give $[TcCl(NNR)(bipy)_2][BPh_4]$ [92].

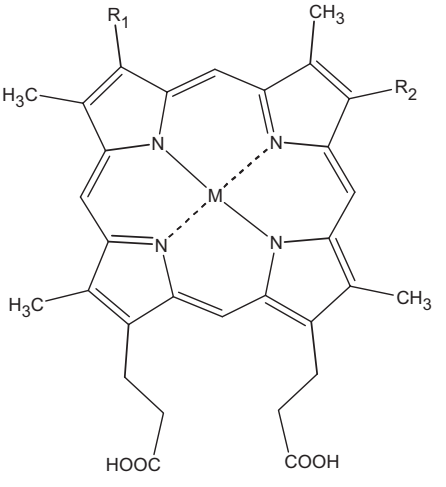
Monocapped boronic acid adducts of Tc(III) with the tris(dioxime) (BATO, boronic acid adducts of technetium dioximes) (X = Cl, Br; dioxime = dimethylglyoxime, cyclohexanedione dioxime; $R = CH_3$, $C_4H_9$) ligand have been prepared [93, 94] by template synthesis starting with $[NBu_4][TcOCl_4]$ or $M_2[TcX_6]$ (M = $NH_4$, K; X = Cl, Br) and stannous ion, yielding seven-coordinate monocapped BATO complexes, **38**. A similar study was performed using methaneboronic acid [94]. It was also observed that reaction of $BCl_2Ph$ or $BH_3ATHF$ with $[TcNCl_2(Me_2PhP)_3]$ generates the corresponding nitride–boron adducts, where the Tc and B atoms are bridged by the nitride group [95]. The compounds are unstable and decomposed at room temperature with cleavage of the N–B bonds.




X = Br, Cl
Y = $CH_3$, n-Bu
R = $-CH_2-CH_2-$, $CH_3$

**38**

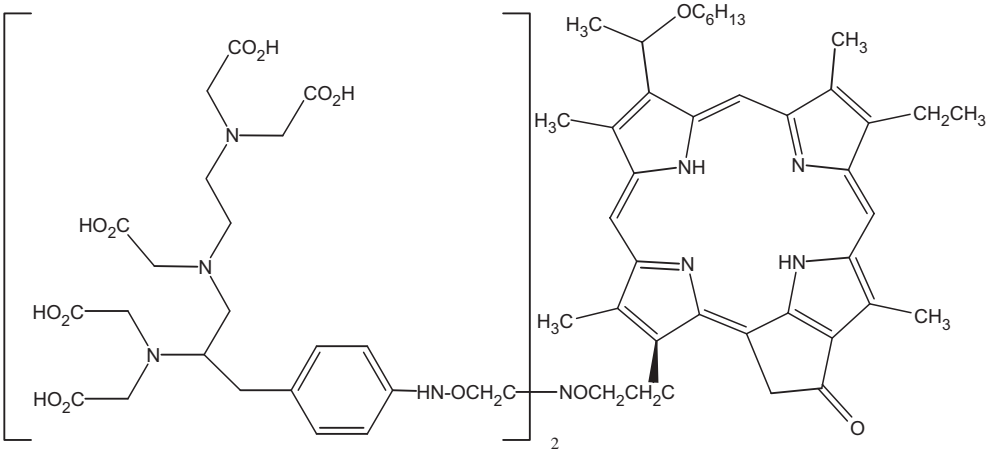
Metal porphyrin complexes **39** carrying radioactive metals, in particular technetium, for bone marrow scintigraphy were reported [96]. The porphyrin was mixed with a physiological saline solution containing Na pertechnetate ($^{99m}$Tc) to give the corresponding $^{99m}$Tc derivative, which gave clear scintigraphic images 5 min, 1 h or 3 h after administration to humans and showed >80% retention in blood 24 h after administration and no adverse effects.




**39**



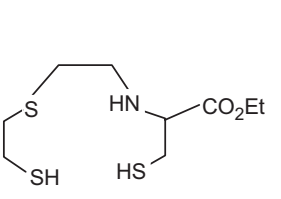
Another Tc macrocyclic complex with porphyrin-type ligand **40**, chlorin and bacteriochlorin-based difunctional aminophenyl DTPA and $N_2S_2$ conjugates was reported [97] for magnetic resonance (MR) contrast media and radiopharmaceuticals, intended for use on MR imaging and photodynamic therapy treatment of tumors and other hyperproliferative tissue.



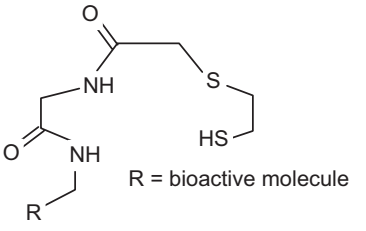

**40**

## 2.4. *Complexes with N,S-containing ligands*

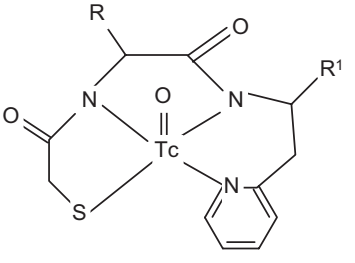
There are three basic classes of $N_xS_{(4-x)}$ chelates: general $N_xS_{(4-x)}$ bifunctional tetradentate chelates with ligands **41** and **42**, complexes with peptide-based ligands **43**, and "3 + 1" class of tridentate and monodentate thiol-containing ligands **44**. The unifying feature in these ligand systems is that all contain thiol groups for coordination to the Tc center and all are used to form Tc(V) mono–oxo complexes [9].



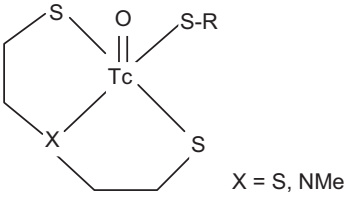

**41**




**42**



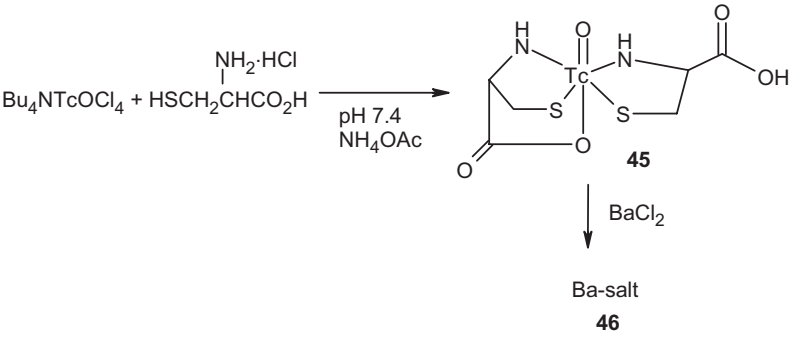

**43**




**44**

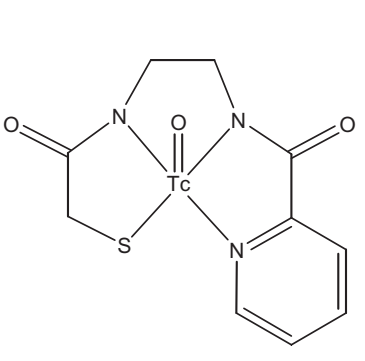
R = H, Me, $CH_2CH_2OH$, $CH_2CH_2COOH$;
$R^1$ = H, COOH

Tc complexes with a $N_2S_2$ moiety seem to be the most common. Thus, sulfur coordinated nitrido and oxo complexes have shown promising myocardial uptake in humans and may be useful as heart imaging agents. Important Tc complexes for biology and medicine, $HTcO(cysteine)_2$ (**45**) and its barium salt $Ba[TcO(cysteine)_2]_2$ (**46**), were prepared and characterized [98].



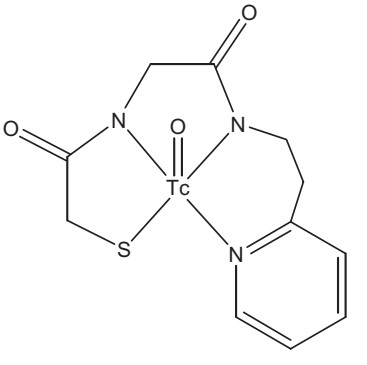
The same products can be obtained from $NH_4TcO_4$ as a precursor and cysteine. Earlier attempts to obtain Tc complexes with cysteine always resulted in the formation of a product contaminated with polymeric species [98]. Other attempts to chelate Tc with polyfunctional ligands that were accompanied by formation of undesired products have also been reported [99–103]. For example, the reaction of $(Bu_4N)[TcOCl_4]$ in methanolic solution with $H_2$pic(acm) [$H_2$pic(acm) = *N*-(2-((2-(((acetylamino)-methyl)thio)acetyl)amino)ethyl)-2-pyridinecarboxamide; pic = 4-picoline; acm = *S*-acetaminomethylaminothioacetal] or $H_2$pyr(Bzm) [$H_2$pyr(Bzm) = *N*-(2-(2-pyridinyl)-ethyl)-*N*′-(2-(((benzoylamine)methyl)thio)-acetyl)glycinamide; pyr = pyridine; Bzm = (benzoylamino)methyl] yields [99] complexes [TcO(pic)] (**47**) and [TcO(pyr)] (**48**). It was postulated that the presence of excess ligand has a degrading effect on the chelate initially formed. This can be avoided by using suitable S-protecting groups (for example: benzyl, acetyl aminomethyl and benzoyl amino methyl) that can undergo metal-induced deprotection, thus avoiding the presence of excess thiolate in the chelate mixture [98]. The $^{99m}$Tc analog of oxorhenium bis-cysteinate has important biological properties, in particular it can be fixed into the kidney [104], which is useful for the diagnosis of the morphological status of that organ [98]. Reaction of cysteine with $^{99m/99}$Tc in a freeze-dried kit, generated the corresponding cysteine complex, which was tested as a renal functional imaging agent [105]. A new $^{99m}$Tc labeled lyophilized single component kit of *N*,*N*′-ethylene-1-dicysteine (EC) for renal imaging, was developed to replace a commercially available multiple step kit; it was done by carefully varying key parameters such as pH, concentration of reducing agents and stabilizers and additives [106].






[TcO(PIC)]

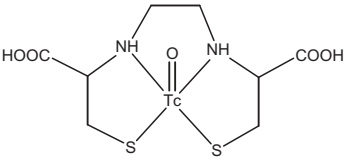
**47**




[TcO(PYR)]

**48**

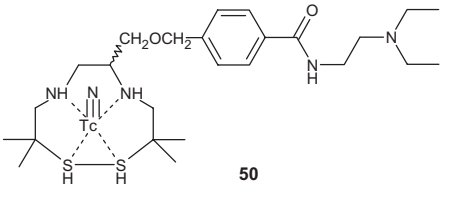
Chelate ligands containing *N*- and S-centers have been used to synthesize potential radiopharmaceuticals for diagnosis of renal function. Carboxylic groups in the ligands favor renal uptake of these compounds. Synthesis from the corresponding ammonium tetrahalo-metal oxo precursors $(NH_4)[TcOX_4]$ and the ligand (2R,7R)-2,7-dicarboxy-3,6-diaza-1,8-octanedithiol ($ECH_3$) yields [107] the $^{99}TcO(ECH_3)$ complex **49**. Unexpected coordination of one of the carboxylate groups *trans* to the oxo-ligand was observed for the Re(V) analog [107].




**49**

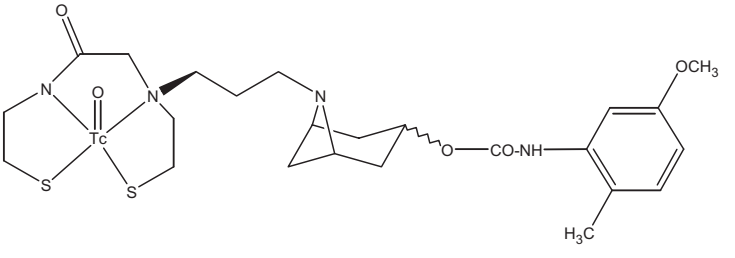
Radioiodobenzamides are the best-known agents under study for the diagnosis of cutaneous melanoma and its metastases. The synthesis of a new BAT derivative radiopharmaceutical in which radioiodine is replaced by $^{99m}$Tc was reported [108]. The cyclic intermediary methyl 4-[3-(4,4,7,7-tetramethyl-5,6-dithia-2,9-diazacyclodecyl)-2-oxapropyl]benzoate occurred in two different conformations identified by spectroscopic analysis. The final BAT ligand was radiolabeled using the nitridotechnetium core by a ligand-exchange reaction. After macroscopic $^{99}$Tc synthesis, *syn* and *anti* isomers **50** were identified.

$^{99g}$Tc complexes containing the *N*-(dialkylaminoalkyl)benzamide fragment were synthesized and evaluated for melanoma uptake. Complexes containing the ligand 4-(S-benzoyl-2-thioacetyl-glycyl-glycylamido)-*N*-(2-diethylaminoethyl)benzamide displayed the highest melanoma uptake [109].




**50**

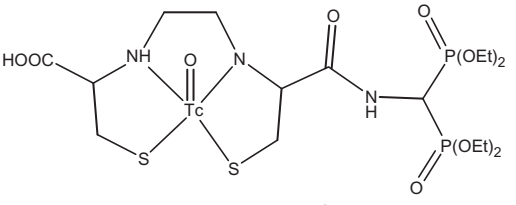
Compound **51**, structurally similar to **50** but containing a bulkier group at $R_1$, has been synthesized and tested as an imaging agent for the sigma-2-receptor status of breast tumors, using single photon emission computed tomography (SPECT) [110]. SPECT clinical efficacy for diabetic foot infection diagnosis in conjunction with Tc-methylene-diphosphonate scintigraphic agents was evaluated in other work, indicating that it is an efficient method for precise diagnosis of osteomyelitis in diabetics [111]. The reaction of $[Bu_4N][^{99m}TcNCl_4]$ with the KYCAR (lysyl-tyrosyl-cystyl-alanyl-arginine) ligand produced a novel nitride Tc complex, which was characterized by NMR and IR spectroscopy. The new complex has a square-pyramidal structure with two KYCARs coordinated to the Tc atom through both an N and a deprotonated S atom of cysteine [112].




**51**

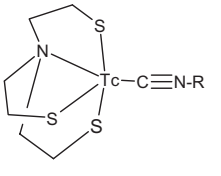
A $^{99m}$Tc complex with a similar chelating core [$N_2S_2$], a derivative of tamoxifen bridged through an amide linker, was synthesized by reacting the ligand and $[TcO_4]^-$ in the presence of sodium acetate [113]. Both the *Z* and *E*-tamoxifen Tc complexes were obtained in good radiochemical yields. *In vivo* and *in vitro* evaluation indicated limited estrogen receptor binding, suggesting that they have some potential for use as breast cancer imaging agents. In the same fashion, two ester-modified $^{99m}$Tc(O)[SN(R)S/S] mixed-ligand complexes, from a $^{99m}$TcO[$C_2H_5OOCCH_2N(CH_2CH_2S)_2$][$SC_6H_4CH_3$] mono-ester compound carrying an Et ester group on the tridentate ligand and the diester compound carrying a second Et ester group on the monodentate ligand {$^{99m}$TcO[$C_2H_5OOCCH_2N(CH_2CH_2S)_2$][$SC_6H_4COOC_2H_5$]}, have been synthesized and evaluated as brain imaging agents [114].

A conjugate **52** of the new renal tracer agent $^{99m}$Tc-EC, covalently bound *via* one of its carboxylates with $H_2$AMDP (AMDP = aminomethylenediphosphonate) was synthesized in seven steps. This study was performed in order to develop better Tc-diphosphonate agents with efficient bone uptake as bone tracers with fast clearance from soft tissues. The new agent showed good quality bone scans, with clear visualization of the skeleton and low soft tissue activity at response times of 1 and 2 h after injection [115].




**52**

A bombesin derived peptide-$^{99m}$Tc chelate complex with a similar chelating moiety to **50** was prepared using a new solid phase synthetic methodology [116]. The desired product was isolated and characterized by NMR spectroscopy. The new methodology could facilitate application of modern drug discovery techniques for the development of new receptor selective Tc radiopharmaceuticals.



