MODERN MEDICINE AND PRACTICE
https://inovatus.es/index.php/ejmmp

EUROPEAN JOURNAL OF MODERN MEDICINE AND PRACTICE
Vol. 4 No. 7 (Jul - 2024) EJMMP ISSN: 2795-921X

THE USE OF ZIRCONIUM COMPOUNDS IN RADIOPHARMACY AND NUCLEAR MEDICINE

Zainab Haidar Shami, Teeba Hamid Wasel, Maryam Ali Jabbar
Department of Chemistry, College of Science, University of Dhi Qar

Baqir Samir Abdel Hussein
Department of Chemistry, College of Science, University of Babylon

Abstract: Zirconium (Zr): It is a transition metal characterized by its silvery gray color. It is a type of flexible, moldable element. It is also included in the composition of many stable compounds. Zirconium is characterized by its high resistance to corrosion. Zirconium and its alloys have been used for centuries in a variety of applications. It is commonly used in corrosive environments, as zirconium alloys can be found in pipes, Chemicool website. Zirconium is aalso fittings, and heat exchangers, according to the used in steel alloys, colored glass, bricks, and ceramics. Abrasives, light bulbs, lamp filaments and gemstones, Synthetic, and some deodorants. Growing interest in using the radioactive isotope of zirconium, zirconium- 89 , for technology, Medical diagnosis by positron emission tomography (PET). This has stimulated significant research into the aqueous chemistry of zirconium with the design of new ligands to achieve the stability required for use in in vivo imaging. This review describes, Educational chemistry that supports the development of new Zr-based imaging agents and also includes related topics such as the synthesis of the radioactive isotope zirconium -89. Principles of PET and the use of monoclonal antibodies (mAbs) The review covers the period from the first reports of the clinical use of zirconium-89 in PET in 2006 to 2017 and is illustrated with examples of the use of radioisotopes. Mainly zirconium 89. In combination with mAbs for PET imaging in both, Preclinical and clinical studies. The standard unit for radioactivity is the Becquerel (Bq), It is necessary to determine the amount of radioactivity present in a medical imaging preparation Using a specific activity This is the measured activity (Bq) in the total amount of the compound, In the preparation of a radioactive compound, there are often unclassified compounds, and in this case the term “specific activity” is used, which is clearly visible and requires a technical technique. Analytical to determine the quantities of classified and unclassified compounds.

Introduction:

Until the last decade of the twentieth century, zirconium chemistry was almost entirely dominated by organometallic complexes and their applications. The main goals were to find new catalysts for reactions such as olefin polymerization, nitrogen fixation and many other transformations of unsaturated molecules. Zirconium (Zr): It is a transition metal characterized by its silvery gray color. It is a type of flexible, moldable element. It is also included in the composition of many stable compounds. Zirconium is characterized by its high resistance to corrosion. Zirconium and its alloys have been used for centuries in a variety of applications.

It is commonly used in corrosive environments, as zirconium alloys can be found in pipes, Chemicool website. Zirconium is aalso fittings, and heat exchangers, according to the used in steel alloys, colored glass, bricks, and ceramics. Abrasives, light bulbs, lamp filaments and gemstones, Synthetic, and some deodorants. Growing interest in using the radioactive isotope of zirconium, zirconium- 89 , for technology, Medical diagnosis by positron emission tomography (PET). This has stimulated significant research into the aqueous chemistry of zirconium with the design of new ligands to achieve the stability required for use in in vivo imaging. This review describes, Educational chemistry that supports the development of new Zr-based imaging agents and also includes related topics such as the synthesis of the radioactive isotope zirconium -89. Principles of PET and the use of monoclonal antibodies (mAbs) The review covers the period from the first reports of the clinical use of zirconium-89 in PET in 2006 to 2017 and is illustrated with examples of the use of radioisotopes. Mainly zirconium 89. In combination with mAbs for PET imaging in both, Preclinical and clinical studies. The standard unit for radioactivity is the Becquerel (Bq), It is necessary to determine the amount of radioactivity present in a medical imaging preparation Using a specific activity This is the measured activity (Bq) in the total amount of the compound, In the preparation of a radioactive compound, there are often unclassified compounds, and in this case the term “specific activity” is used, which is clearly visible and requires a technical technique. Analytical to determine the quantities of classified and unclassified compounds. Due to decay must, Determine the measurement time for the selected activity. The term radiochemical yield (RCY): is the percentage of radioactivity, In the final product to that in the initial compound and both values are corrected to the same starting point.

Zirconium isotopes: Natural zirconium consists of 5 isotopes of zirconium 93 (51.45%), zirconium 91 (11.22%), zirconium 92 (17.15%), zirconium 94 (17.38%), zirconium 96 (2.80%). The first four are stable, but 96Zr is radioactive, although it appears that the Zr that, It has an extremely long half-life of 2.35 x 1020 naturally occurring non-radioactive years for all intents and purposes. There are 38 currently known isotopes of zirconium covering the mass number range 112-78 with four isotopes, Additional stabilizer. Those with mass numbers less than 80 or greater than 100, while the lighter ones decay by showing very short half-lives. Electron capture, the heaviest beta emission among these radioactive isotopes, 89Zr has found wide application because it is a positron emitter with a suitable half-life and energy for positron emission tomography (PET, described in more detail below). Figure 1 shows a simplified decay diagram for zirconium. And 49 neutrons a and it decays to yttrium 89-mRa Zirconium 89 over 40 protons a, Stabilized by a combination of positrons. Simplified decay diagram for zirconium 89, The radioactive isotope of zirconium 89Zr: The isotope zirconium 89 is produced in a cyclotron that accelerates protons onto a path Helical By means of a combination of an alternating electric field and a constant magnetic field, the resulting beam of high-energy protons (about 14 MeV) is directed, Towards a fixed target of yttrium 89, as in Figure (1)



Figure (1): Modern Cyclotron The cyclotron line and crossbar are hidden behind thick semicircular concrete shields.

