An overview on Ga-68 radiopharmaceuticals for positron emission tomography applications

Review Article

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ABSTRACT

Gallium-68 a positron emitter radionuclide, with great impact on the nuclear medicine, has been widely used in positron emission tomography (PET) diagnosis of various malignancies in humans during more recent years especially in neuroendocrine tumors (NETs). The vast number of $^{68}Ge/^{68}Ga$ related generator productions, targeting molecule design (proteins, antibody fragments, affibodies, peptides and small molecules), as well as existing numerous human clinical trials at the registration, continuation and completion levels, are indicative of great importance and future impact of gallium-68 radiopharmaceuticals in human health. A concise review on the recent production and application of ^{68}Ga-tracers with the emphasis on the peptides, biomolecules and also small molecules available for clinical applications, clinical trials or preclinical studies are presented. The importance of Ga-68 radionuclide as a theranostic radionuclide with potential coupling application with therapeutic radioisotopes (such as ^{90}Y and ^{177}Lu) is increasing appreciated. This review describes the present status of availability, application and future horizons on the development of ^{68}Ga-radiopharmaceuticals worldwide.

Key words: ^{68}Ga; PET; Theranostics; Radiopharmaceuticals

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INTRODUCTION

Gallium was discovered by French chemist Paul E. Lecoq de Boisbaudran through a spectroscope in 1875 in Paris. Gallium has 24 isotopes with known half-lives and mass numbers 61 to 84. Of these, two are stable: ^{69}Ga and ^{71}Ga with natural abundances of 60.1% and 39.9% respectively. Simple gallium salts have been used as anticancer agents and still under clinical investigations including gallium maltolate [1], gallium nitrate [2] etc. Among 40 existing Ga radioisotopes, three have paved their way into nuclear medicine field (^{66}Ga, ^{67}Ga and ^{68}Ga), among which Ga-68 possesses the appropriate positron emission to be used in molecular imaging using PET [3] (Table 1). The interesting physical properties and availability of gallium-68 as a generator make it an interesting nuclide for developing new PET tracers [3] offering new opportunities for researchers to design various ^{68}Ga-radiopharmaceuticals due to the availability and commercialization of ^{68}Ge/^{68}Ga generators.

Germanium-68 decays by pure electron capture (EC) to the ground state of ^{68}Ga with a half-life of 270.95 d [4]. Gallium-68 in turn decays with a half-life of 67.71 min by a combination of EC and positron emission primarily to the ground state of ^{68}Zn, but also with a branch to an excited state at 1077 keV with a probability of about 3% and a number of higher excited states with a combined probability of under 0.4 %.

The use of a ^{68}Ge/^{68}Ga generator system ensures direct access to a short lived PET radionuclide within the PET facility or nuclear medicine department for a period of up to one year without the on-site availability of a cyclotron. The 68 min half-life of the high positron emitter ^{68}Ga together with the well-known coordination chemistry of gallium makes it one of the most attractive radionuclides for PET imaging. The interest of the radiopharmaceutical industry is currently focused on the development of ^{68}Ge/^{68}Ga-generators that have recently become routinely available. The development, evaluation and clinical application of ^{68}Ga-radiopharmaceuticalsis still a hot topic in nuclear medicine [5-7].

Gallium co-ordination chemistry

Gallium usually is found in oxidation state of +3 in aqueous solutions and due to high positive charge and small ionic radius is quite acidic (with a *pKa* of 2.6) usually found in hydrated form. Thus Ga cation has low water solubility in normal pH media without the presence of suitable donors. Due to its strong affinity for hydroxide, at very high pH it also has a propensity to demetallate from its complexes and form the gallate anion $Ga(OH)^{4-}$. Aqueous Ga(III) has the most sluggish water exchange rate due to its small size and high charge. Likewise other classic hard acidic cation, Ga(III) is strongly bound to ligands featuring multiple anionic oxygen donor sites, although it has also been shown to have good affinity for thiolates and amines usually forming Ga(III)-chelates up to its maximum coordinate number of 6 in a *pseudo*-octahedral geometry [8]. As a ferric cation bioisoester, Ga(III)has a strong affinity for the biological iron transporter, transferring [9]. Radio-gallium chelator complexes must therefore be sufficiently inert to transchelation by this biomolecule to have efficacy for *in vivo* applications [10] also presence of many thiol groups in the chelating agents is restricted due to oxidation reactions and possible allergic reactions. Most of the commonly used Ga chelates in radiopharmaceutical development consist of amine and phenol groups. Presently the most prevalent bifuntional ligands used in developing ^{68}Ga-labeled compounds are from macrocyclic compounds with nitrogen heteroatoms including –DOTA and –NOTA chelates. Figure 1 demonstrates some simple 1:1 Ga(III):ligand complexes [1, 2] and also Ga(III):chelate macrocycles usually found in Ga-68 radiopharmaceuticals [3, 4].

