



PET Radiochemistry I

Medical Technologies

WS 2014/2015

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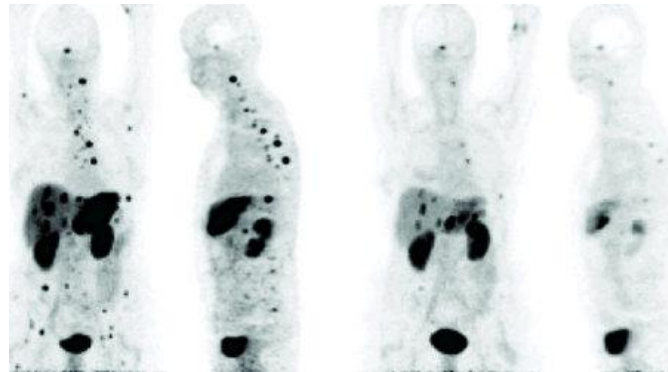
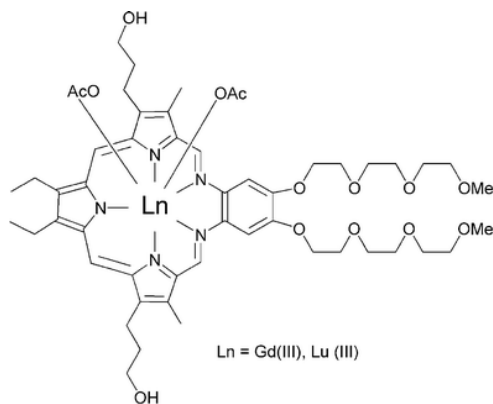
Eberhard Karls University of Tübingen

Tübingen, Germany

- Radiochemistry basics
- F-18 Chemistry
 - Isotope production
 - Tracer production
- C-11 Chemistry
 - Isotope production
 - Tracer production



- Radioactivity
- Radiochemistry
- Radiopharmaceuticals
- Specific activity
- Radioactive decay ($t_{1/2}$)
- Pharmakokinetics
- Metabolism



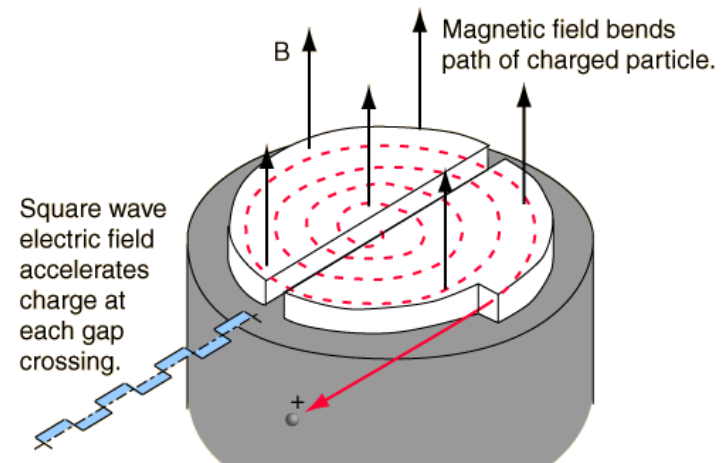
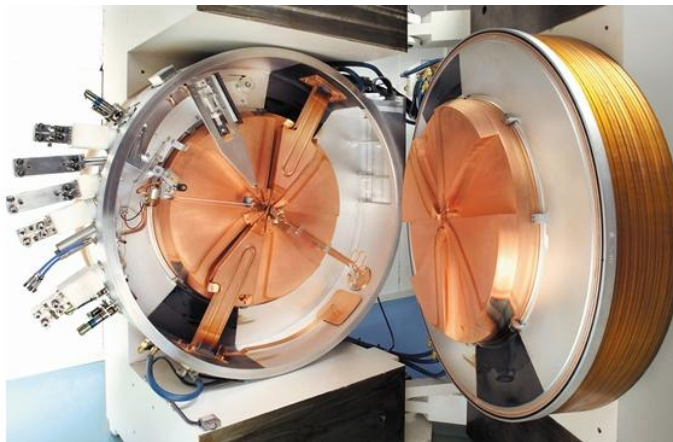
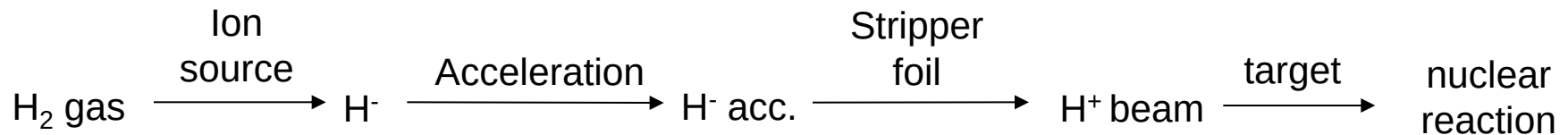
Treatment with Bi-213





A 60 min of bombardment of a water target with protons produces around 40-80 GBq of aqueous [^{18}F]-HF. Depending on the target, the volume is around 1-5 ml.

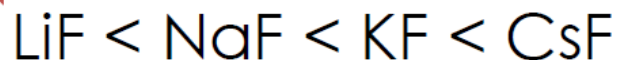
Rule of thumb: The maximum activity within the target is reached after 5-6 half-lives of the radioisotope during an irradiation on the target. But an irradiation of one half-life time gives 50% of the maximum activity.





Common alkali metal fluorides

Increasing ionic strength



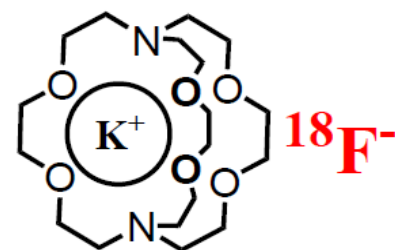
Increasing nucleophilicity
Increasing solubility

$[\text{}^{18}\text{F}]$ fluoride ion/ $[\text{}^{18}\text{O}]\text{H}_2\text{O}$

