Dithiocarbamate complexes as radiopharmaceuticals for medical imaging

David J. Berry, Rafael Torres Martin de Rosales, Putthiporn Charoenphun and Philip J. Blower*

King's College London, Division of Imaging Sciences and Biomedical Engineering, 4th Floor Lambeth Wing, St Thomas Hospital, London SE1 7EH, UK

Abstract: Over the past 30 years dithiocarbamate ligands have found application in radiopharmaceutical metal-ligand complexes to image a range of disease states. The vast majority of research and applications, and the widest range of complex structures, have involved radionuclides of technetium and rhenium. Considering the extent of coordination chemistry of dithiocarbamate ligands described elsewhere in this issue, the extent of radiopharmaceutical application with metallic radionuclides is surprisingly narrow. Here we summarise the types of radiopharmaceutical complexes studied and the uses, and potential uses, to which they have been put in nuclear medicine.

Keywords: Copper, dithiocarbamate, nuclear medicine, radiopharmaceuticals, rhenium, technetium.

INTRODUCTION

Diagnostic and therapeutic nuclear medicine rely on radionuclides of several different metals from both the main groups and transitions series. Gamma- and positron-emitting radioisotopes are used for imaging molecular processes in the body using gamma camera imaging and positron emission tomography (PET). Beta- and alpha-emitting radioisotopes targeted to tumours are used for radionuclide therapy. Many of the radioisotopes employed are metals and have to be complexed in suitable form for targeted *in vivo* delivery to specific organs and disease sites. A wide variety of ligands and chelating agents have been used both to link radiometals to biological targeting molecules and to endow them with useful properties by controlling redox potential, lipophilicity etc. This brief review focuses on use of metal-dithiocarbamate complexes as radiopharmaceuticals. Dithiocarbamate (DTC) ligands are ubiquitous in metal coordination chemistry, as two excellent in-depth reviews of both main group [1] and transition metal [2] dithiocarbamate complexes have shown. It is therefore no surprise that use of metal-dithiocarbamate complexes in nuclear medicine has been researched for over 30 years. However, considering the breadth of experience of general metal-dithiocarbamate chemistry in the literature, research on applications in nuclear medicine has been surprisingly limited in scope and depth. The vast majority of work in this field has focussed on technetium and rhenium. In the 1980s and 1990s the *in vivo* biodistribution and biological targeting properties of simple Tc/Re-dithiocarbamate complexes were evaluated. Over the past decade dithiocarbamate ligands have increasingly been used as co-ligands in mixed ligand ternary complexes used for a variety of purposes such as heart imaging, or for bioconjugation and radiolabelling of biomolecules. Properties of the dithiocarbamate ligands (such as size and lipophilicity) have been varied to optimise the *in vivo* characteristics of the complexes. Study of dithiocarbamate complexes of other radiometals has been limited to thallium and copper radionuclides. Some speculative applications involving radionuclides of bismuth, cobalt and gold have also been included in this review.

*Address correspondence to this author at the King's College London, Division of Imaging Sciences and Biomedical Engineering, 4th Floor Lambeth Wing, St Thomas Hospital, London SE1 7EH, UK; Tel: +442071889513; Fax: +442071885442; E-mail philip.blower@kcl.ac.uk

TECHNETIUM AND RHENIUM

Due to its favourable nuclear properties (half life = 6 h, 140 KeV gamma rays) [3] and convenient supply from the $^{99}Mo/^{99m}Tc$ generator, technetium-99m (^{99m}Tc) is the most widely used radioisotope in nuclear medicine imaging. ^{99m}Tc exists in a range of oxidation states from +1 to +7 and interacts with a wide variety of ligands to form complexes that are used to image many *in vivo* functions and disease states. Its congener rhenium has, in addition to its two naturally occurring isotopes (^{185}Re and ^{187}Re), two potentially useful β-emitting radioactive isotopes (^{186}Re and ^{188}Re) that can be used for radionuclide therapy applications. ^{186}Re has a half-life of 90.6 h and is produced in nuclear reactors by neutron bombardment of stable ^{185}Re [3]. ^{188}Re has a half-life of 16.9 h and is produced from the decay of ^{188}W, and is thus available from a $^{188}W/^{188}Re$ generator [4]. Both isotopes produce imageable gamma rays, which are useful for tracking their biodistribution by gamma camera imaging.

