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AVHANDLINGENS TITTEL: *Development of efficient (radio)fluorination reactions of hypervalent iodinanes for synthesising electron rich [¹⁸F]fluoroarenes for imaging of N-methyl-D-aspartate receptors*

Fluorine-18 is the most important radionuclide in Positron Emission Tomography (PET) due to its excellent decay characteristics and convenient half-life (110 minutes). The only transition metal free radiofluorination methodology for synthesising electron rich [¹⁸F]fluoroarenes is the use of hypervalent iodinanes, specifically iodonium ylides, although in limited yield and in a high yield variation. The methodology was expanded to afford good to high yields for non-activated and deactivated substrates. An oxygen mediated precursor degradation process was found to be the major culprit in the radiofluorination reaction of iodonium ylides. In addition, residual iodine from precursor preparation was identified to cause reduced yields with poor reproducibility. Precursor syntheses and radiofluorination reaction conditions were developed to afford ylides in markedly improved yields and with low yield variability. Furthermore, we found triphenylphosphane to act as a catalyst which assisted radiofluorination of iodonium ylides. In addition, formamides are described as methylamine masking groups, well suited for preparing and radiofluorinating iodonium ylides. The masking group protects basic amines from oxidation.

Hypervalent iodinanes are further described as fluorination precursors for transition metal free preparative synthesis of fluoroarenes. An *ipso*-specific fluorination reaction was developed via carefully selecting solvent and fluoride source. By synthesising anhydrous crypt-222/KF, which has superior solubility properties in organic solvents, we avoided the inefficient *in situ* formation of crypt-222/KF in anhydrous DMF thus affording significantly improved yields.

The developed methodologies are well suited for synthesising *ortho*-fluorinated analogues of electron rich arenes, an abundant motif in NMDA ligands. A focused library of fluorinated

ligands based on NR2B antagonist Ro 04-5595 was constructed. Several potent, fluorinated NMDA/NR2B ligands were identified. Lead compound Ro 04-5595 was radiolabelled with an ^{11}C -methyl group and evaluated via PET imaging. *In vivo* PET data from rat show moderate brain uptake and fast pharmacokinetics with an NR2B like distribution. High-resolution autoradiographic images using [^3H]Ro 04-5595 show retention primarily in NR2B rich regions cortex, hippocampus, thalamus and striatum with very low binding in cerebellum, which is devoid of NR2B receptors. In addition, both enantiomers of Ro 04-5595 were synthesised and individually evaluated via competitive autoradiography. The displacement study indicate that only (*R*)-Ro 04-5595 is a potent NR2B ligand. We believe that future investigation using PET in non-human primates has good chances to validate [^{11}C]-(*R*)-Ro 04-5595 as a suitable ligand for studying NR2B receptors *in vivo*.