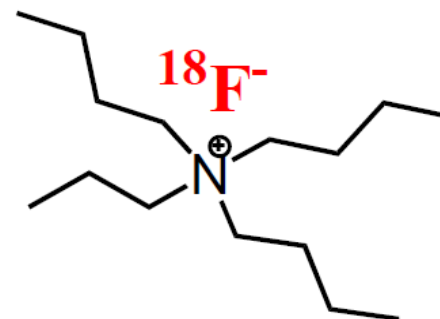


$\text{K}_{2.2.2}/\text{K}_2\text{CO}_3$
or
 $\text{TBAOH}/\text{TBAHCO}_3$

KF/Cryptand

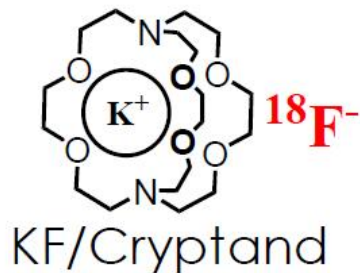


Tetraalkylammonium fluoride

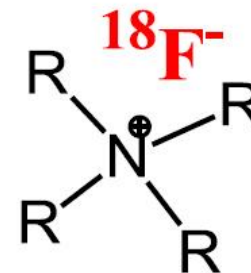


[¹⁸F]fluoride ion/[¹⁸O]H₂O

Kryptofix (K_{2.2.2})
K₂CO₃



Tetrabutylammonium
carbonate
or bicarbonate



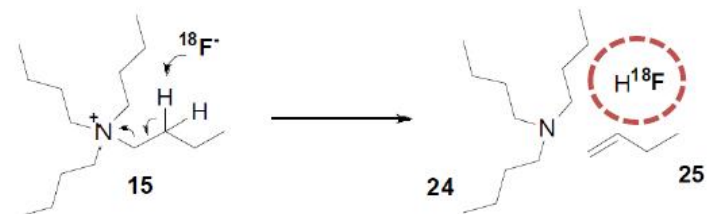
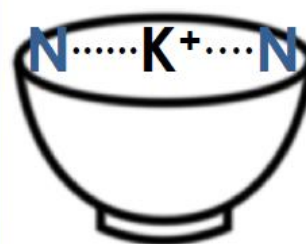
Cesium carbonate
or bicarbonate



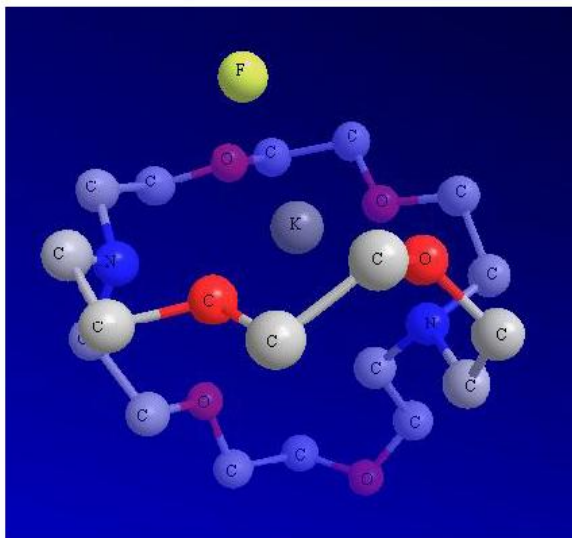
Tetraalkylammonium fluoride



R = methyl, ethyl, butyl

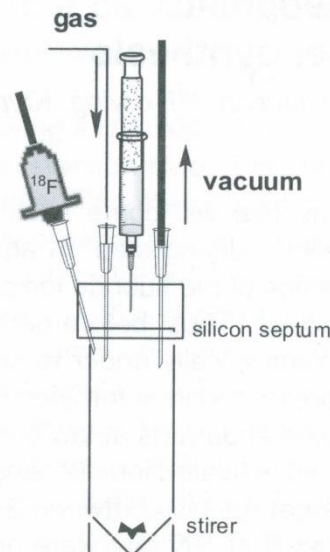


Thermal decomposition of TBAF



Nucleophilic Substitution (most commonly applied method)

[¹⁸F]-HF acquired from a water target is unreactive and requires a laborious drying process, to gain 'water-free' [¹⁸F]-KF. Potassium fluoride is the reactive species for **most nucleophilic substitution reactions** in radiochemistry.

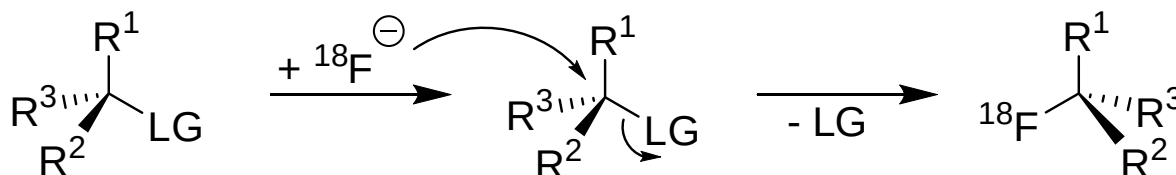


Equipment:

- reaction vial 5 mL + silicon septum lid
- vacuum tubing
- gas tubing for He or N₂
- syringe 1 mL
- gas cylinder (He or N₂)
- oil bath or heating block
- heater with thermometer
- magnetic stirring bar
- QMA light cartridge

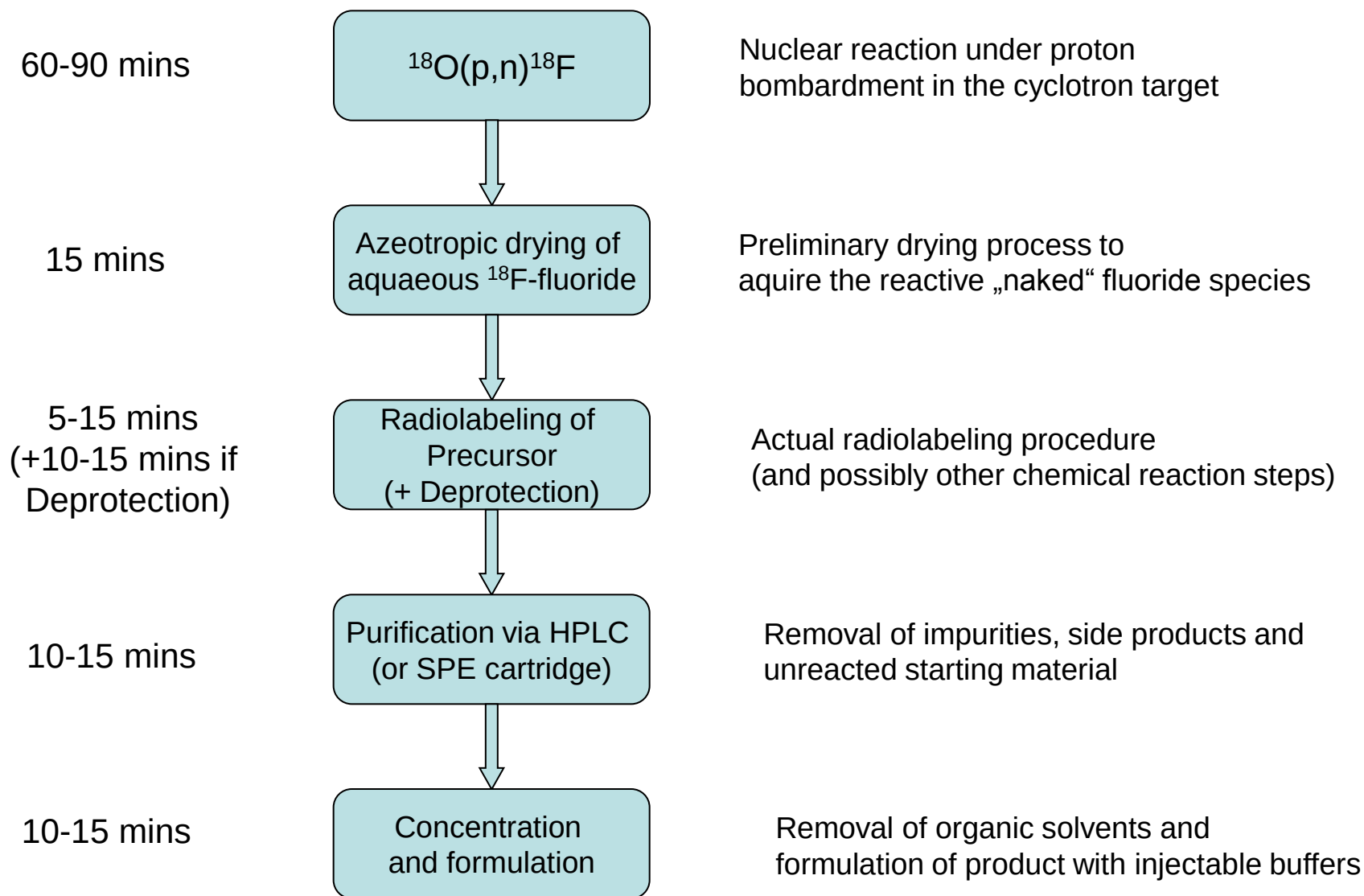
Chemicals:

- Kryptofix 2.2.2 or Cs₂CO₃ or NBu₄⁺HCOO⁻
- K₂CO₃ or potassium oxalate (only when Kryptofix 2.2.2 is used)
- acetonitrile



LG: leaving group

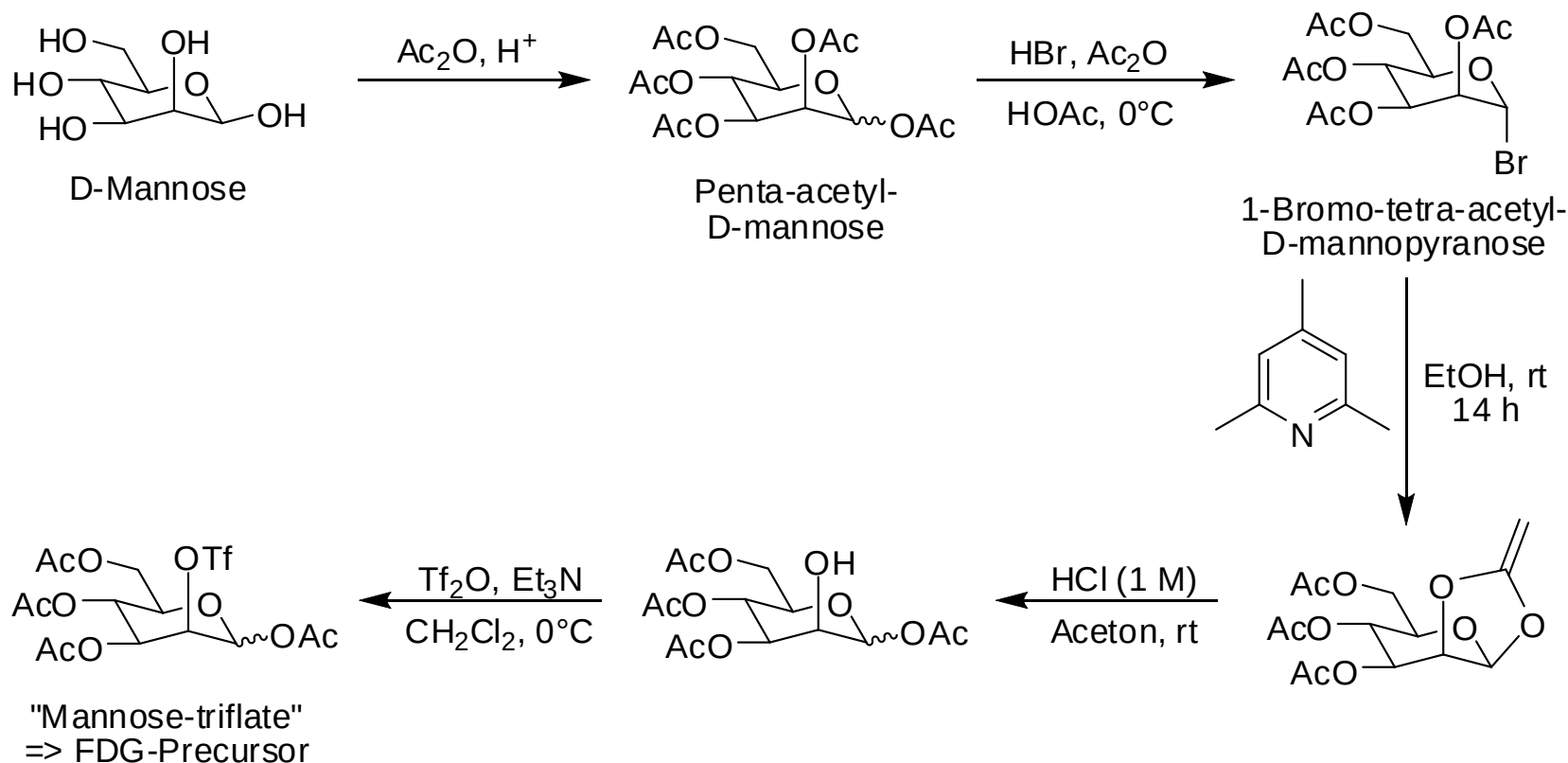
- Cl, -Br, -I
- OMs, -OTs, -ONs
- ⁺NMe₃

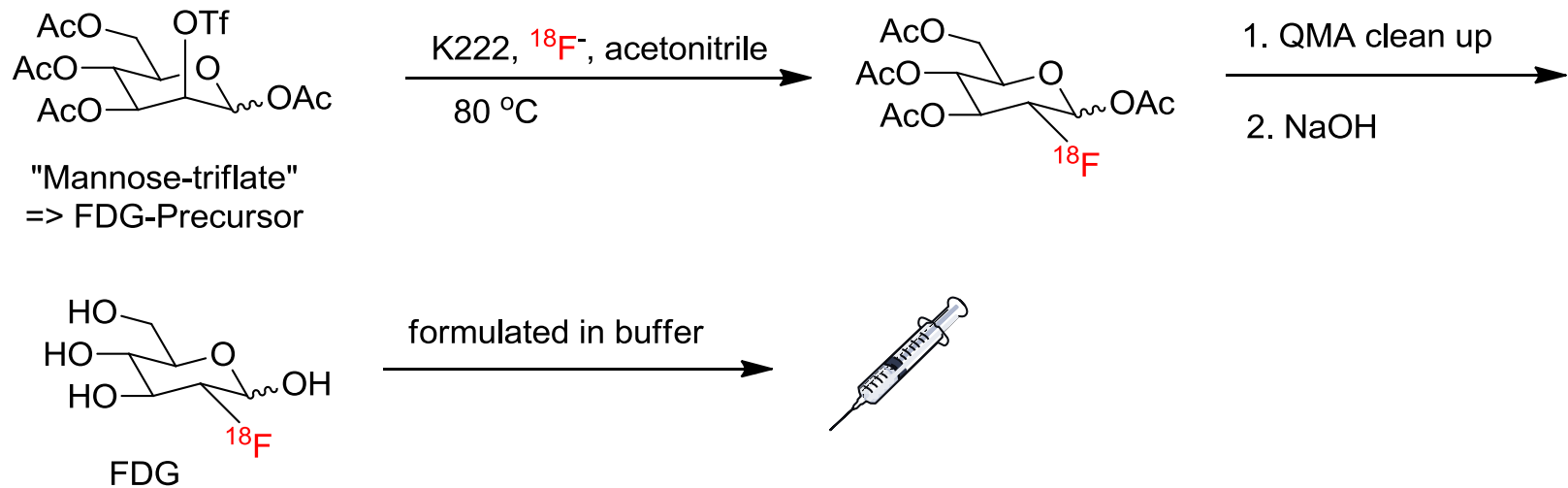


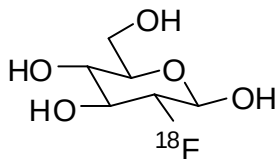


Synthesis of FDG

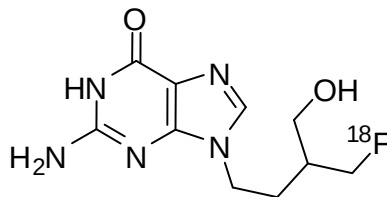
(1) Precursor synthesis



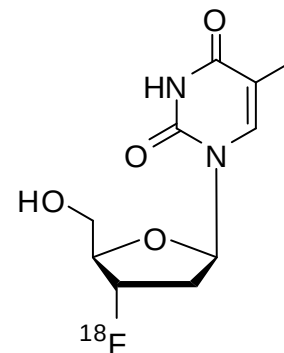




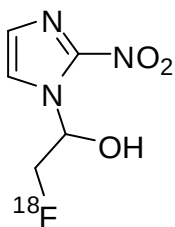
FDG
(2-Fluor-desoxy-glucose)