In the earliest reports of dithiocarbamate ligands in ^{99m}Tc-radiopharmaceuticals, the lipophilic diethyldithiocarbamate (DEDTC) was used (together with formamidine sulfinic acid (FSA) to reduce pertechnetate) to produce a ^{99m}Tc complex whose structure was unknown but which was lipophilic enough to cross the blood brain barrier and clear by the hepatobiliary route [5-7]. A similar complex was produced using stannous tartrate as the reducing agent and used to radiolabel mixed leukocytes *in vitro* [8]. Subsequent studies have placed more emphasis on using structurally well-defined complexes by using well-established Tc and Re cores, such as the pentavalent technetium nitride $[TcN]^{2+}$ system, as precursors around which the dithiocarbamate ligands are assembled. These core systems are designed to produce complexes with reasonable

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stability and control of the chemical characteristics. Their applications may be classified into two general categories: those that are targeted by control of the properties of the complex itself, and those where the dithiocarbamate ligand is used as a bifunctional chelator providing a link to a biological targeting molecule. Each class is discussed separately below. An example of the former are the $[MN(DTC)_2]$ complexes whose lipophilic properties are controlled *via* lipophilic side chains of the dithiocarbamate ligand [9-11]. An example of the latter approach is a dithiocarbamate derivative of an antibiotic such as ciprofloxacin [12,13]. Dithiocarbamate ligands are very well suited to both types as they can be easily synthesised by treatment of molecules that have an existing primary or (preferably) secondary amine group with carbon disulfide [2]. Secondary amines are preferred since dithiocarbamates formed from primary amines have a tendency to decompose into an isothiocyanate [2] or a primary amine and carbon disulfide (CS_2) under acidic conditions [14].

The Nitrido $(M\equiv N)^{2+}$ Core

$[MN(DTC)_2]$ Complexes

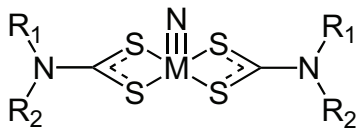
The most commonly used core for Tc and Re with dithiocarbamates in the coordination sphere is the Tc(V) nitrido core, $[TcN]^{2+}$ [15, 16]. Non-radioactive ReN complexes have been known for many decades. $[ReN(DEDTC)_2]$ (**1**) (Fig. **1**) [17] has a square pyramidal structure [18] as does the analogous $[TcN(DEDTC)_2]$ (**2**), the first reported example of a technetium complex with a Tc≡N triple bond [19]. These dithiocarbamate complexes were synthesised at the non-radioactive level in two steps. The rhenium precursor complex $[ReNCl_2(PPh_3)_2]$ [20] was synthesised from $[Re_2O_7]$ [20] or $Na[ReO_4]$ [27] and hydrazine dihydrochloride (as a source of N) and triphenylphosphine (PPh_3) in aqueous ethanol or from $[ReOCl_3(PPh_3)_2]$ by treatment with phenylhydrazine dihydrochloride in aqueous ethanol [28]. $[ReNCl_2(PPh_3)_2]$ was then subjected to ligand exchange with the dithiocarbamate ligands to furnish the dithiocarbamate complex [17]. The radiolabelled ^{99m}Tc complex was similarly prepared in two steps: a $[^{99m}TcN]^{2+}$ intermediate was synthesised by reducing $^{99m}TcO_4^-$ in saline with stannous chloride in the presence of succinic dihydrazide (as a nitrogen atom donor) and the chelator DPTA (1,2-diaminopropane-*N*,*N*,*N*′,*N*′-tetraacetic acid) [12]. The intermediate complex was then incubated with the dithiocarbamate ligands to produce the $[^{99m}TcN(DTC)_2]$ complexes.

