Radiodiagnostické metody

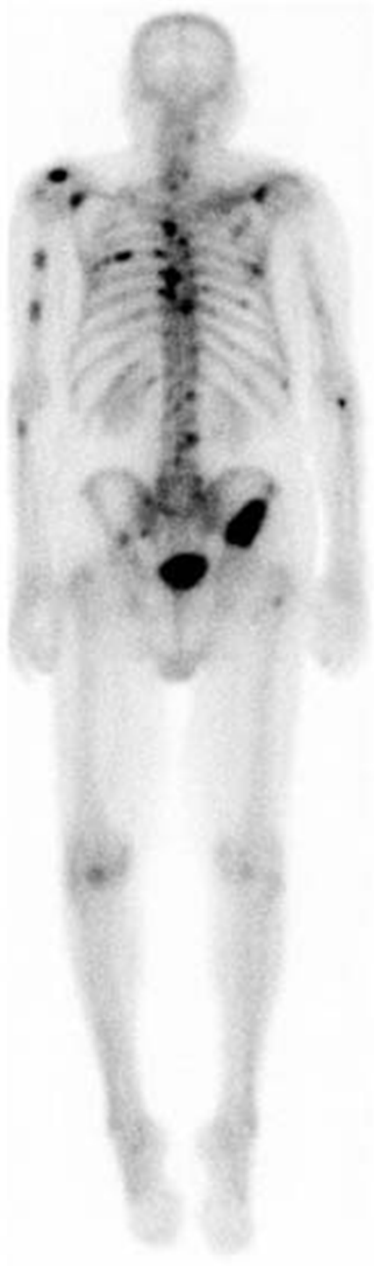
SPECT – single photon emission computer tomography

PET – positron emission tomography

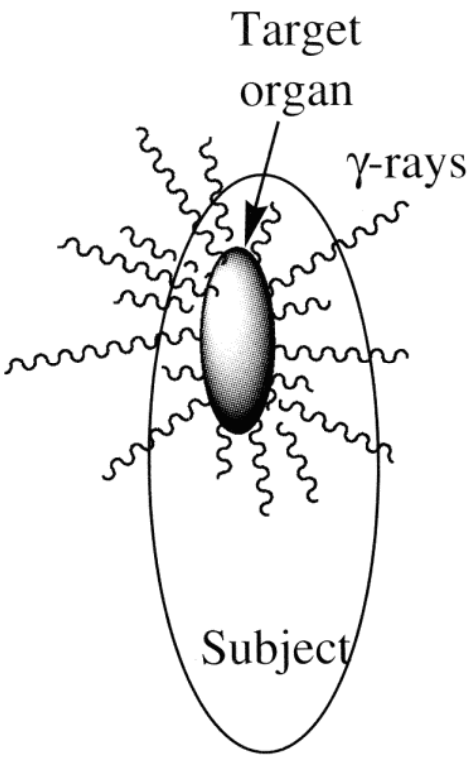
Radiotherapy

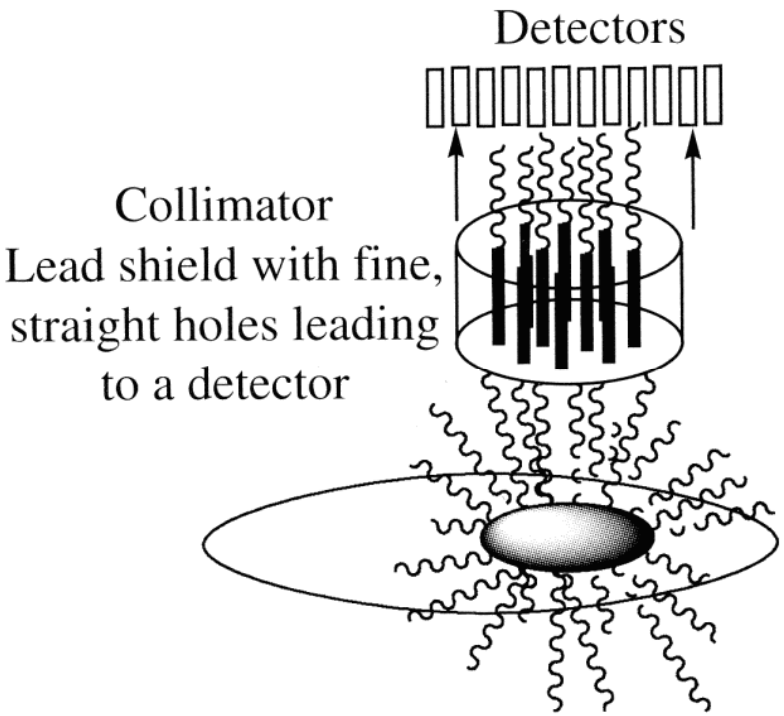
ednofotonová emisní tomografie **(SPECT)**

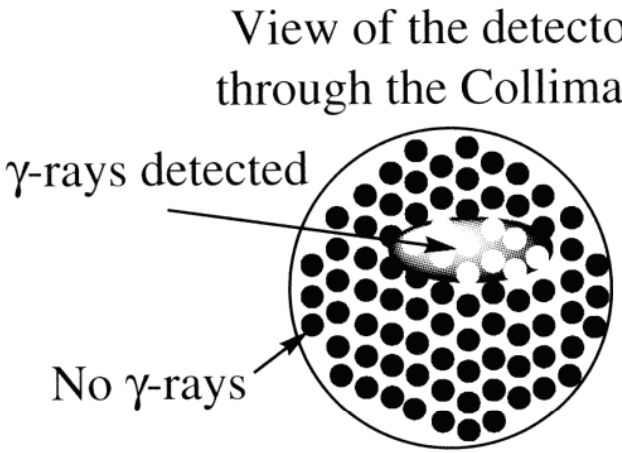
- γ-emitující radioisotopy
- rozlišení ~1 cm3



SPECT







Collimator allows through only γ-rays travelling parallel to holes so creating an image of the radiation source in the detectors

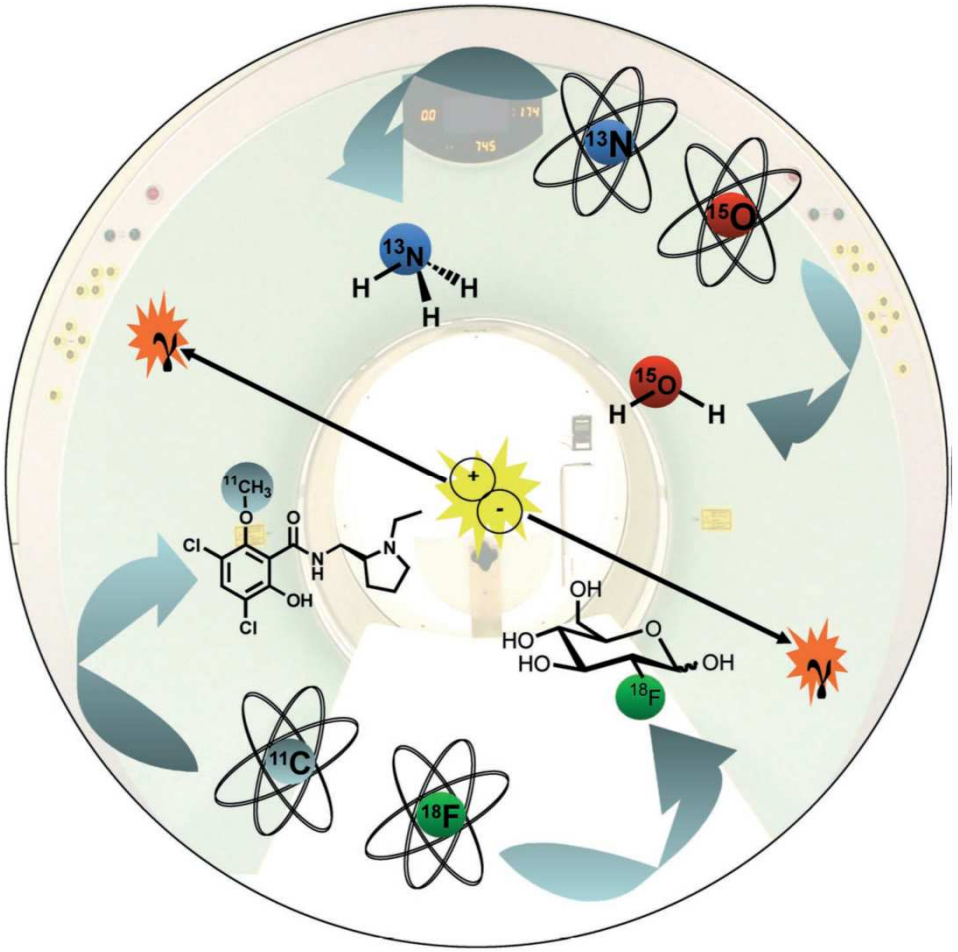
Izotopy pro SPECT

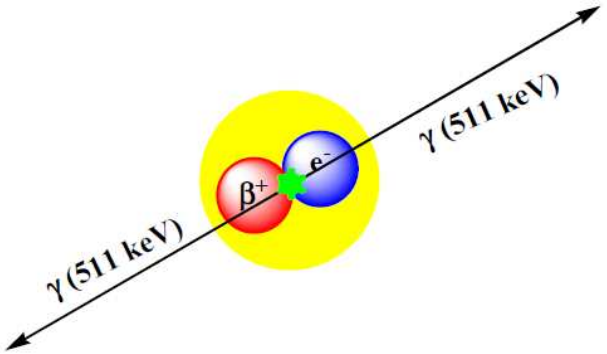
Izotop	Přeměna	Poločas	Zdroj
^{99m}Tc	**γ**	**6 h**	**generátor, ^{99}Mo(β$^-$)^{99m}Tc, 66 h**
^{111}In	**γ**	**68 h**	**cyklotron, ^{111}Cd(p,n)^{111}In**
^{131}I	γ, β$^-$	8 d	reaktor
^{153}Sm	γ, β$^-$	46 h	reaktor
^{166}Ho	γ, β$^-$	26 h	reaktor
^{177}Lu	**γ, β$^-$**	**6.7 d**	**reaktor**

PET

PET

- radioisotopes emitting positrons (β^+-particles)
- annihilation with electrons
- two co-linear photons with an energy of 511 keV
- detection of both photons at the same time
- resolution about 1 mm^3
- low energy → better resolution



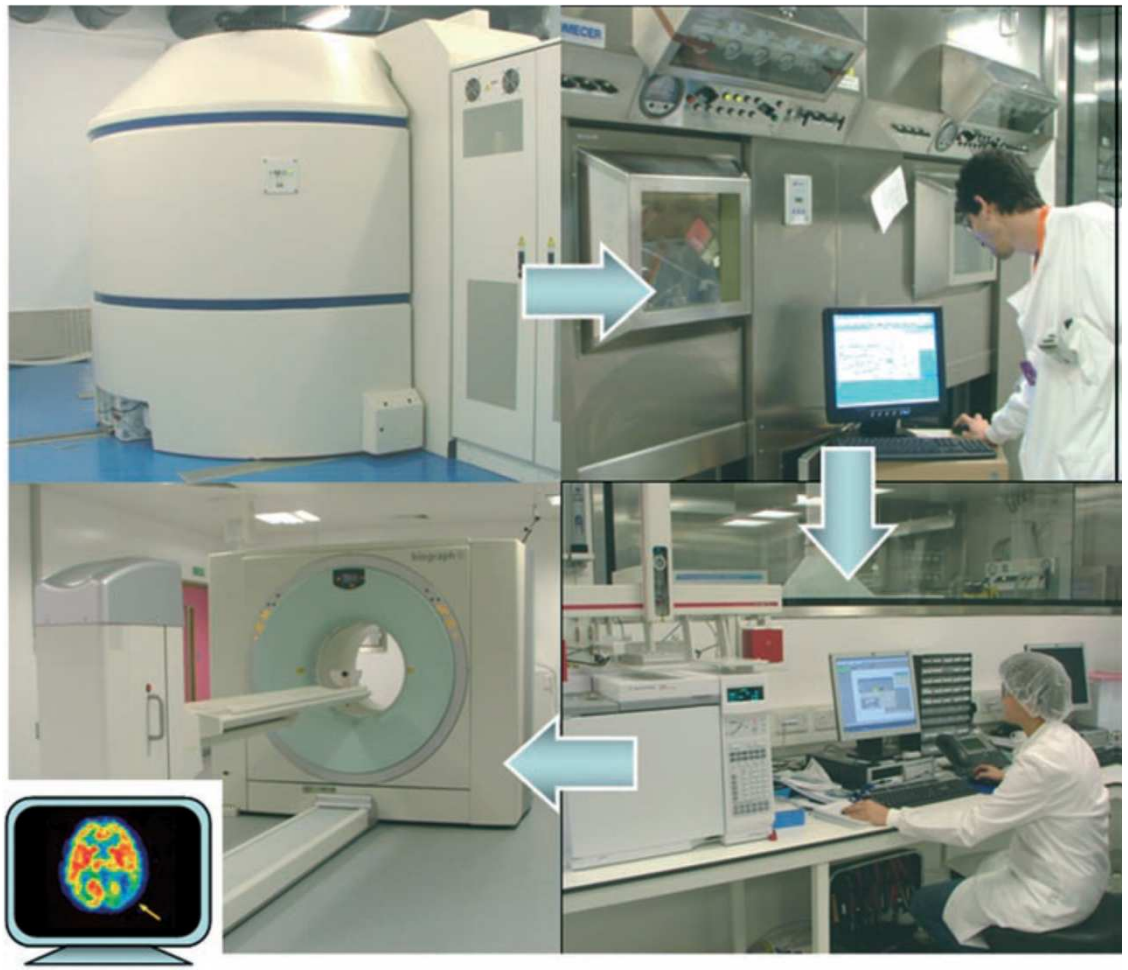


Izotopy pro PET

Izotop	Přeměna	Poločas	Zdroj
^{19}F	**β^+**	**110 min**	**cyklotron, ^{18}O(p,n)^{18}F**
^{11}C	β^+	20 min	cyklotron, ^{14}N(p,α)^{11}C
^{61}Cu	β^+	3.3 h	cyklotron, ^{61}Ni(p,n)^{61}Cu
^{64}Cu	**β^+**	**13 h**	**cyklotron, ^{64}Ni(p,n)^{64}Cu**
^{66}Ga	β^+	9.5 h	cyklotron, ^{63}Cu(α,nγ)^{66}Ga
^{68}Ga	**β^+**	**68 min**	**generátor, ^{68}Ge(β^-)^{68}Ga, 288 d**
^{86}Y	β^+	15 h	cyklotron, ^{86}Sr(p,n)^{86}Y
^{110}In	β^+	69 min	generátor, ^{110}Sn(β^-)^{110}In, 4.11 d

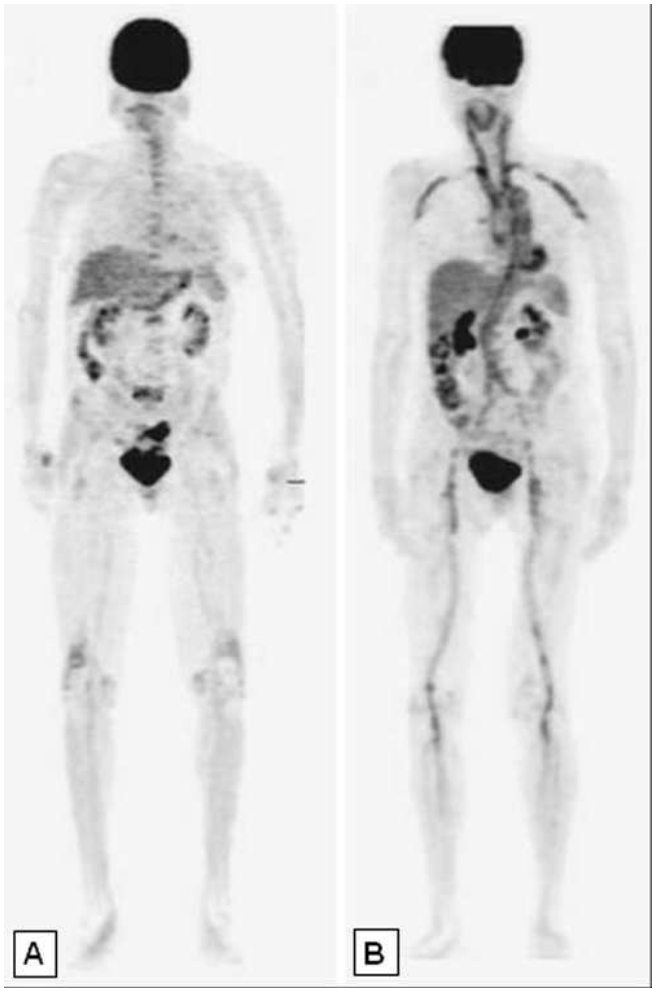
Každá minuta se počítá

- Příprava izotopu
- Izolace izotopu
- Příprava radiofarmaka
- Separace radiofarmaka
- Analýza radiofarmaka
- Doprava k pacientovi
- Aplikace pacientovi
- Dosažení žádané biodistribuce
- Snímkování

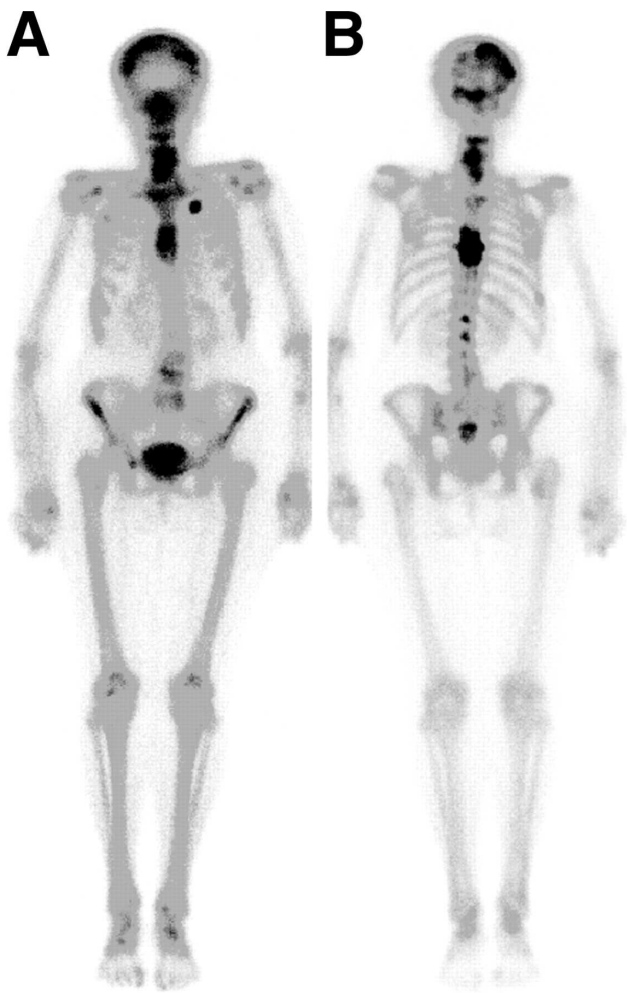


PET vs. SPECT

[^{18}F]-FDG-PET

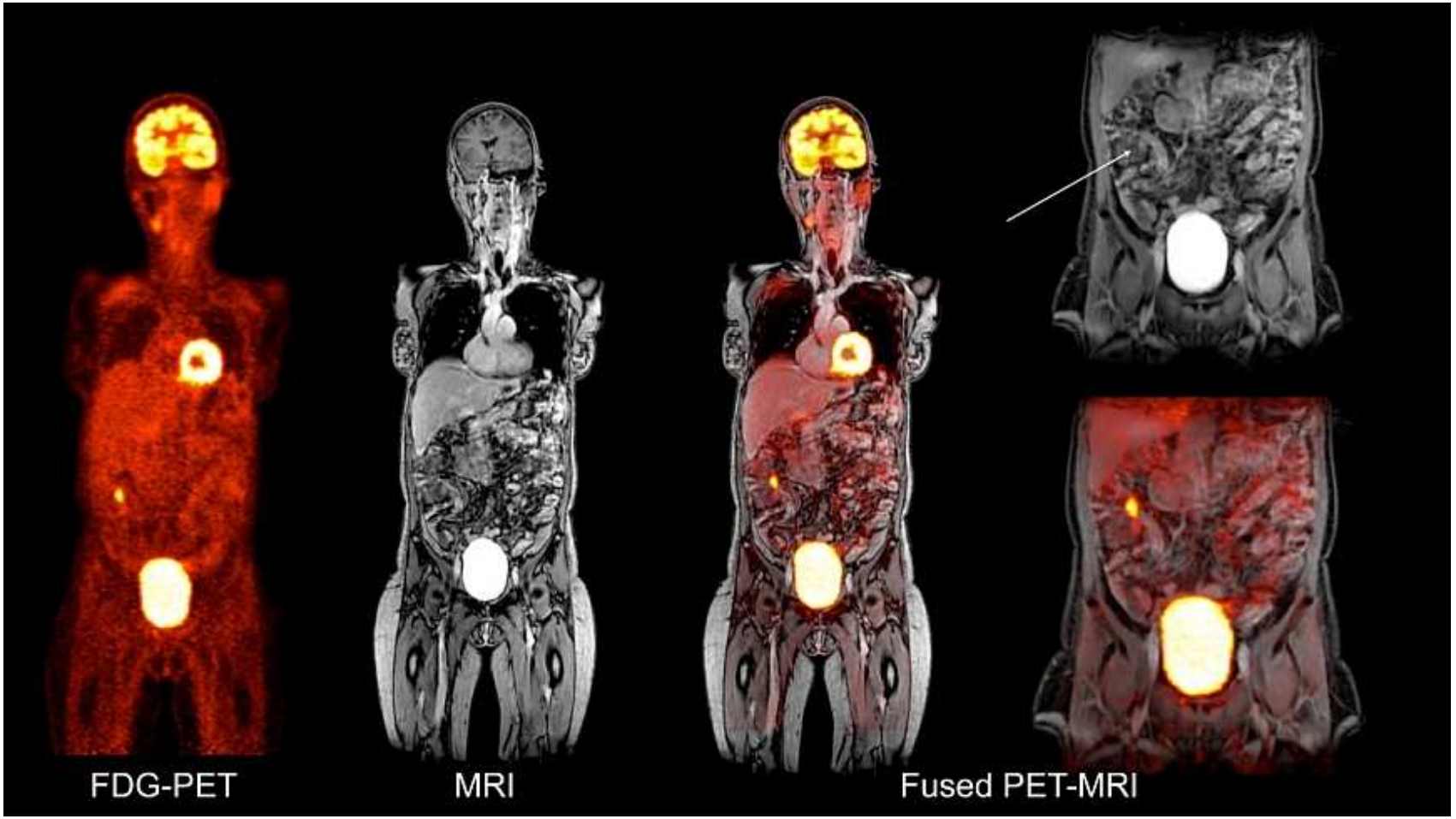


^{99m}Tc-MDP-SPECT



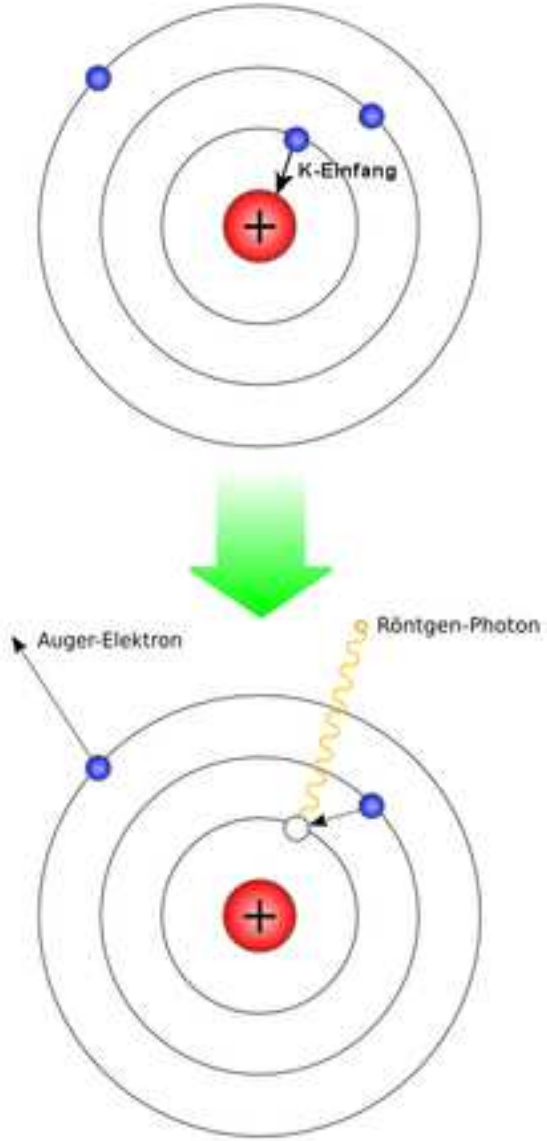
Fused images

- **localization in tissues – combined techniques with CT or MRI**
- **fused images – PET/CT, PET/MRI, SPECT/CT, SPECT/MRI**
- **multimodal contrast agents**



