Beyond FDG

Manufacturing of ^{11}C and ^{18}F Radiopharmaceuticals

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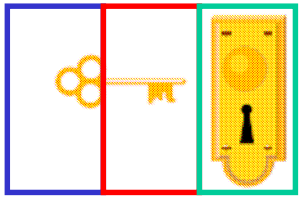
II Symposium on Positron Emission Tomography September 21st - 24th 2014, Jagiellonian University, Kraków, Poland

Outline

- Fluorine chemistry
- Fluorinated PET Radiopharmaceuticals
- ^{11}C labeling
- Carbon labeled Radiopharmaceuticals
- Perspectives

PET Radioisotopes

Radiotracer - chemical compound consists of:



Radioisotope: a radionuclide with physical data suitable for external measurement

Bioconjugate : a molecule with suitable pharmacokinetics, and high concentrations in the target organ or process

PET Radioisotopes

Useful radionuclides

- ^{18}F – half-life 110 min.
- ^{11}C - half-life 20 min.
- ^{15}O - half-life 2 min.
- ^{13}N - half-life 10 min.

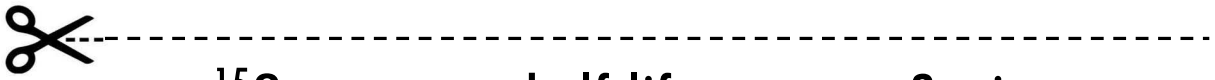
Radionuclide scissors

- Shorter halflife – radiation exposure
- Longer halflife – clinical availability

PET Radioisotopes

Useful radionuclides

- ^{18}F – half-life 110 min.
- ^{11}C - half-life 20 min.



- ^{15}O - half-life 2 min.
- ^{13}N - half-life 10 min.

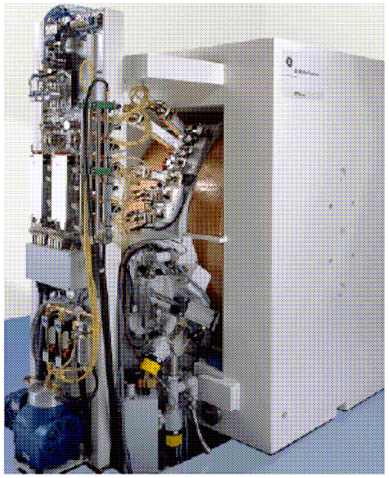
Radionuclide scissors

- Shorter halflife – radiation exposure
- Longer halflife – clinical availability

Isotopes production

Cyclotron

IBA 18/9



GE PETrace 8

Siemens RDS

Isotopes production

Target for liquids

Production ^{18}F :

Reaction: $^{18}O(p,n)^{18}F$

Target: $H_2{}^{18}O$ c, 95% ^{18}O

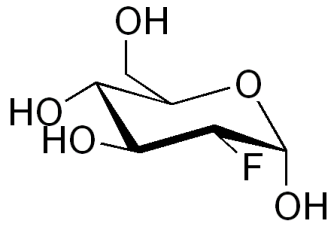
Product: $^{18}F^-$

Application in medicine

Oncology

Principle:

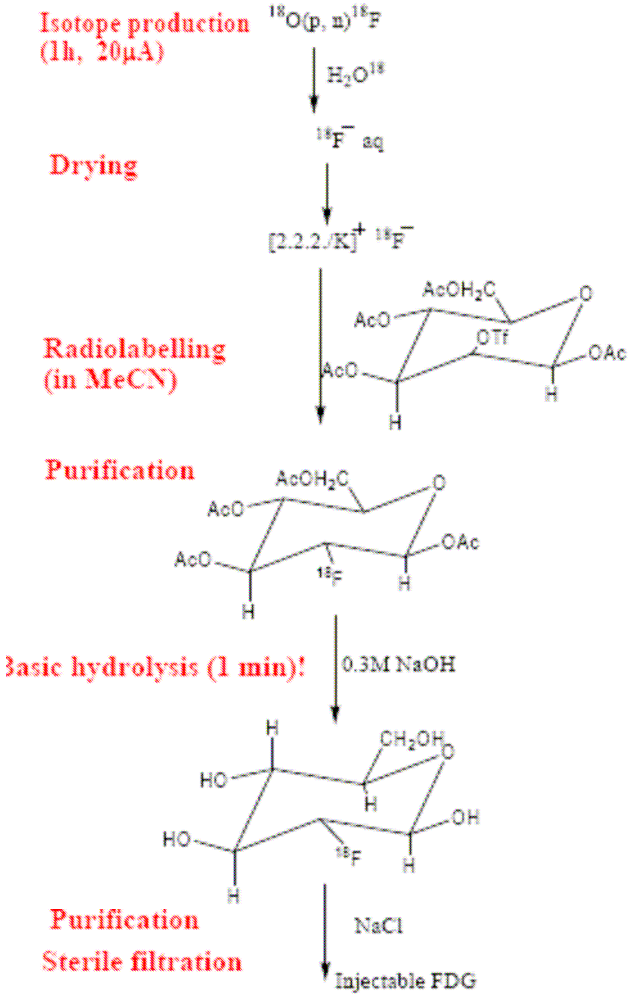
- increased glycolysis in tumor cells – *Warburg phenomenon* – 20-30-times higher glucose metabolism



^{18}F-FDG (2-Deoxy-2-fluoro-D-glucose)

Standard radiopharamceutic in clinical practice: diagnosis of most cancers

^{18}FDG Synthesis



Füchtner et al. App. Radiat. Iso. 47, 61-66, 1996

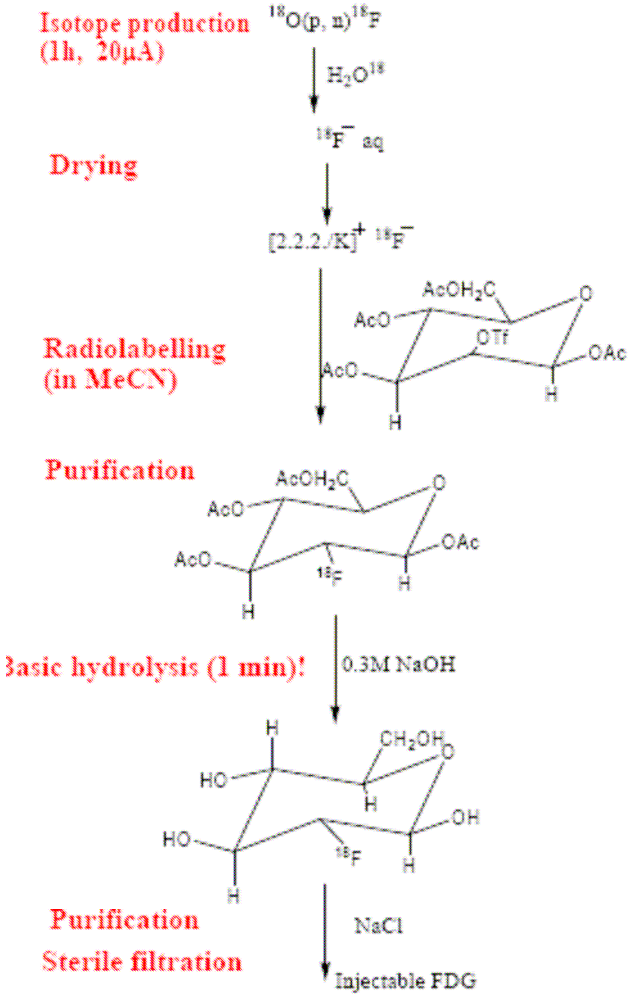
- Step 1: Production ^{18}F
- Step 2: Separation $^{18}F^-$
- Step 3: Drying
- Step 4: Elution ^{18}F
- Step 5: Labeling
- Step 6: Deprotection
- Step 7: Purification
- Step 8: Formulation
- Step 9: Dispensing

^{18}FDG limitations

- FDG: normal increased uptake
  - brain gray matter
  - myocardium
  - active muscle
  - urine tract (bladder)
- FDG: abnormal increased uptake
  - infection
  - inflammation
  - post-treatment areas
- FDG: low uptake : low grade tumors

Problem: When sugar is used by others, or not at all...

Nucleophilic fluorination



Füchtner et al. App. Radiat. Iso. 47, 61-66, 1996

- Step 1: Production ^{18}F
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- Step 3: Drying
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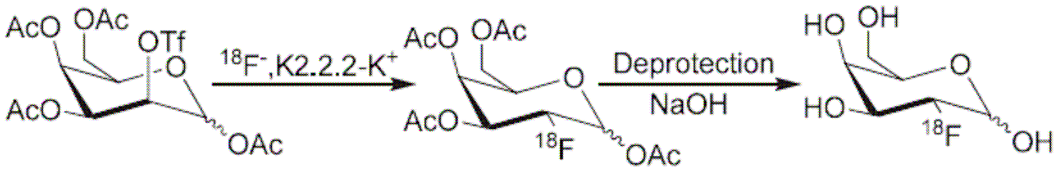
Nucleophilic fluorination

- Aliphatic nucleophylic fluorination $[^{18}F]F^-$ with protection of other groups



- Most popular ^{18}F labeling method:
  - precursor with active group (Br, I, sulphonates, triflates) and protective groups
  - aprotic solvent: acetonitrile, DMF (dimethylfomamide), DMSO, temp.80-180°C, 5-30 min.

Application in medicine

Oncology

Principles:

- increased glycolysis in tumor cells – *Warburg phenomenon* – 20-30-times higher glucose metabolism
- increased permeability of biological membranes of tumor cells
- increased protein synthesis
- specific reactions

Beyond FDG – FDM...

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NATURE MEDICINE | TECHNICAL REPORT

日本語要約

2-deoxy-2-[^{18}F]fluoro-D-mannose positron emission tomography imaging in atherosclerosis

Nobuhiro Tahara, Jogeshwar Mukherjee, Hans J de Haas, Artiom D Petrov, Ahmed Tawakol, Nezam Haider, Atsuko Tahara, Cristian C Constantinescu, Jun Zhou, Hendrikus H Boersma, Tsutomu Imaizumi, Masataka Nakano, Aloke Finn, Zahi Fayad, Renu Virmani, Valentin Fuster, Lisardo Bosca & Jagat Narula

Affiliations | Contributions | Corresponding author

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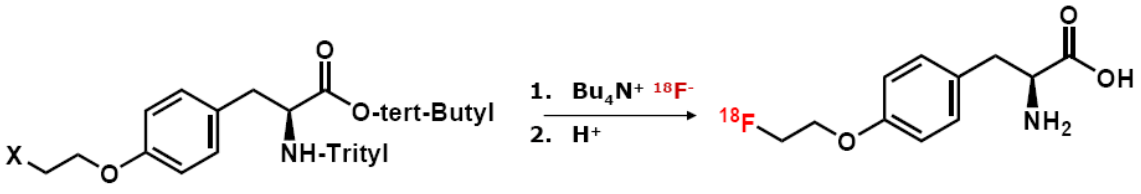
^{18}FET

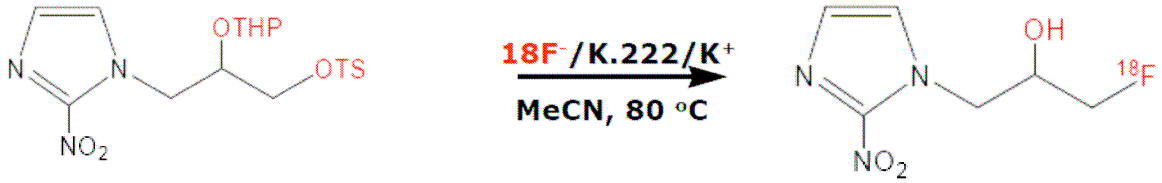
^{18}F Fluoroethylotyrosine [^{18}F] FET



Uptake and metabolism is similar to amino acids and signal is proportional to amino acid uptake and protein synthesis. Mainly used for brain tumor imaging.

