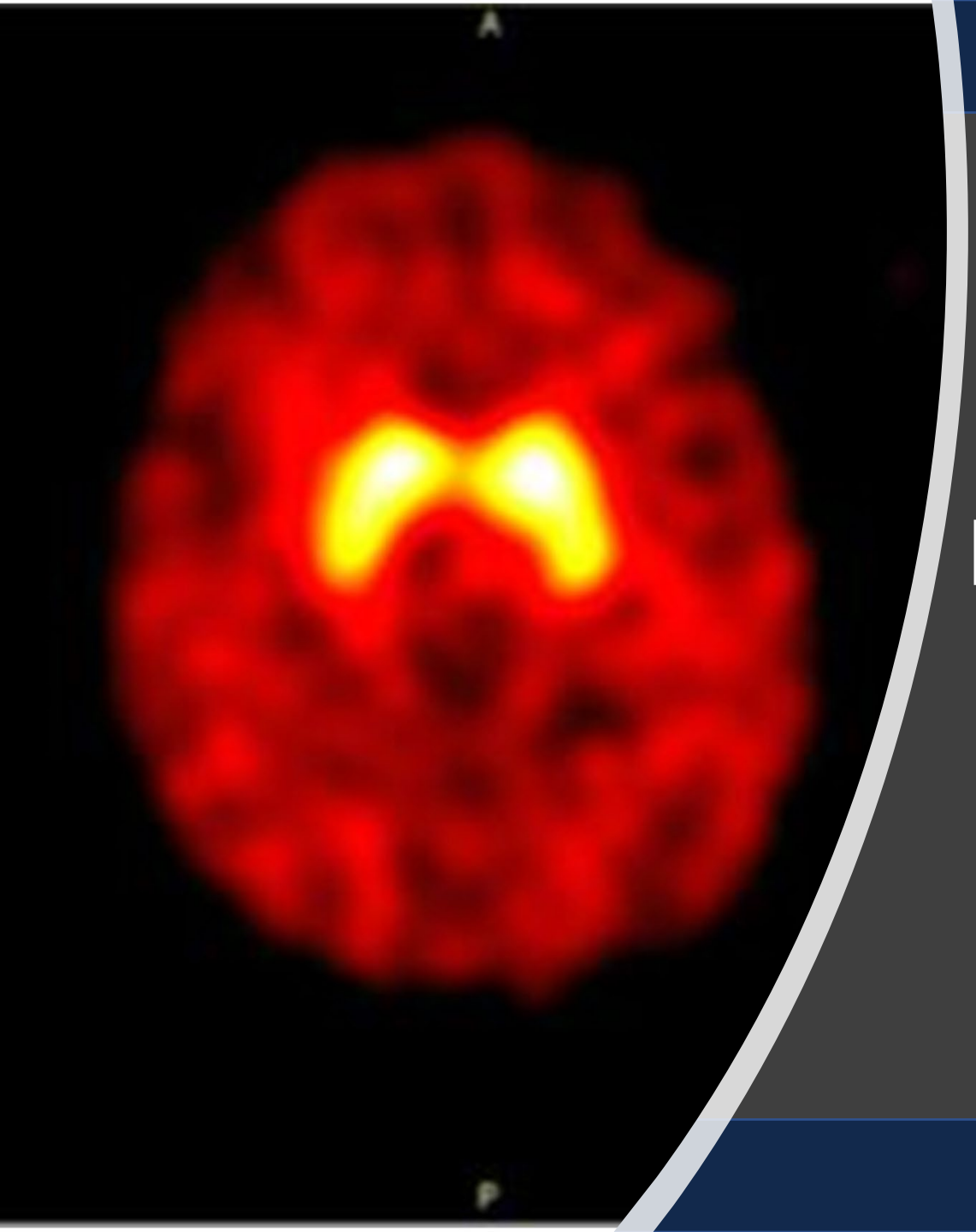


Radioiodination and Its Uses in Radiomedicine

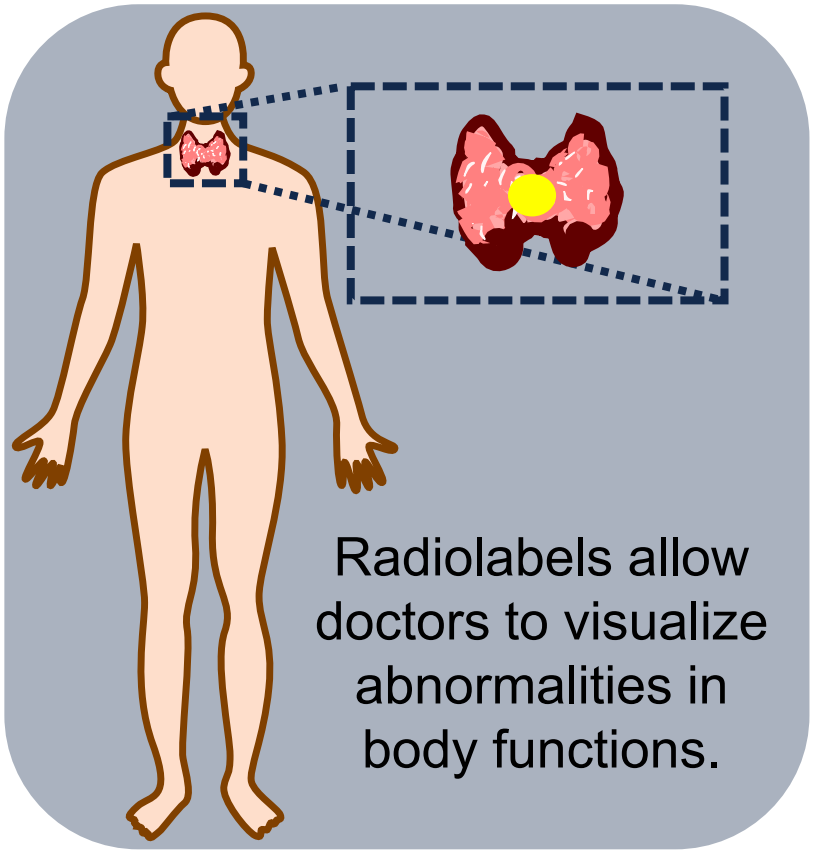
Denmark Lab

February 28th 2023

Jamie Berry

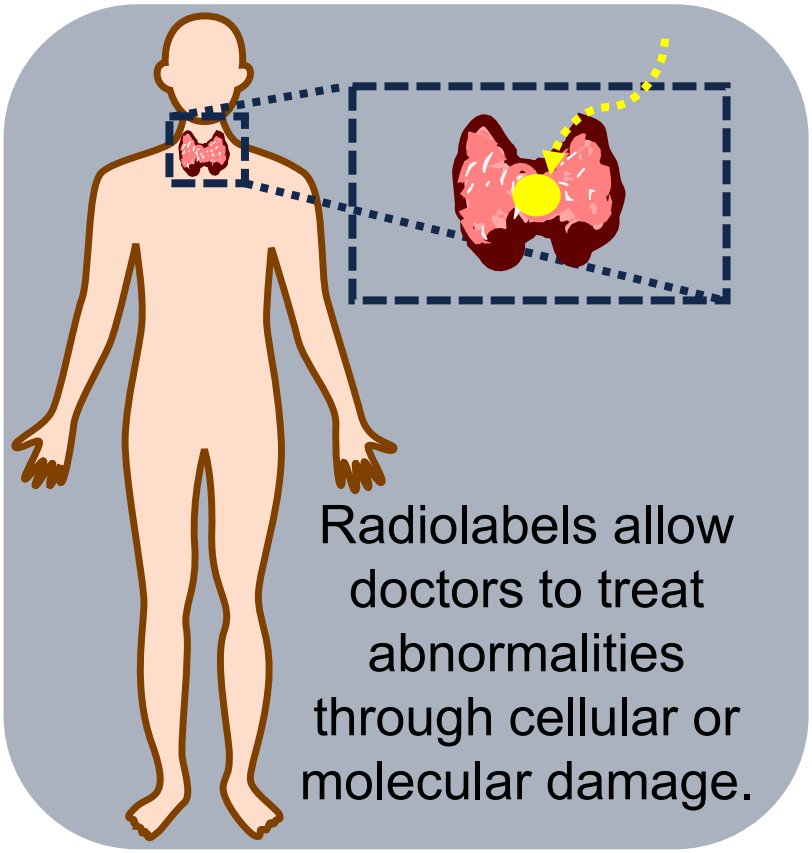
Utility of Radiolabels in Medicine

Imaging



Radiolabels allow doctors to visualize abnormalities in body functions.

Therapeutics



Radiolabels allow doctors to treat abnormalities through cellular or molecular damage.