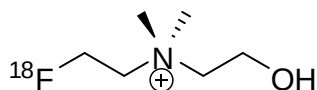
FHBG



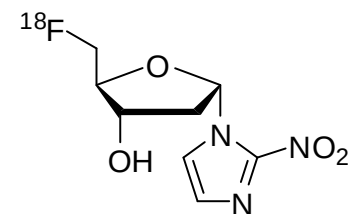
FLT



FMISO

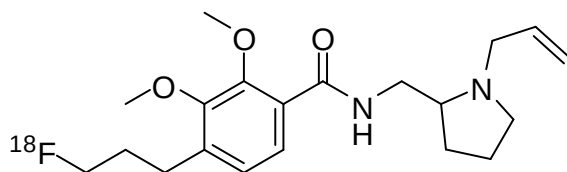


FEC

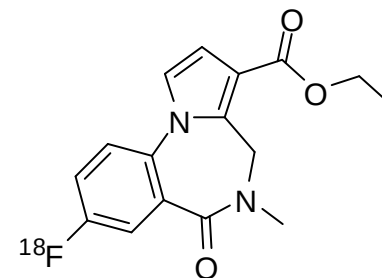


FAZA

Fallypride

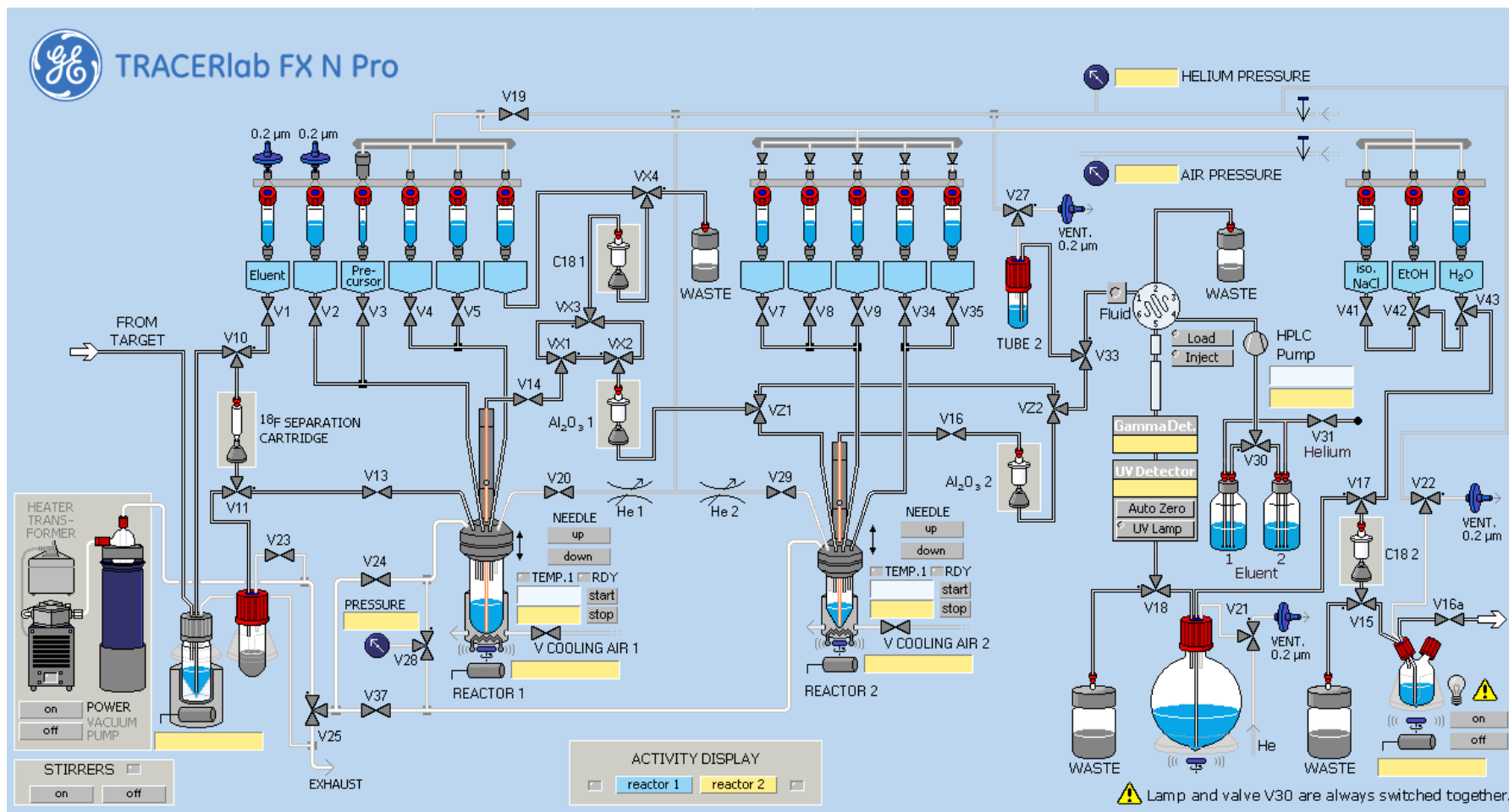


Flumazenil