Radiotherapy

- **Leksell gamma knife**
  - **focuses the radiation from external sources into tumour**
- **internal sources of radiation**
  - **short and defined radius of particles in tissue**
  - **α-emitters**
  - **β^--emitters**
  - **γ-emitters with low energy**
  - **emission of Auger electrons (EC isotopes)**
- **selective deposition in tumors – half-lives in hours**



Radiotherapy

Isotope	Decay	Half-life	Source	Mean range in tissue
^{64}Cu	β^-	12.8 h	cyclotron, ^{64}Ni(p,n)^{64}Cu	0.2 mm
^{67}Cu	β^-	62 h	cyclotron, ^{67}Zn(n,p)^{67}Cu	
^{67}Ga	Auger	3.26 d	cyclotron	
^{89}Sr	β^-	50.5 d	reactor	
^{90}Y	β^-	64 h	generator, ^{90}Sr(β^-)^{90}Y	3.9 mm
^{111}Ag	β^-	179 h	cyclotron	1.1 mm
^{149}Pm	β^-	2.2 d	reactor	
^{153}Sm	β^-	1.9 d	reactor	
^{161}Tb	β^-	166 h	reactor	0.3 mm
^{166}Ho	β^-	1.1 d	reactor	
^{177}Lu	β^-	6.7 d	reactor	
^{186}Re	β^-	90 h	reactor	1.1 mm
^{188}Re	β^-	17 h	generator, ^{188}W(β^-)^{188}Re	3.3 mm
^{212}Pb	β^-/α	10.6 h/1.01h	reactor	0.1 mm

Radiotherapy

Isotope	Half-life	Decay mode	$\bar{E}_\beta$ [MeV] (%)	E_γ [keV] (%)
^{47}Sc	3.35 days	β^-, γ	0.14 (68), 0.20 (32)	159 (68)
^{67}Cu	2.58 days	β^-, γ	0.19 (20), 0.12 (57)	93 (16), 185 (49)
^{90}Y	2.67 days	β^-	0.93 (100)	–
^{111}Ag	7.45 days	β^-, γ	0.36 (93)	342 (6.7)
^{198}Au	2.7 days	β^-, γ	0.31 (99)	412 (95)
^{199}Au	3.1 days	β^-, γ	0.13 (15), 0.08 (66)	158 (37)
^{212}Bi	1.0 h	α	6.1 (25) (α)	727 (12)
		β^-, γ	0.83 (48) (β^-)	
^{213}Bi	46 min	α, γ	5.8 (2) (α), 0.49 (65) (α), 0.32 (32) (α)	440 (27)
^{225}Ac	10 days	α	5.83 (51) (α)	100 (3.5)
Lanthanides				
^{149}Pm	2.21 days	β^-, γ	0.37 (97)	286 (2.9)
^{153}Sm	1.95 days	β^-, γ	0.23 (43), 0,20 (35)	103 (28)
^{166}Dy	3.40 days	β^-, γ	0.12 (91)	82.5 (13)
^{166}Ho	1.12 days	β^-, γ	0.69 (51), 0.65 (48)	80.6 (6.2)
^{177}Lu	6.71 days	β^-, γ	0.15 (79)	208 (11)

Common criteria for radiopharmaceuticals

- Selected molecule must be **amenable to radiolabelling**. Reaction must provide sufficient radiochemical yield, specific activity and must proceed in appropriate time, that means maximally 4, ideally less than 3 half-lives of radioisotope – also depends on half-life itself. Reaction must proceed under reasonable conditions because of automation of procedure in the case of clinical production. Procedure including yield must be reliable and reproducible.

- **Biodistribution** of a radiopharmaceutical must be related to the physiological response to enable measuring functionality of biochemical process under investigation.

- **High affinity** to the target leading to high contrast of a PET image. Interaction between radiopharmaceutical and biomolecules in target tissue must be the major mechanism. Also high specificity for target molecule is essential because interaction with similar targets leads to interference with desired radioactive signal detected by a PET camera.

- The **lipophilicity** (defined as usual partition coefficient between *n*-octanol and water – *log P*) that determines ability to cross cell membranes.
- Optimal passage of lipid bilayers requires *log P* ~ 1.5 – 2. Higher *log P* values result in nonspecific binding caused by hydrophobic interactions with lipids and proteins.

- Certain properties as **passage across the cell membrane** or other barriers like blood brain barrier (BBB). Besides mentioned lipophilicity, also active transport of compounds must be taken in account, e.g. dopamine, serotonin and amino acids.

Common criteria for radiopharmaceuticals

In general, a **low affinity to P-glycoprotein** (P-gp) is a desirable property for most radiopharmaceuticals. P-gp is an ATP-dependent efflux pump naturally expressed in BBB. It can be over-expressed in tumours. P-gp transports compounds that have high affinity for the pump out of the cell and then radiotracers that have high affinity for P-gp show little accumulation in tissues like brain and tumour.

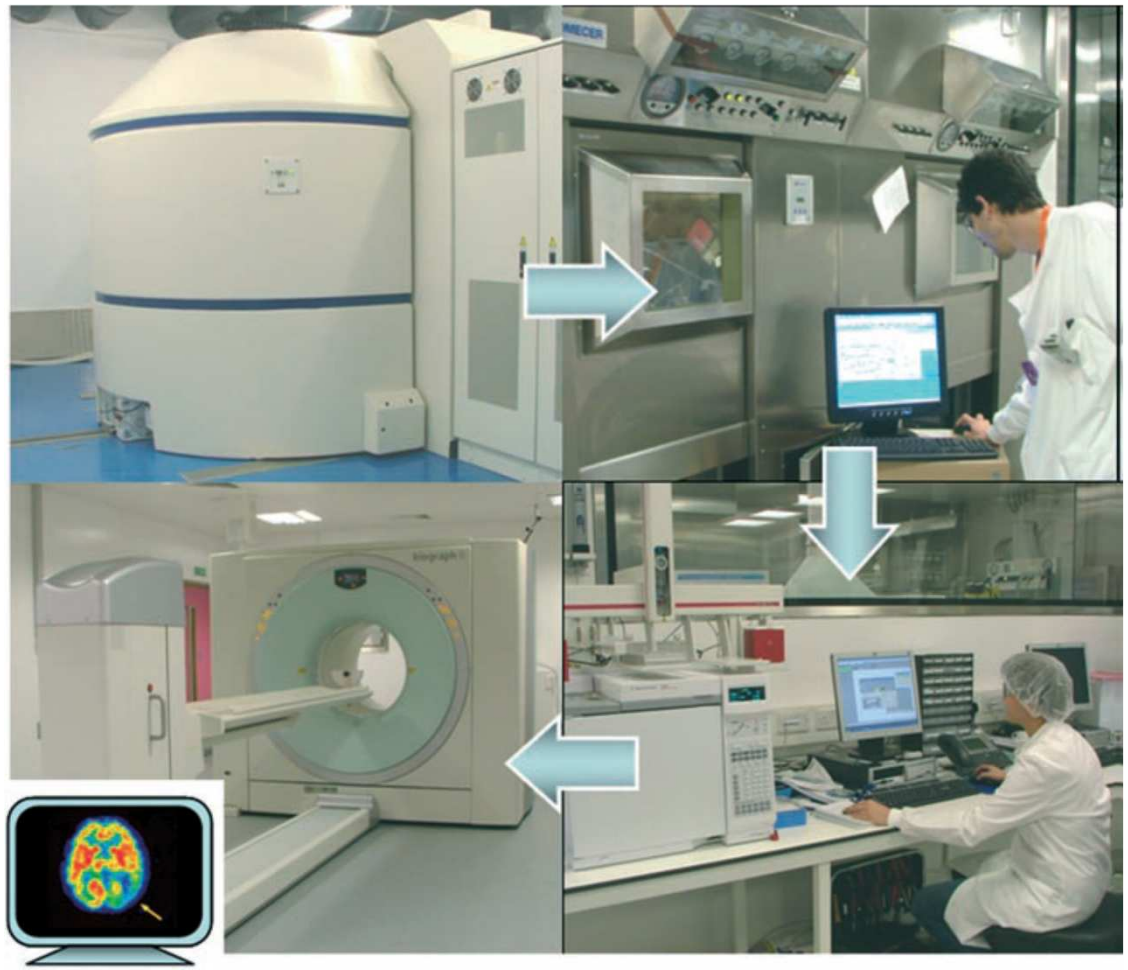
Metabolism of a radiopharmaceutical is a very important point. Rapid metabolism is generally undesirable. Metabolites can then bind to other molecules or take part in other metabolic processes and result in non-specific accumulation of radioactivity. It is preferable to have the radioisotope in the part of molecule which reaches the target at first and after that is further metabolised. In some cases, metabolism of radiotracer is the mechanism underlying the accumulation of radioactivity in tissue.

Clearance of non-specifically bound radioactivity by the time of measurement PET must be discriminated. This is relevant mainly for labelled macromolecules that slowly diffuse into cells and only small portion is bound to the target of interest. The unbound radiolabelled molecules must leave the cells again and be cleared from the circulation.

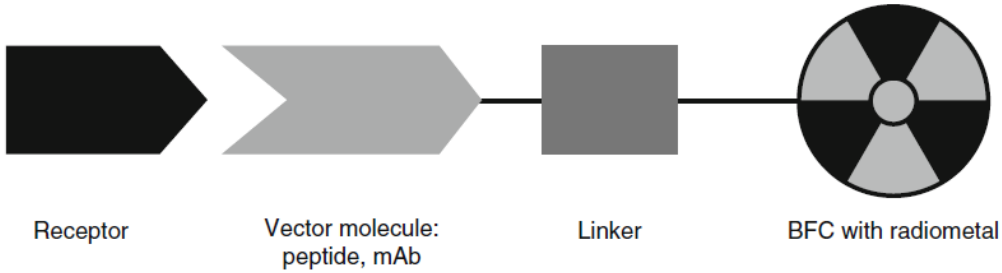
Mutagenicity and toxicity, despite the radiophramaceutical is prepared under non-carrier added (NCA) conditions and small mass is administrated to the patient, must be tested. This differs in different countries according to the law. Usually toxicity tests on rodent species and Ames test for mutagenicity are performed at dosages much higher than those applied in PET studies.

Preparation and administration

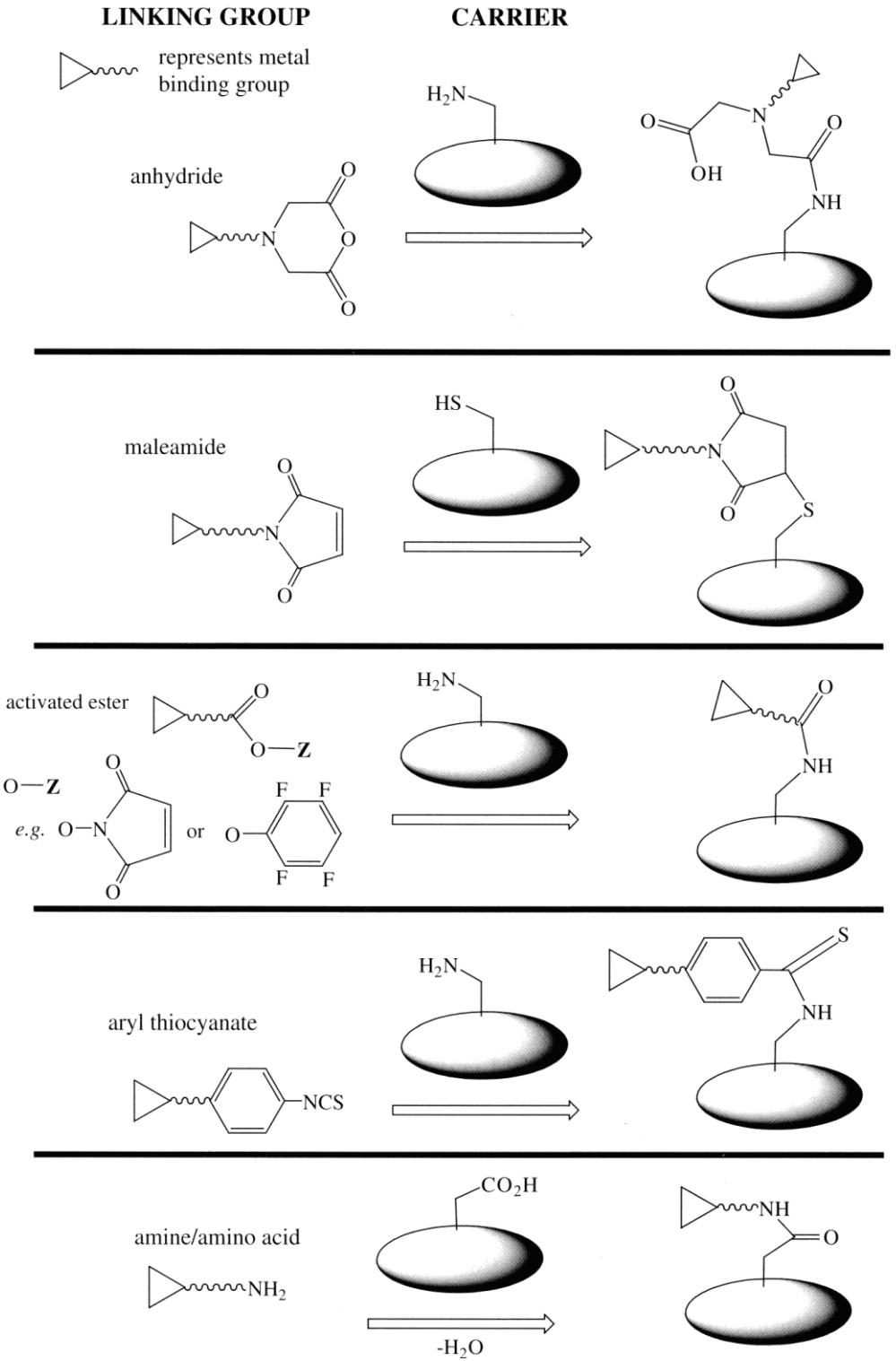
RCY – RadioChemical Yield
CA – Carrier Added
NCA – Non-Carrier Added



Targeting

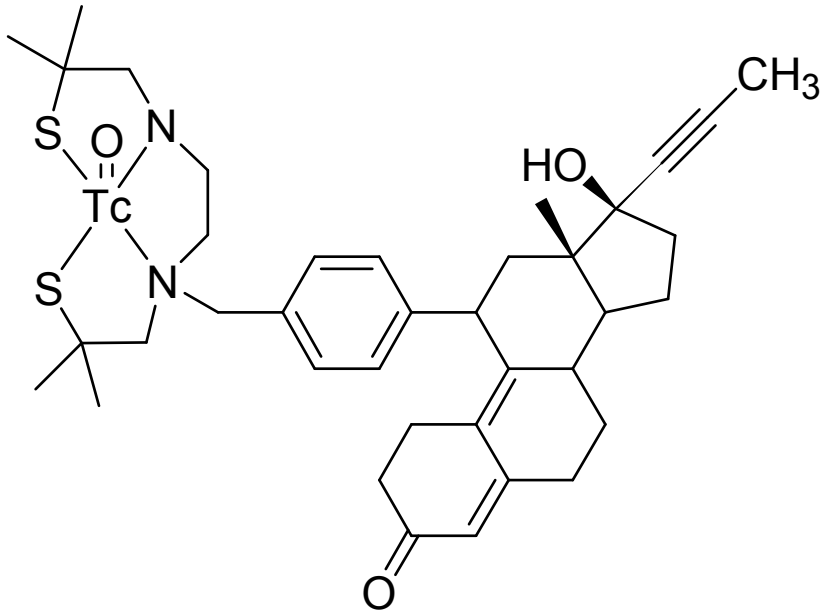


- vector – selectivity for imaged tissue: peptide, oligosacharide, etc.
- chemically sensitive – labelling at mild conditions

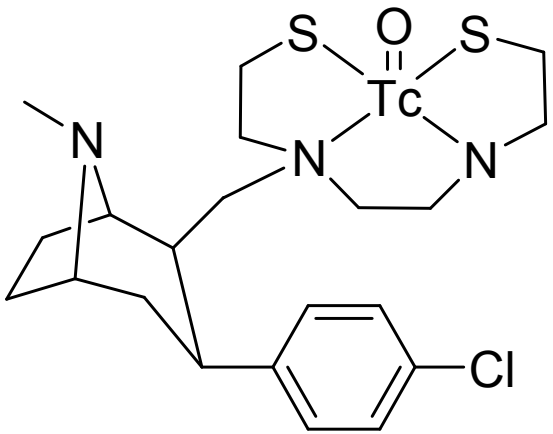


Targeting

- include a biologically active molecule covalently linked to the complex
- e.g.



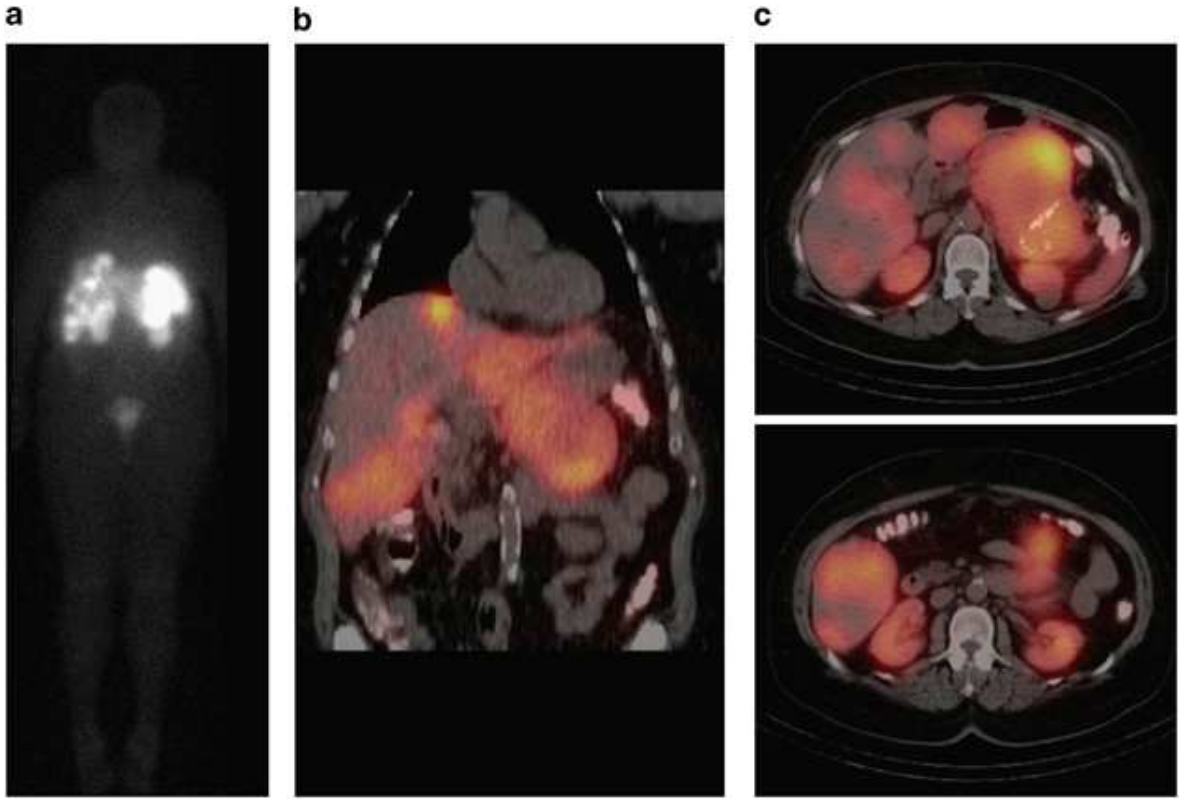
Progesterone receptor analogues
(prostate cancer)

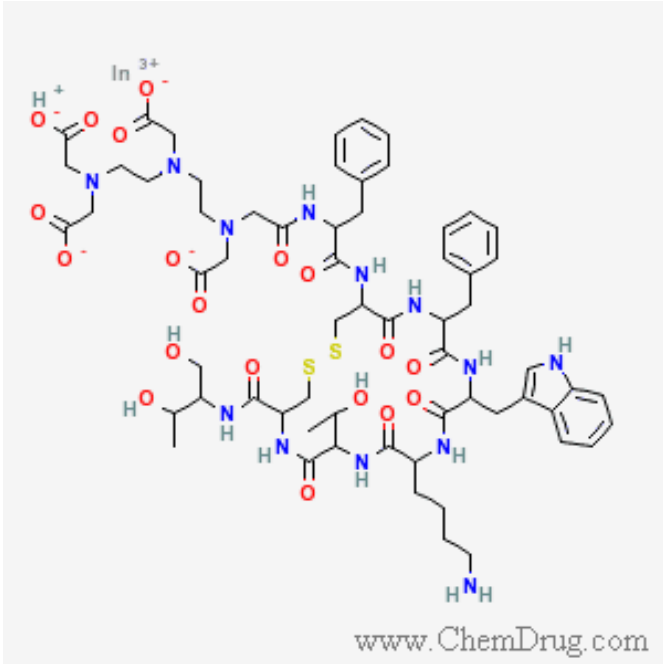


Cocaine analogues
(CNS diseases)

