Development of new precursors for asymmetric preparation of $\alpha$-[11C]methyl amino acids for PET
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5.1 Summary and future perspectives

Positron emission tomography (PET) utilises positron emitting radiopharmaceuticals in the study of metabolic and physiological processes. After the injection of a carbon-11 or fluorine-18 labelled tracer, the space- and time-resolved image of positron annihilations is detected externally using rings of coincidence detectors placed around the subject (a PET scanner). New tomographs allow simultaneously recording of both CT or MRI and PET providing both anatomical information from CT (or MRI) and functionality from PET. PET investigations using 2-[18F]fluoro-2-deoxy-D-glucose (FDG) become available in a large number of hospitals worldwide. FDG-PET is a useful technique for tumour detection, diagnosis of tumour recurrence. However, FDG has disadvantages. It is not only taken up by tumours, but also in the heart and the brain. This phenomenon hampers detection of tumours in these tissues. High physiological FDG uptake can be seen in muscle tissue, macrophages and other cells in inflammatory processes or activated after chemotherapy or radiation therapy causing false positive results. Decreased uptake can cause false negative results in patients with hyperglycaemia. More specific tracers are therefore being developed. The incorporation of labelled amino acids into brain tumours and into some other organ with high physiological consumption of glucose is the superior diagnostic method for its much higher selectivity compared to FDG. The first synthesis of an [11C]amino acid was published in 1973. Enantiomerically pure [11C]amino acids with exception of [11C]methionine are not yet available for routine PET diagnostics. Low availability hampers their evaluation as biological probes. Enantioselective synthesis of large aromatic α-[11C]methyl-α-amino acids by α-methylation of amino acids derivatives is an especially challenging goal due to relatively low steric volume of the methylation agent (methyl iodide or methyl triflate). On the other hand, availability of both [11C]CH3I and [11C]CH3OSO2CF3 as starting materials makes the synthesis and disclosure of α-[11C]methylaminoacids diagnostic impact especially attractive for future routine application in PET diagnostics. Each large aromatic α-[11C]methyl amino acid has specific (potential) advantage based on its metabolic behaviour. In vivo, α-[11C]methyltryptophan is converted to the corresponding 5-hydroxyderivative followed by decarboxylation to α-[11C]methylserotonin. For this reason it is very useful for quantitative measurement of serotonin biosynthesis. Unlabelled α-MeTyr is routinely used for pre-surgery treatment of patients with pheochromocytomas due to its high accumulation in this tumour followed by competitive suppression of uptake of tyrosine leading to lower biosynthesis of catecholamines. Thus α-[11C]MeTyr could be useful for diagnostics of pheochromocytomas, similar to application of fluorine-18 labelled α-MeTyr and the SPECT radiotracer 123I-IMT.

This compound is not decarboxylated in vivo thus being a promising radiodiagnostics drug candidate for measurement of LAT expression in tumour cell membranes. Similarly to widely used FDOPA and β-[1C]DOPA, α-[1C]MeDOPA may be applied for diagnostics of other neuroendocrine tumours and visualisation and possibly quantification of dopamine metabolism in the brain. Application of nickel(II) complexes BPB and α-amino acids for asymmetric synthesis of α-amino acids becomes a popular synthetic method due to cheap starting compounds, easy chromatographic detection of starting and alkylated complexes and re-usage of BPB without loss of enantiomeric purity of its stereogenic centre after several turnovers. The complexes provide easy generation of an intermediate carbanion due to high acidity of α-hydrogen of an amino acid fragment (pKa ≈ 19). The main aims of the work presented in this thesis are:
1. to increase stereochemical output of alkylation of the chiral nickel complexes derived from amino acids in order to avoid or at least simplify separation of diastereomeric products of alkylation;
2. to develop a new approach to create a quaternary asymmetric centre via alkylation of a chiral tertiary carbanion by $^{11}$CH$_3$I or $^{11}$CH$_3$OTf and evaluate the applicability of metallocomplex chiral synthons of $\alpha$-amino acids for asymmetric synthesis of $^{11}$C-labeled $\alpha$-methyl amino acids.