Flowchart GE Tracerlab Fx N Pro



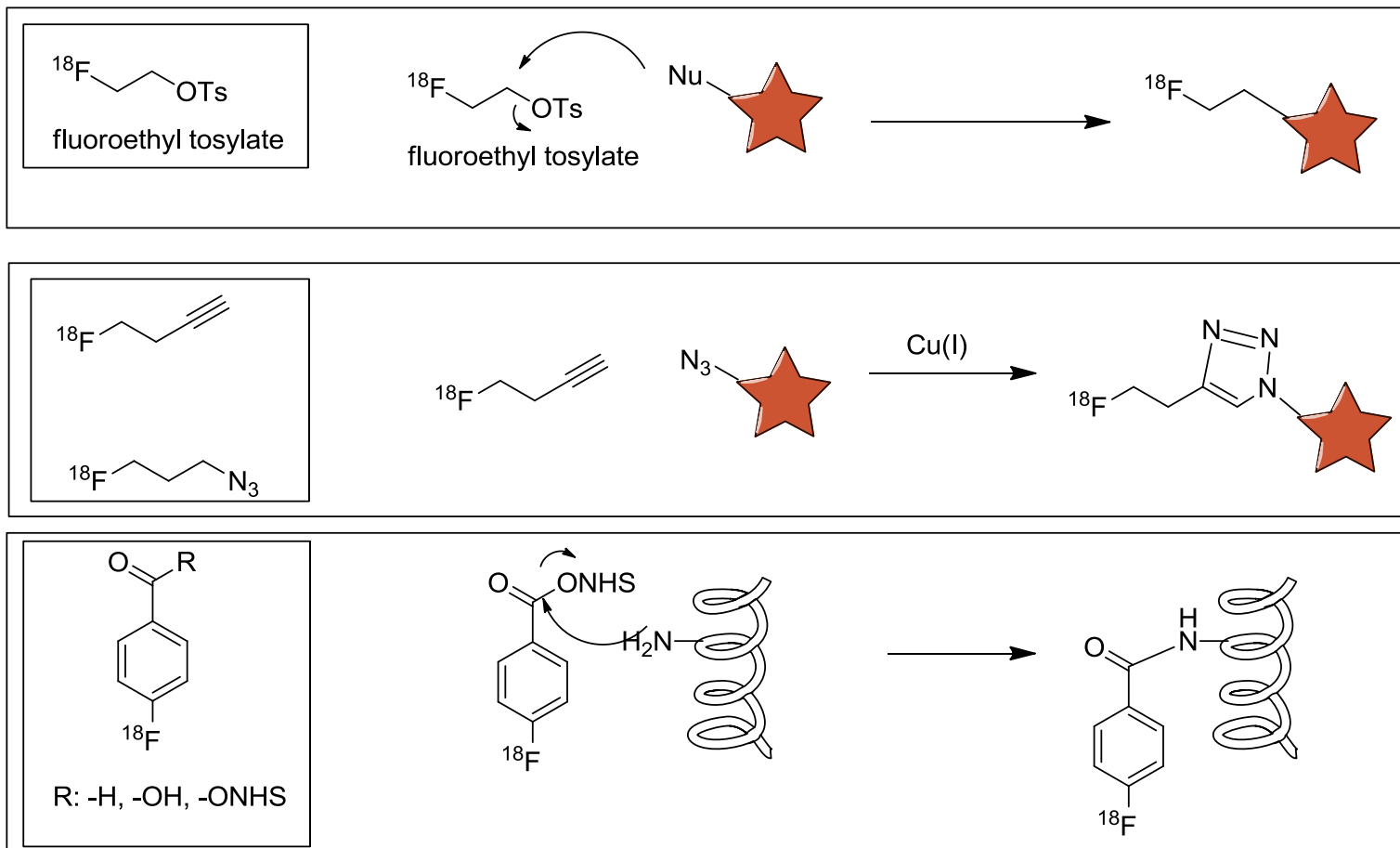




Synthesis of FDG: GE Tracerlab Mx (cartridge system)

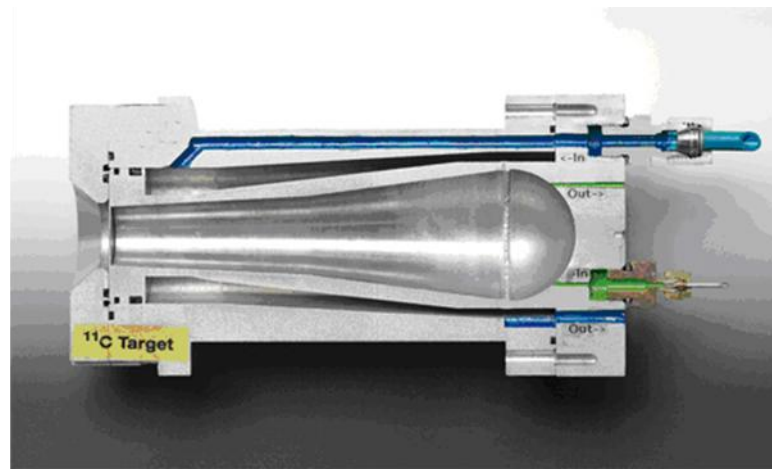


F-18 Prosthetic Groups



Carbon-11 is a synthetic isotope which does typically not occur in nature.

