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New amino acid synthons for preparation of [¹⁸F]FDOPA and α-[¹¹C]methyl amino acids for positron emission tomography

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PET diagnostics using radiolabelled amino acids is an emerging branch of nuclear medicine. This includes visualisation and grading of brain, neuroendocrine and prostata tumours, measurement of protein synthesis rate in tumour cells, quantitative in vivo measurement of dopamine and serotonin metabolism in brain. Development of clinical applications is limited by complexicity of robotic devices necessary for multi-step preparation of the enantiomerically pure amino acids. Robust and reliable approaches not requiring sophisticated separation of radiolabelled intermediates have to be created for everyday clinical routine. Nickel(II) complexes of Schiff bases of (S)-N-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide (BPB) and α-amino acids were developed as artificial analogues of pyridoxal 5'-phosphate (PLP)-dependent enzymes for asymmetric synthesis of amino acids. Current approach using BPB in nickel(II) complex of its Schiff base with glycine allows easy preparation of O-(2'-[¹⁸F]fluoroethyl)-L-tyrosine ([¹⁸F]FET) with 94-97% e. e. with no need for separation of diastereomers of alkylated complexes. Preparation of 6-[¹⁸F]FDOPA using the same starting nickel complex gives only 77±5% e. e. without separation of diastereomers of alkylated complexes while the same preparation of α-[¹¹C]DOPA leads to 92-99% e. e. Preparation of α-methyl DOPA or α-methyltyrosine labelled with carbon-11 or fluorine-18 requires formation of quaternary chiral centre, stereochemistry of which is controlled kinetically. Kinetic control is much less efficient then thermodynamic one, thus diastereomeric excess of complexes of α-methyl amino acids is inferior. Enhancement of stereodivergent power in both thermodynamically and kinetically controlled alkylation reaction is the biggest priority in development of new metallocomplex tools for the preparation of PET amino acids.
In this presentation the evaluation of new amino acids synthons bearing C₂-symmetric benzyl groups with electron-donating and electron-withdrawing substituents will be described. Compatibility of amino acid side chains protective groups will be assessed in relation to the reaction conditions used for preparation of the complexes.

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