Direct no-carrier-added ^{18}F-labelling of arenes via nucleophilic substitution on aryl(2-thienyl)iodonium salts

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Abstract

For *in vivo* imaging of molecular processes via positron emission tomography (PET) radiotracers of high specific activity are demanded. In case of the most commonly used positron emitter fluorine-18, this is only achievable with no-carrier-added [^{18}F]fluoride, which implies nucleophilic methods of ^{18}F-substitution. Whereas electron deficient aromatic groups can be labelled in one step using no-carrier-added [^{18}F]fluoride, electron rich ^{18}F-labelled aromatic molecules are only available by multi-step radiosyntheses or carrier-added electrophilic reactions. Here, diaryliodonium salts represent an alternative, since they have been proven as potent precursor for a direct nucleophilic ^{18}F-introduction into aromatic molecules. Furthermore, as known from non-radioactive studies, the highly electron rich 2-thienyliodonium leaving group leads to a high regioselectivity in nucleophilic substitution reactions.

Consequently, a direct nucleophilic no-carrier-added ^{18}F-labelling of electron rich arenes via aryl-(2-thienyl)iodonium precursors was developed in this work. The applicability of direct nucleophilic ^{18}F-labelling was examined in a systematic study on eighteen aryl(2-thienyl)iodonium salts. As electron rich precursors the *ortho*-, *meta*- and *para*-methoxyphenyl(2-thienyl)iodonium bromides, iodides, tosylates and triflates were synthesised. In addition, *para*-substituted (R = BnO, CH_3, H, Cl, Br, I) aryl(2-thienyl)iodonium bromides were prepared as precursors with a systematically varying electron density.

As first approach, the general reaction conditions of the nucleophilic ^{18}F-substitution procedure were optimised. The best conditions for direct nucleophilic no-carrier-added ^{18}F-labelling via aryl(2-thienyl)iodonium salts were found with dimethylformamide as solvent, a reaction temperature of 130 $\pm$ 3 °C and 25 mmol/l as concentration of the precursor. For the effect of bromide, iodide, tosylate and triflate as counter anion on the radiochemical yield (RCY) the following order was obtained: tosylate < iodide < triflate < bromide. However, based on the kinetics a different order was observed for the initial reaction rates with: tosylate < bromide < iodide < triflate. The influence of the substitution pattern in o*rtho*-, *meta*- and *para*-methoxyphenyl(2-thienyl)iodonium bromide showed an expected strong *ortho*-effect, which led with 60 % of 2-[^{18}F]fluoroanisole to the highest RCY. Also under no-carrier-added conditions, the 2-thienyl group directed to a regiospecific radiofluorination, thus in all ^{18}F-substitutions no 2-[^{18}F]fluorothiophene, but only the desired [^{18}F]fluoroarenes were formed.

With the intention of a systematic examination of electronic factors, the kinetics of the ^{18}F-substitution on substituted aryl(2-thienyl)iodonium bromides were investigated and the determined relative reactivities were compared with the Hammett constants of the corresponding substituents. As result a good linear Hammett correlation and a reaction parameter of ρ = + 1.16 $\pm$ 0.2 were obtained. This confirms the S_NAr-mechanism and a consistent mechanism over the whole range of investigated substituents.

In order to demonstrate the applicability of this method, the ^{18}F-labelling of two pharmacological relevant molecules was carried out. First, n.c.a. 4-[^{18}F]fluorophenol was synthesised via 4-benzyl-oxyphenyl(2-thienyl)iodonium bromide within 40 min and an overall RCY of 34 to 36 %. Second, a complex AMPA receptor antagonist was ^{18}F-labelled via iodonium precursors; however only with low RCY of 1.2 to 3.6 %. For comparison, the radioiodine analogue was labelled via a trimethyltin precursor and [^{131}I]iodide with a very high RCY of 97 $\pm$ 2 % within 2 min, thus it was available for preliminary pharmacological evaluation studies.

In conclusion, the 2-thienyliodonium leaving group proved as highly effective for direct nucleophilic no-carrier-added ^{18}F-labelling even of nucleophilically non-activated arenes. Concerning the ^{18}F-labelling of complex molecules, further optimisation, however, is necessary for this method.