F-MISO

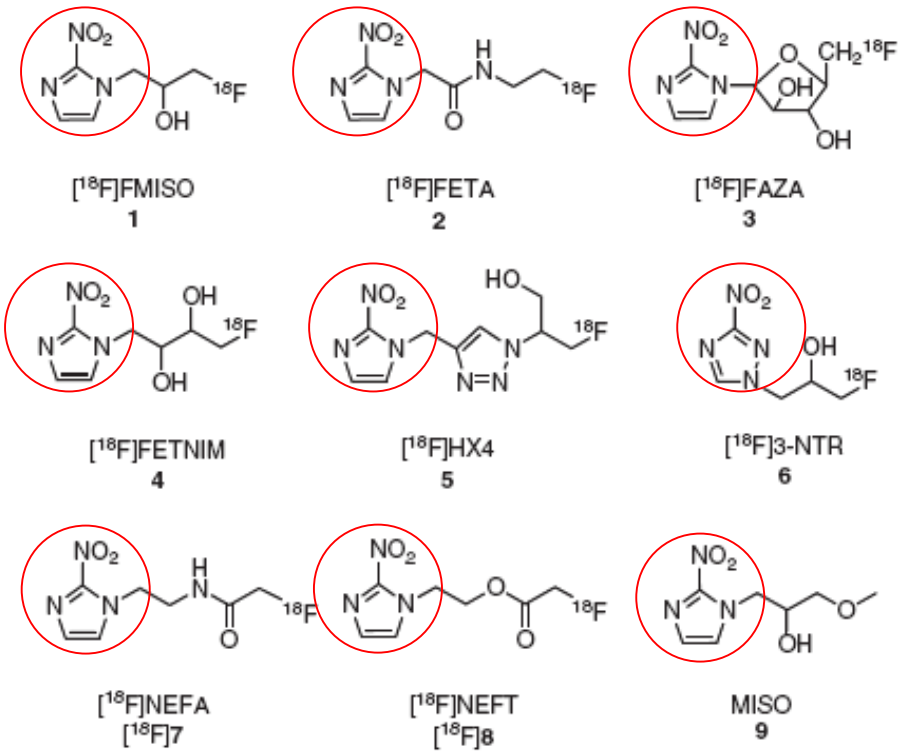
^{18}F fluoromisonidasole [^{18}F]MISO



Demonstrates hypoxia in tumorand distinguishes hypoxic tissues

18F-MISO Analogs

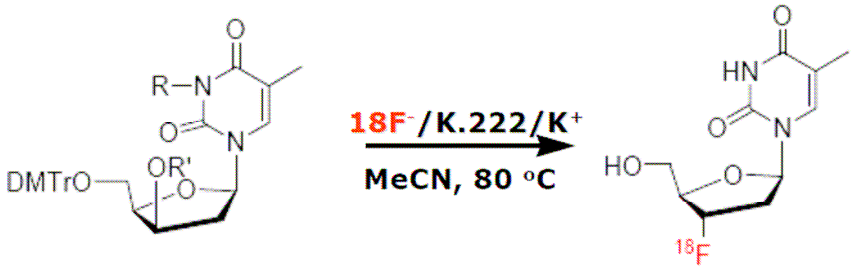
^{18}F-Miso Analogs



Z. Zha et al. / Nuclear Medicine and Biology 38 (2011) 501–508

^{18}FLT

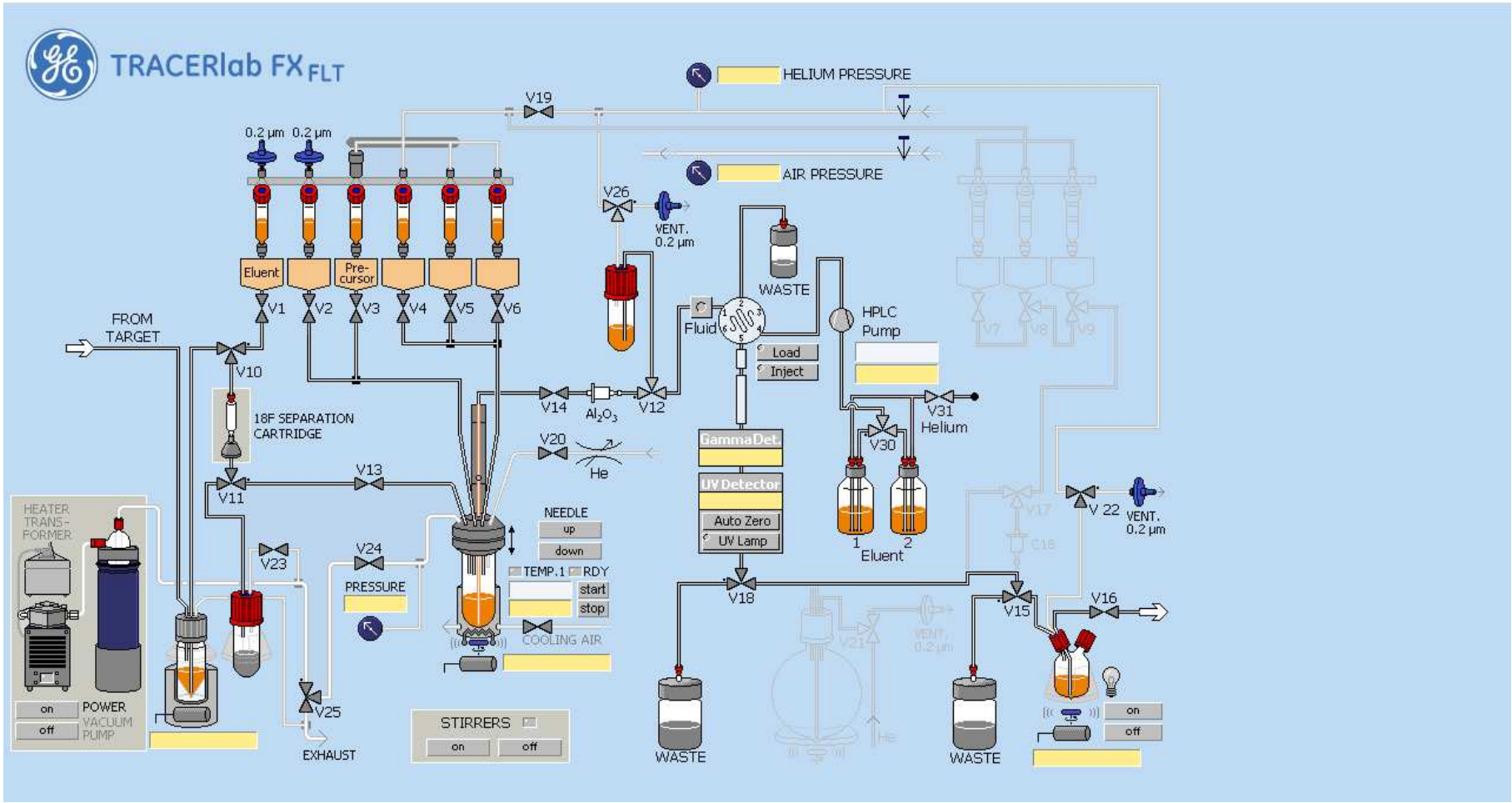
^{18}F Fluorothymidine [^{18}F]FLT



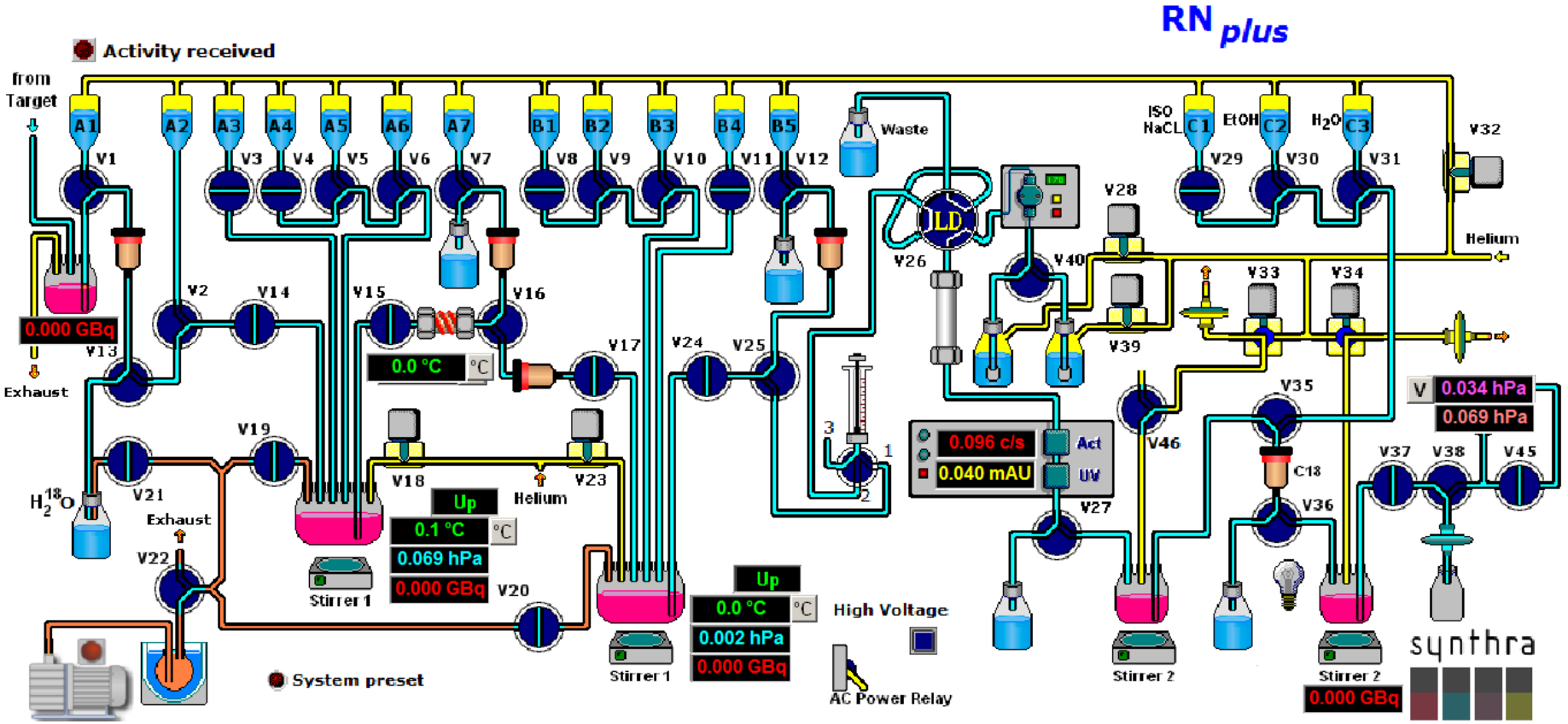
Marker of cell proliferation (thymidine pathway in S2 phase cellular mitosis)

Distinguishes decreased cellular uptake secondary to treatment.

