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A review on evaluation of technetium-99m labeled radiopharmaceuticals

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Abstract In the past few years, substantial progress has been made in technetium chemistry, including the synthesis of a variety of ^{99m}Tc-radiopharmaceuticals. This synthesis can be made feasible by using suitable reducing agents, highly specific ligands, appropriate buffer, and specific pH etc., which results in high radiochemical purity, minimum labeling time, commercial expediency of ^{99}Mo/^{99m}Tc generator and high biological efficacy. ^{99m}Tc-radiopharmaceuticals have confirmed their worth in every span of life, especially in clinical and medical applications. Now ^{99m}Tc based pharmaceuticals are being used as diagnostic agents for a large number of infections caused by bacteria or any pathogens, tumors, cancers, ulcers etc. In this review, we discuss synthesis of a variety of ^{99m}Tc carrying biological molecules (antibiotics/antibodies/peptides/amino acids/macro and micro-organic molecules) along with their applications, to overview key innovations.

Keywords ^{99m}Tc · Labeling · pH · Antibiotics · Antibodies · Peptides · Amino acids

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Introduction

In radiopharmaceuticals, the radioactive tracers are the main components to examining the function of body systems. Many radiopharmaceuticals are available for imaging purposes, which differ in terms of their physical characteristics, bio-distribution and radiation exposure. Medical images provide very helpful information to medical specialists for taking the important and right decision for diagnosis and therapeutic action. The overwhelming applications of radioisotopes in every span of life like agriculture, industry, chemistry, biology and nuclear medicine have made them critically significant. In some diseases radiopharmaceuticals can identify medical abnormalities at an early stage than other diagnostic tests. Synthesis of new radiolabeled agents (radiopharmaceuticals) is the major field of interest of nuclear medicine. Many radionuclides exist in nature, but naturally occurring isotopes do not have suitable half-life for medical use. Radiopharmaceuticals are being used in medical applications for molecular imaging and treatment of various infections, cancer and tumor [1–5]. As far as molecular imaging is concerned, it is a distinct technique capable to visualize, characterize and measure the biological processes at the molecular and cellular level, in humans and other living systems [6–13]. Nonetheless, the major radionuclide used for preparing diagnostic radiopharmaceuticals today is ^{99m}Tc, owing to its physical and chemical properties [14–16].

Salient features of ^{99m}Tc

Depending on clinical requirements, gamma or positron emissions, radiolabeling approaches, kinetics and coordinating systems, a variety of radioisotopes have been explored to develop radiopharmaceuticals. Among these,

^{99m}Tc based radiopharmaceuticals have confirmed their significance with ideal physical characteristics ($t_{1/2}$ 6 h, photon energy 140 keV, no corpuscular radiation), high radiochemical purity, minimum labeling time (10–30 min at room temperature sometimes), low cost, commercial expediency from ^{99}Mo/^{99m}Tc generator and high biological efficacy (maximum assimilation by target organ and favorable pharmacokinetics). So more than 80 % of radiopharmaceuticals being used for diagnostic purposes contain ^{99m}Tc [5, 17]. Technetium (^{99m}Tc) has ideal energy of photons which is able to go inside the tissue and it can be detected easily. Due to the short half-life, it reduces the internal radiation hazard and has high limit of intake as compared to other radioisotopes commonly used in laboratories. The chemistry of ^{99m}Tc is very similar to Re because it is located in the periodic table near Rhenium element. Technetium is the 43 element in the periodic table and it is the member of transition metals group VIIB. The electron configuration of technetium is $4d^5$ $5s^2$. Technetium has seven electrons in its outer most shell just like Krypton's noble gas configuration and enthusiastically loses these electrons to yield the plus seven oxidation state of pertechnetate (TcO_4^-). It has distinguished coordination chemistry with a range of oxidation states between +1 and +7. It facilitates synthesis of technetium based radiopharmaceuticals with diverse ligand environments (O–, C–, Se, N–, P–, S– donor centers and their combinations) [18–31]. Sometimes this diversity does not assist reliable control of the oxidation state and stability of the complexes. On the other hand, it is a matter of fact that this diversity facilitates extensive opportunities for modifying technetium complexes, their structure and properties i.e. altering total charge of the complex, lipophilicity etc. [12, 13, 22–27]. Radiopharmaceuticals are frequently being synthesized with compounds of ^{99m}Tc in oxidation states +1, +3, +4, and +5, using ^{99}Mo/^{99m}Tc generator, and suitable reducing agents like $SnCl_2{\cdot}2H_2O$, SnF, HCl, $NaBH_4$, $Na_2S_2O_4$, Zn dust and $FeSO_4$ etc. From a generator, ^{99m}Tc is eluted in the form of $Na^{99m}TcO_4$. Here negatively charged pertechnetate ion ($^{99m}TcO_4^-$) comprises ^{99m}Tc with +7 oxidation state. But in this form, ^{99m}Tc cannot make a stable complex with ligands, peptides or related molecules. Thus, it is necessary to lower the hepta valency of ^{99m}Tc [32–39]. This lowering of oxidation state is accomplished by using suitable reducing agent, specific ligand(s), and most probably the reaction conditions [40–45]. Previous studies revealed efficient labeling of $^{99m}TcO_4^-$ and $[^{99m}Tc\ (H_2O)_3\ (CO_3)]^+$ with a variety of bidentate and tridentate biologically active ligands having amine, N-heterocycles, aromatic and/or carboxylic donors [6–10, 21, 46]. Due to the ease of access and labeling, high specificity, rapid assimilation at infection or tumor site, i.e. early diagnosis, rapid blood clearance, high target to non-target ratio, less antigenicity, low toxicity, and high compatible half-life of ^{99m}Tc, it is a more desirable labeling radioisotope as compared to others for diagnostic purposes [32]. Also ^{99m}Tc complexes with antibiotics, drugs, peptides, nucleobases like purine and pyrimidine, amino acids etc. have proven their worth in many biochemical systems. These complexes either intercalate DNA or interfere with DNA replication machinery to intervene cancer, tumor, infection etc. The potential to incorporate this radionuclide (^{99m}Tc) into different targeting determinants has been the prime concern in developing specific diagnostic radiopharmaceuticals [5, 16]. Usually radiopharmaceuticals comprising ligands containing N- and S-centers prove to be the best for diagnosis of renal function [6], while that with O-centers are best for myocardial imaging [7]. Those with S- or P-centers are good for CNS receptor imaging, heart imaging and bone scintigraphy [8, 9, 47].

Factors affecting percentage labeling yield

In developing radiopharmaceuticals, maximum labeling yield and radiochemical purity are the main concern of a researcher. Several parameters including pH level, concentration of reducing agent ($SnCl_2$) and coordination moiety i.e. ligand in the solution, and boiling time are optimized for good labeling yield and stable complex. Stability of a labeled moiety is of worth importance in terms of shelf-life and biodistribution. After labeling, in vitro stability, while in vivo stability after injecting in a living body, are of major concern [48–54]. As the radio isotopic atoms of the ligand moieties dissociate, the concentration of the labeled compounds in the shelf decreases. Sometimes such dissociation may continue or even increase in the in vivo domain. As it is much feasible for dissociated radioactive atoms to accumulate in different organs/tissues, the compounds with low labeling yields and/or substantial instability inside the body would not give desired biodistribution. Stability of radiolabeled compound is accomplished by temperature, pH and light etc. [10–13, 22]. An optimum pH with appropriate buffer solution plays significant role to acquire maximum radiochemical yield. Usually Phosphate buffer with pH 7 (6–8 in some cases) is found to be the best for a large number of systems [23–27, 55–59]. It is recommended that the injectable radiopharmaceutical should have pH compatible to blood pH (7.4) [12]. Also the selection of suitable reducing agent and its appropriate concentration is the basic requirement to get maximum radiochemical yield. Technetium in the form of pertechnetate ion ($^{99m}TcO_4^-$) with +7 oxidation state is actually nonreactive in nature and must be reduced to accelerate labeling reactions. Hydrated

stannous chloride ($SnCl_2 \cdot 2H_2O$) is found to be effective in synthesizing most of the radiopharmaceuticals. It is observed that an increase in concentration of $SnCl_2 \cdot 2H_2O$ facilitates increased formation of colloids that leads to decreased yield of the labeled complex [13]. As far as concentration of the starting material (ligands) is concerned, an increase in concentration results in maximum incorporation of ^{99m}Tc because of minimum limit to the volume used [22–25].

