Radiopharmaceutical chemistry with carbon-11

Educational session

NKRV Petten, February 9, 2024

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Radboudumc

History

1939
- First reported use of $[^{11}C]CO_2$
- Photosynthesis mechanism

1945
- First reported in human studies
- Uptake of $[^{11}C]CO$ in red blood cells

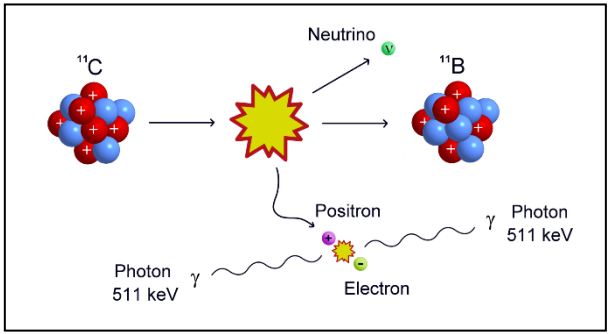
1973
- First reported synthesis of $[^{11}C]$methyl iodide
- Most commonly used synthon

1976
- Synthesis of L-[*methyl*-^{11}C]methionine
- Amino acid used in (brain) tumour imaging

G Antoni, *J. Label. Compd. Radiopharm.* **2015**, *58*, 65-72.

Properties of carbon-11

- Radioactive decay via positron emission (98.1% β^+)



- Short half life: $t_{½}$ = 20 min
  - Demands fast production process
    - **Max. 60 min** from end of proton bombardment in cyclotron to injectable product
    - On-site cyclotron is essential

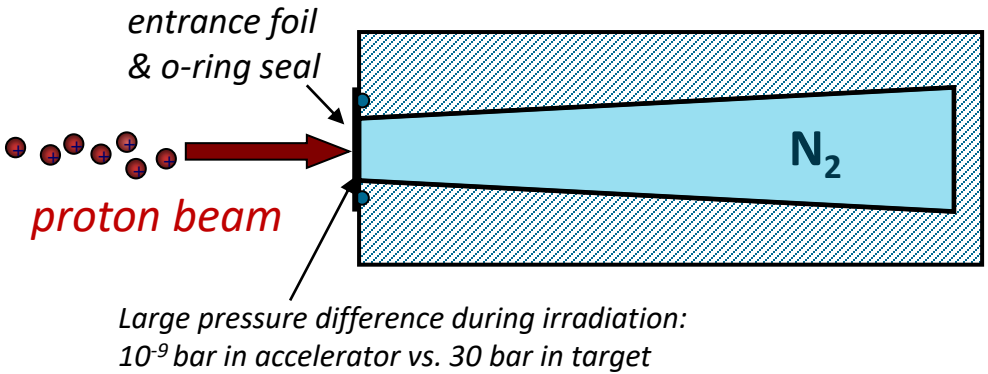
Radionuclide	$t_{½}$ (min)
^{11}C	20.38
^{13}N	9.97
^{15}O	2.04
^{18}F	109.77

Why use carbon-11?

- Essential atoms of life: carbon, nitrogen, oxygen, hydrogen
  - Virtually all (drug-like) molecules contain multiple carbon atoms
- Enables radiolabelling of (drug) molecules without altering molecular structure
  - No effect on binding affinity, pharmacokinetics
  - In case of registered drugs – no need for additional tox studies before clinical PET
- Low radiation burden for patient
- Possibility of doing multiple scans on the same day in (pre)clinical research setting
- Increased sensitivity of digital and whole body PET systems beneficial for use of short-lived isotopes

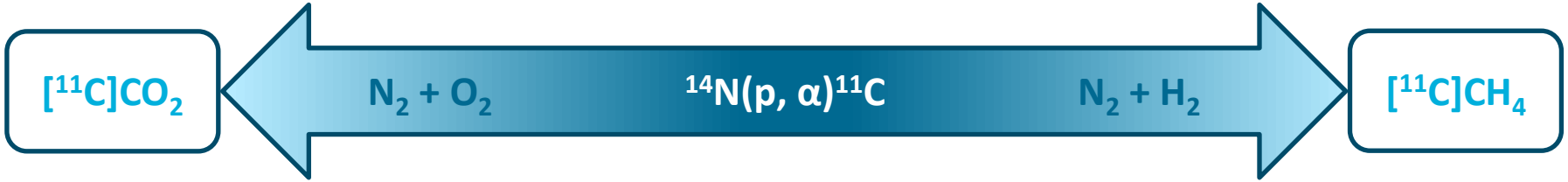
Production of carbon-11

- N_2 gas irradiated with high energy protons (16-18 MeV)
- Nuclear reaction: $^{14}N(p, \alpha)^{11}C$



