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Review article

Approaching Gallium-68 radiopharmaceuticals for tumor diagnosis: a Medicinal Chemist's perspective

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ABSTRACT

Nuclear medicine has revolutionized disease diagnosis and treatment, particularly in oncology, by enabling precise imaging and targeted therapies using radiopharmaceuticals. Recently, Gallium-68 (^{68}Ga) has emerged as a powerful positron emission tomography (PET) imaging agent, with a growing role in theranostics when paired with ^{177}Lu for cancer treatment. The ability to obtain ^{68}Ga from ^{68}Ge/^{68}Ga generators, along with its favorable radiochemical and pharmacokinetic properties, has driven an increasing number of clinical applications, which culminated with the approvals of ^{68}Ga-DOTA-TOC and ^{68}Ga-DOTA-TATE for the treatment of neuroendocrine tumors, and ^{68}Ga-PSMA-11 for prostate cancer over the past decade. This review provides a comprehensive overview of ^{68}Ga radiochemistry, chelators, and key compounds in clinical trials, highlighting the potential of this radionuclide in precision oncology.

1. Introduction

Nuclear medicine plays a crucial role in both the diagnosis and treatment of various diseases, particularly in oncology [1]. The use of radiopharmaceuticals that target specific biological processes enables non-invasive imaging and precise therapeutic interventions. Among the most widely used diagnostic radionuclides, Fluorine-18 (^{18}F) -particularly when labeling ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG)- remains the gold standard for positron emission tomography (PET imaging. Meanwhile, Technetium-99 m (^{99m}Tc) is extensively utilized in single photon emission computed tomography (SPECT), playing a crucial role in various diagnostic applications [2].

On the therapeutic side, both beta-emitting radionuclides, such as Iodine-131 (^{131}I) for thyroid disorders, Lutetium-177 (^{177}Lu) for neuroendocrine tumors and prostate cancer, and Yttrium-90 (^{90}Y) for hepatic malignancies, as well as alpha-emitting radionuclides, such as Radium-223 (^{223}Ra) for bone metastases, have demonstrated significant clinical benefits [3]. In recent years, Gallium-68 (^{68}Ga) has emerged as a powerful diagnostic agent, with growing interest in its theranostic applications paired with ^{177}Lu to enhance cancer treatment. The present review aims to provide Medicinal Chemists with the essential background knowledge needed for designing and synthesizing new compounds suitable for ^{68}Ga labelling. An overview of the chemistry and radiochemistry of Gallium is first reported, followed by a description of the main Gallium chelators focusing on the complex formation. Finally, the review core analyses the most important ^{68}Ga-labeled compounds in clinical trials for diagnostic and theranostic applications.

2. Chemistry and radiochemistry of gallium

Gallium is a chemical element with atomic number **31** and electronic configuration [Ar]3d104s24p1. It is a metal belonging to the 13 p-block group of the periodic table, and its more stable ion is Ga^{3+} [4]. Ga^{3+} presents a short ionic radius (62 p.m.) and high charge density, thus is a hard Lewis acid (pKa = 2.6) [5]. Based on these chemical properties, Gallium (III) preferentially forms coordination compounds by binding hard Lewis bases. The d-orbital completely filled allows Gallium to form complexes with different coordination numbers (i.e., 4, 5, and 6), but the most stable derivatives possess a six-coordination number and an octahedral geometry. Ga^{3+} chelators generally are macrocyclic hexadentate derivatives, including carboxylate, phosphonate, or amines as coordinating groups [4,5].

The ability of Gallium to form complexes is highly dependent on the pH of the medium. At pH values less than 3, Gallium exists primarily as

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Ga^{3+} and can form complexes. At pH values between 3 and 7, it forms the insoluble hydroxide $Ga(OH)_3$, making coordination impossible. At pH values above 7, Gallium exists as gallate ion $[Ga(OH)_4]^-$, which is soluble but unreactive. Although acidic pH may seem like the optimal medium for complexation, most ligands at these pH values are in their protonated form and cannot form complexes with metals. Therefore, Gallium is typically complexed at pH 3–7 using auxiliary complexing agents, such as acetate, citrate, and 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), to prevent precipitation as hydroxide [4–6].

In nature, Gallium is present in the form of two stable isotopes, Gallium-69 (60.11 %) and Gallium-71 (39.9 %). At the same time, its commercially most important radioisotopes are Gallium-67 (gamma emitter, half-life 78 h) and ^{68}Ga (mainly beta plus (β^+) emitter, half-life 68 min) [7]. More specifically, about 89 % of ^{68} Ga day through β^+ decay, with a maximum emitted energy of 1.9 MeV and an average of 0.89 MeV, while approximately 11 % undergoes electron capture decay [5,8]. In both cases, the decay product is the stable isotope Zinc-68. The decay mode and half-life make ^{68}Ga a suitable radionuclide for applications as a radiotracer in PET imaging [9]. Although the energy emitted by ^{68}Ga is higher than that released by ^{18}F (maximum energy of 0.63 MeV, average of 0.25 MeV), and higher energy is usually associated with a decrease in image resolution, experimental evidence has shown that the image quality of the two radionuclides is comparable. Furthermore, the relatively short half-life time is consistent with the pharmacokinetics of most low molecular weight radiopharmaceuticals, allowing limited patient irradiation. Another advantage of using ^{68}Ga is that it can be conveniently obtained from a Germanium-68/Gallium-68 generator [5]. All these properties highlight ^{68}Ga as a promising radiotracer in clinical imaging.

3. Production of ^{68}Ga

^{68}Ga can be produced using either a cyclotron or a generator, each method having advantages and disadvantages. Generators are more easily manageable and can be installed more easily, resulting in a broader distribution. On the other hand, generators produce lower amounts of radioactivity compared to cyclotrons (maximum radioactivity produced in generators is 2.7 GBq, while cyclotrons can produce up to 9.85 GBq or 194 GBq using liquid or solid targets, respectively), limiting the number of patients that can be treated daily [10].

^{68}Ge, needed for synthesizing ^{68}Ga by a generator, can be obtained by a few nuclear reactions in particle accelerators, possesses a half-life of 271 days, and decays to ^{68}Ga with a 100 % electron capture decay [11]. The long half-time of parent nuclide ^{68}Ge allows generators to be used for over one year [10]. The first ^{68}Ge/^{68}Ga generators were initially designed in the 1960s, but numerous modifications have since been introduced, leading to the creation of current equipment. To date, a few ^{68}Ge/^{68}Ga generators are available on the market, and they are all characterized by a solid matrix eluted with HCl, which affords the recovery of Gallium as $^{68}GaCl_3$. The solid matrix can be organic (*e.g.*, N-methylglucamine, pyrogallol-formaldehyde, or Nanoceria-polyacrylonitrile) or inorganic (*e.g.*, SnO_2, TiO_2, CeO_2, nano-zirconia), while the concentration of HCl can span from 0.01 M to 1 M [12]. Generators characterized by an inorganic matrix are more used, and comparative studies have shown that CeO_2- and SiO_2-based phases are more efficient than the TiO_2 and SnO_2 ones [10]. However, it is worth noting that generators on the market typically possess TiO_2 and SnO_2-based matrices. Two examples of commercially available ^{68}Ge/^{68}Ga generators are GalliaPharm® (Eckert & Ziegler Radiopharma GmbH, Germany) and Galli Eo® (IRE Elit, Belgium) [13]. They both are Good Manufacturing Practice (GMP) grade, have Food and Drug Administration (FDA) type II drug master files, and use a sterile solution of 0.1 M HCl for the elution [5]. The GalliaPharm® generator exploits a TiO_2-based matrix, is available to produce ^{68}Ga with activities ranging from 0.74 GBq (20 mCi) to 3.70 GBq (100 mCi) and possesses a shelf-life of 12 months or 700 elutions [14]. Galli Eo® uses an unspecified resin that is suitable for the production of activities in the range between 0.74 GBq (20 mCi) and 1.85 GBq (50 mCi) and shows a shelf-life of 12 months or 450 elutions [15]. Generators can be combined with cold kits (see paragraph **4.2**) to easily prepare ^{68}Ga-based radiopharmaceuticals, although the different eluates' properties make the standardization of cold kits hard.

^{68}Ga production by cyclotron is generally carried out through the reaction ^{68}Zn(p,n)^{68}Ga, *i.e.*, the bombardment of a nucleus of ^{68}Zn by a proton and emission of a neutron and an 11–14 MeV energy [16]. ^{68}Zn can be involved as a liquid target (*i.e.*, a solution of ^{68}Zn in nitric acid) or a solid target (*e.g.*, electrodeposited on copper, platinum, and silver) [16]. The use of a liquid target results in lower radioactivity emissions and lower costs, while solid targets are associated with higher activity despite more difficult purification steps. For these reasons, liquid targets are more suitable for clinical imaging investigations [5]. To date, ^{68}Ga is mainly obtained by a ^{68}Ge/^{68}Ga generator, but the increasing production of ^{68}Ga by cyclotron prompted the insertion of a dedicated monography (number 3109) in the European Pharmacopeia [5,17].

4. Introduction to ^{68}Ga-Radiopharmaceuticals

The application of ^{68}Ga in nuclear medicine is notably increased in the last ten years, as can be appreciated by looking at the pattern of the curve that describes the number of publications as a function of the years. The comparison with ^{18}F publications highlights the potential of ^{68}Ga as first choice PET tracer (Fig. 1).

As further confirmation of the scientific community's interest in this isotope, the annual meeting of the Society for Nuclear Medicine and Molecular Imaging (SNMMI) has selected images obtained with ^{68}Ga radiotracers as "Image of the Year" for several years from 2015 [4]. In particular, the SNMMI, during its 2022 meeting, awarded the image relating to the study entitled "Predicting remodeling and outcome from molecular imaging of fibroblast activation in patients after acute myocardial infarction" by Johanna Diekmann and colleagues of the Department of Nuclear Medicine from Hannover Medical School in Germany. The study compares different imaging techniques, including the application of ^{68}Ga derivatives for evaluating patients who had a myocardial infarction [18]. This increasing importance can be mainly explained by the possibility of easily obtaining ^{68}Ga in generators, the perspective to combine it with other radioisotopes such as ^{177}Lu for theranostic applications, and the development of cold kits for radiopharmaceuticals production [4].

The impact of ^{68}Ga-radiopharmaceuticals is evident from the growing number of review articles published on this topic. Many studies

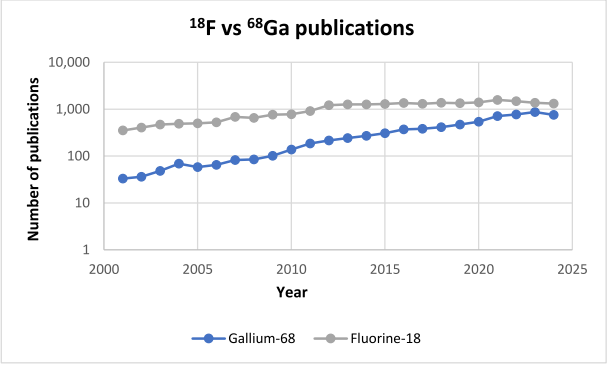


Fig. 1. The trend of the publications involving ^{68}Ga and ^{18}F from 2001 to 2024. Research carried out using Scifinder® on March 3, 2025 and setting these parameters: research topic: "^{68}Ga", refined by document types: article, patent, refined by document year: 2001- combined with research topic: "Gallium-68″, refined by document types: article, patent, refined by document year: 2001-; research topic: "^{18}F″, refined by document types: article, patent, refined by document year: 2001- combined with research topic: "Fluorine-18″, refined by document types: article, patent, refined by document year: 2001-.

focus on the application of ^{68}Ga compounds for detecting various neoplasms. Notably, radiolabeled agents targeting somatostatin receptors (SSTRs) are widely used as the first-line choice for imaging neuroendocrine tumors (NETs) [19] while compounds binding to prostate-specific membrane antigen (PSMA) have become essential tools for diagnosing prostate cancer [20].