^{99m}Tc-labeled antibiotics

Pathogens (bacteria, viruses, parasites, fungi etc.) are regarded as the main source of variety of severe infectious diseases that may lead to mortality or morbidity. Primordial detection and recognition of the infection site allows prompt and successful treatment. Mostly delayed diagnosis of internal infections halts effective treatment and sometimes results in death as well. Actually the diagnosis of inflammatory processes relies on revealing anatomical/structural alterations of the affected organs and these changes are specific to the nature of the inflammation/infection under consideration. There is diversity in sensitivity, accuracy and specificity of various diagnostic techniques that mostly depends on the nature of the disease and pathophysiology operating there. The main objective of different imaging techniques is to incorporate the diagnostic functional data with that of anatomical/structural information in order to describe and characterize site, extent and activity of the disease [60].

After the development of various radiopharmaceuticals, the risk factors of morbidity or mortality accompanying infectious diseases have sharply decreased. ^{99m}Tc based radiopharmaceuticals have a significant role in distinguishing infections from inflammations. Although scintigraphy images are based on functional abrasions of tissues even then inflammatory or infectious progressions can be visualized in their early phases, when anatomical alterations are not yet obvious.

Ciprofloxacin, a frequently used antibiotic is found to be active against most of the gram positive and gram negative bacteria, was labeled with ^{99m}Tc. Ciprofloxacin is a fluoroquinolone-derivative antibiotic that binds to bacterial DNA gyrase and topoisomerase IV, and thus hinders the DNA replication [61]. The infections accurately detected by ^{99m}Tc labeled ciprofloxacin (infector) are septic arthritis, prosthetic device infections, osteomyelitis, endocarditis, deep seated abscesses and extrapulmonary tuberculosis [62]. While ^{99m}Tc-levofloxacin is found to be effective in diagnosing lungs, bone, sinus, airways, skin and joint infections, mostly caused by bacteria [63]. There are other fluoroquinolones derivatives also labeled which provide a higher labeling yield and better results than ciprofloxacin, viz. ^{99m}Tc-clinafloxacin [64], ^{99m}Tc-delafloxacin [65], ^{99m}Tc-fleroxacin [66], ^{99m}Tc-gemifloxacin [67], ^{99m}Tc-norfloxacin [68], ^{99m}Tc-rufloxacin [69] etc.

There are cephalosporins, antibiotics with greater effectiveness against gram-negative bacteria, ^{99m}Tc-cefepime [70], ^{99m}Tc-cefoperazone [26], ^{99m}Tc-ceftizoxime [71], ^{99m}Tc-ceftriaxone [72], ^{99m}Tc-cefuroxime [73], etc. There also certain ^{99m}Tc-antibiotics used to distinguish between sterile inflammation and bacterial infection namely ^{99m}Tc-cefepime [70], ^{99m}Tc-cefprozil [74], ^{99m}Tc-clarithromycin [75]. Whereas ^{99m}Tc-sulfadimidine can differentiate between septic and aseptic inflammation [76]. ^{99m}Tc-daunorubicin, Mitomycin C and ^{99m}Tc-doxorubicin are the only anticancer drugs which are also antibiotics, labeled with ^{99m}Tc for brain imaging [77], liver imaging [16], and tumor detection [78] respectively. There are also many others given in the Table 1.

^{99m}Tc-labeled proteins, peptides, amino acids, and their derivatives

Amino acids are the building blocks of peptides and proteins, which are the major structural and functional units of living systems. Amino acids are present in the body and used in the metabolism. When there are higher energy needs, amino acids are also used for energy fulfilment. Thus in tumors, where there are neoplastic cells with high energy needs, ^{99m}Tc-labeled amino acids or their derivatives prove to be good tumor locating agents. Some instances are ^{99m}Tc-L-carnitine [11], ^{99m}TcN-PRODTC [79], ^{99m}TcN-PHEDTC and ^{99m}TcO-PHEDTC [80].

There are several receptors overexpressed in many types of tumors which can be bound by peptides. ^{99m}Tc-labeled peptides, thus, are used as to target these overexpressed receptors and potentially better tumor localization [81]. Angiogenesis in tumors depends on the integrin $\alpha_v\beta_3$ expression which is overexpressed in various metastasizing cancers [82]. Several ^{99m}Tc-labeled peptides have been synthesized which have high affinity to this receptor [83]. These include ^{99m}Tc-RGD and its derivatives ^{99m}Tc-[E-c(RGDfK)$_2$]$_2$ [83], ^{99m}Tc-3P-RGD2 [84], ^{99m}Tc-EDDA/HYNIC-RGD [85], given here within the Table 2. Other important receptors targeted for tumor imaging are somatostatin, GRP, EGF-R, and IGF-R, which are localized by ^{99m}Tc-octreotide [86], ^{99m}Tc-bombesin [87], ^{99m}Tc-Ior egf/r3 [50], ^{99m}Tc-$Z_{IGF1R:4551}$-GGGC [88] respectively, and their derivatives.

Immunoglobulins or antibodies are proteins synthesized by the body in response to some antigenic stimuli, which specifically bind to those antigens. So in the cases of tumor or infection, antibodies could be used to target the surface antigen of a cancerous cell, or antigens of the inflammatory

