Optimized radiolabeling of ^{11}C–(+)–4–propyl–3,4,4a,5,6,10b–hexahydro–2H–naphto–(1,2–b)(1,4)oxazin–9–ol

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Introduction: Dopamine is an important neurotransmitter in the human central nervous system. Today, radiolabeled neurotransmitter and neuroligands are used for non-invasive imaging of the dopamine system using positron emission tomography (PET). [^{11}C]PHNO, (+)-4-[^{11}C]propyl-3,4, 4a,5,6,10b-hexahydro-2H-naphto-(1,2-b)-(1,4)oxa-zin-9-ol, was developed as D_2-agonist, but it was quickly discovered that it has a 1000-fold higher selectivity to D_3-receptors. The transmembran heli-ces of D_2 and D_3 are 78% identical and the residues which form the binding side are nearly the same. This is the main reason why it took a long time to discover a D_3-agonist. The Synthesis of [^{11}C]PHNO was first described by Alan A. Wilson and colleagues in 2005 [1]. In this study the [^{11}C]PHNO radiosynthesis is optimized.

Methods: [^{11}C]carbondioxide was passed into a solution of 200 µL ethyl magnesium in 200 µL THF at ambient temperature to form propionic acid. After trapping the resulting [^{11}C]acetic acid, 140 µl phtaloyl dichloride in 360 µL THF and 160 µL 2.6-di-*tert*.-butylpyridine in 180 µL DMF and 160 µL THF was added.

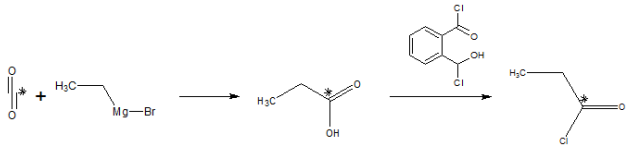

Fig.1: First part of the radiosynthesis of [^{11}C]PHNO.

The reaction mixture was incubated for 2 min and heated to 90 °C to distill [^{11}C]propionyl chloride into a second vial containing the precursor in 50 µl THF.

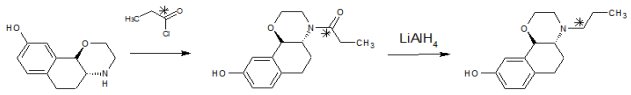

Fig.2: Second part of the radiosynthesis of [^{11}C]PHNO

When the radioactivity peaked in the second vial, the second vial was immersed in an oil bath of 80 °C for 2.5 min. Before adding 100 µL lithium aluminum hydride, the second vial was cooled for one minute in a - 20 °C cooling bath and afterwards heated to 80 °C to remove THF under an argon flow. After total removal of THF from the second vial, 750 µl 1N HCl was added and the resulting mixture was injected into the HPLC.

Results: After 30 min of reaction time [^{11}C]PHNO was synthesized with 90% radiochemical yield. To save very expensive PHNO, *N*-propylbenzylamine and 1,2,3,4-tetra-hydroisoquinoline were used as model compounds at first, but this synthesis modifications required a longer time to achieve the desired results. The Grignard step is very sensitive to moisture, so that all used solvents as well as the vials and the [^{11}C]CO_2 have to be free of water. After the propionyl chloride is assembled, a distillation into a separate vial is required. Depending on the temperature of the oil bath, many byproducts were distilled over. The temperature of the oil bath is further crucial for the evaporation of the THF while controlling the temperature to avoid PHNO to be distilled. As strong reductive agent, lithium aluminum hydride lead to byproducts and required therefore careful controlling of the reaction rate. After adding lithium aluminum hydride to the reaction mixture, one of the resulting by-products is aluminum hydroxide which has to be dissolved by addition of concentrated HCl before the reaction mixture can be injected in the HPLC.

Conclusion: The [^{11}C]PHNO synthesis was successfully reproduced on multiple occasions. In addition to increased radiochemical yields, lower material costs are another benefit which is becoming increasingly important with looming budgetary cuts. The improved radiosynthesis of [^{11}C]PHNO looks promising to warrant PET studies in the near future.

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References

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