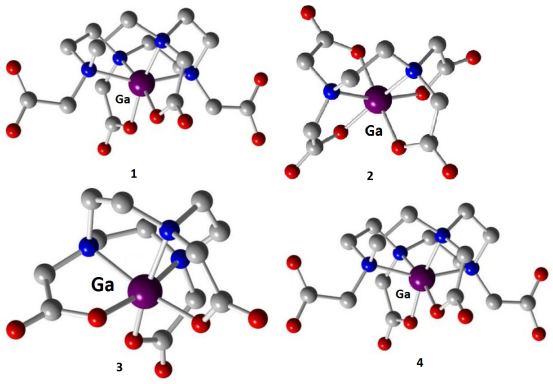


Fig 1. Confirmed structures for some important Ga-complexes used in gallium radiopharmaceutical development; Ga-EC[1] [11], Ga-EDTA[2] [12], Ga-NOTA[3] [13] and Ga-DOTA[4] [14].

Table 1: Physical properties of important gallium radioisotopes.

Radionuclide	Half-life	E_{max} (keV)	Radiation	Production
^{66}Ga	9.5 h	4153	β^+ (56%)	Cyclotron
^{68}Ga	67.6 min	1899, 770	β^+ (89%)	Generator
^{67}Ga	78.26 h	91, 93, 185, 296, 388	γ	Cyclotron

Theranostics properties

Theranostic properties of gallium-68 are an important initiative in the development of ^{68}Ga-radiopharmaceuticals. *"Theranostics"*utilize a combination of therapeutic emissions such as alpha, beta, or Auger ('thera'-) and diagnostic emissions such as gamma or positrons (-'nostic'). The key advantages of theranostics include the personalization of therapy based on uptake of the lower-dose diagnostic. This includes the optimization of a dose based on personal dosimetry, and more importantly the selection of patients who have a high chance of responding to therapy.

One important aspect of Ga-68 radiopharmaceuticals application is its applicability of the multiple-element theranostics, meaning different elements showing similar chemical properties can be used with the same targeting molecule for imaging (in this case ^{68}Ga) and therapy (^{90}Y-90 or ^{177}Lu, etc.). The selection of theranostic potential as a key criterion reflects the increasing interest from the radiopharmaceutical field.

^{68}Ga-radiopharmaceuticals used in clinic

^{68}Ga-citrate

^{67}Ga-citrate has been known as an infection/inflammation imaging agent for decades [15] and its production, quality control as well as its value in the evaluation of various infections has been reported [16]. After development of ^{68}Ga generators the first response to development of Ga-68 citrate was not very enthusiastic since most of ^{67}Ga images were taken far beyond Ga-68 physical half-life, thus for some time the production and application of ^{68}Ga-citrate was ignored. However after implementation of few clinical trials in various centers interests began to develop for ^{68}Ga-infection studies and the preliminary data confirmed a possible role for ^{68}Ga-citrate in the diagnosis of bone infections [17]. These reports concentrated preclinical initiated studies in infectious animals as well as reporting production routes [18-20] and also some groups demonstrated the application of the tracer in atherosclerotic plaques in animal models as possible inflammatory applications [21, 22] (Figure 2) and also its benefit in inflamed rabbit models [23], yet not much data and studies have been reported for the evaluation of inflammation in animal models for determination imaging time as well as other factors. The parallel works have focus on the high scale production of the tracer [24, 25].