^{18}FLT


TRACERlab FX FLT
HELIUM PRESSURE
AIR PRESSURE
V19
V26
VENT. 0.2 µm
0.2 µm 0.2 µm
Eluent
Pre-cursor
V1 V2 V3 V4 V5 V6
WASTE
Fluid
HPLC Pump
Load
Inject
FROM TARGET
V10
18F SEPARATION CARTRIDGE
V14 Al2O3 V12
V31 Helium
V30
V20 He
GammaDet
UV Detector
Auto Zero
UV Lamp
V13
V11
NEEDLE
up
down
TEMP.1 RDY
start
stop
COOLING AIR
V24
PRESSURE
V23
HEATER TRANS-FORMER
POWER
VACUUM PUMP
on
off
V25
EXHAUST
STIRRERS
on
off
V18
WASTE
V15
V16
V 22
VENT. 0.2 µm
1 Eluent 2
WASTE
on
off

^{18}FLT


RN plus
Activity received
from Target
A1
A2
A3
A4
A5
A6
A7
B1
B2
B3
B4
B5
Waste
ISO NaCL
C1
EtOH
C2
H2O
C3
V1
V2
V3
V4
V5
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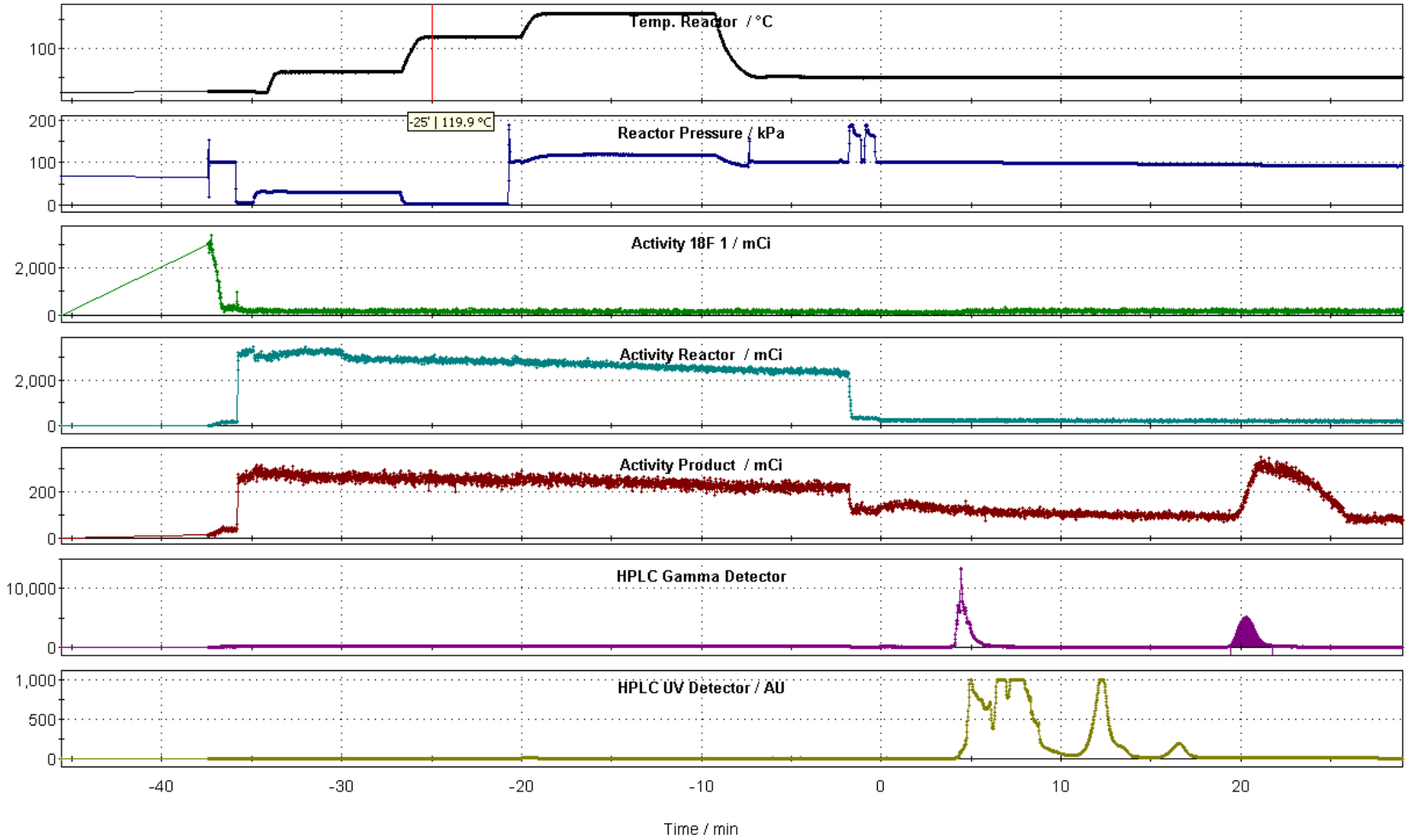
V36
V37
V38
V39
V40
V45
V46
0.000 GBq
Exhaust
0.0 °C
°C
Helium
Up
0.1 °C
0.069 hPa
0.000 GBq
Stirrer 1
H2 18O
Exhaust
System preset
Up
0.0 °C
0.002 hPa
0.000 GBq
Stirrer 1
High Voltage
AC Power Relay
JLD
0.096 c/s
0.040 mAU
Act
UV
C18
V 0.034 hPa
0.069 hPa
Stirrer 2
Stirrer 2
0.000 GBq
Helium
synthra

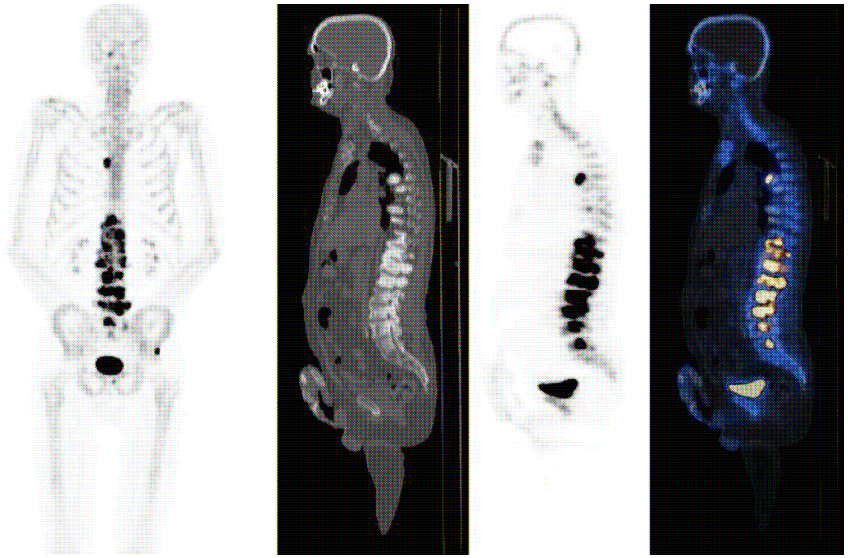
^{18}FLT


Temp. Reactor / °C
100
-25' | 119.9 °C
Reactor Pressure / kPa
200
100
0
Activity 18F 1 / mCi
2,000
0
Activity Reactor / mCi
2,000
0
Activity Product / mCi
200
0
HPLC Gamma Detector
10,000
0
HPLC UV Detector / AU
1,000
500
0
-40
-30
-20
-10
0
10
20
Time / min

Sodium fluoride

^{18}F Sodium fluoride

^{18}F NaF is chemisorbed onto bone surface by exchanging with OH- groups in hydroxapatite crystal of bone to form fluoroapatite.
Mechanism of uptake similar to other bone imaging agents
(Tc – 99m MDP/HDP)



^{18}F Summary

- Well-established use of ^{18}F compounds
- Efficient fluorination scheme
- FDG as a work-horse
- High yields and activities
- Other fluorinated compounds are available
- Regulatory problems

^{18}F vs. ^{11}C

^{11}C

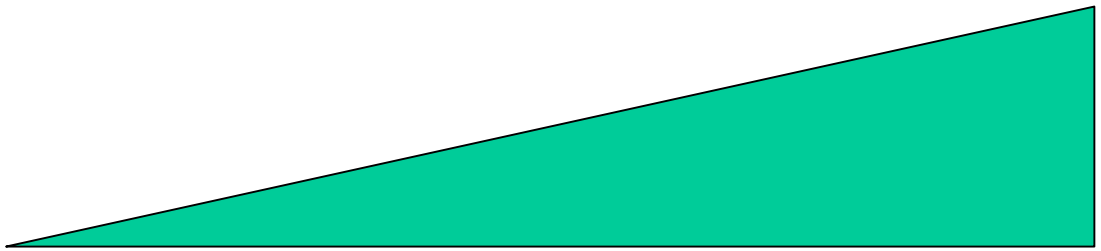
^{18}F

Similarity

Identical to ^{12}C

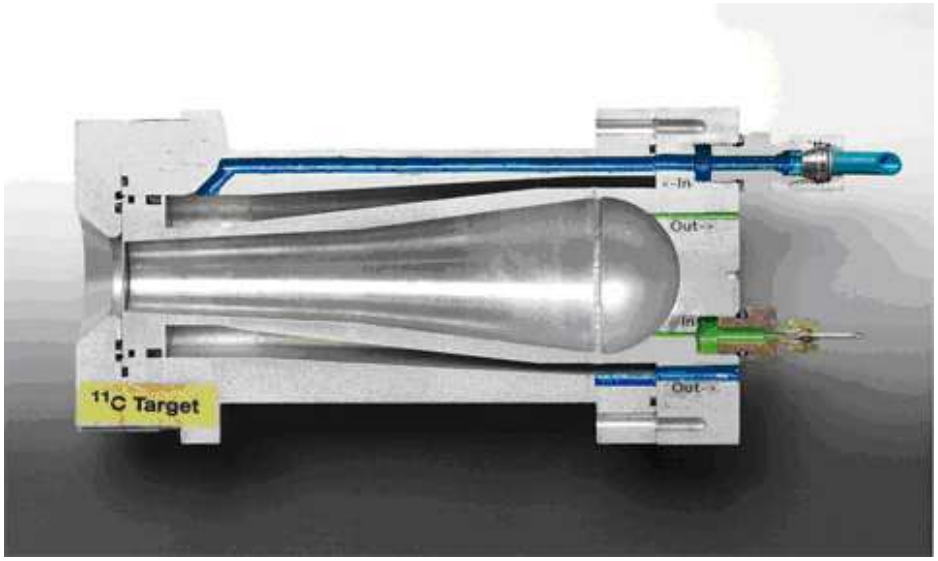
H

OH



Change of biochemical properties

^{11}C Production



Target for gases

Production ^{11}C :