Table 1 ^{99m}Tc-labeled antibiotics and antibiotic derivatives

Compound	Oxidant/reducing agent	Optimum pH	Specific activity ^{99m}Tc (mCi/MBq)	Labeling yield (%)	Application	References
^{99m}Tc-AMOX sodium	$SnCl_2{\cdot}2H_2O$	4.8	37 MBq	>90	Inflammatory process imaging	[115]
^{99m}Tc-azithromycin	$SnCl_2{\cdot}2H_2O$	4.0	400 MBq	97.5 ± 0.9	Bacterial infection imaging	[27]
^{99m}Tc-benzyl penicillin	$SnCl_2{\cdot}2H_2O$	6.0	13 mCi	>99	Liver, spleen and lungs imaging	[58]
^{99m}Tc-BDOQCA	$SnCl_2{\cdot}2H_2O$	6.0	400 MBq	97.3	Used for infection imaging	[116]
^{99m}Tc-cefazolin	$SnCl_2{\cdot}2H_2O$	4.0	400 MBq	89.5	Infection/inflammation imaging	[48]
^{99m}Tc-cefepime	$SnCl_2{\cdot}2H_2O$	8.0	400 MBq	98 ± 1.4	Difference b/w infection/sterile inflammation	[70]
^{99m}Tc-cefoperazone	$SnCl_2{\cdot}2H_2O$	8.0	400 MBq	97.9	Detecting sites of infection	[26]
^{99m}Tc-cefotaxime	$Na_2S_2O_4$	8.5-9.0	370–740 MBq	92 ± 2	Diagnosis of infectious foci	[117]
^{99m}Tc-cefprozil	$SnCl_2{\cdot}2H_2O$	4.0	200–400 MBq	97.5 ± 0.8	Difference b/w bacterial infection/sterile inflammation	[74]
^{99m}Tc-ceftazidime	$Na_2S_2O_4$	8.5-9.0	370–740 MBq	95.4 ± 2.0	Infection imaging	[118]
^{99m}Tc-ceftizoxime	$Na_2S_2O_4$	N/A	370 MBq	92	Investigation of infection processes	[71]
^{99m}Tc-ceftriaxone	$SnCl_2{\cdot}2H_2O$	9.0	~10 MBq	95 ± 2	Infection imaging	[119]
^{99m}Tc-ceftriaxone	$SnCl_2{\cdot}2H_2O$	7.0	~370 MBq	96.2 ± 0.2	Infection imaging	[72]
^{99m}Tc-ceftriaxone	$SnCl_2{\cdot}2H_2O$	5.0	370 MBq	94.2 ± 5.4	*Staphylococcus aureus* detection	[10]
^{99m}Tc-cefuroxime axetil	$SnCl_2{\cdot}2H_2O$	3.0	37–74 MBq	98 ± 1.	Infection imaging	[73]
^{99m}Tc-ciprofloxacin	$SnCl_2{\cdot}2H_2O$	2.5	178 GBq/mmol 370–740 MBq	>90	Infection imaging	[120]
^{99m}Tc-ciprofloxacin	Stannous tartrate	4.0	370 MBq (10 mCi)	95	Bacterial infection imaging agent	[62]
^{99m}Tc-clarithromycin	$SnCl_2{\cdot}2H_2O$	4.0	400 MBq	98 ± 0.2	Infection imaging, differentiating with sterile inflammation	[75]
^{99m}Tc-clinafloxacin	$SnCl_2{\cdot}2H_2O$	5.6	0.5–5.0 mCi	97.55 ± 0.22	*Staphylococcus aureus* infection detection	[64]
^{99m}Tc-clindamycin	$SnCl_2{\cdot}2H_2O$	6.0–7.0	380 MBq	>95	*Staphylococcus aureus* infection detection	[14]
^{99m}Tc-daunorubicin[a]	$SnCl_2{\cdot}2H_2O$	5.0–6.0	~370 MBq	>96	Brain imaging	[77]
^{99m}Tc-delafloxacin	$SnCl_2{\cdot}2H_2O$	6.0	~125 MBq	98 ± 2.1	Methicillin-resistant *Staphylococcus aureus* infection radiotracer	[65]
^{99m}Tc-difloxacin	$SnCl_2{\cdot}2H_2O$	4.0	400 MBq	95.6	Infection site imaging	[57]
^{99m}Tc-doxorubicin[a]	$SnCl_2{\cdot}2H_2O$	6–7	~370 MBq	>92	Tumor imaging	[78]
^{99m}Tc-doxycycline hyclate	$SnCl_2{\cdot}2H_2O$ or Stannous tartate	4.75–7.4	37 MBq	>95	Infection imaging	[23]
^{99m}Tc-enorfloxacin	Stannous tartarate	N/A	120 MBq/mg	72 ± 7	Infection imaging	[121]
^{99m}Tc-erythromycin	$SnCl_2{\cdot}2H_2O$	4.0	400 MBq	97	Infection site imaging	[55]
^{99m}Tc-fleroxacin	SnF_2	5.5	74 MBq	98.10 ± 0.24	*E. coli* infection imaging agent	[66]
^{99m}Tc-gatifloxacin (GTN)	$SnCl_2{\cdot}2H_2O$	10	400 MBq	90 ± 1.8	Infection imaging	[70]
^{99m}TcN-gatifloxacin dithiocarbamate (GTND)	Stannous fluoride	N/A	74 MBq	98.25 ± 0.20	*Streptococcus pneumoniae* (MRSP) infection radiotracer	[122]
^{99m}Tc-gemifloxacin	$SnCl_2{\cdot}2H_2O$	5.4	0.5–5.0 mCi	97.25 ± 0.25	*S. pneumoniae* infection radiotracer	[67]

Table 1 continued

Compound	Oxidant/reducing agent	Optimum pH	Specific activity ^{99m}Tc (mCi/MBq)	Labeling yield (%)	Application	References
^{99m}Tc-garenoxacin (GXN)	$SnCl_2{\cdot}2H_2O$	5.6	3 mCi	97.45 ± 0.18	Localization of multi drug resistant *S.aureus* (MDRSA) and PRSC	[123]
^{99m}TcN-garenoxacin dithiocarbamate (GXND)	$SnCl_2{\cdot}2H_2O$	N/A	1–2 mCi	98.00 ± 0.22	Investigation of MDRSA and penicillin-resistant streptococci (PRSC) infection in human	[124]
^{99m}Tc(CO)$_3$-GXND	N/A	N/A	1–2 mCi	90	Localization of soft tissue MDRSA and PRSC infection	[125]
^{99m}Tc-HQMADA	$SnCl_2{\cdot}2H_2O$	8.0	1–1.5 GBq	91.9	Infection imaging	[126]
^{99m}Tc-kanamycin	$SnCl_2{\cdot}2H_2O$	6–7	370–500 MBq	>98	Infection imaging	[127]
^{99m}Tc-levofloxacin	$SnCl_2{\cdot}2H_2O$	5.0	80-1400 MBq	>95	Infection imaging	[63]
^{99m}Tc-lomefloxacin	$SnCl_2{\cdot}2H_2O$	3.5–5.0	400 MBq	93.6	Infection imaging	[45]
^{99m}TcN-moxifloxacin dithiocarbamate (MXND)	$SnCl_2{\cdot}2H_2O$	N/A	2 mCi	97.55 ± 0.42	Detection of *S. aureus* infectious foci	[128]
^{99m}Tc(CO)$_3$-MXND	N/A	N/A	74 MBq	>90	Infection radiotracer	[129]
^{99m}Tc-nitrofurantoin	$SnCl_2{\cdot}2H_2O$	5.2	2.5 mCi	97.50 ± 0.16	Infection radiotracer	[130]
^{99m}Tc-norfloxacin	$SnCl_2{\cdot}2H_2O$	3.0	400 MBq	95.4	infection imaging agent	[68]
^{99m}Tc-ofloxacin	$SnCl_2{\cdot}2H_2O$	3.5–5.0	400 MBq	96.6	Infection imaging	[45]
^{99m}Tc-pefloxacin	$SnCl_2{\cdot}2H_2O$	4.0	400 MBq	98.1	Infection site imaging	[57]
^{99m}Tc-rifampicin (RMP)	$SnCl_2{\cdot}2H_2O$	5.6	3 mCi	98.95 ± 0.20	In-vivo assessment of MRSA	[131]
^{99m}Tc-rufloxacin	$SnCl_2{\cdot}2H_2O$	6.0	380 MBq	93.4 ± 3	Detecting site of infection	[132]
^{99m}Tc-rufloxacin	$SnCl_2{\cdot}2H_2O$	5.5	2.5 mCi	98.10 ± 0.18	Localization of *S. aureus* infection	[69]
^{99m}Tc-sarafloxacin	$SnCl_2{\cdot}2H_2O$	11.0	400 MBq	96	Localization of infectious foci	[133]
^{99m}Tc-sitafloxacin	$SnCl_2{\cdot}2H_2O$	5.5	3 mCi	98.96 ± 0.10	Infection imaging	[134]
^{99m}TcN-sitafloxacin dithiocarbamate (SFDE)	$SnCl_2{\cdot}2H_2O$	N/A	1 mCi	99.00 ± 0.20	*S. aureus* infection radiotracer	[135]
^{99m}Tc(CO)$_3$-SFDE	N/A	N/A	1–2 mCi	98.45 ± 0.21	*S. aureus* infection tracing in humans	[136]
^{99m}Tc-sparfloxacin	$SnCl_2{\cdot}2H_2O$	10.0	~500 MBq	95	Infection imaging	[137]
^{99m}Tc-sulfadiazine	$SnCl_2{\cdot}2H_2O$	5.0	75 MBq	94.7	Infection imaging	[138]
^{99m}Tc-sulfadimdine	$SnCl_2{\cdot}2H_2O$	4.0	~200–400 MBq	90	Differentiating b/w septic and aseptic inflammations	[76]
^{99m}Tc-temafloxacin complex (TMC)	$SnCl_2{\cdot}2H_2O$	5.5	37 MBq	98 ± 0.34	Infection imaging agent	[139]
^{99m}Tc(CO)$_3$-temafloxacin dithiocarbamate (TAND)	N/A	N/A	74 MBq	98.10 ± 15	*S. aureus* infection radiotracer	[140]
^{99m}TcN-TVND	$SnCl_2{\cdot}2H_2O$	N/A	37 MBq	97.90 ± 0.22	Methicillin-resistant *S. aureus* (MRSA) infection imaging	[141]
^{99m}Tc(CO)$_3$-TVND	$SnCl_2{\cdot}2H_2O$	N/A	1–2 mCi	98.75 ± 0.15	MRSA investigation in human	[142]