^{68}Ga-somatostatin peptide derivatives

Over the last decade ^{68}Ga-labelled, DOTA-conjugated somatostatin (SST) derivatives such as TOC, NOC and TATE for the diagnosis of NETs have been well established.

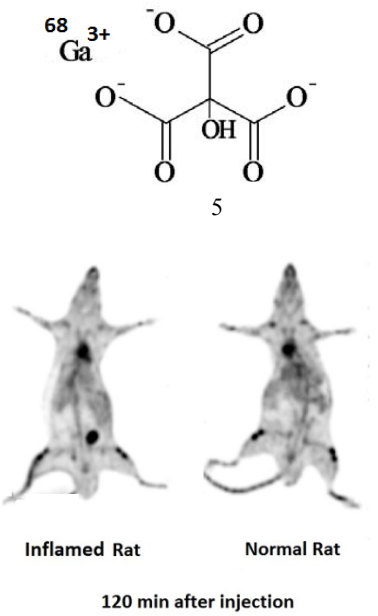


Fig 2. Chemical structure of ^{68}Ga-citrate [5] (above) and PET images of inflammation induced rat and control object 120 min post injection of 3.7 MBq of the tracer (below) [22].

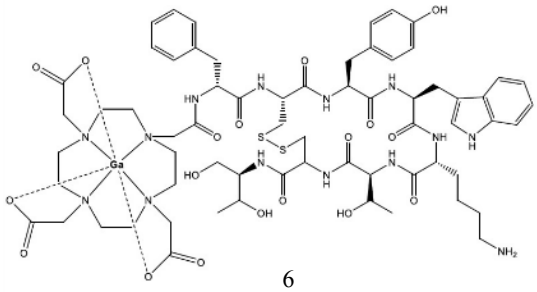
The above radiopharmaceuticals are also increasingly used for planning as well as the monitoring the therapy of NETs. The existence of therapeutic radionuclides forming stable complexes with DOTA chelate including ^{177}Lu, ^{90}Y *etc.* provide the therapeutic/diagnostic couple drugs that can fulfill the clinicians need for the diagnosis-therapy-follow up sequence, usually referred to *"theranostic"* approach as noted earlier.

Various ^{68}Ga-SST complexes have entered clinical applications with interesting pharmacokinetics and pharmacodynamics performance. It is highly beneficial to implement ^{68}Ga based PET imaging agents around the world to enhance the capability of radionuclide therapy.

In the context of the increasing application of Ga-68 radiopharmaceuticals the clinical implementation of the SST analogues based ^{68}Ga-radiopharmaceuticals as well as other potential ^{68}Ga based radiopharmaceuticals is presented:

^{68}Ga-DOTATOC: The development of Ga-68 radiopharmaceuticals was parallel to the development of peptide-based pharmaceuticals in last 2 decades while the physical half-life of this radionuclide with biological half-life of synthetic peptides was in great accordance. Typically, the most important ^{68}Ga-

peptide radiopharmaceuticals are SST analogs [26] as mentioned. The first tracer applied in the detection of malignancies was ^{68}Ga-DOTATOC [27], with high affinities for SSR2 and SSR3 and lower affinity for SSR5 was shown to be highly accurate in the diagnosis of neuroendocrine tumors, meningioma's, thyroid malignancies, and prostatic cancers as well as many other tumors [28] (Figure 3). DOTATOC imaging showed limitations showing false positive data for non-tumor tissues in the pancreas, pituitary gland, and in chronic inflammatory conditions [29].



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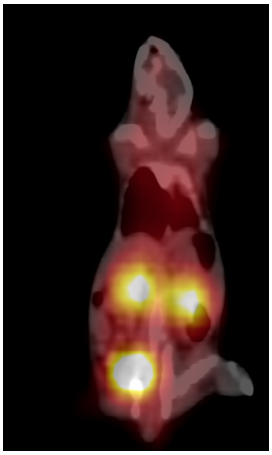
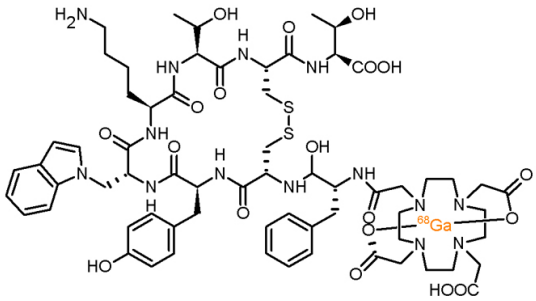


Fig 3. Chemical structure of ^{68}Ga-DOTATOC(6) (above) and PET images of normal rat 30 min post injection of 3.7 MBq of the tracer (below) [30].