Radio Label Comparison

^{99m}Tc

- Many variants used for imaging many parts of the body or therapeutics
- Emits γ rays
- 6 h Half-Life
- Rapid excretion

^{131}I

- NaI used in medicine as a therapeutic for hyperthyroidism and thyroid carcinoma
- Emits γ rays and β particles
- 8 day Half-Life
- Cold Iodine assists excretion

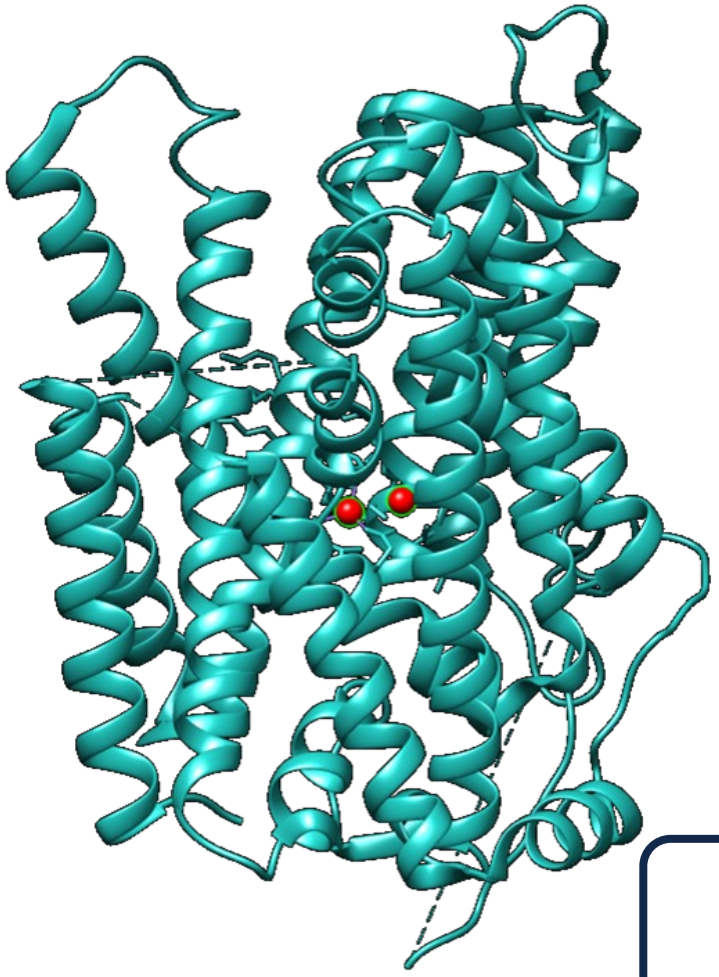
^{18}F

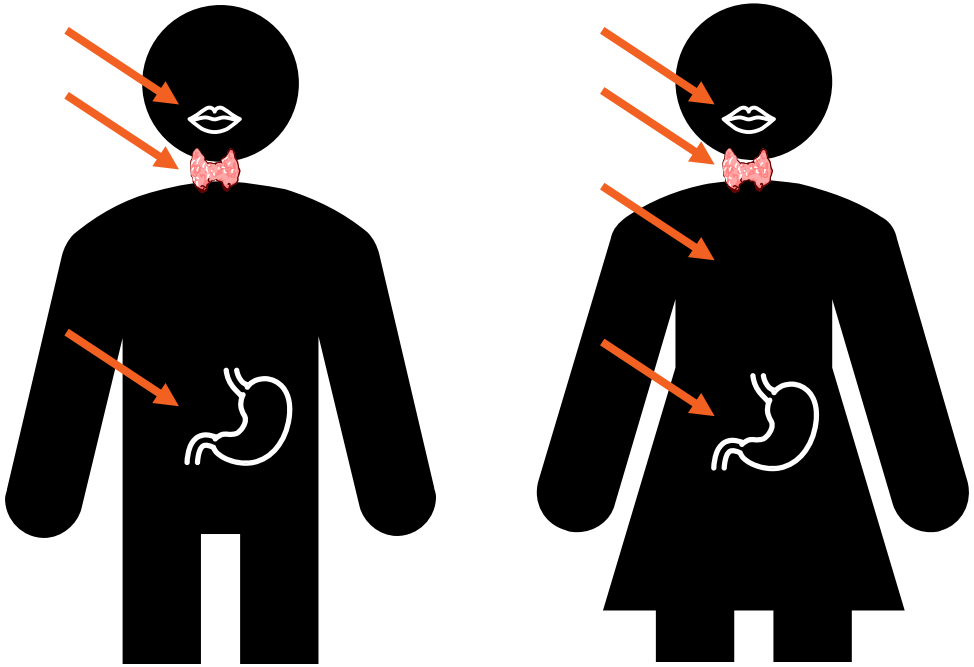
- Variants used for imaging especially through glucose uptake.
- Emits β particles
- 1.8 h Half-Life
- Rapid excretion

Kane SM, Davis DD. Technetium-99m. [Updated 2022 Sep 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559013/*J. Label.; Compd. Radiopharm.* **2021**, *64*, 92-108;
Weeks S, Grossman CE. 131 I Sodium Iodide. [Updated 2022 May 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556145/; Ashraf MA, Goyal A. Fludeoxyglucose (18F) [Updated 2022 Sep 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557653/

Information found on StatPearls Online

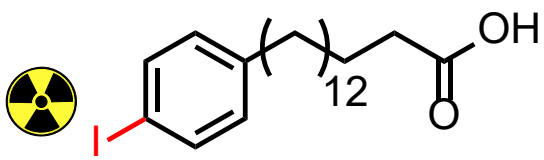
Radioiodide in Medicine



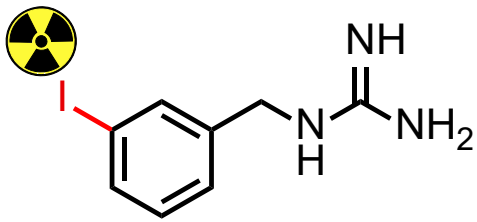


Sodium Iodide Symporter locations limit medicinal possibilities with radioactive NaI.

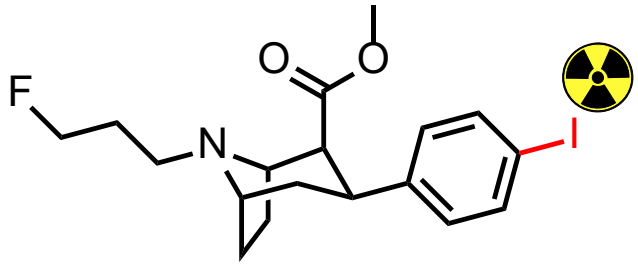
Radioiodine Medications



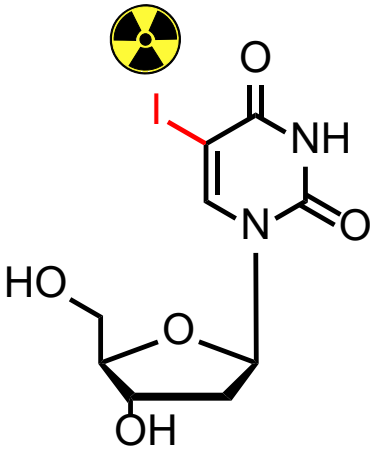
BMIPP
(accepted in Japan)



mIBG (Azedra)

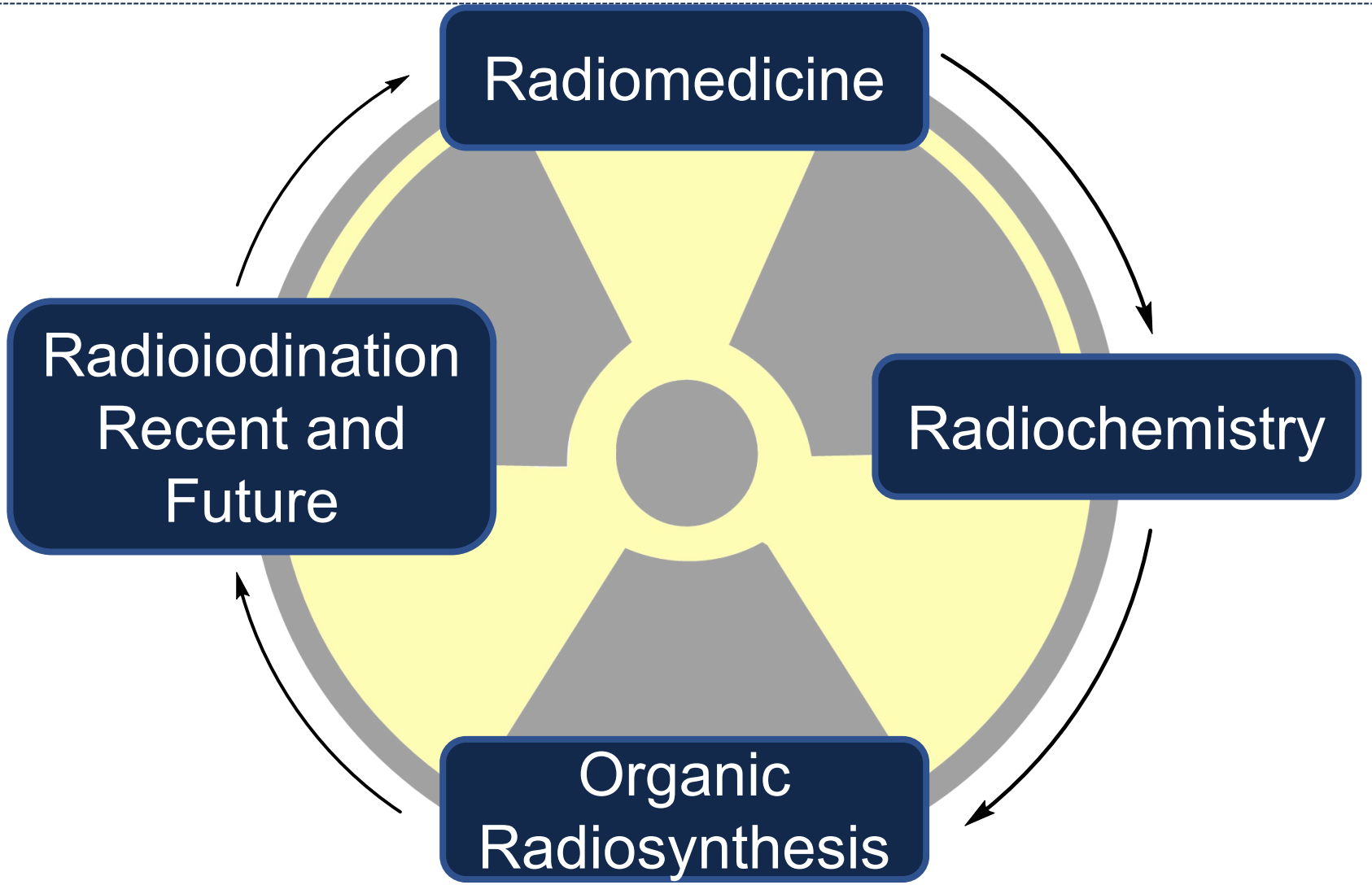


Ioflupane



IUdR
(experimental)