Several nuclear reactions can be used to produce ^{11}C , but the most commonly used and convenient method is the application of a **nitrogen gas target** $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$.



Half-life: 20.3 mins

Decay mode: 99.8% by positron emission

Maximum range (in water): 4.1 mm

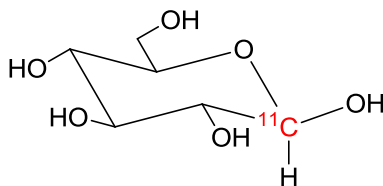


Organic Chemistry with ^{11}C

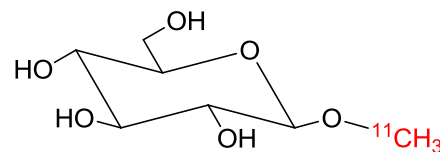
In principle, ^{11}C is a candidate for the isotopic or non-isotopic labeling of any organic compounds and is thus of major importance to PET.

Isotopic labeling: ^{11}C replaces stable $^{12}\text{C}/^{13}\text{C}$ in the molecule. The biological fate of the molecule is virtually unchanged.

Non-isotopic labeling: a group containing ^{11}C is added to the molecule of interest, producing a new compound with different properties to the original.



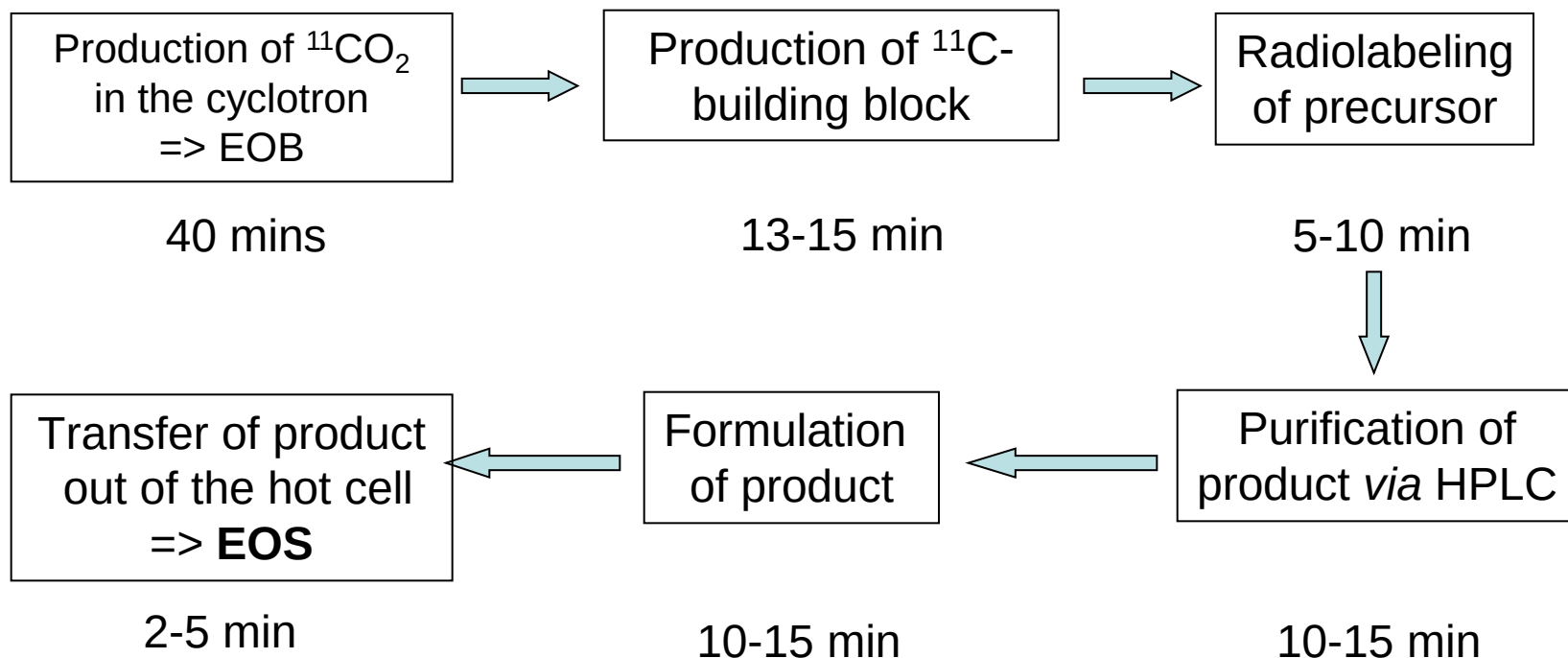
Isotopically-labeled
 ^{11}C -glucose
(substrate glucose-metabolism)



Non-isotopically-labeled
 ^{11}C -methyl-glucose
(tracer for SGLT1)



Sequence of a ^{11}C -radiosynthesis

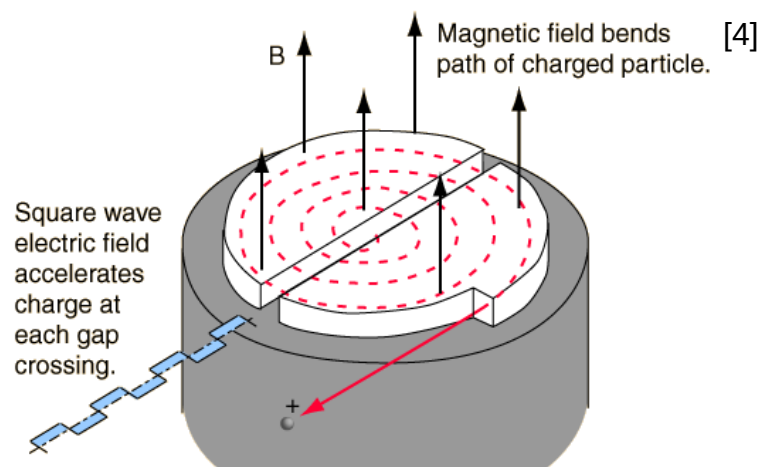
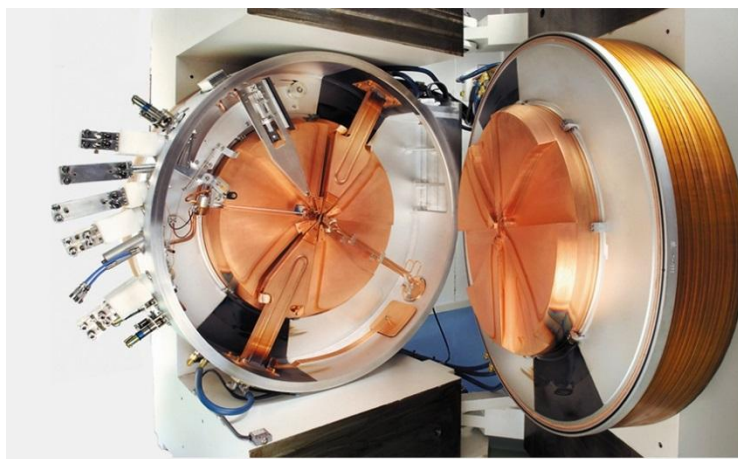
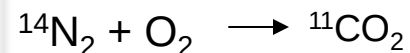
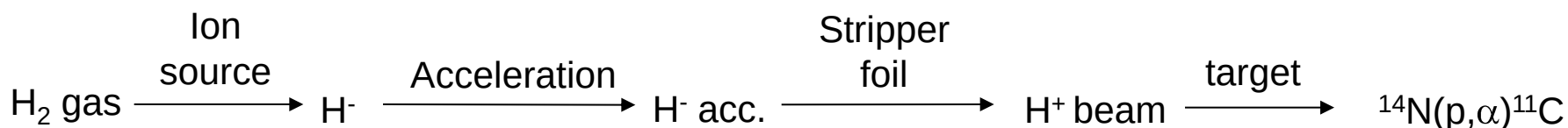