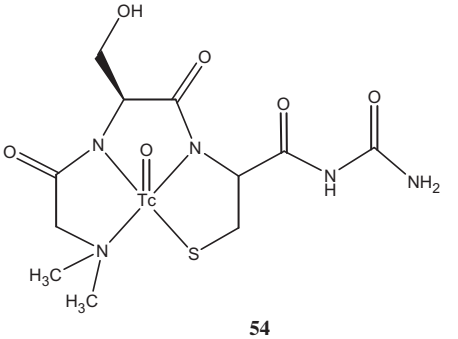

**53**

A series of neutral mixed-ligand Tc(III) complexes of general formula [Tc($NS_3$)(CNR)] (**53**), were synthesized starting from the tripoidal ligand 2,2′,2″-nitrilotris(ethanethiol) ($NS_3$) and isocyanides (CNR) as coligands. The complexes were obtained [117] by a two-step reduction/substitution process from $[TcO_4]^-$. Biodistribution in rats indicates that the compound is lipophilic and has significant brain uptake. No transchelation occurred in the presence of glutathione, so the compound may be useful in the design of new potential lipophilic radiopharmaceuticals.

Complexes where the ligands are biologically important molecules (such as peptides, proteins or antibodies) can have unique application for target-specific

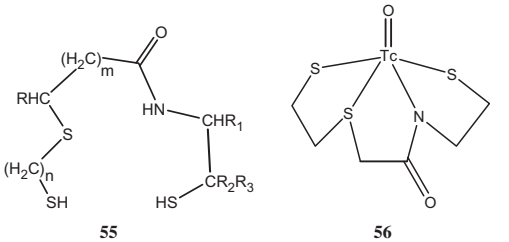
diagnostic radiopharmaceuticals. The reaction of $[TcO_4]^-$ with $SnCl_2$, sodium gluconate and RP294 produced the $^{99}$Tc(V) oxo RP294 complex **54** which exists as the *syn* and *anti* isomers. Crystallographic resolution of the isostructural Re(V) complexes shows that the serine $CH_2OH$ group confers the isomery. The isomers interconvert in solution at room temperature. The $^{99m}$Tc and Re RP294 complexes have similar chemical behavior [118]. An 11-aminoacid neuropeptide of the tachykinin family was labeled with $^{99m}$Tc for imaging SP receptors for inflammatory diseases and neoplasms diagnosis. High specific activity was found when using the 1-imino-4-mercaptobutyl group as a bifunctional chelator [119]. Although macroaggregated albumin has been widely used, a recent report assures higher radiolabeling efficiency (> 98.5%) using a simple procedure [120]. Thus, 85% methanol was used as the mobile phase in paper and ITL chromatography with Whatman #1 and ITLC-SA strips. A system of two solvents (acetone and 1 M NaCl or 0.9% NaCl) was used for 3 MM paper, ITLC-SA and ITLC-SG strips and silica gel plates as the stationary phase. Low-voltage paper electrophoresis with Whatman 3 MM paper sheets soaked in barbiturate buffer and the gel chromatography column method (Sephadex G-25) were also applied.






**54**

The $^{99}$Tc and $^{99m}$Tc complexes with new tetradentate $NS_3$ ligands have been synthesized by refluxing MeOH solutions of the Tc(V) precursor $[TcOCl_4][NBu_4]$ with the appropriate $NS_3H_3$ ligands **55** (table 3) to form Tc(V) species $[TcO(NS_3)][NBu_4]$, such as **56**, in good radiochemical yields. However, the compounds decompose over a period of hours or days. Crystal structures of the analogous Re oxo-complexes indicate that the compound can be considered as a square pyramidal complex with the oxygen at the apical position [121].



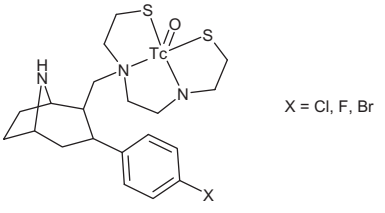

**55** **56**

A series of $^{99m}$Tc labeled tropane systems, **57**, containing bis-(aminoethanethiol) as the neutral complexing moiety were prepared by stepwise reactions adding two aminoethanethiol units and a final deblocking of the 4-methoxybenzyl protecting group with $Hg(OAc)_2$ to obtain free thiol ligands [122]. The biological activities

Table 3. $H_3NS_3$ ligands used [121].

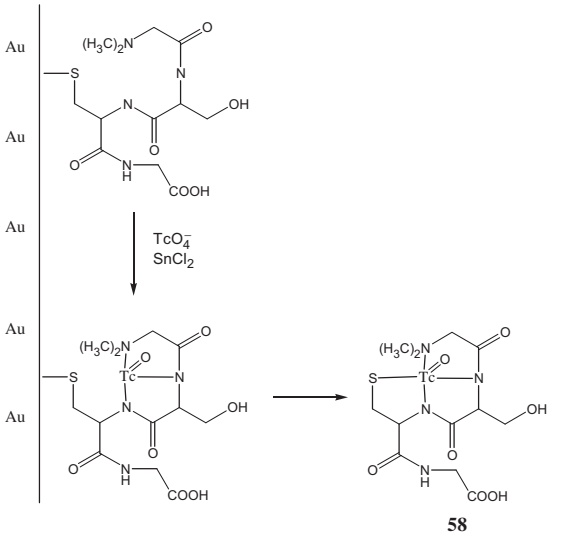
| $H_3NS_3$ ligands | *m* | *n* | $R_1$ | $R_2$ | $R_3$ | R |
|---|---|---|---|---|---|---|
| $H_3L^1$ | 0 | 2 | H | H | H | H |
| $H_3L^2$ | 0 | 3 | H | H | H | H |
| $H_3L^3$ | 1 | 2 | H | H | H | H |
| $H_3L^4$ | 0 | 2 | $CO_2Et$ | H | H | H |
| $H_3L^5$ | 0 | 2 | H | $CH_3$ | $CH_3$ | H |
| $H_3L^6$ | 0 | 2 | H | H | H | $CH_3$ |
| $H_3L^7$ | 0 | 2 | H | $CH_3$ | $CH_3$ | $CH_3$ |
| $H_3L^8$ | 0 | 2 | H | H | H | $C_6H_5$ |
| $H_3L^9$ | 0 | 2 | H | $CH_3$ | $CH_3$ | $C_6H_5$ |
| $H_3L^{10}$ | 0 | 2 | H | H | H | H |

of two diasteromers of [$^{99m}$Tc]TRODAT-1 as an imaging agent for the central nervous system (CNS) were examined. The isomers were separated by high performance liquid chromatography (HPLC) and display different binding affinities toward dopamine transporters and distinct properties of localization in the striatum area of the brain [123].



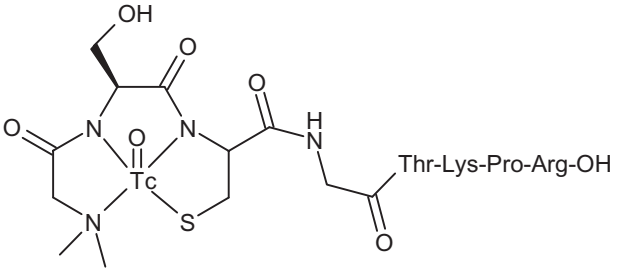

**57**

A method to prepare Tc labeled agents in high specific activity formulations using a solid supported metal chelator **58** has been developed [124]. The use of a gold surface for the attachment of the chelator has several advantages over other solid supported systems, such as easy cleaning and sterility of the surface. The method has good potential to be used in the production of radiopharmaceuticals.



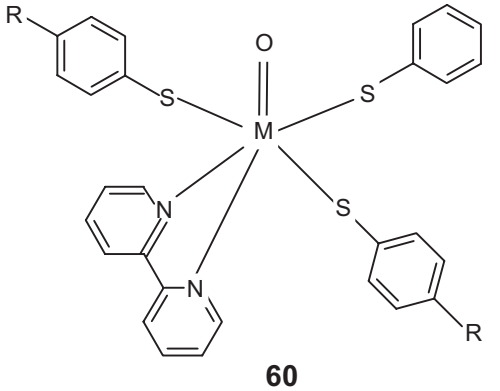

**58**

A Tc(V) complex, **59**, of dimethylglycyl-L-seryl-L-cystyl-glycyl-L-threonyl-L-lysyl-L-prolyl-L-arginine (RP128) was prepared by reacting the deprotected ligand and $NH_4[TcO_4]$ in dry pyridine. The complex was analyzed by NMR and both the *syn* and *anti* isomers were detected. This oxo complex is a potential tuftsin receptor targeting agent [125].




**59**

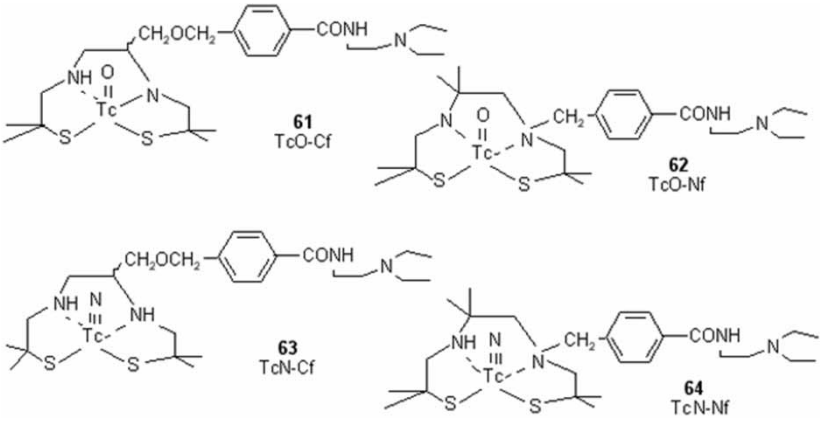
$^{99}$Tc and $^{99m}$Tc complexes **60** from the 2,2′-bipyridine/thiol mixed-ligand system were recently reported [126]. Other Tc(V) chelate complexes with $N_2S_2$ ligands were obtained by the reaction of $[TcNCl_2(PPh_3)_2]_2$ with $HSCR_2CH_2NR'CH_2CH_2NR'CH_2CR_2SH$ (R = Me, Et and R′ = Me, Et) producing the corresponding chelate complex containing the $[Tc{=}N]^{2+}$ core [127]. Similar chemistry of $Mo^{V}O$ and $Tc^{VI}N$ cores has been explored, and mixed ligand complexes such as $[\{TcN(S_2CNEt_2)\}_2(\mu\text{-}O)_2]$, $[\{TcN(S_2CNC_4H_8)\}_2(\mu\text{-}O)_2]$, $[AsPh_4]_2[\{TcN(CN)\}_2(\mu\text{-}O)_2]$ and $[AsPh_4]_2$-$[\{TcN(edt)\}_2(\mu\text{-}O)_2]$ were obtained by reaction of $[\{TcN(OH_2)_3\}_2(\mu\text{-}O)_2]^{2+}$ or $Cs_2[TcNCl_5]$ in $Na_4P_2O_7$ solution with the appropriate ligand [128].



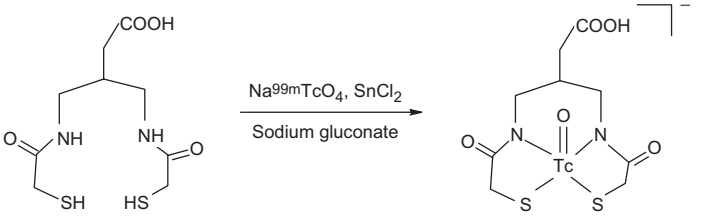

(a) M = $^{99}$Tc, R = Me
(b) M = $^{99}$Tc, R = OMe
(c) M = $^{99m}$Tc, R = Me
(d) M = $^{99m}$Tc, R = OMe

**60**

Four different bis(aminothiol) derivatives **61**–**64** with different octanol/water partition coefficients have been synthesized. The most lipophylic complex **61** TcO-Cf exhibits the highest specificity for the tumor, with a regular increase of its tumor-to-organ ratios with time. The same biological behavior was not previously reported with other $^{99m}$Tc complexes of the same pharmacophore group [129].

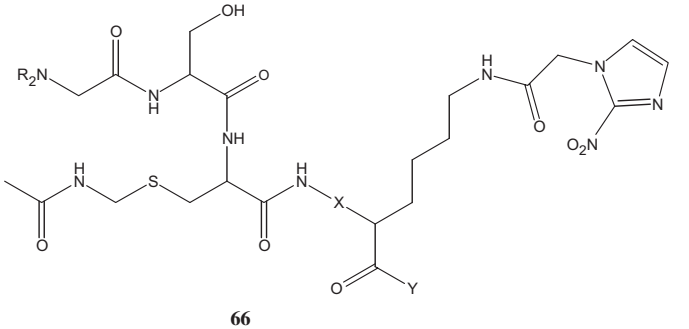



An $N_2S_2$ bifunctional chelator **65** was prepared bearing an $N_2S_2$ core for binding Tc and a carboxylic acid group for conjugation to amino groups of biomolecules. Its $^{99m}$Tc complex was isolated at the tracer level by reaction of the ligand with $^{99m}TcO_4^-$, tin(II) chloride and sodium gluconate, giving a mixture of two isomers, but showing a preference for the *anti* isomer [130].

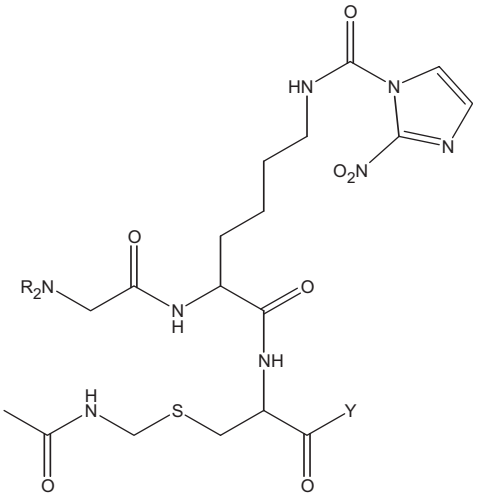



**65**

Among various Tc complexes and their precursors with moieties different from $N_2S_2$, the following compounds have been reported. Two novel peptidic $N_3S$ ligands, **66** and **67**, ($R = CH_3$–, $C_6H_5$–, $-(CH_2)_5$–; X = gly, val; Y = gly acid, dibenzylamide, amide, acid) containing 2-nitroimidazole groups were developed and their chelating properties toward $^{99m}$Tc studied. The chelators were prepared by automated solid-phase peptide synthesis and labeled by transchelation from [$^{99m}$Tc]gluconate at a range of temperature of 22–100°C [131].

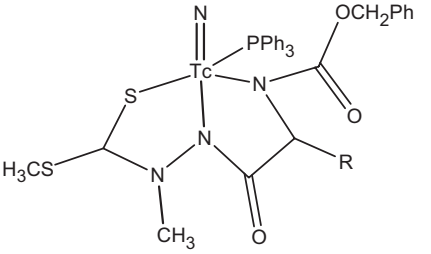


**66**



**67**

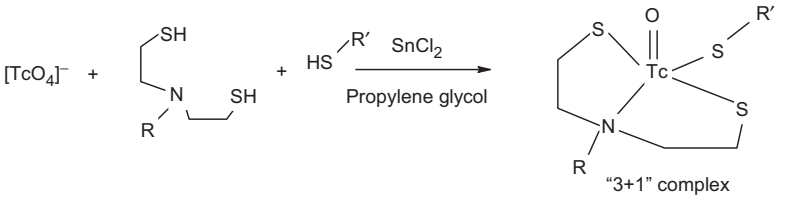
Tc-nitrido complexes with *N*-protected aminoacid derivatives of 2,5-dimethyldithiocarbazoic acid (Hdtc) were reported [132] as compounds for radiopharmaceutical applications. A series of five complexes $[TcN(L^n)(PPh_3)]$ (**68**) [where $L^n =$ z-Gly-dtc ($n = 1$), z-Ala-dtc ($n = 2$), z-Phe-dtc ($n = 3$), z-Val-dtc ($n = 4$) and z-Leu-dtc ($n = 5$)], was synthesized and characterized by spectroscopical methods and X-ray crystallography.



R = -H, $-CH_3$, $-CH_2C_6H_5$,
$-CH(CH_3)_2$, $CH_2CH(CH_3)_2$

**68**

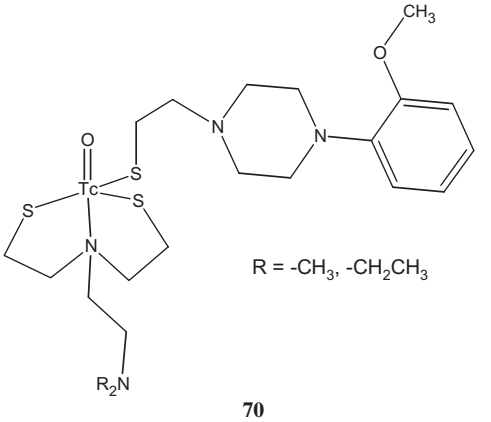
Complexes of oxotechnetium(V), one tridentate ligand, and an additional monodentate thiolato ligand, the so called "3 + 1" mixed-ligand system, mentioned at the beginning of this section, have been extensively studied for the labeling of biomolecules [5]. Complexation of $^{99m}Tc$ with a mixture of *N*-R(3-azapentane-1,3-dithiol) [R = Me, Pr, Bn, $Et_2N(CH_2)_2$] and *N*-(2-dialkylamino)ethanethiol (alkyl = X = Et, Bu, morpholinyl] using $Sn^{2+}$ as reducing agent resulted in the formation of mixed ligand $NS_3$ complexes $[Tc(O)(SN(R)S)(SNX_2)]$ (**69**), with high radiochemical yield (60–98%). *In vivo* evaluation suggests that small Tc complexes could be useful as melanoma-imaging agents [133].