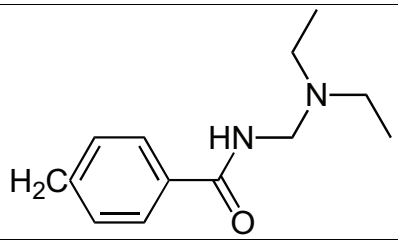
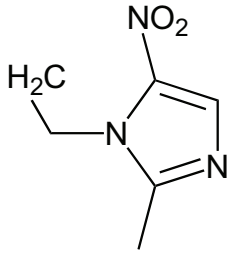
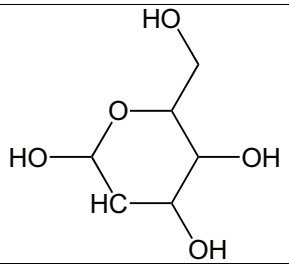
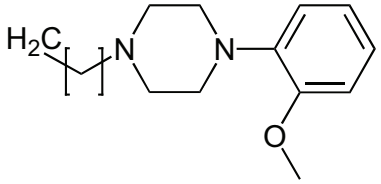
The $[TcN]^{2+}$ core has been used to create ^{99m}Tc-dithiocarbamate complexes with a range of uses in nuclear medicine. $[^{99m}TcN(NOET)_2]$ (**3**) was the first clinically tested example of a $[^{99m}TcN]$ tracer for imaging the myocardium [9,29]. It was found to be the most effective myocardial imaging agent among a number of lipophilic $[^{99m}TcN(DTC)_2]$ complexes including $[^{99m}TcN(DEDTC)_2]$ (**2**) [21]. Although $[^{99m}TcN(NOET)_2]$ is uncharged, its myocardial uptake properties in dogs [30] and humans [31,32] are similar to those of the $^{201}Tl^+$ ion, which behaves as a potassium ion analogue and is taken up by cardiomyocytes *via* the sodium-potassium ATPase pump. Its subcellular distribution in rat myocardium [33] showed localisation in the hydrophobic parts of the cells. Both the ^{99m}Tc complex and its ^{188}Re analogue have been used to radiolabel blood cells [34,35] and a number of lipophilic $[^{99m}TcN(DTC)_2]$ complexes including **2** were shown to be taken up in cultured tumour cells *in vitro* [9]. Lipophilic $[^{99m}TcN(DTC)_2]$ complexes containing dithiocarbamate ligands derived from primary amines [10,11,36-45] and a few secondary amines [10,46,47] have been shown to cross the blood brain barrier, suggesting applications in brain perfusion imaging.

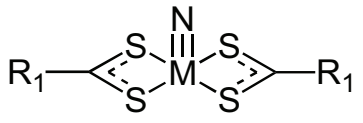
More recently the dithiocarbamate ligand has been used as a bifunctional linker to attach technetium to specific targeting molecules. Dithiocarbamate derivatives of a number of antibiotic molecules based on the fluoroquinolene group have been synthesised by addition of CS_2 to a native amine group, and their $[^{99m}TcN(DTC)_2]$ complexes have been evaluated as infection imaging agents. These include $[^{99m}TcN(Ciprofloxacin\text{-}DTC)_2]$ (**4**) [12] and analogues based on Norfloxacin [48], Garenoxacin [49], Trovafloxacin [50], Moxifloxacin [51], Tosufloxacin [52], Sitafloxacin [53] and Gatifloxacin [54]. A $[^{99m}TcN(DTC)_2]$ complex based on a benzamide structure (**5**) was synthesised and evaluated for diagnosis of malignant melanoma [22], however, tumour/organ ratios in mice were lower than for the more established [^{123}I-BZA]. A $[^{99m}TcN(DTC)_2]$ complex was synthesised for imaging of sigma receptors, which can be overexpressed in a variety of cancers; but tumour uptake in mice was low [55]. $[^{99m}TcN(DTC)_2]$ complexes containing the nitroimidazole functionality (e.g. **6**) have also been synthesised for hypoxia imaging but did not show promise [23,24]. $[^{99m}TcN(glucosamine\text{-}DTC)_2]$ (**7**) showed tumour uptake in mice [25] and $[^{99m}TcN(DTC)_2]$ complexes based on the 2-methoxyphenylpiperazine moiety (**8**) have been tested for 5-HT_{1A} receptor binding for imaging brain disorders [26].