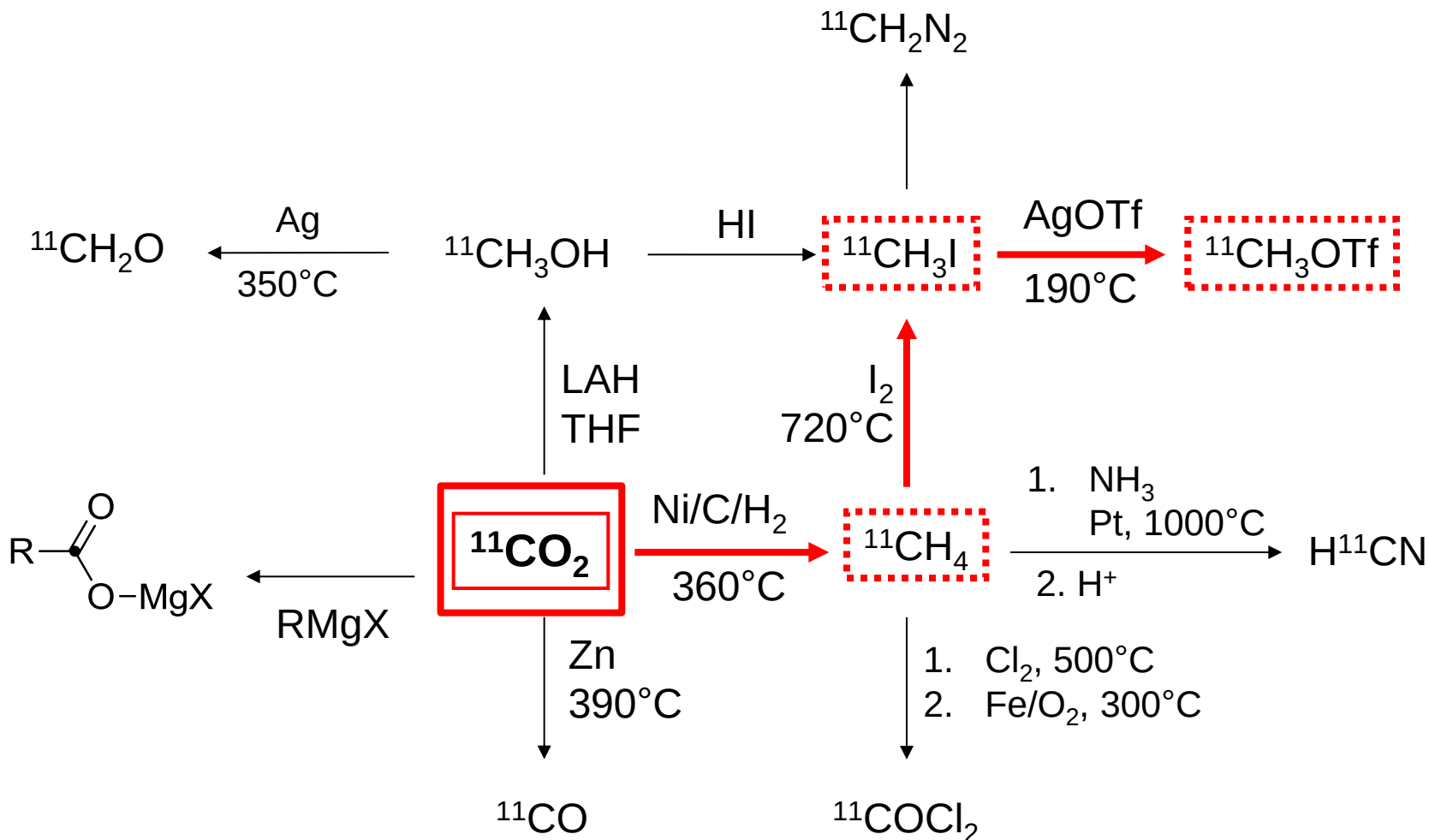
Minimum time for ^{11}C -radiosynthesis: ~30 min (without irradiation time)

Typical time for ^{11}C -radiosynthesis: ~60 min (without irradiation time)

Typical $^{11}\text{CO}_2$ activity after irradiation: ~ 200 GBq (EOB)

Source of isotopes for PET radiochemistry is mostly a cyclotron. A cyclotron is a proton / deuteron accelerator, which accelerates protons / deuterons on a spiral trajectory.