**69**

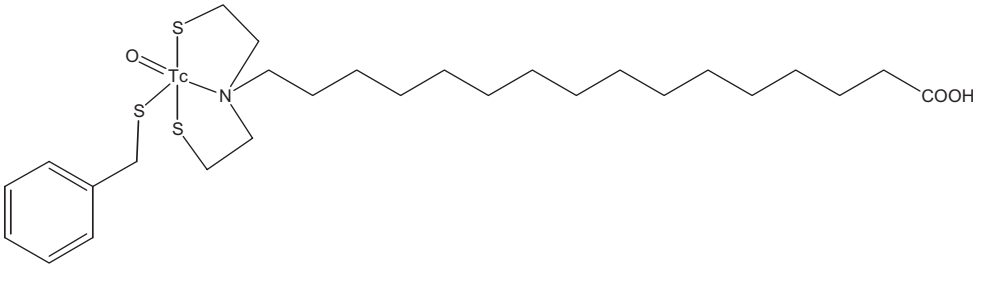
A "3 + 1" complex of Tc and a $S_3$ chelating ligand and dopamine was synthesized and tested as dopamine transporter imaging agent. Biodistribution in mice demonstrate that the compound can penetrate the blood brain barrier (1.03%/g) at 5 min after injection [134]. Two more "3 + 1" complexes bearing the 1-(2-methoxyphenylpiperazine) moiety, $TcO[((CH_3)_2CH)_2NCH_2CH_2N(CH_2CH_2S)_2][o\text{-}CH_3OC_6H_4N(CH_2CH_2)_2NCH_2CH_2S]$ and $TcO[(CH_3CH_2)_2NCH_2CH_2N(CH_2CH_2S)_2][o\text{-}CH_3OC_6H_4N(CH_2CH_2)_2NCH_2CH_2S]$ (**70**), were prepared, by using $^{99m}$Tc-glucoheptonate as precursor [135].





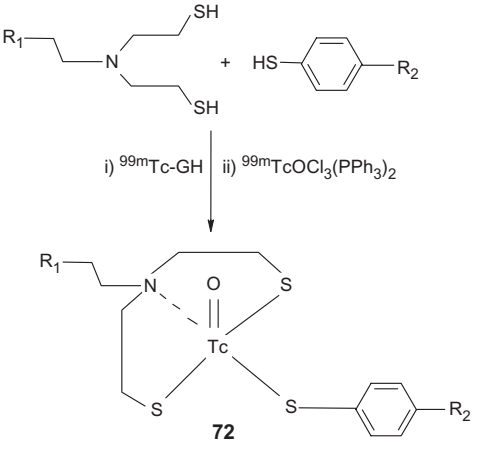

**70**

Studies in mice showed the ability of the complexes to cross the intact blood-brain barrier. This "3 + 1" design was also exploited for the preparation of two series of compounds incorporating fatty acid components. The complex $[TcO\{\eta^3\text{-}(SCH_2CH_2)_2N(CH_2)_{15}CO_2H\}\{\eta^1\text{-}SCH_2C_6H_5\}]$ (**71**), was isolated; its biodistribution in heart and blood indicated that it was not useful for heart imaging applications [136].



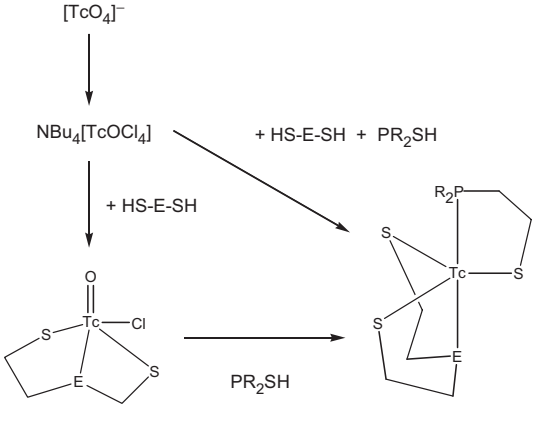

**71**

Two series of [$^{99m}$Tc](SNS/S) mixed-ligand complexes **72** each carrying the *N*-dimethylaminoethyl or the *N*-ethyl-substituted bis(2-mercapthoethyl)amine ligand (SNS) were produced at tracer level using tin chloride as reductant and glucoheptonate as transfer ligand. The elucidation of brain retention mechanism of these complexes has revealed the potential of the SNS/S mixed-ligand system in diagnosis of several pathologies interfering with intracellular glutathione (GSH) levels [137].




**72**

Novel mixed-ligand Tc(III) complexes, [Tc($SCH_2CH_2$-E-$CH_2CH_2S$)($PR_2S$)] (**73**) (E = S, N($CH_3$); $PR_2S$ = phosphinothiolate with R = aryl, alkyl) were described [138]. These "3 + 2"-coordination complexes can be prepared in a two-step reduction/substitution procedure *via* the appropriate chloro-containing oxotechnetium(V) complex [TcO(SES)Cl] {E = S, N($CH_3$)}. The substituents at the bidentate P, S ligand significantly influence the biodistribution pattern. Remarkable differences are observed especially in brain, blood, lungs, and liver. All the complexes are able to penetrate the blood-brain barrier of rats and showed a relatively fast washout from the brain.

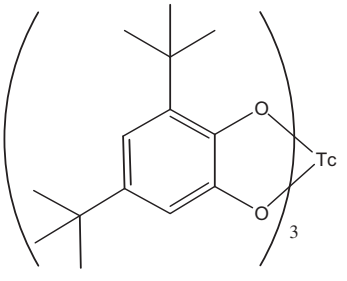



I. E = S
II. E = N-$CH_3$
R = $C_6H_5^-$, $C_6H_{11}^-$, $CH_3^-$

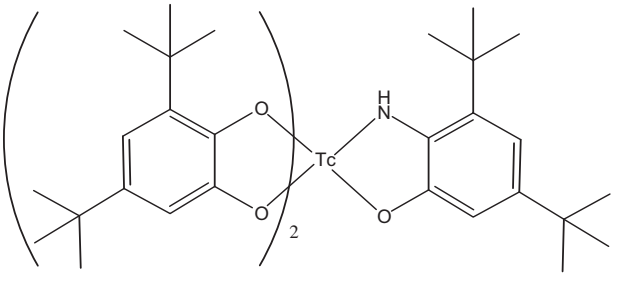
**73**

### 2.5. *Complexes with O-containing ligands*

It has been known for a long time, that a mixture of $\{Tc^{VI}(DBCat)_3\}$ (**74**) and $\{Tc^{VI}(DBCat)_2(DBAP)\}$ (**75**) (DBAP = di-*tert*-butylamidophenolate) is produced by the reaction of 3,5-di-*tert*-butylcatechol (DBCat) and ammonium pertechnate in MeOH [139]. Schiff-base condensation of ammonia (from ammonium) and the catechol is responsible on the formation of the di-*tert*-butylamidophenolate (DBAP) ligand. Electron paramagnetic resonance (EPR) spectroscopy and X-ray crystallographic data are consistent with a Tc(VI) complex, the least common oxidation state of Tc. The catecholate ligand serves as both a reducing and a chelating agent.

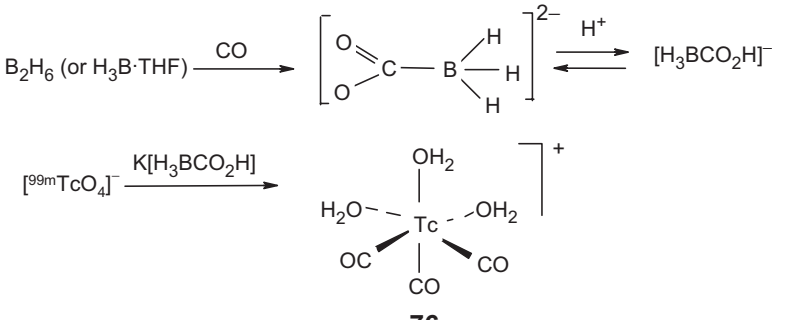



**74**




**75**

Functionalization of biologically relevant molecules for labeling with the *fac*-$[^{99m}Tc(OH_2)_3(CO)_3]^+$ precursor **76** has gained considerable attention lately. This precursor was obtained [5, 6] by direct reduction of pertechnetate with sodium borohydride in aqueous solution in the presence of CO, readily undergoing ligand exchange reactions with a variety of chelators. Another scheme for obtaining **76** from $[^{99m}TcO_4]^-$ is as follows [140]:

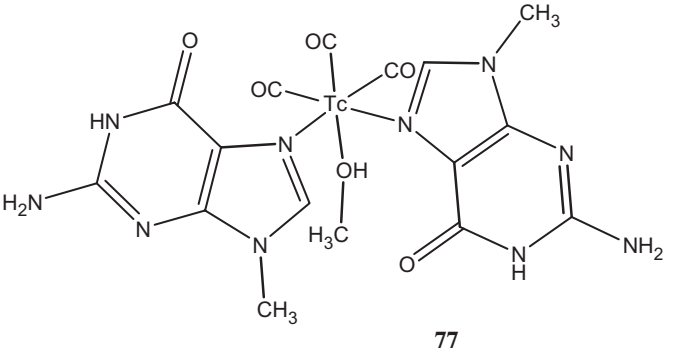



**76**

The compound $[H_3BCO_2]^{2-}$ combines the possibility of *in situ* CO formation and reducing properties (moderately powerful reducing agent). As will be shown later, complex **76** is widely used as a precursor for a series of Tc complexes, in particular with cyclopentadienyl ligands (see section 2.9). Also, this potential labeling agent may be useful in the preparation of several radiopharmaceutical imaging agents for nuclear medicine [141, 142]. The rate constant of ligand exchange for this complex

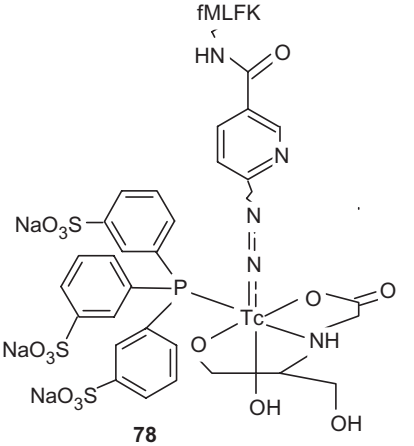
has been determined by means of multinuclear NMR spectroscopy under pressurized conditions in aqueous media [143]. The basic aqueous chemistry of this complex for radiopharmaceutical applications has been reviewed before [144]. Reactivity toward a bifunctional ligand was tested, obtaining a picolinamine-*N*,*N*-diacetic acid (PADA) complex in good yields, where the water ligands have been easily exchanged with the PADA ligand [141]. Preliminary work on the use of this precursor with ligands in bioorganometallic chemistry was performed using several ligands containing *N*,*N*-coordinating functionalities, which were designed for binding to the hypothalamic serotonergic receptors (5-HT1A) in the CNS [145].

Seven different tridentate (hidstidine, inimodiacetic acid, *N*-2-picolylamineacetic acid, *N*,*N*-2-picolylaminediacetic acid) and bidentate (histamine, 2-picolinic acid, 2,4-dipicolinic acid) ligand systems were tested with precursor **76**, allowing mild radiolabeling conditions (30 min, 75°C) and yields higher than 95% of the corresponding organometallic complexes [146]. Complexes with bidentate ligands showed significantly higher retention times in liver, kidneys and blood, compared to those with tridentate ligands. Similar work has been reported for bidentate ligands and their *in vivo* and *in vitro* evaluation, using water-soluble phosphine ligands as anchor groups [147]. In other work, glucose and 2-deoxyglucose were derivatized to generate transition metal complexes ($^{99m}$Tc and Re) at position C-1 in high yields. The products are water-soluble and water-stable, and the coordination was verified using one-dimensional (1D) and two-dimensional (2D) $^1$H NMR spectroscopy, mass spectroscopy and IR spectroscopy. The products have excellent stability both in physiological conditions (pH 7.4, phosphate buffer) and in human plasma (24 h at 37°C). Potential uses in diagnostic nuclear medicine were investigated [148]. The precursor was also involved in the synthesis of the complex $[Tc(CO)_3(TBI)_3]^+$ (TBI = *t*-butyl-isonitrile) with yields higher than 90%. The product is stable over 6 h at room temperature, and is well accumulated and maintained in the heart after injection in normal mice (after 5 and 60 min post-injection time, (19.07 ± 0.81)%(ID/g) and (18.24 ± 2.41)%(ID/g) uptakes were determined), making this compound a promising myocardial imaging agent [149]. $[^{99m}Tc(OH_2)_3(CO)_3]^-$ was reacted with 9-methylguanine (9-MeG), (yielding $[^{99}Tc(CH_3OH)(9\text{-MeG})_2(CO)_3]^+$ (**77**)), and also with guanosine (G) and 2′-deoxyguanosine (2dG), in order to study the reaction of this precursor with DNA bases. The purine bases are coordinated to the metal center through the N-7 atoms. Kinetic studies indicated that the rates of substitution of those bases in solution are comparable to that of one of the active forms of cisplatin [150].




**77**

Among other technetium oxygen-containing complexes with a mixed-ligand environment, the electronic structure of a binuclear technetium chloroacetate cluster $Tc_2(CH_3COO)_4Cl$ was elucidated [151]. As a result, formation of a polymeric chain $[Tc_2(CH_3COO)_4Cl]_n$ was suggested instead of isolated ions $[Tc_2(CH_3COO)_4^+ \cdots Cl^-]$. A stabilized $^{99m}Tc$ complex RP463 **78** of a hydrazine nicotinamide derivatized chemotactic peptide for infection imaging was reported [152].

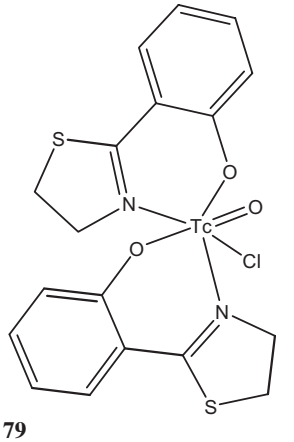



**78**

RP463

(fMLFK is a derivative of N-formyl-methionyl-leucyl-phenylalanine)

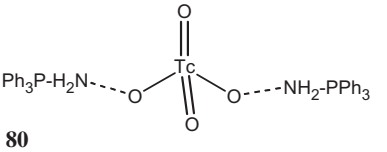
The reactions of $[NBu_4][TcOCl_4]$ with naturally occurring oxazoline and thiazoline ligands [HL = 2-(2′-hydroxyphenyl)-2-oxazoline, 2-(2′-hydroxy-3-mehtylphenyl)-2-oxazoline, 2-(2′-hydroxyphenyl)-2-thiazoline and 2-(2′-hydroxyphenyl)-2-benzoxazoline] yield the hexacoordinate complexes $TcOClL_2$ (**79**) in refluxing alcoholic solutions (MeOH, EtOH) [153].




**79**

Finally, a presumed hydrogen bonding network between a phosphinimine and technetium(VII), $[Ph_3P{=}NH_2]^+[TcO_4]^-$ (**80**), was reported [154]. Although the authors

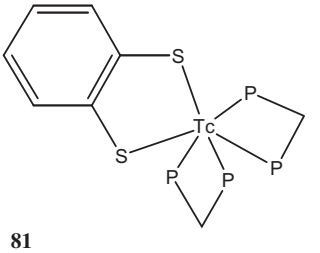
report strong hydrogen-bond interactions among the $[TcO_4]^-$ units and the phosphin-imine fragments, no neutron diffraction data were presented (just X-ray diffraction data), so electrostatic interactions may be assumed as the main force holding the three-dimensional (3D) structure together.