Moreover, the innovative potential of ^{68}Ga-based radiopharmaceuticals, particularly in combination with therapeutic radiometals such as ^{177}Lu and Actinium-225 (^{225}Ac) for theranostic applications, has increasingly attracted the attention of researchers [21,22]. Beyond oncology, the utility of ^{68}Ga extends further. ^{68}Ga-PET imaging is emerging as a non-invasive tool for visualizing inflammatory disorders, with the ability to detect most major pathophysiological mediators of inflammation. This opens promising applications in cardiovascular diseases such as myocardial infarction, cardiac sarcoidosis, and myocarditis [23,24] Additionally, ^{68}Ga shows promise in supporting the transition from SPECT to PET imaging for evaluating regional lung function [25].

4.1. General structure of ^{68}Ga-radiopharmaceuticals

As previously mentioned, radiolabeling with ^{68}Ga is accomplished by utilizing specific chelators that can complex with this metal. Therefore, Gallium radiopharmaceuticals comprise an organic carrier for selective drug delivery to the site of interest and a chelating agent (ligand) to allow the labeling. Ligands must form stable complexes with ^{68}Ga. The organic carrier is generally a peptide; however, small molecules or antibodies have been recently reported [26]. Sometimes, a linker is used to conjugate chelators and carriers. Furthermore, a bifunctional chelating agent (BFCA) suitable for complexing gallium and binding the carrier can be exploited. BFCAs are molecules endowed with a portion to coordinate a metal and a group to form a covalent bond with the carrier [27,28]. Usually, radiopharmaceuticals are synthesized in two steps: first, the chelator is linked to the biomolecule, and then the radiolabelled reaction is carried out. In some cases, the radiometal-chelate complex is first synthesized and then conjugated [8].

Characteristics of these chelating agents have been extensively reviewed elsewhere [5,8]. We can briefly summarize that the labeling process must be fast (necessary for isotopes characterized by a short half-life), quantitative, and selective, and it requires mild conditions of the reaction.

Herein, we report some examples of the most used ligands for ^{68}Ga complexes, classifying them into cyclic and acyclic ligands.

4.1.1. Most common ligands for ^{68}Ga-Radiopharmaceuticals

4.1.1.1. Cyclic ligands. NOTA is the acronym for the macrocyclic chelator 1,4,7-triazacyclononane-*N, N′, N″*-triacetic acid (Fig. 2A). NOTA is a hexadentate ligand and coordinates Ga^{3+} through the three nitrogen atoms of the cycle and three oxygens of the carboxylate groups of the acetate side (N_3O_3) (Fig. 2B). NOTA-Ga^{3+} complexes are stable, as confirmed by the value of the formation constant (logK calculated ranging from 29.63 to 31.0, depending on references) [4,29,30]. A series of NOTA derivatives has been developed, including NOTA-bis(*t*Bu)ester, NOTA-NHS ester, and NODA-GA derivatives (Fig. 2A), which allows for greater versatility in conjugation reactions.

NOTA-bis(*t*Bu)ester presents two carboxylic groups protected as esters and allows mono-functionalization. NOTA-NHS compounds possess an *N*-hydroxysuccinimide (NHS) functional group that facilitates the activation of the carboxyl moiety as an NHS ester, allowing the reaction with primary amines under mild reaction conditions and consequent formation of an amide bond [31]. NODA-GA is the acronym of 1,4,7-triazacyclononane,1-glutaric acid-4,7-diacetic acid. NODA-GA compounds present a nitrogen atom of the macrocycle functionalized with a glutaric acid (GA) unit instead of an acetic acid unit [32]. Several NODA-GA derivatives are reported in the literature, such as NODA-GA(*t*Bu)$_3$ or NODA-GA-NHS ester (Fig. 2A).

DOTA is the acronym for the cyclic chelator 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (Fig. 2A). It is an octadentate ligand, but it coordinates Ga^{3+} as a hexadentate ligand, using only four nitrogen atoms and two oxygen atoms (N_4O_2) (Fig. 2B). DOTA possesses a constant of stability with Ga^{3+} slightly lower than NOTA (logK for the DOTA-Ga^{3+} complex has been calculated between 21.30 and 26.05, depending on references) [4,29,33], but is one of the most employed chelators in medicinal chemistry. Its success in Ga^{3+} chelation is related to PET radiotracers for the diagnosis of tumors that overexpress SSTRs [34].

DOTA's primary limitations include its low selectivity for ^{68}Ga compared to other metals, leading to purification challenges, and the requirement for high temperatures for complexation, which precludes its use with thermolabile compounds [4].

Although the DOTA macrocycle can be used as a BFCA itself [28], its derivatives are most commonly used for conjugation reactions. Among these chelators, it is worth mentioning DOTA-tris(*t*Bu)ester, DOTA-NHS ester, maleimide-DOTA, and DOTA-GA derivatives (Fig. 2A). This variety offers the opportunity to select the best chelator based on the functional groups on the substrate, affording selective reactions. For instance, in mild conditions, the maleimide group of maleimide-DOTA selectively reacts with the thiol group (such as cysteine SH groups) [28,35], while the isothiocyanate group of *p*–NCS–Bz-DOTA-GA can react with primary amino groups, affording a thiourea linker.

DATA is the acronym of 6-amino-1,4-diazepine-triacetate. Different DATA chelators have been synthesized, the simplest is DATA^{M} (Fig. 2A), where M refers to a methyl on the C6 position. DATA^{M} forms a slightly distorted octahedral structure with Gallium, where the Ga^{3+} ion is coordinated by the three nitrogen atoms of the amino groups and three oxygen atoms of the carboxylic groups (N_3O_3) (Fig. 2B) [36,37]. These ligands can be defined as hybrid chelators possessing both a cyclic moiety and an acyclic portion (the nitrogen not included in the ring) and, although they have been introduced quite recently, are very promising for Ga^{3+} complexation. Indeed, they are stable *in vivo* and allow for radiolabeling at room temperature, being suitable for developing cold kits for Gallium labeling [38,39].

4.1.1.2. Acyclic ligands. HBED is the acronym for *N,N′*-bis(2-hydroxybenzyl)ethylenediamine-*N,N′*-diacetic acid (Fig. 3A). This acyclic ligand complexes Ga^{3+} its four oxygen atoms and two nitrogen atoms (N_2O_4) (Fig. 3B) and possesses a high formation constant for this metal (LogK 38.51–39.57) [4,32]. Nevertheless, during the complexation, the formation of three geometric isomers (each one characterized by a couple of enantiomers), endowed of different profiles of activity and pharmacokinetic properties, has been observed [29], pointing out a limitation of this ligand. On the other hand, HBED allows radiolabeling at room temperature, and is applicable to heat-sensitive molecules [4].

Among HBED derivatives, *N,N′*-bis[2-hydroxy-5-(carboxyethyl) benzyl]ethylenediamine-*N,N′*-diacetic acid (HBED-CC) (Fig. 3A) possesses significant importance because is the ligand which coordinates Ga^{3+} in [^{68}Ga]Ga-PSMA-11, the only Ga^{3+}-radiopharmaceutical approved for PET imaging in diagnosis of prostate tumors [20]. HBEDD-CC presents two acetic functions on the aromatic rings, increasing the versatility in conjugation with carrier compounds.

THP, *i.e.*, tris(hydroxypyridinone) derivatives are new ligands disclosing excellent properties in Ga^{3+} complexation. Indeed, the THP moiety allows quick and quantitative chelation of this ion at soft pH conditions (pH ~6.5) and room temperature [20]. The oxygen atoms of the three hydroxypyridinone rings are involved in the complexation (Fig. 3B). An example of a THP chelator is THP-NCS (Fig. 3A).

4.1.1.3. Stability of Ga^{3+} complexes. The stabilization of Ga^{3+} complexes in aqueous solution, particularly within the pH range suitable for radiolabelling reaction, remains a key challenge in the synthesis of these

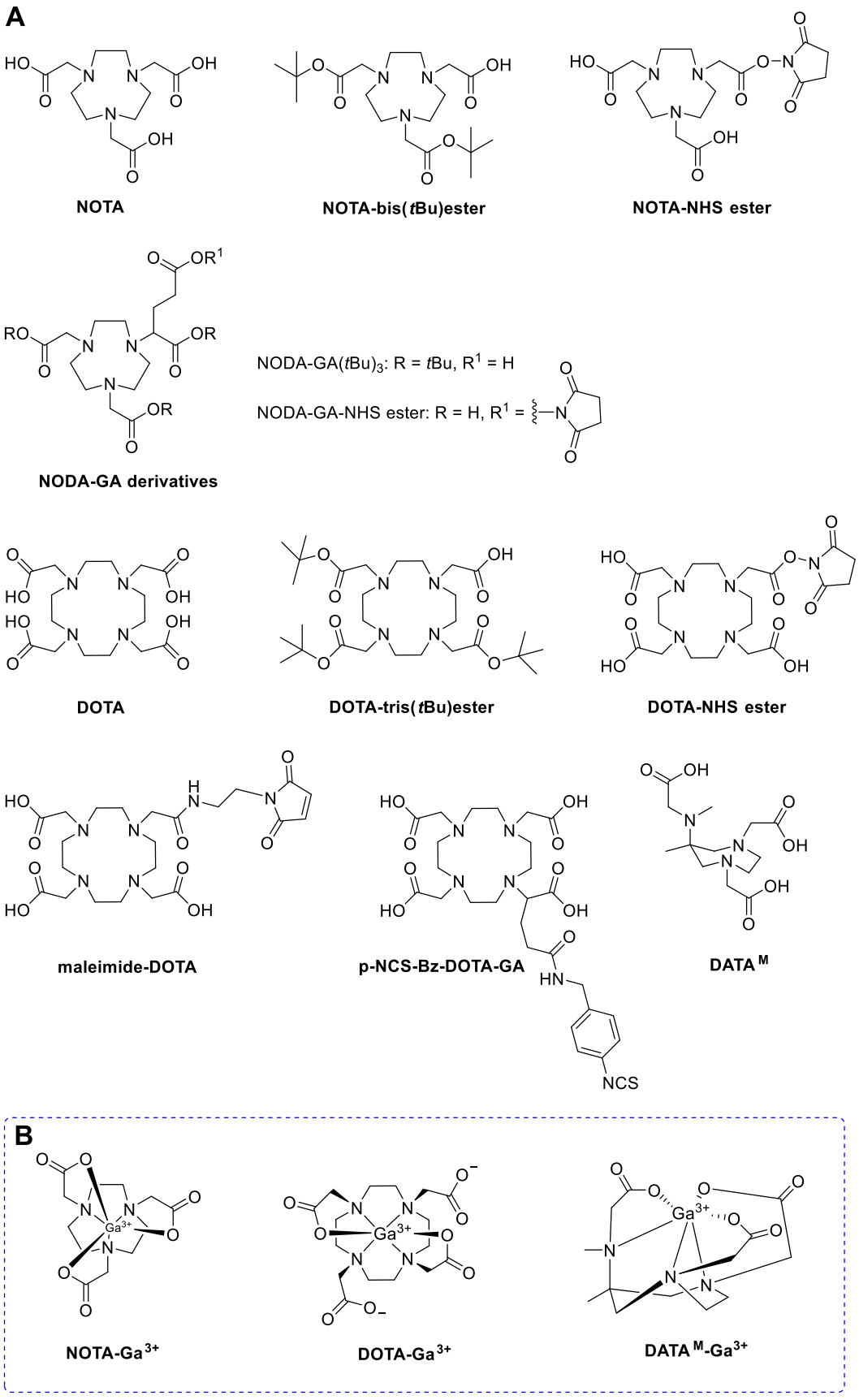


Fig. 2. **A.** Structure of the main cyclic chelating agents. **B.** Structure of the complexes of NOTA, DOTA and DATA^{M} with Ga^{3+}.