^{68}Ga-DOTATATE: The other developed SST ligand for PET SST receptor imaging is ^{68}Ga-DOTATATE. The recent studies showed while ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE considered equally well for staging and patient selection for peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE, the slight difference in the healthy organ distribution and excretion may render ^{68}Ga-DOTATATE preferable [31]. The facile production and quality control of ^{68}Ga-DOTATATE has been reported using automated and semi-automated methods [32, 33] (Figure 4). In many other studies in neuroendocrine tumors, ^{68}Ga-DOTATATE demonstrated high sensitivity and specificity [34].



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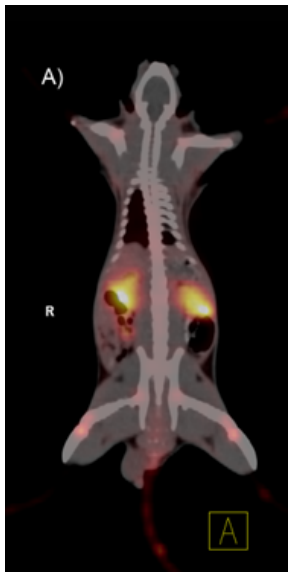

Fig 4. Chemical structure of ^{68}Ga-DOTATATE(7) (above) and PET/CT fused images of [^{68}Ga]DOTA-TATE in a male rats 45 min post injection (below) [32, 34].

Also preliminary results showed that ^{68}Ga-DOTATATE has a higher lesion uptake even in well-differentiated thyroid cancer patients and may have potential advantage over ^{68}Ga-DOTANOC, the other known Ga-68 SST ligand [35]. These findings encouraged the initiation of many clinical trials in many centers using ^{68}Ga-DOTATATE [36, 37].

^{68}Ga-DOTANOC: Recent data indicated that ^{68}Ga-DOTANOC positron emission tomography computed tomography may yield improved images in a shorter acquisition protocol than ^{111}In-DTPA-octreotide in the evaluation of NETs (Figure 5). Interestingly, The SST 2,3,5-specific radiotracer ^{68}Ga-DOTANOC detected significantly more lesions than the SST 2-specific radiotracer (^{68}Ga-DOTATATE) in the

patients with NETs. The clinical relevance of these finding has to been proven in larger studies [38-40].

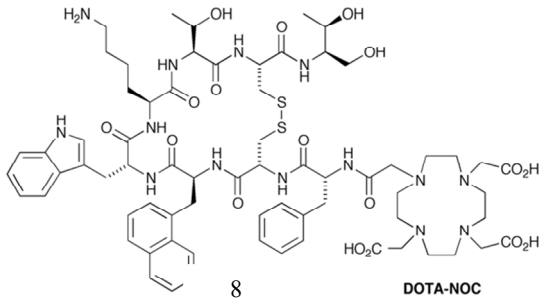

Fig 5. Chemical structure of ^{68}Ga-DOTANOC[8].

^{68}Ga-radiopharmaceuticals in clinical trials

In addition to SST analogues several other ^{68}Ga based radiopharmaceuticals are under development. These include, ^{68}Ga-labelled peptide ligands targeting other receptors and their corresponding peptides such as bombesin, RGD peptides, melanocyte stimulating hormones (MSH) *etc.*, however have not yet found their way to routine clinical applications. In addition, development of ^{68}Ga non-peptide tracers could also have significant use. These could include tracers for tumor diagnosis such as bone seeking agents, inflammation markers, or myocardial perfusion imaging tracers.

However, these agents are yet to reach significant clinical impact and need further research support. The advantages of the easy availability of the positron emitter ^{68}Ga from the generator combined with the superior imaging quality of PET and the uniqueness of the ^{68}Ga-radiopharmaceuticals hold important promises towards the future management of cancer and other diseases. Some of the tracer's data are presented in Table 2 and chemical structures of some ligand also shown in Figure 6.