**80**

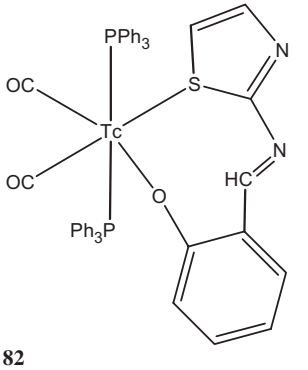
## 2.6. *Complexes with S-containing ligands*

Among compounds with sulfur-poor ligands, $S_2$–thiolato–Tc(IV) complexes can be obtained [155] by reduction of $[Tc(OH)O(dmpe)_2]^{2+}$ in excess of 3,4-toluendithiol ($H_2tdt$) yielding $[Tc(tdt)(dmpe)_2](PF_6)$ (**81**), [dmpe = bis(dimethylphosphino)ethane]. The product was characterized by spectroscopical methods and X-ray diffraction. The coordination geometry around the Tc atom is intermediate between octahedral and trigonal prismatic [Tc–S, 2.318(6) Å, S–Tc–S bite angle 84.49(4)°, Tc–P, 2.902(7) Å].



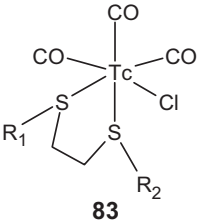

**81**

A Tc(I) complex was synthesized by reacting $[Tc(PPh_3)_2(CO)_3Cl]$ with the lithium salt of the Schiff base *N*-orthohydroxybenzyl-idene-2-thiazolylimine in boiling tetrahydofuran (THF) to yield $[Tc(PPh_3)_2(CO)_2\{(C_3H_2NS)N{=}CHC_6H_4O\}]$ (**82**). The chemistry of Tc(I) complexes is relatively unexplored and only a few examples are fully characterized and identified. This compound has a six-coordinated distorted octahedral geometry, with *trans*-$PPh_3$, *cis*-CO groups and one chelate bidentate anion [156].




**82**

Four dithioether tricarbonyl complexes **83** of the rarely exploited $^{99m}$Tc(I) have been synthesized from $[^{99m}Tc(H_2O)_3(CO)_3]^+$ in good yields. They have advantages over Tc(V) analogous complexes, as resistance to transchelation or ligand exchange is increased, making them better candidates for CNS receptor imagining [157]. The same complexes were also studied by extended X-ray absorption, fine structure (EXAFS), spectroscopy in solution, in order to estimate the structural parameters of the complexes and their reaction products [158].

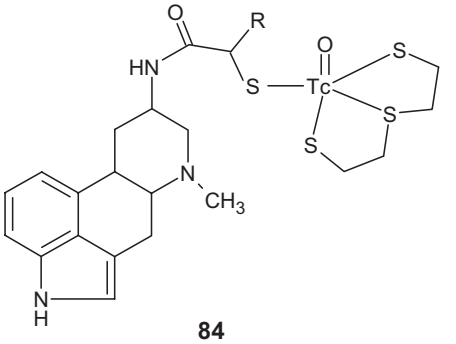



**83**

(a) $R^1 = R^2 = CH_3$;
(b) $R^1 = CH_3$, $R^2 = C{\equiv}CH$;
(c) $R^1 = CH_3$, $R^2 = CH_2CH_2COOH$;
(d) $R^1 = CH_2COOH$, $R^2 = CH_2COOH$

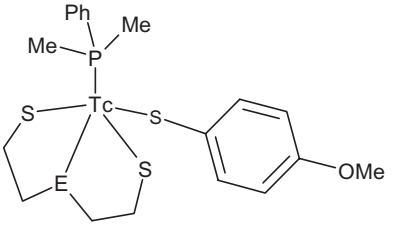


8$\alpha$-Amino-6-methyl-ergoline, a synthetic ergot alkaloid that can act as agonist or antagonist at neurotransmitter receptors, was mercaptoacetylated in order to form a Tc–$S_4$-coordinated complex, **84**. This complex was studied in order to determine its receptor-binding ability. The resulting complex biodistribution was studied on Wistar rats showing significant accumulation in liver and kidneys and low brain uptake [159].



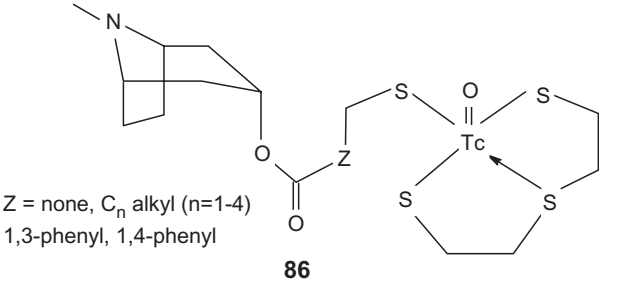

**84**

$S_3$–Tc(III) complexes of the general formula [Tc(SES)(RS)($PMe_2Ph$)] (**85**) (SES = tridentate dithiol ligand, E = S, O, NMe; RSH = monothiol ligand) were isolated in a one-step procedure from pertechnetate and the corresponding ligands in stoichiometric proportions. They can be also produced by a two-step procedure in similar yields [160]. The compounds oxidize in solution, losing the monothiolato ligand and resulting in the corresponding oxotechnetium(V) complex. The complexes were characterized by X-ray diffraction, cyclic voltammetry and multinuclear NMR spectroscopy [161]. This type of complexes is intended to be analyzed as glutathione or protein radiotracers for nuclear medicine.



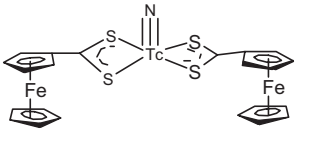

**85**

Tc complexes with tridentate/bidentate S,E,S/P,S coordination cores (E = O, $N(CH_3)$, S) were synthesized from the appropriate chloro-containing oxotechnetium(V) complex *via* a two-step reduction/substitution procedure. In this way, complexes $[Tc(SCH_2CH_2–E–CH_2CH_2S)(PR_2S)]$ (E = S, $N(CH_3)$; $PR_2S$ = phosphinothiolate with R = alkyl, aryl) were prepared. All complexes are able to penetrate the blood-brain barrier of rats and showed a relatively fast washout from the brain [162]. The "3 + 1" ligand system for $TcO^{3+}$ was derivatized with a tropane analog [163] for targeting the DAT (dopamine transporter which is the most promising for a successful $^{99m}$Tc-labeled neuroreceptor targeting moiety [9]). The corresponding [$^{99m}$Tc]-3 + 1-$\alpha$-tropanol complex **86** uses the dithiolthioether tridentate ligand and a monodentate thiol with an appended $\alpha$-tropanol moiety.

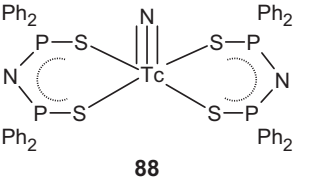



**86**

$S_4$–Nitrido complexes with a ferrocene dithiocarboxylate ligand were isolated by reacting $[Tc(N)Cl_2(PPh_3)_2]$ with the piperidinium salt of the ligand $FcCS_2$, resulting in the $Tc(N)[Fe(C_5H_4CS_2)(C_5H_5)]_2$ (**87**) complex. The two ferrocene units behave as independent redox centers bridged by the [Tc=N] core, as seen by cyclic voltammetry [164]. Complexes with the chelating ligand $N(SPPh_2)_2$ synthesized by the reaction of $[TcN(Cl)(PPhMe_2)_3]$ or $[TcNCl_2(PPh_3)_2]$ with the sodium salt of the ligand, yield [165] $[TcNL_2]$ (**88**) and $[TcN(Cl)(PPhMe_2)L]$, respectively ($L = N(SPPh_2)_2$].

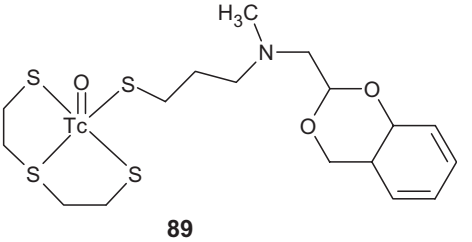



**87**



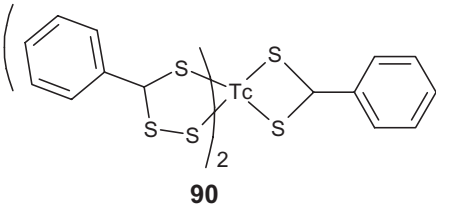

**88**

Among other similar nitride–dithiocarbamate complexes, a Tc–nitrido complex, $[^{99m}TcN(MECHDTC)_2]$ was synthesized by a ligand-exchange reaction starting from $[^{99m}TcO_4]^-$ and succinic dihydrazide in the presence of stannous chloride as reducing agent and propylenediamine tetraacetic acid as complexant [166]. After successive additions of the sodium salt of *N*-methyl, *N*-cyclohexyl dithiocarbamate (MECHDTC), the complex was obtained in over 90% yield. The complex has good biodistribution in mice (heart and brain), suggesting that this compound is a potential myocardial and cerebral imaging agent. Seeking a new class of brain perfusion imaging agents, the Tc–nitrido $[^{99m}TcN(CBDTC)_2]$ complex (CBDTC = *N*-cyclodithiocarbamato) was synthesized from $[^{99m}TcO_4]^-$ through a simple and efficient method which can be used for preparation of radiopharmaceuticals through a lyophilized kit formulation [167]. The complex was significantly retained in the brain suggesting it can potentially be a good imaging agent. A nitrido $^{99m}Tc$ complex $[^{99m}Tc(N)(IBDTC)_2]$ was synthesized from $[^{99m}TcO_4]^-$ reduced to $[^{99m}Tc(N)]^{2+}$ with stannous chloride as reducing agent, in the presence of succinic dihydrazide and propyelendiamine tetraacetic acid, followed by the addition of the sodium salt of *N*-isobutyl-dithiocarbamato (IBDTC) [168]. This good lipophilic complex has a good brain uptake and retention, suggesting that may be useful as a brain perfusion imaging agent. Among other complexes with the $S_4$–moiety, the $[^{99m}Tc]$-3 + 1-containing methylamine and ether-containing phenylalkyl groups of ketanserin **89** were reported [169].



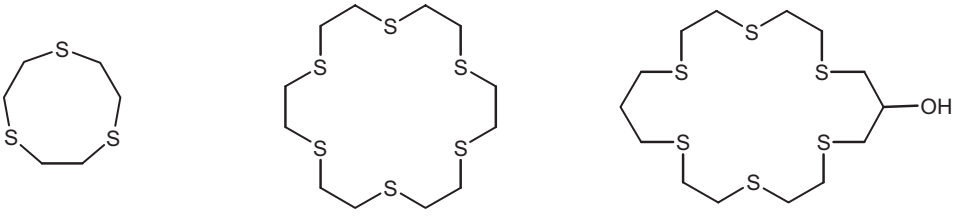

**89**

Sulfur-rich $^{99g}Tc$ complexes derived from reactions of $[^{99g}Tc(O)Cl_4](NBu_4)]$ and $[^{99g}Tc(N)Cl_4](NBu_4)]$ with a dithiobenzoate piperidinium salt in $CH_2Cl_2$ were obtained and one crystallographically characterized [170]. The same product, $[TcO_4][Tc(S_3CPh)_2(S_2CPh)]$ (**90**), can be obtained from the reaction of $^{99m}Tc$ pertechnetate in the presence of a strong reducing agent (HCl/tertiary phosphine, $SnCl_2 \cdot 2H_2O$) and radiopharmaceutical dithiobenzoate ligands. This complex is analogous to the corresponding Re compound and represents a rare example of fully sulfur-coordinated Tc complex. This compound may be useful for diagnosis of inflammatory processes [171].




**90**

Complexes bearing the *fac*-[Tc(CO)$_3$] moiety and macrocyclic thioethers **91**–**93** of various ring sizes were synthesized and X-ray structurally characterized [172]. In complex **94**, the metal is coordinated through two sulfur atoms.



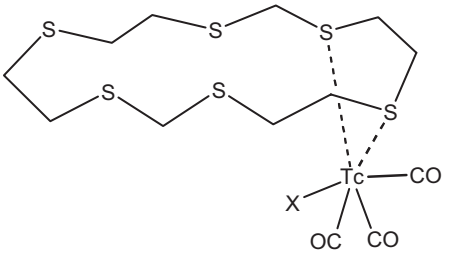
**9-one-S$_3$**
**91**



**18-one-S$_6$**
**92**



**20-one-S$_6$-OH**
**93**

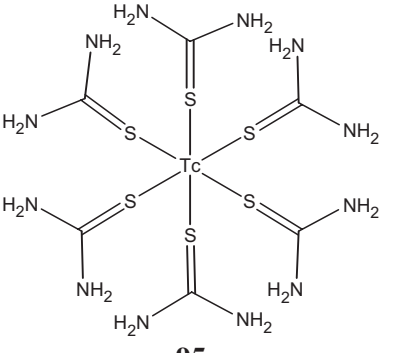


X = Cl, Br, tosylate

**94**



A hexakis(thiourea-S)technetium(III) (**95**), complex was prepared [173] from $[TcO_4]^-$ in an acidic solution with thiourea as reductant. This complex was used as a precursor for preparation of Tc-humic acid complexes in almost 80% yield *via* a thiourea displacement reaction, under nitrogen at pH 5.5.



**95**

## 2.7. *Complexes with P-containing ligands*

Phosphine-containing ligands are of interest as heart imaging agents, and Tc complexes with them could be useful for the pharmaceutical industry. Among the simple

phosphine-containing compounds, the complexes $[TcO_2(PR_3)_3](BPh_4)$ (R = Et, Pr) [26], have a distorted trigonal bipyramidal structure with the two oxo ligands in the trigonal plane. The salts of the cation $[TcO_2(PR_3)_3]^+$ are good starting reagents for the preparation of other dioxo mixed-ligand species:

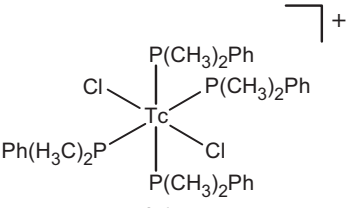
$$[TcO_2(PR_3)_2]^+ + py \rightarrow [TcO_2(PR_3)_2(py)_2]^+ \quad (\text{in } CH_3OH)$$

If R = Me, the $[TcO_2(PMe_3)_2(py)_2]^+$ complex can be prepared directly from $[TcO_4]^-$ by a one-pot method, which could probably be adapted to the commercial kits used in hospitals for the preparation of the $^{99m}$Tc radiopharmaceuticals:

$$NH_4[TcO_4] + py + PMe_3 \rightarrow [TcO_2(PMe_3)_2(py)_2]^+ \quad (\text{in } CH_3OH)$$

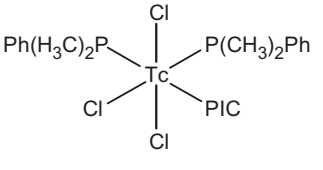
The compounds containing the cation $[TcO_2(PR_3)_2(py)_2]^+$ are diamagnetic, indicating an important deformation from ideal octahedral geometry [26]. Two other Tc complexes with the $N_2P_2$ coordination core were synthesized from diamido-dihydroxymethylene-phosphine and 4,4-bis[di-hydroxymethyl-phosphonyl-propylcarbonmolyl]-butyric acid [174].

New ionic Tc complexes of the type *trans*-$[Tc(PR_3)_4Cl_2]^+$ (**96**) were synthesized by reacting $[TcO_4]^-$ with the phosphine in methanol in the presence of a chloride salt [175]. Complexes containing the less bulky phosphine ligands can be prepared from bulkier phosphines. Mixed-ligand complexes may be synthesized by substitution of the chloride ligands.

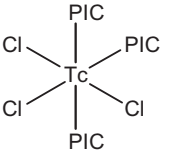


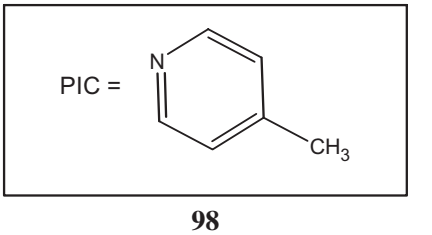

**96**

Similar complexes of Tc(III) where O-atom transfer occurs by reacting $[TcOCl_4]^-$ with several phosphine ligands in 4-picoline as solvent, yield the *mer*-$[Cl_3(pic)(PMe_2Ph)_2Tc]$ (**97**) and *mer*-$[Cl_3(pic)_3Tc]$ (**98**) complexes. The products were characterized by X-ray diffraction and spectrophotometric methods [176].