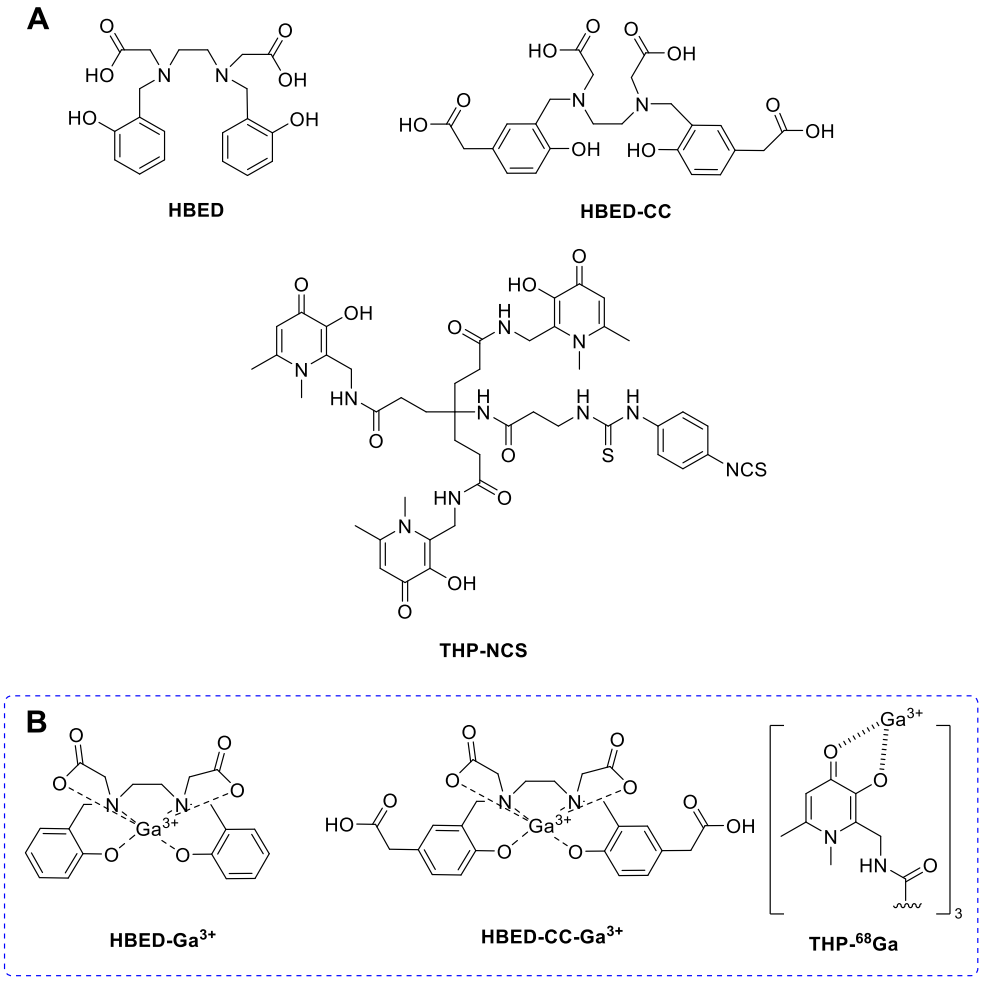


Fig. 3. A. Structure of the main acyclic chelating agents. **B.** Structure of the complexes of HBED, HBED-CC and THP with Ga^{3+}.

radiopharmaceuticals. Although this topic has been reviewed in detail elsewhere [5,40], we provide here a concise summary of the stability of these complexes. Specifically, we highlight the thermodynamic stability constants, the media used, and the typical pH conditions for radiolabeling reactions, where such data are available (Table 1).

From the table, it is evident that acyclic chelating agents generally form more stable complexes than cyclic ligands. Furthermore, the radiolabeling conditions are similar across different ligands, typically requiring a pH of around 4 and the use of HEPES buffer. It is worth noting that the pH of the solution is commonly adjusted prior to injection to ensure it falls within a physiologically acceptable range, typically between 4 and 8. Commonly used buffers for this adjustment include bicarbonate and phosphate [49,50].

Table 1
Thermodynamic complex formation stability constant for Ga^{3+} (logK), medium, and pH values for radiolabeling reactions.

Ligand	logK	Medium	pH	Reference
NOTA	31.0	1 M HEPES buffer	3.5	[30]
NODA-GA		Different buffers		[41]
DOTA	21.3	1 M HEPES buffer	4.8	[33]
DOTA-tris(*t*Bu)ester		1 M sodium acetate		[42]
DOTA-NHS ester		1 M HEPES buffer		[43]
$DATA^{M}$	21.7	0.2 M sodium acetate	4–7	[44]
HBED	38.5	2.1 M HEPES buffer	4.2	[45]
HBED-CC		2.1 M HEPES buffer	4.2	[46]
THP	35.0		7.0	[47]
THP-NCS		1 M ammonium acetate		[48]

4.2. Preparation of ^{68}Ga radiopharmaceuticals: automated synthesizers and cold kits

^{68}Ga radiopharmaceuticals can be obtained by using automated synthesis devices or cold kits.

Automated synthesizers represent a significant advancement over traditional manual synthesis methods. These instruments enable the radiolabeling of drugs with various isotopes and consist of modular units that accommodate vials containing the appropriate reagents. Through a network of tubes, three-way valves, and pumps, controlled by specialized software, these reagents are mixed in the reactor, allowing the synthesis to be conducted safely and efficiently. Additionally, purification can be performed using the device, if required. Most synthesizers also support the use of disposable cassettes for each reagent, which minimizes the risk of contamination [4].

Cold kits are freeze-dried formulations of buffers and ligands designed for reconstitution by adding a solution of the appropriate radioisotope, resulting in the generation of radiopharmaceuticals. This method has achieved considerable success in the synthesis of compounds labeled with ^{99m}Tc due to its simplicity and rapid application. However, the use of cold kits for labeling compounds with ^{68}Ga is more complex due to the variable properties of ^{68}Ga solutions eluted from generators, which exhibit differing concentrations and radioactivity levels, depending on the instrument model. Indeed, the quantity of ligand in the kit must be correlated with the activity of the eluate, and the type and volume of the buffer must be determined based on the HCl concentration of the radioisotope solution. Consequently, various cold

kits are marketed with different instructions for radiopharmaceutical reconstitution, tailored to the specific properties of the eluate [5,51].

5. ^{68}Ga radiopharmaceuticals for tumor diagnosis

Because of its decay and chemical and radiochemical properties, ^{68}Ga has already found a wide range of applications in PET investigations, and its use is still increasing ^{68}Ga derivatives became a gold standard for diagnosing neuroendocrine and prostate tumors, as reported. The use of ^{68}Ga for the detection of other neoplasias, such as gliomas and breast cancers (see paragraph **5.3**), is also under investigation.

Herein, we provide an overview of 68Ga radiopharmaceuticals, focusing on their applications in various cancers. We focus on already approved compounds and molecules in clinical trials, and describe the most promising compounds published in the last five years. Finally, we discuss the use of ^{68}Ga in theranostics.

5.1. ^{68}Ga labeled radiopharmaceuticals for NET diagnosis

Neuroendocrine tumors (NETs) are a heterogeneous class of tumors which can affect various organs. Lungs, gastrointestinal tract, and pancreas are the most commonly affected, while thymus, thyroid, and pituitary glands are less frequently involved [52,53]. Most NETs are characterized by an overexpression of somatostatin (SST) and its receptors (SSTRs) [54,55], with subtype 2 (SSTR2) being the most commonly detected [56–59].

Although treatment with SST has shown inhibition of tumor growth, the short half-life of the endogenous peptide has limited its clinical use. To overcome this limitation, a family of somatostatin analogs has been developed for the treatment of NETs [57]. Among them, octreotide, **1** (OC) (Fig. 4), a cyclic octapeptide that can be administered orally, was the first identified. Octreotide has a 20-fold greater activity profile and a longer half-life than SST, making it more suitable for clinical use [60].

Besides the application in therapy, the evidence that SST receptors are overexpressed in NET prompted the scientists to label SSTR ligands with a radionuclide for the diagnosis of these tumors [61]. In 1994, the FDA approved the ^{111}In-pentreotide (which structurally presents the octreotide conjugated to the ligand diethylenetriaminepentaacetic acid (DTPA)), namely Octreoscan®, for the scintigraphic investigation of NET [61]. For more than a decade, this radiotracer was the golden standard for NET diagnosis, but it was lately replaced by ^{68}Ga-derivatives whose PET imaging showed superior qualities and better predictive value [61].

To date, the ^{68}Ga-DOTA-conjugated peptides targeting SSTRs that have gained more attention are ^{68}Ga-DOTA-TOC, **2**, ^{68}Ga-DOTA-TATE, **3**, and ^{68}Ga-DOTA-NOC, **4** (Fig. 4). In particular, ^{68}Ga-DOTA-TOC received the orphan designation from the FDA in 2014 [62] and was successively approved in 2019 [63], ^{68}Ga-DOTA-TATE was approved in 2016, [64], while ^{68}Ga-DOTA-NOC is in different phases of clinical trials for PET imaging of NET and pulmonary diseases [65].

From a structural point of view, the peptide moiety of these compounds differs from the octreotide in the amino acid at 3 and/or eight position(s). In ^{68}Ga-DOTA-TOC (^{68}Ga-DOTA-[D-Phe1, Tyr3]octreotide), the phenylalanine (Phe^3) of octreotide is replaced by a tyrosine (Tyr^3), hence the acronym TOC (Tyr3-Octreotide). This peptide is also called edotreotide. ^{68}Ga-DOTA-TATE (^{68}Ga-DOTA-[D-Phe1, Tyr3]-octreotate) is the oxidized analog of ^{68}Ga-DOTA-TOC possessing a carboxylic acid function at threonine 8 (Thr8) instead of the primary alcohol present in the latter. This peptidic structure, also called octreate, gives rise to the name TATE (Tyr3-octreotate). Finally, ^{68}Ga-DOTA-NOC (^{68}Ga-DOTA-(1-Nal3)-octreotide) presents a 3-(2-naphthyl)-alanine (Nal) instead of Phe^3 of octreotide, hence the acronym NOC (Nal3 octreotide).

All these radiotracers present a good safety profile [66–68] and high affinity (IC_{50} in the nanomolar-low nanomolar range) for SSTR2. ^{68}Ga-DOTA-TOC and ^{68}Ga-DOTA-TATE are quite selective toward this receptor subtype, showing only a slight activity towards SSTR5, possessing IC_{50}s of 2.5 and 0.2 nM for SSTR2, respectively, and about 30- and 1900-fold higher values for SSTR5. In contrast, ^{68}Ga-DOTA-NOC also has a good binding affinity for SSTR5 and SSTR3, showing IC_{50} values of 1.9, 40, and 7.2 nM for the SSTR2, SSTR5, and SSTR3, respectively [69].

The potential of the approved radiopharmaceuticals ^{68}Ga-DOTA-TOC and ^{68}Ga-DOTA-TATE is supported by several clinical trials involving the two compounds for the diagnosis of different NET subtypes [70,71]. Overall, no significant differences have been detected in the application of these two octreotide derivative radiotracers [69], that have already been extensively reviewed elsewhere [72]. Interestingly, due to the overexpression of SSTRs in inflammatory cells [73], ^{68}Ga-DOTA-TOC and ^{68}Ga-DOTA-NOC have also been explored as imaging agents for myocardial disease diagnosis. However, no results have been reported yet [74].