Proximity of ortho-protons of the benzyl group to both the $\alpha$-proton of the proline residue and substituents in $\alpha$-position of the amino acid fragment in CDCl$_3$ solution of the simplest studied complex led to formulation of the first hypothesis about structure of the improved synthon providing higher asymmetric induction. It should carry substituents in ortho-positions of the benzyl group. The donation of electron density from the $\pi$-system of the benzyl ring to nickel orbitals should influence the stereochemical result of alkylation of the complexes under thermodynamically controlled conditions. Replacement of the $N$-benzyl group by a polyalkyl-substituted benzyl group should also result in steric hindrance of 'ring-edge' bonding (between the $\eta^2$-bonded aromatic ring and the metal atom), compared to 'ring-centre' bonding where the polyalkyl-substituted benzyl group is a $\eta^6$-ligand. The polyalkyl-substituted benzyl group may also increase steric hindrance with respect to alkylation of the $\alpha$-carbon of the glycine or the alanine fragment, thereby enhancing the diastereoselectivity of the reaction. X-Ray charge density studies of the Ni(II) complex of the Schiff base of BPB proved an interaction between Ni$^{2+}$(d$^z$$_2$) orbital and benzyl $\pi$-electron density. Due to occupation of the d$^z$$_2$ orbital with two electrons no donation of electron density from the $\pi$-system of the benzyl ring to nickel orbitals is possible. Instead, polarisation of the $\pi$-system of the benzyl ring by a positive charge of the nickel atom leads to electrostatic attraction between the benzyl group and the nickel atom. Introduction of -C(CH$_3$)$_3$ substituents in meta-positions of the benzyl group or use the pentamethylbenzyl group in Ni(II) complexes of Schiff bases of (S)-N-(2-benzoylephynyl)-1-benzopyrrolidine-2-carboxamide and glycine and alanine gave very efficient synthons of glycine and alanine capable of stereospecific preparation of $\alpha$-monosubstituted glycines or highly stereoselective synthesis of $\alpha$-methyl $\alpha$-amino acids. A synthetic procedure suitable for the routine preparation of (S)-$\alpha$-[$^{11}$C]methylDOPA and (S)-$\alpha$-[($^{11}$C)methylyrosine was developed, final radiochemical synthetic steps are now being optimised. Search for a suitable protective group for the indole nitrogen atom of similar tryptophan synthon for the preparation of enantiomers of $\alpha$-[($^{11}$C)methylyryptophan and, in the case of success, for preparation of enantiomers of $\alpha$-[($^{11}$C)methyl-5-hydroxytryptophan, is in progress. Preparation of the complexes was optimised with respect to minimisation of amount of nickel compounds in waste water.

Differences in pharmacokinetics of $\beta$-[($^{11}$C]DOPA and 6-[($^{18}$F]fluoroDOPA were studied in a number of publications. One potential difference was omitted in these studies – the fluorine atom present in 6-[$^{18}$F]fluoroDOPA is potentially able to form a (strong) hydrogen bond with surrounding biologic structures including receptors and other parts of biomembranes thus resulting in different behaviour of 6-fluoroDOPA and 6-fluorodopamine compared to the non-fluorinated analogues. Accurate quantum-chemical modelling of such interactions is not easy due to uncertainty of which biological structure to choose, their unknown in vivo conformations and high computational cost of calculation for large systems. Modelling of an intramolecular hydrogen bond between the fluorine atom of fluorodopamine and the hydrogen
atoms of the amino group which mimics an amino group of a protein could be an attractive alternative. The small size of the system enables accurate geometry modelling at MP2 level with low computational cost. Indeed, geometry optimisation of both dopamine and 6-fluorodopamine revealed significant differences in intramolecular interactions in vacuum. In dopamine, the only intramolecular hydrogen bond exists in – H … OH between two phenolic hydroxy groups. In 6-fluorodopamine there are two kinds of intramolecular hydrogen bonds H … OH and F … HN. One should expect similar F … H interaction in real biological systems. In vivo the interactions could lead to differences in the biodistribution and metabolic rates of dopamine and 6-fluorodopamine.