$[TcN(PNP)(DTC)]^+$ Complexes

Several mixed ligand cationic complexes with the general structure $[MN(PNP)(DTC)]^+$ (e.g. **9 - 13**) (Fig. **2**) have been evaluated (where PNP is a potentially tridentate amino bisphosphine ligand) with dithiocarbamates as co-ligands [56,58,59]. Characterisation of some of the rhenium complexes indicated a square pyramidal geometry with two phosphorus and two sulfur donor atoms as well as the nitride ligand. In addition, a weak interaction between the metal atom and the tertiary nitrogen atom on the backbone of the phosphine ligand [57] is believed to significantly stabilise the complexes; if the diphosphine ligands containing only methylene groups in the chain were used, no pure stable compounds could be isolated [65]. $[^{99m}TcN(PNP)(DTC)]^+$ complexes were stable to transchelation for up to 4 hours in serum and in solutions of excess cysteine or glutathione [61]. They can be the basis of lipophilic cationic tracers for myocardial perfusion imaging and both $[^{99m}TcN(PNP3)(DBODC)]^+$ (**10**) and $[^{99m}TcN(PNP5)(DBODC)]^+$ (**11**) show favourable myocardial uptake [60-62], with heart/lung and heart/liver ratios much higher than those of the commercially available agents ^{99m}Tc-tetrofosmin and ^{99m}Tc-sestamibi [61] and more favourable dosimetry [66]. Rapid myocardial uptake was



	M	R_1	R_2	Ref
1	Re	Et	Et	[17,21]
2	Tc	Et	Et	[9,19,21]
3	Tc	Et	OEt	[9, 21]
5	Tc		H	[22]
6	Tc		H	[23,24]
7	Tc		H	[25]
8	Tc		H	[26]



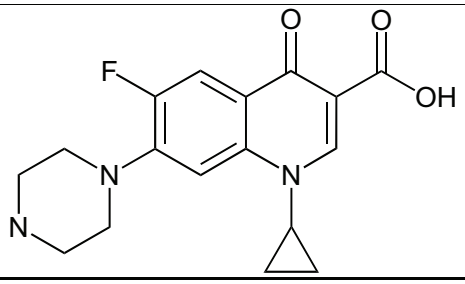
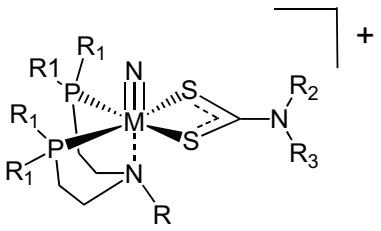
	M	R_1	Ref
4	Tc		[12]

Fig. (1). $[MN(DTC)_2]$ complexes.

further improved by incorporating an alicyclic dithiocarbamate ligand (e.g. **12**) (Fig. **3**) [67]. The analogous complex $[^{99m}TcN(PNP5)(NOET)]^+$ (**13**) also shows myocardial uptake [63]. A bifunctional nitroimidazole-dithiocarbamate derivative was used with this ligand system to produce $[^{99m}TcN(PNP5)(MNIE\text{-}DTC)]^+$ (**14**) which has been used to image hypoxia [64].

In a related series of complexes the $[MN]^{2+}$ core was replaced by N-phenylhydrazine to give complexes with the structure $[TcNNPh(PNP)(DTC)]^+$ (**15**) [68] in which the phenylhydrazine acted as a surrogate for the bifunctional linker HYBA (4-hydrazinobenzoic acid). Combinations of crown ether-derived dithiocarbamates and bisphosphine ligands were evaluated in the metal coordination sphere to optimise the lipophilicity and stabilise the cationic charge [68, 69].