Production of carbon-11

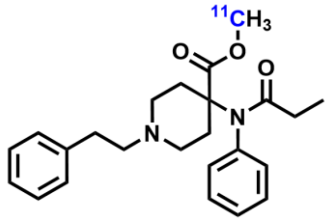
- Product obtained after irradiation dependent on target gas:



- Starting point for virtually all carbon-11 radiopharmaceutical chemistry

Molar activity (A_m)

- Amount of radioactivity per unit mass of element/compound in GBq/µmol
- Maximum theoretical molar activity: 340918 GBq/µmol
  - For 40 GBq $[^{11}C]CO_2$ this equals 0.12 nmol
- In practice, 40 GBq $[^{11}C]CO_2$ equals 20-100 nmol at end of bombardment
  - A_m = 400-2000 GBq/µmol
- Minimal required molar activity for clinical use: 18.5 GBq/µmol at end of tracer synthesis



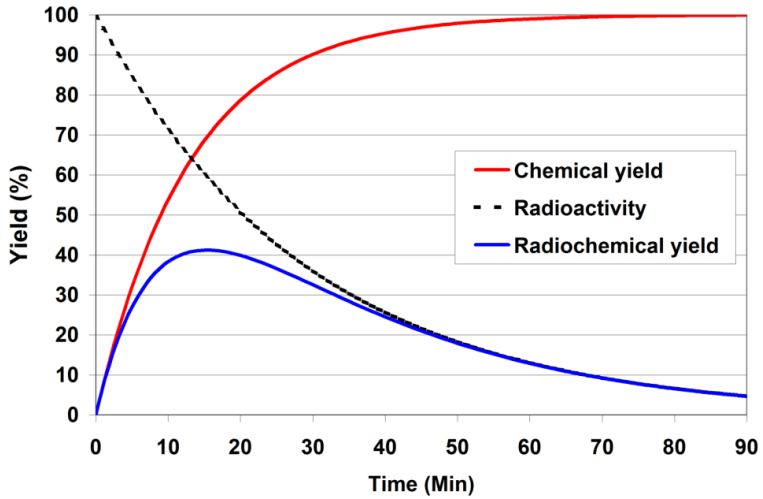
[^{11}C]carfentanil

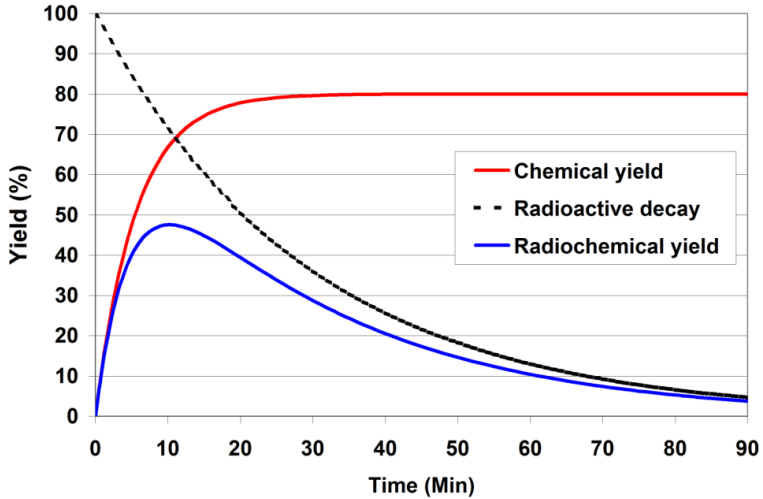
µ-opioid receptor (K_i = 0.051 nM)

Sources of isotopic dilution

- CO_2 from air (380 ppm), impurities in process gasses
  - Demands use of closed, leak tight systems and high purity gasses
- Processes yielding CO_2 during target irradiation
  - Combustion of carbonous materials
  - Migration and desorption of CO_2 from target holder bulk metal
- Use of reagents reactive towards CO_2 at ambient temperatures
  - E.g. Grignard, organolithium compounds
- Generally, use of $[^{11}C]CH_4$ yields products with higher A_m compared with $[^{11}C]CO_2$