N/A not associated

[a] Anticancer drugs

Table 2 ^{99m}Tc labeled Proteins, peptides and amino acid derivatives

Compound	Oxidant/reducing agent	Optimum pH	Specific activity ^{99m}Tc (mCi/MBq)	Labeling yield (%)	Application	References
$(^{99m}Tc(NS_3)(CN))_2$-SP	$SnCl_2{\cdot}2H_2O$	N/A	50–100 MBq	>85	Efficient radio-pharmaceutical	[143]
$^{99m}Tc(CO)_3$-hexapeptide [Asp-Gly-Arg-D-Tyr-Lys-His]	Mixture of Na/K-tartrate, Na_2CO_3, $NaBH_4$	6.5–7.0	185–370 MBq	>97	Tumor imaging (especially $\alpha_v\beta_3$-receptor positive tumors)	[53]
$^{99m}Tc(CO)_3$-tetrapeptide 1 (Asp-Gly-Arg-His)	Mixture of Na/K-tartrate, Na_2CO_3, $NaBH_4$	6.5–7.0	185–370 MBq	>97	Tumor imaging (especially $\alpha_v\beta_3$-receptor positive tumors)	[53]
$^{99m}Tc(CO)_3$-tetrapeptide 2 (Asp-Gly-Arg-Cys)	Mixture of Na/K-tartrate, Na_2CO_3, $NaBH_4$	6.5–7.0	185–370 MBq	>97	Tumor imaging (especially $\alpha_v\beta_3$-receptor positive tumors)	[53]
$^{99m}Tc(CO)_3$-triazolyl pep-3 [Asp-Gly-Arg-His]	$SnCl_2{\cdot}2H_2O$	6.5–7.0	74–185 MBq	96.74 ± 1.10	Imaging of tumors (integrin-positive receptor sites)	[144]
^{99m}Tc-(Nα-His)Ac-NT(8–13)	$NaBH_4/NaHCO_3$/Na/K-tartrate	7.0	11.1–33.3 GBq	>98	Imaging of oncogene receptors overexpressed in SCLC	[145]
^{99m}Tc(Sn) P.Val	$SnCl_2{\cdot}2H_2O$	8–9	5–10 mCi	N/A	Hepatobiliary imaging	[146]
^{99m}Tc(Sn) P.isoL	$SnCl_2{\cdot}2H_2O$	8–9	5–10 mCi	N/A	Hepatobiliary imaging	[146]
^{99m}Tc-$[E\text{-}c(RGDfK)_2]_2$	$SnCl_2{\cdot}2H_2O$	~5	~15 MBq	>95	Imaging $\alpha_v\beta_3$-integrins in tumors	[83]
^{99m}Tc-3P-RGD2	N/A	N/A	370–1111 MBq	>95	Detection of head and neck squamous cell carcinoma	[84]
^{99m}Tc-5-FU-Ab-NPs	$SnCl_2{\cdot}2H_2O$	Phosphate buffer	550–740 MBq	95.1	Targeting tumor proliferation/angiogenesis	[147]
^{99m}Tc-alafosfalin	$SnCl_2{\cdot}2H_2O$	6.1	12–504 MBq	>95	Imaging of osteomyelitis	[148]
^{99m}Tc-anti-*S. aureus* antibody	$SnCl_2{\cdot}2H_2O$	7.4	60 mCi	98.09 ± 1.81	Endocarditis imaging, also diagnosis of infectious diseases	[149]
^{99m}Tc-bombesin derivative (HYNIC-BB 5-14)	$SnCl_2{\cdot}2H_2O$	N/A	81 GBq/μmol	>98	Imaging of GRP receptor-positive tumors	[87]
$^{99m}Tc\text{-}C_3(BHam)_2$-annexin A5	Sn(II) gluco-heptonate	8.0	37–740 MBq	~95	Detection of apoptosis after chemotherapy	[150]
^{99m}Tc-CpTT-octreotide	$CrCl_3/Cr(CO)_6$	N/A	26.0 mCi	100	Imaging of somatostatin receptor positive tissue (adrenals and pancreas)	[86]
^{99m}Tc-CXCL8	$SnSO_4$	6.5–8.2	400 MBq	>90	Monitoring disease activity in inflammatory bowel disease	[151]
^{99m}Tc-Cys-annexin V	$SnCl_2{\cdot}2H_2O$	7.2	37 MBq	94 ± 1	Apoptosis imaging	[152]
^{99m}Tc-D-AM-Fab	$Na_2S_2O_4$	8.0	20–40 mCi	>80	In vivo applications (also in myocardial infarction)	[89]
^{99m}Tc-D-HF	$Na_2S_2O_4$	8.0	20–40 mCi	87.2 ± 4.6	In vivo applications (also in coagulation)	[89]
^{99m}Tc-EC-225	$SnCl_2$	7.4	80 mCi	~100	Assessment of tumor EGFR expression	[52]
^{99m}Tc-ECD	N/A	N/A	100 mCi	>90	Brain imaging (cerebral perfusion examinations)	[153]
^{99m}Tc-ECDG	$SnCl_2{\cdot}2H_2O$	N/A	0.5 Ci/mmol	~96.4	Functional metabolic imaging agent	[154]
^{99m}Tc-EC-guanine	$SnCl_2{\cdot}2H_2O$	8.5	37–370 MBq	>90	Tumor proliferation imaging	[25]
^{99m}Tc-EDDA-HYNIC-TOC	$SnCl_2{\cdot}2H_2O$	6–7	0.5–2.0 GBq	>90	Somatostatin receptor (SSTR) scintigraphy of neuroendocrine tumors	[155]
^{99m}Tc-EDDA/HYNIC-RGD	$SnCl_2{\cdot}2H_2O$	6–7	800 MBq	93.9	Imaging $\alpha_v\beta_3$-integrin receptor expression in tumors	[85]
^{99m}Tc-ghrelin peptide	$NaBH_4$/K-tartrate/K_2CO_3	7.0–8.0	300–1500 MBq	>95	Diagnostic radiopharmaceutical	[156]
^{99m}Tc-Gly-L-Pro	$SnCl_2{\cdot}2H_2O$	9.7	100 MBq	>96	Imaging status of collagen homeostasis	[157]
$^{99m}Tc\text{-}(CO)_3$-HEHEHE-$Z_{HER3:08,699}$	N/A	N/A	200–320 MBq	>80	Imaging of malignant tumors (HER-3 imaging)	[158]