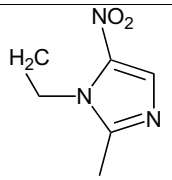
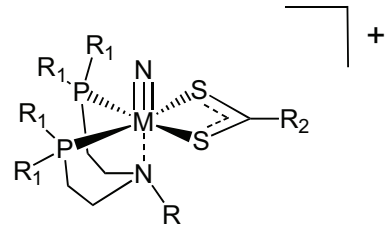
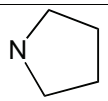
	M	R	R_1	R_2	R_3	Ref
9	Re	$(CH_2)_2OEt$	$(CH_2)_4OMe$	$(CH_2)_2OEt$	$(CH_2)_2OEt$	[58,59]
10	Tc	$(CH_2)_2OMe$	$(CH_2)_3OMe$	$(CH_2)_2OEt$	$(CH_2)_2OEt$	[60-62]
11	Tc	$(CH_2)_2OEt$	$(CH_2)_4OMe$	$(CH_2)_2OEt$	$(CH_2)_2OEt$	[60-62]
13	Tc	$(CH_2)_2OEt$	$(CH_2)_4Me$	Et	OEt	[63]
14	Tc	$(CH_2)_2OEt$	$(CH_2)_4OMe$		H	[64]

Fig. (2). $[MN(PNP)(DTC)]^+$ complexes.



	M	R	R_1	R_2	Ref
12	Tc	$(CH_2)_2OMe$	$(CH_2)_3OMe$		[67]

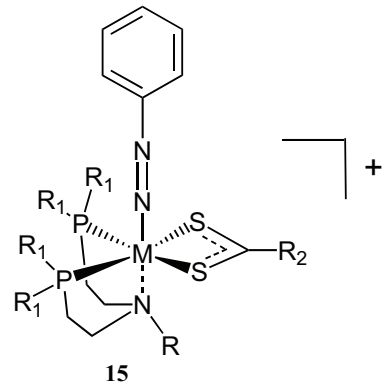


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Fig. (3). $[MN(PNP)(DTC)]^+$ and $[MNNPh(PNP)(DTC)]^+$ complexes.

TcN(PS)(DTC) Complexes

A series of complexes based on the $[TcN]^{2+}$ core with one bidentate phosphine-thiol (PS) ligand and one dithiocarbamate with the general square pyramidal structure [TcN(PS)(DTC)] (**16**) (Fig. **4**) has been reported [70-72]. Analogues of these complexes containing lipophilic dithiocarbamates such as DEDTC and dipropyldithiocarbamate (DPDTC) and lipophilic side chains on the PS ligand were able to cross the blood brain barrier [71], but attempts to exploit this by incorporation of dithiocarbamate derivatives of 2-methoxyphenylpiperazine to produce agents for imaging $5HT_{1A}$ receptors in brain led to reduced blood brain barrier penetration [72].

The Tricarbonyl $[M(CO)_3]^+$ Core

The $[^{99m}Tc(CO)_3]^+$ core with a dithiocarbamate ligand has been utilised for radiolabelling biomolecules with ^{99m}Tc [73]. The coordination sphere consisted of the three CO ligands plus one monodentate co-ligand such as isonitrile or phosphine (**17**) (Fig. **5**), and one bidentate dithiocarbamate co-ligand. The link to the biomolecules was through either the monodentate ligand or the dithiocarbamate. Conjugation of the dithiocarbamate ligand to a model amino acid using a dithiocarbamate-carboxylate-NHS ester **18** (Fig. **6**) was only possible if the CS_2 functionality was first protected using a non-radioactive $[M(CO)_3]^+$ fragment as shown in (Fig. **6**) to avoid decomposition under the acidic conditions needed for the conjugation step [73]. Alternatively, a monodentate phosphine ligand could be used as the bifunctional linker (**17**) [74]. $[^{99m}Tc(CO)_3]^+$ has also been used to radiolabel a range of dithiocarbamate compounds including brain perfusion agents [75], 5-HT_{1A} receptor imaging agents [26] and dithiocarbamate derivatives of Ciprofloxacin [13], Tosufloxacin [52] and Sitafloxacin [76] for infection imaging. Whilst it is expected that the dithiocarbamate ligand coordinates to the technetium in bidentate mode, the identity of the ligand in the sixth coordination site, and the overall structure of the complex, remains unknown.