Targeting

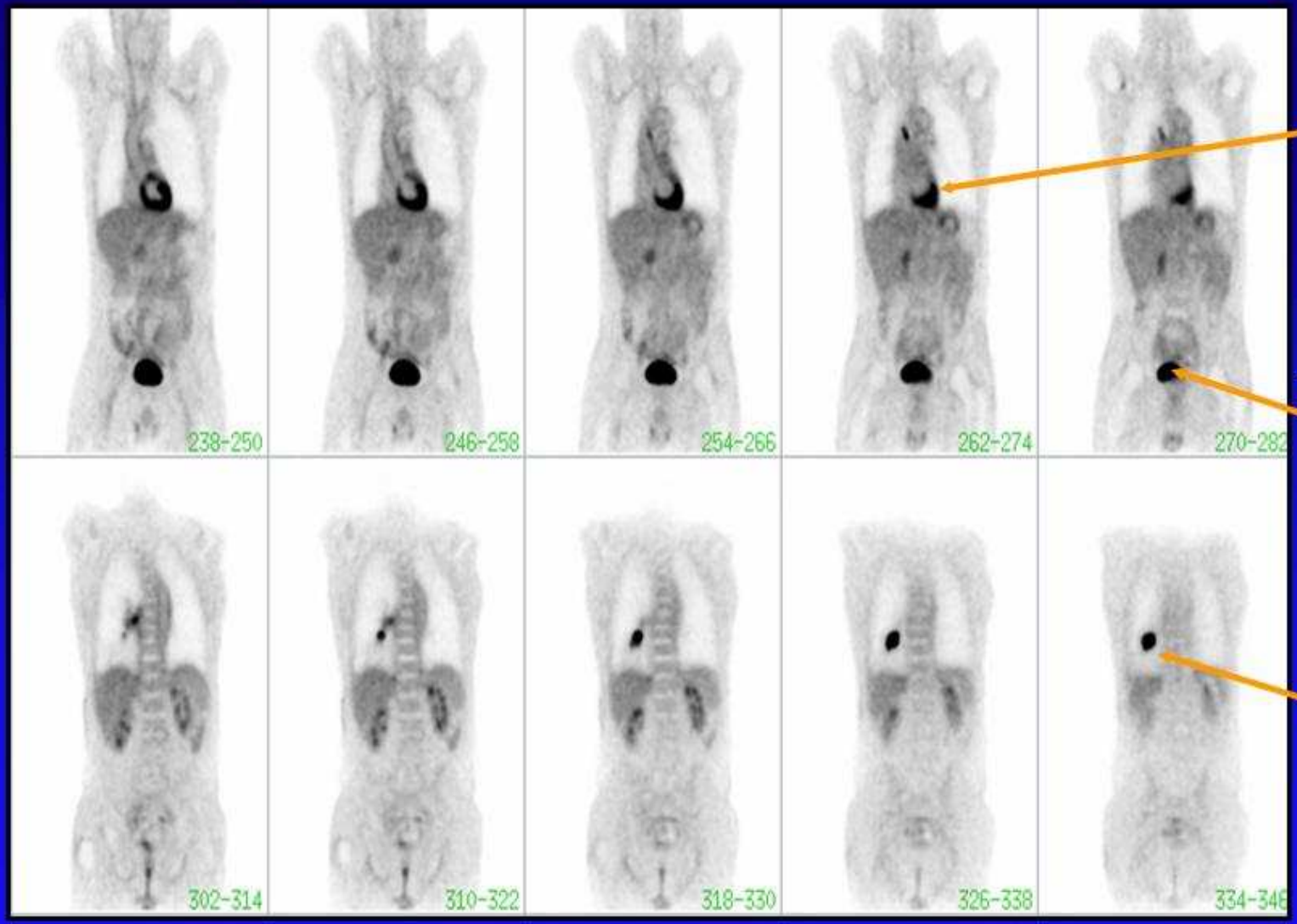
Octreoscan – ^{111}In –DTPA-Octreotide





Octreoscan imaging for neuroendocrine tumors.
a) Coronal octreoscan image demonstrating radiotracer uptake in multiple liver metastases and a large pancreatic primary neuroendocrine carcinoma.
(b) Coronal octreoscan fusion images with single photon emission tomography (SPECT) providing increased anatomic detail.
(c) Axial octreoscan fusion images with SPECT.

PET Scan: An Example



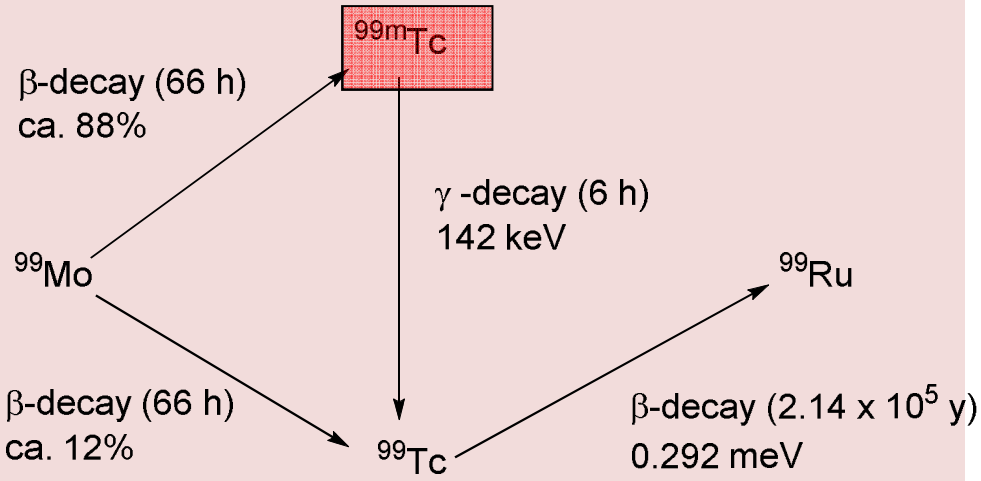
Heart activity (normal)

Tracer in bladder (normal)

Lung Cancer (abnormal)

Technetium ^{99m}Tc

- predicted by Mendeleev
- first isolated 1938
- 20 isotopes (7 relatively stable)
- used extensively (>90% of all diagnostic nuclear medicine)
- $t_{1/2}$ = 6 h
- γ-ray emission energy of 141 keV
- versatile coordination chemistry
- multiple oxidation states
- easily generated from ^{99}Mo ($t_{1/2}$ = 66 h)



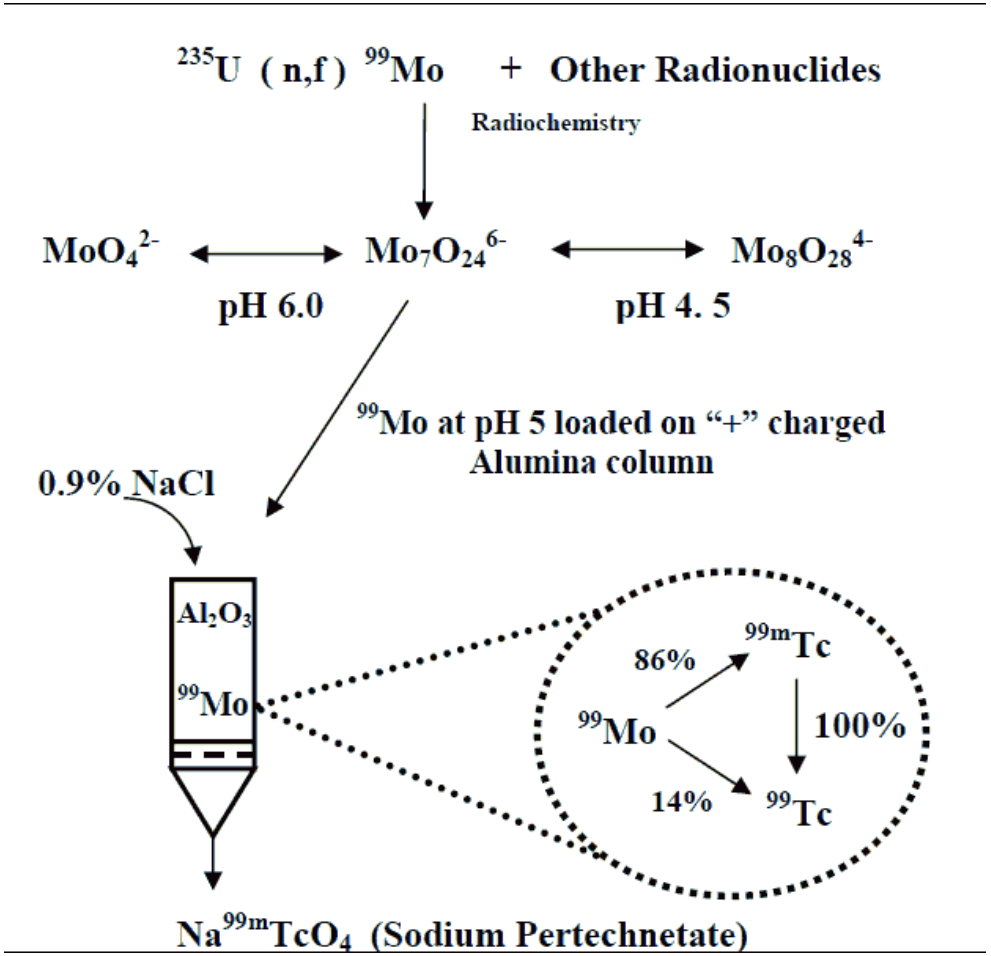
Rhenium

- ^{186}Re, $t_{1/2}$ = 90 h, available from reactor
- ^{188}Re, $t_{1/2}$ = 17 h, available from ^{188}W(β$^-$)^{188}Re generator
- chemical properties similar to Terchnetium: diagnostic/therapeutic isotop-pair

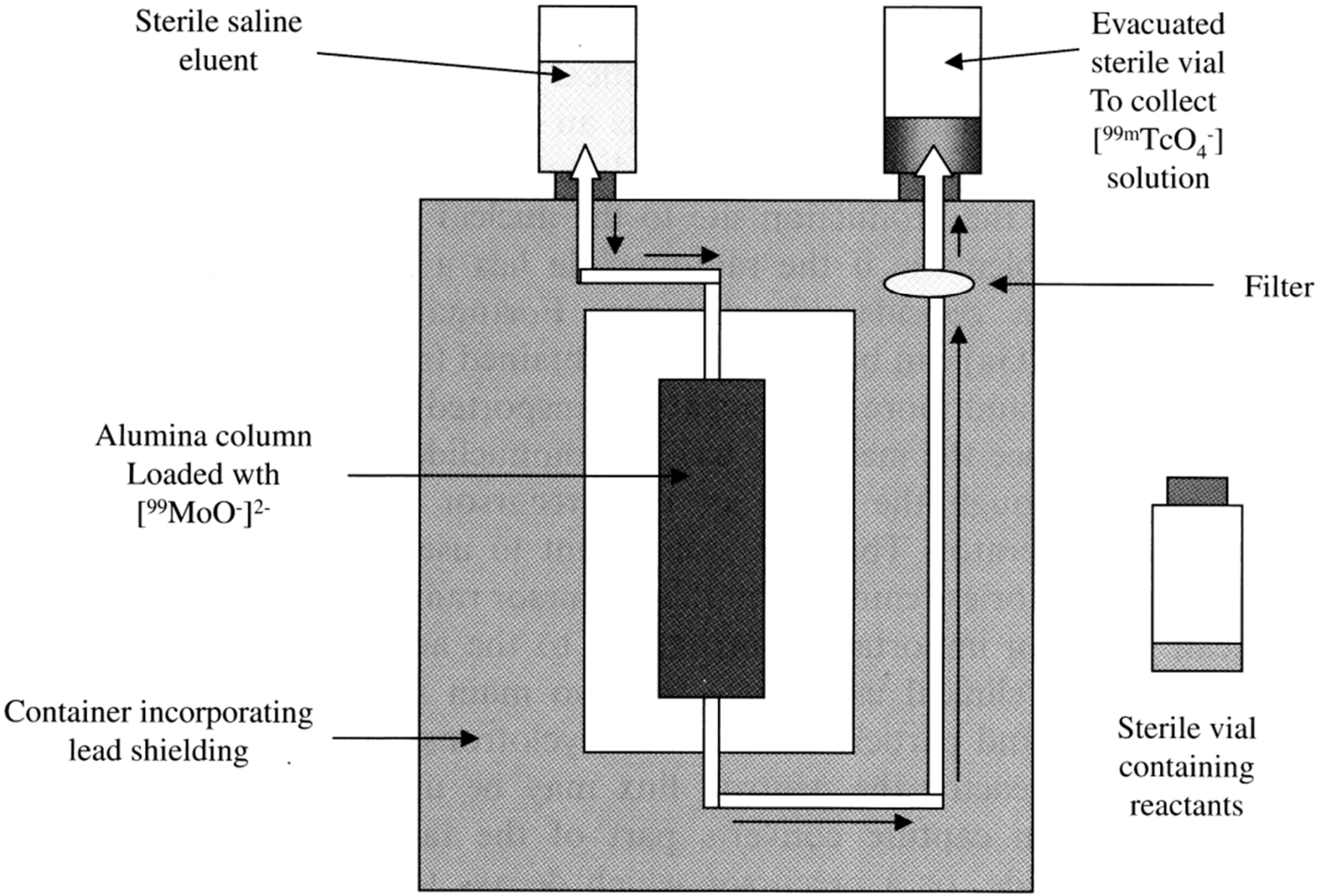
Technetium ^{99m}Tc

^{99}Mo/^{99m}Tc Generator

- patented in 1958
- fission-produced ^{99}Mo is processed and purified to anionic molybdate
- loading on the positively charged alumina (Al_2O_3) column

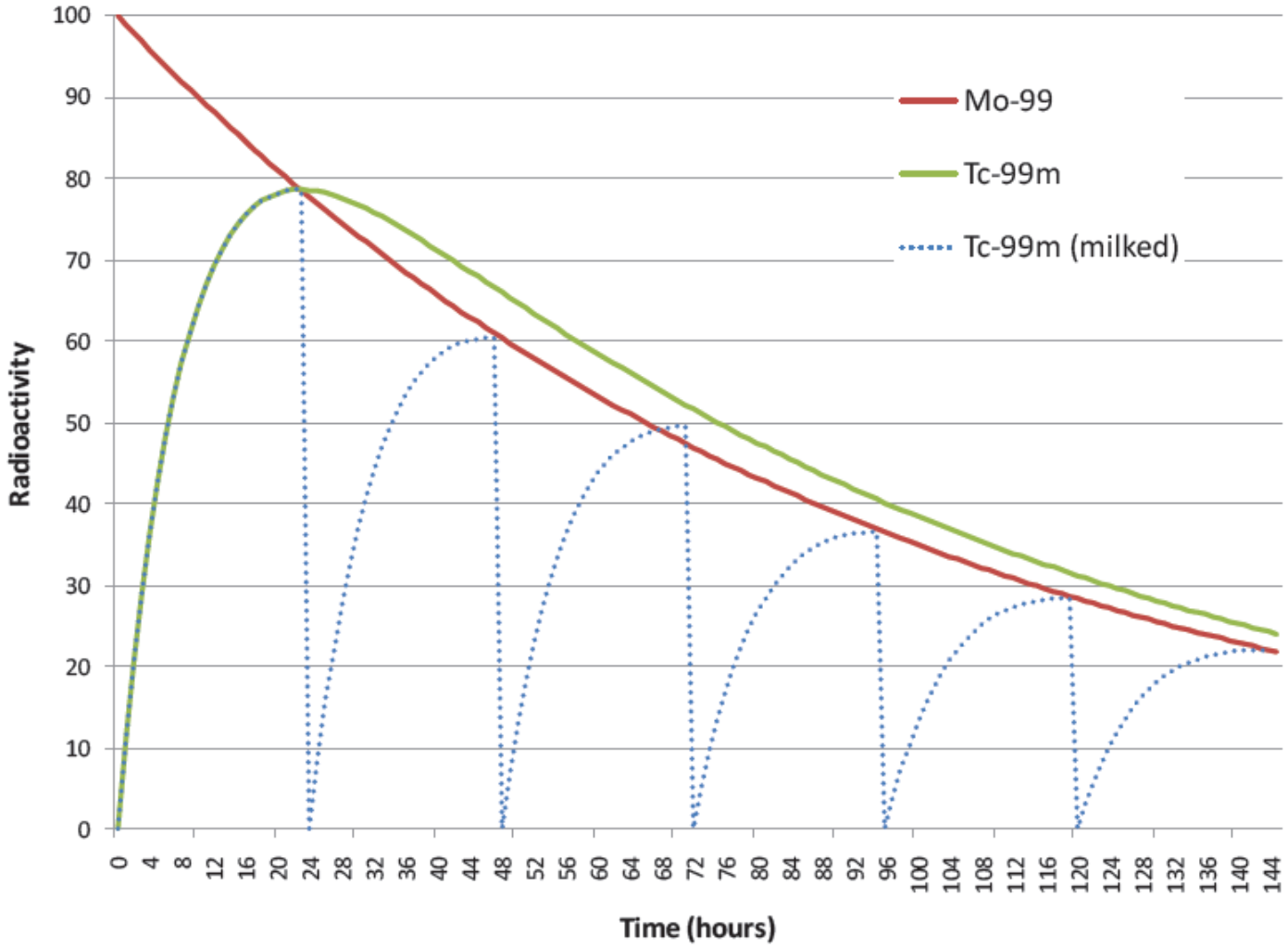


Technetium ^{99m}Tc



Radionuklidový generátor

Technetium ^{99m}Tc



Počty elucí z generátoru

^{99m}Tc

Technetium ^{99m}Tc

Chemistry

- TcO_4^- most stable oxidation state, produced in generator, can not be complexed
- insoluble TcO_2
- reduction with ascorbic acid, $FeCl_2$, $NaBH_4$, $Na_2S_2O_4$, **$SnCl_2$**
  - oxidation states IV, V – oxocation technecyl
    (disproportionation V → IV + VII)
  - oxidation states I, II, III (oxidation → IV)
- stabilization of oxidation states with ligands

Technetium kit

- reducing agent
- coordinating ligand
- antioxidants
- buffers
- lyophilized and sealed under inert atmosphere

Technetium ^{99m}Tc

Pharmacology

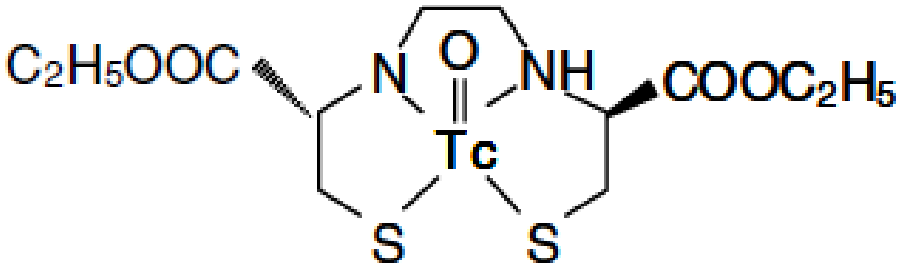
- bio-distribution and targeting depends much on size and charge:
  - neutral – brain
  - cationic – hart
  - anionic – bones and kidney
- so called technetium essential or first generation agent
- targeting of other organs requires designer ligands:
  - must traverse the blood brain barrier
  - moderately lipophilic
  - neutral charge

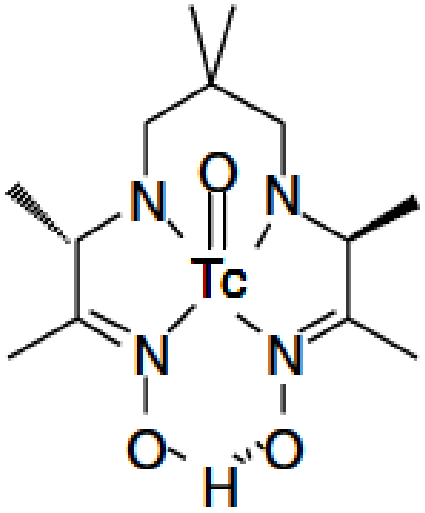
Technetium ^{99m}Tc

Neutral complexes

– brain imaging

– oxidation states IV, V

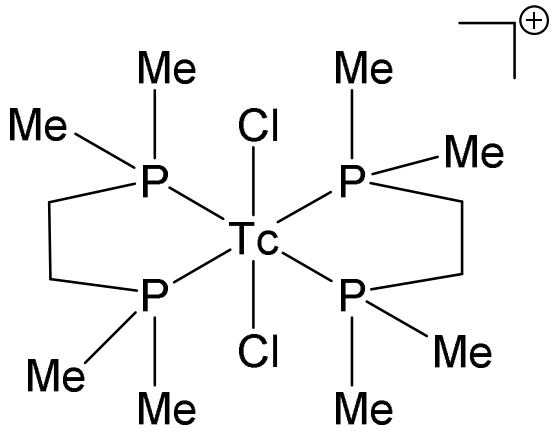




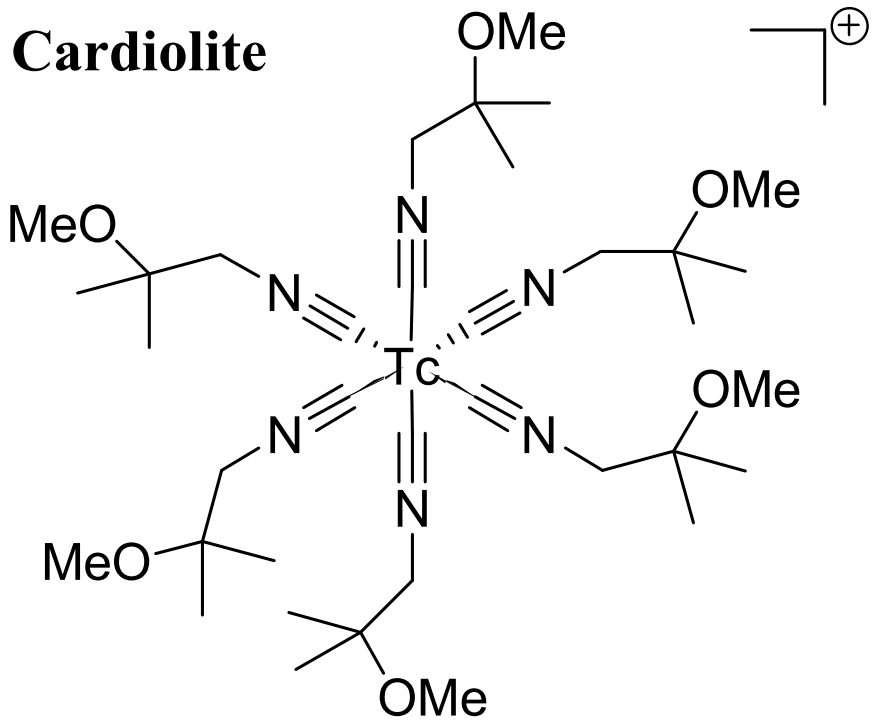
Technetium ^{99m}Tc

Cationic complexes

- hart imaging
- uptake via Na-K ATPase pump as K^+ mimics



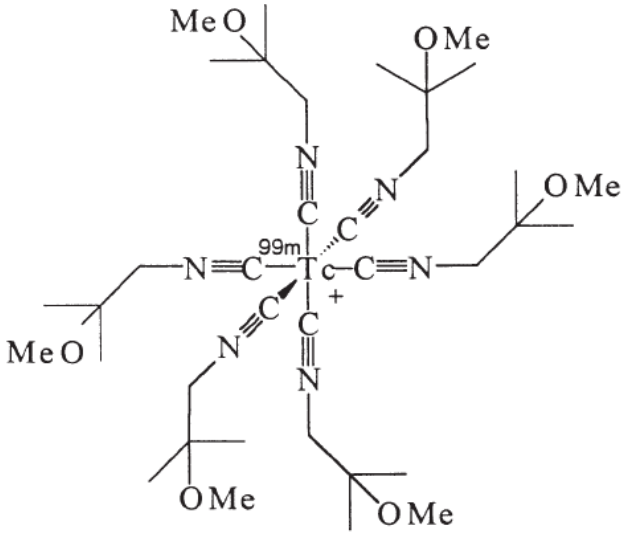
Cardiolite



Technetium ^{99m}Tc

SCAN RESULTS (at stress)	Annualized Risk of Cardiac Events	Potential Treatment Implications**
Normal	<1% risk of both MI and cardiac death[1,6]	Risk factor modification in addition to current regimen[14]
Mildly Abnormal	Low risk of cardiac death; intermediate risk of MI[13]	• Aggressive risk factor modification[1,4] • Medical treatment[3]
Moderately to Severely Abnormal	Intermediate-to-high risk of both MI and cardiac death[7,15]	• Aggressive RFM[14] • Medical treatment[14] • Catheterization — dependent on severity of scan[14]

Scans contributed by Howard Lewin, MD, of Cardiac Imaging Associations



Cardiolite

Each 5 mL vial contains a sterile, non-pyrogenic, lyophilized mixture of:

- Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate – 1.0 mg
- Sodium Citrate Dihydrate – 2.6 mg
- L-Cysteine Hydrochloride Monohydrate – 1.0 mg
- Mannitol – 20 mg
- Stannous Chloride, Dihydrate, minimum ($SnCl_2 \cdot 2H_2O$) – 0.025 mg

Prior to lyophilization the pH is 5.3 to 5.9. The contents of the vial are lyophilized and stored under nitrogen.

This drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate ^{99m}Tc Injection. The pH of the reconstituted product is 5.5 (5.0 - 6.0). No bacteriostatic preservative is present.

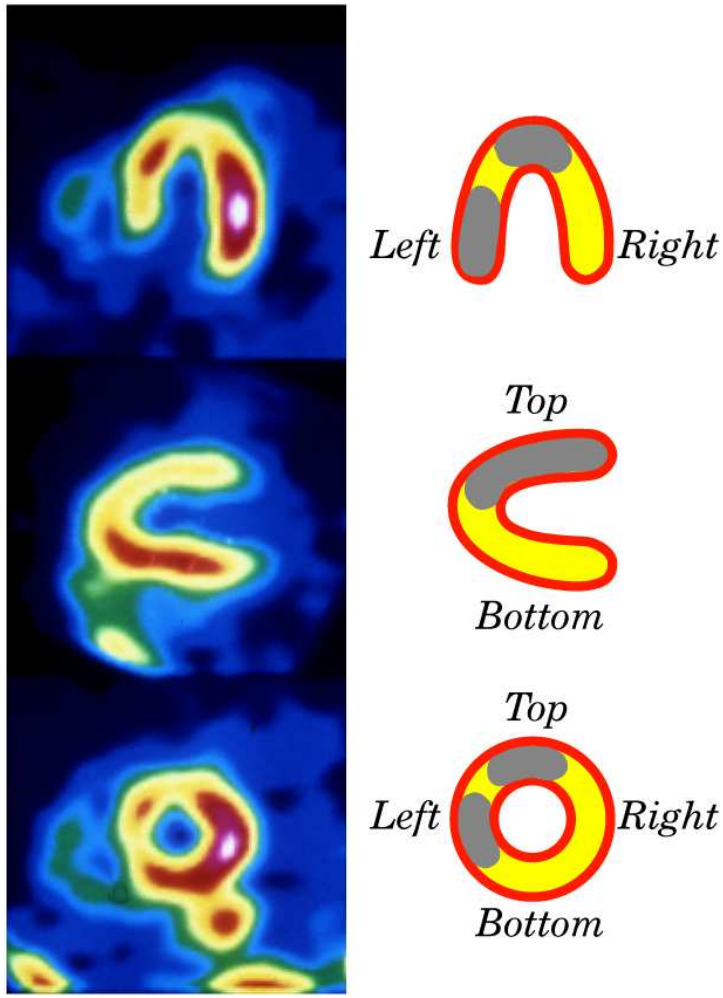
The precise structure of the technetium complex is $^{99m}Tc[MIBI]^{6+}$ where MIBI is 2-methoxy isobutyl isonitrile.

Over 40 million people have received cardiac scans using Cardiolite.

Technetium ^{99m}Tc

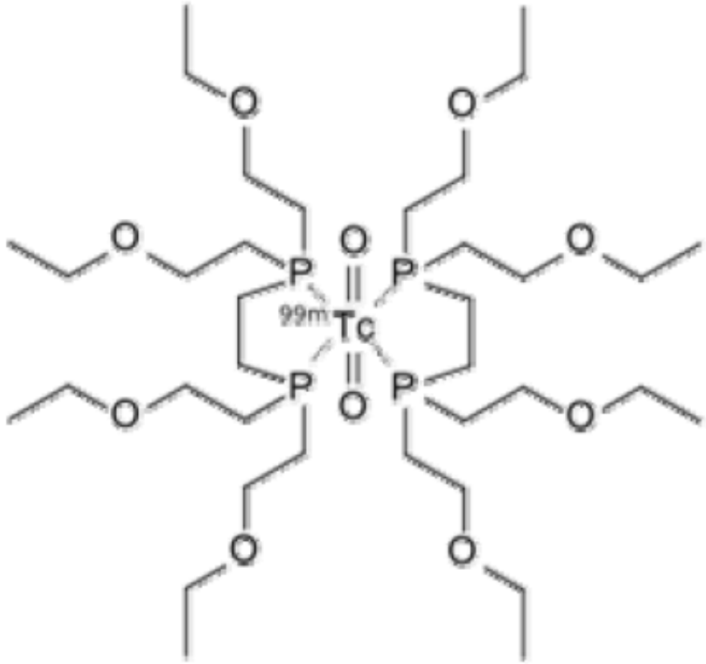
Scans of a human heart under stress taken with the ^{99m}Tc-based imaging agent Myoview™

Area with inadequate blood supply give less intense signals (the grey areas on the idealised images)



Heart scans courtesy of Amersham plc

Imaging agents in action

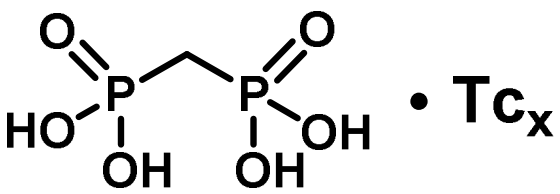


Myoview = tetrofosmin

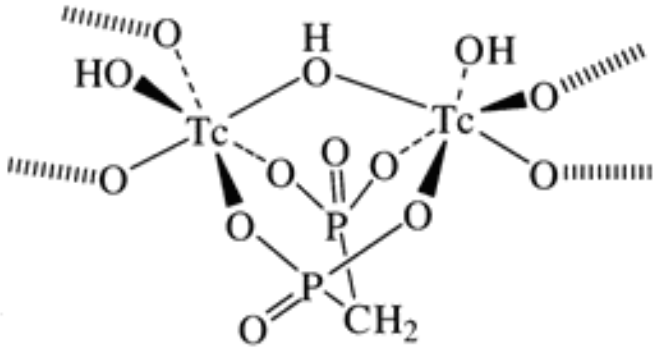
Technetium ^{99m}Tc

Bone imaging

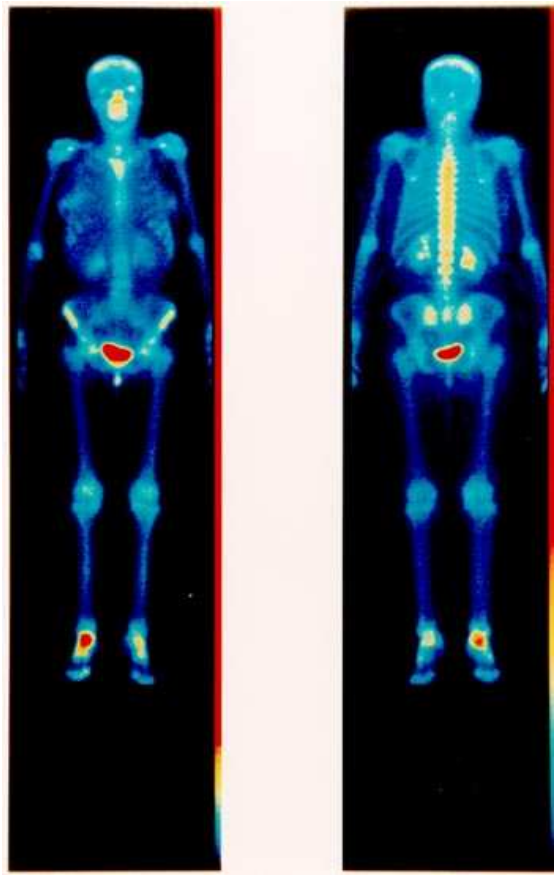
- hydroxyapatite principal mineral component of bones $Ca_{10}(PO_4)_6(OH)_2$
- phosphate (PO_4^{3-}) and pyrophosphate ($P_2O_7^{2-}$) bone seeking anions
- diphosphonates give improved performance



• Tc_x



- absorption via calcium coordination to phosphonate
- stressed bone has higher calcium concentration
- main use to detect cancer metastasis into bone



arthritic right ankle

Carbon ^{11}C

- half-life 20.40 min
- decay mode: 99.8 % β^+, 0.2 % EC
- max β^+ energy: 0.96 MeV
- range in tissue: 0.96 mm
- decay product: ^{11}B

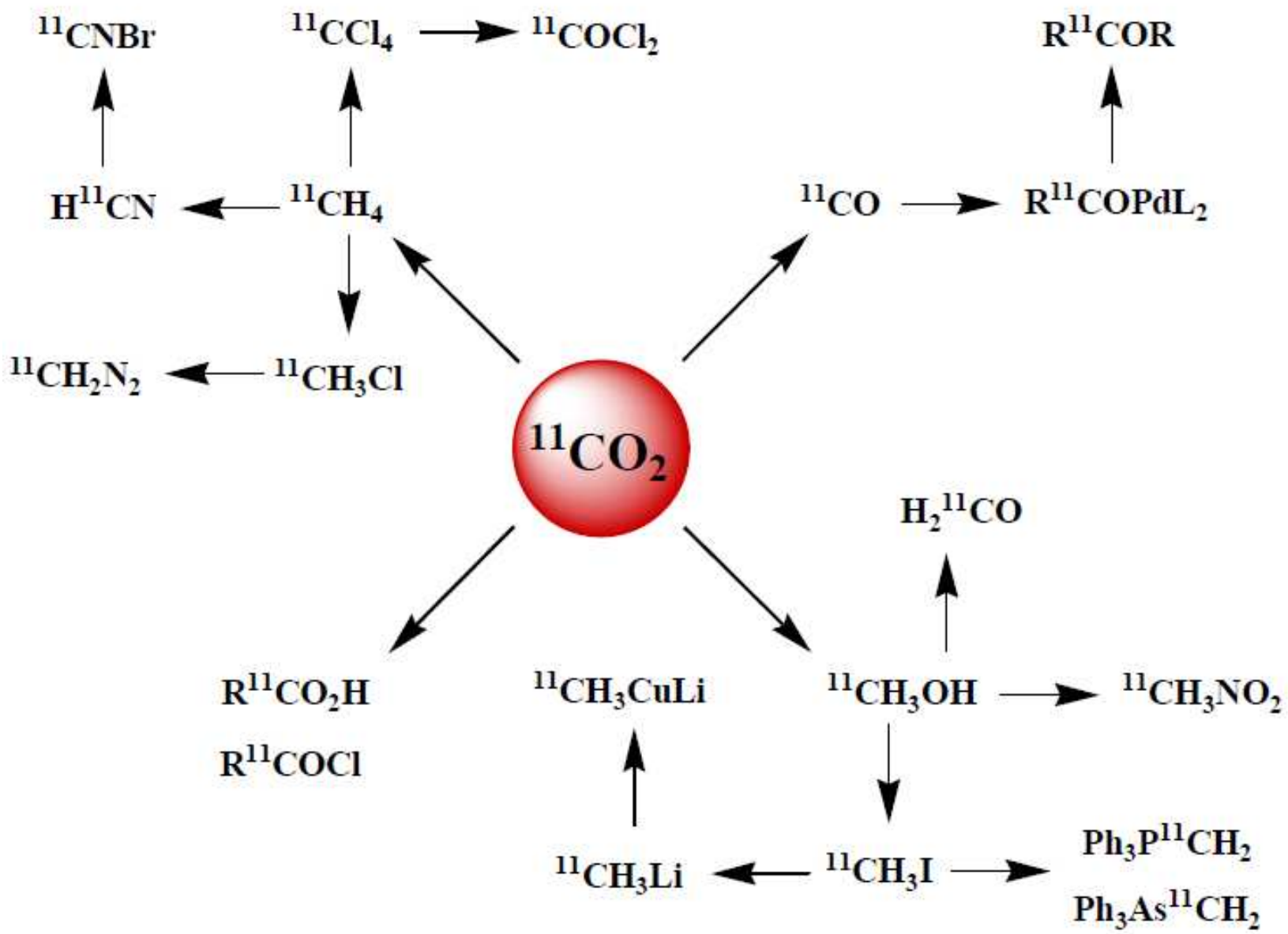
Production

- cyclotron-generated: mainly produced by the proton bombardment of ^{14}N
- $^{14}N(p,\alpha)^{11}C$ nuclear reaction
- target gas:

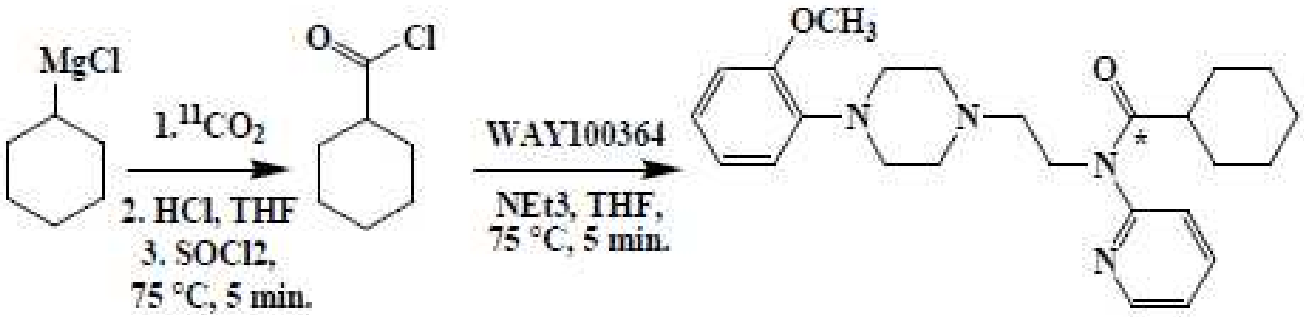
  2% O_2 in N_2 → $^{11}CO_2$

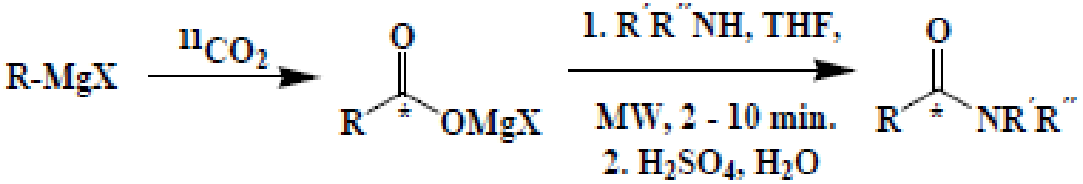
  5% H_2 in N_2 → $^{11}CH_4$

Carbon ^{11}C

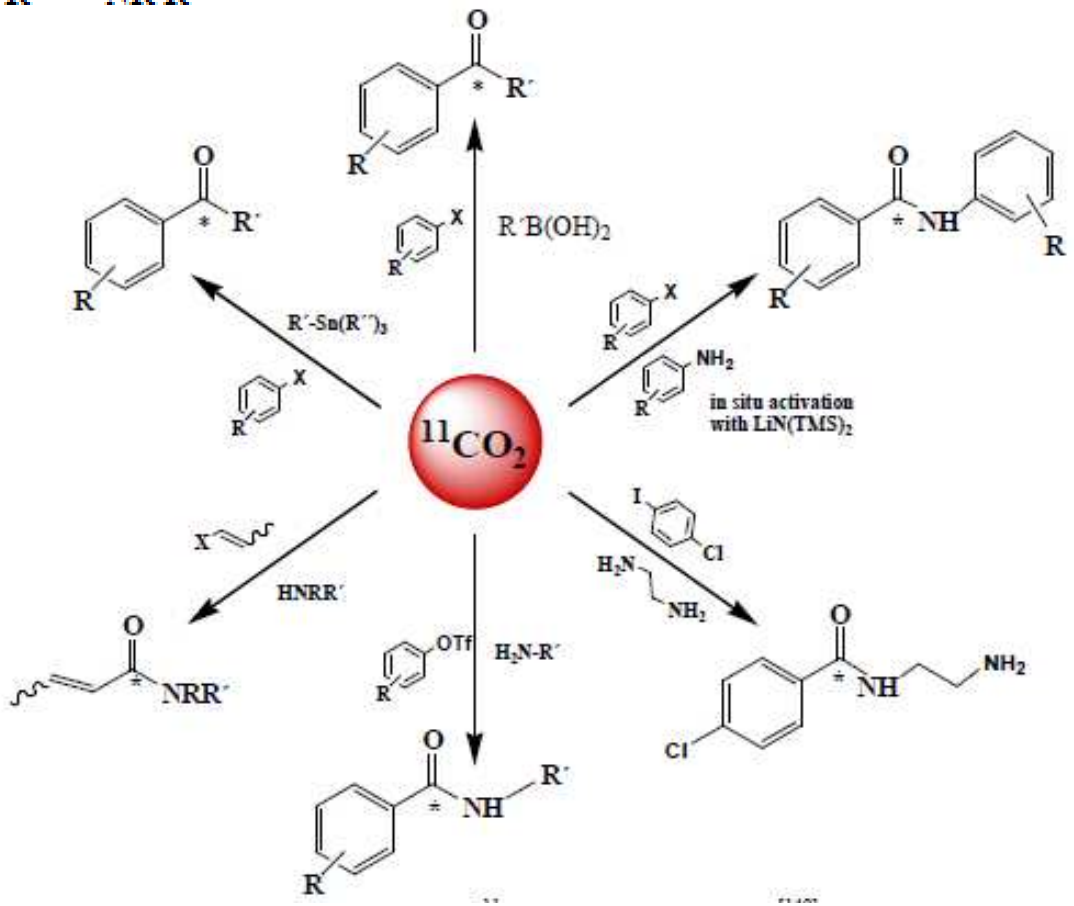

$^{11}CNBr$
$^{11}CCl_4$
$^{11}COCl_2$
$R^{11}COR$
$H^{11}CN$
$^{11}CH_4$
^{11}CO
$R^{11}COPdL_2$
$^{11}CH_2N_2$
$^{11}CH_3Cl$
$^{11}CO_2$
$H_2{}^{11}CO$
$R^{11}CO_2H$
$R^{11}COCl$
$^{11}CH_3CuLi$
$^{11}CH_3OH$
$^{11}CH_3NO_2$
$^{11}CH_3Li$
$^{11}CH_3I$
$Ph_3P^{11}CH_2$
$Ph_3As^{11}CH_2$

Carbon ^{11}C





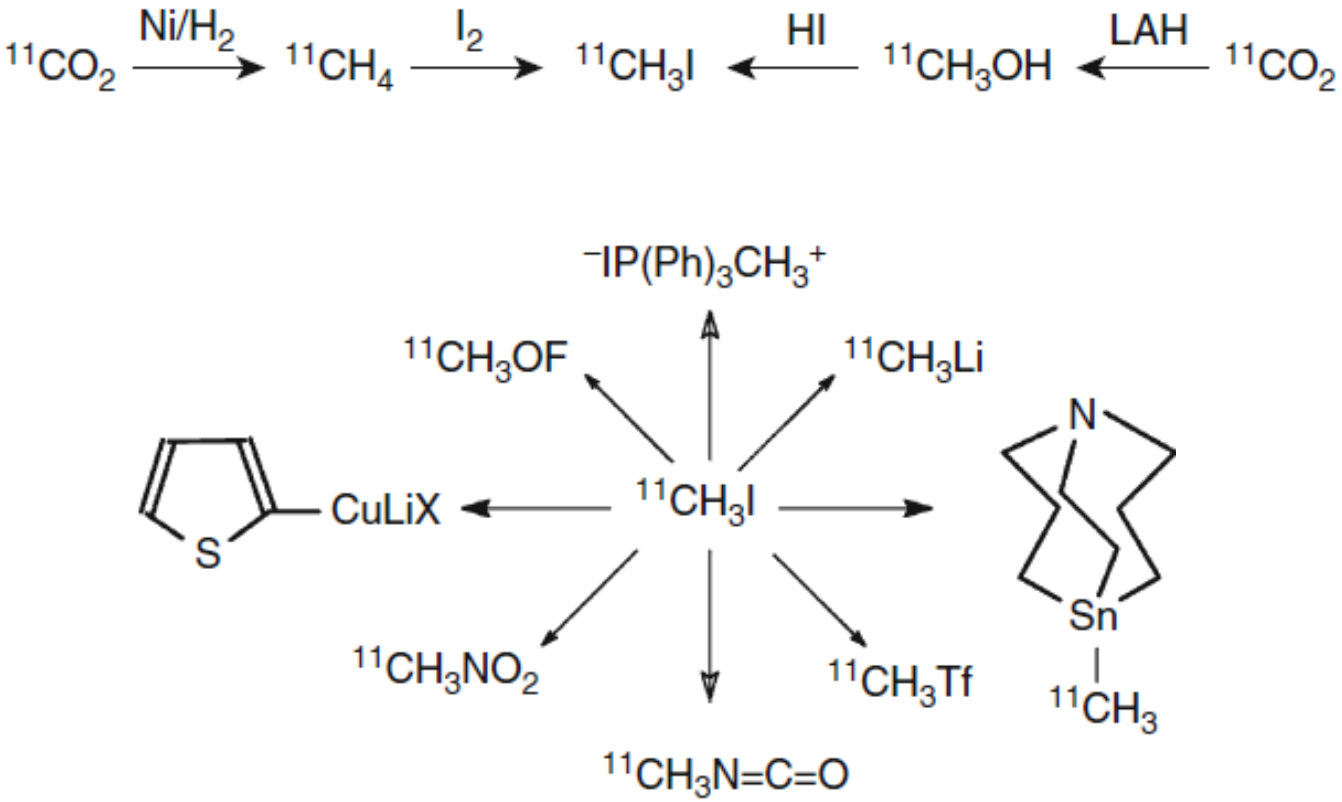
Palladium mediated reactions



Carbon ^{11}C

$^{11}CH_3I$

- methylation of N –, O –, S – compounds



Carbon ^{11}C

Synthesis of [^{11}C]alkyl halides

$$^{11}CO_2 \xrightarrow[2.\ LAH\ \ 3.\ HI]{1.\ RMgBr} R^{11}CH_2I$$

Synthesis of 1,2-[^{11}C]dibromoethane

$$^{11}CO_2 \xrightarrow[2.\ LAH\ \ 3.\ H_2O]{1.\ CH_3MgBr} CH_3{}^{11}CH_2OH \xrightarrow[Heat]{Quartz}$$