^{68}Ga-radiopharmaceuticals at preclinical studies

^{68}Ga-tracers used in bone imaging

The FDA approved ^{153}Sm-EDTMP [56, 57] and recent clinically used ^{177}Lu-EDTMP [58, 59], have demonstrated high bone uptake and fast urinary clearance and have paved the way for developing other EDTMP-based radiopharmaceuticals. In a homology to the mentioned therapeutic compounds, ^{68}Ga-EDTMP[15] has been prepared for clinical imaging of bone metastases [60, 61] occurring in many patients with solid malignant tumors.

Table 2: Novel ^{68}Ga-tracers entering in clinical evaluation studies.

Ligand	Chemical category	Diagnostic applications	Type of study	Ref.
^{68}Ga-NEB	Protein (Albumin)	Arteriovenous Malformation; Hemangioma; Neoplasms Lymph Nodes; Lymphedema	IV, SGA	[41]
^{68}Ga-BNOTA-PRGD2	Peptide	Evaluation of Stroke	IV	[42]
^{68}Ga-RM2[9]	Peptide	Primary Prostate Cancer	IV,NR	[43]
^{68}Ga-ABY-025	Affibody	Metastatic Breast Cancer	IV, SGA	[44]
^{68}Ga-DOTA-Bombesin[10]	Peptide	Prostate Cancer	IV, SGA	[45]
^{68}Ga-NOTA-AE105[11]	Peptide	Invasive Cancer Phenotype	IV, SGA	[46]
^{68}Ga-AlfatideII[12]	Peptide	Lung Cancer and Lung Tuberculosis	PA	[47]
^{68}Ga-NOTA-NFB[13]	Peptide	Glioma or Breast Cancer	O	[48, 49]
^{68}Ga-PSMA	Peptide	Prostate Cancer	IV, SGA	[50, 51]
^{68}Ga-IMP-288[14]	Peptide	Recurrence of HER2 Negative Breast Carcinoma Expressing CEA	IV	[52, 53]
^{68}Ga-F(ab') 2- Trastuzumab	Antibody fragment	Breast cancer	IV	[54]
^{68}Ga-MSA	Protein (Albumin)	Atherosclerosis	O	[55]

(IV: Interventional, SGA: Single group assignment, NR:Non-randomized, PA: Parallel assignment, O: Observational)