It is advantageous that this is a natural isotope. Care must be taken with the irradiation time to avoid the formation of zirconium 88 as an impurity. Zirconium 89 is then filtered into the target. Using 2 ml of HCI is then loaded onto a column of hydroxamate resin which, Zirconium 89 binds in the form of a hydroxamate compound. Then remove the addition of acid, Oxalate 1 ml Zirconium 89 as an oxalate derivative. , Appear that, But it has been suggested that it is an eight-coordinate anionic compound Zr (oxalate) and with electrophoresis studies of (oxalate-Zr) that both negatively and positively charged species indicate the presence of a mixture of species. [Zr]Zr chloride was developed as being preferable to oxalate because it avoids the presence of, Oxalic acid is potentially toxic. However used in radiopharmaceuticals of zirconium 89, this toxicity is not a problem. Zirconium 89 has significant gamma emissions during decomposition It is handled in hot cells, which have a heavy lead shield (usually 10-8). cm) and the contents are displayed through thick glass windows. Standard combinations are currently performed manually, but methods for use are being developed. Principles of positron emission tomography (PET) for 89Zr:, A positron emitted by zirconium-89 has a maximum energy of 890 kv with an average energy of 390 kv. The energy is important because it determines the distance the positron will travel before annihilating. By taking an electron from a surrounding atom. This leads to uncertainty in the exact location of the positron emission source. This annihilation event results in the emission of two 511 kev photons, At 180 degrees. to each other which are then detected almost simultaneously by a ring of thousands of tiny scintillation crystals coupled to photodetectors. Figure 2 A modern cyclotron. The cyclotron line and crossbar are hidden behind shields Thick semi-circular concrete that can be returned for access via existing rails, On the floor. Chance events occur at a rate of about one million per second. Schematic diagram of a PEa T scanner. Figure 3 shows

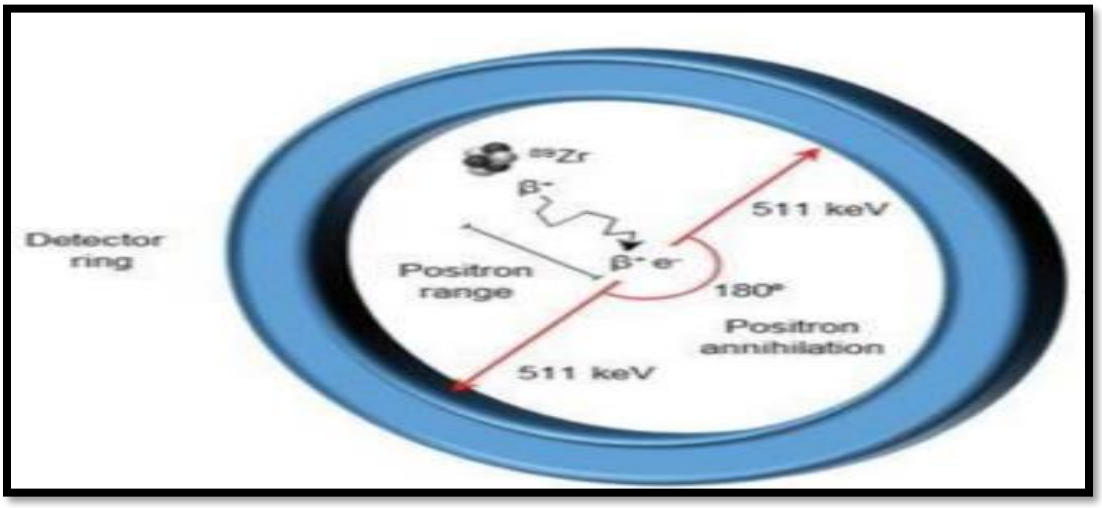


Figure No. (2) PET scanner

Sophisticated computer algorithms that take into account factors such as attenuation and scattering are then deployed to determine the spatial coordinates of the annihilation point and then develop a 3D image (slices across the object being scanned) of the location of the zirconium isotope 89. PET scanners are often Modern side-by-side X-ray computed tomography (SPECT) scanner, Co-registered images allow the anatomical location of the radioisotope with 4 mm accuracy. A special advantage of PET over SPECT is that the amount of radioactivity in a unit volume can, It is quantified, allowing the fraction of radioactivity directed to the target site to be determined. Biochemistry of zirconium: Oligomeric metal marks and other impurities It is also necessary to add gentisic acid (2,5- dihydroxybenzoic acid) to the final labeled product. Radioactive to prevent damage to the union by autoradioactive decay. As Table 1 shows, large amounts of zirconium are found in organisms, The snake. Zirconium is generally specified. The estimated daily intake of Zr is 4.2. mg, daily intake of food and water and is eliminated exclusively through the digestive system with feces rather

than the kidneys. This is in marked contrast to other transition metals that are eliminated through the urinary system. This is attributed to Zr being strongly bound to proteins, Therefore, it cannot pass through the renal filtration system.