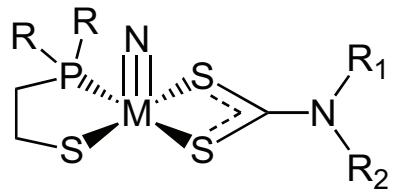


Fig. (4). A [TcN(PS)(DTC)] complex.

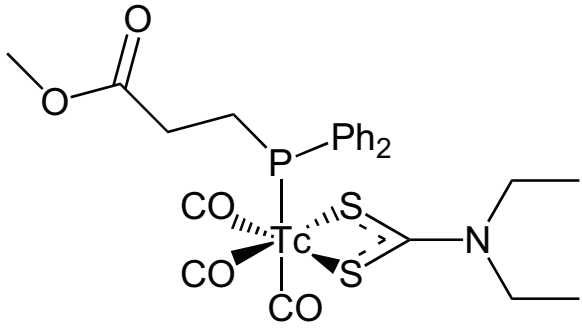


Fig. (5). A $[Tc(CO)_3]^+$ dithiocarbamate complex.

Miscellaneous Technetium and Rhenium Complexes

Ternary ligand complexes such as **19** (Fig. **7**) have also been evaluated for the development of new potential rhenium radiopharmaceuticals. The core consisted of a diazenide ligand, triphenylphosphine and some simple dithiocarbamates [77]. The seven-coordinate distorted pentagonal bipyramidal complex $[Re(DEDTC)_3(CO)]$ (**20**) [78] and its technetium analogue (**21**) [79] have been reported. Further radioactive ^{99m}Tc complexes of the general formula $[^{99m}Tc(DTC)_3(CO)]$ were produced [80]. These highly lipophilic complexes were rapidly cleared by the hepatobiliary system and showed potential as hepatobiliary imaging agents. The same authors have also published the structures of $[Tc(DEDTC)_2Cl_2(NS)]$ (**22**) [81] and $[Tc(DEDTC)_2Br_2(NS)]$ (**23**) [82].

COPPER

Copper has four radionuclides useful for molecular imaging, ^{60}Cu, ^{61}Cu, ^{62}Cu and ^{64}Cu. ^{64}Cu is the most widely used thanks to its favourable properties for PET imaging and radionuclide therapy (half-life 12.7 h, 18 % β^+, 39 % β^-, 43 % electron capture). Dithiocarbamate ligands are well known as effective ligands for Cu(II), forming square-planar $[Cu(II)(DTC)_2]$ complexes, but their use as chelating groups for copper radionuclides has been somewhat neglected to date [2,83]. The radiolabelled complexes are formed very rapidly in high yield but lack kinetic stability in biological media. $[^{62}Cu(DMDTC)_2]$ (**24**) (Fig. **8**) and $[^{62}Cu(DEDTC)_2]$ (**25**) [84] readily cross the blood brain barrier and have potential utility as brain perfusion imaging agents [85]. Because of their lipophilicity and kinetic lability these complexes are taken up and trapped in cells, and complexes of dimethyldithiocarbamate (DMDTC), DEDTC and DPDTC (**26**) were used to label a mouse macrophage cell line (J774) with very high efficiency depending on the dithiocarbamate used. $[^{64}Cu(DMDTC)_2]$ showed the most rapid and efficient uptake [86]. However, the wash-out rates were too rapid for imaging cell trafficking *in vivo* and were the same for all the complexes, suggesting rapid intracellular dissociation of all the complexes.