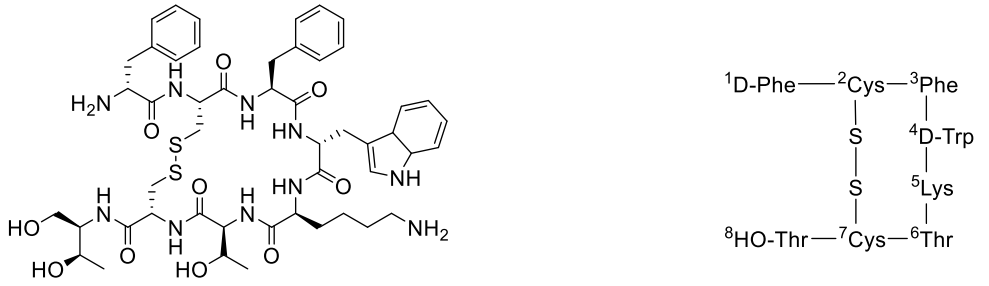
Among SSTR agonists currently in development, ^{68}Ga-DATA-TOC, **5** (Fig. 5) deserves a mention. In a paper published in 2019, the first human application for diagnosis in a patient affected by NET was reported. The authors reported that the radiopharmaceutical was efficiently prepared by using an instant kit and afforded results comparable to ^{68}Ga-DOTA-TOC, pointing out the potential of this compound [75]. These results were further supported by another comparative study on ^{68}Ga-DATA-TOC and ^{68}Ga-DOTA-NOC, which showed that the definition of images obtained with the two tracers is superimposable, with lower cost and easier procedure for the preparation for ^{68}Ga-DATA-TOC [39]. Besides these compounds, SSTR antagonists labeled with ^{68}Ga are currently in clinical trials for NET imaging. SSTR antagonists, despite a lower internalization rate, show better pharmacokinetic properties and improved image definition compared to the agonists [76,77].

From a structural point of view, these derivatives, analogously to SSTR agonists, generally present a peptide moiety responsible for the interaction with the target and a chelating agent to complex Ga^{3+}. For instance, ^{68}GaNODAGA-JR11 (also known as ^{68}Ga-OPS202, ^{68}Ga-satoreotide trizoxetan, and ^{68}GaIPN01070) **6** (Fig. 5) is an octapeptide derivative selective for SSTR2 possessing an IC_{50} of 1.2 nM [77] which has been submitted to different phase 1 and phase 2 clinical trials [78,79]. Some results already published from these studies showed that ^{68}GaNODAGA-JR11 has high sensitivity and reproducibility in the diagnosis of gastroenteropancreatic NETs (NCT02162446) [79] and identified the best dose for PET application at 100–200 MBq (NCT03220217) [80].

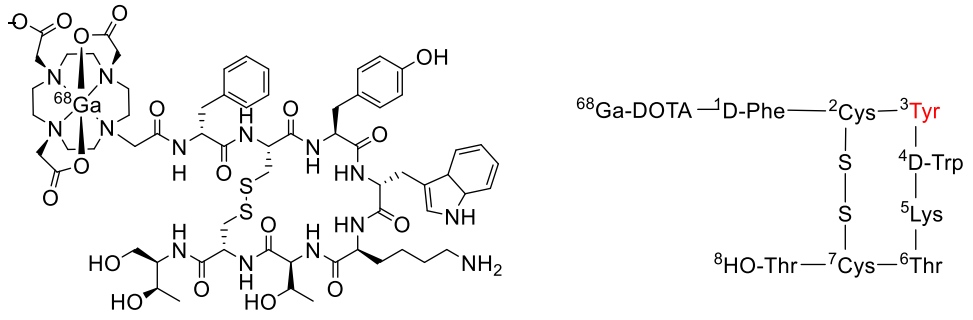
Although SSTR2 is the primary target for NET imaging, other proteins also serve as markers for detecting these tumors. Notable examples include integrin $\alpha_v\beta_3$, the urokinase-type plasminogen activator receptor (uPAR), and CXC chemokine receptor 4 (CXCR4). While these molecules were initially developed for the treatment and diagnosis of other tumors (see paragraph **5.3**), they have recently been applied to NETs and are now advancing to the clinical phase.

Integrins are a family of heterodimeric receptors that regulate the macromolecular network of the cell-extracellular matrix (ECM), mediating cell-cell adhesion, motility, and invasion. These receptors are composed of different combinations of α- and β-subunits and are overexpressed in various types of cancer [81]. Among integrin subtypes, the $\alpha_v\beta_3$ subtype has been first identified as a promising target for pathologies characterized by neovascularization [82]. $\alpha_v\beta_3$ integrin, like other members of the family, recognizes the sequence Arg-Gly-Asp (RGD) [81]. Consequently, RGD-based peptides have been leveraged to develop PET tracers.

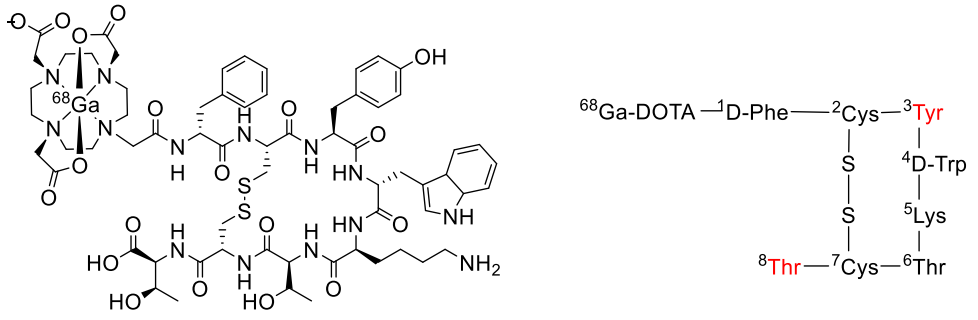
One such tracer, ^{68}Ga-NODAGA-E[c(RGDyK)], **7** (Fig. 6), has been identified as a valuable tool for NET diagnosis. This compound consists of two moieties of the cyclic peptide Arg-Gly-Asp-D-Tyr-Lys [c(RGDyK)], conjugated to a single equivalent of ^{68}Ga-NODA-GA. In a comparative study with its ^{64}Cu-labeled counterpart, compound **7** emerged as the optimal choice due to its slightly enhanced stability in tumor retention and the greater availability of ^{68}Ga [83]. Furthermore, a



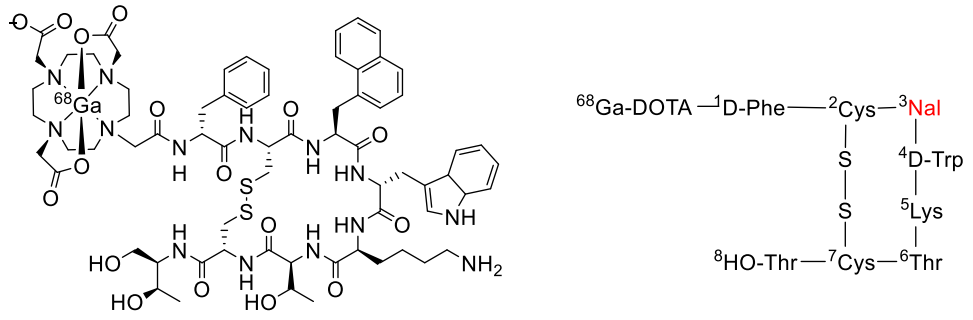
1 Octreotide (OC)



2 ^{68}Ga-DOTA-TOC



3 ^{68}Ga-DOTA-TATE



4 ^{68}Ga-DOTA-NOC

Fig. 4. Chemical structure of octreotide **1** and its representation using amino acid abbreviations. Chemical structures of ^{68}Ga-DOTA-TOC **2**, ^{68}Ga-DOTA-TATE **3**, and ^{68}Ga-DOTA-NOC **4**, along with their representations using amino acid abbreviations. Differences in the peptide moiety compared to octreotide are highlighted in red.

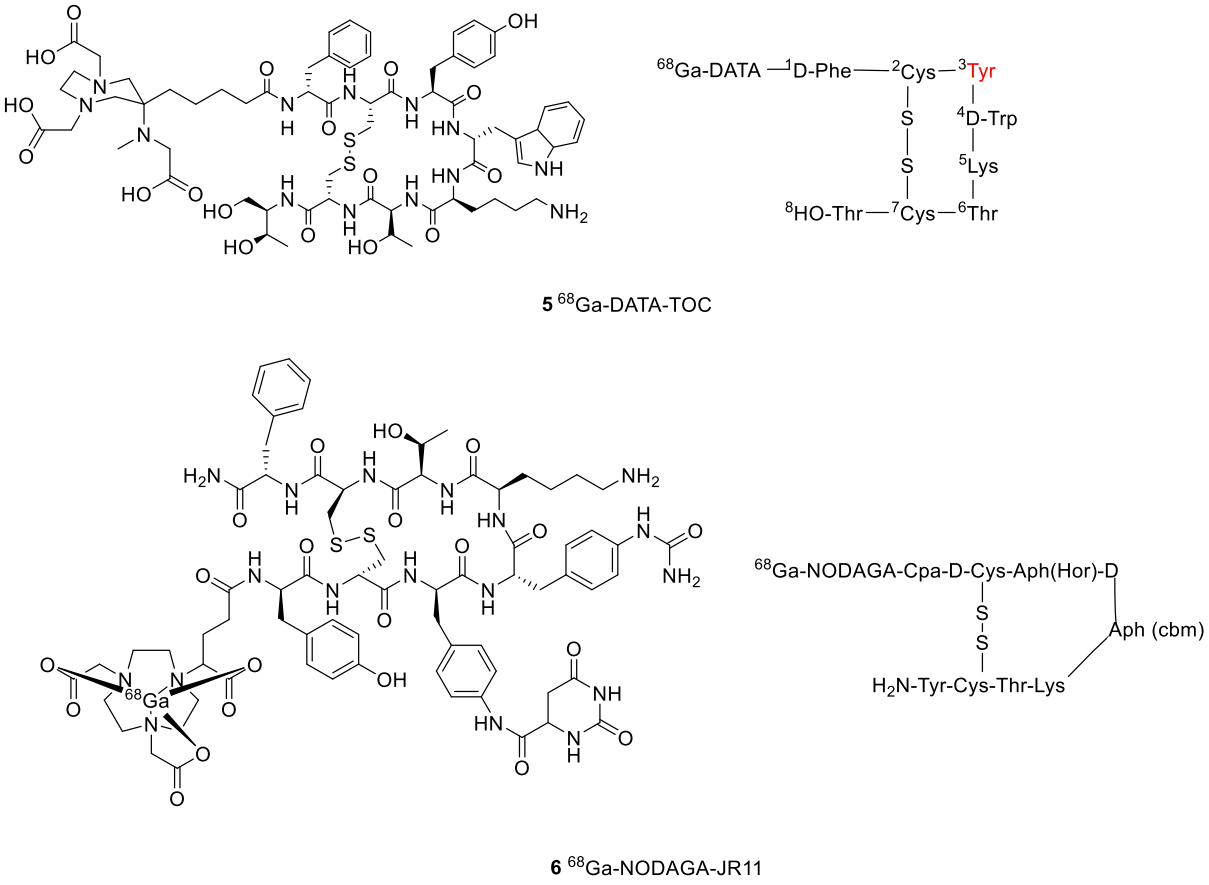


Fig. 5. Chemical structures of the SSTR ligands ^{68}Ga-DATA-TOC **5**, and ^{68}GaNODAGA-JR11 **6**, along with their representations using amino acid abbreviations. Differences in the peptide moiety compared to octreotide are highlighted in red. Cpa = 4-Chloro-phenylalanine; Aph(Hor) = 4-Amino-L-hydro-ortho-phenylalanine; D-Aph (Cbm) = D-4-Amino-carbamoyl-phenylalanine.

recent phase II clinical trial demonstrated that ^{68}Ga-NODAGA-E[c(RGDyK)] **7** is effective in detecting all grades of neuroendocrine neoplasms. This compound warrants further investigation to determine its potential as a predictive tool for integrin $\alpha_v\beta_3$ inhibition-based therapy [84].