Table 2 continued

Compound	Oxidant/reducing agent	Optimum pH	Specific activity ^{99m}Tc (mCi/MBq)	Labeling yield (%)	Application	References
^{99m}Tc-HYNIC-annexin A5	N/A	7.4	3.7–7.4 MBq/μg	~95.7	Detection and direct quantification the degree of intramedullary and splenic apoptosis	[159]
^{99m}Tc-HYNIC-GABA-bombesin	$SnCl_2{\cdot}2H_2O$	N/A	370–1480 MBq	>98	Imaging of GRP-receptor-positive organs (prostate, breast, colon, small-cell lung cancer)	[160]
^{99m}Tc-HYNIC-Tyr3-octreotide (TOC)	$SnCl_2{\cdot}2H_2O$	N/A	37–370 MBq	>98	Somatostatin receptor-positive tumor imaging	[161]
^{99m}Tc-HYNIC-βAla-bombesin	$SnCl_2{\cdot}2H_2O$	7.0	37 MBq	96.2	Identification of bombesin-positive tumors (breast cancers)	[162]
^{99m}Tc-insulin complex	$SnCl_2{\cdot}2H_2O$	7.0	19 mCi	>99	Liver, lungs, kidney and bladder imaging.	[59]
^{99m}Tc-Ior egf/r3	$SnCl_2{\cdot}2H_2O$	N/A	39.59–2301.4 MBq	>95	Tumor diagnosis	[50]
^{99m}Tc-lanreotide	$SnCl_2{\cdot}2H_2O$	2.8	~444 MBq (12 mCi)	>97	Scintigraphic imaging of specific tumors (neuroendocrine)	[163]
^{99m}Tc-L-carnitine	$SnCl_2{\cdot}2H_2O$	7	200–400 MBq	93	Diagnosis of tumors	[11]
^{99m}Tc-maEEE-$Z_{HER2:342}$	$SnCl_2{\cdot}2H_2O$	11	10 MBq	90 ± 2	Molecular imaging of targets in abdominal area	[164]
^{99m}Tc-maESE-$Z_{HER2:342}$	$SnCl_2{\cdot}2H_2O$	11	10 MBq	87 ± 8	Molecular imaging of targets in abdominal area	[164]
^{99m}Tc-maEES-$Z_{HER2:342}$	$SnCl_2{\cdot}2H_2O$	11	10 MBq	90 ± 6	Molecular imaging of targets in abdominal area	[164]
^{99m}Tc-maSEE-$Z_{HER2:342}$	$SnCl_2{\cdot}2H_2O$	11	10 MBq	92 ± 0.4	Molecular imaging of targets in abdominal area	[164]
^{99m}Tc-neurotensin analog	$SnCl_2{\cdot}2H_2O$	5.0	370–1110 MBq	98.6 ± 0.54	Diagnostics of malignant tumors	[165]
^{99m}Tc-p5 + 14	$SnCl_2{\cdot}2H_2O$	N/A	1–10 mCi	75 ± 7.7	Detection of systemic visceral amyloidosis disease	[166]
^{99m}Tc-PADS	$SnCl_2{\cdot}2H_2O$	7.0	100 MBq (2 mCi)	95	Liver and kidney imaging	[29]
^{99m}TcN-PHEDTC	$SnCl_2{\cdot}2H_2O$	N/A	370 MBq	>90	Tumor imaging	[80]
^{99m}TcO-PHEDTC	$SnCl_2{\cdot}2H_2O$	N/A	370 MBq	>90	Tumor imaging	[80]
^{99m}TcN-PRODTC	$SnCl_2{\cdot}2H_2O$	N/A	370 MBq	>90	Tumor imaging	[79]
^{99m}Tc-trifoban	$SnCl_2{\cdot}2H_2O$	7.3	100 MBq	95	Imaging of deep venous thrombosis	[167]
^{99m}Tc-trastuzumab[a]	$SnCl_2{\cdot}2H_2O$	7.3	7.4 MBq/0.1 ml	95 ± 1.7	Her-2 receptor imaging in cancers	[168]
^{99m}Tc-ubiquicidin (UBI) 29-41	$SnCl_2{\cdot}2H_2O$	6–7	370–400 MBq (10 mCi)	>95	Localization of infectious foci	[38]
^{99m}Tc-USPIO-bevacizumab[a]	$SnCl_2{\cdot}2H_2O$	~8.4	370 MBq	>90	Imaging agent for SPECT/MRI of HepG2 HCC	[169]
^{99m}Tc-vasopressin	$SnCl_2{\cdot}2H_2O$	N/A	200–1000 MBq	>95	Diagnosis of patients with small-cell lung cancer	[170]
^{99m}Tc-$Z_{IGF1R:4551}$-GGGC	$SnCl_2{\cdot}2H_2O$	7.4	600 kBq	97 ± 3	Visualizing the IGF-1R expression in human tumor xenografts	[88]