Reaction : $^{14}N(p,\alpha)^{11}C$

Target : 99,6%^{14}N (0,1-5%H_2)

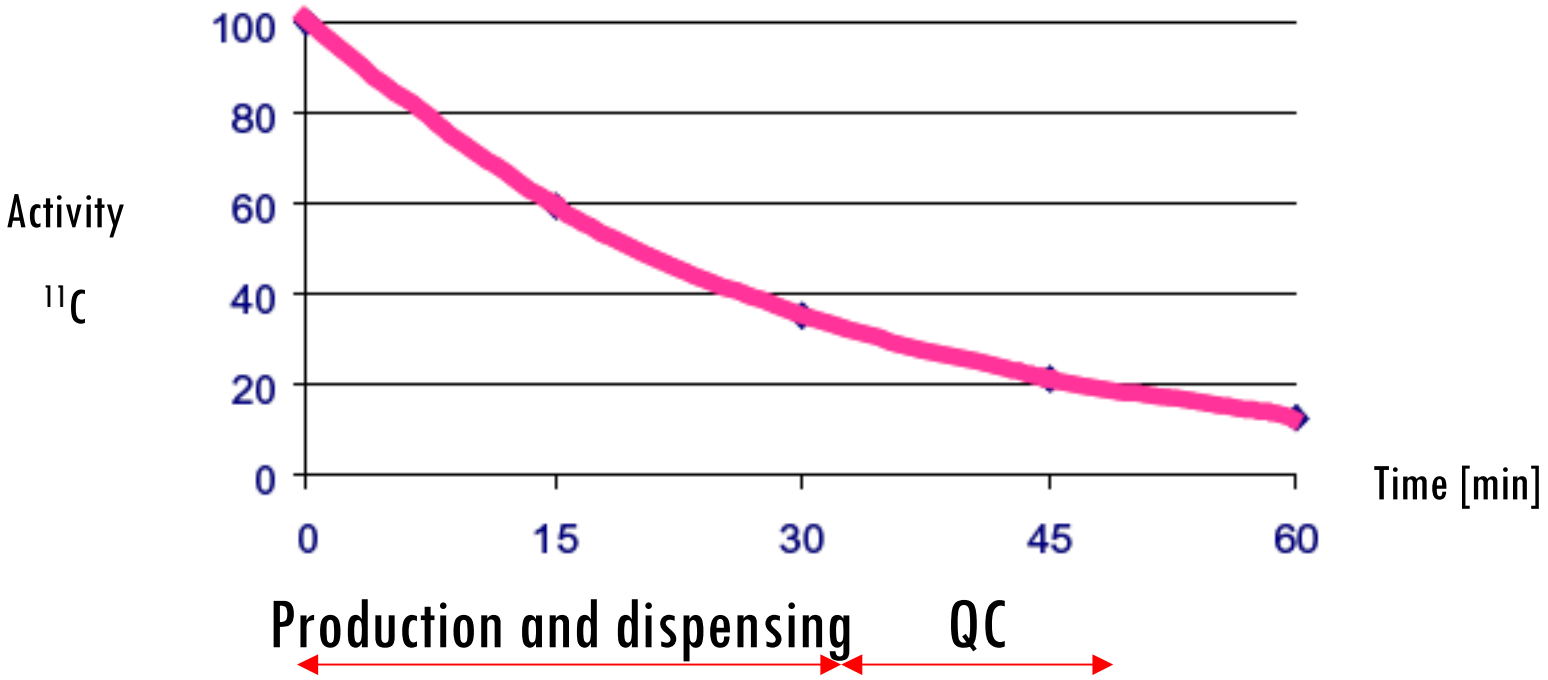
Product : HCN, CH_4

or

Target : ^{14}N (O_2)