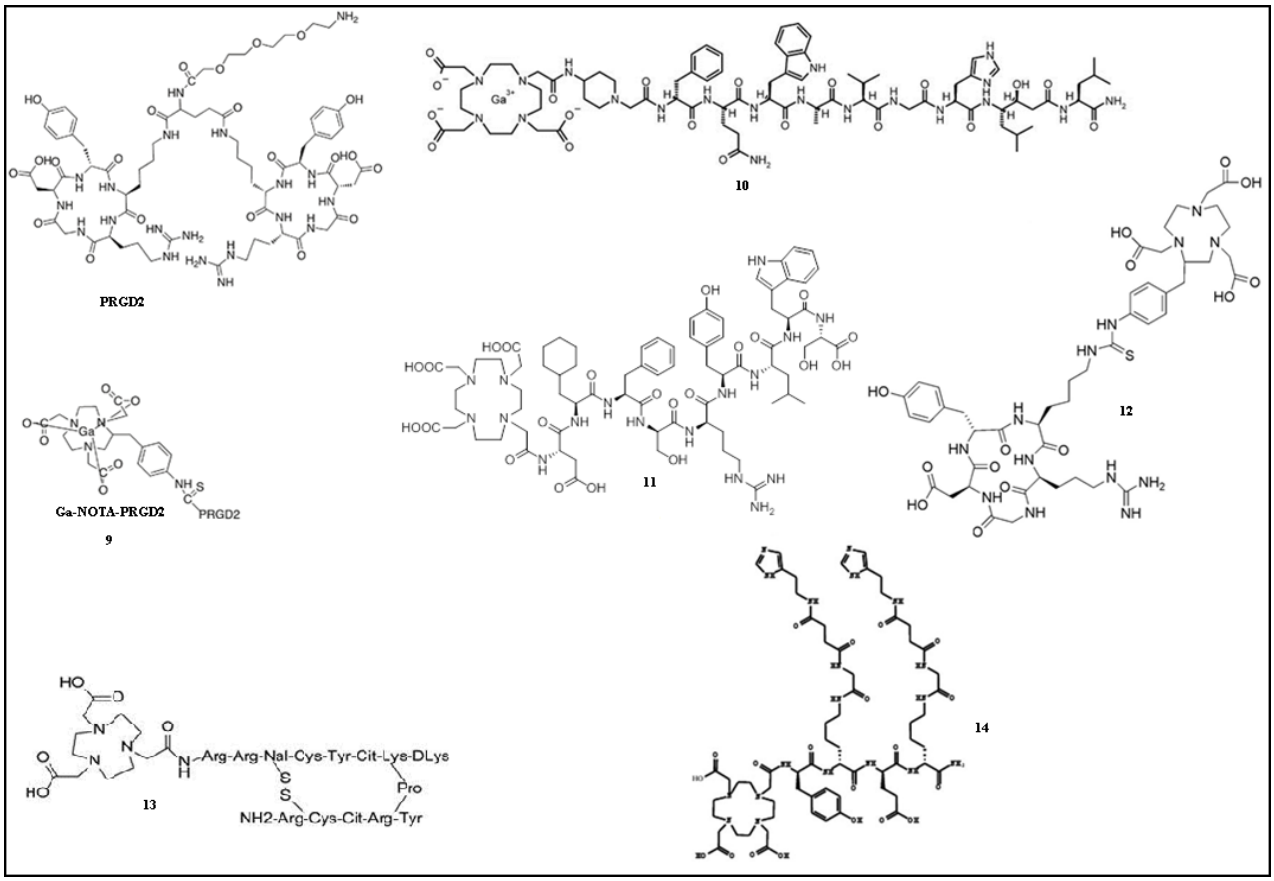

Fig 6. Chemical structure of some ^{68}Ga-tracers in the clinical trials.

The longer half-life and intensive radiation dose to the patients from F-18 sodium fluoride has led to develop ^{68}Ga-based bone radiopharmaceuticals including ^{68}Ga-EDTMP. Recently, novel radiogallium-labeled bone imaging agents using oligo-aspartic moieties have been presented due to their high affinity for hydroxyapatite [62]. Another interesting research project has been initiated using ^{68}Ga-BPAMD(16), presenting a possible PET/CT imaging agents as a theranostic approach [63, 64] leading to few human studies [65-67].

Other ^{68}Ga-tracers

May other tracers have been designed and went through preclinical studies based on the research groups scientific scopes for the detection of malignancies, functional tissue performance, neurological problems, cardiac imaging, rheumatoid arthritis *etc.* In most cases the new molecules are designed based on the homology of the kit-based Tc-99m radiopharmaceuticals. Still a major research and development capacity of these groups is focused on the peptide cores due to high target:non target ratio, rapid clearance end low toxicity and possibility of solid phase synthesis with high purity grade. Table 3 demonstrates the details and status of some these developed tracers. Also the chemical formulas of some of the mentioned ligands are presented in Figure 7.

FUTURE PERSPECTIVES

Regarding the potential of molecular imaging based on PET/CT technique, the research and development of PET tracers will be the major area of interest and development in the field of radiopharmacy in developed and developing countries. ^{68}Ga as an available source of radioisotope, in form of radionuclide generator with almost a year shelf life, is a secure, non-expensive and easy-to-use source of PET radiotracers unlike other cyclotron produced radionuclide with short half-lives. With respect to the available kit technology in many countries, development of ready-to-prepare radiopharmaceuticals similar to ^{99m}Tc-kits is possible for ^{68}Ga radiotracers.

Table 3: The details of the potential Ga-68-tracers/research small molecules.