N/A not associated

[a] Anticancer drug

Table 3 Miscellaneous ^{99m}Tc-labeled organic molecules

Compound	Oxidant/reducing agent	Optimum pH	Specific activity ^{99m}Tc (mCi/MBq)	Labeling yield (%)	Application	References
$[^{99m}Tc(CO)_3(PA\text{-}TZ\text{-}CHC]^+$	N/A	7.4	185 MBq	>95	Tumor targeting (H22 liver cancer)	[171]
$^{99m}Tc(CO)_3$-(1-azido-1-deoxy-β-D-glucopyranoside)	N/A	N/A	20 mCi	97.9 ± 1.5	Tumor diagnosis	[106]
$^{99m}Tc(CO)_3$-2-nitroimidazole-triazole	$NaBH_4/Na_2CO_3$/sodium potassium tartrate	7.5	105.55 ± 1.11 μCi/μmol	95.0 ± 1.00	Tumor imaging	[92]
$^{99m}Tc(CO)_3$-4-nitroimidazole-triazole	$NaBH_4/Na_2CO_3$/sodium potassium tartrate	7.5	107.03 ± 0.64 μCi/μmol	96.3 ± 0.57	Tumor hypoxia imaging	[92]
$^{99m}Tc(CO)_3$-5-nitroimidazole-triazole	$NaBH_4/Na_2CO_3$/Na/K-tartrate	7.5	107.77 ± 1.11 μCi/μmol	97.0 ± 1.00	Tumor hypoxia imaging	[92]
$^{99m}Tc(CO)_3$-folic acid derivative	$NaBH_4/Na_2CO_3$/Na/K-tartrate	6.0	~37 MBq	>95	Imaging of folate receptors in tumors	[108]
$^{99m}Tc(CO)_3$-Gua	$NaBH_4/Na_2CO_3$/Na/K-tartrate	7.0	60 MBq	94 ± 3	Imaging agent for in vivo application	[172]
^{99m}Tc-2-aminoestrone-3methyl ether	$SnCl_2{\cdot}2H_2O$	1.0	400 MBq	98.5 ± 3.4	Inflammation imaging	[112]
^{99m}Tc-5-ALA	$SnCl_2{\cdot}2H_2O$	6.9	~100 MBq	98	Liver imaging agent	[101]
^{99m}Tc-AQCD	$SnCl_2{\cdot}2H_2O$	7.0	200–400 MBq	97.5	Tumor imaging	[173]
^{99m}Tc-5FU	$SnCl_2{\cdot}2H_2O$	7.0	555 MBq	98.1 ± 1.2	Diagnosis of advanced breast cancer	[30]
^{99m}Tc-5FU/EDDA	$SnCl_2{\cdot}2H_2O$	7.0 ± 0.5	500 ± 20 MBq/0.5 ml	95.7	Brain imaging	[174]
^{99m}Tc-ALD (aldronate sodium)	$SnCl_2{\cdot}2H_2O$	N/A	1 mCi	>90	Bone cancer diagnosis	[175]
^{99m}Tc-amine-thiophene-dione	$SnCl_2{\cdot}2H_2O$	8–8.5	740 MBq (~20 mCi)	98.1 ± 1.2	Brain imaging	[97]
^{99m}Tc-BAT-AV-45	$SnCl_2{\cdot}2H_2O$	5–6	~0.5 mCi	95 ± 1	Aβ plaques (brain imaging)	[15]
^{99m}Tc-BIDP	$SnCl_2{\cdot}2H_2O$	6.0	92.50 MBq	>95	Bone scanning agent	[90]
^{99m}Tc-BIPeDP	$SnCl_2{\cdot}2H_2O$	6.0	92.5 MBq	>95	Bone imaging agent	[91]
^{99m}Tc-BPIDA	$SnCl_2{\cdot}2H_2O$	6.0	1–1.5 GBq	85.4 ± 3	Hepatobiliary imaging (hepatocyte functionality, biliary duct patency)	[102]
^{99m}Tc-celecoxib	$SnCl_2{\cdot}2H_2O$	7.0	~750 MBq	99.67	Inflammation detection imaging	[113]
^{99m}Tc-clomiphene citrate	$SnCl_2{\cdot}2H_2O$	7.0	400 MBq	94.4	Diagnosis of breast cancer	[107]
^{99m}Tc-CMC	$SnCl_2{\cdot}2H_2O$	8.0	1.2 mCi	97.9	Liver imaging agent	[176]
^{99m}Tc-CSA-107	$SnCl_2{\cdot}2H_2O$	4.0	370 MBq	>95	Infection imaging	[114]
^{99m}Tc-DES-P	$SnCl_2{\cdot}2H_2O$	7.0	37 MBq/100μL	99 ± 0.17	Imaging of estrogen receptor (ER) rich tumors (e.g. uterus, prostate etc.) and their metastases in bone	[109]
^{99m}Tc-diclofenac	$SnCl_2{\cdot}2H_2O$	7.0	400 MBq	~96	Inflammation imaging (differentiation of inflammation from bacterial infection)	[56]
^{99m}Tc-DHP-DG	$NaBH_4/Na_2CO_3$/Na/K-tartrate	7.4	46 mCi	93	Heart imaging	[28]
^{99m}Tc-DMIDA	$SnCl_2{\cdot}2H_2O$	6.0	1–1.5 GBq	93.1 ± 2	Hepatobiliary imaging	[177]
^{99m}Tc-DMSA	$SnCl_2{\cdot}2H_2O$	N/A	740 MBq	>95	Imaging of functional renal cortical mass, and nephrotoxicity	[178]
^{99m}Tc-DTPA-CHC	$SnCl_2{\cdot}2H_2O$	6–6.5	111 MBq	~67	Tumor imaging	[179]

Table 3 continued

Compound	Oxidant/reducing agent	Optimum pH	Specific activity ^{99m}Tc (mCi/MBq)	Labeling yield (%)	Application	References
^{99m}Tc-DTPA-estradiol	$SnCl_2{\cdot}2H_2O$	N/A	37 MBq	64.5 ± 2.8	Assessment of estrogen receptors(ERs) expression in tumors	[180]
^{99m}Tc-ECB-DG	$NaBH_4/Na_2CO_3$/Na/K-tartrate	7.4	46 mCi	96	Brain imaging	[28]
^{99m}Tc-EDTADG	$SnCl_2{\cdot}2H_2O$	7–8	370 MBq	>95	Tumor imaging	[181]
^{99m}Tc-EIBDP	$SnCl_2{\cdot}2H_2O$	6.0	74 MBq	96 ± 2	Bone metastasis diagnosis	[47]
^{99m}Tc-EIPeDP	$SnCl_2{\cdot}2H_2O$	6.0	74 MBq	96 ± 2	Bone metastasis diagnosis	[47]
^{99m}Tc-EIPrDP	$SnCl_2{\cdot}2H_2O$	6.0	74 MBq	96 ± 2	Superior bone imaging agent	[47]
^{99m}Tc-*fac*(S)-[Rh(aet)$_3$]	$SnCl_2{\cdot}2H_2O$	~2	5–10 mCi	~99	Used as imaging agent	[182]
^{99m}Tc-famotidine	$SnCl_2{\cdot}2H_2O$	N/A	74 MBq	>95	Diagnosis of diseases involving H-$_2$-receptor (dyspepsia, stomach ulcer)	[51]
^{99m}Tc-fluconazole[b]	$SnCl_2{\cdot}2H_2O$	7.5	200 MBq	~90	Marker for *C. albicans* infections	[183]
^{99m}Tc-gabapentin	$SnCl_2{\cdot}2H_2O$	7.0	20–50 mCi	80	Brain receptor imaging	[98]
^{99m}Tc-gemcitabine	$SnCl_2{\cdot}2H_2O$	9.0	400 MBq	96 ± 0.3	Solid tumor imaging	[184]
^{99m}Tc-histamine	$SnCl_2{\cdot}2H_2O$	4.0	~400 MBq	98.0 ± 0.34	Brain imaging and brain SPECT	[99]
^{99m}Tc-HYNIC-AMDP	$SnCl_2{\cdot}2H_2O$	8.0	15 MBq	>95	Bone imaging	[185]
^{99m}Tc-HYNIC-CHC	$SnCl_2{\cdot}2H_2O$	7.0	54 MBq	95.8 ± 0.54	Diagnostics of malignant tumors	[110]
^{99m}Tc-HYNIC-MN	$SnCl_2{\cdot}2H_2O$	7.0	1.85–185 MBq	>95	Imaging of tumor hypoxia	[186]
^{99m}Tc-IBDP	$SnCl_2{\cdot}2H_2O$	N/A	180–210 MBq	>95	Bone scintigraphy	[187]
^{99m}Tc-IPeDP	$SnCl_2{\cdot}2H_2O$	N/A	180–210 MBq	>95	Superior bone scintigraphy agent	[187]
^{99m}Tc-labetalol	$SnCl_2{\cdot}2H_2O$	4.0	400 MBq	98	β_1-adrenoreceptor-mediated myocardial imaging	[104]
^{99m}Tc-lapatinib	$SnCl_2$	N/A	25–30 GBq/μmol	>97	Breast cancer imaging (status of Her-2)	[188]
^{99m}Tc-LCMC	$SnCl_2{\cdot}2H_2O$	5.0	1.2 mCi	93.6	Hepatocyte targeted molecular imaging	[176]
^{99m}Tc-losartan	$SnCl_2{\cdot}2H_2O$	7.0	35–70 kBq	~98	Myocardial imaging agent	[105]
^{99m}Tc-MAG-$_2$-FA	$SnCl_2{\cdot}2H_2O$	10	370–555 MBq	≥80	Tumor imaging	[189]
^{99m}Tc-MAG$_2$-MTX	$SnCl_2{\cdot}2H_2O$	10	370–555 MBq	≥75	Tumor imaging	[189]
^{99m}Tc-MAG$_3$-FA	$SnCl_2{\cdot}2H_2O$	10	370–555 MBq	≥75	Tumor imaging (also breast cancer)	[189]
^{99m}Tc-MAG$_3$-MTX	$SnCl_2{\cdot}2H_2O$	10	370–555 MBq	≥75	Tumor imaging (also breast cancer)	[189]
^{99m}Tc-methotrexate[a] (MTX)	Stannous tartarate	8.2–8.5	555 MBq	98.2 ± 0.5	A strong tumor diagnostic agent	[31]
^{99m}Tc-metronidazole	$SnCl_2{\cdot}2H_2O$	7.0	200–400 MBq	93.0 ± 0.32	Tumor diagnosis	[22]
^{99m}Tc-MIBI-PCL NC	N/A	N/A	37 MBq	92.95 ± 0.21	Intramammary study	[190]
^{99m}Tc-MIBI-CS-PCL NC	N/A	N/A	37 MBq	89.82 ± 0.76	Intramammary study	[190]
^{99m}Tc-misonidazole	N/A	7.4	107.2 ± 1.2 μCi/μmol	>95	Tumor hypoxia	[93]
^{99m}Tc-mitomycin C[a]	$SnCl_2{\cdot}2H_2O$	7.0	15 mCi	100	Liver imaging	[16]
^{99m}Tc-nebivolol	$SnCl_2{\cdot}2H_2O$	6.0	195 MBq	95 ± 2.87	Specificity for β_1-adrenergic receptors, myocardial imaging	[191]
^{99m}Tc-NIDA	$SnCl_2{\cdot}2H_2O$	6.0	1–1.5 GBq	94.2 ± 2	Hepatobiliary imaging	[177]
^{99m}Tc-NTP 15-5	$SnCl_2{\cdot}2H_2O$	N/A	25 MBq/μmol	~100	Human cartilage molecular imaging, also osteoarthritis monitoring	[192]
^{99m}TcN-OHPP-DTC	$SnCl_2{\cdot}2H_2O$	5.0	10 mCi (370 MBq)	>90	Imaging of 5HT$_{1A}$ receptor (a serotonin recptor), Brain PET/SPECT	[193]