Kurzzusammenfassung

Zur *in vivo* Bildgebung molekularer Prozesse mittels Positronen-Emissions-Tomographie (PET) besteht eine große Nachfrage nach Radiotracern mit hohen spezifischen Aktivitäten. Im Fall des dafür meistgenutzten Positronenstrahlers Fluor-18 sind diese nur mittels trägerarmen [^{18}F]Fluorids erreichbar, so dass nukleophile ^{18}F-Markierungsmethoden erforderlich sind. Elektronenarme aromatische Gruppen können leicht mit trägerarmen [^{18}F]Fluorid direkt markiert werden, wohingegen elektronenreiche [^{18}F]Fluoraromaten nur über mehrstufige Radiosynthesen oder geträgerte elektrophile Methoden zugänglich sind. Hier stellen Diaryliodoniumsalze eine Alternative dar, seit sie sich als Vorläufer für die direkte nukleophile ^{18}F-Markierung von aromatischen Verbindungen als vorteilhaft erwiesen haben. Weiterhin ist von nicht-radioaktiven Untersuchungen bekannt, dass die 2-Thienyliodonium Abgangsgruppe in nukleophilen Substitutionen zu einer hohen Regioselektivität führt.

Daher wurde die direkte nukleophile, trägerarme ^{18}F-Markierung von elektronenreichen Arenen mittels Aryl(2-thienyl)iodoniumsalzen in dieser Arbeit entwickelt. In einer systematischen Studie wurde ihre Anwendbarkeit auf direkte nukleophile ^{18}F-Substitutionsreaktionen an achtzehn Aryl(2-thienyl)-iodoniumsalzen untersucht. Als elektronenreiche Vorläufer wurden die *ortho*-, *meta*- und *para*-Methoxyphenyl(2-thienyl)iodonium Bromide, Iodide, Tosylate und Triflate synthetisiert. Zusätzlich wurde eine Gruppe von *para*-substituierten (R = BnO, CH_3, H, Cl, Br, I) Aryl(2-thienyl)iodonium Bromiden als Vorläufer mit systematisch variierender Elektronendichte hergestellt.

Zunächst wurden die allgemeinen Reaktionsparameter der nukleophilen ^{18}F-Substitutionsreaktion optimiert. Als beste Bedingungen für den direkten trägerarmen ^{18}F-Austausch mittels Aryl(2-thienyl)iodoniumsalzen ergaben sich Dimethylformamid als Lösungsmittel, eine Reaktionstemperatur von 130 $\pm$ 3 °C und eine Vorläuferkonzentration von 25 mmol/l. Für den Einfluss von Bromid, Iodid, Tosylat und Triflat als Gegenion auf die radiochemische Ausbeute (RCA) wurde die folgende Abstufung erhalten: Tosylat < Iodid < Triflat < Bromid. Basierend auf den Reaktionskinetiken ergab sich jedoch aus den initialen Reaktionsgeschwindigkeiten eine andere Reihenfolge mit: Tosylat < Bromid < Iodid < Triflat. Der Einfluss des Substitutionsmusters in o*rtho*-, *meta*- and *para*-Methoxyphenyl(2-thienyl)iodonium Bromid äußerte sich wie erwartet als starker *ortho*-Effekt, der bei 2-[^{18}F]Fluoranisol zur höchsten RCA von 60 % führte. Die 2-Thienyl Gruppe führte auch im trägerarmen Fall zu regiospezifischen Radiofluorierungen, so dass in allen ^{18}F-Substitutionen kein 2-[^{18}F]Fluorthiophen, sondern nur die gewünschten [^{18}F]Fluorarene gebildet wurden.

Für eine systematische Untersuchung des elektronischen Einflusses wurden die Kinetiken der ^{18}F-Substitution an substituierten Aryl(2-thienyl)iodonium Bromiden untersucht und die erhaltene relative Reaktivität mit den Hammett Konstanten der jeweiligen Substituenten verglichen. Es ergab sich eine gute lineare Hammett-Korrelation mit einem Reaktionsparameter von ρ = + 1,16 $\pm$ 0,2. Dies bestätigt den S_NAr-Mechanismus und eine hohe Reaktivität der Aryl(2-thienyl)iodoniumsalze.