Influence of reaction kinetics on radiochemical yield

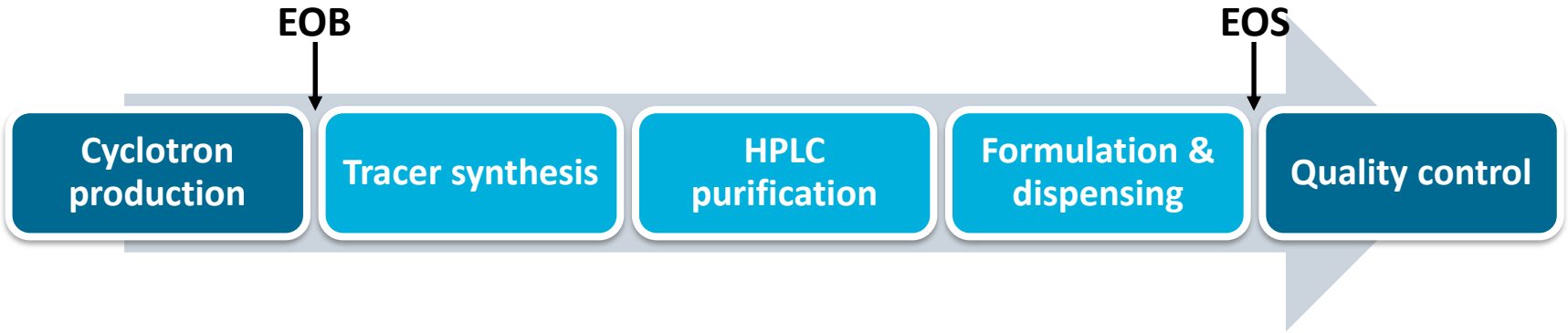




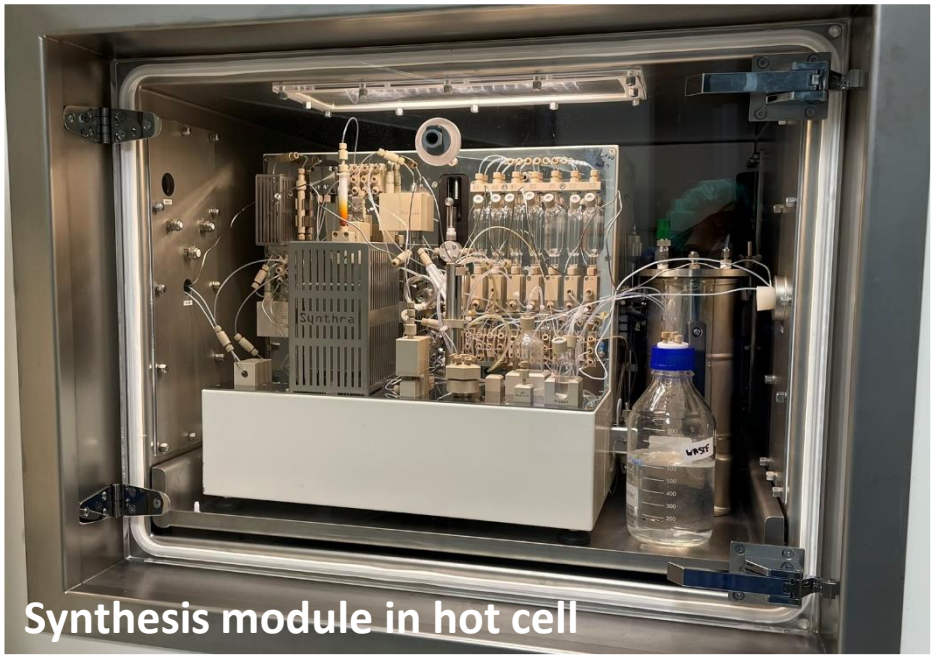
Maximum chemical yield ≠ maximum radiochemical yield