Table 3 continued

Compound	Oxidant/reducing agent	Optimum pH	Specific activity ^{99m}Tc (mCi/MBq)	Labeling yield (%)	Application	References
^{99m}Tc-omeprazole	$SnCl_2{\cdot}2H_2O$	9.0	200–400 MBq	~96	Ulcer imaging	[94]
^{99m}Tc-ornidazole xanthine (ONXT)	$SnCl_2{\cdot}2H_2O$	N/A	37 MBq	~90	Targeting tumor hypoxia	[194]
^{99m}Tc-oxybutynin	$SnCl_2{\cdot}2H_2O$	4.0	400 MBq	93.5	Imaging of urinary bladder (specificity for M_3-G-proteins)	[195]
^{99m}Tc-PAAS	$SnCl_2{\cdot}2H_2O$	5–6	20–400 MBq (0.5–10 mCi)	>95	Bone imaging agent	[196]
^{99m}Tc-paclitaxel[a]	Sodium borohydride	7.4	111 MBq	~95	Potential radiotracer of paclitaxel (in chemotherapy)	[197]
^{99m}Tc-pantoprazole	$SnCl_2{\cdot}2H_2O$	10	400 MBq	~96.5	Stomach ulcer imaging	[95]
^{99m}Tc-phytochlorin	$SnCl_2{\cdot}2H_2O$	10	400 MBq	98.4 ± 0.6	Selective radiotracer for solid tumor imaging	[54]
^{99m}Tc-piracetam	$SnCl_2{\cdot}2H_2O$	6.0	200–400 MBq	>97	Brain imaging	[100]
^{99m}Tc-piroxicam	$SnCl_2{\cdot}2H_2O$	11	~750 MBq	97.3 ± 1.6	Scintigraphy of inflammatory lesions	[198]
^{99m}Tc-PQQ	SnF_2	6.0	40 MBq	>95	Brain imaging	[199]
^{99m}Tc-PyDA	$SnCl_2{\cdot}2H_2O$	8.0	195 MBq	96 ± 3	Tumor hypoxia imaging	[200]
^{99m}Tc-rabeprazole	$SnCl_2{\cdot}2H_2O$	9.0	~400 MBq	98.5 ± 0.4	Stomach ulcer imaging	[96]
^{99m}Tc-sestaMIBI	$SnCl_2{\cdot}2H_2O$	N/A	925–1100 MBq	97	Evaluation of acute myocardial infarction	[201]
^{99m}Tc-siRNA (^{99m}Tc-HYNIC-siRNA)	$SnCl_2{\cdot}2H_2O$	8.5	74–185 MBq	61.26 ± 2.47	Visualization of CXCR4 expression in cancers	[111]
^{99m}Tc-shikonin	$SnCl_2{\cdot}2H_2O$	5.0	400 MBq	96.5 ± 4.75	Cancer imaging	[202]
^{99m}Tc-spermine	$SnCl_2{\cdot}2H_2O$	9.0	37 MBq	96.5 ± 1.3	Tumor imaging	[203]
^{99m}Tc-SV (scorpion venom)	$SnCl_2{\cdot}2H_2O$	7.0	40–120 MBq	97	Monitoring toxins biodistribution, also in vivo studies	[204]
^{99m}Tc-sucralfate	$SnCl_2{\cdot}2H_2O$	7.0	1000 mCi	>95	Detection of gastrointestinal ulcers	[205]
^{99m}Tc-tannic acid	$SnCl_2{\cdot}2H_2O$	7.0	200–400 MBq	90	Stomach ulcer imaging	[49]
^{99m}Tc-tannic acid	$SnCl_2{\cdot}2H_2O$	7.0	200–400 MBq	95.5	Stomach ulcer imaging	[206]
^{99m}Tc-tetrofosmin	$SnCl_2{\cdot}2H_2O$	6.4	200 mCi	>90	Heart imaging	[207]
^{99m}Tc-TOR-G	$SnCl_2{\cdot}2H_2O$	8.0	370 MBq	90.0 ± 0.07	Imaging of ovarian tumors	[208]
^{99m}Tc-TRODAT-1	$SnCl_2{\cdot}2H_2O$	7.0	20–30 mCi	>93	Localization of dopamine transporters in brain	[209]
^{99m}Tc-vincristine[a]	$SnCl_2{\cdot}2H_2O$	4.0	10 mCi	99.6 ± 0.4	Liver and spleen imaging	[210]
^{99m}Tc-UDCA	$SnCl_2{\cdot}2H_2O$	8.0	400 MBq	97.5	Hepatobiliary imaging	[103]

N/A not associated

[a] Anticancer drugs

[b] Anti-fungal drug

agent, respectively. Monoclonal antibodies (Mabs) are the candidate for radiolabeling because they provide enough binding specificity for localization of the target. Certain ^{99m}Tc-labeled Mabs are available for certain receptors or proteins, like ^{99m}Tc-Ior egf/r3 [50], ^{99m}Tc-D-AM-Fab and ^{99m}Tc-D-HF [89]. There are other proteins that specifically bind to other proteins like affibodies. Affibodies are non-antibody low molecular weight proteins. ^{99m}Tc-labeled affibody molecules serve as very good at localization of certain receptors overexpressed in tumors or other diseases, like ^{99m}Tc-$Z_{IGF1R:4551}$-GGGC affibody which targets insulin growth factor type-1 receptors [88]. There are also many other protein and peptide derivatives labeled and given in the table 2.