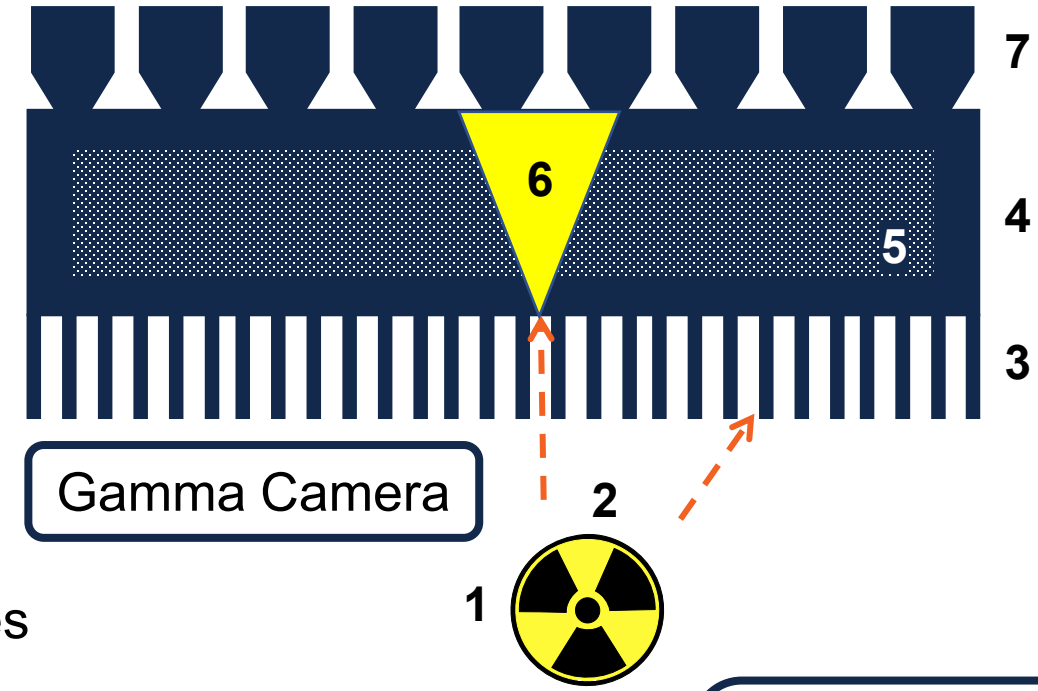
Outline


Radiomedicine
Radiochemistry
Organic Radiosynthesis
Radioiodination Recent and Future

SPECT Detector

Single Photon Emission Computed Tomography

1. Radio label
2. γ Rays
3. Collimators
4. Detector
5. Scintillation Crystal
6. Light Pulse
7. Photomultiplier Tubes

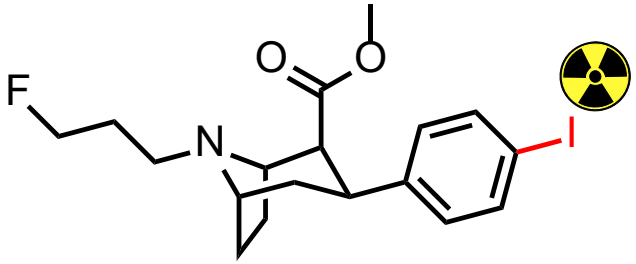


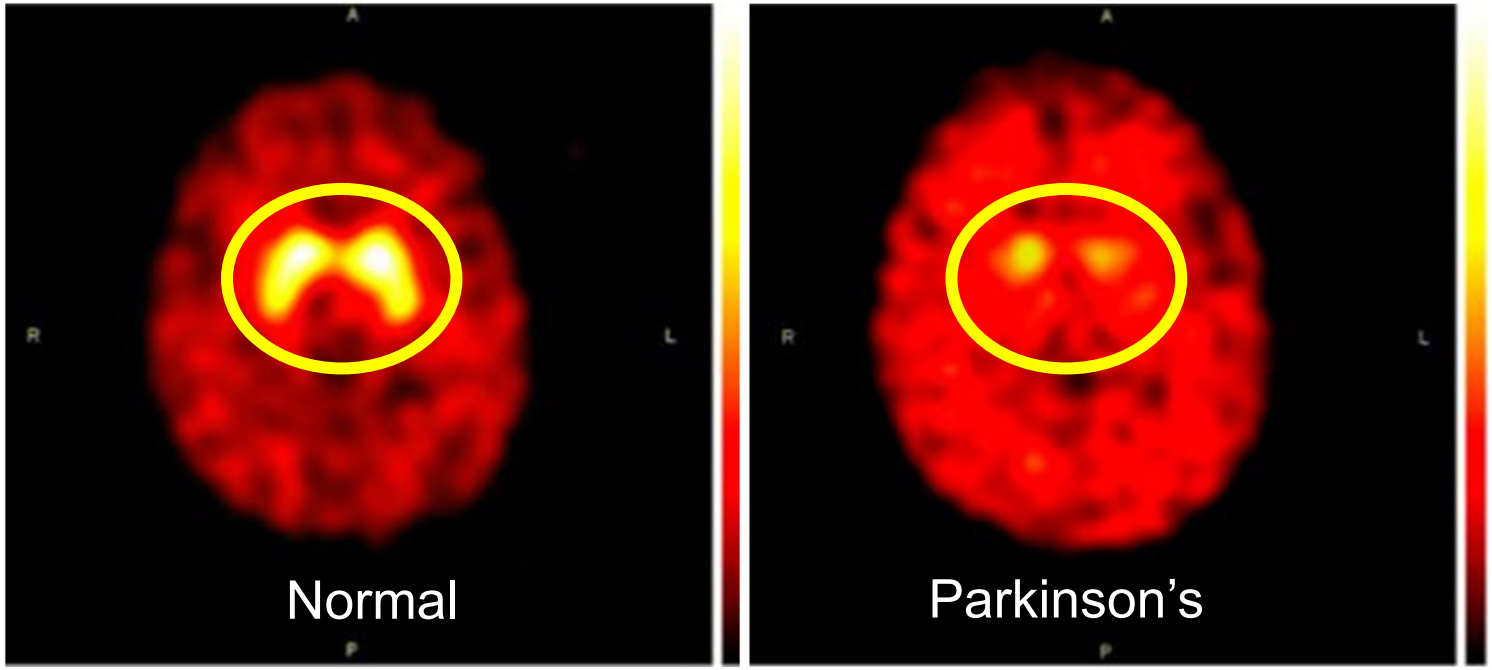
Emission → Conversion → Amplification

The camera is moved around the subject to give a 3D image.

SPECT Parkinson's Diagnosis

Dopamine Transporter Imaging with Ioflupane

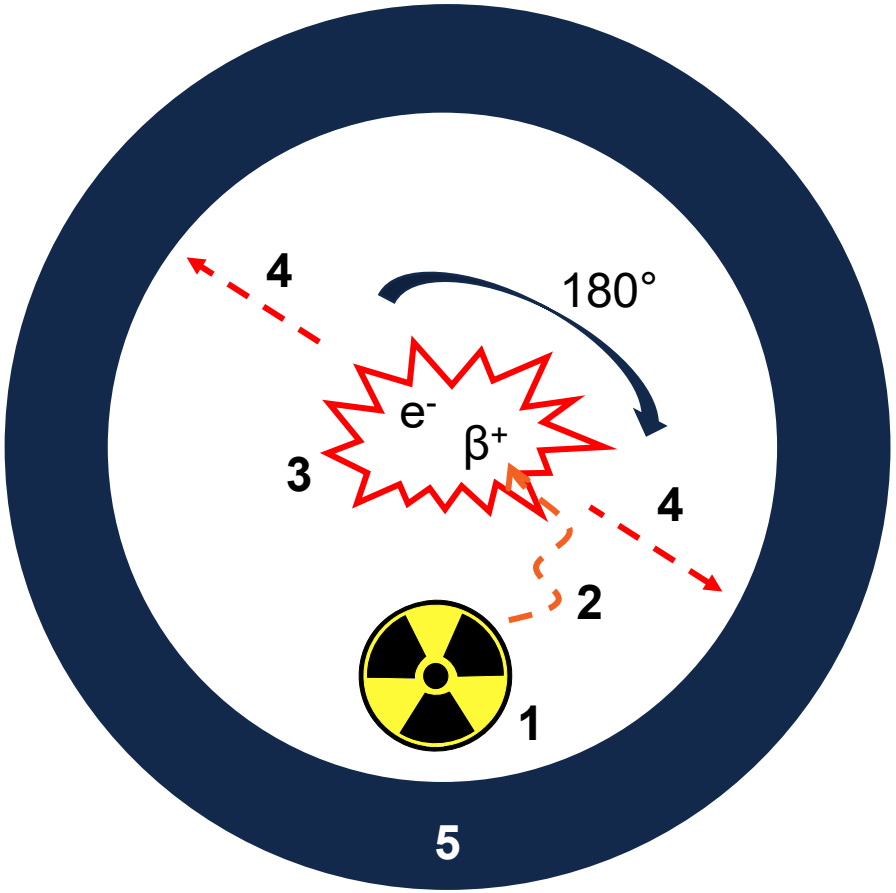




This research was originally published in *JNM*. Chaudhry, A.; Gul, M.; Franceschi, D.; Matthews, R. Pearls and pitfalls of I-123 Ioflupane (DATscan) SPECT imaging. J Nucl Med. 2013;54:1284. © SNMMI.

