^{18}F labeling of insulin via click chemistry

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Introduction: As a positron emission tomography probe, a new ^{18}F-bearing insulin derivative was prepared by an original labeling method. This tracer was required as a radiolabelled active principle model compound to perform biodistribution imaging studies of new pulmonary administrable formulations.

Methods: A 1,3-dipolar azide/alkyne cycloaddition (click chemistry) approach was developed for the mild and efficient linking of the radioactive probe onto insulin (Fig1).

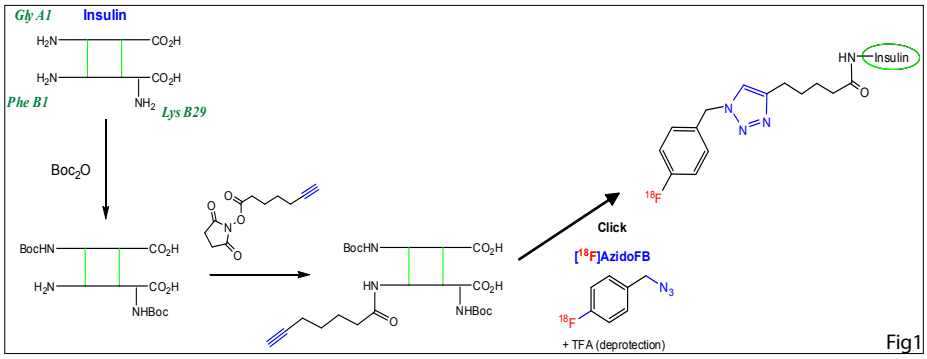

Fig1

As an initial step, native insulin had to be derivatized in order to present an accessible alkyne group at an appropriate position. For this, two of the three amino functions available on the molecule (Glycine A1 and Lysine B29) were first protected as N-Boc derivatives. An alkyne bearing prosthetic group could then be selectively grafted on the phenylanine B1 residue which does not interfere in the insulin-receptor binding process [1]. The final [^{18}F] fluorine insertion step was carried out by reacting this insulin derivative with the radioactive azide synthon 1-(azidomethyl)-4-[^{18}F]-fluorobenzene[2]under Cu(I) catalysis conditions.

Results: The clickable ^{18}F azide 1-(azidomethyl)-4--[^{18}F]-fluorobenzene was obtained in 65 minutes with good radiochemical yield (40-45% decay-corrected) and radiochemical purity (>90%) thanks to a fully automated preparation method developped on remote-controlled commercial radiosynthesis unit. Subsequent copper catalyzed click reaction on the alkyne bearing insulin derivative was performed at room temperature in less than 20 minutes with current radiochemical yields of 70-80% (decay-corrected).

Conclusions: A mild and efficient radiolabelling strategy of insulin was succesfully developped using click chemistry. This radiotracer can now be incorporated in new inhalable pharmaceutical formulations for biodistribution imaging studies.

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References:

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