Characteristics of carbon-11 radiochemistry

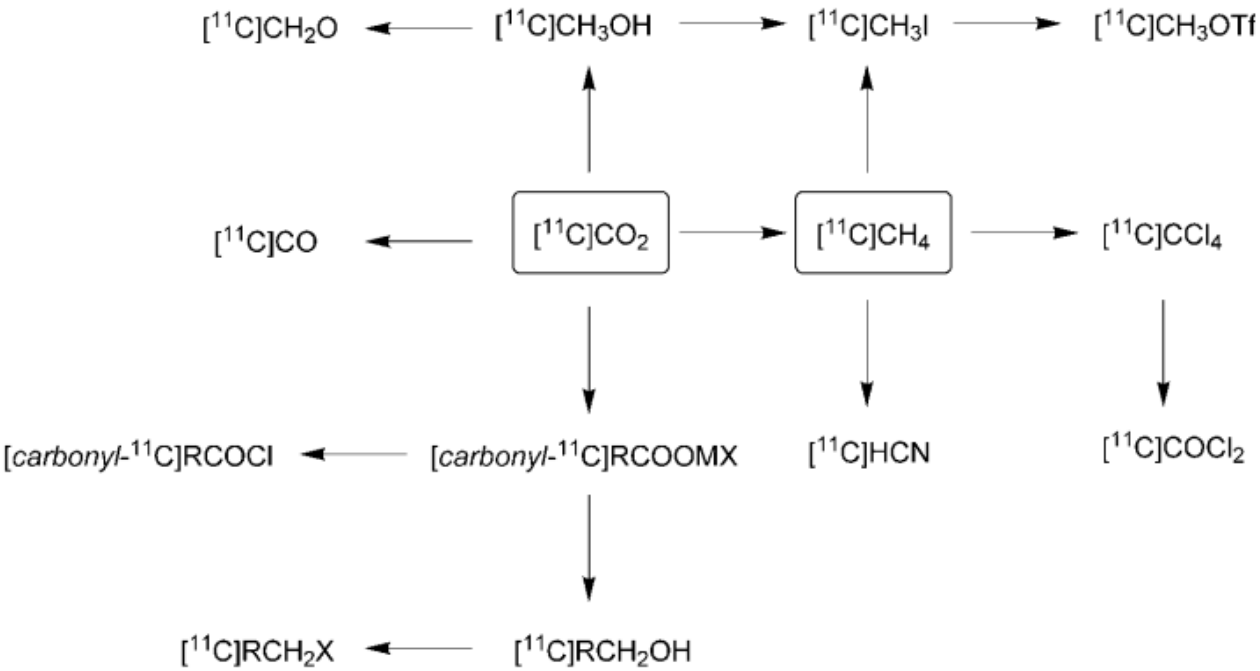
- Late stage incorporation of carbon-11 in target structure
- Fast reaction kinetics
- Remote controlled and automated synthesis devices
- Reliable – especially important for clinical practice!
- Total synthesis time EOB→EOS <60 min



Facilities & Equipment



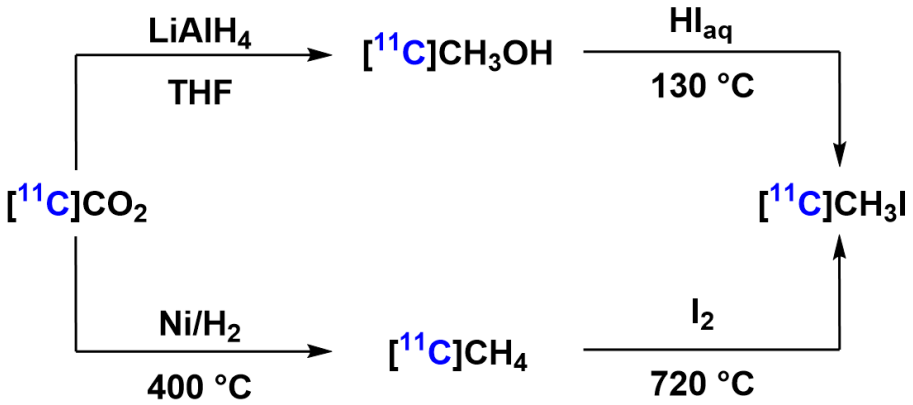
Carbon-11 synthons



PW Miller *et al.*, *Angew. Chem. Int. Ed.* **2008**, *47*, 8998-9033.

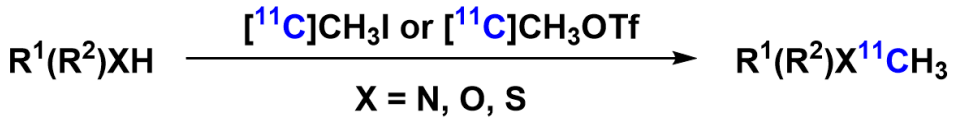
[^{11}C]methyl iodide ([^{11}C]CH_3I)

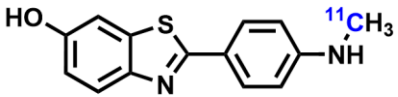
- Most used secondary carbon-11 precursor
- Two commonly applied synthesis routes: “wet” vs “gas phase” method
- [^{11}C]CH_3I can be converted on-line to more reactive [^{11}C]CH_3OTf