Um die Anwendbarkeit als Markierungsmethode zu demonstrieren, wurden die ^{18}F-Radiosynthesen zweier pharmakologisch relevanter Moleküle durchgeführt. Zunächst wurde trägerarmes 4-[^{18}F]Fluorphenol mittels 4-Benzyloxyphenyl(2-thienyl)iodonium Bromid dargestellt, für das nach 40 min eine radiochemische Gesamtausbeute von 34 - 36 % erhalten wurde. Weiterhin wurde ein komplexer AMPA Rezeptor Antagonist über Iodoniumvorläufer ^{18}F-markiert; allerdings nur mit einer geringen RCA von 1,2 – 3,6 %. Zum Vergleich wurde das Radioiodanalog mittels eines Trimethylzinnvorläufers und [^{131}I]Iodid innerhalb von 2 min mit sehr hoher RCA von 97 $\pm$ 2 % hergestellt, womit es für erste pharmakologische Evaluierungsstudien zur Verfügung stand.

Insgesamt erwies sich die 2-Thienyliodonium Abgangsgruppe als sehr effektiv, auch nukleophil nicht-aktivierte Aromaten direkt trägerarm zu radiofluorieren. Bezüglich der ^{18}F-Markierung komplexer Moleküle sind jedoch weitere Optimierungen der Methode notwendig.

Contents

Introduction

1.1 Radionuclides in Nuclear Medicine

In 1896 Antoine Henri Becquerel noticed the blackening of photographic films by uranium ore whereby he discovered the radioactivity. This was the basis for a new branch of natural sciences and Becquerel received the physics Nobel price in 1903. Consequently, the sub-field of nuclear chemistry was established in 1898 by the researcher couple Marie and Pierre Curie, who isolated the radioactive elements polonium and radium from pitchblende by radiochemical procedures [1].

With the first *in vivo* examinations of biological processes using radionuclides by Georg de Hevesy in 1920, the way of radionuclides into life sciences was opened [2]. Hevesy and Adolf Paneth developed the radiotracer principle which is based on the identical chemical and biochemical behaviour of stable elements and their radioactive isotopes. Since that time Hevesy is known as the “Grandfather of Nuclear Medicine” and he received the medicine Nobel price in 1943 for his life’s work.

As far as 1930, the radionuclides were limited to the natural occurring nuclides and only very few were suitable as radiotracers in life sciences. By the development of the first cyclotron (Ernest Orlando Lawrence, 1930), the discovery of the induced nuclear fission (Otto Hahn and Fritz Strassmann, 1938/39, chemistry Nobel price 1944) and the construction of the first nuclear reactor (Enrico Fermi and Leo Szilard, 1942), the production of artificial radionuclides in large scale became possible [3]. Since then their applications in life science have increased rapidly [4].

Today only a selected minority of more than 2400 available radionuclides are employed in life sciences. Their number is strictly limited by special requirements in half-life, achievable chemical and radiochemical purity and radiation type and energy. Especially the field of nuclear medicine calls for high standards in these aspects, more than other domains in life sciences.

Application in Nuclear Medicine classifies radionuclides generally in diagnostic and therapeutic nuclides. For *in vivo* diagnostic investigations only short-lived single photon and positron emitters are used to guarantee as small as possible radiation exposure for the patient, but well detectable signals to get the important information [5, 6]. In contrast, for the *in vivo* therapeutic use (e.g. for brachytherapy and endoradiotherapy) longer-lived corpuscular emitting radioisotopes with high LET-values (Linear-Energy-Transfer) are in demand, with the intention that the α- and β^--particles accomplish a local degeneration of the pathogen tissues. In addition, Auger electron emitting nuclides are of therapeutic interest, they cause degeneration in a very small radius of the emitting nuclide. Thus they are able to induce apoptosis, when they are brought into the cell nucleus and cause radiation damage of DNA [5, 7, 8].

The application of radiolabelled biomolecules or pharmaceuticals with *in vivo* examinations enables the visualisation of physiological or pathophysiological processes on a molecular level. Besides *in vivo* techniques, many *in vitro* procedures (e.g. radioimmunoassay (RIA) and autoradiography) have been developed and became important tools in biochemistry, physiology and pharmacology.

The radiotracer method now extends over widespread fields of physiology and pharmacology and has played a key role e.g. in investigations on metabolic principles, on the function and dysfunction of physiological processes and in the development of pharmaceuticals.

