Synthesis und radioactive labelling of N-(2-[^{18}F]Fluoroethyl)2β-carbomethoxy-3β-(4-iodophenyl)nortropane (β-CIT-FE)

P. Riss, M. Piel, S. Höhnemann, F. Rösch
Institut für Kernchemie, Johannes Gutenberg-Universität, Fritz-Strassmann-Weg 2, 55128 Mainz

Introduction: Dopaminergic neurotransmission plays an important role in the central nervous system. The dopamine transporter (DAT) is a membrane bound protein at the presynaptic terminal of dopaminergic neurons, which is important for the regulation of dopamine (DA) at the synaptic gap. DAT related reuptake of DA into neurons is an essential feedback signal in dopaminergic signal transmission. Pathologic alterations of dopaminergic functions or morphology, e.g. decreased biotransformation of L-DOPA into DA or an increase of DA-receptor or DAT availabilities are very closely related to several neuropsychiatric disorders, including parkinsonism, schizophrenia or ADS. Beside suitable L-DOPA mimics and DA-receptor ligands, fluorine-18 labelled DAT ligands are of certain interest for clinical diagnosis of neuropsychiatric diseases. Moreover, quantification and localisation of monoamine transporters useing positron emission tomography (PET) are important tools in understanding or defining functions and pharmacology of the dopaminergic system.
N-(2-[^{18}F]fluoroethyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (β-CIT-FE) **7** is a selective DAT ligand, based on cocaine. Some ^{123}I-labelled analogues of β-CIT became diagnostic radiotracers for SPECT (e.g. DaTSCAN®). Its fluorine-18 labelled counterparts,however, will enable full quantification, in addition to improved temporal and spatial resolution by the use of PET.
Aim: Aim of this study was to establish a synthetic route leading from commercially available cocaine to the labelling precursor 2β-carbomethoxy-3β-(4-iodophenyl) nortropane (β-norCIT). This compound subsequently had to be fluorinated via [^{18}F]fluoroalkylation using 2-[^{18}F]fluoroethyl-tosylate ([^{18}F]FETos).

Synthesis: Commercially available cocaine hydrochloride **1** was hydrolysed with diluted hydrochloric acid to afford ecgonin **2** in excellent yield. After elimination of water and reesterification with methanol, anhydro-ecgoninmethylester **3** was obtained in good yield. Stereoselective addition of phenylmagnesiumbromide yielded 2β-carbomethoxy-3β-phenyl-tropane **4** which was iodinated in position 4 of the phenyl ring to obtain 2β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT) **5**. Demethylation with 1-chloroethylchloroformate afforded the desired labelling precursor 2β-carbomethoxy-3β-(4-iodophenyl)nortropane **6** in good yields.

Radiolabelling: [^{18}F]Fluorine was incorporated via ^{18}F-fluoroalkylation using [^{18}F]FETos. 2-[^{18}F]FETos was prepared in an automated radio-synthetic module by reacting ethylene-1,2-ditosylate with potassium carbonate [$K^+ \cap 2.2.2$]$^{18}F^-$ complex (MeCN, 88°C, 3 min). The product was purified using semi-preparative RP HPLC (MeCN:H_2O, 1:1), separated by solid phase extraction and eluted in DMSO.

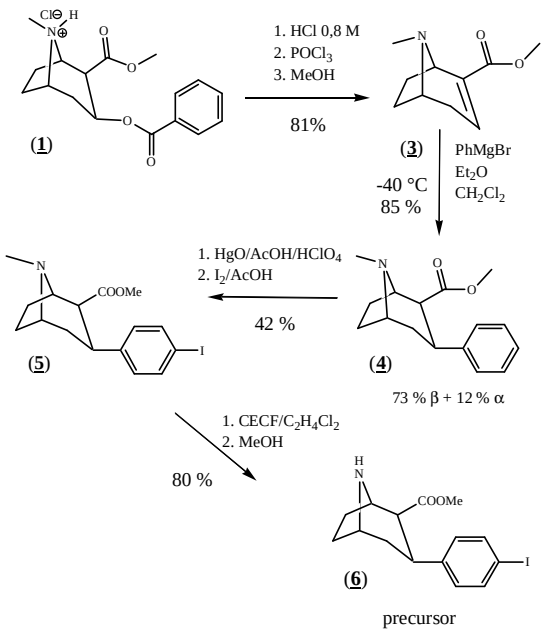

Fig.1: Synthetic route from cocaine hydrochloride **1** to 2β-carbomethoxy-3β-(4-iodophenyl)nortropane **6**.

Radiolabelling of **6** was performed in 5 mL wheaton reaction vials by reacting 50 MBq [^{18}F]FETos with 3 mg of **6** (DMSO, 80-120°C, 20 min).

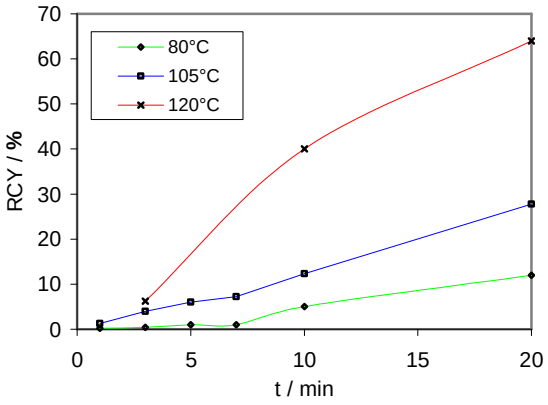

Fig.2: Radiochemical yields versus reaction time at different temperatures. (3 mg precursor, 20 min reaction time, DMSO, 80°C, 105°C, 120°C)

Results: The labelling precursor **6** was obtained in a good yield of 25% after 6 steps. A maximum RCY of about 65% was achieved after a reaction time of 20 min at 120°C using DMSO as solvent.

References:

[1] Neumeyer, J. L. et al., J. Med. Chem., 37, (1994), 1558 f
[2] Xu, L. et al., Heterocyclic Chemistry, 33, (1996), 2037 ff
[3] Swahn, C.-G. et al., J. Label. Compd. Rad., 38, (1996), 675 ff
[4] Clarke, R. L. et al., J. Med. Chem., 16, (1973), 1260 ff
[5] Meltzer, P. C. et al., J. Med. Chem., 36, (1993), 855 ff