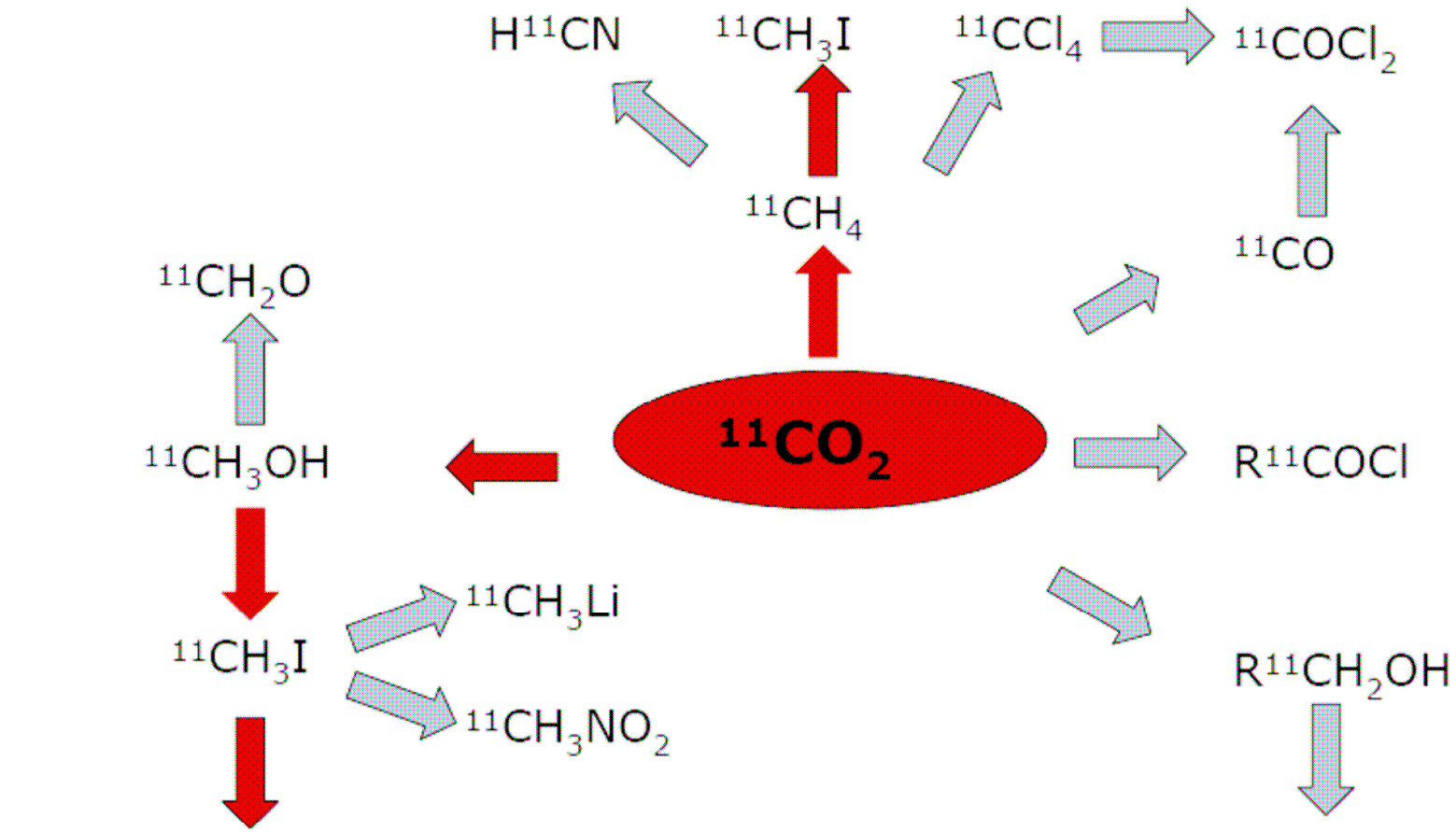
Product : CO, CO_2

^{11}C Production cycle



^{11}C Synthons

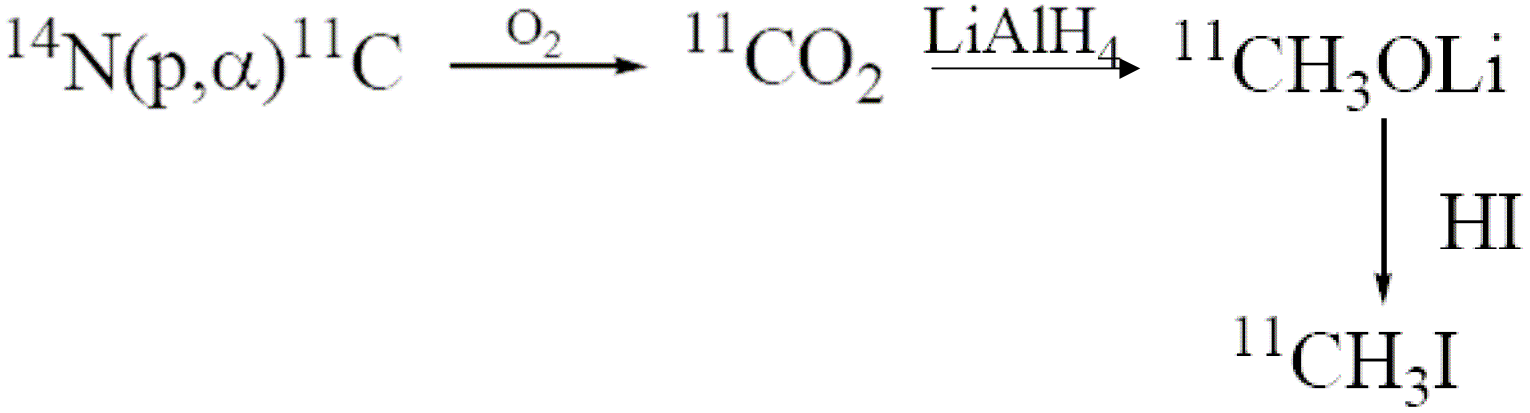
$^{11}CO_2$ Synthons



11C-Methyltriflate

Methyl iodide synthesis

Wet method

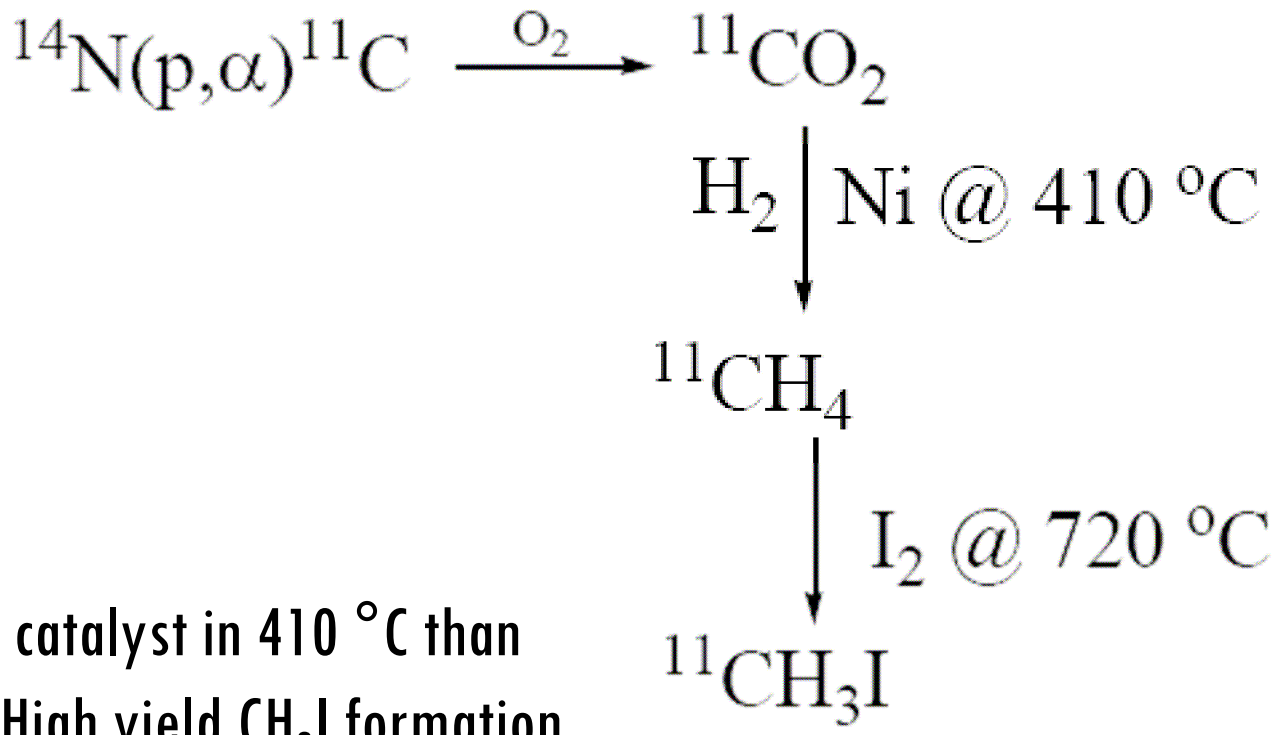


Iodination in THF or diethyl ether, high yield,

contaminiation with $^{12}CO_2$, HI is corosive

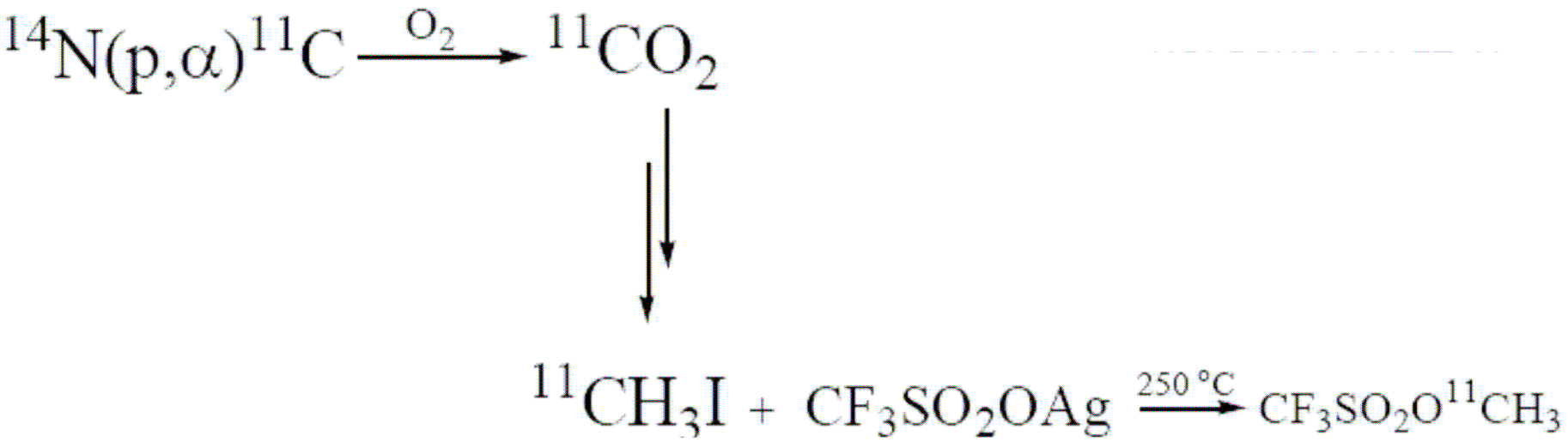
Methyl iodide synthesis

Dry method



Reduction of $^{11}CO_2$ on Ni catalyst in 410 °C than iodination I_2 in 720 °C. High yield CH_3I formation. No corrosive HI.