Tracer	Application	Probe	imaging	Ref.
^{68}Ga-ECC	Renal perfusion imaging	Rodent	PET/CT	[68]
^{68}Ga–ECD	Renal perfusion imaging	Rodent	PET/CT	[69]
^{68}Ga-MAA	Lung imaging	Rodent	PET/CT	[70]
^{68}Ga-EDTMP(15)	Bone imaging	Rodent	PET/CT	[61, 62]
^{68}Ga-EDTA(17)	Glomerular filtration rate	Human	PET/CT	[71]
^{68}Ga-DOTA-Siglec-9	Inflammation imaging	Rodent	PET/CT	[72]
^{68}Ga-[3-isopropoxy-ENBDMPI]$^{+}$(18)	Myocardial imaging	Rodent	PET/CT	[73]
^{68}Ga-NOTA-folate (19)	Tumor imaging	KB xenografts nude mice	Distribution	[74]
^{68}Ga-anti-CD163-antibody	Arthritis imaging	Rodent	PET	[75]
^{68}Ga-labeled fatty acid	Myocardial imaging	Rodent	PET	[76]
^{68}Ga-NO2AP	Bone imaging	Rodent	PET/CT	[77]
^{68}Ga-DOTA-triptorelin	Tumor imaging	Rodent	Distribution	[78]

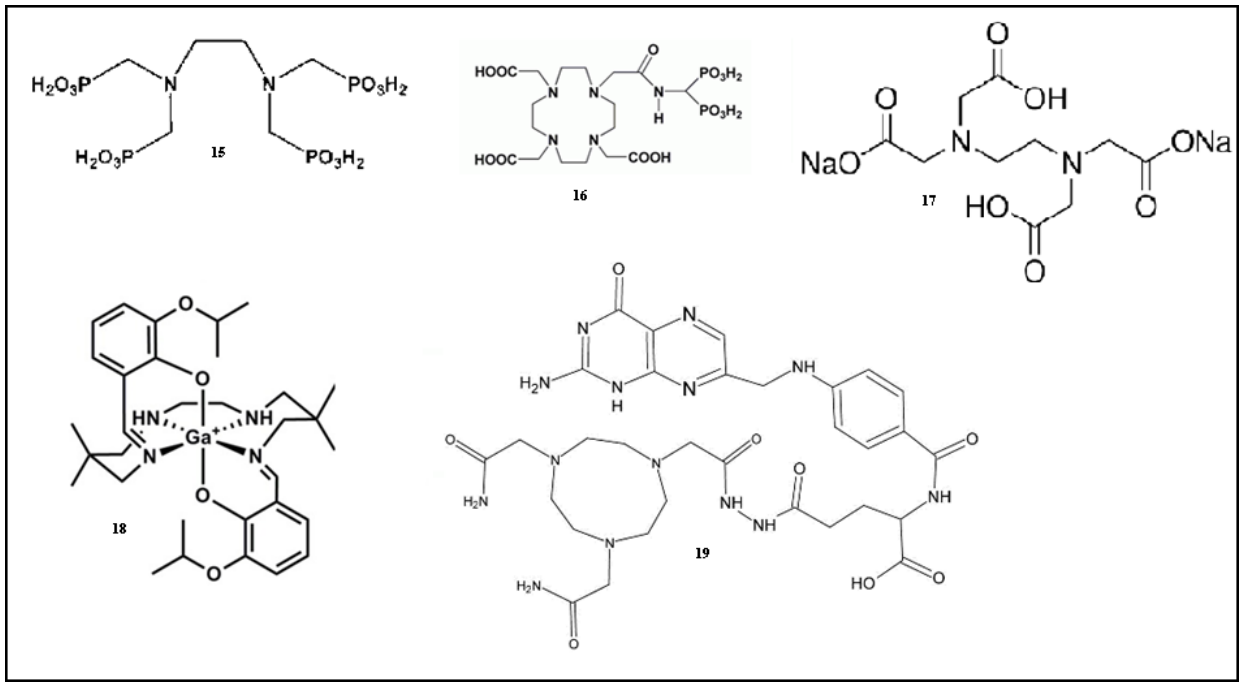

Fig 7. Chemical structures of various ^{68}Ga-ligands at preclinical stages.

Peptides as stable, non-expensive targeting molecules with well studied chemistry, pharmacology and pharmacokinetics continue to be the best targeting molecules in ^{68}Ga-radiotracer development and more than 80% of future clinically established ^{68}Ga-tracers will be based on peptides. The next candidates will be affibodies and other small molecules.

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