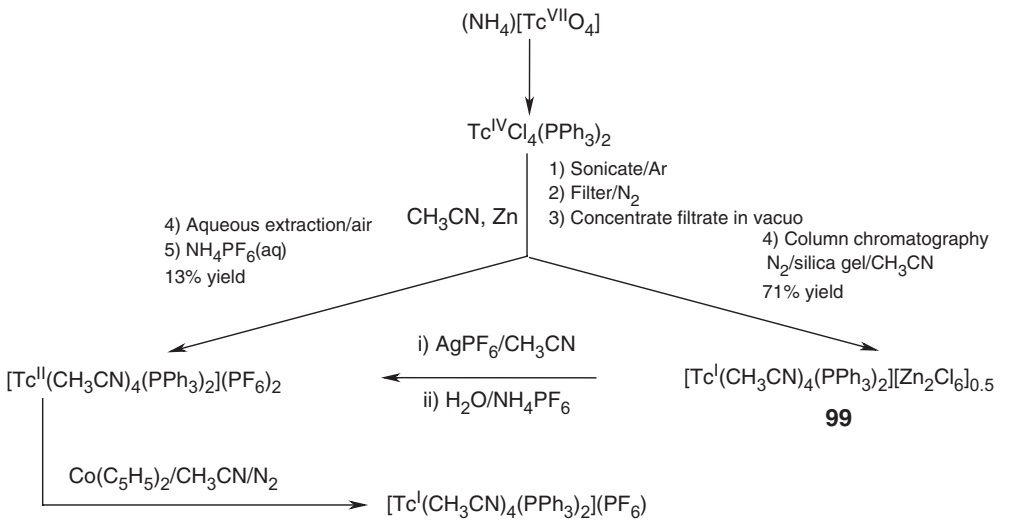



**97**




**98**

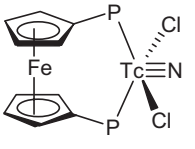



Scheme 1. Synthesis of technetium acetonitrile complexes.



An acetonitrile-containing Tc(III) complex $[TcCl_3(MeCN)\{PR_3\}_2]$ ($R = C_6H_5$, $C_6H_4Me$-3) was synthesized by zinc reduction of $[TcCl_4(PPh_3)_2]$ in acetonitrile in the presence of $PPh_3$. The acetonitrile complex is a useful Tc(III) precursor to obtain other compounds. The reaction of this complex with bipy, phen, and tpy gives the Tc(III) dicationic complexes $[Tc(bipy)_3]^{2+}$, $[Tc(phen)_3]^{2+}$ and $[Tc(tpy)_3]^{2+}$ as their $[BPh_4]^-$ or $[PF_6]^-$ salts [177]. A new route to low-valent technetium complexes containing multiple acetonitrile ligands has been reported [178]. The reduction of $TcCl_4(PPh_3)_2$ with zinc metal dust (scheme 1) in acetonitrile resulted in the formation of $[Tc(CH_3CN)_4(PPh_3)_2][Zn_2Cl_6]_{1/2}$ (**99**). A similar complex, $[Tc(NC_6H_4CH_3)Cl_3(PPh_3)_2]$, containing *p*-methylpyridine instead of acetonitrile was reported [179].

Two novel Tc nitride complexes bearing a diphenylphosphinoferrocenyl (dppf) fragment were synthesized by the reaction of dppf with $[TcNCl_4]^-$ or $[Tc(NPh)Cl_3(PPh_3)_2]$ in benzene, yielding the monomeric mono-substituted $[TcNCl_2(dppf)]$ (**100**), and $[Tc(NPh)Cl_3(dppf)]$ complexes [180]. The dppf fragment is coordinated on the equatorial plane of a distorted square pyramid or a distorted octahedron, respectively.



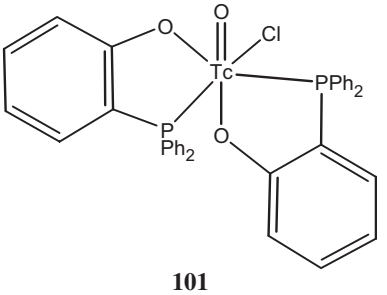

**100**

Pertechnetate reacts with derivatized phosphinocarboxylate ligands {L = 2-(diphenylphosphine)benzoic acid $[Ph_2P(C_6H_4COOH)]$, 3-(diphenylphosphine) propionic acid $[Ph_2P(C_2H_4COOH)]$ and (diphenylphosphine)acetic acid $[Ph_2P(CH_2COOH)]$} producing the corresponding $[TcL_3]$ complexes. Spectroscopic and structural characterization of the compounds indicates that the complexes have a distorted octahedral geometry

in *mer*-configuration, with two pairs of like donor atoms *trans* to each other and the remaining phosphorus atom *trans* to the oxygen atom [181]. Complexes of the short-lived isotope $^{99m}$Tc were prepared by similar procedures and their physical and chemical properties agreed with those of the $^{99}$Tc complexes. These compounds show significant brain uptake in biological tests.

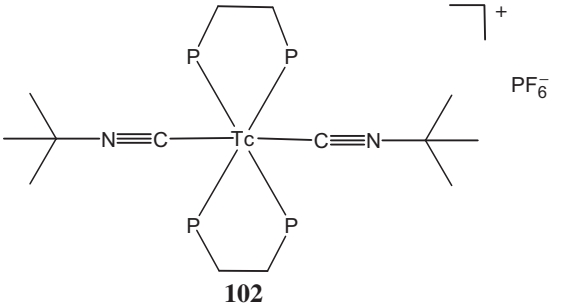
Reaction of precursor **76** with tris-(hydroxymethyl)phosphine (THP) and 1,2-HMPE [HMPE = bis(di(hydroxymethyl)phosphino)ethane] yields the corresponding complexes, with coordination of the phosphine groups to the Tc(I) at all three sites *trans* to the carbonyl ligands [182]. The same precursor was reacted with triphenylphosphine or tetrofosmin [$(C_2H_5OC_2H_4)_2PC_2H_4P(C_2H_4OC_2H_5)_2$] for the preparation of two novel Tc-phosphine complexes whose biodistribution was studied in mice, indicating low uptake in blood and fast clearance from blood [183]. A $^{99m}$Tc–nitride–tetrofosmin complex was prepared and its biodistribution in mice studied, showing accumulation in myocardium with high retention and rapid blood and lung clearance [184].

Technetium(V) complexes with HMPE and (*o*-hydroxyphenyl)diphenylphosphine (corresponding complex **101**) ligands were prepared by metathesis reactions with the appropriate Tc(V) precursor and/or by reduction/ligand-exchange reactions with ammonium pertechnetate [185]. It was expected that the combination of one soft phosphine P-donor and two hard phenolate O-donors in the chelate would stabilize Tc centers in intermediate oxidation states.




**101**

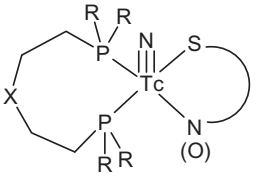
A Tc thiourea complex $[Tc(tu\text{-}S)_6]Cl_3 \cdot 4H_2O$ was used [186] as precursor in preparation of $[Tc(dppe)_2(t\text{-}BuNC)_2](PF_6)$ (**102**). The preparation involves mixing of both the corresponding ligand and the Tc(III) precursor in ethanol under reflux and it is a more convenient synthetic route to these compounds than using sodium amalgam, bis(diphenylphosphino)ethane (dppe) and $[TcCl_4(PPh_3)_2]$. The Tc atom has a distorted octahedral coordination geometry with the isocyanide ligands *trans* to each other.



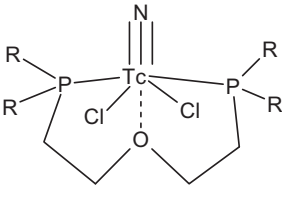

**102**

Three mixed-ligand neutral Tc complexes with monodentate phosphine and NCS ligands were synthesized by reaction of $[TcO_4]^-$ or $[TcO_2(PR_3)_3]^-$ in the presence of both NaNCS and $P(OR)_3$, or just NaNCS [187]. The complexes were structurally characterized by X-ray crystallography, showing all with a tetragonal distortion from ideal octahedral geometry.

A new labeling approach was designed in order to incorporate bioactive peptides into a $^{99m}$Tc coordination complex of type $[^{99m}Tc(N)(PXP)]^{+2}$ (**103**), where PXP is an ancillary diphosphine ligand (X = N, O) [PXP = $((C_6H_5)_2)(P(CH_2)_2)O$; $((C_6H_5)_2)P(CH_2)_2)$-$N(CH_2)_3CH_3$; $((C_6H_5)_2)(P(CH_2)_2)N(CH_2)_2OCH_3$; $((CH_3O(CH_2)_2)$-$P(CH_2)_2)N(CH_2)_2OCH_3$; $((CH_3)_2)(P(CH_2)_2)NCH_3$]. This molecular building block selectively reacts with monoanionic and dianonic bidentate ligands (YZ) having soft $\pi$-donor coordinating atoms such as cystein and other short peptides having a cystein group available [188].




**103**

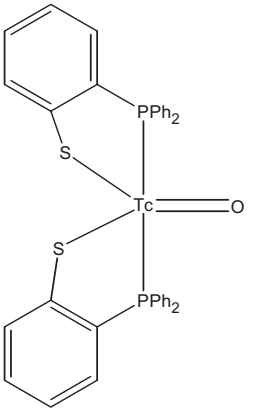



**104**

An efficient route for introducing two different bidentate chelating ligands into a nitrido Tc(V) complex was described [189]. The *cis* (yellow) isomer, **104**, was isolated from reaction of the diphosphine ligand [bis(2-diphenylphosphinoethyl)ether (POP)] with a precursor complex $[Tc(N)Cl_2(PPh_3)_2]$. This complex spontaneously converts to the *trans* (orange) isomer in acetonitrle. This procedure allows preparation of asymmetrical nitrido complexes potentially useful for production of new $^{99m}$Tc radiopharmaceuticals. Bidentate phosphine ligands such as bis(diphenylphosphino)-methane (dppm) and diphenyl-2-pyridylphosphine have been used for investigation of pertechnetate anion reduction in refluxing ethanol/HCl [190].

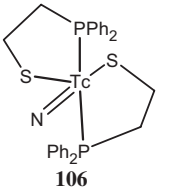
Monosubstituted $[Tc(N)Cl_2(POP)]$ and $[Tc(N)Cl_2(PNP)]$ complexes were prepared by reaction of $[Tc(N)Cl_4]^-$ and $[Tc(N)Cl_2(PPh_3)_2]$ with the diphosphine ligands POP and bis(2-diphenylphosphinoethyl)methoxyethylamine (PNP) in refluxing dichloromethane/methanol solutions. The heteroatom of the diphosphine ligand was invariably located *trans* to the nitrido linkage, as established by X-ray diffraction analysis [191, 192]. The neutral $[TcNCl_2(Ph_2PNH)_2]$ complex was prepared from $[TcNCl_4]^-$ and $CH_3SiNPPh_3$ in dichloromethane, but only produced $[TcNCl_4]^-$ when the reaction was performed in acetonitrile [193].

Neutral Tc(III) complexes with S,P-bidentate phosphine-thiolate ligands [2-(diphenylphosphino)ethanethiolate, 2-(diphenylphosphino)propanethiolate, and 2-(diphenylphosphino)thiophenolate, (complex **105**)] were obtained from reaction of $[TcO_4]^-$ with an excess of the ligand [194]. The neutral compounds have a five-coordinate trigonal-bipyramidal geometry, with two phosphorus donors of two chelates coordinated mutually *trans* in the axial positions.

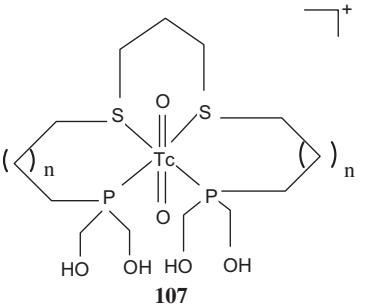



**105**

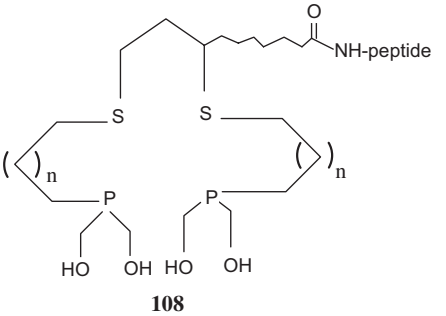
Reactions of [$^{99g}$Tc(N)$Cl_2(PPh_3)_2$] and [$^{99g}$Tc(N)$Cl_4$] with phosphine-thiol ligands ($HL^n$) of the type $R_2PCH_2CH_2SH$ (R = phenyl, methoxypropyl), $R'_2PCH_2CH_2SH$ (R = phenyl, tolyl) and $R''_2P$-*o*-$C_6H_4SH$ (R = phenyl) produced five-coordinate, disubstituted nitrido Tc(V) complexes [$^{99g}$Tc(N)$(L^n)_2$] [195]. The complexes possess a rare trigonal-bipyramidal geometry in contrast with the common square-pyramidal geometry of other Tc nitride complexes. The structural changes are related to the nature of the donor atoms, both at the axial or the equatorial positions [195]. Among other $P_2S_2$–Tc complexes, water-soluble phosphine chelates **106**–**108** were reported [9]. Complex **107** has a general $P_2S_2$ tetradentate ligand and compound **108** is a bifunctional $P_2S_2$ tetradentate ligand, appended to a peptide [9].




**106**




**107**




**108**

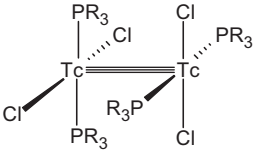
The neutral technetium(V) phosphoraneimine complex [$TcNCl_2(Ph_2PNH)_2$] is formed from ($NBu_4$)[$TcOCl_4$] and $Me_3SiNPPh_3$ in $CH_2Cl_2$. The same reaction yields the [$TcNCl_4$]$^-$ anion when it is performed in acetonitrile [196].

## 2.8. *Complexes containing M–M bonds*

The identification of metal–metal (M–M) multiple bonds belongs among the most important discoveries in coordination chemistry. Single and multiple bonds between metal centers have been characterized for many elements. Rhenium complexes containing multiple metal–metal bonds are prototypes in developing an understanding of the physical and chemical properties of such bonds between metal atoms. However, for its analog, technetium, the development of its coordination chemistry is strongly limited by the fact that all its isotopes are radioactive. The existence of metal–metal bonds is not very extensive in Tc chemistry; however, some key compounds have been characterized and reviewed [5].

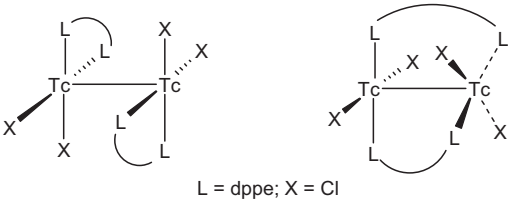
A comparative calculation of the $[Tc_2Cl_8]^{m-}$ ($m = 2, 3, 4$) and $[Mo_2Cl_8]^{m-}$ ($m = 4, 5$) clusters has been carried using the SCF $X_\alpha$-scattered wave approximation [197]. No correlation was found between the formal order of the M–M bond and the calculated electronic characteristics of the clusters or the position on the potential curve minima. For a classic cluster $[Tc_2Cl_8]^{3-}$, the Tc–Tc bond consists of one $\sigma$-, two $\pi$-, one $\delta$-bond, and one electron residing in the antibonding $\delta^*$ orbital (bond order is 3.5). The band between 6000 and 8000 $cm^{-1}$ was attributed to the $\delta \rightarrow \delta^*$ transition [198].

Reported data on Tc–Tc multiple bonds are rare [18, 20, 29, 199]. A series of triple metal–metal bonded diamagnetic ditechnetium(II) phosphine complexes $Tc_2Cl_4(PR_3)_4$ (**109**), ($PR_3 = PEt_3$, $PPr^n_3$, $PMePh_2$, $PMe_2Ph$) was reported in the same work [199]. These compounds are the first examples of phosphine complexes that contain a Tc–Tc multiple bond and are formed as a result of the reduction of $TcCl_4(PR_3)_2$ under heating (50–55°C) in toluene or by sonication in benzene (>90% yield in both cases). Ligand dependence of metal–metal bonding in the $d^3$–$d^3$ dimers $Tc_2X_9^{n-}$ (X = F, Cl, Br, I) was described [200].




**109**

The extended polymeric chain structure of $[Tc_2Cl_6]_n^{2n-}$ [201], also contains metal–metal triple bonds. Triple Tc–Tc bonds were also found in the $\alpha$ and $\beta$ forms of $Tc_2Cl_4(dppe)_2$ [202]. The $\alpha$ isomer **110** has an eclipsed conformation and a Tc–Tc distance of 2.15(1) Å, while the $\beta$ isomer **111** has a twist angle of 35(2)° and a Tc–Tc distance of 2.117(1) Å. These last two isomers were prepared by refluxing $Tc_2Cl_4(PR_3)_4$ (R = Et, $Me_2Ph$) in toluene, with and without, an excess of dppe, respectively.