The uPAR plays a crucial role in the proteolytic cascade that converts inactive plasminogen into plasmin. This pathway, closely interconnected with the integrin signaling pathway, contributes significantly to ECM regulation. uPAR overexpression has been detected in different cancers, where it drives cell proliferation, migration, and tumor angiogenesis, often correlating with poor prognosis [85,86].

^{68}Ga-labeled radiopharmaceuticals targeting uPAR have recently been explored as tracers for NET diagnosis. As already seen for other ^{68}Ga labeled compounds, tracers consist of a peptidic moiety for target binding and a chelating agent for gallium complexation. For instance, ^{68}Ga-NOTA-AE105, **8** (Fig. 6) was recently evaluated in a phase II clinical trial in patients affected by NET, emerging as a suitable tracer for the detection of these types of neoplasia [87]. ^{68}Ga-NOTA-AE105 is composed of a linear decapeptide (AE105) conjugated to NOTA. AE105 is a uPAR antagonist (IC_{50} of 11 nM) and has been identified by Ploug and colleagues from a library of peptide derivatives [88]. Both ^{68}Ga-NOTA-AE105 and ^{68}Ga-NODAGA-AE105 (structure not reported) emerged as promising alternatives to ^{64}Cu labeled analogs [89].

CXC chemokine receptor 4 (CXCR4) is a G protein-coupled receptor (GPCR) implicated in several cancers [90], including gastro-entero-pancreatic neuroendocrine tumors [91]. Notably, the CXCR4-targeting probe ^{68}Ga-pentixafor, **9** (also known as CPCR4-2, Fig. 6) has been successfully tested for NET diagnosis. ^{68}Ga-pentixafor, developed by Gourni et al., is a ^{68}Ga-labeled cyclic CXCR4-binding pentapeptide conjugated to DOTA by a 4-(aminomethyl) benzoic acid linker [92]. This tracer possesses an IC_{50} of 4.99 nM, high *in vivo* stability, and elevated and specific tumor accumulation [92,93]. Furthermore, ^{68}Ga-pentixafor showed favorable dosimetry and a lower absorbed dose compared to ^{18}F-FDG or ^{68}Ga-labeled somatostatin receptor ligands, supporting its potential as a superior imaging agent for NET detection [94].

Interestingly, a comparative study between ^{68}Ga-DOTA-TOC and ^{68}Ga-pentixafor showed that the latter, despite a lower sensitivity in well-differentiated NETs, led to the identification of 80 % of patients affected by grade 3 NETs, emerging as a promising tool for theranostic approach targeting CXXR4 in undifferentiated SSTR-negative tumor patients [95]. An early phase 1 clinical trial (NCT03335670) is currently ongoing to evaluate ^{68}Ga-pentixafor in patients with NETs [96]. Among tracers applied for the detection of NET and not characterized by a peptide moiety, we can enumerate compounds targeting fibroblast activation protein (FAP). FAP is a transmembrane serine protease and a member of the prolyl peptidase family. It is overexpressed in several diseases, including cancer. In particular, high levels are detected in more than 90 % of carcinomas, leading to the development of various fibroblast activation protein inhibitors (FAPI). Although FAP overexpression is well established, its precise role in cancer progression remains incompletely understood [97,98].

The most active FAPIs reported in the literature feature a quinolinoyl scaffold linked to a 2-cyanopyrrolidine moiety via a glycyl chain and exhibit IC_{50} values for FAP in the nanomolar range [99]. These compounds have been conjugated with DOTA through an *O*-alkyl or *N*-alkyl piperazine linker, affording a series of FAPI suitable for diagnostic or therapeutic applications. FAPIs that gained more success and reached

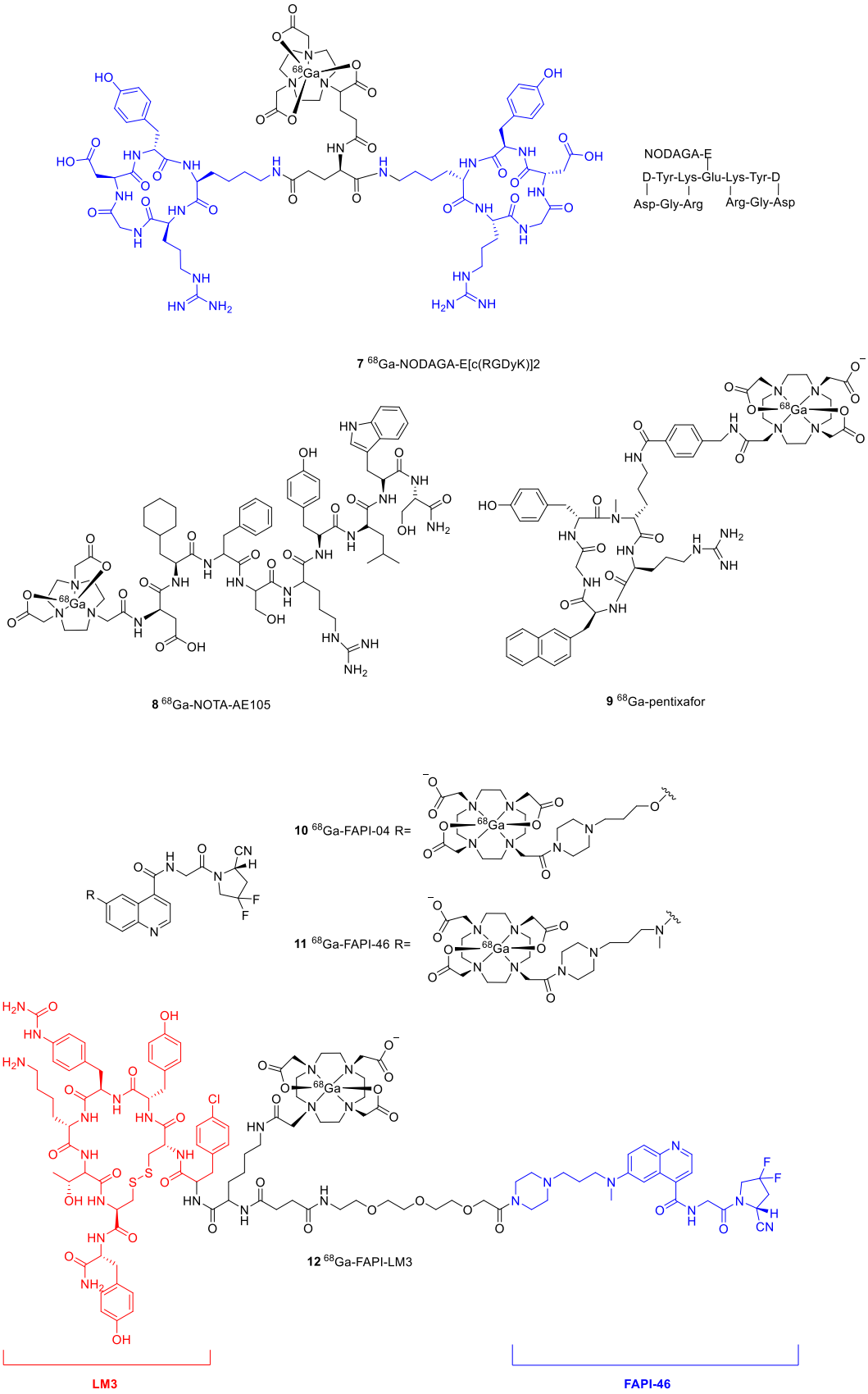


Fig. 6. Chemical structures of ^{68}Ga-labeled compounds binding targets different from SSTR2. For compound ^{68}GaNODAGA-JR11 **7**, the representation using amino acid abbreviations is reported.

the clinical phase are FAPI-04 [100] and FAPI-46 [101]. In particular, the corresponding labeled derivatives ^{68}Ga-FAPI-04, **10** and ^{68}Ga-FAPI-46, **11** (Fig. 6) are in phases 1 and 2 clinical trials for the diagnosis of several solid tumors and other diseases [102,103]. Furthermore, ^{68}Ga-FAPI-04 has been recently compared with ^{18}FDG in a case of a patient affected by a neuroendocrine tumor with hepatic metastasis with promising results [104].

Interestingly, in 2023, started a clinical trial (NCT05873777) aimed at evaluating the dual SSTR2 and FAP inhibitor ^{68}Ga-FAPI-LM3, **12** (Fig. 6) (LM3 is another peptide derivative endowed with activity towards SSTR2) in SSTR2 positive diseases in terms of safety, biodistribution and radiation dosimetry of in healthy volunteers and the potential usefulness in PET [105,106].

5.2. ^{68}Ga-labeled radiopharmaceuticals for the diagnosis of prostate cancer

Prostate cancer is a heterogeneous illness that affects millions of men worldwide. This neoplasia, which usually has a favorable prognosis when detected in the early stage, is commonly characterized by elevated levels of the biomarker prostate-specific membrane antigen (PSMA) [107].

Various PSMA-specific tracers have been developed to facilitate diagnosis and management. Among these, the monoclonal antibody ^{111}In-capromab pendetide (ProstaScint®) was the first to receive FDA approval in 1996. However, ^{111}In-capromab pendetide was associated with poor image quality due to the limitations of the ^{111}Indium, such as its long half-life and suboptimal dosimetry profile. These issues prompted the development of radiotracers labeled with different isotopes, including ^{68}Ga-PSMA-11, **13** (also known as ^{68}Ga-HBED–CC–PSMA or ^{68}Ga-gozetotide) (Fig. 7) [108].

^{68}Ga-HBED–CC–PSMA consists of three portions: i) HBED-CC as a gallium chelator, ii) 6-aminohexanoic acid (Ahx) as a linker, and iii) a peptide derivative as a PSMA-specific ligand. The latter is characterized by the sequence Glu–NH–CO–NH–Lys and thus falls among the inhibitors with a urea structure. HBED-CC was chosen for its lipophilic characteristics, while the pharmacophore group, which possesses a hydrophilic nature, allows a good balance of the compound's pharmacokinetic properties. This compound was published in 2012 and has an IC_{50} of 7.5 nM (calculated based on affinity in an enzyme assay) and a K_i of 12.0 nM (calculated based on affinity in a cell assay). In addition, it showed good pharmacokinetic properties, such as rapid clearance in blood and organs, low hepatic accumulation, and enhanced specific absorption in tissues that overexpress PSMA [109]. It is worth noting that ^{68}Ga-PSMA-11 is currently the only ^{68}Ga-labeled drug approved by the FDA for the diagnosis of prostate cancer. Specifically, the FDA has approved the use of three kits based on gozetotide, Illuccix® (Telix), approved in 2021 [110] Locametz® (Novartis), approved in 2022 [111], and Gozellix® (Telix), approved on March 20, 2025 [112].

Locametz® consists of a vial of white lyophilized powder for an injectable solution containing 25 μg of gozetotide and 28.97 mg of sodium. By adding a radionuclide solution, reconstitution yields the radiopharmaceutical, which can exhibit radioactivity up to 37 mCi. This kit is compatible with ^{68}Ga solutions produced by various generators, including Eckert & Ziegler GalliaPharm®. Depending on the type of generator used, the conditions for reconstitution change [113].

Interestingly, a comparative study on the synthesis of ^{68}Ga-PSMA-11 using both a generator and a cyclotron as sources for the radionuclide was conducted. The results demonstrated no significant differences in clinical imaging between the compounds produced by the two methods. However, the cyclotron-based approach appears the most promising strategy to meet the growing demand for this radiopharmaceutical, ensuring a more scalable and reliable production [114].

Several clinical trials involving ^{68}Ga-HBED–CC–PSMA for the diagnosis of other malignancies, such as liver, ovarian, breast, thyroid, and brain cancers [115], are currently underway since PSMA is also expressed in different tumors.