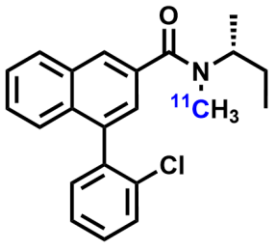
Carbon-11 methylation

- Most commonly used labelling method using [^{11}C]methyl iodide
- N-, O- or S- methylation reactions (nucleophilic substitution)
  - Mostly primary and secondary amines and phenols

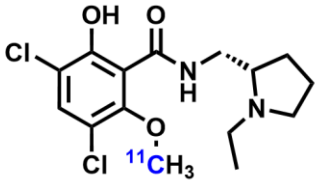




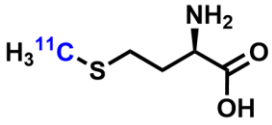
[^{11}C]PiB
Amyloid β plaques



(*R*)-[^{11}C]PK11195
Translocator protein (TSPO)



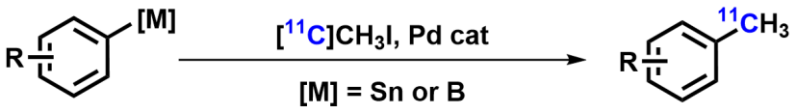
[^{11}C]Raclopride
Dopamine receptors

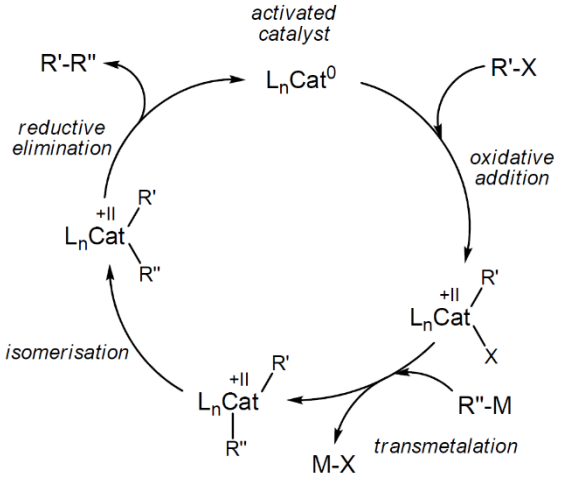


L-[*methyl*-^{11}C]methionine
amino acid transport

Cross coupling reactions with $[^{11}C]CH_3I$

- Transition metal mediated C-C bond formation
  - Well known examples are Stille, Suzuki and Sonogashira reactions





Cat - catalyst (e.g. Pd)

L - ligand

R', R'' - organic moities

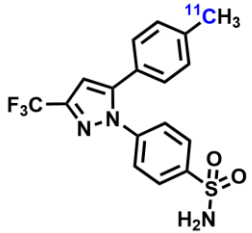
X - halide

M - (transition)metal

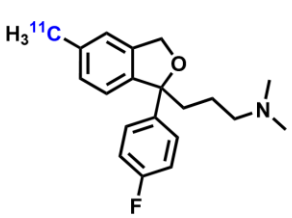
n - number of ligands

Cross coupling reactions with $[^{11}C]CH_3I$

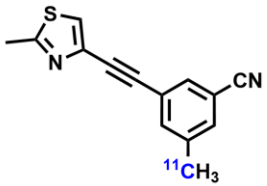
- Stille and Suzuki cross coupling yield the same product
  - Use of different precursor: tin (Stille) vs boron (Suzuki) based
    - Suzuki not restricted to aromatic methyl groups



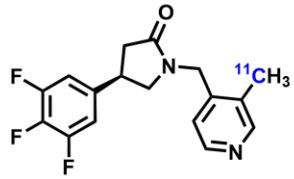
[^{11}C]celecoxib
Cyclooxygenase 2 inhibitor



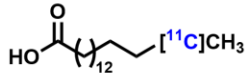
[^{11}C]citalopram analogue
Selective serotonin reuptake inhibitor