$$^{11}CH_2{=}CH_2 \xrightarrow{Br_2/CCl_4} Br^{11}CH_2CH_2Br$$

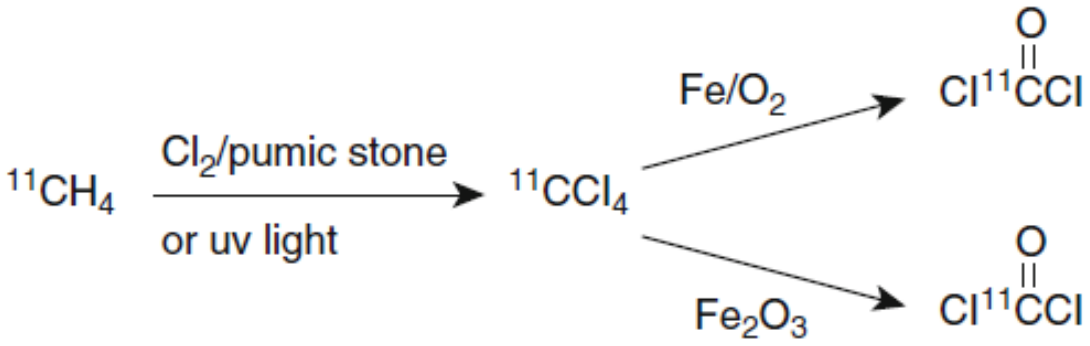
Synthesis of [^{11}C]nitroalkanes

$$R^{11}CH_2I \xrightarrow{AgNO_2} R^{11}CH_2NO_2$$

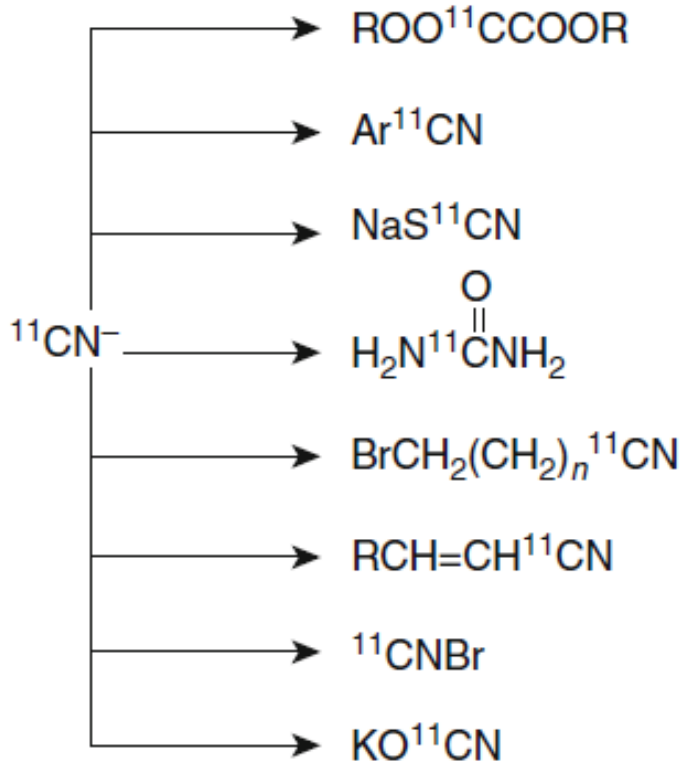
R=H, CH_3, CH_3CH_2

Carbon ^{11}C

Synthesis of [^{11}C]phosgene

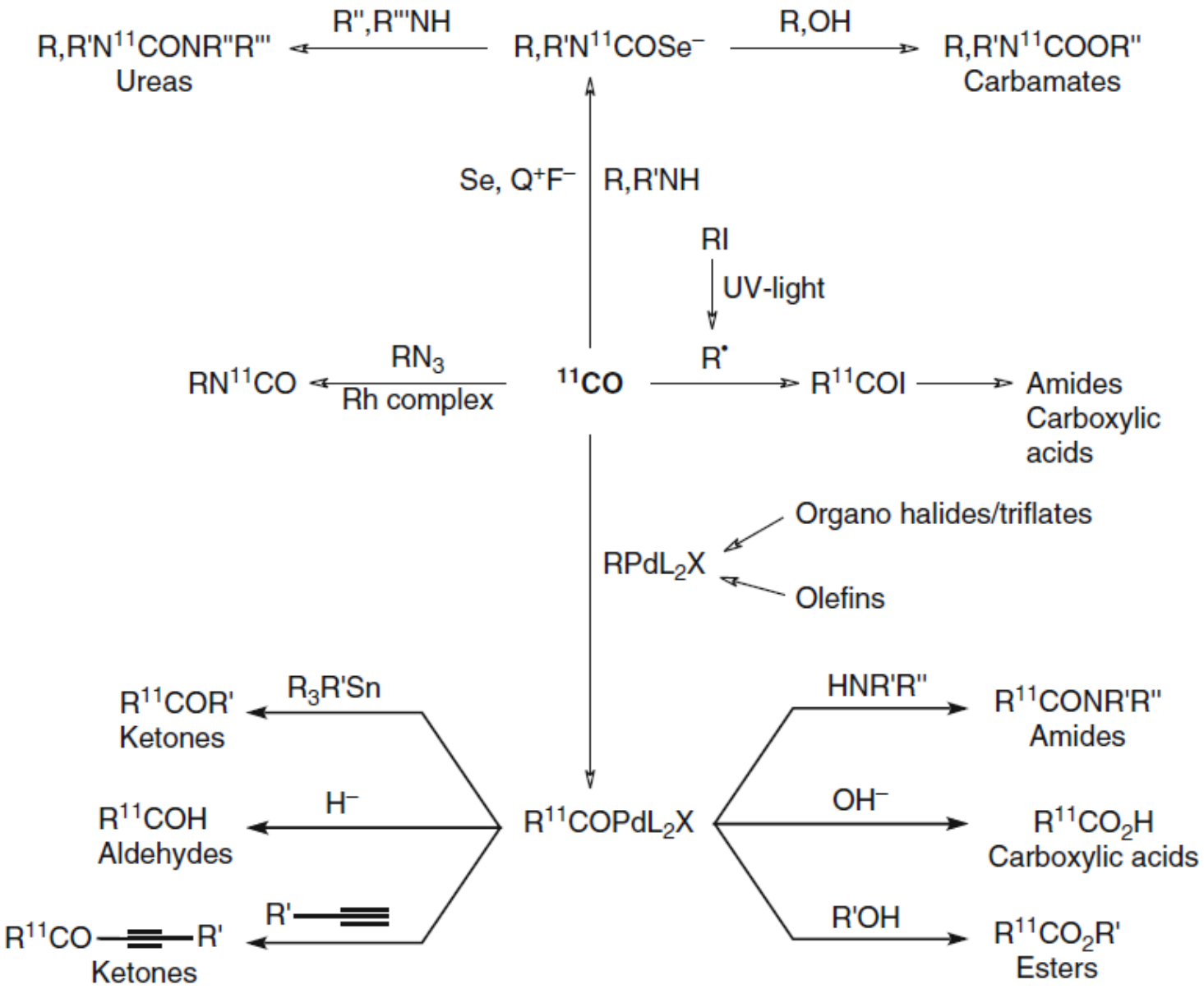


Some examples of possible synthetic transformations from [^{11}C]cyanide



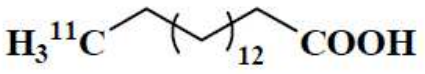
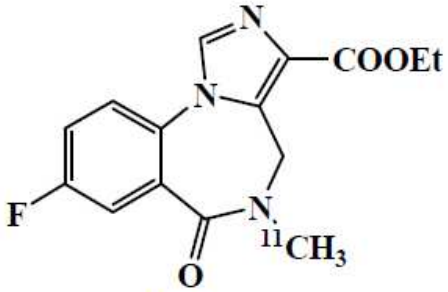
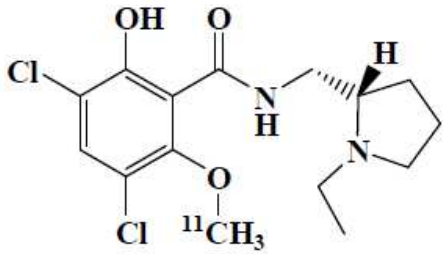
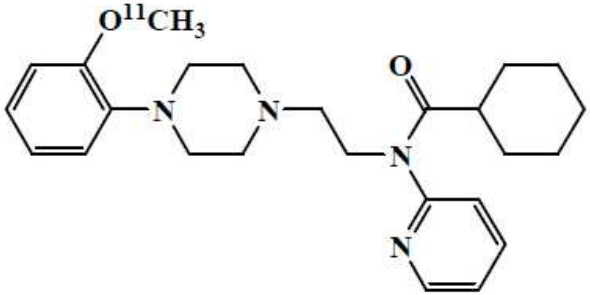
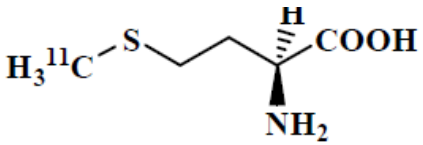
Carbon ^{11}C

Possible chemical transformations using [^{11}C]carbon monoxide



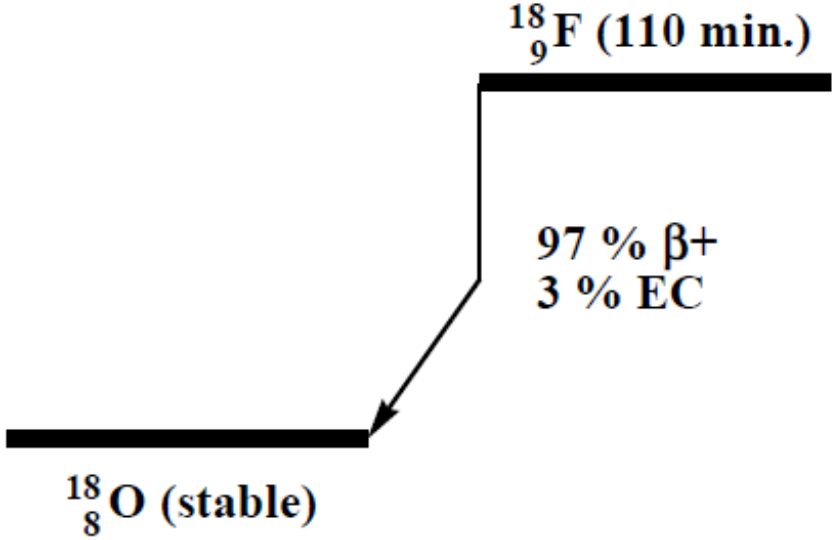
X= halide or triflate

Carbon ^{11}C

[^{11}C]Palmitic acid		myocardal metabolism of fatty acids
[^{11}C]Flumazenil		benzodiazepine receptors
[^{11}C]Raclopride		dopamine receptors D_2
[^{11}C]WAY-100635		seronin receptors $5HT_{1A}$
[^{11}C]Methionine		protein synthesis, metabolic abnormalities

Fluorine ^{18}F

- half-life 109.7 min
- decay mode: 96.9 % β^+, 3.1 % EC
- max β^+ energy: 0.63 MeV
- range in tissue: 0.54 mm
- decay product: ^{18}O



^{17}F	β^+	64.5 s
^{18}F	β^+	109.7 min
^{20}F	β^-	11.0 s
^{21}F	β^-	4.4 s
^{22}F	β^-	4.1 s
^{23}F	β^-	2.2 s
^{24}F	β^-	0.34 s
^{25}F	β^-	59 ms

Fluorine ^{18}F

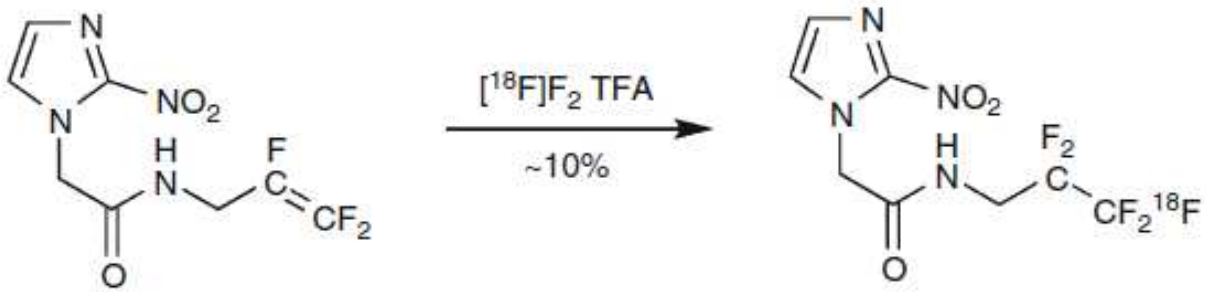
Production

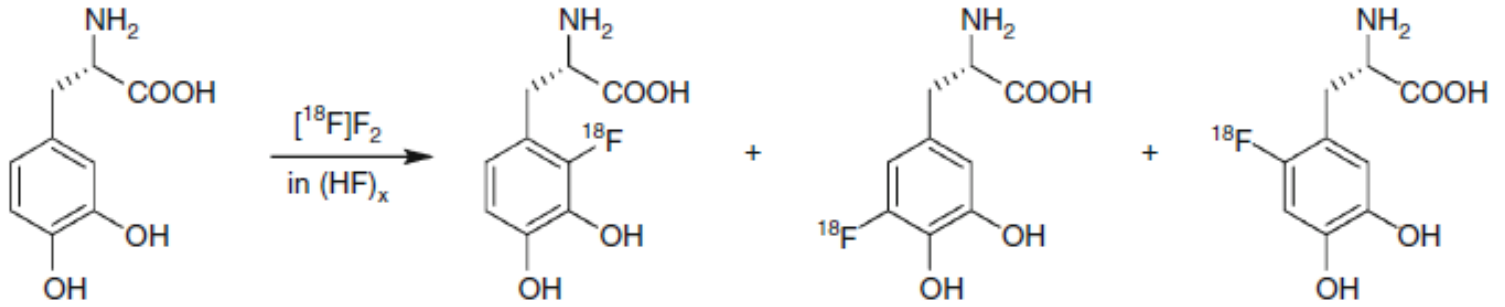
Product	Target	Beam energy (MeV)	Reaction	Specific activity
$[^{18}F]F_2$	0.1 % $F_2/^{20}Ne$	18 or 23	$^{20}Ne(d,\alpha)^{18}F$	30 - 370 MBq/μmol
$[^{18}F]F_2$	0.1 % $F_2/^{18}O$	16	$^{18}O(p,n)^{18}F$	600 MBq/μmol
$[^{18}F]HF$	15 % $H_2/^{20}Ne$	14	$^{20}Ne(d,\alpha)^{18}F$	0.1 - 1 TBq/μmol
$[^{18}F]F^-$	$H_2{}^{18}O$	15	$^{18}O(p,n)^{18}F$	0.01 - 7 TBq/μmol
$[^{18}F]F^-$	H_2O	36	$^{6}Li(n,\alpha)^{3}H/^{16}O(^{3}H,n)^{18}F$	50 GBq/μmol
$[^{18}F]F^-$	2-fluoroaniline	25	$^{19}F(\gamma,n)^{18}F$	not published

Fluorine ^{18}F

Electrophilic ^{18}F-Fluorination

- reaction of highly polarized fluorine with an electron rich reactant, e.g., an aromatic system, an alkene, or a carbanion
- starting with $[^{18}F]F_2$ – 50% RCY (molecule compsition ^{18}F–^{19}F)
- other fluorination agents $[^{18}F]XeF_2$, $[^{18}F]AcOF$





Fluorine ^{18}F

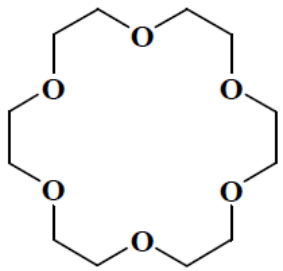
Nucleophilic ^{18}F-Fluorination

- [^{18}F]fluoride
- protonation at low pH
- formation of ion pairs with cations – decrease of reactivity

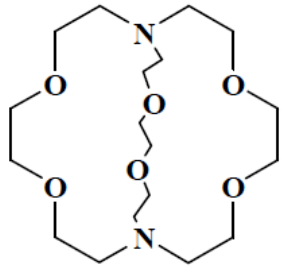
→ phase transfer catalysis or use of crownethers and cryptands

Nucleophilic Aliphatic Fluorination

$$R\text{–}X + F^- \longrightarrow R\text{–}F + X^-$$

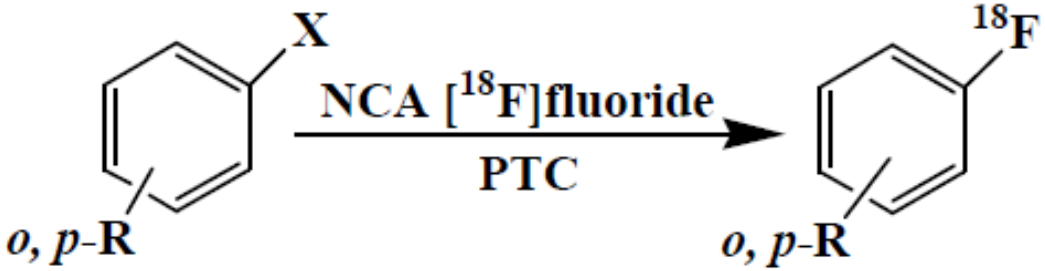


18-crown-6



Kryptofix 2.2.2.

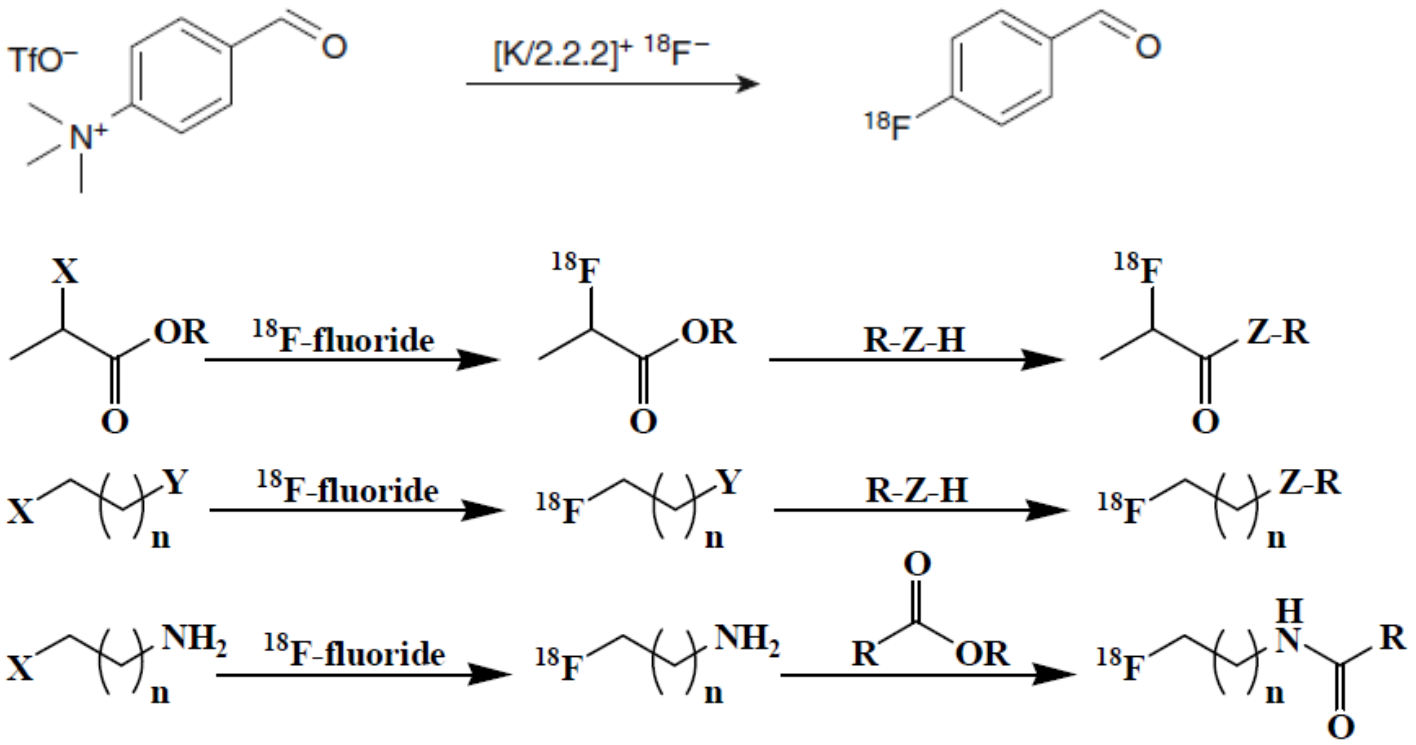
Nucleophilic Aromatic Fluorination



Fluorine ^{18}F

Prosthetic groups (PG)

- labelled compound containing reactive moiety
- fluoromethylation with $[^{18}F]FCH_2I$ or $[^{18}F]FCH_2Br$
- fluoroethylation with $[^{18}F]FCH_2CH_2X$
- other precursors