For instance, the Mayo Clinic in Rochester, United States, initiated a phase II clinical trial in 2022 to evaluate ^{68}Ga-PSMA-11 for liver cancer (NCT05176223). A phase II clinical trial to assess 68Ga-PSMA-11 in glioma (NCT06444412) was also started in 2024. Both the studies are currently in the recruitment phase.

Alongside ^{68}Ga-PSMA-11, a series of analogs have been developed. All feature the Glu–NH–CO–NH–Lys sequence as the pharmacophore but vary in their chelators and linkers. These analogs include ^{68}Ga-PSMA-617, **14**, ^{68}Ga-P16-093, **15**, and ^{68}Ga-THP-PSMA, **16** (Fig. 7).

^{68}Ga-PSMA-617, **14** (also reported as DKFZ-PSMA-617) has the peptidemimetic moiety bioconjugated with the DOTA by a linker bearing a naphthyl substituent. The compound has K_i values of 0.37 ± 0.21 and 52.34 ± 2.94 nM, determined in enzymatic and LNCaP cell assays, respectively. Furthermore, it has a favorable pharmacokinetic profile, showing specific uptake in prostate cancer cells and kidneys [116]. This compound is currently evaluated in several clinical trials, basically for the diagnosis of prostate cancer [117].

^{68}Ga-P16-093, **15** is a new radiotracer for PSMA-PET, an analog of ^{68}Ga-PSMA-11 developed in 2018 by Five Eleven Pharma Inc. ^{68}Ga-P16-093 has an *O*-(carboxymethyl)-L-tyrosine linker and showed an optimal affinity for PSMA (IC_{50} = 16.5 nM), specific uptake by PSMA-expressing tumors, and rapid clearance [118]. Recently, a comparison study between ^{68}Ga-P16-093 and ^{68}Ga-PSMA-11 revealed that the former shows better diagnostic properties, allowing complete visualization of lesions in 71 % of patients and determining a revision of the treatment protocol in 42 % of patients [119]. Currently, ^{68}Ga-P16-093 is in clinical trials for the diagnosis of prostate cancer, carcinoma renal, glioma, and breast cancer [120].

^{68}Ga-THP-PSMA, **16** is a selective tracer for PSMA that utilizes tris (hydroxypyridinone) (THP) as chelator moiety. THP is a novel chelating agent that enables rapid, quantitative, and efficient ^{68}Ga complexation at room temperature, across a wide pH range, and at low concentrations [121]. As described in Fig. 7, three hydroxypyridinone rings coordinate the Ga^{3+} ion, ensuring high stability. ^{68}Ga-THP-PSMA demonstrated >6 h of stability in human serum and specific binding to PSMA-expressing cells.

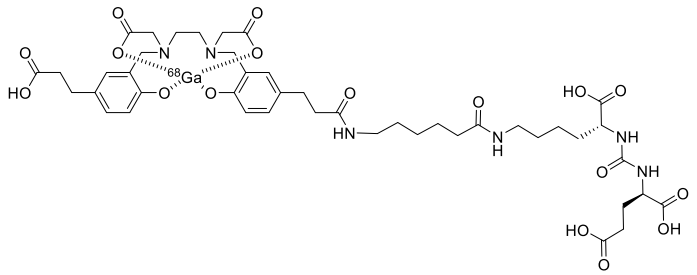
In preclinical studies with PSMA-positive mice, the tracer selectively accumulated in neoplastic tissues, providing image resolution comparable to that of ^{68}Ga-PSMA-11 [122]. However, a comparative analysis with ^{68}Ga-PSMA-11 revealed that ^{68}Ga-THP-PSMA exhibits approximately 10 times lower activity than the approved compound (IC_{50} = 361 ± 60 nM vs. IC_{50} = 34.3 ± 4.1 nM), which may impact its clinical utility [121].

A phase I clinical study (NCT04158817) and a phase II clinical study (NCT03617588) on ^{68}Ga-THP-PSMA have been completed to assess this tracer for prostate cancer detection. In approximately 50 % of patients, diagnosis with ^{68}Ga-THP-PSMA PET/CT resulted in a change in treatment protocol, underscoring the value of this radiopharmaceutical in optimizing therapy [123].

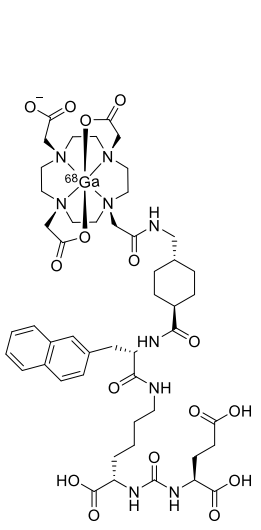
Several radiopharmaceuticals targeting PSMA have been developed, including derivatives of the "HTK" series by Dr. Bernard et al. at the University of British Columbia, Vancouver. The researchers initially modified PSMA-617, adjusting the linker to optimize lipophilicity. Specifically, they varied the naphthyl moiety by incorporating additional fused aromatic rings or an alkyl chain.

This study led to the identification of ^{68}Ga-HTK03141, **17** (Fig. 7), which exhibited a K_i of 0.63 ± 0.06 nM in LNCaP cells and achieved the highest uptake (23 % of the injected dose) among the synthesized analogs [124].

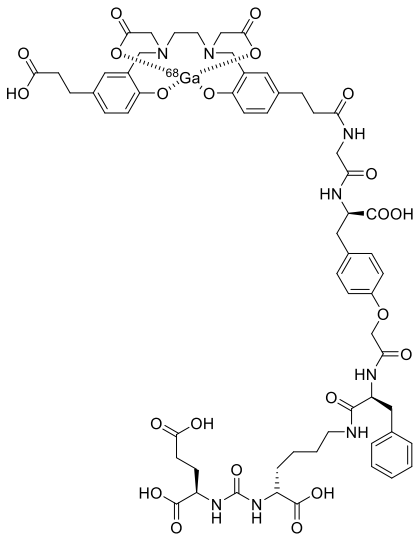
However, HTK03141 also demonstrated uptake in the kidneys and salivary glands. To address this issue, the researchers investigated the effect of replacing glutamate in the pharmacophoric portion with an alternative amino acid. Specifically, substituting Glu with Aad (L-2-aminoadipic acid) led to the identification of ^{68}Ga-HTK03149, **18** (Fig. 7) [125].



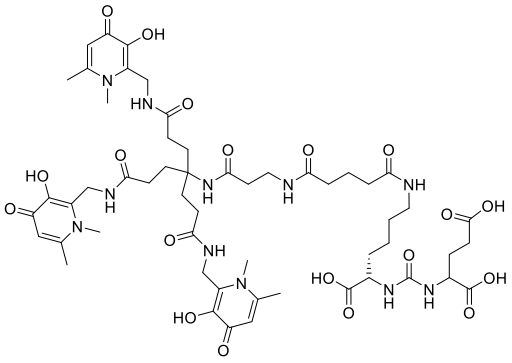
13 ^{68}Ga-PSMA-11 (^{68}Ga-HBED-CC-PSMA, ^{68}Ga-GOZETOTIDE)



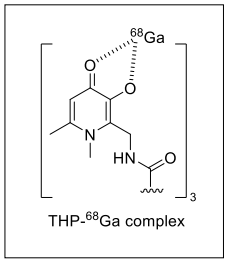
14 ^{68}Ga-PSMA-617

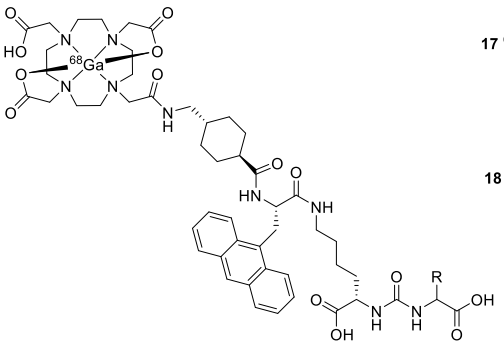


15 ^{68}Ga-P16-093

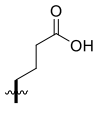


16 ^{68}Ga-THP-PSMA





17 ^{68}Ga-HTK03141 R =



18 ^{68}Ga-HTK03149 R =

Fig. 7. Chemical structures of ^{68}Ga-labeled compounds **13**–**18** targeting PSMA.

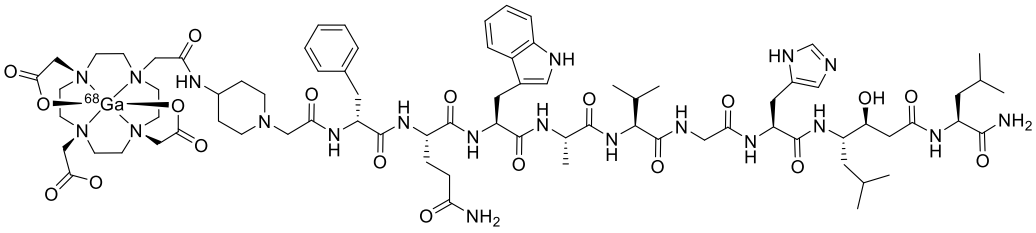
PET imaging demonstrated that ^{68}Ga-HTK03149 exhibits high uptake in LNCaP tumor cells, with primary renal excretion and minimal off-target accumulation, including in the kidneys and salivary glands. In the context of theranostic applications, the compound was labeled with both ^{68}Ga and ^{177}Lu, yielding PSMA binding affinities of 6.99 ± 0.80 nM and 1.57 ± 0.42 nM, respectively [125].

Selective gastrin-releasing peptide receptor (GRPR) antagonists have been developed for prostate cancer imaging. GRPR, a G protein-coupled receptor (GPCR), is overexpressed in various malignancies, including prostate cancer, and belongs to the bombesin receptor family. Bombesin is a 14-amino acid peptide (Pyr-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2) that binds to GRPR with high affinity [126]. The unusual name of this peptide comes from the original terminology used by V. Erspamer et al. to name a tetradecapeptide isolated from the skin of the European frog *Bombina bombina*.

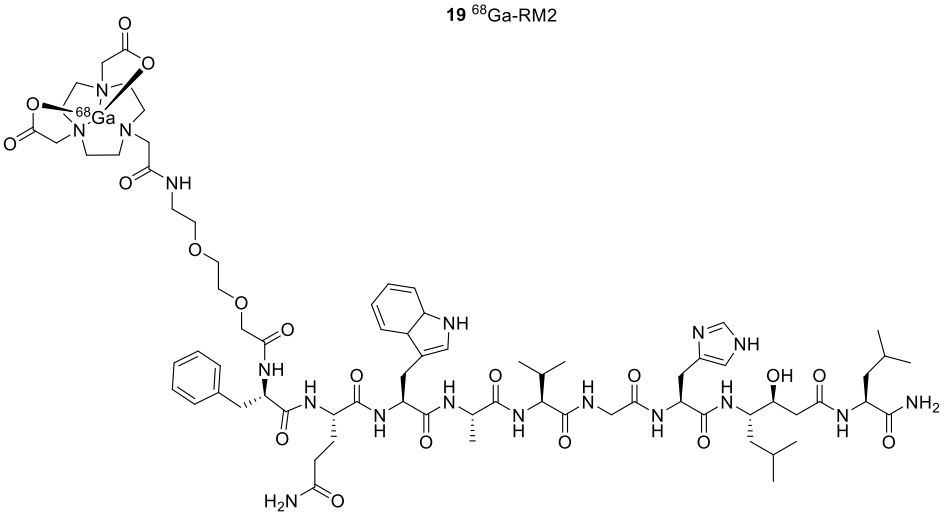
Later, two bombesin-like peptides were identified in mammals: gastrin-releasing peptide (GRP) and neuromedin B (NMB). GRP, a 27-amino acid peptide, was initially isolated from pig stomach and shares the same seven C-terminal amino acids with bombesin, explaining their similar biological activity [127].