PET Detector

Positron Emission Tomography

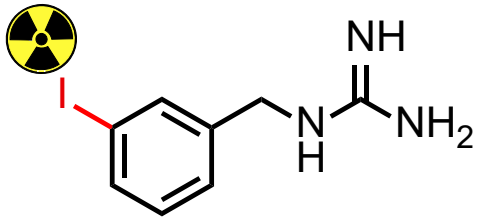


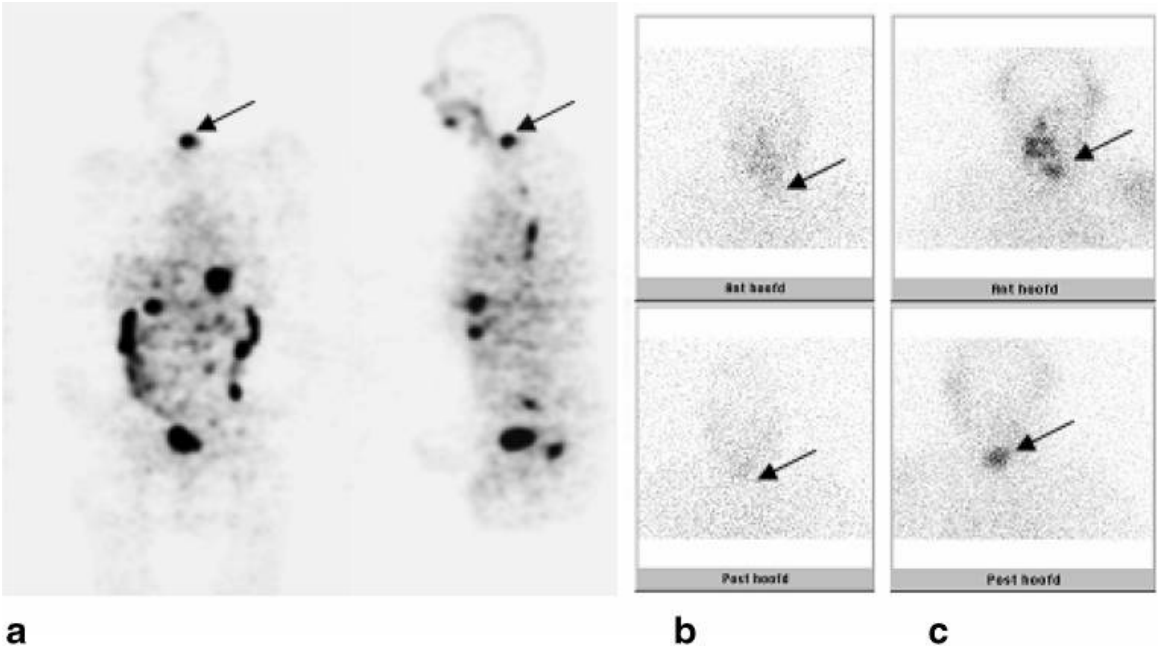
1. Radio label
2. Positron
3. Annihilation
4. γ Rays
5. Detector

The detector is the same as the SPECT detector with no collimators.

PET Image

Thyroid lesion with mIBG (a) and NaI (b & c)





Reused from *Eur. J. Nucl. Med. Mol. Imaging.* ***2008,*** 35, 958-965

Comparison of SPECT to PET

SPECT

- Radio Label Releases
- Re
- $50
- Us
  Distance Accuracy of the Scan

PET

- Radio Label Releases
- gnals
- s
- ble at
- le
- Incident Signals Provide More Reliability in Distances

❖ The choice of radiolabel is dependent on the scan type and the bodily function being analyzed.

Chem. Rev. 2022, 122, 10266-10318; Carle. *Carle Hoopeston Regional Health Care*, Carle, 2022. https://carle.org/patients-visitors/transparent-pricing-and-estimates

Radioiodine Properties

^{123}I

SPECT

^{124}I

PET

^{125}I

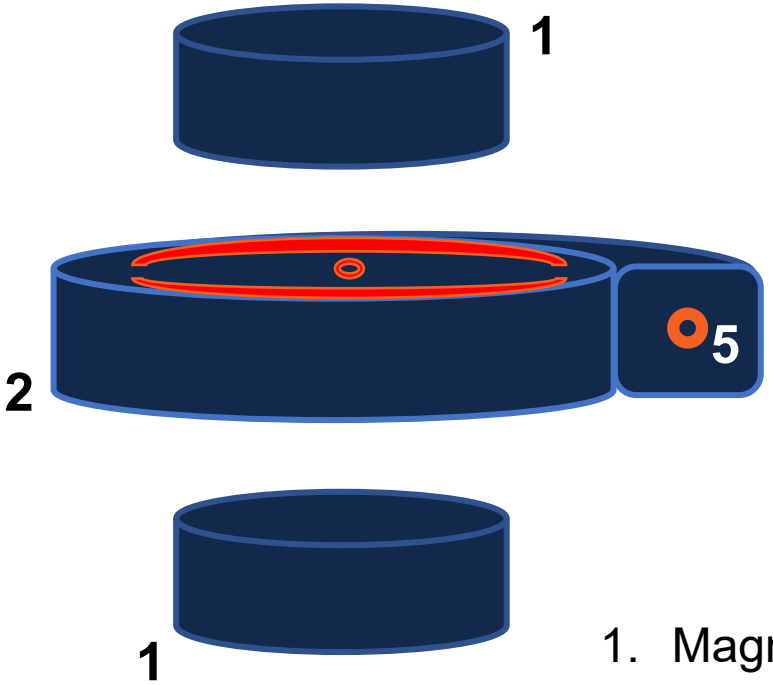
SPECT or Therapeutics

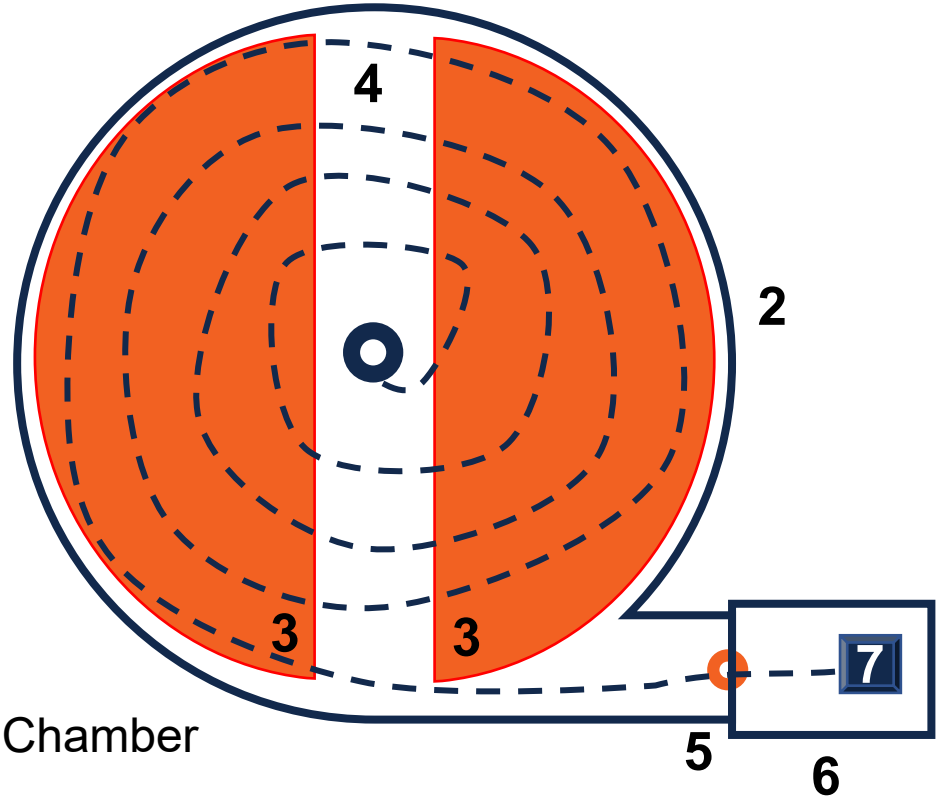
^{131}I

Therapeutics

J. Label. Compd. Radiopharm. **2021**, *64*, 92-108

Radiochemical Cyclotron Bombardment

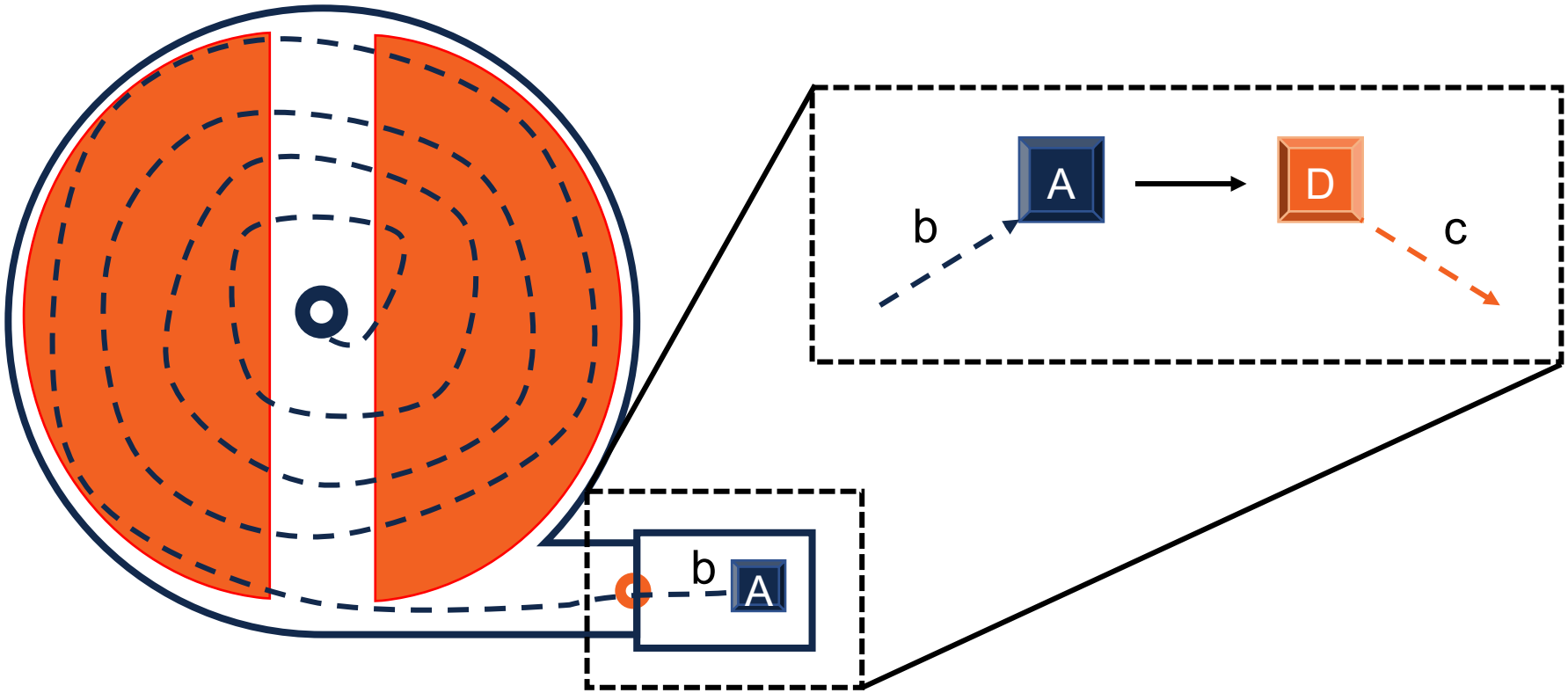




1. Magnet
2. Air-Tight Chamber
3. Dees
4. Particle Path
5. Window
6. Bombardment Chamber
7. Sample

NASA Cyclotron Operation Webpage. https://www1.grc.nasa.gov/historic-facilities/cyclotron/cyclotron-operation/#:~:text=Cyclotrons%20accelerate%20charged%20particles%20and,fields%20to%20accelerate%20the%20particles.