[^{11}C]M-MTEB
Metabotropic glutamate receptor subtype 5



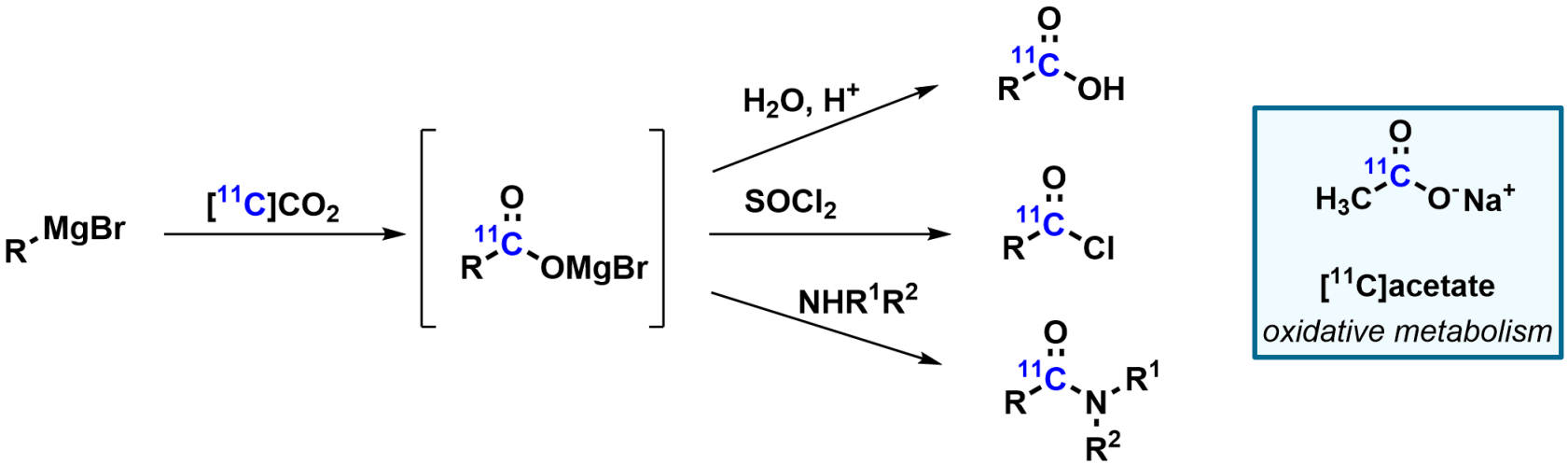
[^{11}C]UCB-J
Synaptic vesicle glycoprotein 2A



[^{11}C]palmitate
Fatty acid metabolism

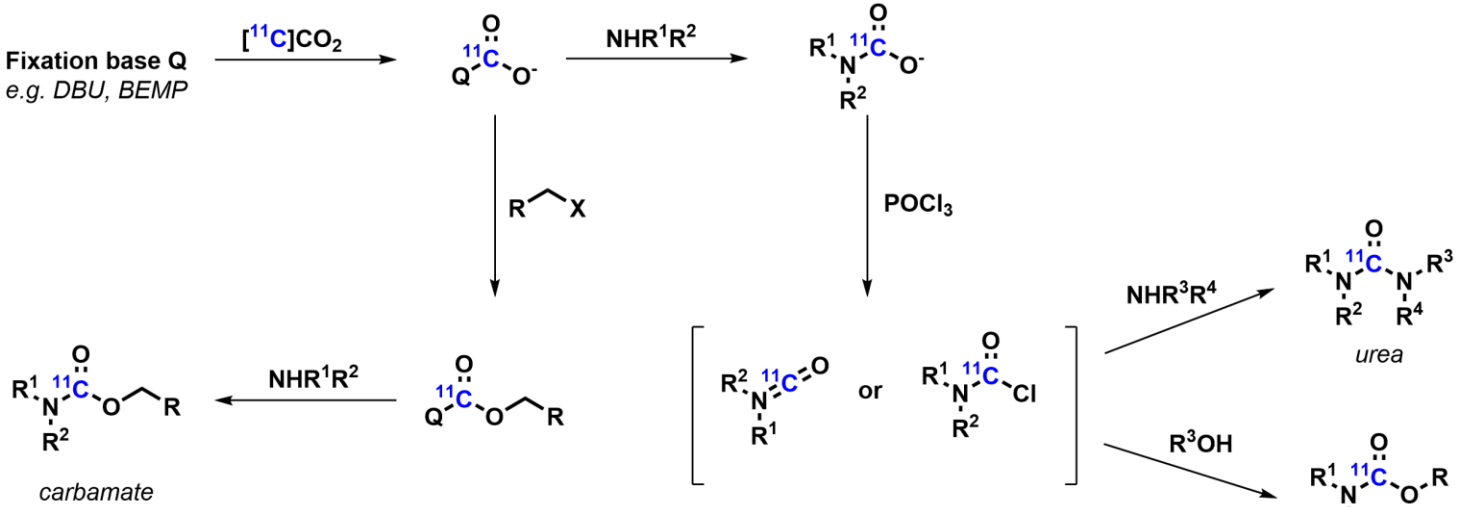
Organometallic chemistry with [^{11}C]CO_2