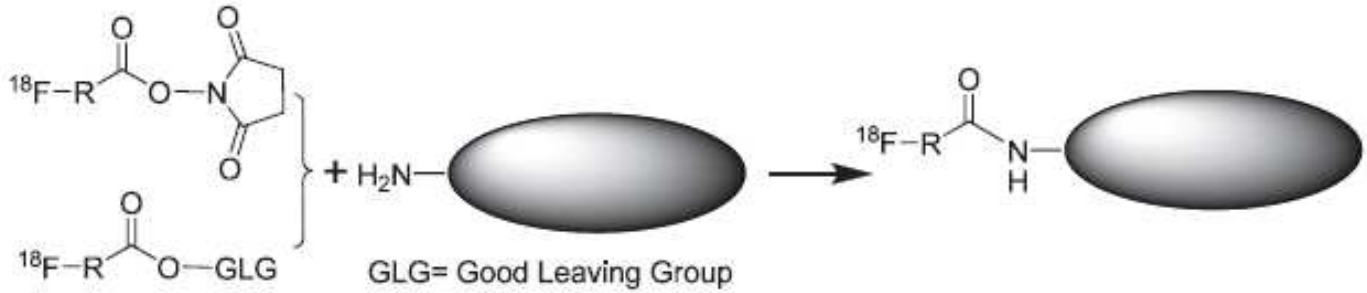


Fluorine ^{18}F

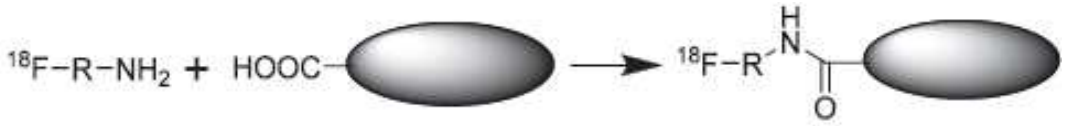
Prosthetic groups for biomolecules

- enable labelling of peptides and proteins

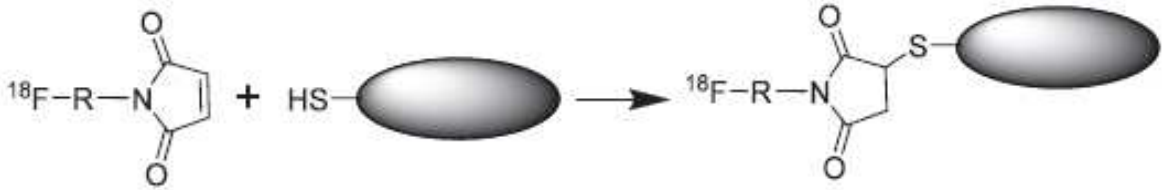
Amine reactive PGs



Carboxylic acid reactive PGs

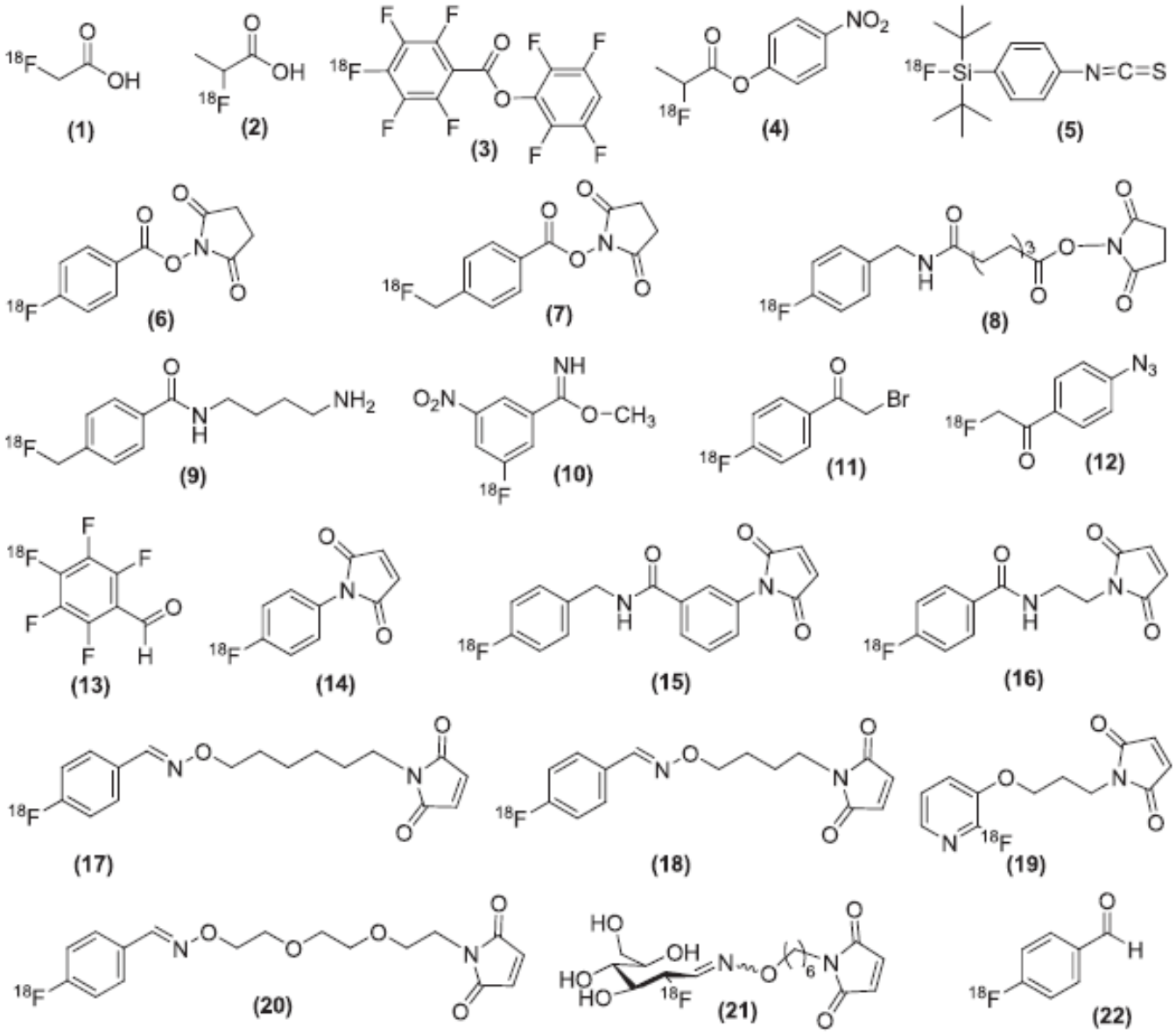


Thiol reactive PGs



Fluorine ^{18}F

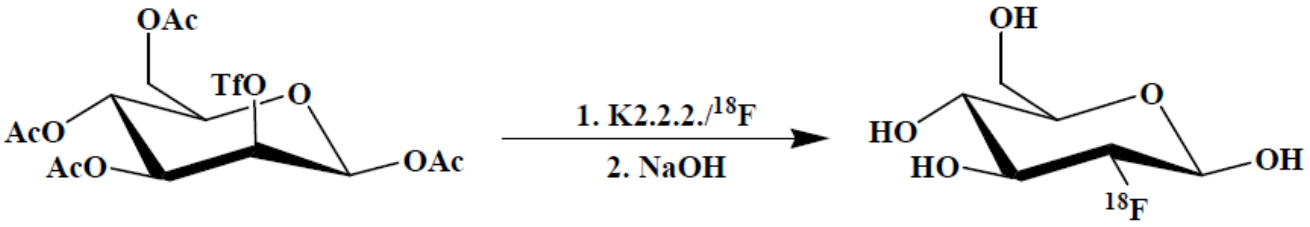
Prosthetic groups (PG)

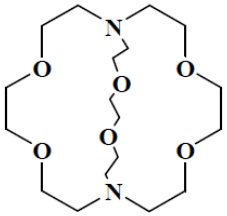


Fluorine ^{18}F

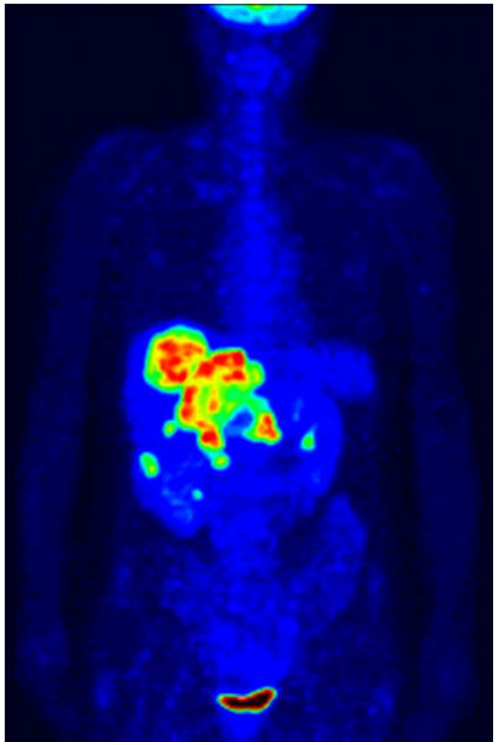
^{18}F-FDG: [18F]fluoro-2-deoxy-D-glucose – **vyrábí se cyklotronicky v MOÚ**

- 1968, J. Pacák and M. Černý, Department of Organic Chemistry, UK
- the most common PET tracer
- distribution similar to glucose
- can not be metabolized
- accumulation in metabolically-active tissues



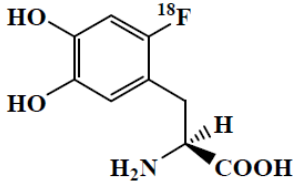
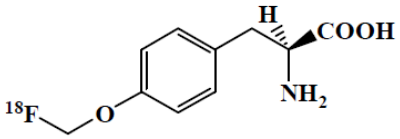
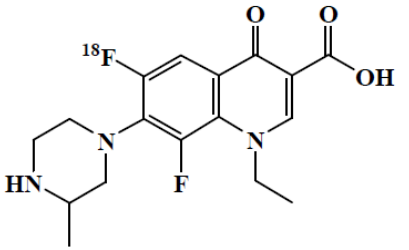
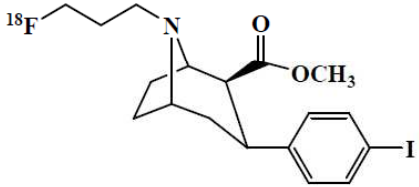
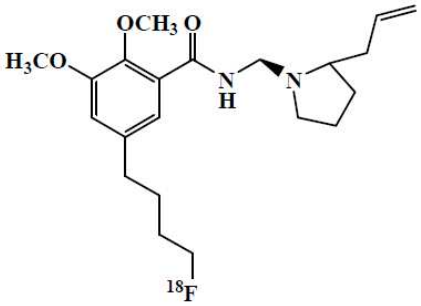
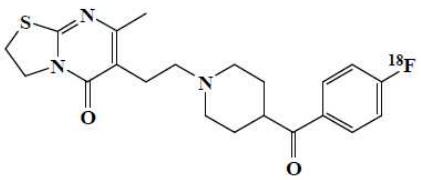


Kryptofix 2.2.2.



Whole-body PET scan using ^{18}F-FDG to show liver metastases of a colorectal tumor

Fluorine ^{18}F

Radiopharmaceutical	Formula	Clinical utility
6-[^{18}F]Fluoro-DOPA		dopamine metabolism Parkinson disease, schizophrenia, neurodegenerative desease
[^{18}F]Fluoro-α-methyltyrosine		tumour imaging
[^{18}F]Lomefloxacin		antibiotic pharmacokinetics
[^{18}F]FP-CIT		dopamine transport
[^{18}F]Fluoro-fallypride		post-synaptic D_2/D_3 receptors
[^{18}F]Setoperone		serotoninergic receptors ($5HT_2$)

Iodine isotopes

Isotope	Production	Modes of decay	Half-life	E_γ/E_β[a]	Specific activity[b]	Application
^{123}I	Cyclotron	EC	13.2 h	159/–	>600[c]	Imaging
^{124}I	Cyclotron	EC/β^+ (25%)	4.18 days	603/ 1,530	>30[d]	Imaging
^{125}I	Nuclear reactor	EC	59.4 days	35/–	>90	In vitro and therapy
^{131}I	Nuclear reactor	β^-	8.04 days	364/606	110	Imaging and therapy

$$^{123}\mathrm{I}: \quad ^{124}\mathrm{Xe}(\mathrm{p}, 2\mathrm{n})^{123}\mathrm{Cs} \xrightarrow{(\beta^+,\ 0.1\ \mathrm{h})} {}^{123}\mathrm{Xe} \xrightarrow{(\beta^+,\ 2.08\ \mathrm{h})} {}^{123}\mathrm{I}$$

$$^{124}\mathrm{I}: \quad ^{124}\mathrm{Te}(\mathrm{d}, 2\mathrm{n})\mathrm{or}(\mathrm{p}, \mathrm{n})^{124}\mathrm{I}$$

$$^{125}\mathrm{I}: \quad ^{124}\mathrm{Xe}(\mathrm{n}, \gamma)^{125}\mathrm{Xe} \xrightarrow{(\mathrm{EC},\ 17\ \mathrm{h})} {}^{125}\mathrm{I}$$

$$^{131}\mathrm{I}: \quad ^{235}\mathrm{U}(\mathrm{n}, \mathrm{fission})^{131}\mathrm{I}, {}^{99}\mathrm{Mo}, {}^{117}\mathrm{Pd}, {}^{137}\mathrm{Cs}, \ldots$$

Metalic nuclides (non-Tc, non-Re)

Metal	Ionic radius [pm],octahedral	Nuclides
Sc^{3+}	75	^{47}Sc
Ga^{3+}	62	^{66}Ga, ^{67}Ga, ^{68}Ga
Y^{3+}	90 (105)	^{86}Y, ^{90}Y
In^{3+}	80	^{111}In, ^{110}In
Dy^{3+}	105	^{166}Dy
Ho^{3+}	104	^{166}Ho
Lu^{3+}	100	^{177}Lu
Bi^{3+}	103	^{212}Bi, ^{213}Bi
Ac^{3+}	126	^{225}Ac
Sm^{3+}	110	^{153}Sm
Cu^{2+}	87	^{67}Cu, ^{64}Cu, ^{62}Cu, ^{61}Cu, ^{60}Cu
Ag^{+}	129	^{111}Ag

Complex stability

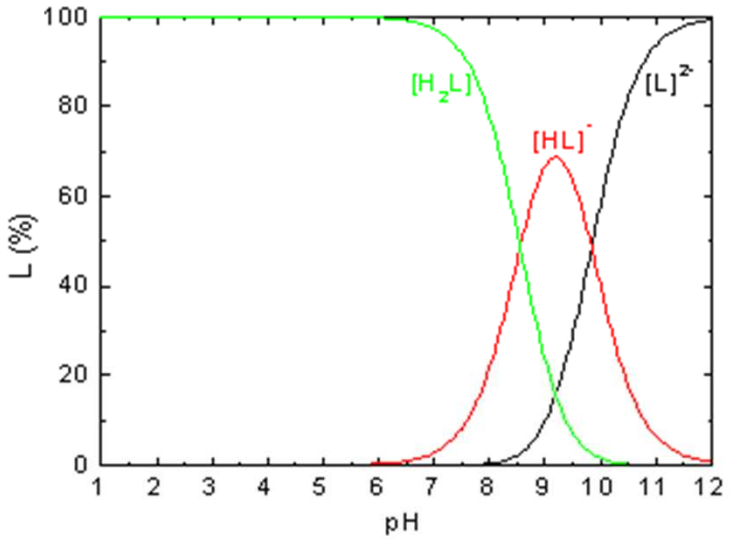
Thermodynamic stability

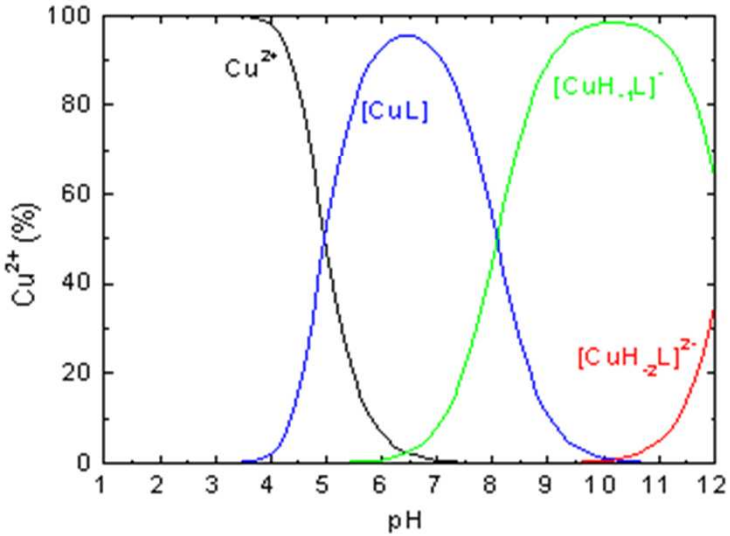
- proton vs. metal competition
- ligand basicity

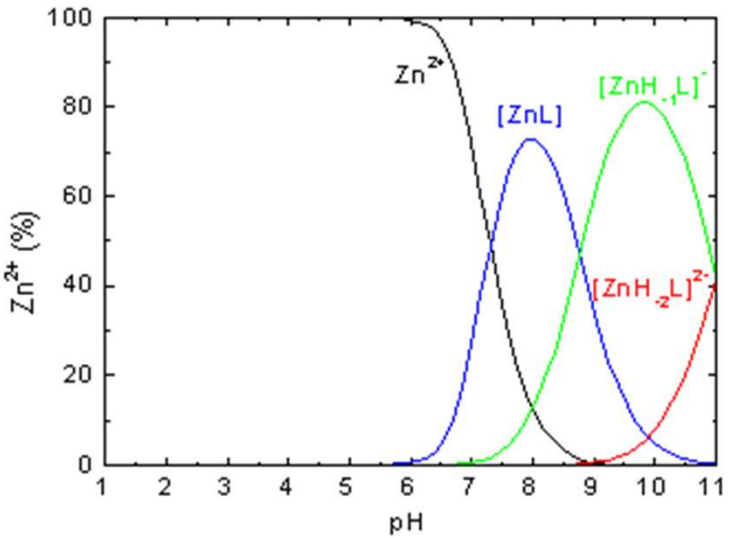
$$K_a = \frac{[H]\times[L]}{[HL]}$$

- stability constants

$$K = \frac{[ML]}{[M]\times[L]}$$







Complex kinetics

Formation kinetic

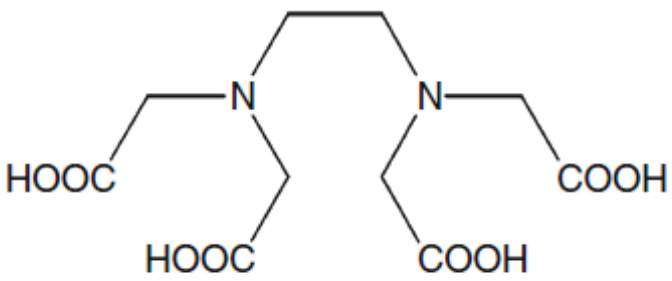
- chemistry – high concentrations; NMR, UV-VIS
- radiochemistry – low concentrations

Kinetic inertness

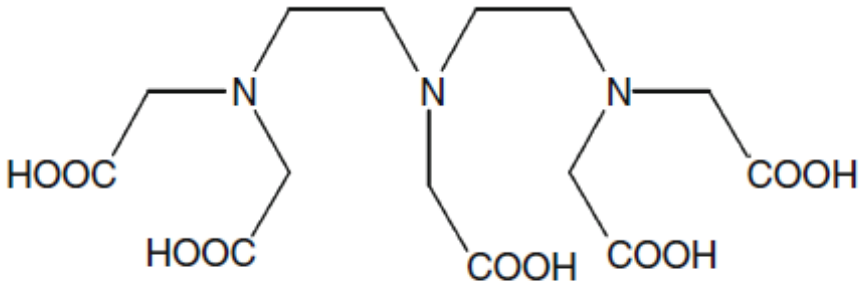
- *in vitro* experiments
  - transmetallation (Zn(II))
  - decomplexation in acidic solutions
  - incubation in plood plasma

Open-chain ligands

- high thermodynamic stability
- kinetically labile
- fast complexation
- applied in large excess



EDTA

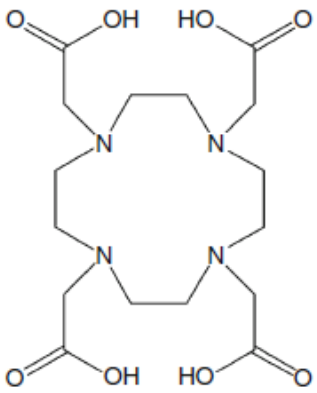


DTPA

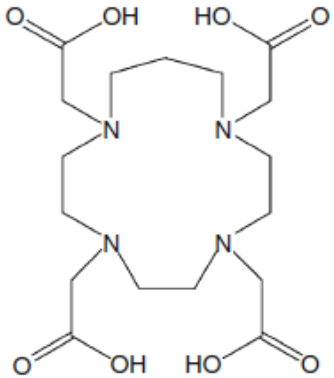
Macrocyclic ligands

- high thermodynamic stability
- kinetically inert
- slow complexation
- variation of pendant arms
  - carboxylates, alcohol, amine, phosphorus derivatives
  - changes in stability, inertness, complexation rate, charge,

lip



DOTA



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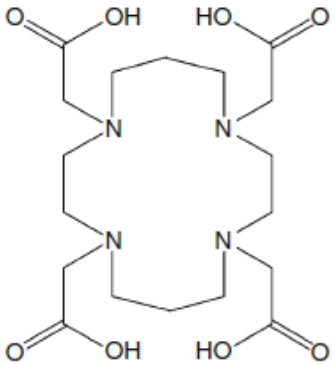

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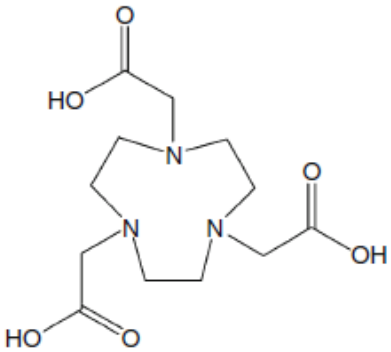
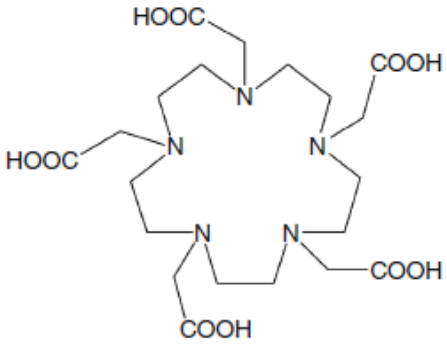
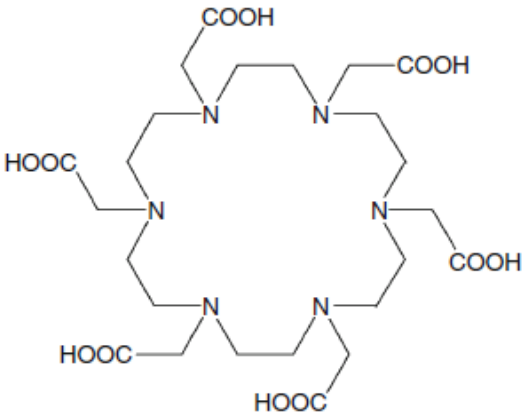