Radiochemical Reaction



A(b,c)D

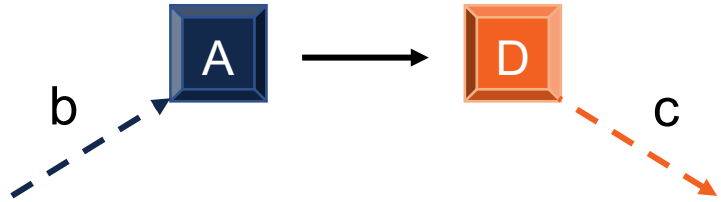
A+b→c+D

p = proton
n = neutron
d = deuteron

α = α particle (^4He)
β = β particle (e^-)
γ = γ ray

NASA Cyclotron Operation Webpage. https://www1.grc.nasa.gov/historic-facilities/cyclotron/cyclotron-operation/#:~:text=Cyclotrons%20accelerate%20charged%20particles%20and,fields%20to%20accelerate%20the%20particles.

Synthesis of Radioiodine (NaI)



^{123}I

$^{121}Sb(\alpha,2n)^{123}I$
$^{124}Te(p,2n)^{123}I$
$^{123}Te(p,n)^{123}I$
$^{127}I(p,5n)^{123}Xe \rightarrow {}^{123}I$

^{124}I

$^{124}Te(d,2n)^{124}I$
$^{124}Te(p,n)^{124}I$

^{125}I

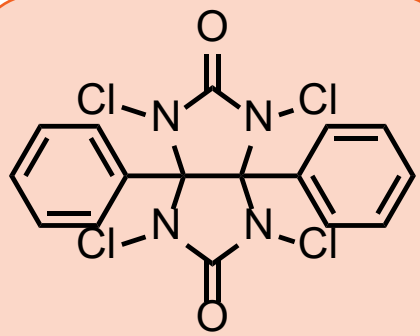
$^{124}Xe(n,\gamma)^{125}Xe(57s) \rightarrow {}^{125}I$
(^{125}Xe metastable)
$^{124}Xe(n,\gamma)^{125}Xe(19.9h) \rightarrow {}^{125}I$
(^{125}Xe gas)

^{131}I

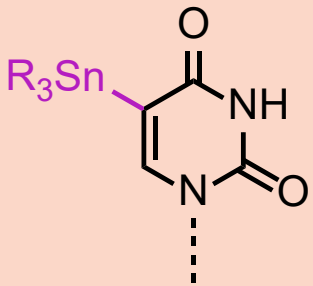
$^{130}Te(n,\gamma)^{131}Te(\beta-) \rightarrow {}^{131}I$
$^{235}U(n,f) \rightarrow {}^{99}Mo$ (^{131}I byproduct)
f = fission

Implications to Organic Synthesis

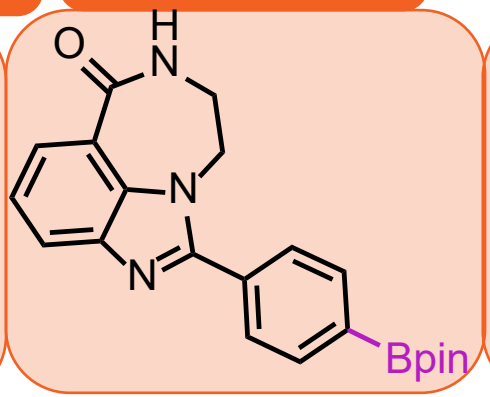
Iodogen



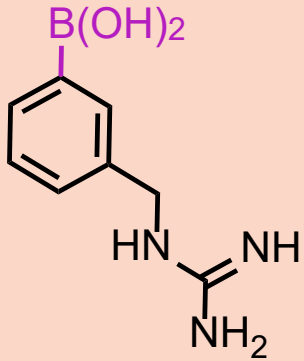
Iododestannylation



Copper Catalyzed



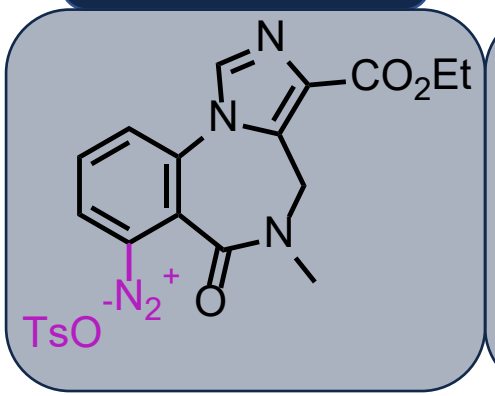
Gold Catalyzed



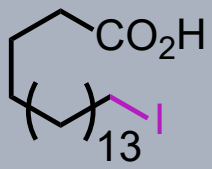
Electrophilic

Nucleophilic

Nucleophilic Exchange



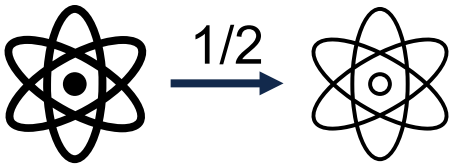
Finkelstein Reaction



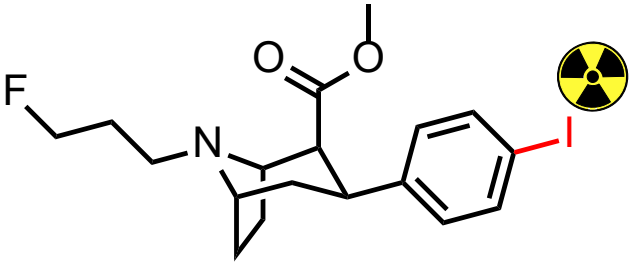
Considerations for Reaction Development

Reactions must be done in house to reduce nuclear decay.

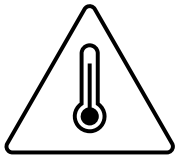
Long Reaction Times



Late Stage Synthesis

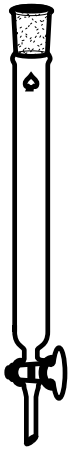


High Temperatures



Organic Solvents

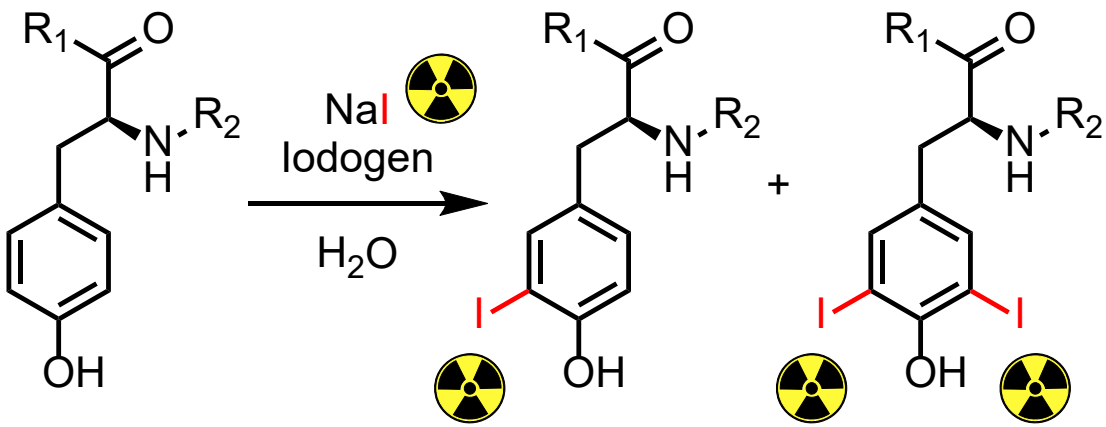
Long Purifications

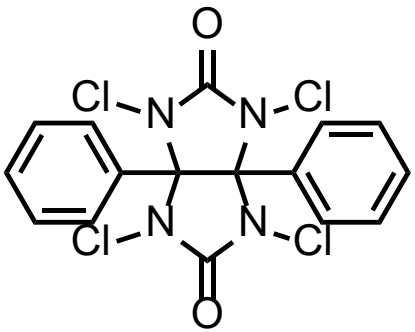


Hazardous Byproducts

Iodogen Radiolabeling

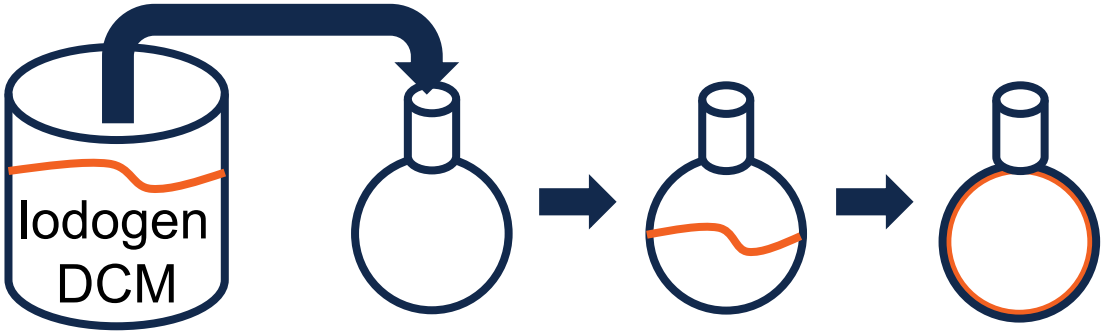
The Most Widely Used in Medicinal Chemistry



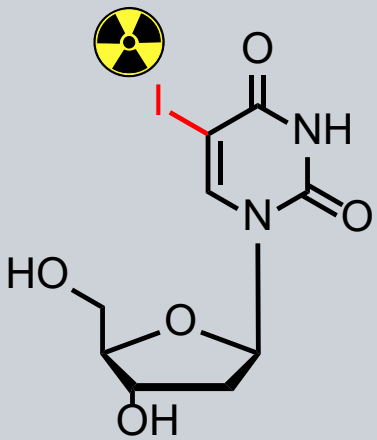


Iodogen

Iodogen is hydrophobic leading to low rates of over-iodination.