- Cyclotron produced primary precursor
  - Mostly used in Grignard chemistry to obtain carboxylic acids and derivatives
    - Well known example: [^{11}C]acetate



$[^{11}C]CO_2$ "fixation" chemistry

- Increased chemical utility for $[^{11}C]CO_2$
  - Availability of carbamates and ureas



BH Rotstein *et al.*, *Chem. Commun.* **2013**, *49*, 5621.

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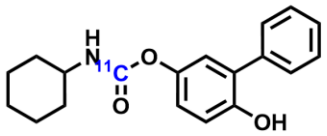
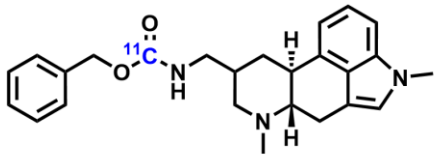
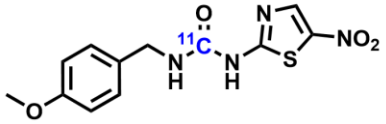


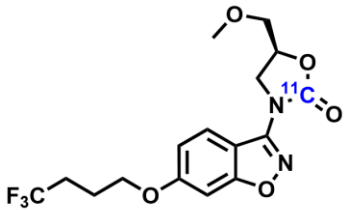
[^{11}C]CURB
Fatty acid amide hydrolysis



[^{11}C]metergoline
serotonin 5HT antagonist



[^{11}C-*carbonyl*]AR-A014418
selective GSK-3β inhibitor

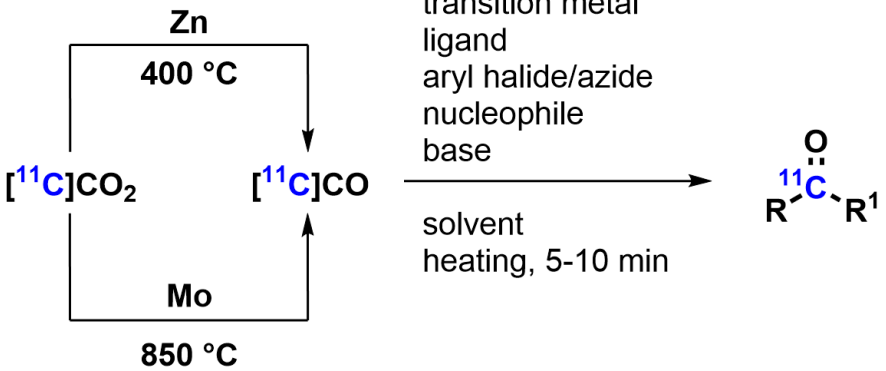


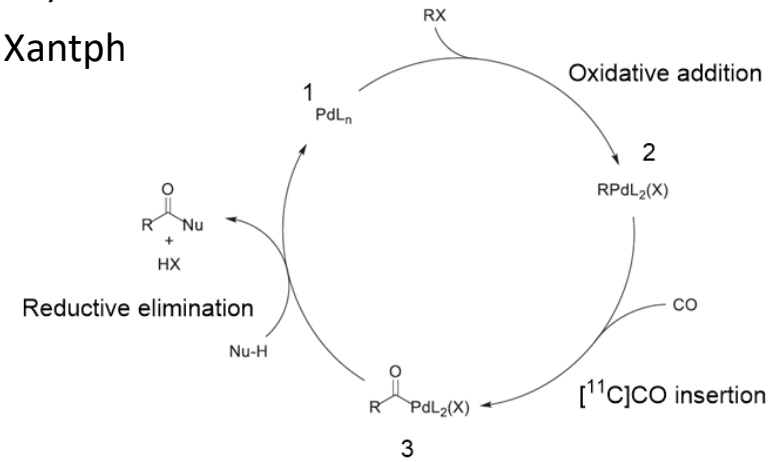
[^{11}C]SL25.1188
monoamine oxidase-B inhibitor

BH Rotstein *et al.*, *Chem. Commun.* **2013**, *49*, 5621.