5.1.1 Perspectives of development of chiral nickel complexes for preparation of radiolabelled α-disubstituted glycines

New complex design incorporating a D-proline residue N-alkylated with a C2v-symmetrically substituted benzyl group will be used for preparation of α-[11C]methyl amino acids. High efficiency of such complexes has been demonstrated in model reaction with non-radioactive electrophiles. Diastereomeric excesses of the methylation reaction should be higher, but the radiochemical yields can be influenced by electron rich “benzylic umbrellas” proximate to the nickel atom and the methylated α-carbon. Commercial potassium hydroxide used in the methylation reaction usually contain significant amount of water. This water present in the reaction mixture is responsible for hydrolysis of main part of [11C]methyliodide yielding [11C]methanol. Potassium hydroxide will be dried by melting in a platinum crucible under argon or will be prepared by controlled hydrolysis of tert-BuOK followed by evaporation of tert-butanol. The influence of its dryness to the radiochemical yields of the [11C]methylation reactions will be evaluated. Low stability of Boc indolyl N-protective group of the studied tryptophan synthon led to the failure of its α-methylation. New indolyl N-protective groups will be evaluated for preparation of enantiomers of α-[11C]methyltryptophan and, in the case of success, for preparation of enantiomers of α-[11C]methyl-5-hydroxytryptophan. A new tryptophan synthon where the nitrogen is protected with -Si(i-Pr)3 has been recently prepared and its structure has been confirmed by MS/MS. Non-labelled (S)-methyltyrosine is used for preoperational treatment of pheochromocytoma patients due to its high specific uptake into these tumour cells and its ability to inhibit catecholamine synthesis. Efforts will be made towards evaluation of enantiomers of α-[11C]methyltyrosine for imaging of pheochromocytomas and for in vivo comparison of α-[11C]MeDOPA and FDOPA.

5.1.2 Perspectives of development of chiral nickel complexes for preparation of radiolabelled α-monosubstituted glycines

During the course of development of new chiral nickel complexes for radiosynthesis of α-methyl amino acids, the evaluation of the complexes for preparation of α-amino acids was also performed. In the most stereochemically challenging synthesis of alanine, several new compounds demonstrated stereospecific alkylation reaction according to NMR analysis of the reaction mixtures. Usage of the complexes for preparation of “α-monosubstituted glycines” (e. g. substituted large aromatic amino acids) could be an attractive option. An example of such approach to FDOPA using complexes developed by a group led by Krasikova has been
recently published (Scheme 5.1) [1]. New stereospecific glycine synthons described in the Chapter 3.3 are candidates for evaluation in this FDOPA synthesis with no need for separation of the diastereomers of the alkylated complexes. The methodology could be a complimentary tool to existing enzymatic approaches fitted to individual large aromatic amino acids like β-11C-labelled L-5-hydroxytryptophan and L-DOPA or L-5-[18F]fluorotryptophan [2, 3].

Scheme 5.1 Asymmetric synthesis of FDOPA from 18F employing chiral nickel complexes

5.1.3 Perspectives of physical chemical investigations
Deeper physical chemical research of the chiral nickel complexes will cover crystal structures determination and deformational electron density mapping using diffraction of neutrons in combination with synchrotron X-ray diffraction data; MP2 modelling of structures of nickel complexes and carbanions generated from them both in vacuum and in aprotic solvents; more accurate “atoms-in-molecules” topologic analysis of intramolecular bonding based on results of MP2 modelling. Search for long-range 15N-13C and 13C-13C interactions in NMR spectra will be extended to wider variety of the complexes carrying a C2v-symmetrically substituted benzyl group. This research can disclose properties of the complexes, especially intramolecular interactions, which will give new insight to design of new precursors of radionlabelled amino acids for PET.

MP2 modelling of interactions of fluorine labelled radiopharmaceutical will cover not only hydrogen bond formation, but also assessment of Van-der-Waals interactions with other biomolecules. It would be also useful to access weakness of the DFT approach for such calculations.