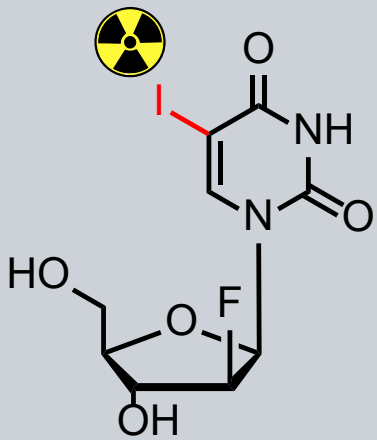


IUdR and FIAU Case Study



IUdR

Delivery to DNA of rapidly dividing tumor cells.



FIAU

Imaging of bacterial infections and tumors associated with herpes.

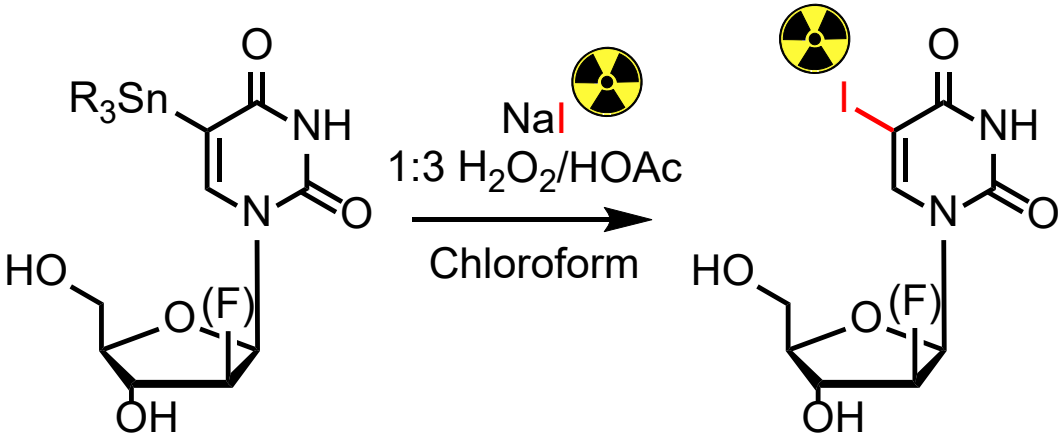
Nomenclature:

RCY: Radio Chemical Yield **RCC**: Radio Chemical Conversion

RCP: Radio Chemical Purity $\mathbf{A_m}$: Molar Activity

J. Org. Chem. **2008**, *73*, 8236-8243, *Nuclear Medicine & Biology.* **1998,** *25*, 487-496

Iododestannylation



R = Me or *i*Pr

85% – 90% RCY

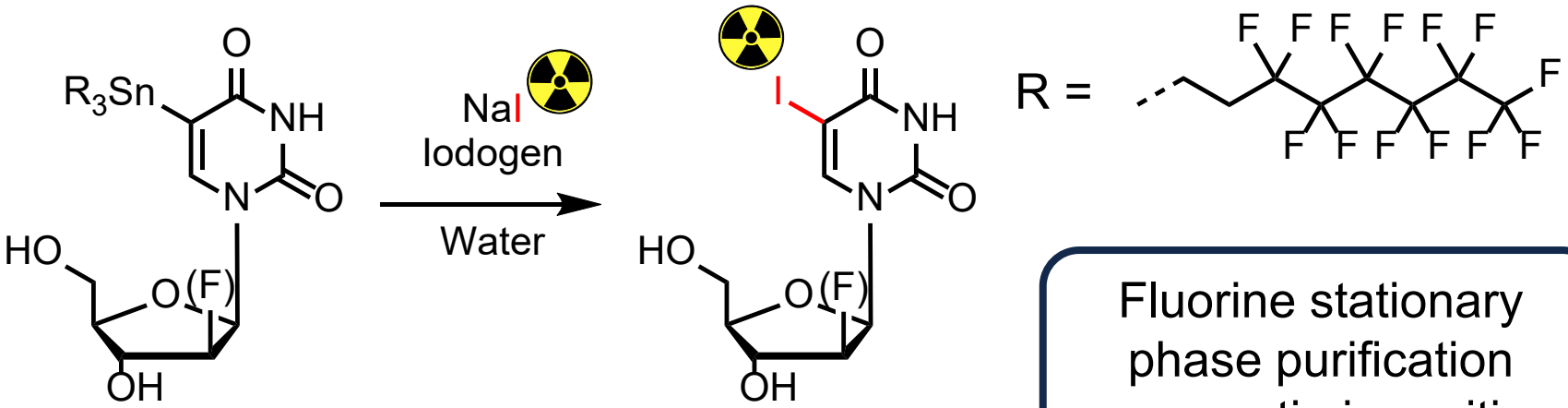
Positives

- High Radio Chemical Yield
- Relatively simple precursor

Negatives

- Results in tin impurities
- HPLC purification required

Flow Purified Iododestannylation



88% - 94% RCY

Fluorine stationary phase purification removes tin impurities.

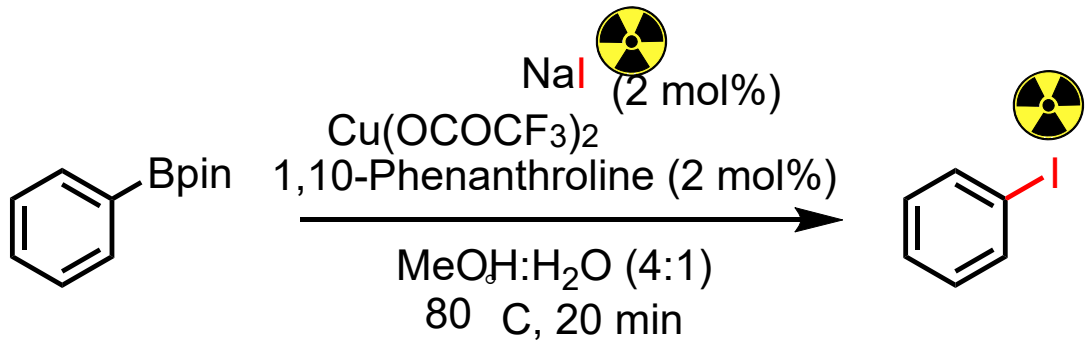
Positives

- High Radio Chemical Yield
- Easy and Fast Purification
- Possible route for solid phase synthesis

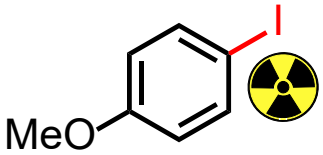
Negatives

- More Difficult Precursor Synthesis
- Still uses hazardous starting materials.

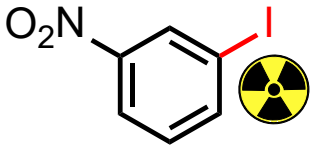
First Copper Catalyzed Conditions



Under Chloramine-T Conditions:

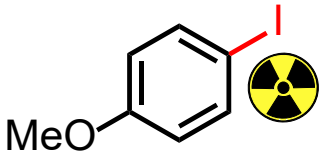


93% RCC

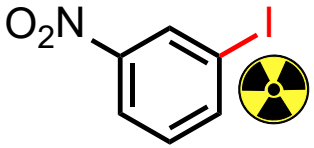


0% RCC

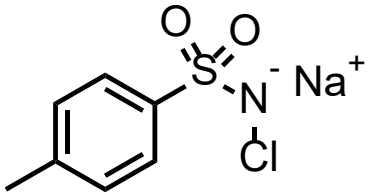
Under Copper Conditions:



80% RCC

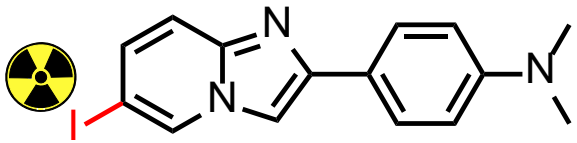


84% RCC



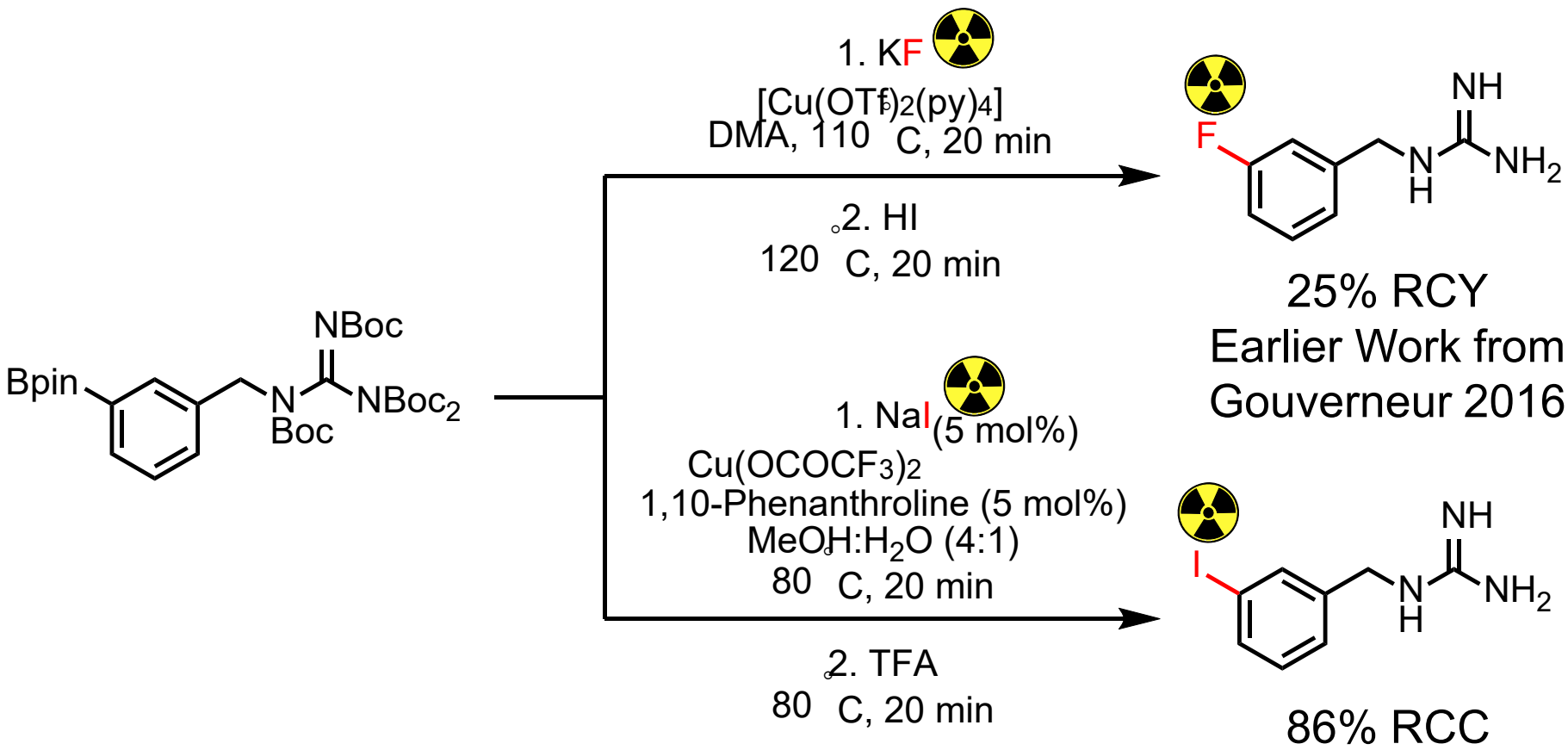
Chloramine-T

Radio Tracers



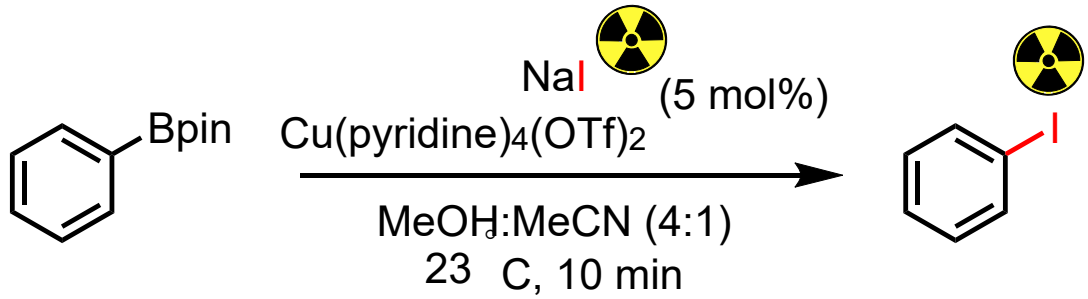
IMPY
89% RCC

Divergent Synthesis



Fast and easy divergent syntheses could be practically useful for diagnostic imaging services.

Modified Copper Catalyzed Conditions



Modifications Made:

Solvent

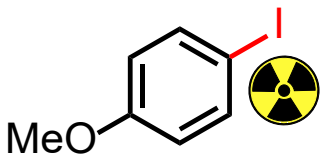
From: $MeOH:H_2O$

To: MeOH:MeCN

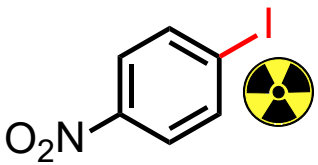
Catalyst

From: $Cu(OCOCF_3)_2$

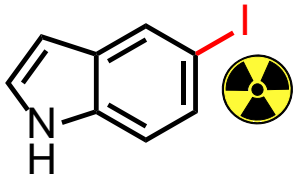
To: $Cu(pyridine)_4(OTf)_2$



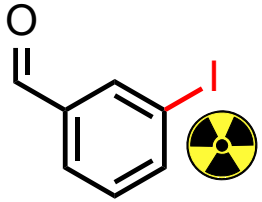
99% RCC



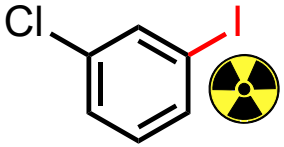
100% RCC



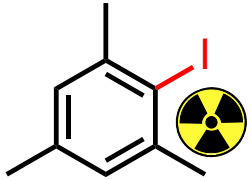
93% RCC



60% RCC

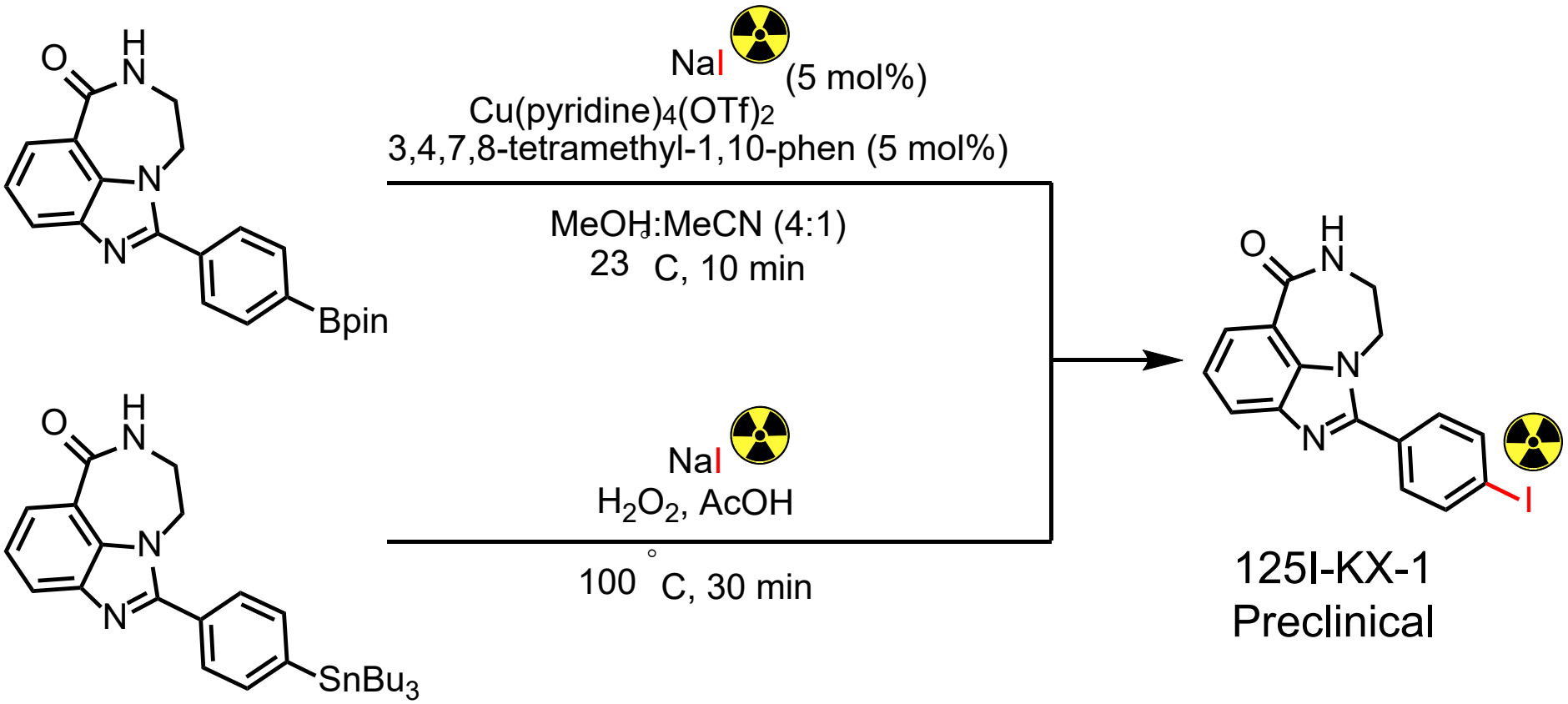


99% RCC



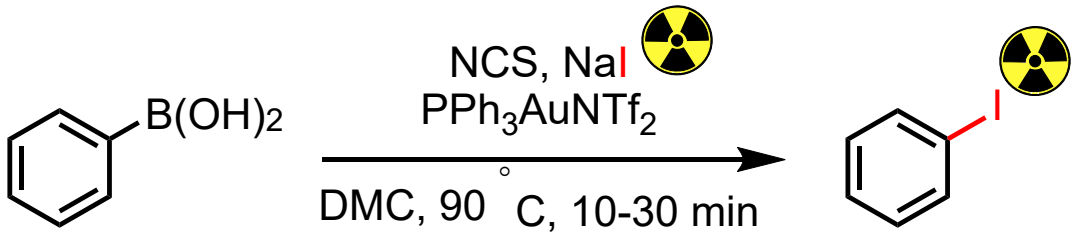
92% RCC

Comparison to Iododestannylation



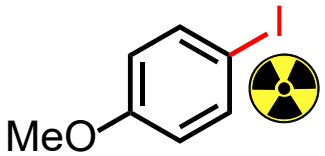
Destannylation: 70% RCC
Copper Catalyzed: 99% RCC