Transition metal mediated carbonylation with [^{11}C]CO

- Reduction of [^{11}C]CO_2 over Zn or Mo at high temperatures
  - Challenge: trapping of [^{11}C]CO in reaction mixture
    - Use of high pressure systems (e.g. autoclave)
    - More recently: low pressure systems (Xe, Xantph

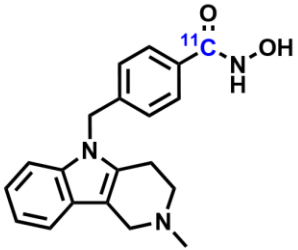




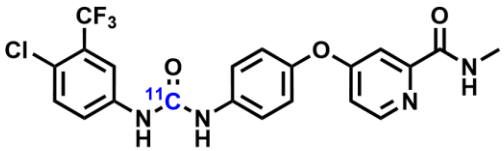
J Eriksson *et al.*, *Nuc. Med. Biol.* **2021**, *92*, 115-137; K Dahl *et al.*, *Eur. J. Org. Chem.* **2013**, 1228-1231.

Transition metal mediated carbonylation with [^{11}C]CO

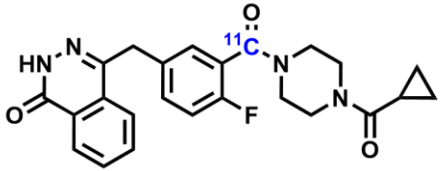
- Wide variety of functional groups, e.g. amides, ureas, ketones, hydroxylamines, acrylamides, acylsulfonamides
- Most reported reactions Pd- or Rh-mediated



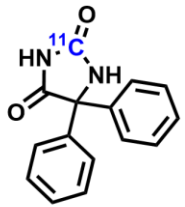
[^{11}C]tubastatin A
Histone deacetylase 6 inhibitor



[^{11}C]sorafenib
Tyrosine kinase inhibitor



[^{11}C]olaparib
PolyADP ribose polymerase inhibitor

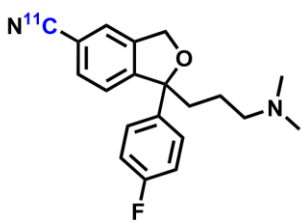


[^{11}C]phenytoin
P-gp substrate

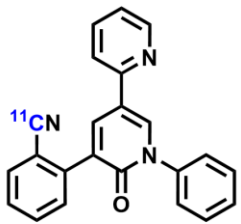
J Eriksson *et al*., *Nuc. Med. Biol.* **2021**, *92*, 115-137.

[^{11}C]hydrogen cyanide

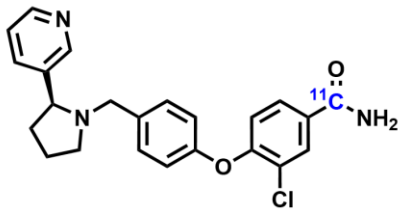
- Synthesis of aliphatic and aromatic nitriles, amino acids



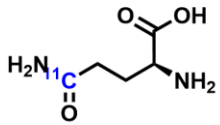
[^{11}C]citalopram
Selective serotonin reuptake inhibitor



[^{11}C]perampanel
AMPA receptor antagonist



[^{11}C]LY2795050
κ opioid receptor



L-[^{11}C]glutamine
amino acid

[^{11}C]phenylalanine
amino acid

X Deng *et al.*, *Angew. Chem. Int. Ed.* **2019**, *58*, 2580-2605.

Take home messages

- Carbon-11 is a versatile PET radioisotope that can be incorporated in various drug-like molecules
- Development of new carbon-11 radiopharmaceutical methodology allows for expanding number of molecules that can be labelled
- Carbon-11 allows for multiple scans a day with low radiation burden – especially interesting for (pre)clinical research purposes

Further reading

- G Antoni, *J. Label. Compd. Radiopharm.* **2015**, *58*, 65-72.
- PW Miller *et al.*, *Angew. Chem. Int. Ed.* **2008**, *47*, 8998-9033.
- X Deng *et al.*, *Angew. Chem. Int. Ed.* **2019**, *58*, 2580-2605.
- BH Rotstein *et al.*, *Chem. Commun.* **2013**, *49*, 5621.
- J Eriksson *et al.*, *Nuc. Med. Biol.* **2021**, *92*, 115-137.

- **Book**: Radiopharmaceutical Chemistry (chapters 11 & 12), Lewis, Windhorst, Zeglis Eds., Springer, 2019.

Acknowledgements

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