	[Zr] (μg g^{-1})
Serum	0.68[a,b]
Aorta	9.49
Liver	6.28
Brain	2.61
Urine	0
Red blood cells	6.18

12

[a] Average values over several patients. [b] Corresponds to 5 μM Zr.

Table No. (1): Zr concentrations in humans (mg) per patient population.It has been suggested that the presence of large amounts of Zr in naturally protected brain tissue It may indicate that Zr has an as yet unknown biological role. (See Figure 4) This illustrates a major potential problem with the use of zirconium-89 complexes as any dislodgement of the complexes will lead to unwanted accumulation of zirconium-89 in the bone with potentially long- term radiation dose.

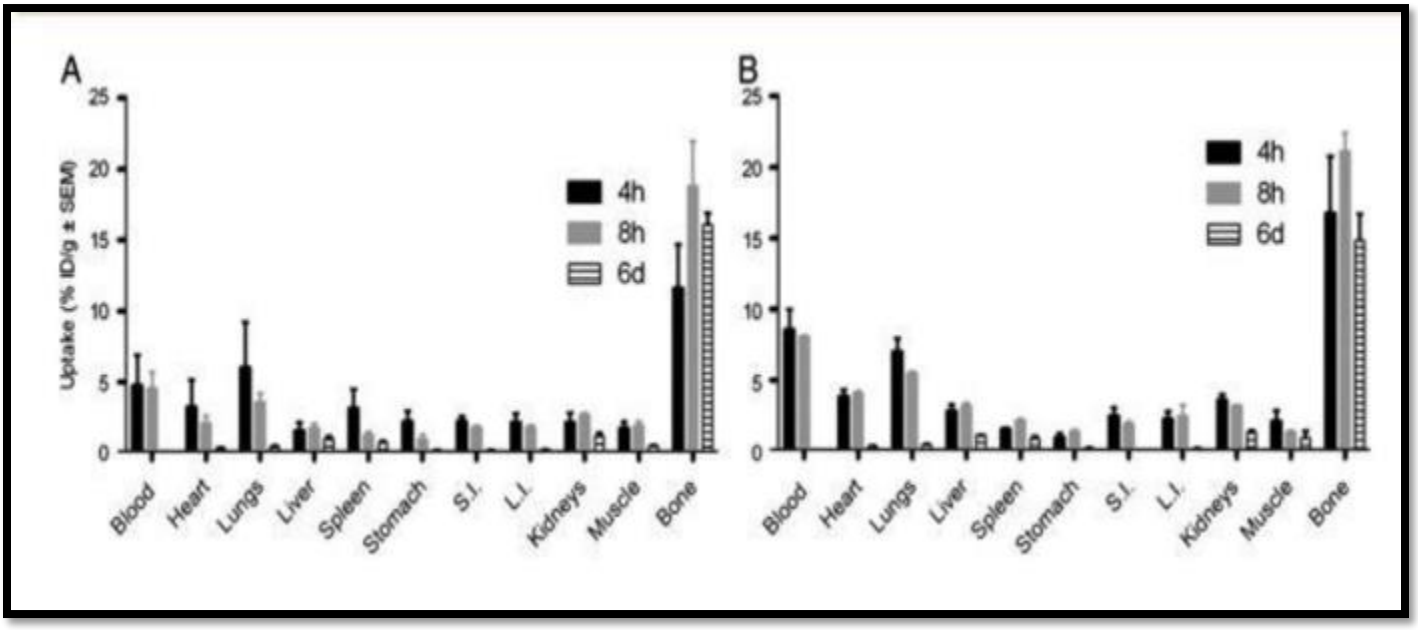


Figure No. (3) Biodistributions in mice of 89 Zr.

Hydroxamate donor groups : Desferrioxamine (DFO): A bacteriophore produced by a fungus-like bacterium called.In poetic series. DFO is widely used in the clinic (often under the name. Desferral (for the treatment of patients with iron overload) is therefore available It is widely commercially available at a modest cost and

there are no toxicological problems associated with its use in patients. The formation of a monocation is predictable, but in reality under the conditions used to prepare ZrDFO complexes, the pendant amino group is protonated and the total charge is +2. No crystal structure has been determined. X-rays . zr is of the DFO-Zr complex, but the DFT calculation predicts the lowest energy structure, Three hydroxamate bonds and two water molecules located in 8-coordinate with, With total anti-flammable deformed square structure. Of the cis positions, the two monodentate water molecules are likely labile and their loss is thought to be the initial stage of demineralization that is observed to a small but significant extent in vivo, With the metal chelator delivered, the next stage is to pair this with a targeting agen (monoclonal antibody (mAbs) that provide Biological, which is generally a body, The amino group attached to DFO can interact with the standard peptide conjugate, Carboxyl group on mAbs. Unfortunately, hydroxamate residues interfere with. This coupling needs to be protected by DFO pre-coordination of the iron. This It has been used successfully for long-term studies but with the cumbersome and time- consuming approach piloted on animals and humans using an antibody called zirconium 89.(8mAb-)DFO(Zr]Zr). An alternative coupling method was then developed using. Benzene.isothiocyanato-di This involves reacting DFO with a stoichiometric amount of benzene to give the thiourea derivative BzNCS-DFO. The remaining NCS moiety can then be used to conjugate to amino residues on the mAb (usually lysine) for administration, The mAb-DFO conjugated product is as shown in Figure (4)