Triflate synthesis

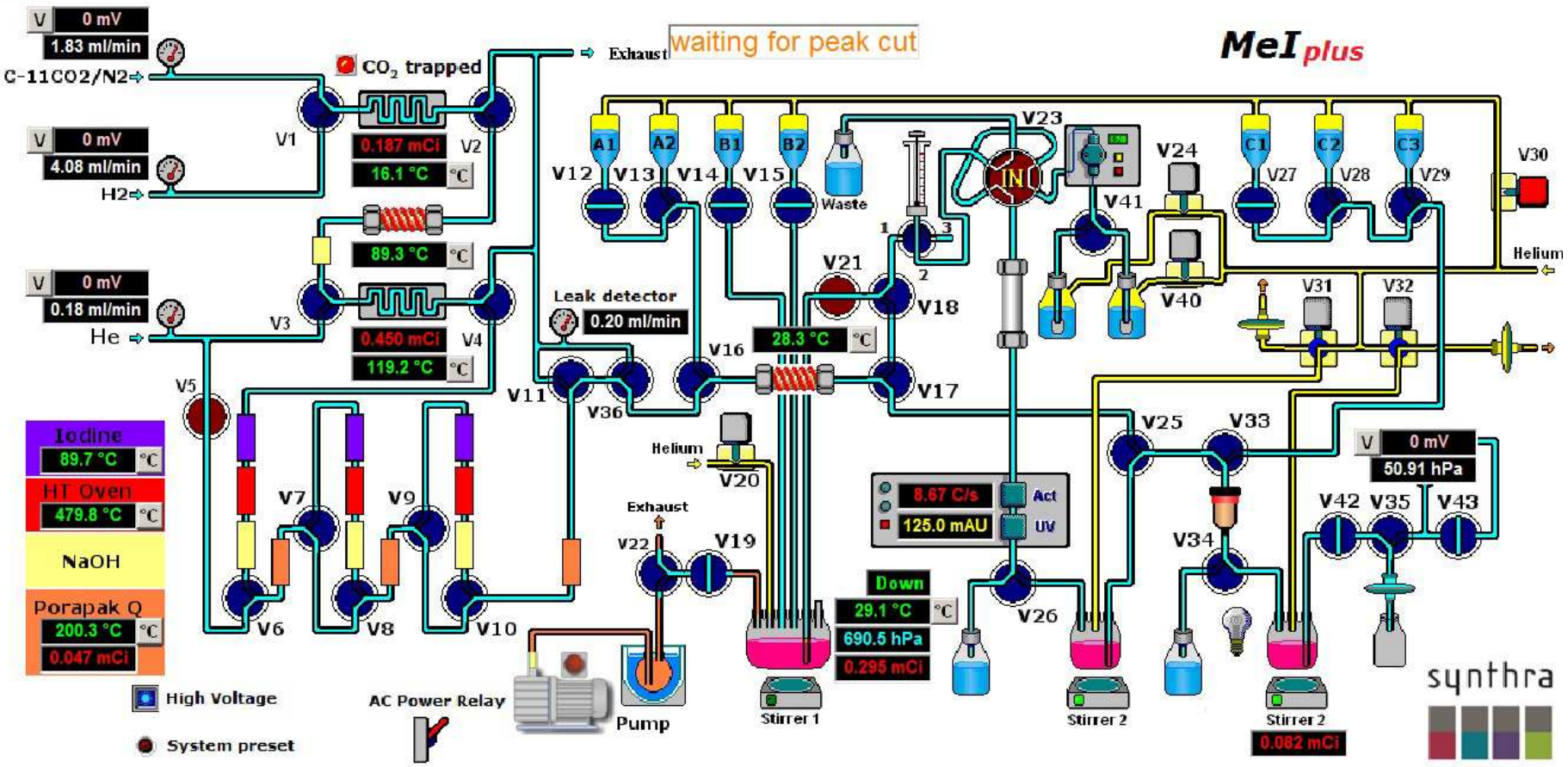


Methyl triflate

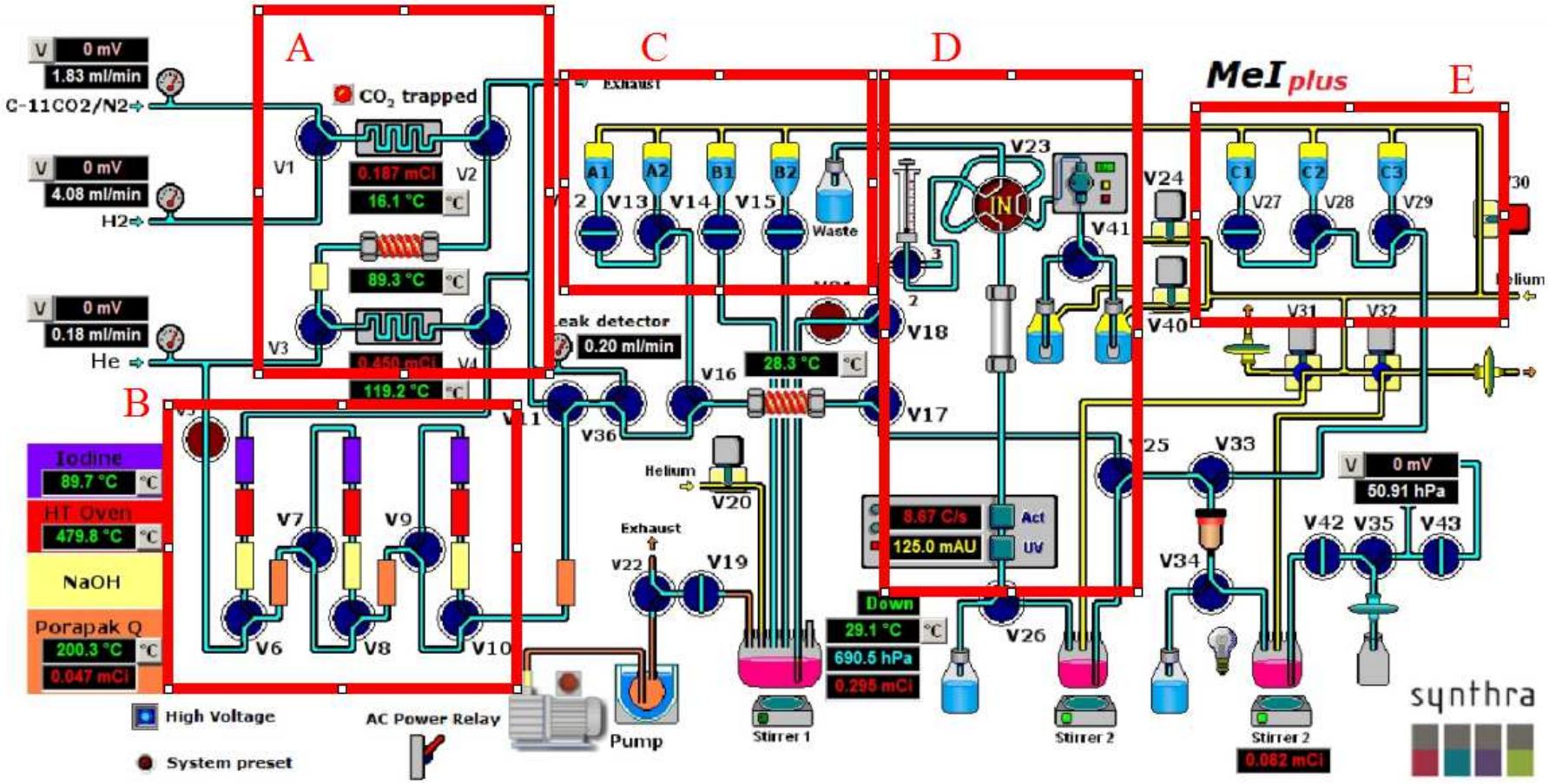
Advantages:

- 10^4-10^5 times more reactive than CH_3I
- For unstable or unreactive substances

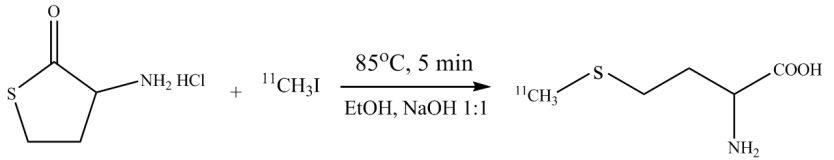
^{11}C Synthesis unit



^{11}C-methionine

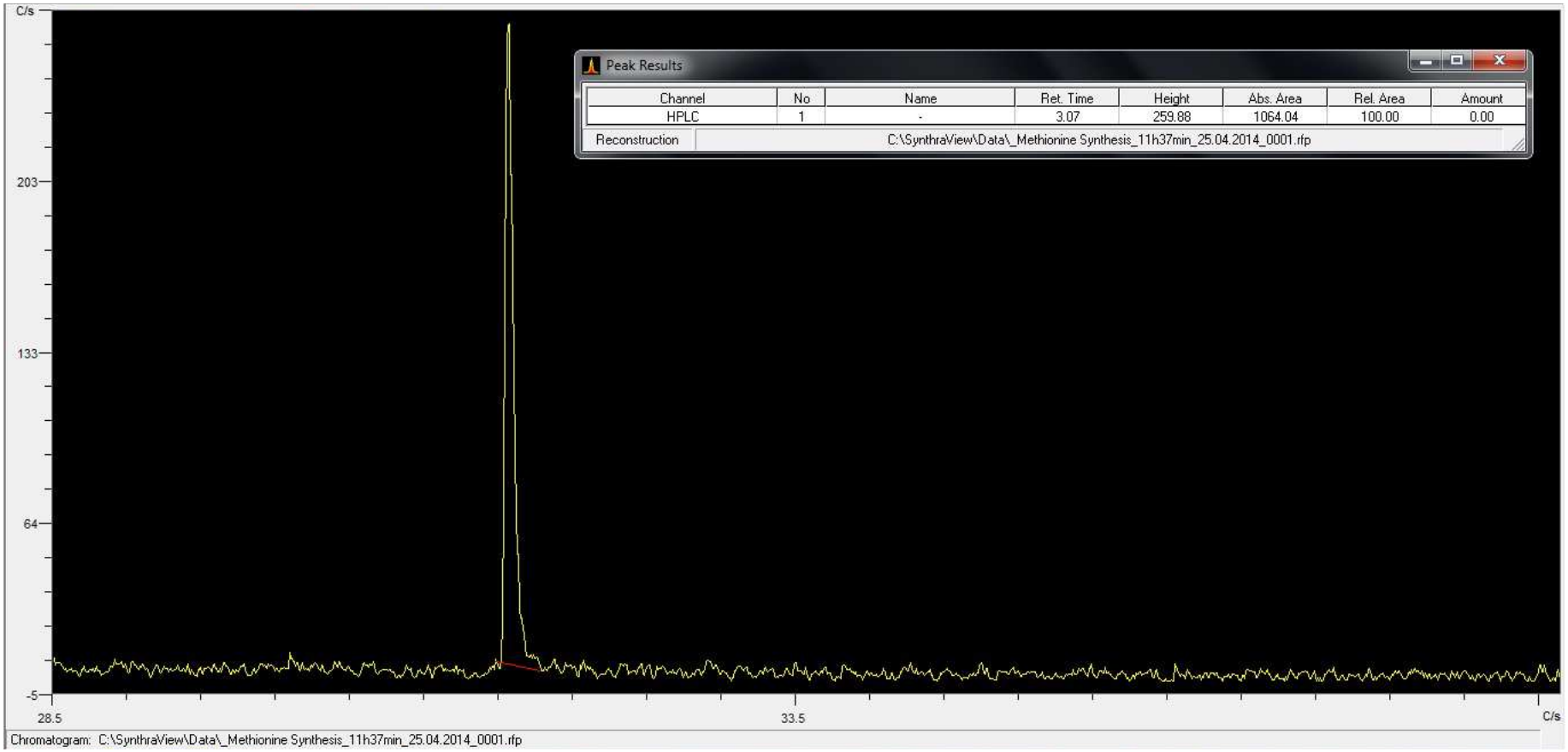


$$^{11}CO_{2(g)} \xrightarrow{-165^{o}C} {}^{11}CO_{2(s)} \xrightarrow[425^{o}C]{H_2,\ Ni} {}^{11}CH_4 \xrightarrow[750^{o}C]{I_2} {}^{11}CH_3I$$