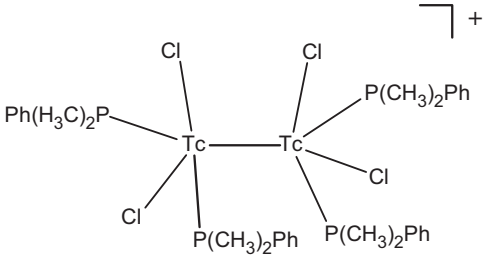



**110** **111**

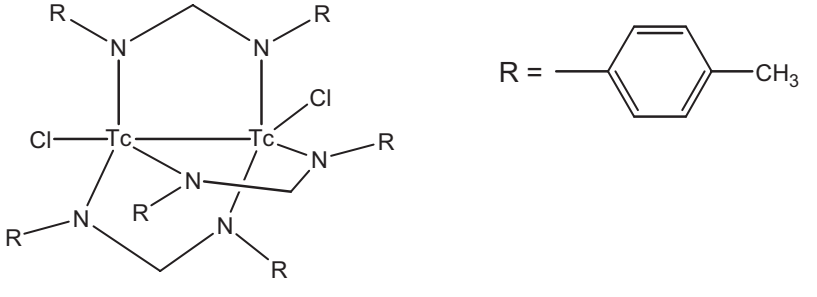
A Tc nitrido dimer $(Bu_4N)_2[\{TcNCl_2\}_2(\mu\text{-}O)_2]$ bearing a Tc–Tc single bond (Tc–Tc distance of 2.5493(10) Å) was synthesized by heating a mixture of water/acetone and $[TcNCl_4](NBu_4)$ [203]. According to the opinion of authors, this finding can be important on designing new Tc-based radiopharmaceuticals as $[^{99m}TcNCl_4]^-$ is widely used as a synthon and Tc nitrido chemistry is a developing area in radiopharmaceutical research.

Complexes with Tc–Tc multiple bond of orders of 3.5 were synthesized in high yield by one electron chemical oxidation of $Tc_2Cl_4(PMe_2Ph)_4$ with ferrocenium hexafluorophosphate in acetonitrile, producing $[Tc_2Cl_4(PMe_2Ph)_4][PF_6]$ (**112**) or neutral $[Tc_2Cl_5(PMe_2Ph)_3]$ when oxidized in the presence of bis(triphenylphosphine)iminium [204]. When $Tc_2Cl_4(PR_3)_4$ ($PR_3 = PEt_3$, $PMe_2Ph$, $PMePh_2$) reacts with molten formamidines (diphenylformamidine, di-*p*-tolylformamidine), mixtures of *tris* and *tetrakis*-bridged formamidinate complexes of general formula $Tc_2(L)_mCl_n$ (**113**) ($m = 3$, 4; $n = 1$, 2) are produced in modest yield [205]. However, triply bonded complexes of Tc such as $[Tc_2(MeCN)_{10}][BF_4]_4$ [206] can be photodissociated in acetonitrile solutions to give $[Tc(MeCN)_6]^{2+}$ in almost quantitative yield [207]. This deca-acetonitrile, triply bonded Tc binuclear complex was synthesized by acidification of $Tc_2Cl_4(PR_3)_4$ with $HBF_4 \cdot Et_2O$ in a mixture of acetonitrile and methylene chloride, in very good yields [5].






**112**

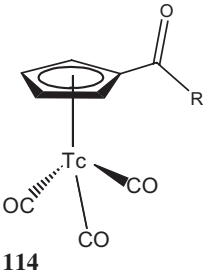



**113**

## 2.9. *Other technetium complexes*

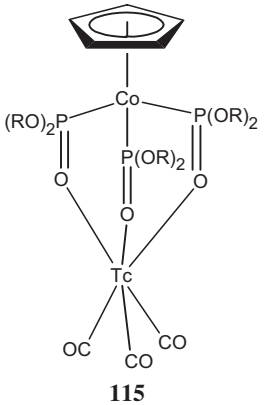
**2.9.1. Complexes containing Tc–C bonds.** *Cyclopentadienyl complexes.* Efforts to obtain complexes $\eta^5$-cyclopentadienyl-tricarbonyl technetium(I) and rhenium(I) were made [6, 208]. Half-sandwich complexes of the type $[(RCOCp)^{99}Tc(CO)_3]$ (**114**) were synthesized from **76** in water. The R group can be an organic residue or a receptor

binding biomolecule with a spacer to Cp. This provides [208] a general route to Cp complexes of technetium without the need for starting from $[TcBr(CO)_5]$. Other cyclopentadienyl $^{99m}$Tc complexes have been reported [209, 210].

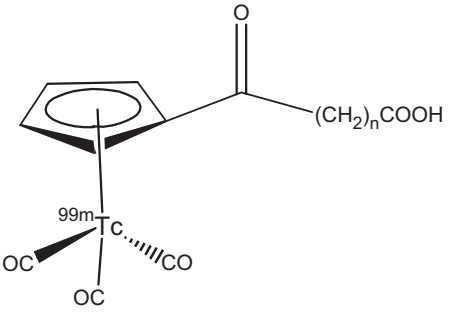



**114**

The reaction of $[Tc(H_2O)_3(CO)_3]^+$ with $Na[CpCo[PO(OR)_2]_3]$ (R = Me, Et) in water produced the compounds $[Tc(CO)_3(CpCo[PO(OR)_2]_3)]$ (**115**) as yellow solids in yields ranging from 55 to 89%. The complex was crystallographically characterized and can be used as a structural model for triaqua-like, weak-field ligands coordinated to the *fac*-$[Tc(CO)_3]^+$ core [211].




**115**

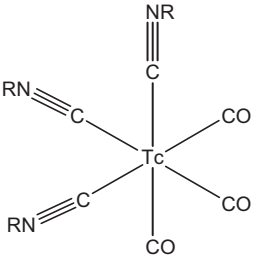



**116**

A novel Cp-containing radiotracer for evaluation of medium chain fatty acid metabolism in the liver, $^{99m}$Tc-CpTTOA (8-cyclopentadienyltricarbonyl $^{99m}$Tc 8-oxo-octanoic acid) and similar complexes **116** were reported [212].

**2.9.2. Complexes with a $Tc(CO)_3$ core and other carbonyls.** Bifunctional single amino acid chelates for labeling of biomolecules with the $[Tc(CO)_3]^+$ core were reported [213]. A novel $^{99m}$Tc(I)–tricarbonyl complex, $[Tc(CO)_3(MIBI)_3]$ (**117**), was prepared for MDR1 P-glycoprotein (Pgp) recognition, showing a 60-fold higher accumulation in drug-sensitive cells compared to colchicine-selected drug-resistant KB 8.5 cells. Biodistribution analyses showed delayed liver clearance as well as enhanced brain uptake, demonstrating that the Tc–CO–MIBI complex is a functional probe

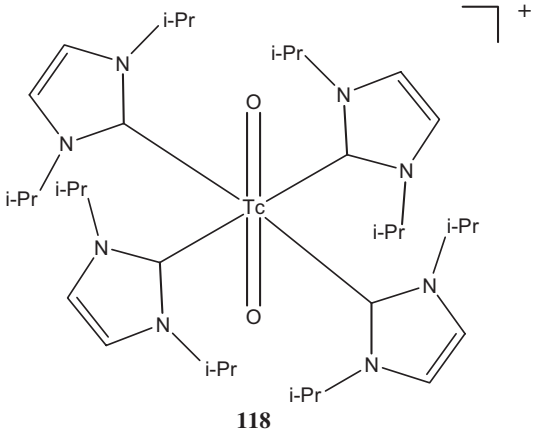
of Pgp transport activity *in vivo*. Biodistribution data compared normal mice with MDR1 knock out mice [214].




**117**

When $[Tc(CO)_4]^-$ reacts with $BH_3 \cdot THF$ under 1 atm of CO, the water soluble dianionic complex $[TcCl_3(CO)_3]^{2-}$ complex is formed [215]. The unusual, hydride-bridged, trinuclear complex $[Tc_3(\mu\text{-}H)_3(CO)_{12}]$ was structurally characterized [142]. Other types of Tc carbonyl derivatives were reported [216–218]. Thus, the $Tc(CO)_5I$ complex, which is isostructural to the $Mn(CO)_5I$, exists as orthorhombic crystals. Its crystal structure consists of $Tc(CO)_5I$ molecules. The crystals of $[Tc(CO)_4I]_2$ are monoclinic and are also built of individual $[Tc(CO)_4I]_2$ molecules. The complexation processes of $[Tc(CO)_3(H_2O)_3]^+$ with halide and thiocyanate ions in aqueous solutions were studied [219]. Among these ligands, the $NCS^-$ anion forms the most stable complexes with the $Tc(CO)_3^+$ ion. $^{99m}Tc(CO)_3$–mebrofenin complex is formed [220] (mebrofenin = trimethyl-bromoacetanilido-iminodiacetic acid) in 95% yield from *fac*-$[^{99m}Tc(OH_2)_3(CO)_3]^+$ and mebrofenin in phosphate-buffered saline at 70°C for 1 h.

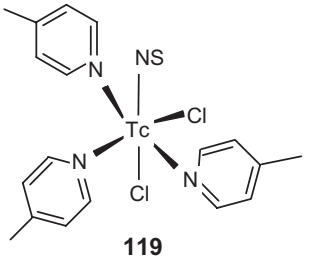
The first complex with *N*-heterocyclic carbenes, cationic dioxotechnetium complex $[TcO_2(L^1)_4]^+$ (**118**) ($L^1$ = 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene) and its Re analog were prepared from $[NBu_4][MOCl_4]$ and an excess of $L^1$ and studied by X-ray crystallography. The metal–carbon distances in these Re and Tc complexes range from 2.216(4) to 2.232(4) Å indicating mainly $\sigma$-bonding [221]. Other organometallic complexes of technetium are covered in a recent review [222].




**118**

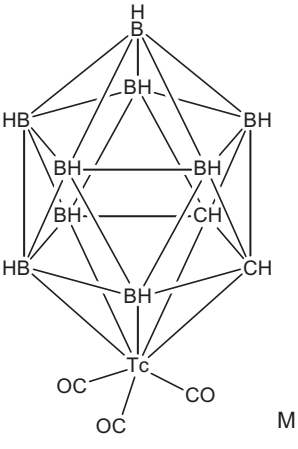
**2.9.3. $H_2$ and $N_2$-complexes.** The first $\eta^2$-$H_2$ complex of technetium was prepared from $[TcCl_4(PPh_3)_2]$, Zn powder and dppe giving 16-electron species $[TcCl(H_2)(dppe)_2]$. This strong Lewis acid is stable under an inert gas atmosphere, but readily forms the yellow $N_2$ complex $[TcCl(N_2)(dppe)_2]$, when exposed to nitrogen [223]. The hydrido complex $[TcH(N_2)(dppe)_2]$ can be prepared from $[TcCl_4(PPh_3)_2]$ by reduction in benzene with sodium amalgam under an $N_2$ atmosphere, in the presence of dppe [224].

**2.9.4. NS complexes.** The direct reaction of $[TcNCl_4]^-$ with heterocyclic amines as solvent and $[S_2O_4]^{2-}$ as reducing agent produces *mer*-$[TcCl_2(NS)(py)_3]$ and *mer*-$[TcCl_2(NS)(pic)_3]$ (**119**), respectively [225].

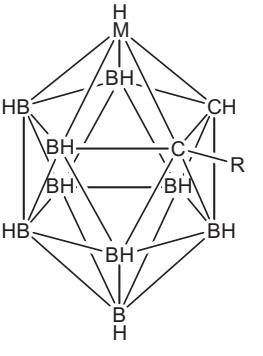



**119**

Carboranes as ligands for the preparation of organometallic Tc radiopharmaceuticals have been used for the synthesis of $[Tc(CO)_3(\eta^5\text{-}2,3\text{-}C_2B_9H_{11})]$ (**120**) and the bifunctional rac-$[Tc(CO)_3(\eta^5\text{-}2\text{-R-}2,3\text{-}C_2B_9H_{10})]$ ($R = CH_2CH_2CO_2H$), starting from $[Tc(CO)_3Br_3]^{2-}$. It was achieved by slow addition of the *nido*-$[C_2B_9H_{12}]$ or the acid substituted analog to the Tc precursor in the presence of TlOEt in THF. Preparation in water was possible using sodium carbonate in place of TlOEt [226]. Similar boron-containing structures **121** were reported [227] and applied for preparation of radiopharmaceuticals at the tracer level.




**120**

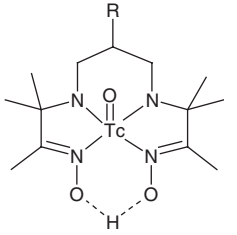



M = Tc, Re; R = H, $CH_2COOH$

**121**

More detailed information on these and other technetium coordination and organometallic compounds is covered in a review [6]. Synthetic methods for the main types of Tc complexes are presented in table 4.

Table 4. Preparation of selected technetium complexes.

| Metal or its compound | Reaction system | Products | Reference |
|---|---|---|---|
| *Complexes with O-containing ligands* | | | |
| $(Nbu_4)[TcOCl_4]$ | Oxazoline and thiazoline ligands, refluxing MeOH, EtOH | $TOCl(L)_2$ complexes | [153] |
| $KTcO_4$ | 3,5-di-*t*-butylcathechol, $CH_3OH$ | Tris(3,5-di-*t*-butylcathecholato) technetium(VI) ($Tc(DBCat)_3$) and bis(3,5-di-*t*-butylcatecholato) (di-*t*-butylamido phenolato) technetium(VI) {$Tc(DBCat)_2$ (DBAP)} | [139] |
| $[TcO_4]^-$ | Aqueous solution, CO bubbling | $[^{99m}Tc(OH_2)_3(CO)_3]$ | [141, 142] |
| *Complexes with N-containing ligands* | | | |
| $TcCl_3(PPh_3)_2(MeCN)$ | *t*-Butyl$_3$tpy, DME | $TcCl_3$(*t*-butyl$_3$tpy) | [48] |
| $TcCl_3(tpy)$ | TlOTf, adventitious water | Oxo bridged Tc(III) polypyridil [(tpy)($Me_2$bpy)](OTf)$_4$ complex | [49] |
| $[TcOCl_4]^-$ | Alanine | Monooxotechnetium(V) complex of cyclic tetraalanine | [55] |
| $NH_4(TcO_4)$ | PnAO-6-R, reductive conditions, pH ~ 8.5 |  **29** | [65] |
| $NH_4TcO_4$ | 2-hydrazinopyridine · 2HCl, $CH_3OH$ | $[TcCl_3(\eta^1\text{-}NNC_5H_4NH)(\eta^2\text{-}HNNC_5H_4N)]$ | [67] |
| $[TcOCl_4]^-$ | Hydrazine dihydrochloride, toluene, refluxing $CH_2Cl_2$ | $[TcCl_2(C_8H_5N_4)(PPh_3)_2] \cdot 0.75C_7H_8$, $[TcNCl_2(PPh_3)_2] \cdot 0.25CH_2Cl_2$ | [76] |
| $[Tc(CH_3CN)(PPh_3)_2Cl_3]$ | HYPY | $[Tc(NNC_5H_4N)(PPh_3)_2Cl_2]$ | [77] |
| $NH_4TcO_4$ | Organohydrazona-2-hydrazinopyridine | $[Tc(NNC_5H_4N)(PPh_3)_2Cl_2]$ | [77] |
| $[TcNCl_2(PPh_3)_2]_2$ | Tetra-azamacrocycles (L′) | $[TcN(L')(H_2O)] \cdot 2H_2O$ | [88] |

| | | | |
|---|---|---|---|
| $[TcCl_4(PPh_3)_2]$ | Zn reduction, $CH_3CN$, $PR_3$ | $[TcCl_3(CH_3CN)(PR_3)_2]$ ($R=C_6H_5$, $C_6H_4CH_3$) | [177] |
| $[Bu_4N][TcOCl_4]$ | Cysteine monohydrochloride monohydrate, aqueous solution | $[HTcO(Cys)_2]$ | [98] |
| $[Tc_2Cl_4(PR_3)_4$ ($R_3 = Et_3$,$PMe_2Ph$, $PMePh_2$) | MeCN, $HBF_4$ | $[Tc_2^{II}(MeCN)_{10}]\,[BF_4]_4$ The product is an excellent precursor for the synthesis of other low-valent mono- and dinuclear technetium complexes. 50% yield. Tc–Tc multiple bond is present. | [228] |
| $[TcCl_6]^{2-}$ | Reduction by $Bu_3SnH$ or Zn, then treatment with $MeCN + HBF_4$ | | |
| *Complexes with S-containing ligands* | | | |
| $[TcNCl_2(PPh_3)_2]$ | Piperidinium salt of $FeCS_2$ | $\{TcN[Fe(C_5H_4CS_2)](C_5H_5)]_2\}$ | [164] |
| $[TcNCl(PPh_3)_3]$, $[TcNCl_2(PPh_3)_2]$ | Sodium salt of L ($L = N(SPPh_2)_2$) | $[TcNL_2]$ or $[TcN(Cl)(PPhMe_2)L]$ | [165] |
| $[TcO_4]^-$ | Sodium salt of IBDTC, succinic dihydrazide, propyelenediamide tetraacetic acid | $[Tc(N)(IBDTC)_2]$ | [168] |
| $[TcO_4]^-$ | HCl, $PR_3$, $SnCl_2 \cdot 2H_2O$, dithiobenzene | $[TcO_4][Tc(S_3CPh)_2(S_2CPh)]$ | [157] |
| *Complexes with P-containing ligands* | | | |
| $NH_4[TcO_4]$ or $[TcO_2(PR_3)_3]^+$, $R = Et$, $Pr$ | $PR_3$, $CH_3OH$ | $[TcO_2(PR_3)_3]^+$ or $[TcO_2(PR_3)_2(py)_2]^+$ in presence of py yields 60–70%. An excess of ligand is used (about 10×). No reducing agent is needed. $NH_3$ is produced in the reaction. | [26] |
| $[Tc(PPh_3)_2(CO)_3Cl]$ | Lithium salt of the Schiff base *N-o*-hydroxybenzylidene-2-thiazolylimine, boiling THF. $[(LiOC_6H_4)(CH{=}N(CSNC_sH_2)]$ | $[Tc(PPh_3)_2(CO)_2\{(C_3H_2NS)N{=}CHC_6H_4O\}]$ | [156] |
| $TcCl_3(PPh_3)_2(MeCN)$ | tmeda, DME, Toluene Py | $TcCl_3(PPh_3)_2(tmeda)$ | [48] |
| | | *mer*-$TcCl_3(py)_3$ Reflux | [176] |
| $[TcNCl_4]^-$ | dppf or POP | $[TcNCl_2(dppf)]$ or $[TcNCl_2(POP)]$ | [180, 191] |