Several GRPR-targeting PET radiopharmaceuticals have been developed, including ^{68}Ga-RM2, **19**, ^{68}Ga-RM26, **20**, and ^{68}Ga-DOTA-NeoBOMB1, **21** (Fig. 8). Studies in healthy volunteers have shown that these tracers exhibit stable biodistribution and effective dose levels comparable to other PET radiopharmaceuticals. The available data are promising, both for initial prostate cancer diagnosis and for detecting disease recurrence [126].

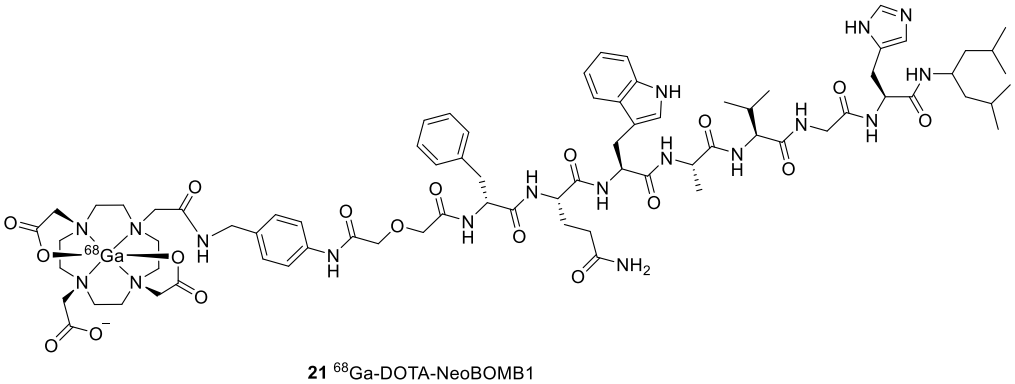
^{68}Ga-RM2, **19** (also reported as BAY86-7548) is a GRPR antagonist developed by Bayer, featuring the structure ^{68}Ga-DOTA-4-amino-1-carboxymethylpiperidin-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2. It exhibits a high affinity for GRPR (IC_{50} = 7.7 ± 3.3 nM) [128]. A recent study has identified ^{68}Ga-RM2 as a promising PET tracer for prostate cancer diagnosis [129]. Several clinical trials are ongoing or have been completed to evaluate its performance, including comparative studies



19 ^{68}Ga-RM2



20 ^{68}Ga-RM26



21 ^{68}Ga-DOTA-NeoBOMB1

Fig. 8. Chemical structures of ^{68}Ga-GRPR antagonists **19**–**21** developed for prostate cancer imaging.

with ^{68}Ga-PSMA-11 for prostate cancer imaging [130].

^{68}Ga-RM26, **20**, another GRPR-targeting tracer, shares the same pharmacophoric portion as RM2 (D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH_2) but presents a PEGylated linker and NOTA as the chelator instead of DOTA. ^{68}Ga-RM26 is an antagonist of GRPR with a high affinity for this receptor ($IC_{50} = 0.9 \pm 0.2$ nM) [131,132].

Early clinical studies have confirmed its potential for detecting both primary and metastatic prostate cancer [133], and further research is underway to evaluate its use in glioma, gastrointestinal, and breast cancer imaging [134]. A pilot study involving 22 glioma patients (NCT06412952) demonstrated the safety and efficacy of ^{68}Ga-RM26 in detecting and staging this tumor [135], while a comparison with ^{18}F-FDG highlighted ^{68}Ga-RM26 as a promising tracer for gastrointestinal stromal tumors (GISTs). Notably, no radiopharmaceutical-related adverse events were observed, and ^{68}Ga-RM26 showed higher uptake and detection rates for GISTs than the traditional PET tracer [136].

^{68}Ga-DOTA-NeoBOMB1 **21** is another GRPR antagonist, bioconjugated with DOTA for gallium labeling. It demonstrates a high affinity for GRPR ($IC_{50} \sim 1$ nM), strong metabolic stability, and high tumor-specific uptake in PC-3 xenograft mouse models (33 % of the injected dose) [137].

NeoBOMB1 has been labeled with multiple radionuclides, including ^{68}Ga (for PET), ^{111}In (for SPECT), and ^{177}Lu (for theranostics), expanding its potential for diagnostic and therapeutic applications [138]. A few clinical trials have been conducted to evaluate ^{68}Ga-DOTA-NeoBOMB1 for diagnosing GRPR-overexpressing cancers, including prostate, breast, and gastrointestinal cancers [139].

5.3. ^{68}Ga-labeled radiopharmaceuticals for the diagnosis of other tumors

^{68}Ga is being evaluated for the diagnosis of various solid and hematological tumors, as well as for different pathological conditions, including fibrosis and inflammation [140]. For these applications, the same radiotracers described so far are often used based on the evidence that certain markers are present in several pathologies. Below are key examples of ^{68}Ga-based radiotracers that have been investigated in clinical trials, mainly focusing on brain and breast tumors, the malignancies for which ^{68}Ga has been most widely studied.

Primary brain tumors are a heterogeneous group of neoplasms. While diagnosis can often be anticipated based on medical history, confirmation via neuroimaging is essential. Carefully interpreted nuclear medicine imaging aids in predicting and monitoring tumor response while enabling personalized dosimetry [141].

Notably, somatostatin receptor expression has been identified in several pediatric brain tumors, including medulloblastoma and meningioma, which affect the central nervous system, and neuroblastoma, which affects the peripheral nervous system [142,143]. Over 90 % of these rare pediatric tumors can be visualized with targeted imaging techniques [143]. Early pediatric imaging studies utilized SPECT with ^{111}In-DTPA-octreotide, but PET with ^{68}Ga-labeled tracers has largely replaced it. The most commonly used radiopharmaceuticals in this field are ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTA-NOC [144]. For instance, 68Ga-DOTA-TOC is currently in the clinical phase for the diagnosis of several brain tumors in both adults and children [145].

Additionally, new compounds such as ^{68}Ga-FF58 (structure not disclosed), developed by Novartis, are in clinical evaluation. This tracer targets αvβ3 and αvβ5 integrins and is being investigated for glioblastoma, as well as breast, gastroesophageal, and pancreatic cancers. A phase I trial (NCT04712721) concluded at the end of 2024, but results have not yet been published [146].

Breast cancer (BC) is the most common cancer among women worldwide, with approximately 270,000 new cases reported in the United States in 2018 [147]. Diagnostic imaging plays a crucial role in BC management, and over the past decade, immunological PET (immuno-PET), combining PET's high resolution with the specificity and selectivity of monoclonal antibodies (mAbs), has emerged as a powerful tool for improving detection. Among targets not yet mentioned, carcinoembryonic antigen (CEA), particularly the cell adhesion molecule CEA-5, represents an interesting target in BC, being expressed in 50 %–60 % of patients with metastatic disease [148]. Notably, the bifunctional peptide ^{68}Ga-IMP288 **22** (Fig. 9A) has demonstrated promising immuno-PET performance in this context [148,149]. This molecule is utilized in an immuno-PET approach based on pre-targeting, which involves a two-step process. First, a monoclonal antibody is administered and allowed to bind to its target. Once binding is complete, a radiolabeled peptide containing a hapten is introduced. A hapten is a small molecule that triggers an antibody response only when attached to an appropriate carrier.

In the case of ^{68}Ga-IMP288, pre-targeting begins with TF2, a specific antibody that binds divalently to CEA-5. Once TF2 is attached to the tumor, ^{68}Ga-IMP288 is administered. This molecule comprises DOTA as a chelating agent for ^{68}Ga and a tetrapeptide core, which carries two histamine-succinylglycine (HSG) sequences acting as haptens. Each HSG sequence binds with high affinity to specific anti-HSG Fab fragments on TF2, stabilizing the structure (Fig. 9B). The pretargeting approach shortens the waiting time before analysis can be performed and leads to a stable complex with good uptake at the tumor site [149–151]. ^{68}Ga-IMP288 has been tested in the clinical phase for the diagnosis of breast, colorectal, lung, and thyroid cancers [152].

In the context of breast cancer diagnosis, an additional class of compounds known as affibodies has emerged. Affibodies are a class of antibody-mimetics. In particular, they are medium-sized (6.5 kDa) engineered proteins that exhibit high-affinity binding to their targets, often comparable to or even exceeding that of traditional antibodies [153]. One notable example is ABY002, **23** (Fig. 10), an affibody specific for HER2, a protein overexpressed in breast cancer. ABY002 consists of a 58-amino acid chain and incorporates DOTA as a chelating agent for ^{68}Ga labeling.

The first human use of ^{111}In- and ^{68}Ga-labeled ABY002 in patients with recurrent breast cancer was reported Baum et al. in 2010 [154]. Labeled ABY002 showed rapid blood clearance, allowing imaging 2–3 h after application, and high uptake, being internalised only in metastatic lesions, liver and kidney. In addition, the tracer allowed the detection of nine of the eleven metastases observed on ^{18}FDG-PET scanning [153]. ABY025, **24** (Fig. 10) is a second-generation affibody with a structure comprising a maleimide-DOTA chelator linked via a cysteine residue to a 61-amino acid peptide chain [35,155]. ABY025 binds specifically to domain III of the HER2 receptor, allowing a non-competitive interaction with trastuzumab and pertuzumab and enabling rapid treatment monitoring. In addition, it exhibits reduced non-specific hepatic uptake. ABY025 has been successfully labeled with ^{68}Ga and ^{111}In, making it suitable for use in both PET and SPECT imaging [154].

Finally, it is worth mentioning that ^{68}Ga-labeled nanobodies emerged as effective probes for detecting neoplasia. Nanobodies, or single-domain antibodies, are constituted by a single monomeric variable antibody domain and offer distinct advantages such as small size, high stability, and strong target specificity. Recently, ^{68}Ga-NODAGA-SNA006, **25** (Fig. 10) has been evaluated as a PET tracer in solid malignancies overexpressing $CD8^+$ T cells [156]. In this compound, the nanobody SNA006 was conjugated to NODAGA-maleimide and radiolabelled with ^{68}Ga [157] In an early phase 1 clinical trial [158], ^{68}Ga-NODAGA-SNA006 proved to be safe, feasible, and well tolerated, exhibiting favorable pharmacokinetics. This approach provides a reliable method for non-invasive, quantitative assessment of $CD8^+$ T-cell tumor infiltration and enables monitoring of the immunotherapy response [156]. Chen et al. reported the nanobody-based radiopharmaceutical ^{68}Ga-MY6349, **26** (Fig. 10) as a promising agent for the detection of epithelial tumors [159]. MY6349 consists of the nanobody Nb4, previously described by Xu et al. [160], conjugated via an amino acid linker to the THP chelator, enabling efficient complexation with Ga^{3+}. This nanobody selectively targets trophoblast cell-surface antigen 2 (Trop2), a protein overexpressed in various human epithelial cancers.

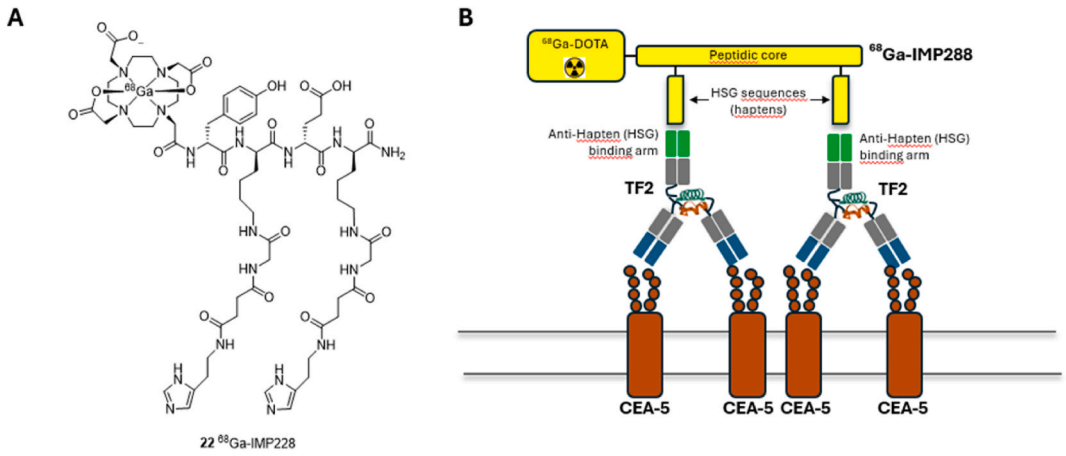


Fig. 9. A. Structure of ^{68}Ga-IMP288 **22**. **B.** Schematic representation of the interaction of ^{68}Ga-IMP288 with the target. The image serves solely to illustrate the mechanism of action; the scale of the compounds is not maintained.