Gold Catalysis

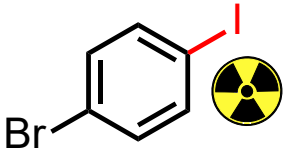


DMC = Dimethylcarbonate

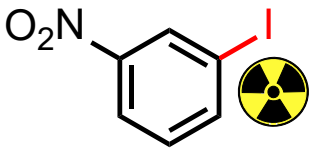
Originally Optimized with cold NIS



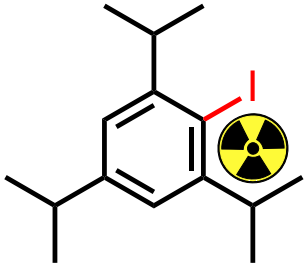
100% RCY



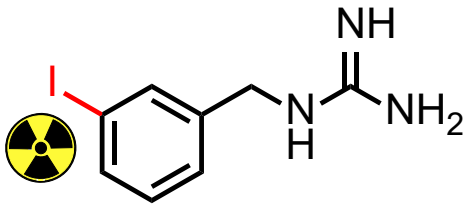
97% RCY



100% RCY

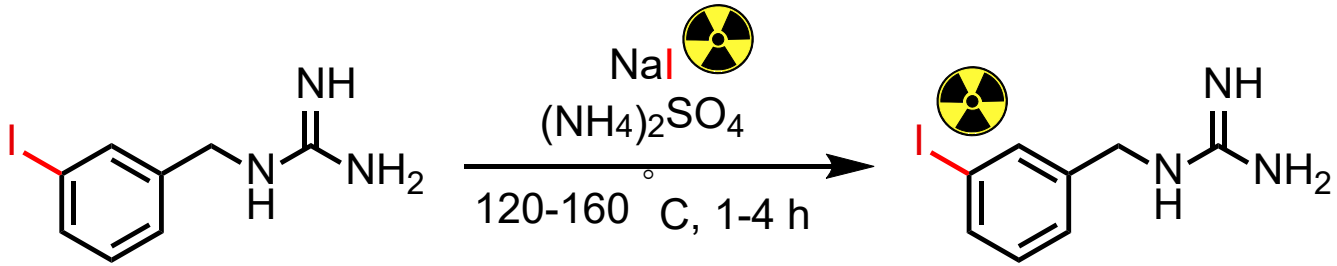


0% RCY



91% RCY

Halogen Exchange



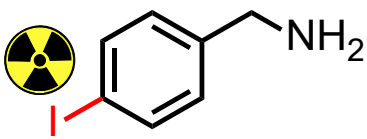
Reaction driven by loss of ammonia and pH stability.

Positives

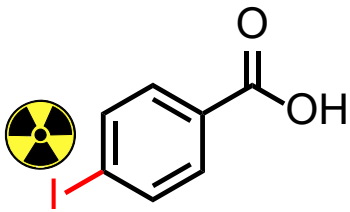
- Requires no organic solvents
- High yielding for similar structures

Negatives

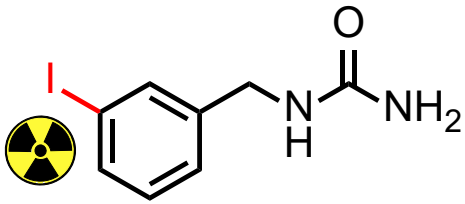
- Purification of nonquantitative products can be difficult
- High reaction temperatures
- Long reaction times
- Limited substrate scope



90% RCY

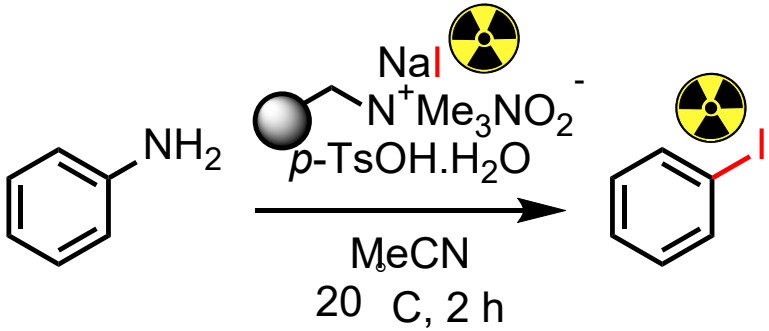


96% RCY



70% RCY

Diazonium Salt Assisted Exchange



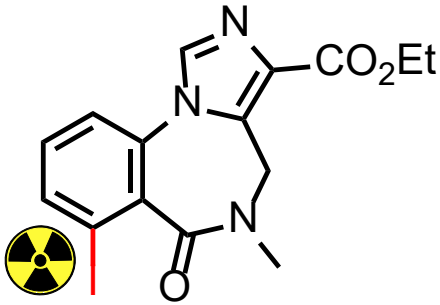
Polymer supported diazonium avoids hazardous intermediates and could allow for solid phase synthesis

Positives

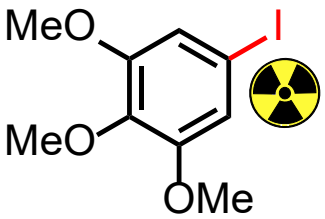
- Easier purification
- High yields on varying substrates
- Wider substrate scope

Negatives

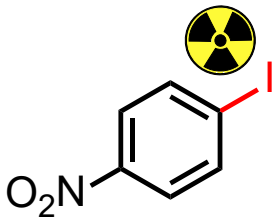
- Uses organic solvent
- Long reaction times



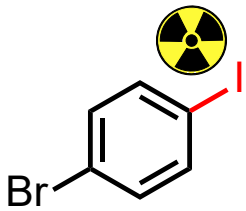
92% RCY



94% RCY

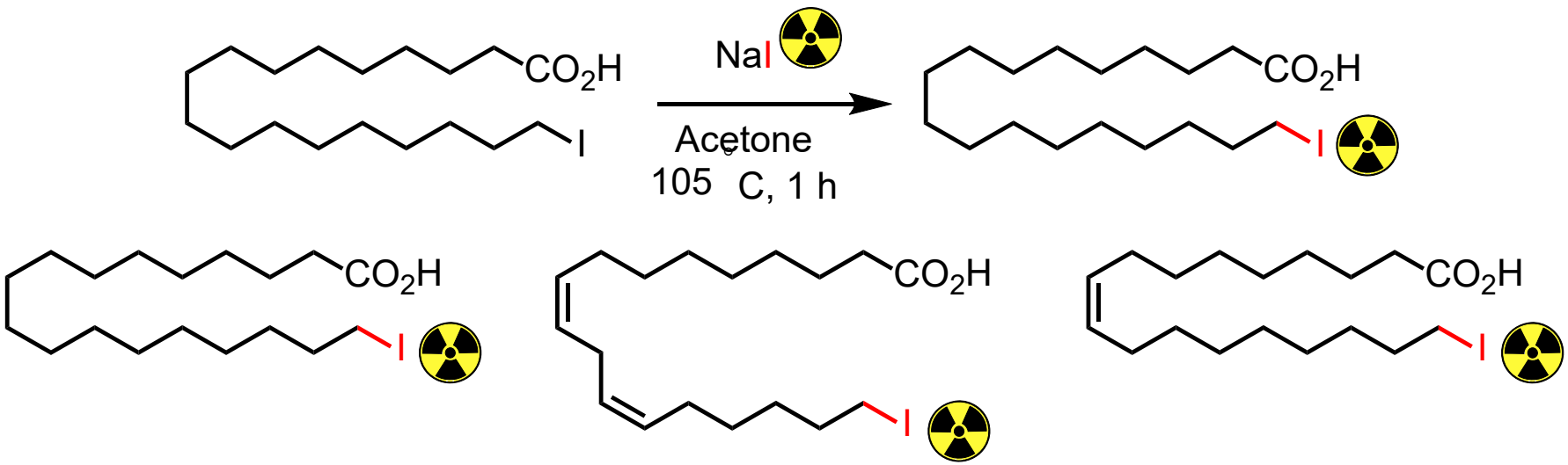


93% RCY



73% RCY

Finkelstein Reaction



All products obtained at >95% RCY

Positives

- Simple procedure
- Can use alkyl iodides or alkyl bromides
- Generally high yielding
- Allows for easier imaging

Negatives

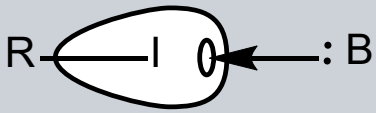
- May not be widely feasible for imaging.

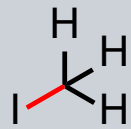
Important Structural Considerations

Organic iodides are susceptible to deiodination in vivo.

van der Waals radius (Å):
C :1.70 I : 2.15

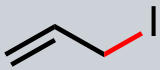
σ-hole weakening





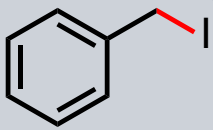
BDE 237.72 kJ/mol

BDE 201.87 kJ/mol

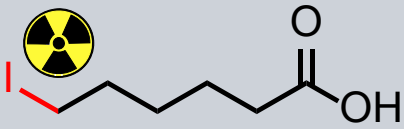


BDE 184.51 kJ/mol

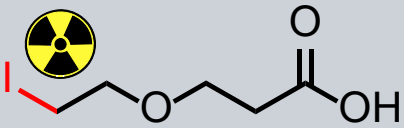
BDE 206.27 kJ/mol



BDE 167.36 kJ/mol



Unstable In Vivo

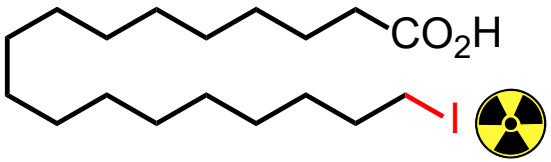


Stable In Vivo

Novel medicine must take into account possible decomposition and route of decomposition.

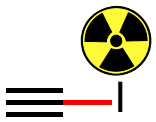
Future of Radioiodination

Csp^3 Radioiodination



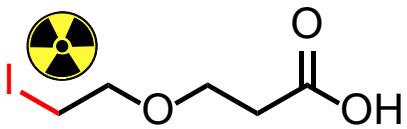
Larger scope expanding past halogen exchange

Csp Radioiodination



Csp radioiodination is largely unknown.

Logical Medicinal Design



Biologists and organic chemists need to work together for the most optimal reaction design.

Questions?