(*Continued*)

Table 4. Continued.

| Metal or its compound | Reaction system | Products | Reference |
|---|---|---|---|
| $[Tc(NPh)Cl_3(PPh_3)_2]$ | dppf, benzene or PNP, refluxing $CH_2Cl_2$ | $[Tc(NPh)Cl_3(dppf)]$ or $[Tc(NPh)Cl_3(PNP)]$ | [180, 193] |
| $[TcNCl_4]^-$ | $CH_3SiNPPh_3$, $CH_2Cl_2$ | $[TcNCl_2(Ph_2PNH)_2]$ | [193] |
| $[TcO_4]^-$ | $PR_3$, MeOH, in presence of a chloride salt | *trans*-$[Tc(PR_3)_4Cl_2]$ | [175] |
| $TcCl_4(PPh_3)_2$ | $PEt_3$ or P(*n*-Pr)$_3$, THF | $3TcCl_4(PR_3)_2$ | [199] |
| $TcCl_4(PEt_3)_2$ | Zn, benzene, sonication | $Tc_2Cl_4(PEt_3)_4$ | [199] |
| $Tc_2Cl_4(PMe_2Ph)_4$ | $[Cp_2Fe][PF_6]$ | $[Tc_2Cl_4(PMe_2Ph)_4][PF_6]$ Tc–Tc multiple bond. | [204] |
| *Complexes containing M–M bonds* | | | |
| $Tc_2Cl_4(PR_3)_4$ | Molten formamidines | $[Tc_2(L)_4Cl_n$ ($n = 1$, 2) L = $PEt_3$, $PMe_2Ph$, $PMePh_2$ | [205] |
| $[TcCl_6]^{2-}$ | Metallic zinc, conc. HCl | $[Tc_2Cl_8]^{3-}$ (with $NH^{4+}$ or $Y^{3+}$ counterions). Tc oxidation state is +2.5. Bond order is 3.5. The formation of $[Tc_2Cl_8]^{2-}$ was also reported. Tc–Tc bond in different similar complexes is 2.10–2.13 Å. | [229, 230] |
| $[TcO_4]^-$ | Conc. HCl, $H_3PO_2$ | $[NBu_4]_2[Tc_2Cl_8]$ | [231] |
| $[NH_4]_3[Tc_2Cl_8]$ | Pivalic acid. 150°C, 36 h. | $[Tc_2Cl_2(piv)_4]$, piv = $O_2CCMe_3$. The Tc–Tc bond is quadruple, 2.192 Å. | [232] |
| $K[TcO_4]$ | HCl, acetic acid (Hac), organic solvents | $[Tc_2Cl_2(ac)_4]$ | [233] |
| $[Tc_2Cl_8]^{2-}$ | Acetic anhydride, $HBF_4$ | $[Tc_2(ac)_2Cl_4(OH_2)_2]$ DMF, DMA, DMSO, py (L) can substitute water ligands giving $[Tc_2(ac)_2Cl_4(L)_2]$. $[Tc_2(ac)_2Cl_4(OH_2)_2]$ can also be produced from $[TcOCl_4]^-$, $[NBu_4][BH_4]$, $HBF_4$ in acetic anhydride at −50°C. | [234] |
| $[Tc_2Cl_8]^{2-}$ | $CH_3CN$, $HBF_4 \cdot Et_2O$ | $[Tc_2(NCCH_3)_{10}]^{4+}$ (major product). It can also be obtained from $[Tc_2Cl_4(PEt_3)_4]$, $CH_3CN$ and $HBF_4 \cdot Et_2O$ or from $[TcCl_6]^{2-}$, toluene, (*n*-Bu)$_3$SnH and subsequent acidification with $HBF_4 \cdot Et_2O$. The product contains a triple Tc–Tc bond of 2.122 Å. The reduction of $[Tc_2(NCCH_3)_{10}](BF_4)_4$ with cobaltocene in acetonitrile leads to a mixed-valence $Tc^{I}/Tc^{II}$ complex $[Tc_2(NCCH_3)_{10}](BF_4)_3$. | [207, 235] |

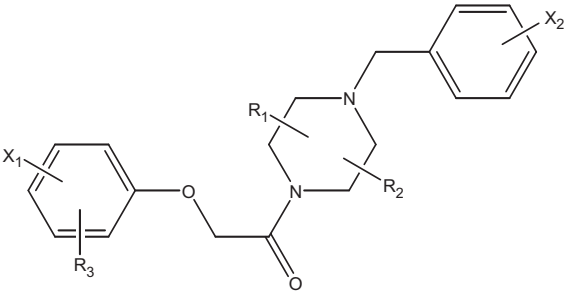
## 3. Applied aspects of technetium complexes

Table 5 presents the principal applications of technetium coordination compounds for medical purposes. Other applications of metallic Tc and its compounds are covered in a recent review [8].

## 4. Concluding remarks

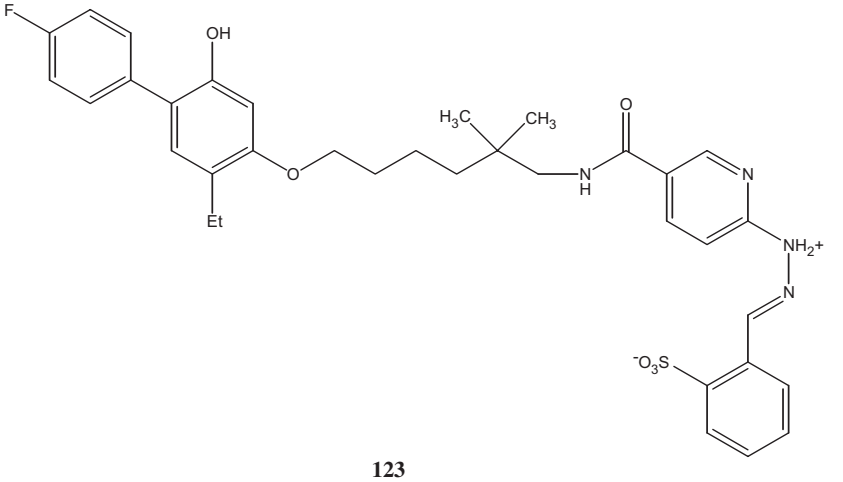
The technetium is the most studied element among non-*f* radioactive ones for medical and technical purposes [31]. Theoretical interest for Tc is caused, in part, by its periodic relationship to its heavier congener rhenium. This element (Re) forms a variety of multiple metal–metal bond complexes and has been intensively studied in order to achieve a better understanding of the physical and chemical properties of multiple bonds between metal atoms [199]. In comparison with their analogous Re complexes, Tc complexes generally react faster following a dissociative mechanism [236].

The growing importance of Tc complexes, for radiopharmaceutical, imaging and medical treatment is evident from the increasing number of patents on these complexes [96, 97, 227, 237–256]. Some ligands **122**–**125** reported in recent patents for Tc complex formation, are as follows:

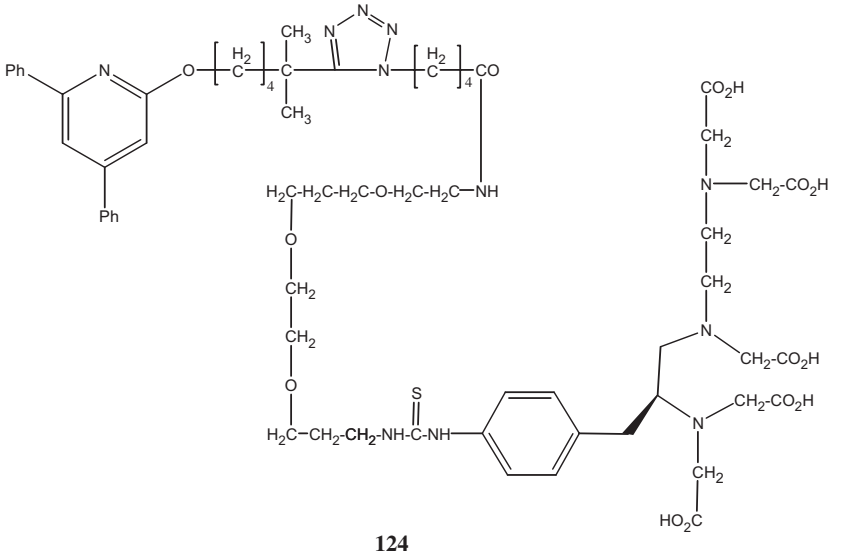



$X_1$, $X_2$ = Halogen; $R_1$, $R_2$ = H or alkyl; $R_3$ = H, amino, R-amino derivative

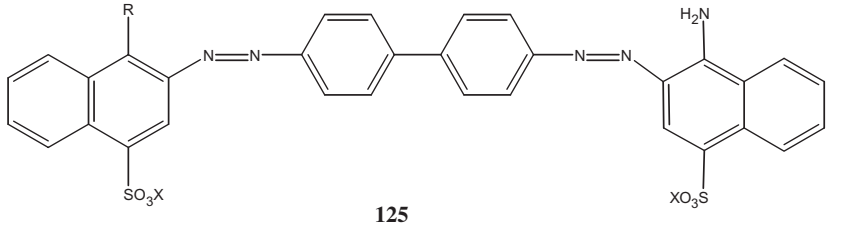
**122**



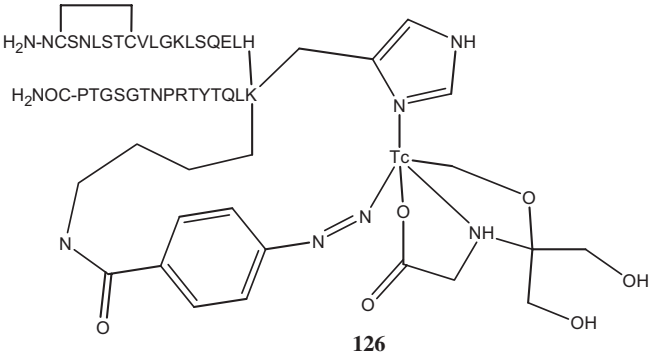

**123**



**124**



**125**



**126**

Among the preceding complexes, the Tc complex **122** is used for diagnosis of AD [250]. Compound **123** is applied to form complexes of Tc(tricine)(TPPTS)(4-ethyl-2-(4-fluorophenyl)-[5-[5,5-dimethyl-6-[[[6-diazenido-3-pyridyl]carbonyl]amino]hexyl]-oxy]-phenol) [TPPTS = tri(3-sulfonatophenyl)phosphine, sodium salt] to detect inflammation/infection in guinea pig and rabbit focal infection models [246]. The ligand **124** is used for formation of Tc complexes for simultaneous dual isotope imaging of perfusion and inflammation [244]. A patent [242] reports a Tc complex with "Congo Red" **125** and diamide dithiolate ligand system for radioimaging amyloid in animals and man *via* intrathecal administration. An efficient $^{99m}$Tc labeling of

Table 5. Medical applications of Tc complexes.

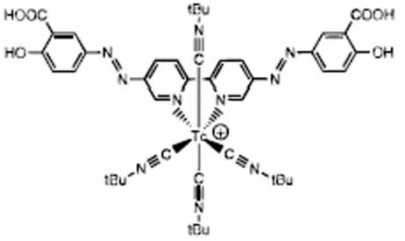
| Metal complex or compound | Observations | Reference |
|---|---|---|
| *Labeling agent of biomolecules and small molecules* | | |
| $^{99m}$Tc labeled somastostatin | $^{99m}$Tc somatostatin, lanreotide, and P829 are all neuroendocrine tumor imaging agents targeting somatostatin receptors. The key point of this reference is that the $^{99m}Tc(CO)_3(OH_2)_3$ precursor was used to label the somatostatin thus avoiding the use of any reductant in the presence of somatostatin; i.e. protecting the disulfide bond. | [56] |
| $^{99m}$Tc–labeled lanreotide | Direct $^{99m}$Tc labeling of a somatostatin analog is described in which the disulfide bond, in a difference with the data of [56], is intentionally broken to coordinate the $^{99m}$Tc. | [58] |
| $[Tc(C_5H_4NS)_2(NNC_5H_4NH)(HNNC_5H_4N)]$ | The reduction of pertechnetate with 2-hydrazinopyridine dihydrochloride in methanol has led to the preparation of $[TcCl_3(NNC_5H_4NH)(HNNC_5H_4N)]$, whose reaction with with pyridine-2-thiol yielded a complex $[Tc(C_5H_4NS)_2(NNC_5H_4N)(HNNC_5H_4N)]$ having a monoclinic structure. The first complex serves as model for the binding of Tc(V)-oxo species to hydrazino-nicotinamide (HYNIC)-conjugated chemotactic peptides. | [67] |
| $[^{99m}Tc(OH_2)_3(CO)_3]$ | An organometallic aqua complex, obtained directly from $[^{99m}TcO_4]^-$ in saline aqueous solution under 1 atm of CO; the compound is useful to obtain carbonyl complexes by substitution of the labile water ligands for nuclear medicine applications, e.g. probes for nucleic acids, cancer diagnosis or therapy involving DNA–DNA pretargeting. | [141] |
| $^{99m}$Tc(oxo) RP294 | The reaction of $^{99}TcO_4^-$ with $SnCl_2$, sodium gluconate, and peptide dimethylglycyl-L-seryl-L-cysteinylglycinamide (RP294) produced the $^{99}$Tc(V) oxo RP294 complex, [$^{99}$TcO(RP294)]. Like the [ReO(RP294)] complex, [$^{99}$TcO(RP294)] also exists in the *syn* and *anti* conformations in a ratio of approximately 1 : 1. The $^{99m}$Tc complex of RP294 was prepared at the tracer level from the reaction of $Na[^{99m}TcO_4]$ with excess $SnCl_2$, sodium gluconate, and RP294. These compounds may be useful for therapeutic radiopharmaceuticals. | [118] |
| $[Tc(SES)(RS)(PMe_2Ph)]$, SES = tridentate dithiol ligand, E = S, O, NMe; RSH = monothiol ligand | Glutatione or protein radiotracers. Stability studies show that the $^{99m}$Tc complexes undergo some alteration in solution. They are oxidized to the 3 + 1 oxotechnetium(V) complexes and/or decompose in aqueous solution. In challenge experiments performed with glutathione, exchange of the monothiolato ligand occurs in the same manner as known for the 3 + 1 complexes. | [160] |
| $[^{99m}Tc(N)(PXP)]^{+2}$ | A new labeling approach for incorporating bioactive peptides into a $^{99m}$Tc coordination complex is described. This method exploits the chemical properties of the novel metal-nitrido fragment $[^{99m}Tc(N)(PXP)]^{2+}$, composed of a terminal Tc≡N multiple bond bound to an ancillary diphosphine ligand (PXP). These results were conveniently employed to devise a new, efficient procedure for labeling short peptide sequences having a terminal cysteine group available for coordination to the $[^{99m}Tc(N)(PXP)]^{2+}$ fragment. | [188] |