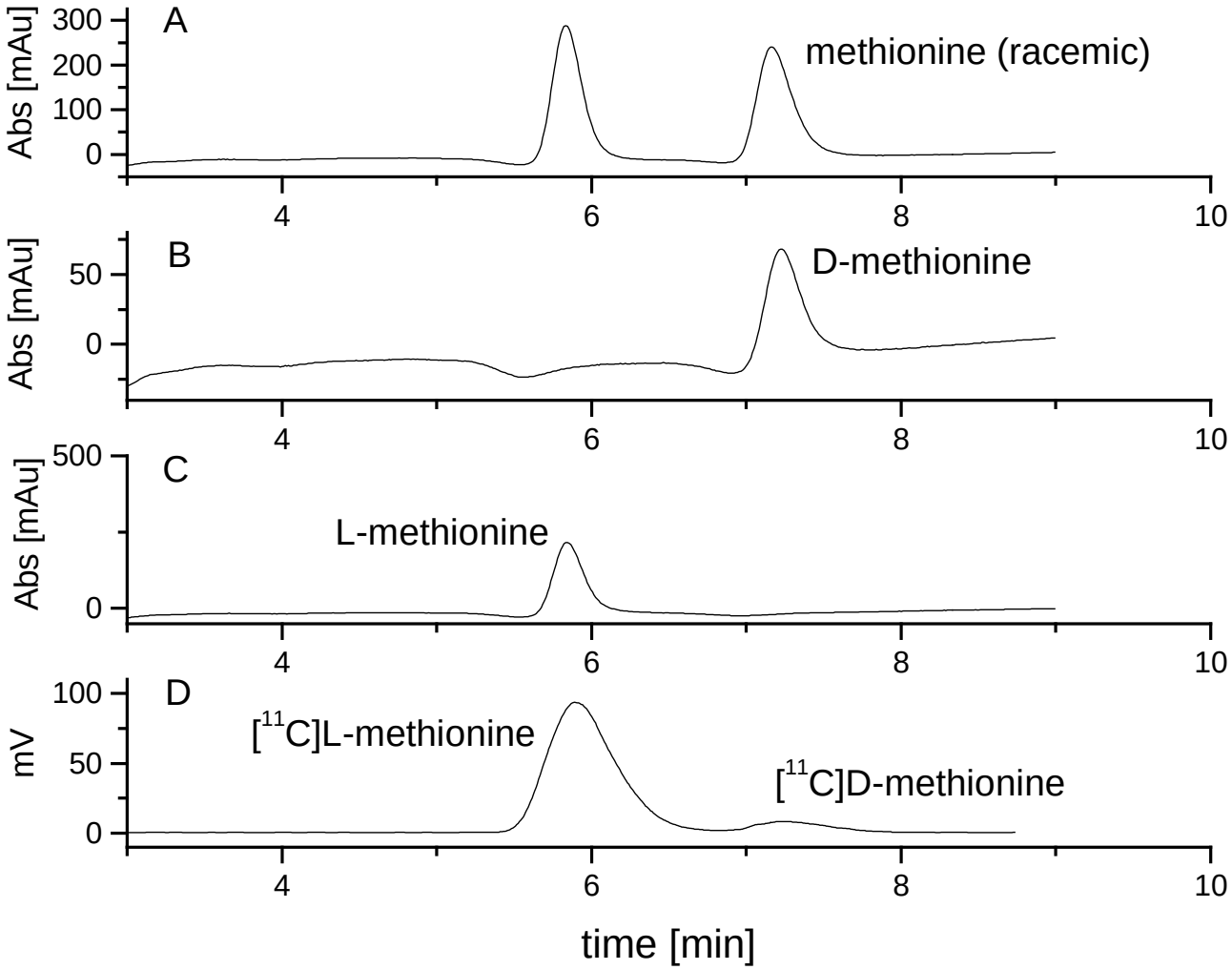
^{11}C-methionine

Radiochemical purity



^{11}C-methionine

Enantiomeric purity

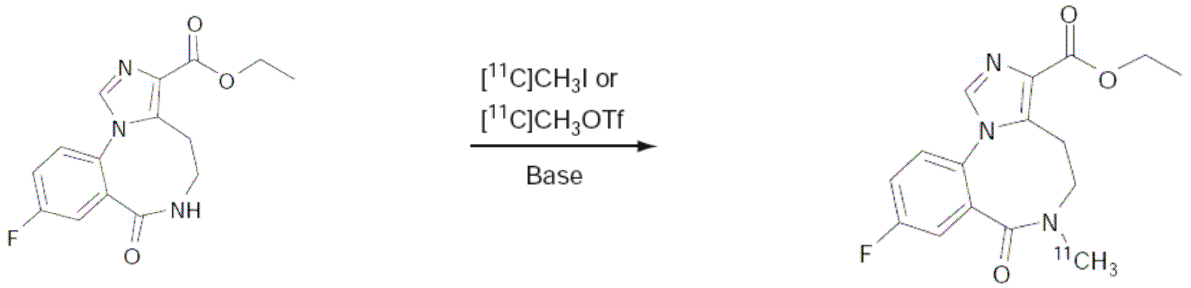


$^{11}CH_3I$ -methylation

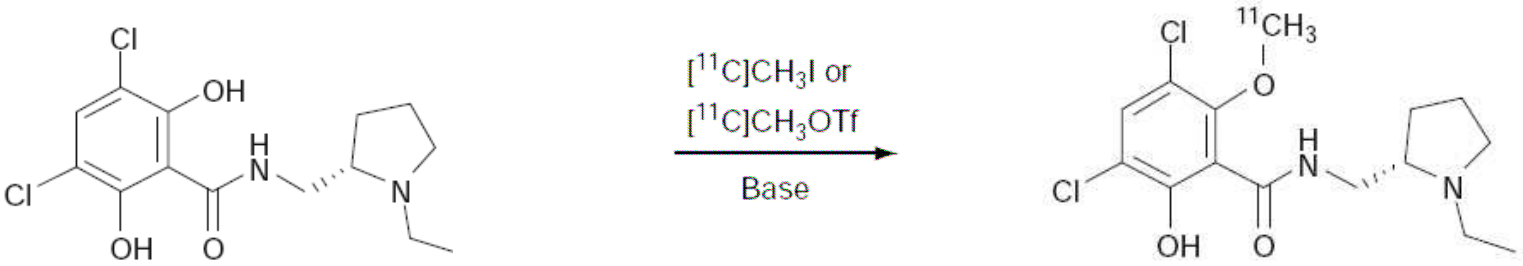
- Methyl iodide or methyl triflate metylation - most popular ^{11}C labeling method:
  - precursor with heteroatom active group (N, O, S) and protective groups
  - Basic, organic solvent: NaOH, EtOH.

Practical applications

Receptor imaging (agonist/antagonist/modulator)



[11C]WAY100635 – behavioral disorders

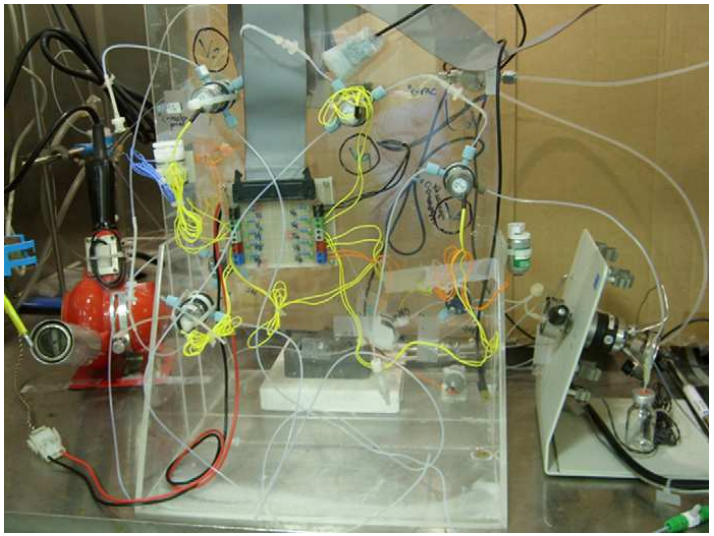


^{11}C raclopride – neurodegradation, schizofrenia

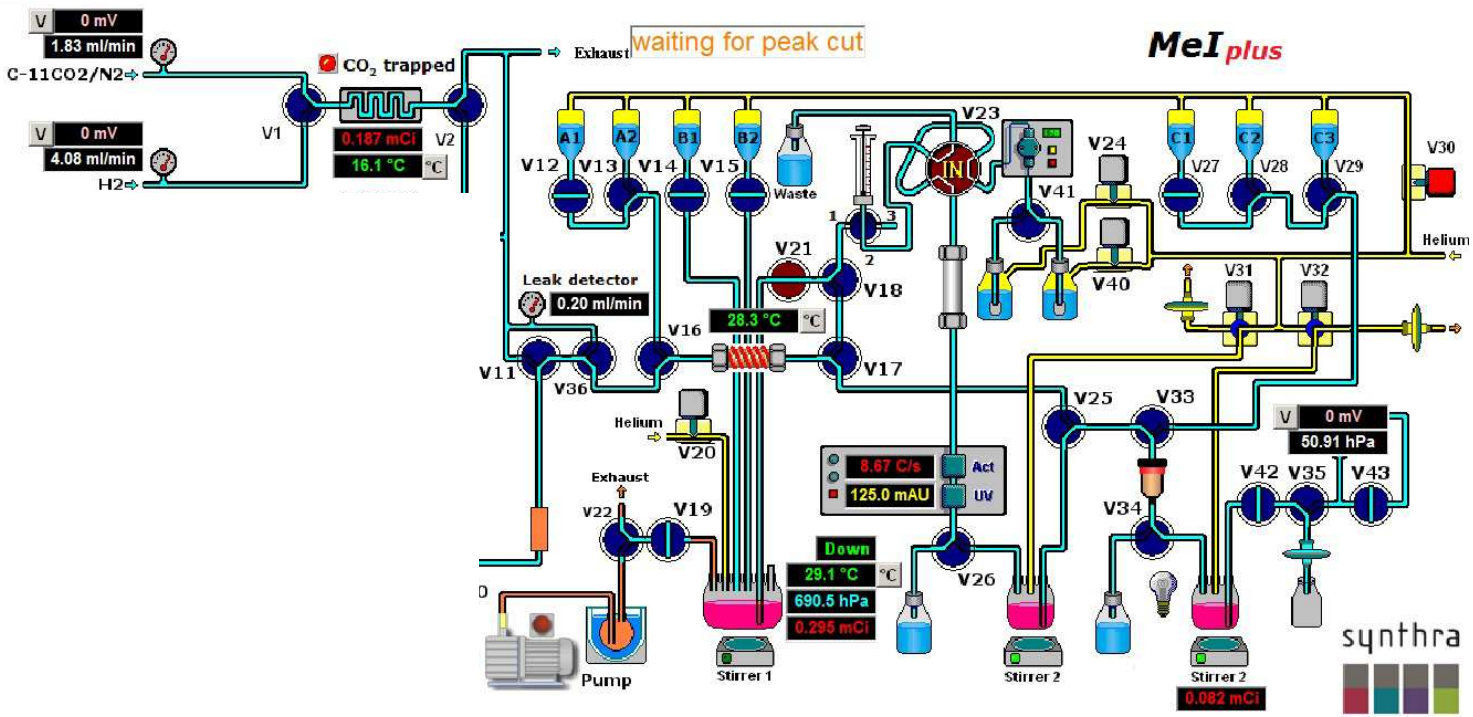
Practical applications

Receptor imaging (agonist/antagonist/modulator)

Neurotransmitter system	Radioligand
Dopamine D_1	[^{11}C]SCH 23390
	[^{11}C]NNC 112
Dopamine D_2	[^{11}C]raclopride
	[^{11}C]NMSP
	[^{11}C]FLB 457
	[^{18}F]fallypride
Dopamine transporter	[^{11}C]methyl-phenidate
	[^{11}C]PE2I
Serotonin 5-HT_{1A}	[^{11}C]WAY-100635
Serotonin 5-HT_{2A}	[^{11}C]NMSP
	[^{11}C]MDL 100907
Serotonin transporter (5-HTT)	[^{11}C]McN
	[^{11}C]DASB
	[^{11}C]MADAM
Opiate	[^{11}C]diprenorphine
	[^{11}C]carfentanil
Neurokinin-1	[^{11}C]SPA-RQ
GABA–benzodiazepine	[^{11}C]flumazenil
Peripheral benzodiazepine	[^{11}C]PK11195



^{11}C Flexibility - ^{11}C -acetate

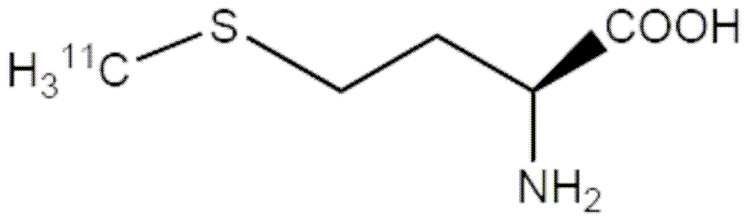


Reaction with Grignard compounds:

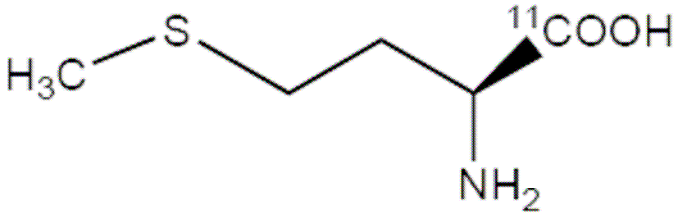
$$^{11}CO_2 + CH_3MgBr \xrightarrow{THF} CH_3{}^{11}COOH$$