Bifunctional dithiocarbamate ligands have been developed incorporating a bisphosphonate group for strong binding of copper radionuclides to several inorganic materials of interest to the biomedical imaging and engineering fields [87]. The copper complex $[^{64}Cu(DTCBP)_2]$ (**27**) is obtained instantly at room temperature by simple addition of the radionuclide to the ligand. This is in contrast to most macrocyclic chelators commonly used for ^{64}Cu chemistry, such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) or 4,11-bis(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (CB-TE2A) in which complex formation is relatively slow and heating (*ca.* 95 ºC) is necessary [83]. When conjugated to surfaces of inorganic materials *via* its bisphosphonate groups, $[^{64}Cu(DTCBP)_2]$ resists transchelation reactions *in vivo* [87].

THALLIUM

^{201}Tl-DEDTC was introduced in the 1980s as a lipophilic radiotracer for imaging cerebral blood flow [6, 7, 88-90]. The structure of the complex was not determined, although thallium is known to form [Tl(I)(DTC)] and $[Tl(III)(DTC)_3]$ complexes [1]. The tracer was found to have higher retention in rabbit brain and much lower blood protein binding than

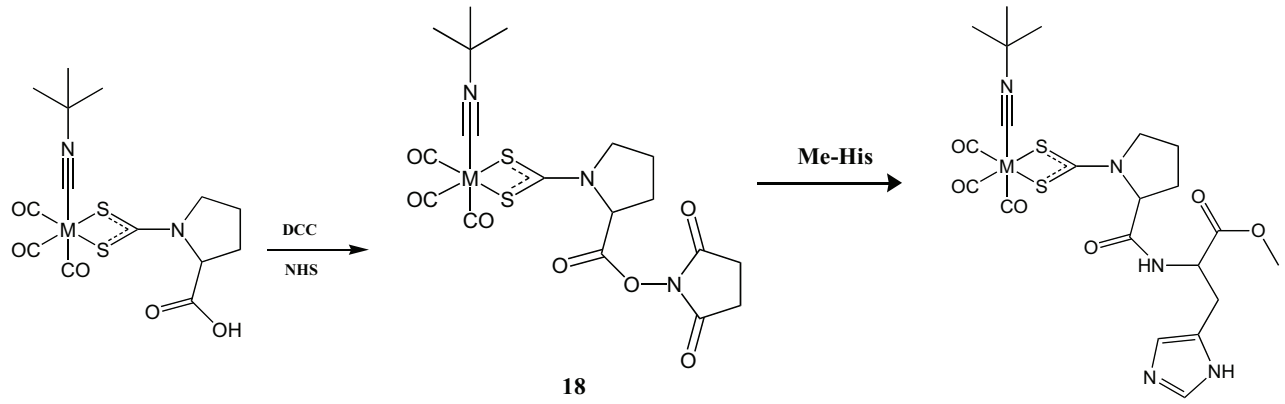
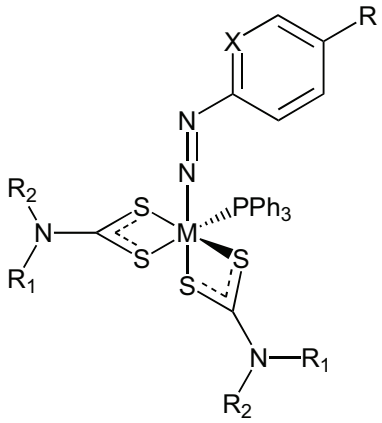
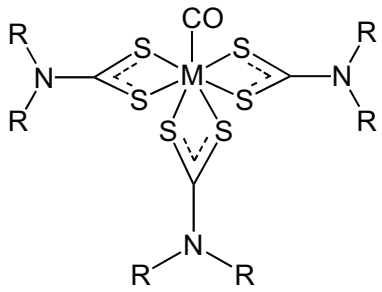


Fig. (6). Dithiocarbamate ligand synthesis with $[M(CO)_3]^+$ as a protecting group.