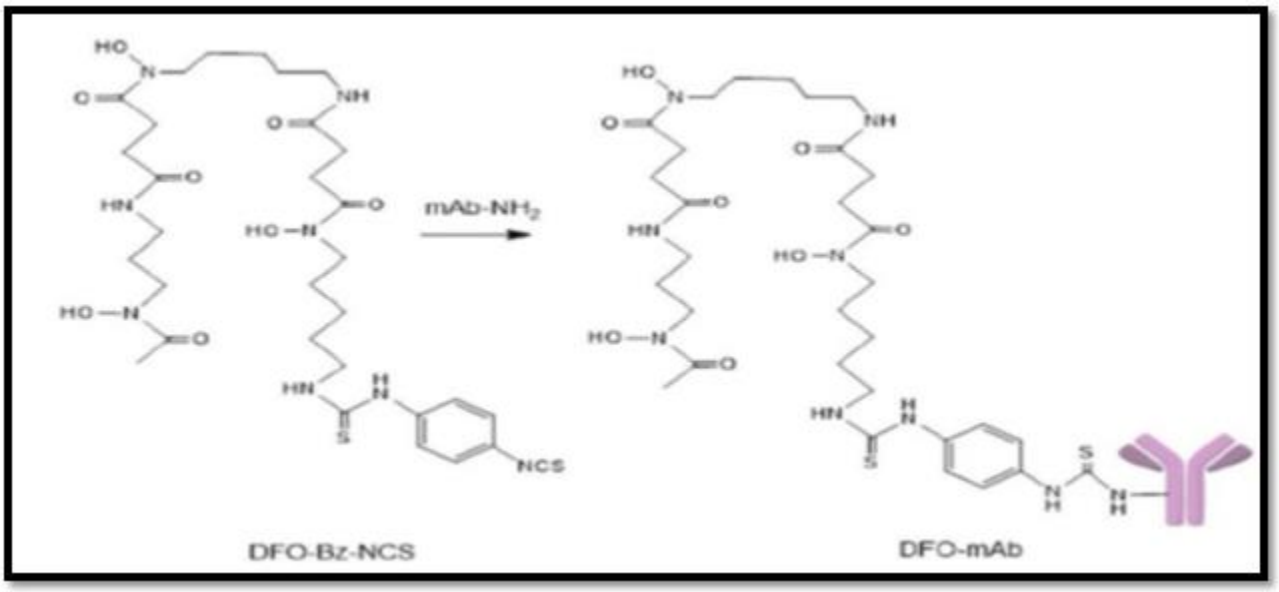


Figure No. (4) Structure of BzNCS-DFO alone and with conjugated antibody.

Design of a dual-functional claw for zirconium coordinate engineering: When considering the design of bifunctional chelators, its chemical properties must be taken into account. Zirconium, at its highest oxidation state of four, is a calcic solid or a Class A acceptor and as such will have a strong preference for strong donors e.g. Oxygen and nitrogen. It is frequently stated that Zr is a small metal ion when in fact the ^{1}Zr ion has the largest radius (87 m) among the tetravalent cations, The metallicity of the second row is as expected with an increase in the effective nuclear charge. Zirconium does not bind as strongly to the targeting groups commonly used in zirconium-89 PET imaging as it does with multi-metal chelators. This means that it can, Procedure for radiolabeling of zirconium 89- After collection and chromatographic size exclusion purification of the label by inductively coupled plasma emission or mass spectroscopy. The chelator targeting kit unit is used to remove any products with oligomeric metal traces and other impurities. It is also necessary to add gentisic acid (2,5-dihydroxybenzoic acid) to the final labeled product. Radioactive to prevent damage to the union by autoradioactive decay. Zirconium 89 applications will be multi-dentate with 6-8 teeth with oxygen or nitrogen donor atoms and a charge at 3 or 4 when the proton is removed to reduce the charge. The

total on the complex. Although the stability of the zirconium compound in media is also important. The results of biological accumulation are crucial, however, the in vivo distribution of any conjugate is significant in non-target organs and its prolonged presence in the blood pool. With additional radiation doses and the possibility of blocking the tumor or metastasis of the target.