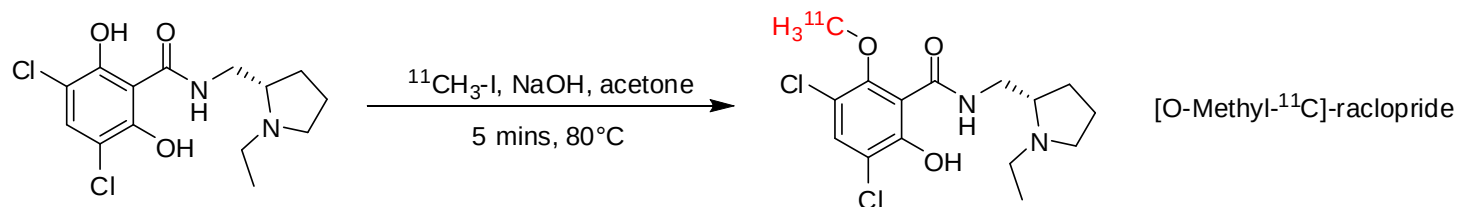




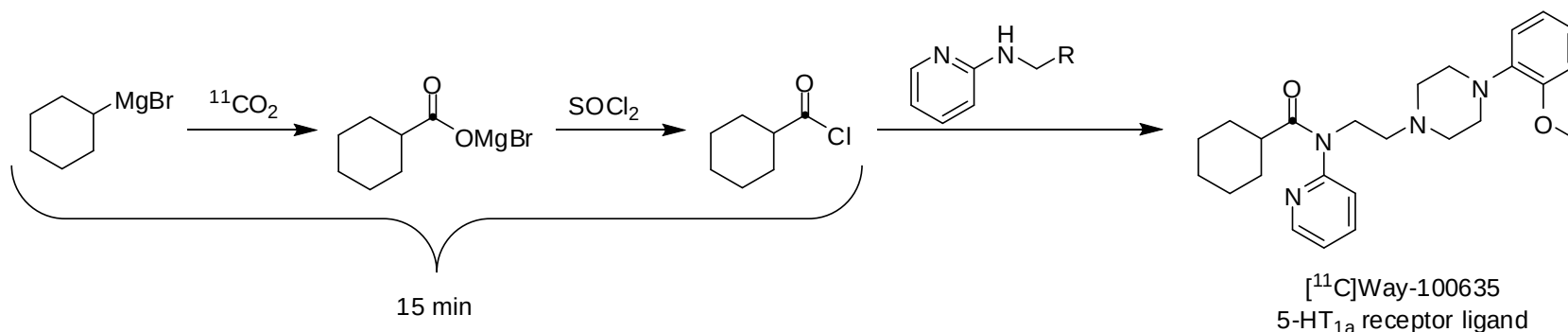


Based on the building blocks and the physical half-life time of carbon-11 the following reaction types are available:

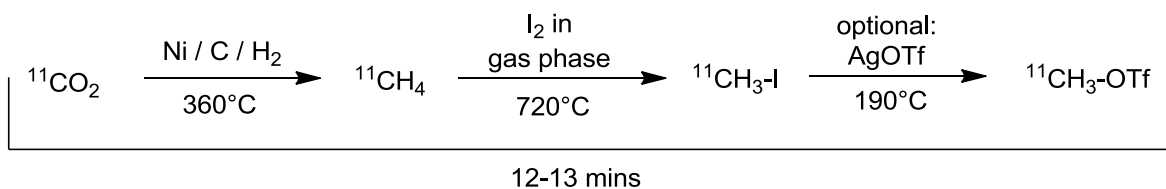
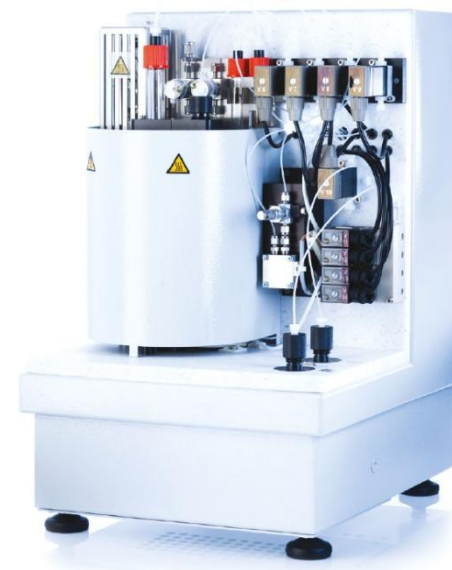
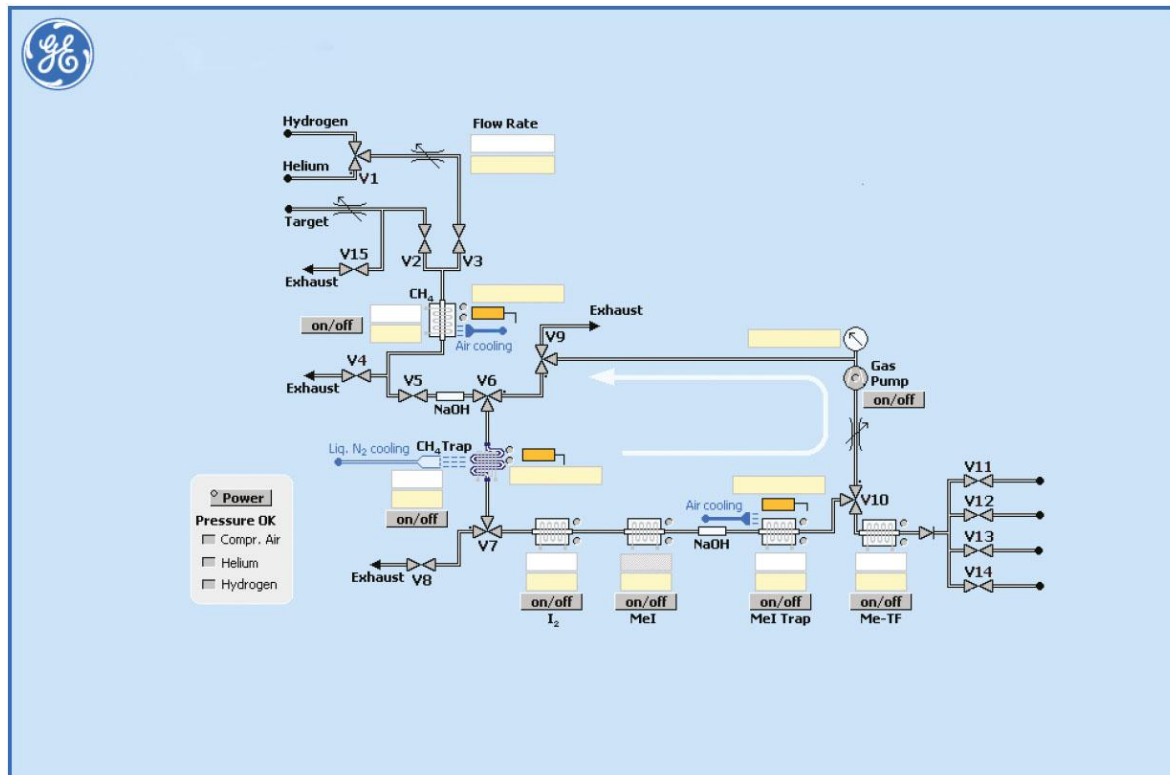
- N-, O- and S-Methylation reactions (either with ¹¹C-CH₃I or ¹¹C-CH₃OTf)



- Preparation of carboxylic acids or synthesis of acylating agents (typically ¹¹C-acetylchloride) with Grignard Reagents



Synthesis of ^{11}C -CH₃I



Flowchart of a ^{11}C -radiosynthesis