^{11}C acetate- prostate cancer diagnostics

^{11}C Flexibility – labeling position



L-[S-methyl 11C]-methionine



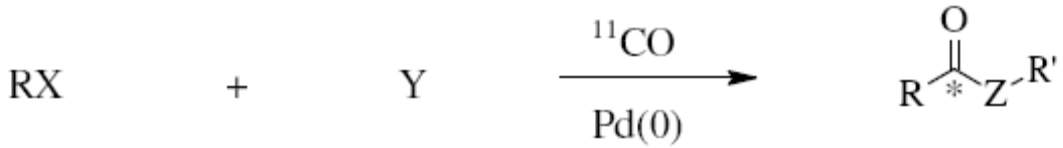
L-[11C]methionine

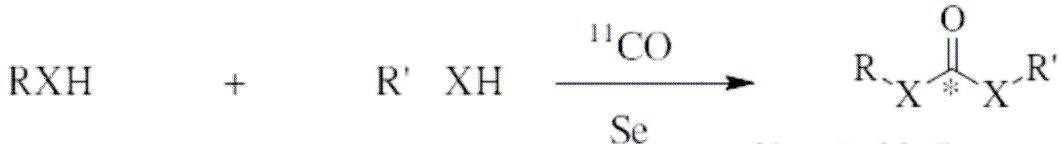
^{11}C-methionine imaging:

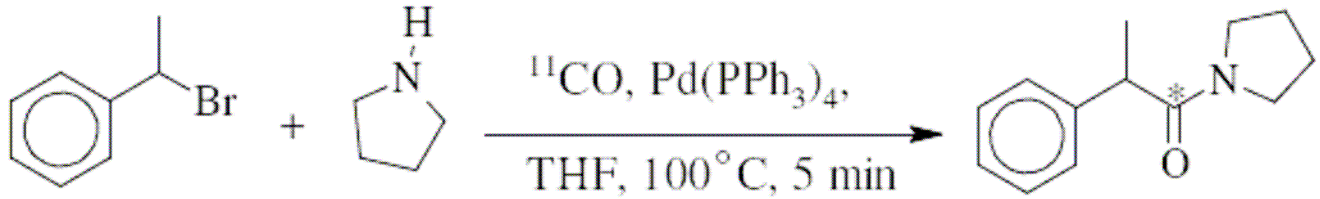
- aminoacids transport - (L-[S-methyl 11C]-methionine)
- protein synthesis – (L-[11C]methionine)
- transmethylation– (L-[11C]methionine)

^{11}C – modern organic chemistry

Reaction of CO catalyzed with Pd and Se:



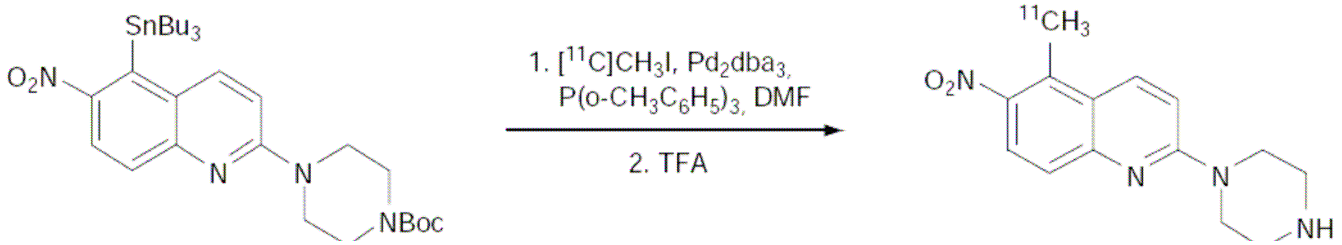




1-(2-phenylo-[carbonyl-11C]propanoyl)pirolidine – histamine receptors modulator

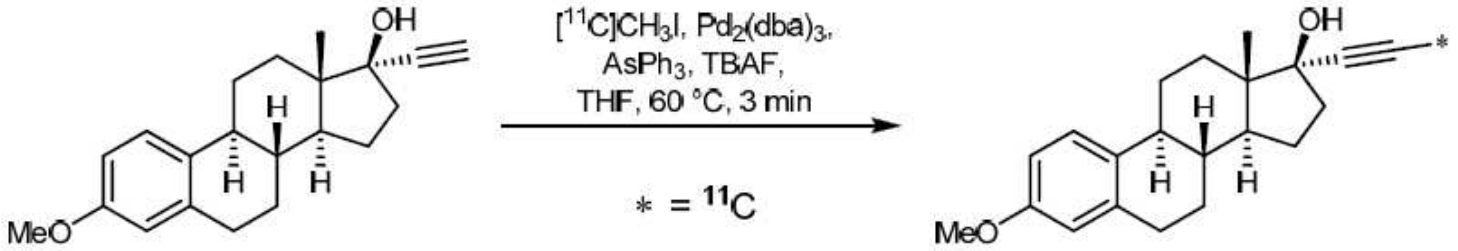
^{11}C – modern organic chemistry

Stille reaction



[^{11}C] MNQP - [11C]5-methyl-6-nitroquipaizine - serotonine transport

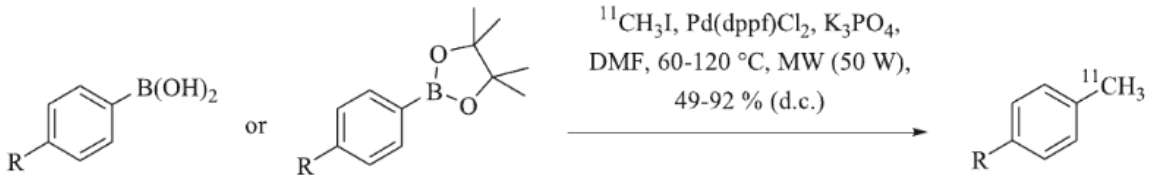
Sonogashira reaction

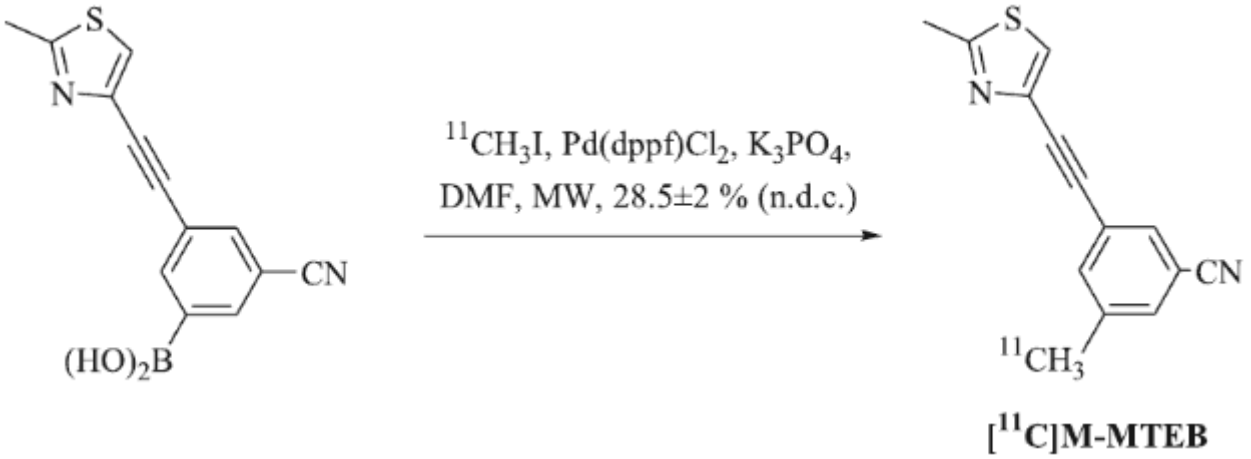


17α-(3'-[11C]prop-1-yn-1-yl)-3-methoxy-3,17β-estradiol – estrogene receptors – breast cancer imaging

^{11}C – modern organic chemistry

Suzuki reaction





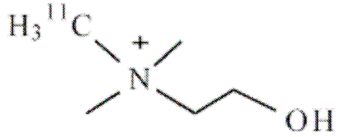
[^{11}C] M-MTEB – glutamate receptors

^{11}C Summary

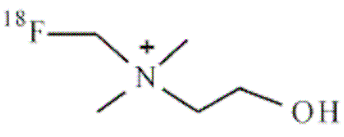
- Short ^{11}C half-life requires on-site imaging
- Well-recognized synthons - CH_3I
- Wide range of compounds with poorly understood function
- Clinical and preclinical trials

In place of conclusions

Tracers of membrane proliferation - increased permeability of biological membranes of tumor cells.



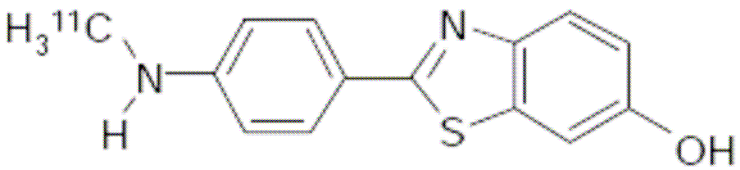
^{11}C -choline



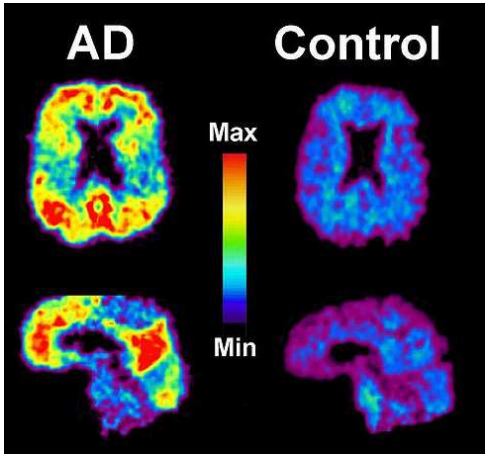
^{18}F-choline

The most used compounds for prostate cancer

In place of conclusions

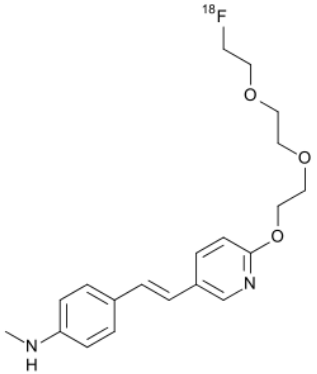


[11C]PIB (Pittsburgh Compound B) –Alzheimer disease imaging



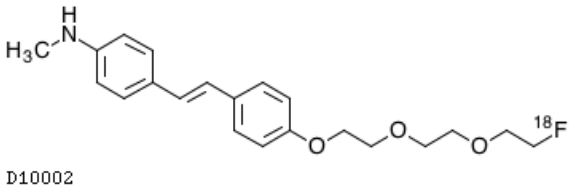
^{18}F Florbetapir

Amyvid ®



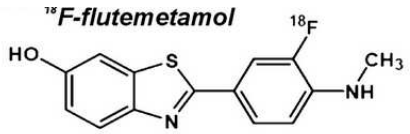
^{18}F Florbetaben

Neuraceq ®



^{18}F Flutemetamol

Vizamyl®



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and people from AAA Poland

Thank you for attention