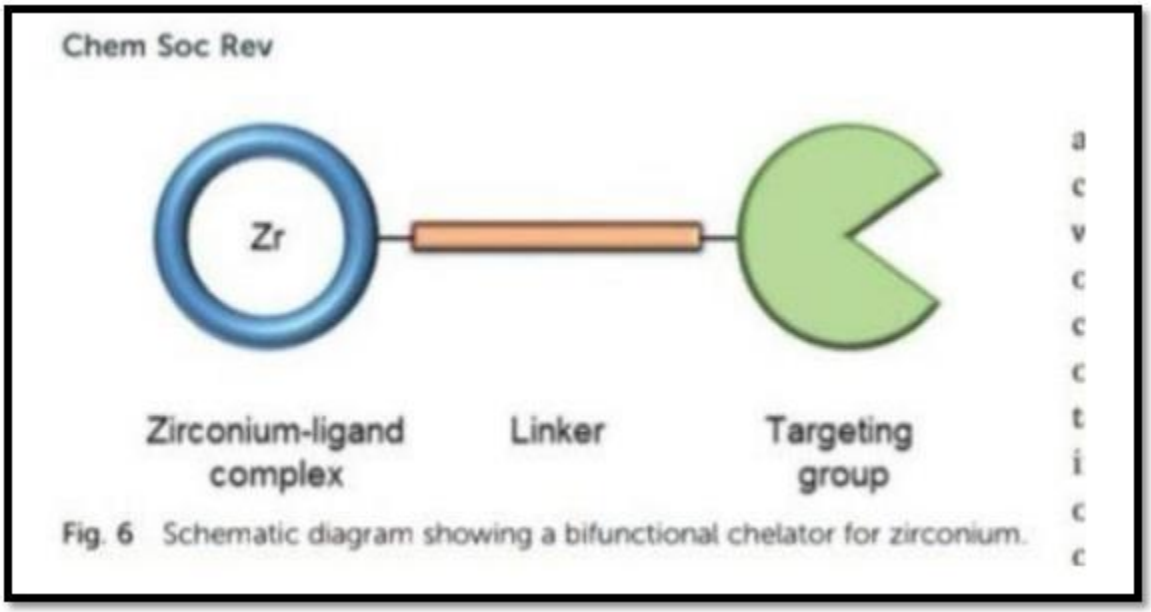


Figure (5) A diagram showing a two-functional chelate for the total charge of zirconium.

Preclinical studies with DFO-Zr derivatives:

Of all the bifunctional chelators mAbs derived from antibody-linked zirconium-89- and clinical a labeled DFO have been the most investigated in both preclinical contexts. In this section, three examples were selected, Arbitrary to illustrate how agents are made and what type of information can be derived from positron emission tomography scans in both animals and humans. The antibody labeled [591J-BzNCS-)DFO (Zr) was examined for imaging of tumors, Implantable prostate cancer (LNCAP, PSMAP positive and -3PC, PSMA negative), In mice. In vivo studies were performed in mice bearing mAbs implanted with either LNCAP or -3PC tumors using an injection dose of approximately 11 mAb corresponding to approximately 60 ÿg of mAb. Stronger uptake was observed in PSMA (a radioactive substance or antigen that targets a protein) that LnCaP tumors express, unlike those, Found in 3PC tumors (human prostate cancer), Absorption increased to 48% of the injected dose after 144 hours. Operations appear, Typical PET test or scan, which shows the significant difference in LNCaP, (Lymph nodes prostate cancer), And tumors -3pc. In contrast to studies of solution stability in brine, it was found, Approximately 5% of the dose injected into the mice in the bones after 96 hours is consistent, DFO crowbar. Low stability seen in vivo. With some disintegration of System B, This is not uncommon for mineral-based imaging agents and caution is required in extrapolating results from solution studies. These imaging results indicate that this agent has real potential for imaging PSMA-positive tumors in vivo. Similar studies were performed in mouse using the same mAb 591J but this time combined with DFO via previously described non-catalyzed click chemistry26. The results were very similar to those described above demonstrating that the nature of the ligand group, It does not contain a large number of links. Clinical studies with "DFO-Zr" derivatives: Non-isotope-labeled mAbs such as cetuximab are used in clinical treatment, For cancers including colorectal cancer. These treatments are expensive and prior indication of the potential efficacy of the mAb is clearly desirable. Strong uptake of radiolabeled antibodies assessed by PET at the site of tumor or metastasis suggests that the therapeutic use of this mAb

Unlabeled mAb is likely to be effective. This is an increasingly important application for, Zirconium-labeled mAbs.89a, An alternative treatment method is to disseminate a MAb labeled with a radioisotope Bxor that is capable of killing cancer cells. This is known as radioimmunotherapy or RAIT and is finding increasing use especially for cancers that have proven resistant to alternative treatments. evidence as to whether RAIT will btehenefit Again, the use of [Zr]-mAbs can provide useful the patient. It has been examined across a range of cancers such as head and neck, breast, gliomas, lung, pancreas, ovary, colorectal and renal cells. The technetium agent is a diphosphonate compound that is also strongly bound to hydroxyl, a form of apatite.Apatite is a naturally occurring phosphate mineral, Calcium. The mineral has the chemical formula (OH(3)4PO(5Ca), in bone and is maximally absorbed where the bone is under stress and is widely used for imaging bone metastases. Labeled FDG mainly depicts the elevated metabolism of cancerous areas. Unlike an antibody Named, none of these factors, Designed for prostate cancer. Figure 7 shows all three scan types for a patient with metastatic prostate cancer. The images show that 59289J-DFO-Zr highlights more sites of bone metastasis than either of the other two agents. Selected lesions seen on the zirconium 89 scans were biopsied to confirm They were PSMA positive. Taken together, the results show that 5918J-DFO-Zr is well tolerated in patients and may be valuable in imaging prostate cancer lesions that are not easily detected by other imaging methods. Disease progression was observed in 3 of 4. Patients showed no tumor uptake of the labeled mAb. 9.2 Derivatives, Desferrioxamine Bone resorptions of up to 5% i.d. per gram indicate that the DFO chelate has limited stability in vivo.