NOTA



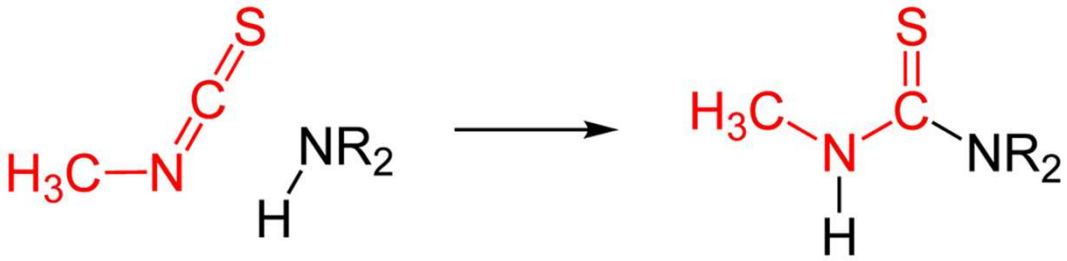
PEPA

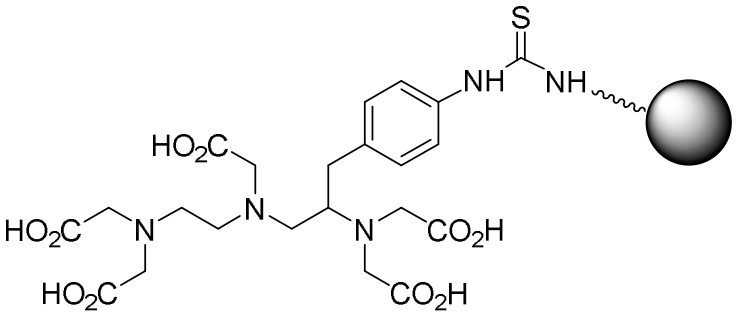


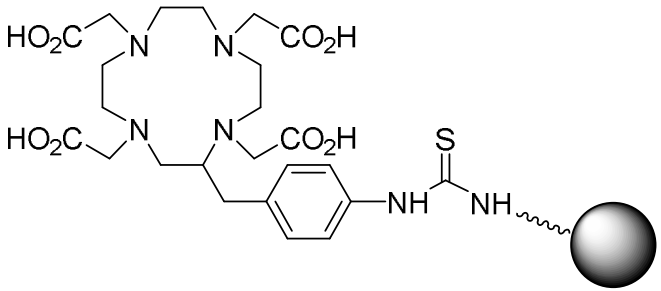
HEHA

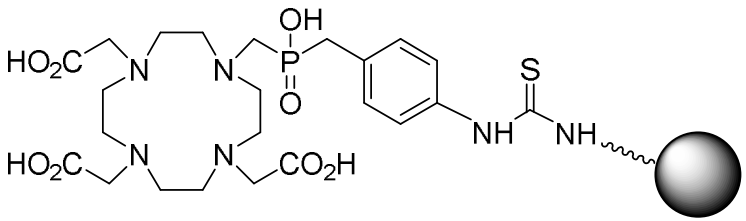
Bifunctional chelators

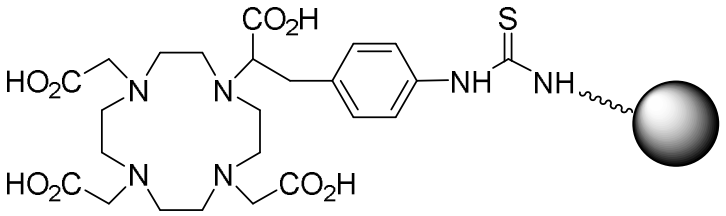
Thiourea bond



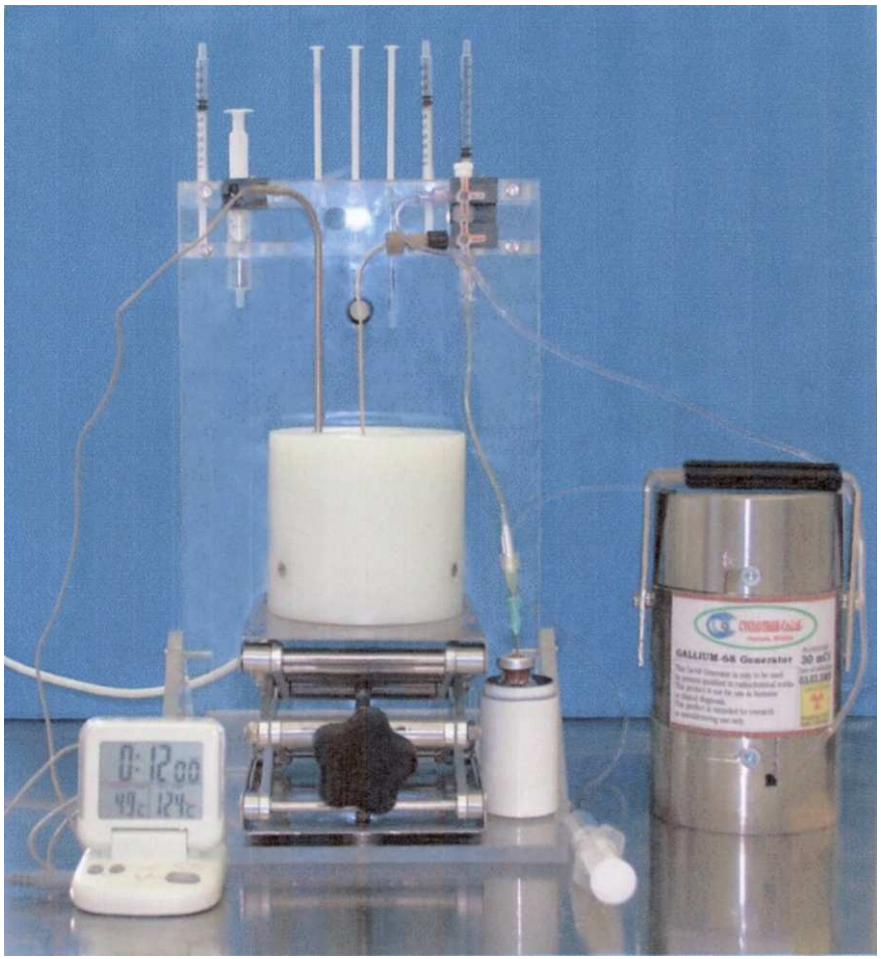








Gallium ^{68}Ga



- half-life 67.6 min
- decay mode: 89 % β^+, 11 % EC
- max β^+ energy: 1.90 MeV
- range in tissue: 2.12 mm
- decay product: ^{68}Zn

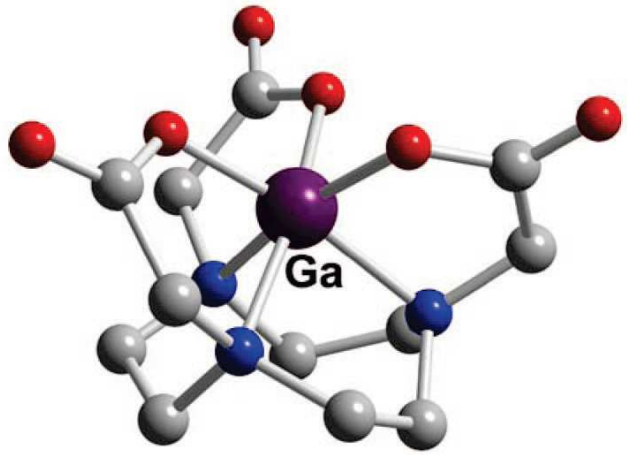
Generator produced

- source ^{68}Ge ($T_{1/2}$ = 271 d)
- adsorbed on TiO_2 or SnO_2
- elution with HCl or citric acid

Chemistry

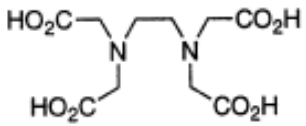
- trivalent
- hexacoordination
- hard metal ion
- precipitation of hydroxide at wide pH range
- formation of tetrahydroxido complex at high pH

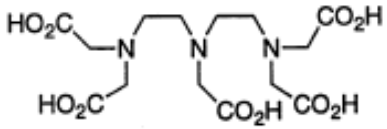
Gallium ^{68}Ga

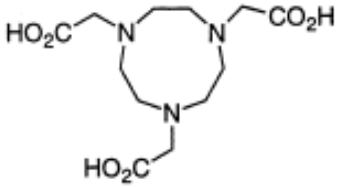


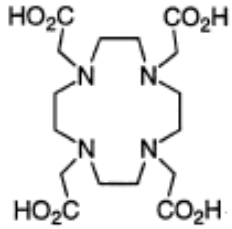
Ligands for ^{68}Ga complexation

Aminocarboxylates

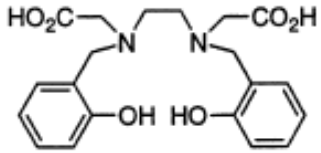


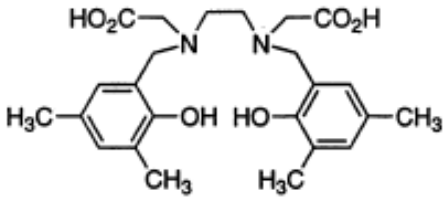


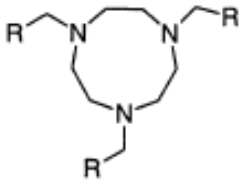


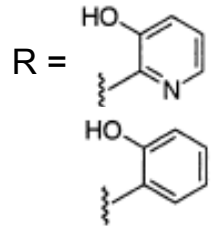


Hydroxybenzyl and hydroxypyridyl derivatives

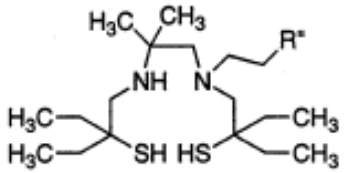


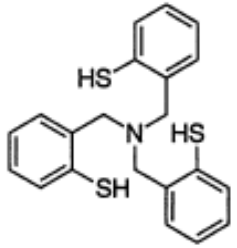


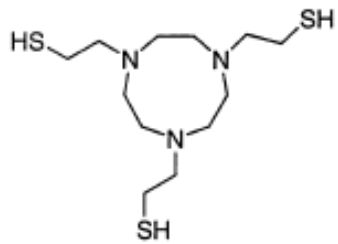


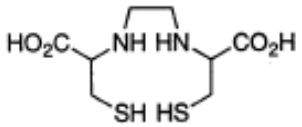


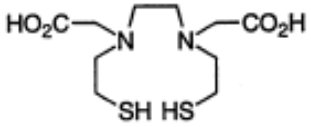
Thiol and amino-thiol chelates











Copper isotopes

Isotope	Decay	Half-life	Source
^{60}Cu	β^+	24 min	cyclotron, ^{60}Ni(p,n)^{60}Cu
^{61}Cu	β^+	3.3 h	cyclotron, ^{61}Ni(p,n)^{61}Cu
^{62}Cu	β^+	9.74 min	generator, ^{62}Zn(β^-)^{62}Cu, 9.3 h
^{64}Cu	β^+ (61%), β^- (39%)	12.8 h	cyclotron, ^{64}Ni(p,n)^{64}Cu
^{67}Cu	β^-	62 h	cyclotron, ^{67}Zn(n,p)^{67}Cu

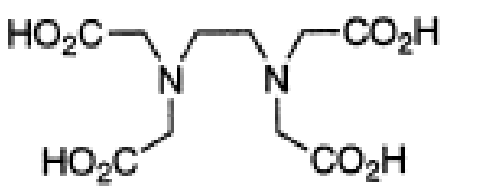
- isotopes 60, 61, 62 and 64 – PET
- isotopes 64 and 67 – SPECT and therapy
- difficult production and isolation

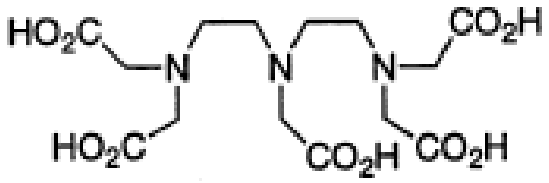
Chemistry
- divalent
- hexacoordination
- Jahn-Teller effect

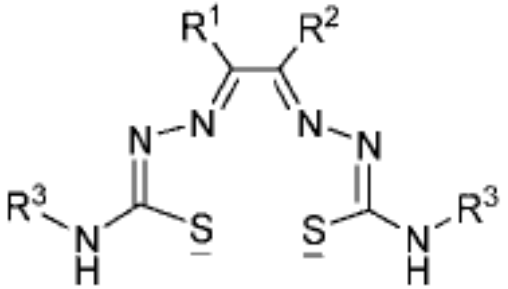
Copper isotopes

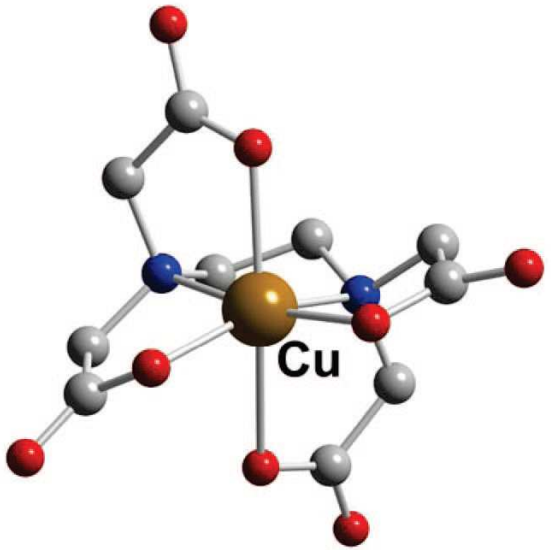
Ligands for copper complexation

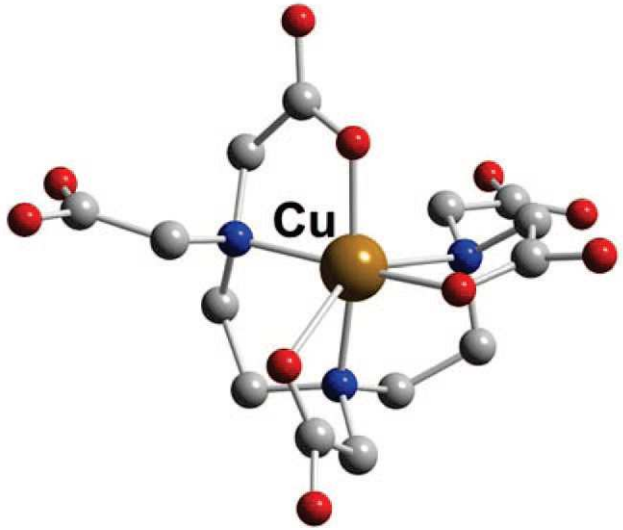
Open-chain ligands

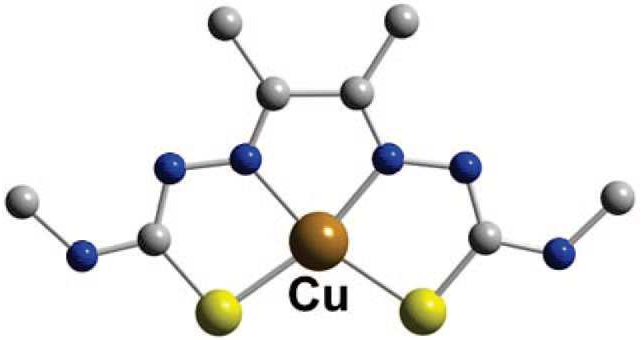








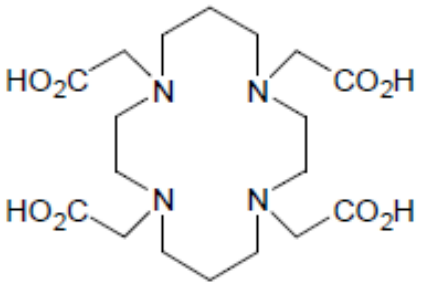




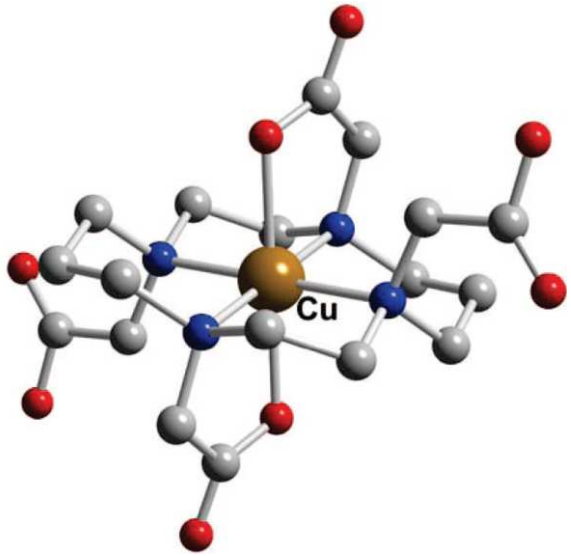
Copper isotopes

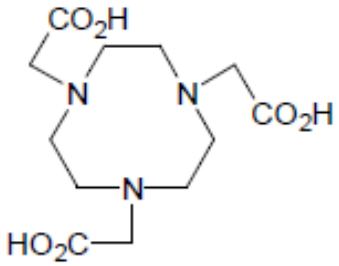
Ligands for copper complexation

Macrocyclic ligands

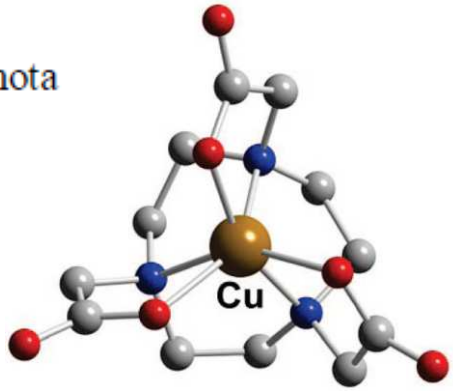


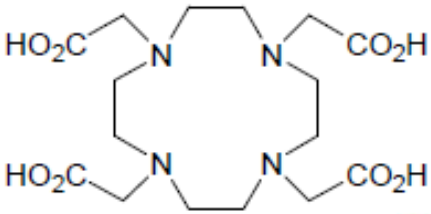
H_4teta



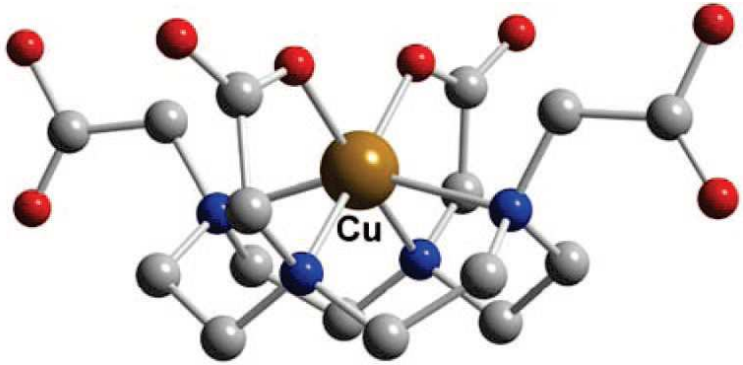


H_3nota





H_4dota



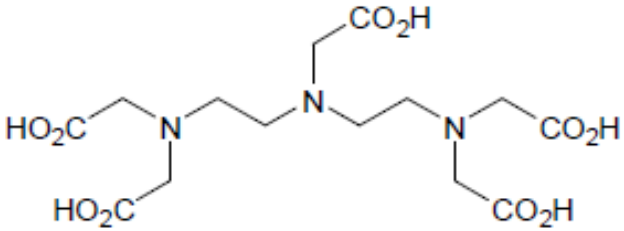
Sc, Y, In and Lanthanoides

	Decay	Half-life	Source
Diagnotic isotopes			
^{44}Sc	β^+	3.93 h	generator, $^{44}Ti(EC)^{44}Sc$, 59 y or cyclotron, $^{44}Ca(p,n)^{44}Sc$
^{86}Y	β^+	14.7 h	cyclotron, $^{86}Sr(p,n)^{86}Y$
^{110}In	β^+	69.0 min	generator, $^{110}Sn(\beta^-)^{110}In$, 4.11 d
^{111}In	γ	68 h	cyclotron, $^{111}Cd(p,n)^{64}In$
^{134}La	β^+	6.70 min	generator, $^{134}Ce(\beta^-)^{134}La$, 3.0 d
^{140}Pr	β^+	3.39 min	generator, $^{140}Nd(\beta^-)^{140}Pr$, 3.3 d
Therapeutic isotopes			
^{90}Y	β^-	64 h	generator, $^{90}Sr(\beta^-)^{90}Y$, 28.8 y
^{149}Pm	β^-	2.2 d	reactor
^{153}Sm	β^-	1.9 d	reactor
^{161}Tb	β^-	166 h	reactor
^{166}Ho	β^-	1.1 d	reactor
^{177}Lu	β^-	6.7 d	reactor

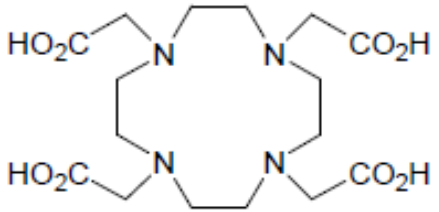
Sc, Y, In and Lanthanoides

Chemistry

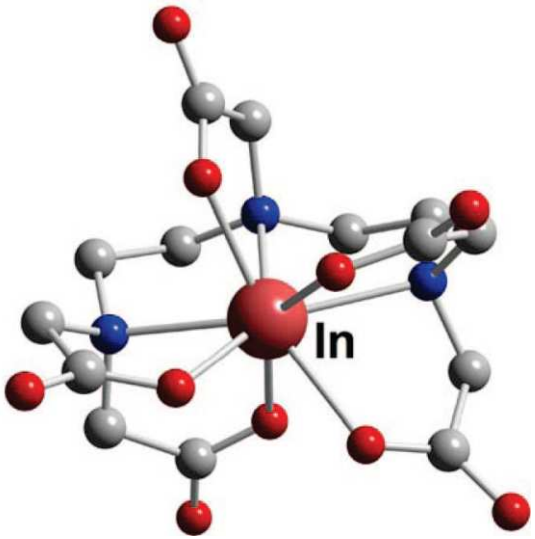
- octa- or nona-coordination
- octadentate ligands
- hard metal ions

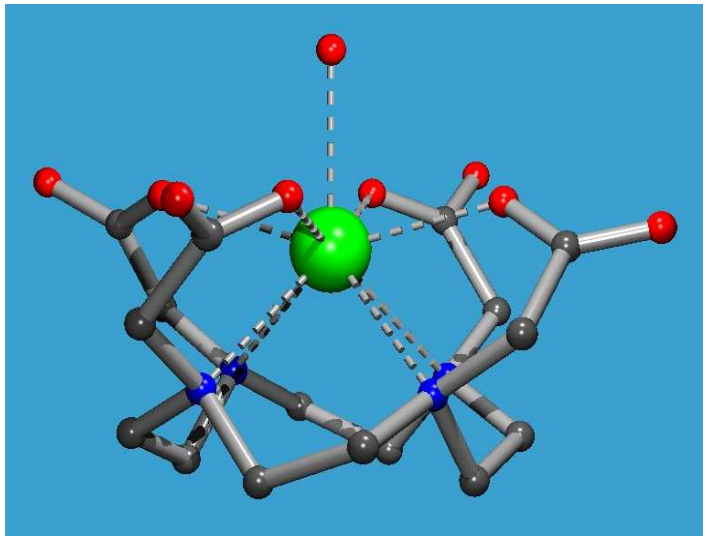


H_5dtpa

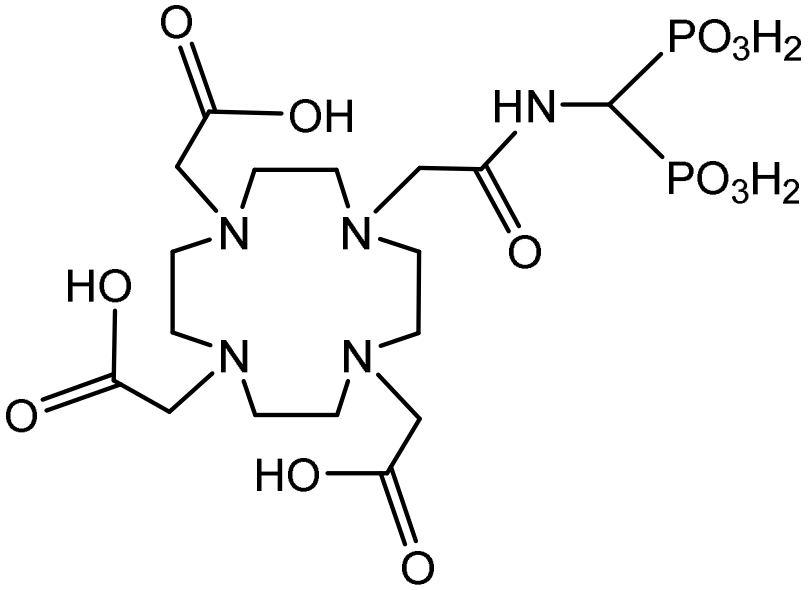


H_4dota





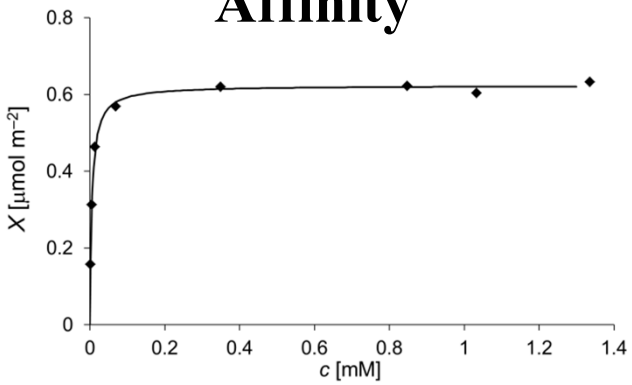
Radiochemical research



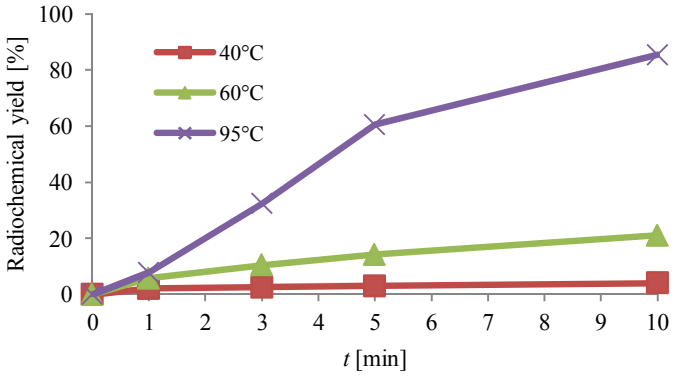
Bisphosphonate-containing dota-amides

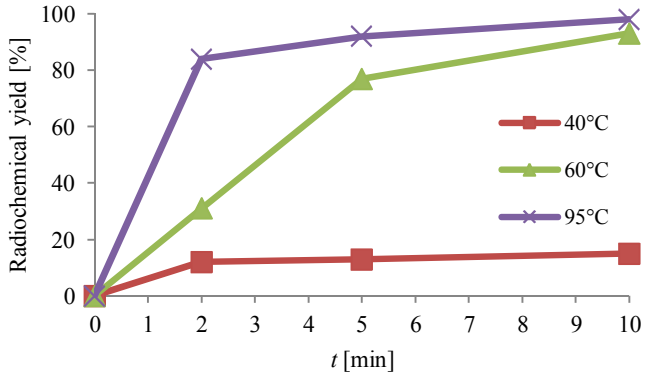
- ligand synthesis and characterization
- chemical complexation study
- labelling (complexation of radionuclide)
  - pH, temperature, ligand concentration
- affinity and stability study