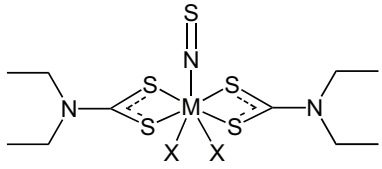
the technetium "analogue" ^{99m}Tc-DEDTC of unknown structure [7]. The low energy and low abundance of gamma rays from ^{201}Tl along with a long half-life of 3 days make the imaging properties and dosimetry of this radionuclide less ideal for SPECT imaging than the ^{99m}Tc complexes such as ^{99m}Tc-HMPAO [91] which replaced it.



	M	X	R	R_1	R_2	Ref
19	Re	CH	OMe	Me	Me	[77]

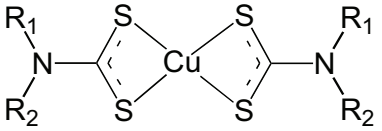


	M	R	Ref
20	Re	Et	[78]
21	Tc	Et	[79,80]



	M	X	Ref
22	Tc	Cl	[81]
23	Tc	Br	[82]

Fig. (7). Miscellaneous technetium and rhenium dithiocarbamate complexes.



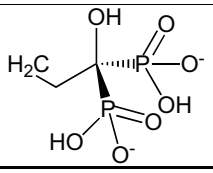
	R_1	R_2	Ref
24	Me	Me	[84]
25	Et	Et	[84]
26	Pr	Pr	[86]
27		Me	[87]

Fig. (8). [Cu(DTC)$_2$] complexes.

BISMUTH

A selection of bismuth complexes [Bi(DTC)$_3$] have been synthesised and evaluated *in vitro* and *in vivo* for their anti-cancer properties [92]. Their *in vivo* mechanism of action is unknown as there is no known biological target. Nevertheless, if they are able to selectively enter tumour cells then radioactive analogues using the α-emitters ^{212}Bi and ^{213}Bi [93, 94] could be potential candidates for radionuclide therapy.

COBALT

Cobalt-55 is a positron-emitting isotope ($t_{½}$ = 18.2 h) that has been scarcely explored for nuclear medicine. It has been used to mimic calcium influx in ischaemic tissue and for

carbohydrate and platelet labelling [95-97]. Dithiocarbamate ligands are well known to form kinetically inert Co(III) complexes $[Co(DTC)_3]$ [2]. Thus, ^{55}Co derivatives could provide stable PET imaging agents with potentially very low transchelation rate *in vivo*. The extremely long half life of the radioactive daughter isotope (^{55}Fe, $t_{½}$ = 2.7 years), however, represents a significant obstacle for the successful development of these agents, as it may result in unnecessary long-term radiation doses to subjects and represents an environmental issue.

GOLD

Radioisotopes of gold are available and occasionally used in medicine. The $^{195m}Hg/^{195m}Au$ generator was developed to produce ^{195m}Au, a short half-life gamma emitter [98] that can be used as a tracer for imaging blood flow. Beta emitters ^{198}Au and ^{199}Au, produced from either nuclear reactor or cyclotron [99], have potential for radionuclide therapy [100,101]. Chelators for use with gold isotopes are underdeveloped but since gold (III) dithiocarbamate complexes have demonstrated high anti-tumour cytotoxicity with less non-target toxicity than the common anticancer drug cisplatin [102], and have good stability in physiological conditions [103], radioactive gold dithiocarbamate complexes may have potential as radiopharmaceuticals.

SUMMARY

Dithiocarbamate ligands have found application in radiopharmaceuticals containing metallic radionuclides to image a range of disease states. The vast majority of research and applications, and the widest range of complex structures, have involved technetium and rhenium. Considering the extent and variety of coordination chemistry of dithiocarbamate ligands described elsewhere in this issue, the extent of radiopharmaceutical application with metallic radionuclides that has been realised is surprisingly narrow and confined to just a few complex types. The potential for application of these ligands in nuclear medicine remains great, as the field of molecular imaging as whole is evolving and clinical utility and availability of positron emission tomography is growing rapidly. Radionuclide therapy is also a growing field and dithiocarbamate ligands have the potential to contribute, especially with radionuclides of rhenium which offer a particularly wide range of stable, well-defined dithiocarbamate complex types.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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