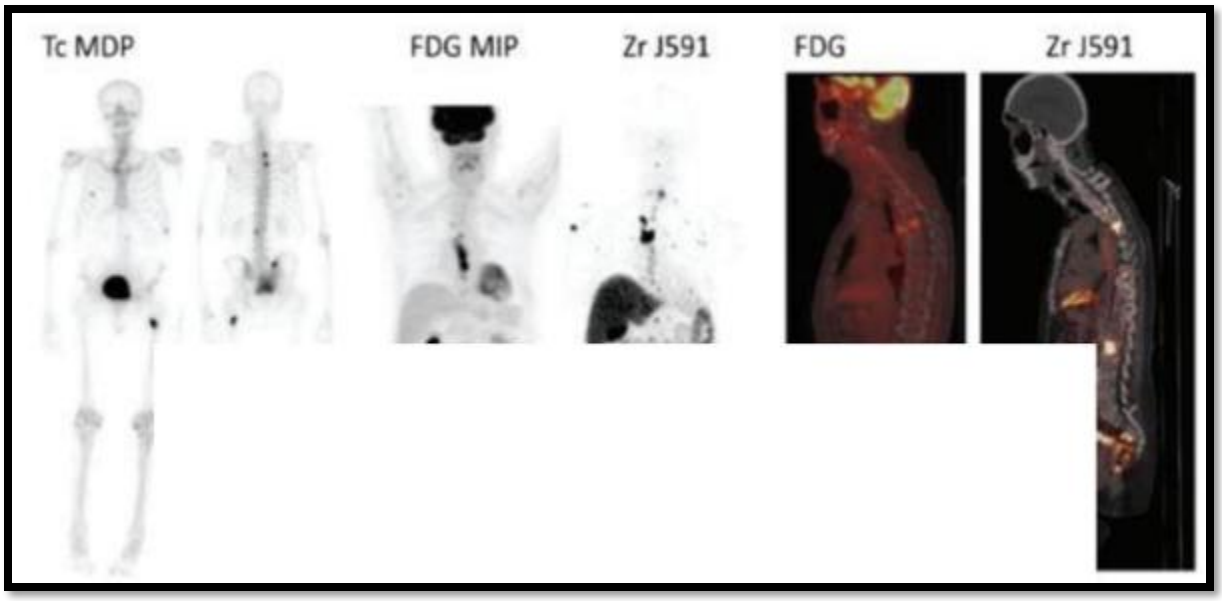


Figure No. (6) Positron emission tomography and photon emission computed tomography One SPECT (for a patient with extensive metastases due to prostate cancer).

Possibility of removing metal: One approach is to attach additional hydroxamate residues. The resulting DFO variable is designated DFO. The optimal DFT figure for [ZrDFO] is shown and confirms that the zirconium is, Already eight coordinates. The addition of additional hydroxamates was achieved relatively simply by a peptide conjugation reaction and after deprotection of the additional group there is a pendant amino group that can be functionalized for conjugation by reaction with -1,4-diisothiocyanatobenzene to give BzNCS-DFO, similarly to DFO as previously described. a. In paper with BNCS-DFO was combined with trastuzumab and a subsequent detailed comparison was performed." BZNCS-DFO. In both cases approximately one label was associated with each ms, Ampere. Radiolabeling of both was performed using standard protocols and comparative stability in vitro studies were performed in saline, sucrose histidine

buffer and serum. Blood, the DFO derivative showed significantly increased stability in serum and salt, then, The behavior of both mAbs in mice bearing 87N tumors was examined by, Positron emission tomography and organ dose measurements. Both agents showed good tumor uptake at 24, 72 and 144 h p.i. with uptake at 72 h being significantly higher for the 45% DFO derivative. ID per gram) compared to analogue DFO (35% of ID per gram).