Affinity

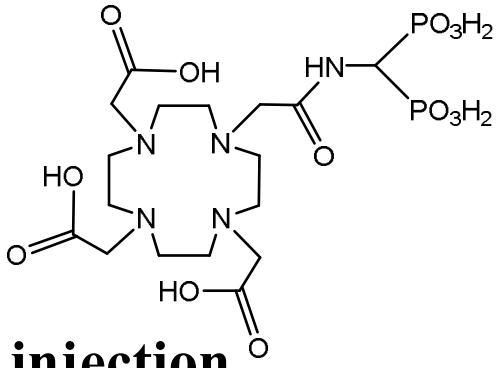


Labeling

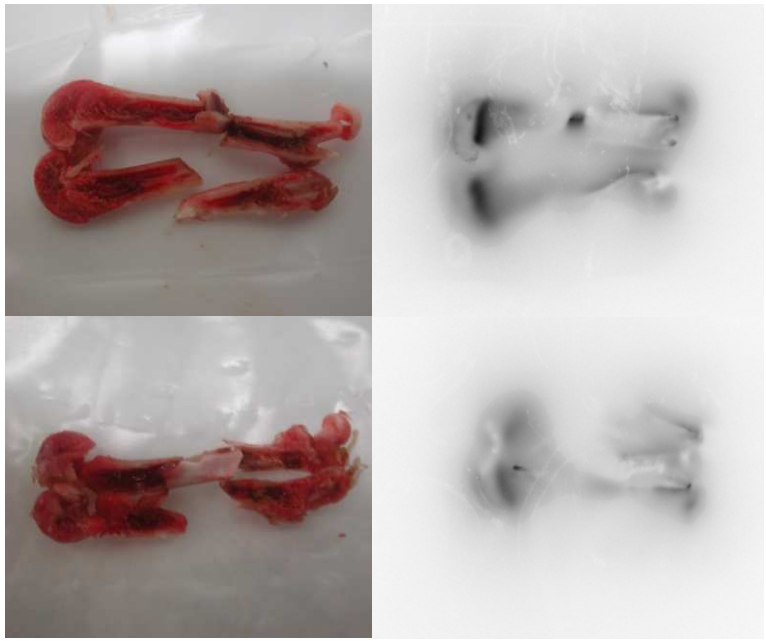


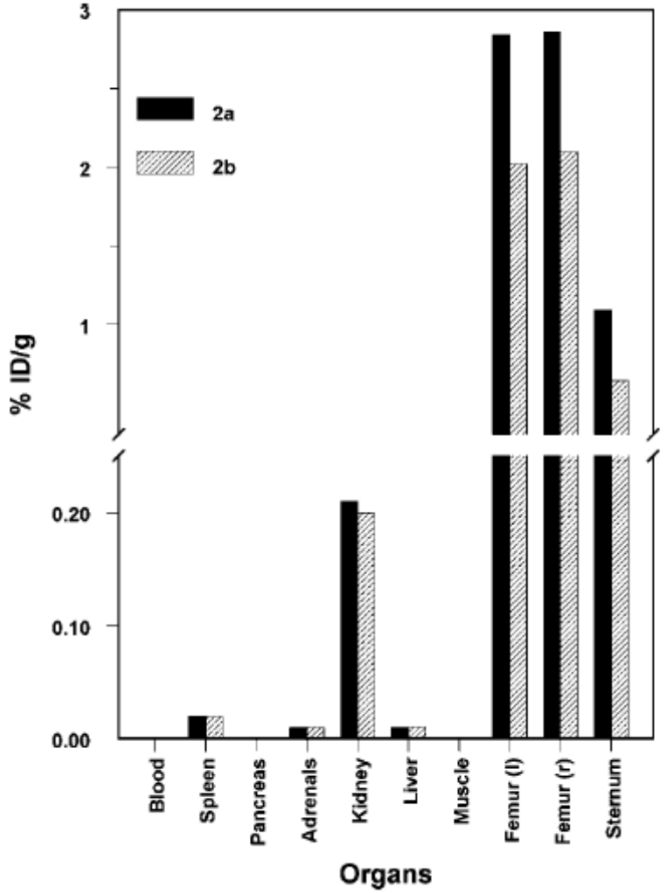


Radiochemical research

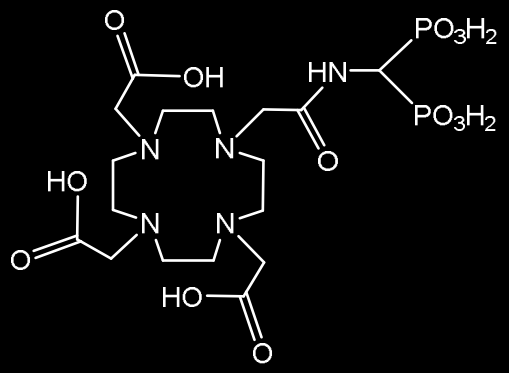


Biodistribution of ^{177}Lu-complexes in Lewis rat 24 h after injection

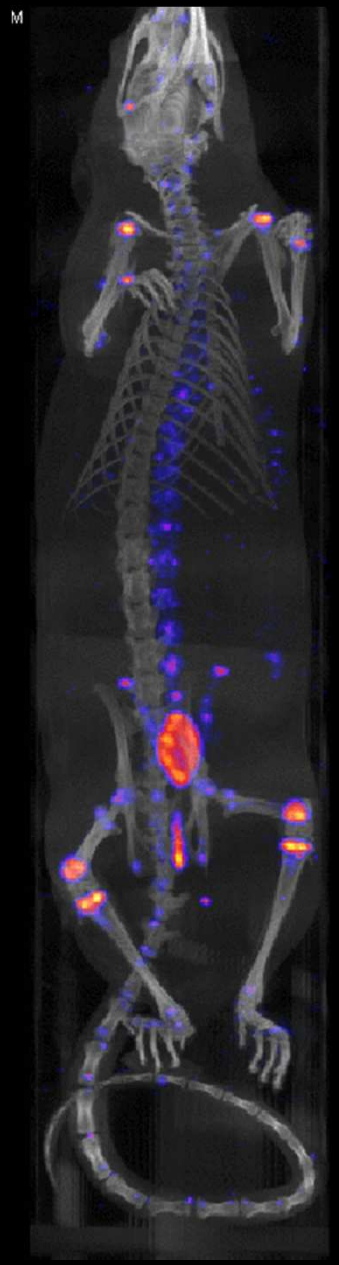




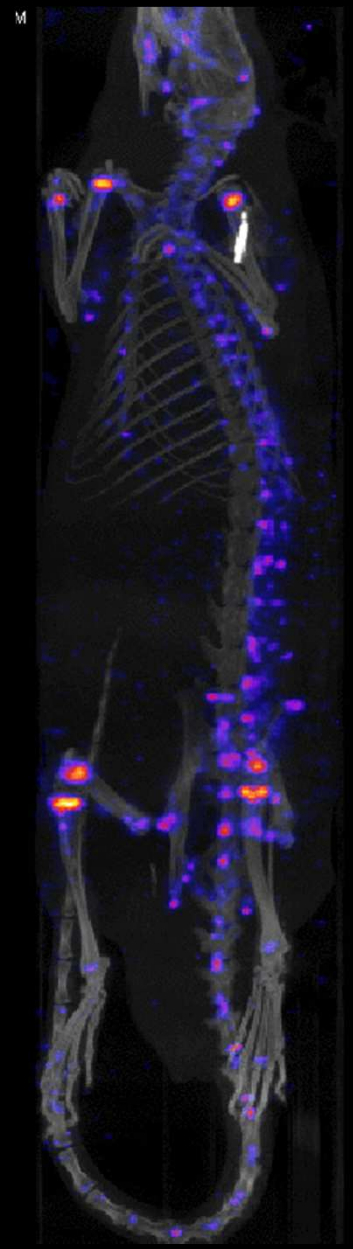
Radiochemical research



In vivo SPECT/CT visualization of ^{177}Lu-complex

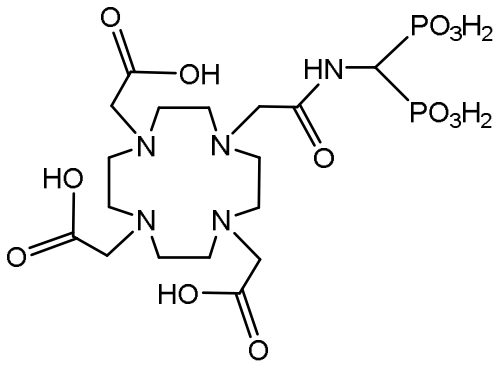


1 h *p.i.*

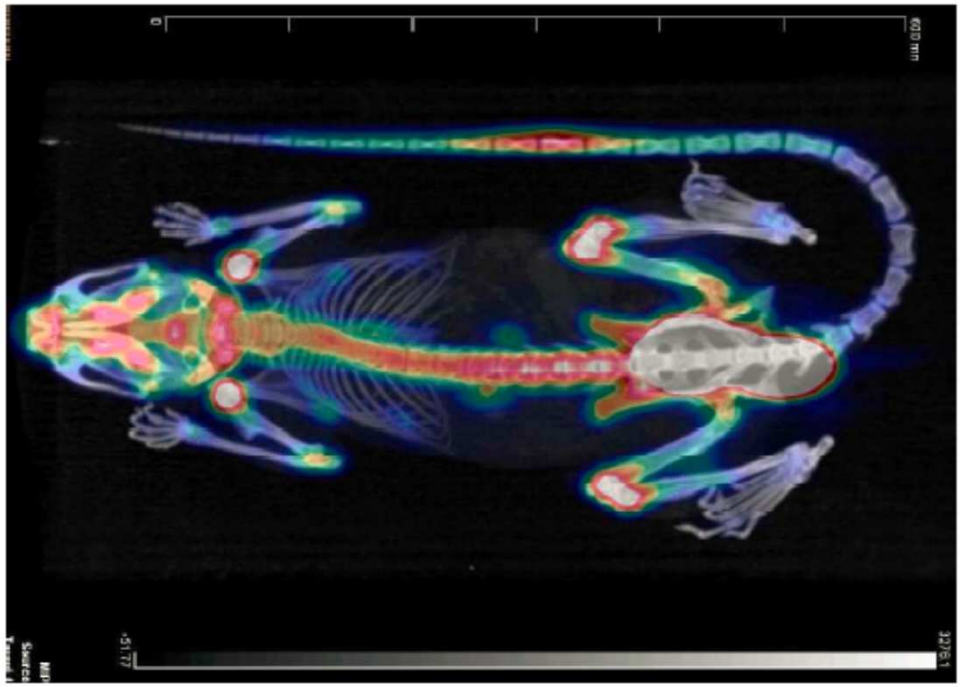


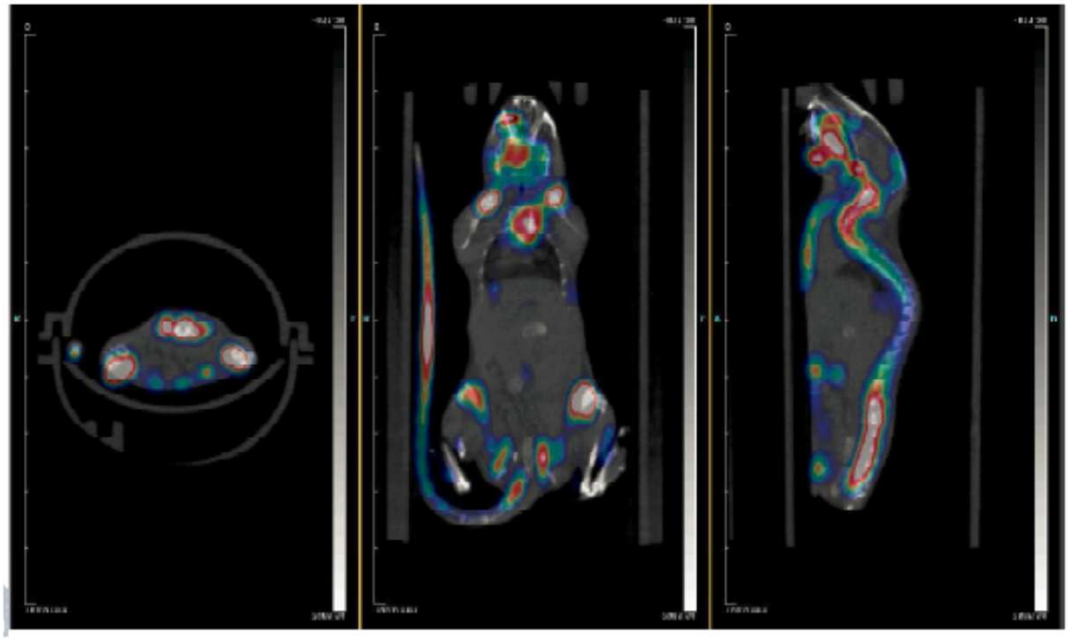
24 h *p.i.*

Radiochemical research

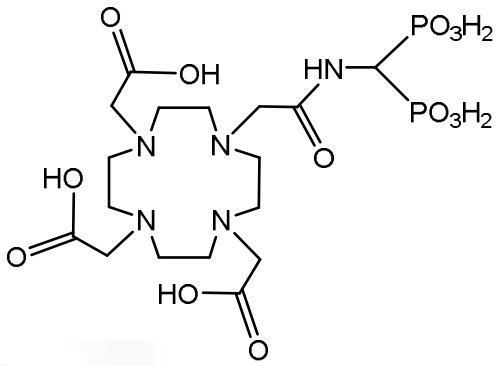


^{64}Cu complex

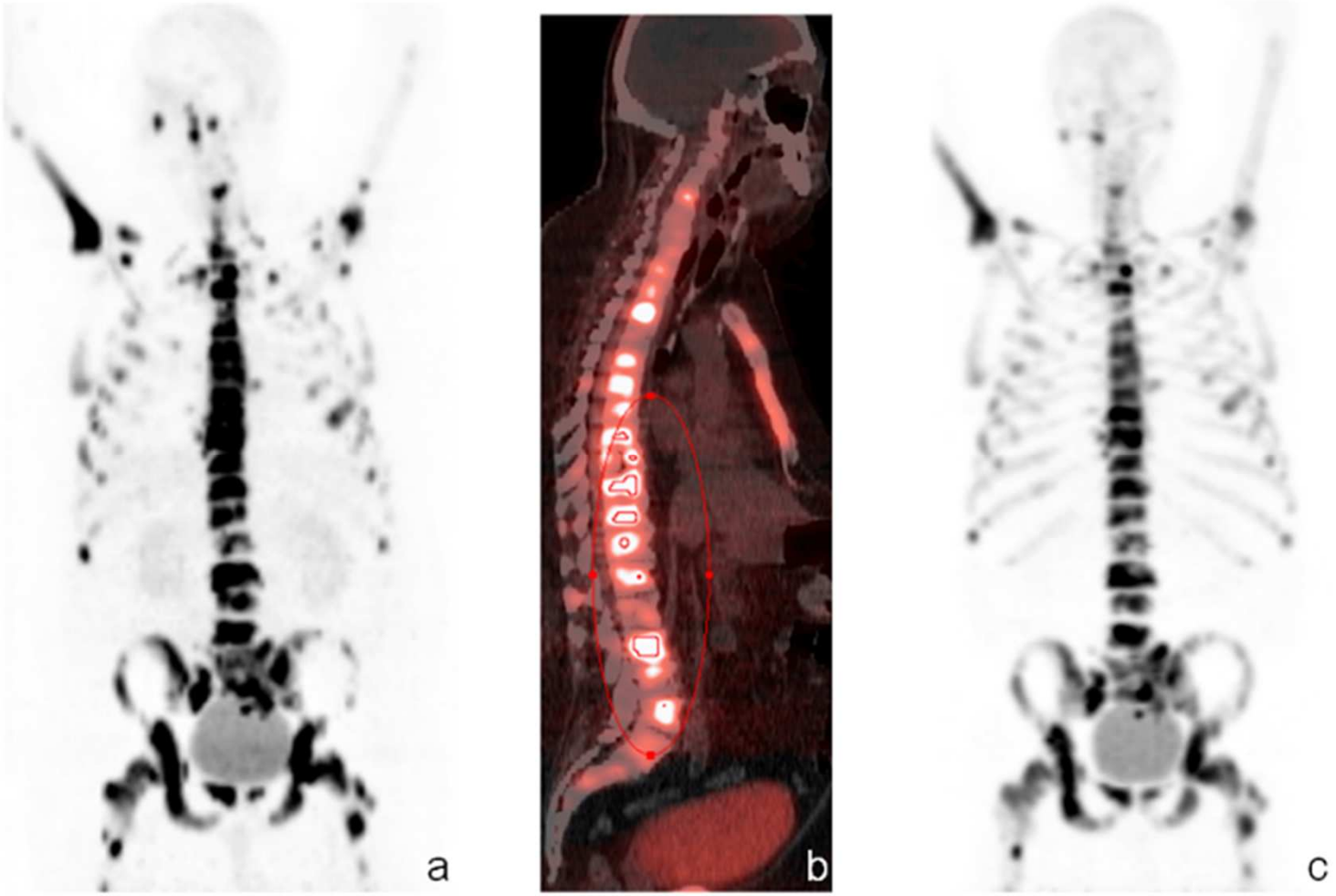




Radiochemical research



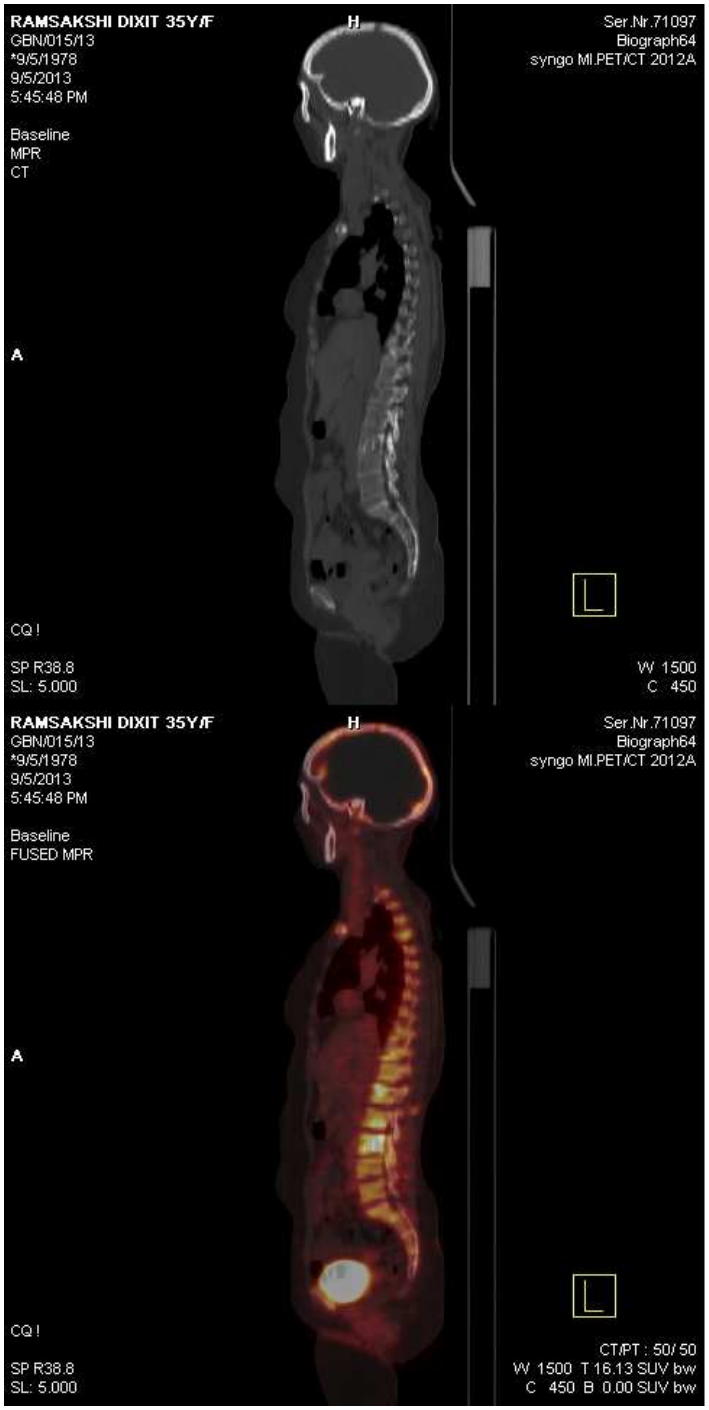
PET/CT imaging of bone metastases with ^{68}Ga-complex

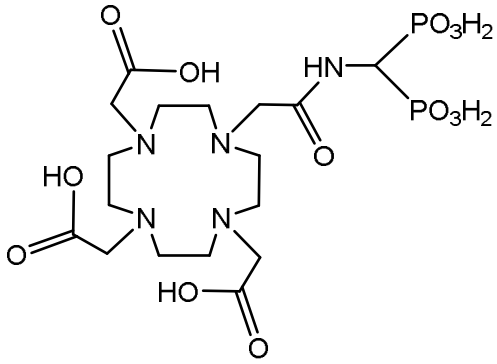


(a) = coronal PET, (b) = sagittal PET/CT. For comparison (c) shows ^{18}F-fluoride PET.

University of Mainz, Zentral Klinik Bad Berka

Radiochemical research





^{68}Ga-complex