Miscellaneous ^{99m}Tc-labeled organic molecules

Miscellaneous macro and micro-organic compounds have been labeled with ^{99m}Tc, as dictated by the nature and type of the ligand. Diphosphonates or bisphosphonates have affinities for bones. Many of their derivatives are labeled with ^{99m}Tc in search of a superior bone scintigraphy imaging agent, e.g. ^{99m}Tc-BIDP [90], ^{99m}Tc-BIPeDP [91], ^{99m}Tc-EIPrDP [47]. Nitroimidazoles have an affinity for hypoxic microenvironments of tumors, that's why ^{99m}Tc-nitroimidazole [92], and its derivatives e.g. 99mTc-metronidazole [22], ^{99m}Tc-misonidazole [93], are used for tumor hypoxia imaging. There are other imidazoles like ^{99m}Tc-omeprazole [94], ^{99m}Tc-pantoprazole [95] and ^{99m}Tc-rabeprazole [96] used for stomach ulcer localization. Also there is ^{99m}Tc-tannic acid, one good radiotracer of stomach ulcer [49].

Our brain has billions of neurons which operate with nerve impulse. Nerve impulse is mediated as neurotransmitters bind to their receptors on the neuronal surface. Thus any ligand, might it be a neurotransmitter or its analog that can bind to these receptors, could be labeled for brain imaging. ^{99m}Tc-amine-thiophene-dione [97], ^{99m}Tc-gabapentin [98], ^{99m}Tc-Histamine [99], ^{99m}Tc-piracetam [100] are such examples. As the brain uses high energy for its functioning, glucose is a crucial requirement. Deoxyglucose derivatives are used for brain imaging like ^{99m}Tc-ECB-DG [28]. While hepatobiliary imaging is facilitated by organic acids like ^{99m}Tc-5-ALA [101], ^{99m}Tc-BPIDA [102], ^{99m}Tc-UDCA [103] etc. Cardiovascular diseases are detected and characterized by labeled β_1-receptor and other myocardial receptor antagonists. Labeled β_1-receptor antagonists are ^{99m}Tc-labetalol [104] and ^{99m}Tc-nebivolol. Another receptor angiotensin II is imaged by its ^{99m}Tc-antagonist i.e. ^{99m}Tc-losartan [105].

There are many ^{99m}Tc-labeled ligand preparations that help to detect and characterize many types of tumors. They usually detect tumors by receptor-specific binding. For example ^{99m}Tc$(CO)_3$-(1-azido-1-deoxy-β-D-glucopyranoside) for tumor detection [106], ^{99m}Tc-clomiphene citrate is an estrogen receptor (ER) antagonist (breast and uterine cancers) [107], ^{99m}Tc$(CO)_3$-folic acid derivative for folate receptors [108], ^{99m}Tc-DES-P [109], ^{99m}Tc-HYNIC-CHC for tubulin binding [110], ^{99m}Tc-methotrexate (MTX) for folate receptors [31], ^{99m}Tc-siRNA for chemokine receptor 4 expression [111] etc. Table 3 contains details of these and others. There are also non-antibiotic steroidal or non-steroidal compounds labeled with ^{99m}Tc for infection or inflammation imaging like ^{99m}Tc-2-aminoestrone-3-methyl ether [112], ^{99m}Tc-celecoxib [113], ^{99m}Tc-CSA-107 [114], ^{99m}Tc-diclofenac [56].

Conclusion and perspectives

^{99m}Tc labeled radiopharmaceuticals have an important place in medicine and health sciences. Because the role of ^{99m}Tc in the diagnostics is very well established owing to its physical and chemical properties (half-life of 6 h, gamma ray energy of 140 keV, easily obtained from a ^{99}Mo/^{99m}Tc generator, low cost, minimal dose to the patient and negligible environmental impact). High labeling yield with minimal harsh conditions like low specific activity, neutral pH etc. make a radiopharmaceutical best for practical applications.

By looking at the data presented here in this article, we can conclude that there are some superior diagnostic agents than the others. Superior ^{99m}Tc-antibiotics include ^{99m}Tc-benzyl penicillin, ^{99m}Tc-cefepime, ^{99m}Tc-cefuroxime axetil, ^{99m}Tc-clarithromycin, ^{99m}Tc-delafloxacin, ^{99m}Tc-fleroxacin, ^{99m}TcN- GTND, ^{99m}Tc-kanamycin, ^{99m}TcN-MXND, ^{99m}Tc-pefloxacin, ^{99m}Tc-rifampicin, ^{99m}Tc-rufloxacin, ^{99m}Tc-sitafloxacin, ^{99m}TcN-sitafloxacin dithiocarbamate (SFDE), ^{99m}Tc$(CO)_3$-SFDE, and ^{99m}Tc-temafloxacin complex (TMC).

Superior labeled proteins and peptide radiotracers include ^{99m}Tc$(CO)_3$-hexapep, ^{99m}Tc$(CO)_3$-tetrapep 1, ^{99m}Tc$(CO)_3$-tetrapept 2, ^{99m}Tc-(Nα-His)Ac-NT(8–13), ^{99m}Tc-3P-RGD2, ^{99m}Tc-anti-*S. aureus* antibody, ^{99m}Tc-bombesin derivative (HYNIC-BB 5-14), ^{99m}Tc-CpTT-octreotide, ^{99m}Tc-Cys-annexin V, ^{99m}Tc-EC-225, ^{99m}Tc-ECDG ^{99m}Tc-ghrelin peptide, ^{99m}Tc-HYNIC-annexin A5, ^{99m}Tc-HYNIC-GABA-Bombesin, ^{99m}Tc-HYNIC-Tyr3-octreotide (TOC), ^{99m}Tc-HYNIC-βAla-bombesin, ^{99m}Tc-insulin complex, ^{99m}Tc-Ior egf/r3, ^{99m}Tc-neurotensin analog, ^{99m}Tc-PADS, ^{99m}Tc-trifoban, ^{99m}Tc-trastuzumab, ^{99m}Tc-ubiquicidin 29-41, ^{99m}Tc-vasopressin and ^{99m}Tc-$Z_{IGF1R:4551}$-GGGC.

Superior ^{99m}Tc-labeled organic molecules from Table 3 include a heterogeneous group of compounds. ^{99m}Tc-EIPrDP and ^{99m}Tc-IPeDP are superior bone scintigraphy agents. Superior liver imaging agents include ^{99m}Tc-5-ALA, ^{99m}Tc-CMC, ^{99m}Tc-Mitomycin C, ^{99m}Tc-Vincristine

and ^{99m}Tc-UDCA. While a superior renal imaging agent is ^{99m}Tc-DMSA. Some, very suitable, brain imaging agents are ^{99m}Tc-amine-thiophene-dione, ^{99m}Tc-BAT-AV-45, ^{99m}Tc-histamine, ^{99m}Tc-piracetam and ^{99m}Tc-TRODAT-1. Some superior radiopharmaceuticals for gastrointestinal ulcer imaging are ^{99m}Tc-famotidine, ^{99m}Tc-omeprazole, ^{99m}Tc-pantoprazole, ^{99m}Tc-rabeprazole and ^{99m}Tc-tannic acid.

Superior tumor imaging agents are ^{99m}Tc-5FU, ^{99m}Tc-DES-P and ^{99m}Tc-methotrexate. While superior tumor hypoxia imaging agents are $^{99m}Tc(CO)_3$-4-nitroimidazole-triazole, $^{99m}Tc(CO)_3$-5-nitroimidazole-triazole, ^{99m}Tc-HYNIC-MN, ^{99m}Tc-misonidazole and ^{99m}Tc-PyDA. Some very efficient infection/inflammation imaging agents are ^{99m}Tc-2-aminoestrone-3-methyl ether, ^{99m}Tc-celecoxib, ^{99m}Tc-diclofenac, ^{99m}Tc-piroxicam, and ^{99m}Tc-fluconazole which is a fungal infection marker. Some superior and efficient heart imaging agents are ^{99m}Tc-labetalol, ^{99m}Tc-losartan, ^{99m}Tc-nebivolol and ^{99m}Tc-SestaMIBI.

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