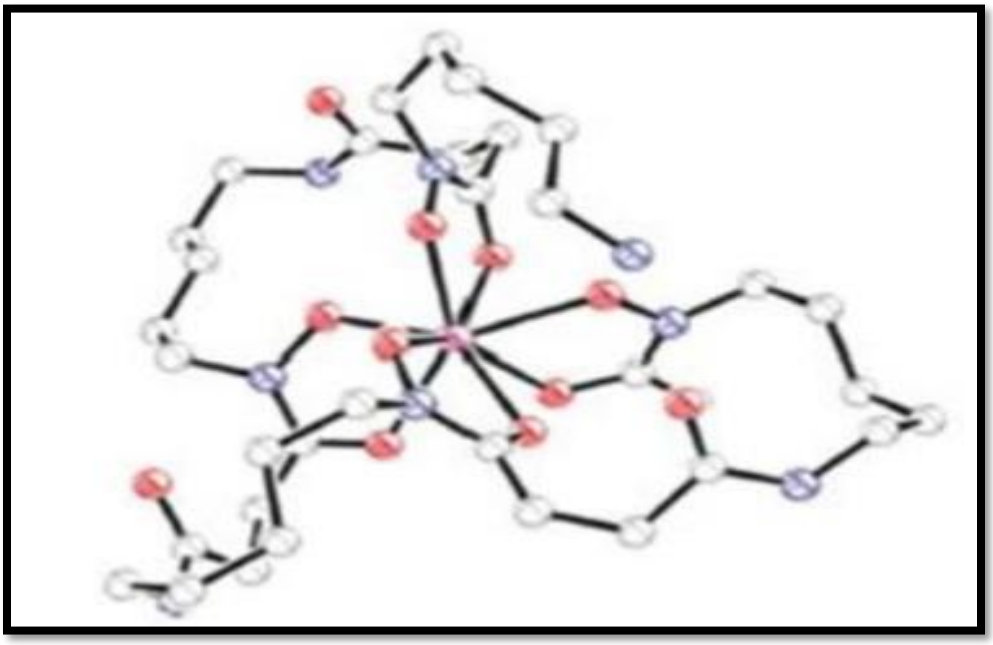


Figure No. (7) : mAb-Sq-DFO synthesis

One important observation was that bone uptake of the DFO comparator. It was lower in time points consistent with in vitro studies that showed higher stability, For DFO factor. Octa core. No clinical studies have been reported at this stage. But the evidence so far suggests that DFO offers some real advantages over DFO, For positron emission tomography using mAbs. One potential disadvantage of DFO is that it is relatively insoluble in water which leads to difficulties in purification, Both DFO. And its bio comparisons. In mice with xenografted 21M tumors, one tumor contained a positive integrin and the other contained a negative integrin. The stunning images obtained are shown in this was closely Figure (9), and it is clear that absorption is highly correlated linked to integrin expression and this was confirmed by performing imaging in the presence of a derivative blocking factor of RGD which significantly reduced tumor uptake, confirming its specificity. not done reported bone resorption but in light of the results of solution stability, it is likely, To be much lower than the DFO-based factors. Conjugation to antibodies has not yet been reported and it will be necessary to reduce conjugation sites on the FSC from Three to one to achieve good chelator to mAb ratios and to avoid cross-linking problems. Also, long-term in vivo experiments are needed as required for action marking mAb to confirm stability over long periods of time. Although long-lived zirconium 89 is mainly used with antibodies, this shows that it is also very effective in targeting peptides with faster pharmacokinetics.

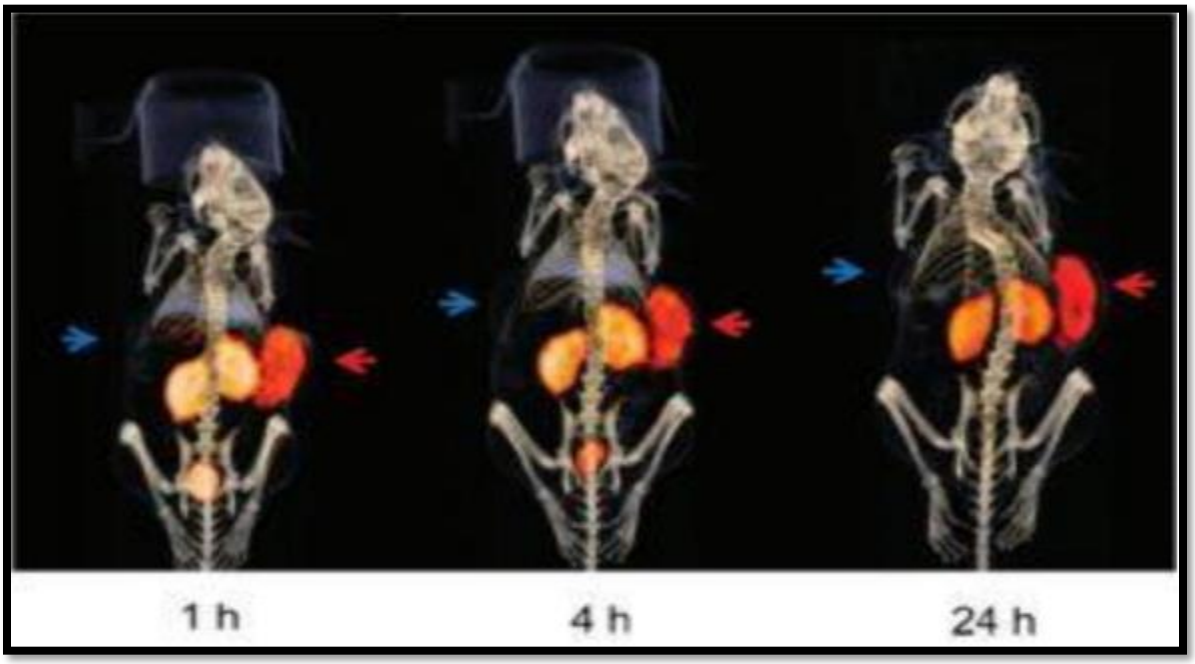


Figure No. (8) CT/PET scan of 21M tumor-bearing mice using [89] 3. (arrows indicate succRGD (-FSC-Zr-) Red arrows indicate strong uptake in integrin-expressing positive tumors, while blue arrows indicate no Uptake in integrin-negative tumors.