A clinical trial completed in August 2024 (NCT06188468) [161] demonstrated that ^{68}Ga-MY6349 PET/CT provides a non-invasive method for assessing Trop2 expression in tumors, thereby enhancing diagnostic accuracy, staging, and potentially supporting personalized treatment strategies for cancer patients [159].

6. Radiopharmaceuticals labeled with ^{68}Ga as theranostic agents

The term "theranostic" refers to integrating therapy and diagnostics. Theranostic action is often achieved by labeling the same or very similar molecules with radioisotopes with different emission characteristics. This approach is referred to as a theranostic pair and allows for predicting treatment response and tissue toxicity, enabling the optimization of the therapeutic protocol [162]. For example, ^{68}Ga and ^{177}Lu are often combined for this aim [8,12,163]. In this pairing, ^{177}Lu provides the therapeutic effect as it undergoes β^- decay, while ^{68}Ga, which undergoes β^+ decay, enables monitoring of ^{177}Lu therapy progression via PET imaging [8,162]. Other radionuclides often used for their therapeutic counterparts are Yttrium-90 (^{90}Y), which, like ^{177}Lu, undergoes β^- decay, and Bismuth-213 (^{213}Bi), which is an α-emitting radionuclide [162] Since the previous section thoroughly described the ^{68}Ga labeling for diagnosis, we will now focus on the corresponding therapeutic counterpart.

6.1. Theranostic pairs for the treatment of NETs

Several radiopharmaceuticals are available for the theranostic treatment of NETs. Some of these agents have received regulatory approval, while others are still undergoing clinical trials. Among the radiopharmaceuticals selectively targeting the SSTR2 receptor, the most notable are DOTA-TATE and DOTA-TOC, which have been appropriately labeled for theranostic applications.

DOTA-TATE has been labeled with ^{177}Lu, resulting in the radiopharmaceutical ^{177}Lu-DOTA-TATE, which Novartis markets under the brand name Lutathera®. ^{177}Lu-DOTA-TATE was approved by the EMA in 2017 [164]and by FDA in 2018 [165]. It is indicated for the treatment of inoperable, well-differentiated, SSTR receptor-positive metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults [166]. DOTA-TOC has been labeled with ^{123}Bi, ^{177}Lu, or ^{90}Y for therapeutic purposes, and with ^{68}Ga for diagnostic imaging. ^{123}Bi-DOTA-TOC has been evaluated in phase 1 clinical trials for the treatment of refractory liver metastases [166].

Among the molecules active on the CXCR4 receptor, the compound which gained the most success as a theranostic agent is pentixather, **27** (Fig. 10). Pentixather is an iodinated analogue of pentixafor, **9**. It is a radiopharmaceutical approved for compassionate use in Germany for the treatment of lymphoma and multiple myeloma. It employs ^{177}Lu as a therapeutic isotope and ^{68}Ga as a diagnostic counterpart [166].

6.2. Theranostic pairs for the treatment of prostate cancer

The theranostic approach to prostate cancer involves several radiopharmaceuticals targeting PSMA or GRPR. One such example is the theranostic pair ^{68}Ga/^{177}Lu-PSMA-617 [166]. ^{177}Lu-PSMA-617, also known as ^{177}Lu vipivotide tetraxetane, is a radiopharmaceutical recently approved by the FDA (March 23, 2022) and the EMA (December 9, 2022) [167,168]. Marketed by Novartis under the brand name Pluvicto®, it is indicated for the treatment of PSMA-positive, metastatic, castration-resistant prostate cancer [167]. The corresponding diagnostic radionuclide is ^{68}Ga-PSMA-617.

Theranostic approach targeting GRPR include ^{68}Ga/^{177}Lu-NeoBOMB1. This couple has been preclinically evaluated by Dalm et al., showing excellent tumor uptake, good pharmacokinetic properties in a PC-3 xenografted mouse model of prostate cancer [138].

In addition to conventional radiopharmaceuticals, nanoparticles have emerged as a promising strategy for PSMA-targeted imaging and therapy. While low molecular weight radiopharmaceuticals offer high tumour affinity and penetration, their rapid clearance can necessitate high or repeated dosing, increasing the risk of off-target toxicity. Nanoparticles, including inorganic particles, liposomes, and macromolecules, enhance drug solubility, stability, and pharmacokinetics. For instance, iron oxide nanoparticles have been explored for ^{68}Ga-PSMA-targeted PET/MR imaging in prostate cancer [169].

6.3. Theranostic pairs for the treatment of other tumors

Regarding the use of theranostic pairs in diagnosing and treating gliomas, many studies are underway involving specific molecules on different targets. For instance, pilot studies on ^{68}Ga- and ^{90}Y-labeled molecules specific for SSTR2, including DOTA-TOC, are ongoing.

Interestingly, PSMA antigen overexpression was also detected in gliomas, leading to different studies evaluating the use of prostate cancer-specific molecules in brain tumors [170]. Particularly, recent studies have highlighted promising findings for the ^{68}Ga/^{177}Lu-PSMA theranostic pair [171]. Nevertheless, additional prospective analyses are necessary to thoroughly assess the diagnostic value of PSMA-targeted radiotracers in glioblastoma imaging.

In addition, molecules targeting FAP and labeled with ^{68}Ga and ^{90}Y or ^{177}Lu are also being investigated as theranostic agents for various tumour types, including gliomas, breast cancer, pancreatic adenocarcinoma, and lung cancer [166].

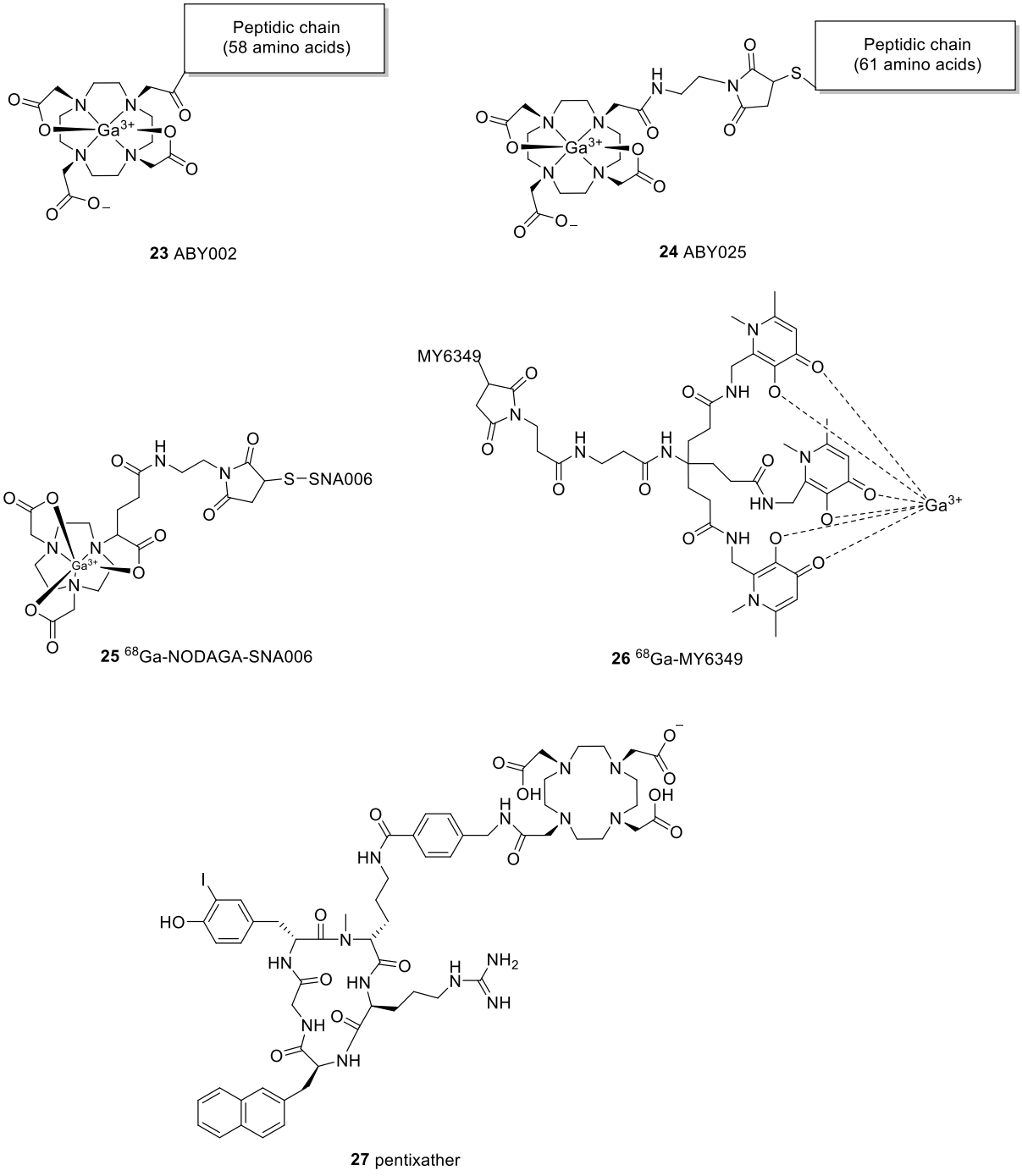


Fig. 10. Schematic representation of the ABY002 **23** and ABY025 **24** affibodies, nanobodies ^{68}Ga-NODAGA-SNA006 **25** and ^{68}Ga-MY6349 **26**, and pentixather **27**.

7. Conclusions

Gallium-68 (^{68}Ga) is rapidly emerging as a cornerstone in clinical nuclear medicine, demonstrating exceptional promise in both diagnostic imaging and theranostics. Since 2016, the FDA has approved three ^{68}Ga-labeled PET tracers - ^{68}Ga-DOTA-TOC and ^{68}Ga-DOTA-TATE for neuroendocrine tumor diagnosis, and ^{68}Ga-PSMA-11 for prostate cancer imaging - marking a significant step forward in oncological imaging. Beyond these approved agents, a growing pipeline of ^{68}Ga-based radiotracers is in clinical development, broadening its applications across various malignancies and reinforcing its role in precision medicine.

One of the most exciting applications of ^{68}Ga is in theranostics, where it serves as the diagnostic counterpart to therapeutic radionuclides such as ^{177}Lu. This pairing supports the transition from imaging to targeted radiotherapy, enhancing treatment efficacy while minimizing systemic toxicity.

Despite its rapid advancement, ^{68}Ga-based radiopharmaceuticals still face challenges in clinical adoption. A major drawback is the small number of validated targets suitable for ^{68}Ga applications, currently restricted to somatostatin receptors and the prostate-specific membrane antigen. However, emerging targets such as FAP hold great potential to expand its use across multiple cancer types.

Looking ahead, the expanding clinical adoption of ^{68}Ga suggests that additional regulatory approvals are imminent, reinforcing its position as a pivotal PET imaging agent alongside ^{18}F.

CRediT authorship contribution statement

Francesca Musumeci: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Alessandro Fasce:** Writing – original draft, Software. **Marta Falesiedi:** Visualization. **Federica Oleari:** Visualization. **Giancarlo Grossi:** Writing – review & editing. **Anna Carbone:** Writing – review & editing. **Silvia Schenone:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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