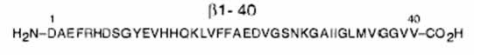
(*Continued*)

Table 5. Continued.

| Metal complex or compound | Observations | Reference |
|---|---|---|
| *Tumor tissues imaging agent* | | |
| $^{99m}$Tc labeled annexin V-122 and V-123 | The use of $^{99m}Tc(CO)_3(OH_2)_3$ for labeling Annexin V, a protein that binds to phosphatidyl serine (PS) on the cell membrane, is reported. PS is exposed on cell membranes undergoing apoptosis or cell death. Labeling Annexin with $^{99m}$Tc tricarbonyl did not alter the binding of Annexin to apoptotic cells. | [53] |
| $^{99m}$Tc–Sulesomag complex | The compound is used as an *in vivo* granulocyte labeling agent for imaging inflammation. The complex is obtained by radiolabeling of the antibody fragment sulesomag with $^{99m}$Tc in a 5-min procedure. It is then added to anticoagulated blood, incubated and the $^{99m}$Tc activity associated with leukocytes measured. | [59] |
| $^{99m}$Tc-P829 somatostatin analog | This new somastostatin analog was compared with $^{111}$In-pentetreotide. In patients with endocrine tumors, the detection rate of $^{99m}$Tc-P829 scintigraphy was lower than that of $^{111}$In-pentetreotide scintigraphy, especially for liver metastases. | [60] |
| $^{99m}$Tc labeled (cyclam AH 2123) | $^{99m}$Tc labeled cyclam *N*-2′-methoxyethyl-2-(3′-nitro-1′-triazole) acetamide (cyclam AK 2123) has been synthesized, radiolabeled and characterized as a hypoxic tumor imaging agent. *In vivo* distribution and scintigraphic imaging studies were performed after *in vivo* injection into mammary tumor-bearing rats using a gamma camera and associated computer. The increased concentration of radioactivity in these tumors suggests that this agent could be labelling hypoxic cells and have utility as an imaging agent. | [61] |
| $^{99m}$Tc labeled cyclam acid porphyrin (5,10,15,20-*tetrakis*[4-{4′,8′,11′-*tris*(carboxymethyl)-1′-(1′,4′,8′,11′-tetraazacyclotetradecane) amidomethyleneoxy}phenyl]porphyrin) | *In vivo* distribution studies of this compound were performed in $C_6$-gliomas and *N*-nitroso-*N*-methylurea (NMU) induced mammary tumour bearing rats and scintiimages were obtained at 5 h post-administration of the labeled ligand using gamma camera computer system. Tumour to muscle (T/M) ratios were determined and compared with currently available tumour seeking radiopharmaceuticals such as $^{99m}$Tc(V)–DMSA, $^{99m}$Tc–Citrate and $^{201}$TlCl. | [62] |
| $^{99m}$Tc complexes analogs to $^{123}$I-BZA {[$^{123}$I]-*N*-(2-diethylaminoethyl)-4-iodobenzamide} | The synthesis of a new BAT derivative radiopharmaceutical, in which radioiodine is replaced by $^{99m}$Tc (radioiodobenzamides are the best-known agents under study for the diagnosis of cutaneous melanoma and its metastases), is reported in this work. The BAT ligand was radiolabeled using the nitridotechnetium core by a ligand-exchange reaction. The biodistribution of two formed complexes was evaluated in mice bearing murine B16 melanoma. Extensive liver and kidney uptake was observed, but the benzamide tropism for the tumor was partially preserved. | [108] |
| $^{99m}$Tc complex with tamoxifen | To produce an imaging agent for breast cancer using a $^{99m}$Tc-labeled agent specific for estrogen receptors, an $N_2S_2$ bifunctional chelator was conjugated to *Z*- and *E*-aminotamoxifens through an amide linker. These bioconjugates have been chelated with $^{99m}$Tc. Both *in vitro* and *in vivo* biological evaluation of the tamoxifen chelates indicated very limited estrogen receptor binding. | [113] |

| | | |
|---|---|---|
| Bombesin derived peptide-$^{99m}$Tc chelate complex | This compound was prepared using a solid phase synthetic methodology. The Tc chelate–peptide conjugate was subsequently isolated from the solid support. The goal of the approach was to develop a versatile solid phase synthetic procedure that would facilitate the future application of modern drug discovery techniques for the development of receptor selective Tc radiopharmaceuticals. | [116] |
| $^{99m}$Tc complex with peptidic $N_3S$ ligands | Radiolabeled 2-nitroimidazoles have been used for imaging hypoxia, and the octanol/water partition coefficient (*P*) of these compounds appears to play a crucial role in their suitability for imaging. A series of 11 2-nitroimidazoles coupled to peptidic chelators (dialkyl-Gly-Ser-Cys-linker-2-nitroimidazole (Class I) and dialkyl-Gly-Lys(2-nitroimidazole)-Cys (Class II)) for $^{99m}$Tc with divergent *P* was developed and evaluated in an *in vitro* system. The chelators were labeled by transchelation from [$^{99m}$Tc]gluconate. The peptidic class of 2-nitroimidazoles, with flexible design and convenient solid-phase synthesis, deserves further study as agents for imaging hypoxia in tumors. | [131] |
| Amine-dioxime chelators for $^{99m}$Tc | A series of 11 2-nitroimidazoles coupled to peptidic chelators for $^{99m}$Tc with divergent partition coefficient (octanol/water) was developed and evaluated *in vitro*. Two clases of chelators were used: dialkyl-Gly-Ser-Cys-linker-2-nitroimidazole and dialkyl-gly-lys(2-nitroimidazole)-cys. Four of the 11 compounds showed selective accumlation in hypoxic cells, and may be useful as agents for imaging hypoxia in tumors. | [131] |
| $[Tc(O)(SN(R)S)(SNX_2)]$ | *In vitro* uptake studies in B16 murine melanoma cells indicated tumor-cell accumulation of the prepared compounds after a 60-min incubation. *In vivo* evaluation of some synthesized compounds in the C57Bl6/B16 mouse melanoma model demonstrated tumor localization. The results suggest that small technetium-99m complexes could be useful as potential melanoma-imaging agents. | [133] |
| *Thrombosis imaging agent*<br>$[^{99}Tc(HYPY)(PPh_3)_2Cl_2]$,<br>$[^{99}Tc(HYPY)(PPh_3)_2(tricine)]$ | Ternary ligand technetium complexes of 2-hydrazinopyridine (HYPY), $PPh_3$ and $^{99}$Tc were prepared as structural models for the HYNICtide and triphenylphosphine-3,3′,3″-trisulfonate $^{99}$Tc complexes, which were also prepared. The last compounds have shown to be efficient venous thrombi imaging agents in canine arteriovenous and deep vein thrombosis models. | [78] |
| *AD chemotherapeutics*<br>$^{99}$Tc complex with bis-diazo ligand. | The affinity of technetium complexes for $\beta$1-40 amyloid fibrils was determined. | [83] |






(*Continued*)

Table 5. Continued.

| Metal complex or compound | Observations | Reference |
|---|---|---|
| *Heart imaging agent* | | |
| The bis(*N*-methyl, *N*-cyclohexyl dithiocarbamato) nitrido technetium-99m complex [$^{99m}$TcN(MECHDTC)$_2$] (MECHDTC: *N*-methyl,*N*-cyclohexyl dithiocarbamato) | The two-step procedure consisted of an initial reaction of $^{99m}TcO_4^-$ with succinic dihydrazide in the presence of stannous chloride as reducing agent and propylenediamine tetraacetic acid as complexant, and successive addition of sodium salt of *N*-methyl, *N*-cyclohexyl dithiocarbamate. According to realized studies, this compound is a potential myocardial and cerebral imaging agent. | [166] |
| $^{99m}$Tc–nitride–tetrofosmin complex | Myocardium specific, high retention and rapid blood and lung clearance. | [184] |
| *Renal function diagnosis* | | |
| $^{99m/99}$Tc–cysteine complex | Cysteine was chelated with $^{99m/99}$Tc in a freeze-dried kit containing Sn(II) ions, separating the green $^{99m/99}$Tc–cysteine complex. The biodistribution of this complex in mice was studied. Kidney was confirmed as the target organ. The protein-bound Tc–cysteine complex was the primary form in excreta, and renal tubular secretion was the excretory pathway. | [105] |
| $^{99}TcO(ECH_3)$ complex | Carboxyl groups are important for efficient renal uptake of small anionic molecules. $[^{99m}TcO(ECH)]^{2-}$ (ECH = pentaanionic form of (2R,7R)-2,7-dicarboxy-3,6-diaza-1,8-octanedithiol ($ECH_6$) is a potentially useful radiopharmaceutical for diagnosis renal function. | [107] |
| $HTcO(cysteine)_2$, $Ba[TcO(cysteine)_2]_2$ | The technetium-99m analogue of rhenium chelate $[Ph_4P]^+[\{ReO(Cys)_2\}^-\{HReO(Cys)_2\}]\cdot 4H_2O$ exhibited renal tubular transport and renal retention, which makes this radiopharmaceutical useful for evaluation of the clinical status of renal patients. | [98] |
| *Brain imaging agent* | | |
| [2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo [3.2.1]oct-2-yl]methyl](2-mercaptoethyl)amino] ethyl]amino]ethanethiolato(3-)-*N*2,*N*2′,*S*2,*S*2′] oxo-[1R-(exo-exo)]- [$^{99m}$Tc]technetium, [$^{99m}$Tc]TRODAT-1 | This complex displayed the highest initial uptake in rat brain. TRODAT-1 forms at least two diastereomers after complexing with a metal(V)-oxo (M = $^{99m}$Tc, Re) center core. The two isomers display different binding affinities toward dopamine transporters and distinct properties of localization in the striatum area of the brain where the transporters are located. Such compounds may provide a convenient source of short-lived imaging agents for routine diagnosis of CNS diseases (i.e. Parkinson's disease) in which changes in the dopamine transporter concentration are implicated. | [122, 123] |
| Bis(*N*-cyclobutyl-dithiocarbamato)nitrido technetium-99m complex [$^{99m}$TcN(CBDTC)$_2$] (CBDTC: *N*-cyclobutyl dithiocarbamato) | The complex was significantly retained in the brain. The brain uptake (ID %/g) was 3.61, 3.15 and 2.62 and the brain/blood ratio was 1.00, 1.44 and 1.30 at 5, 30 and 60 min post-injection, respectively. These results suggest that this compound could be a potential brain perfusion imaging agent. | [167] |
| Bis(*N*-isobutyl-dithiocarbamato)nitrido technetium-99m complex [$^{99m}$TcN(IBDTC)$_2$] (IBDTC: *N*-isobutyl dithiocarbamato) | The complex accumulated in the brain with high uptake and good retention. The brain uptake (ID%/g) was 6.22, 5.45 and 3.88 and the brain/blood ratio was 1.51, 2.24, 1.84 at 5, 30 and 60 min post-injection, respectively. These results suggest potential usefulness of the complex as a brain perfusion imaging agent. | [168] |

| | | |
|---|---|---|
| Dithioether tricarbonil complexes of $^{99m}$Tc(I) | The no-carrier-added preparation of the $^{99m}$Tc(I) carbonyl thioether complexes (with bidendate dithioethers (L) of the general formula $H_3C–S–CH_2CH_2–S–R$ (R = –$CH_2CH_2COOH$, $CH_2–C{\equiv}CH$) and $R'–S–CH_2CH_2–S–R'$ (R′ = $CH_3CH_2$–, $CH_3CH_2$–OH, and $CH_2COOH$)) could be performed using the precursor *fac*-$[^{99m}Tc(H_2O)_3(CO)_3]^+$. Biodistribution studies in the rat demonstrated for the neutral complexes $[^{99m}TcCl(CO)_3(CH_3CH_2–S–CH_2CH_2–S–CH_2CH_3)]$ and $[^{99m}TcCl(CO)_3(CH_2–S–CH_2CH_2–S–CH_2–C{\equiv}CH)]$ a significant initial brain uptake (1.03 ± 0.25% and 0.78 ± 0.08% ID/organ at 5 min p.i.). Challenge experiments with glutathione clearly indicated that no transchelation reaction occurs *in vivo*. | [157] |
| Neutral and paramagnetic $[TcL_3^n]$ complexes with O,P-bidentate phosphinocarboxylic acid ligands $HL^n$ [$n$ = 1,2-(diphenylphosphino) benzoic acid; $n$ = 2,3-(diphenylphosphino) propionic acid; $n$ = 3, (diphenylphosphino) acetic acid; $n$ = 4,3-(diethylphosphino)propionic acid]. | Similar reduction–substitution reactions have been performed utilizing the short-lived isotope $^{99m}$Tc. The physicochemical properties of the resulting $^{99m}$Tc-labelled species match very well those exhibited by the analogues prepared with the long-lived isotope $^{99}$Tc. Thus the chemical structures of $[^{99m}TcL_3^n]$ and $[^{99}TcL_3^n]$ analogues are identical. Female Sprague–Dawley rats were injected with pre-purified $[^{99m}TcL_3^n]$ ($n$ = 1, 2 or 4) and the resulting biodistributions evaluated at different times post injection. All the complexes undergo very low, but significant, brain uptake which decreases with time. | [181] |
| *Liver and kidney imaging agent* | | |
| PnAO-glucoronide Tc-labeled molecule | Biological evaluation of this complex indicated selective binding to hypoxic EMT-6 cells, and cytotoxicity to fibroblasts and HeLa, sk24, sk23, and g361 cancer cell lines, at an $IC_{20} < 2.5^{\circ}\mu g\,mL^{-1}$. *In vivo* biodistribution of two formulations of the complex in Balb/c mice with EMT-6 tumor produced diverse results, with one formulation showing no tumor preference, and the other providing a tumor/blood ratio of 2.3 at 4 h post-injection. The latter formulation delineated tumor, large intestine and liver in scintigraphic images. | [63] |
| $^{99m}$Tc amino acid complexes | Four amino acids (alanine, 2,3-diaminopropionic acid, cystine and cysteine) were chelated with $^{99m}$Tc and their renal excretion patterns studied in rabbits in the presence and absence of two renal tubular transport inhibitos, probenecid and 2,4-dinitrophenol. The compounds may be useful for evaluation of effective renal plasma flow. | [104] |
| 8α-Amino-6-methyl-ergoline Tc complex | The amino groups of 8α-amino-6-methyl-ergoline were mercaptoacetylated in order to prepare their Tc complexes. The coordination compounds have more affinities in binding test on cloned human dopamine $D_2$ receptors than the parent compound. Biodistribution on Wistar rats show a blood clearance with substantial accumulation and retention in liver, kidneys and low brain uptake. | [159] |

salmon calcitonin was effected [257] using a solid phase peptide synthesis (complex **126**). The product showed good serum stability and specific affinity for human calcitonin receptors. These and other patents show the high applied importance of the coordination chemistry of this element. The range of ligands (mainly *N*-containing), used for Tc complexation, is very wide: from the simplest acetonitrile [228] to novel bifunctional agents such as 3-hydroxy-4-[2-(2′-pyridinecarboxamido)acetylamino]benzoic acid [258] or the ligands earlier.

The recent reviews [5, 9, 10, 259] contain additional information on medical uses of similar and other Tc compounds. In addition to its medical use, other Tc applications [8] in industry make this element one of the most promising among the radioactive series. We expect further developments of technetium coordination chemistry during this decade, in particular on the design of new water-soluble complexes and complexes with novel ligands.

During evaluation of this manuscript in the journal, a number of related publications have appeared. Among the flow of the most recent articles, we would like to note first the review [260], dedicated to the coordination chemistry of $^{99m}$Tc and its core structures. Experimental reports are dedicated to the preparation, characterization and medical applications of various series of technetium compounds, such as, for example, complexes of the "3 + 1" type [261, 262], those with $[Tc(CO)_3]^+$ core [263–271] and representing a new core $[M(CO)_2(NO)]^{2+}$ (M = Tc, in particular) in bioorganometallic chemistry [272–274], and much more.



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