Hydroxyisophthalimide (IAM):

Some biological iron acid compounds and lanthanide sequestering agents rely on hydroxyisophthalimide (IAM) donor groups and thus also have the ability to, Formation of stable zirconium complexes. The structure of the total octacyclic ligand is described The octet through a series of low-yield, multi-stage reactions in detail. A ¹5L analogue with a pendant IAM array has also been reported. Prepared, Cold Zr complexes [¹4ZrL] and [¹5ZrL] of Zr acetylacetonate in methanol, They were characterized by H¹NMR and PESI FTMS. There are no X-ray crystal structures. Available but the structure of ¹4ZrL was calculated via DFT. Two isomers with similar energies that differ in the amide coordination were found. This is the only example among imaging agents where six-membered rather than five-membered chelating rings are attached. With zirconium. The seeded complexes were then subjected to a standard challenge with excess DTPA vs. [89DFO(Zr]Zr) for comparison. After 7 days, 72% of [¹489ZrL]Zr remained silicate versus 40.6% for [9DFO(Zr]Zr). (Indicating higher stability, but this stability order was reversed in human serum.), [89Zr]¹5ZrL was lower. Animal studies were performed in wild-type mice with the three compounds named above and in, For organ distribution at 2, 4, 48, and 72 h after anatomy definition. [89Zr]¹4ZrL showed higher kidney retention (about 6 and higher) and liver retention (about 4 times higher) than labeled DFO. Relative to ¹5L Liver retention was higher but kidney retention was closer to [89DFO(Zr]Zr). Brother ra, bone retention after 72 hours for ¹L was significantly higher than labeled DFO ¹5L was higher. In general, the high solution stability of [¹489ZrL]Zr did not translate into, Decreased bone resorption in vivo and forced radiolabeling conditions are problematic and retention of activity in the liver and kidneys is not ideal. Results of in vivo mAb conjugate studies are awaited, but some will be needed, Interconnection design modifications to compete with DFO.

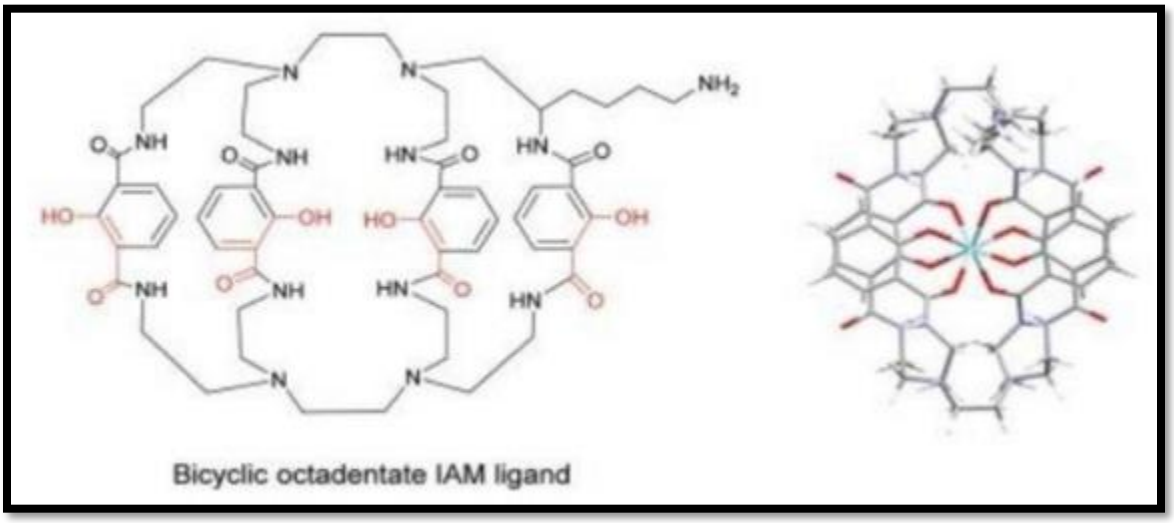


Figure No. (9) Structures of 14L hydroxyisophthalimide (IAM) and DFT Optimized structure of its Zr complex

Conclusion

References

1. Verel, G.W.M. Visser, R. Boellaard, M. Stigter-vanWalsum, G. B. Snow and GAMS van Dongen, J. Nucl. Med., 2003,44, 1271-1281.
2. S. Heskamp, R. Raave, O. Boerman, M. Rijkpema, V. .2 Goncalves and F. Denat, Bioconjugate Chem., 2017, 28, 2211-2223.
3. Y. Zhang, H. Hong and W. Cai, Curr. Radiopharm., 2011, 4,
4. GW Severin, JW Engle, TE Barnhart and RJ Nickles,131-139. Med. Chem., 2011, 7, 389-394.
5. TJ Wadas, EH Wong, GR Weisman and CJ Anderson,chem. Rev., 2010, 110, 2858-2902.
6. E. W. Price and C. Orvig, The Chemistry of Molecular.6 Imaging, John Wiley & Sons, Inc., 2014, pp. 105-135.
7. T. K. Nayak and M. W. Brechbiel, Bioconjugate Chem., 2009, 20, 825-841.
8. MA Deri, BM Zeglis, LC Francesconi and JS Lewis, Nucl. Med. Biol., 2013, 40, 3-14.
9. D. S. Abou, T. Ku and P. M. Smith-Jones, Nucl. Med. Biol., 2011, 38, 675-681.
10. J.P. Holland, Y. Sheh and J.S. Lewis, Nucl. Med. Biol., 2009, 36, 729-739.
11. DBN Lee, M. Roberts, C. G. Bluchel and R. A. Odell, ASAIO J., 2010, 56, 550-556.
12. H. A. Schroeder and J. J. Balassa, J. Chronic Dis., 1966, 19, 573-586