1.2 Emission tomography

In general, the non-invasive imaging techniques magnetic resonance tomography (MRT) and x-ray computed tomography (CT) give information about tissue structure. Hereby the MRT includes the sub-fields of magnetic resonance spectroscopy and imaging (MRS and MRI). An enhancement of MRI, the functional MRI (fMRI), is a step to observe specific physiological functions, particularly for brain imaging. fMRI is based on the so-called Bold-effect, an increase in blood flow of a local vasculature that accompanies neural activity in the brain. fMRI is versatile tool for mapping the brain and supports the clinical management in neurosurgery [9].

In contrast to the above mentioned methods, the emission tomography technology shows special advantage of visualising pathophysiological, physiological and metabolic processes. The use of compounds, which are involved in this biochemistry and labelled with suitable radionuclides, helps to understand the mechanisms and the processes of e.g. degenerative brain diseases such as Alzheimer's, Parkinson's and Huntington's disease. Furthermore, in oncology radiotracers are widely employed for diagnoses as well as for controlling and monitoring endoradiotherapy. Additionally, the very sensitive traceability of radioactivity and radiotracers with high specific activities allow the use of substrate quantities in subnanomolar scales. In consideration of this fact, the implementation of highly potent or even toxic compounds is possible without any pharmacodynamic effects and a physiological or pathophysiological system can be studied without disturbance. [10-13]

Emission tomography is possible as single photon emission tomography (SPET) and positron-emission tomography (PET). Both are routinely used in nuclear medicine and pharmacological research.

SPECT is the more popular technique, by reason that here the focus is on the artificial radionuclide ^{99m}Tc. ^{99m}Tc has favourable properties: a monoenergetic 140 keV single photon emission and an opportune half life of 6 h. However, the major advantage is the availability of ^{99m}Tc generator systems, thus its application is independent of nearby cyclotrons or reactors.

Moreover, one-step-labelling systems (so-called kits) containing precursors and all necessary reagents were developed by the pharmaceutical industry and make practical application very convenient. More single photon emitting radionuclides such as ^{111}In, ^{123}I and ^{201}Tl are also in routine use for SPECT, but not to the extension of ^{99m}Tc.

Although SPECT became more developed in recent years and even attempts for quantitative analyses were made, PET is still the advanced technology. PET shows a higher sensitivity (more than 100-fold of SPECT) and its quantitation methods are well-elaborated. The characteristics of the positron decay itself establish the basic for a quantitative measurement of radioactivity. Nonetheless, an exact independent transmission measurement and attenuation correction is necessary. Consequently, radiotracer concentrations and their kinetics in organs and the regions of interest can be measured quantitatively and used with appropriate bio-mathematical models to evaluate (patho)physiological processes [14].

For labelling PET radiotracers, short-lived, neutron deficient positron emitters are of primary interest. From the decaying nucleus a positron (β^+) and a neutrino (ν) are emitted synchronously by the conversion of a proton into a neutron. Neutrinos show practically no interaction with matter and PET cameras are not able to detect them [15]. The positron loses its kinetic energy by collisions and interactions with matter along a short distance. The range depends on the β^+-energy, which is specific for the employed isotope (Table 1.1 shows the β^+_{max}-energies of important positron emitters used for PET) and reaches from less than 1 mm to several millimetres. When the positron is nearly at rest, it is able to interact with an electron, its anti-particle. Positron and electron compose an intermediary positronium, an exotic atom showing similarities to hydrogen. In the positronium the proton in the hydrogen's nucleus is replaced by a positron. Positronium atoms exist as para-positronium in a singlet state (antiparallel spins, angular moment: 0, mean life: $1.25 \cdot 10^{-10}$ s) or as ortho-positronium in a triplet state (parallel spins, angular moment: $\hbar = h/2\pi$, mean life: $1.39 \cdot 10^{-7}$ s). In the positronium the particles "spiral" closer to each other until they are terminated by annihilation. By annihilation, γ-rays are released with a total energy of 1.022 MeV, the sum of the masses of positron and electron, 511 keV each. As a result of the conservation of energy, parity and angular momentum the singlet state emits two γ-rays and the triplet state emits three γ-rays. The two γ-rays from the singlet state show a nearly 180° distribution and each carries a characteristic energy of 511 keV. Due to different numbers of quantum states of ortho- and para-positronium their probability of creation is 3:1. However, in matter the ortho-positronium merge into para-positronium by the so-called pick-off process, where it interacts with electrons of its environment. In matter, the high efficiency of the pick-off process leads to a strong depression of the triplet state, thus only the two γ-rays annihilation is relevant here and the three γ-rays annihilation is negligible [16].

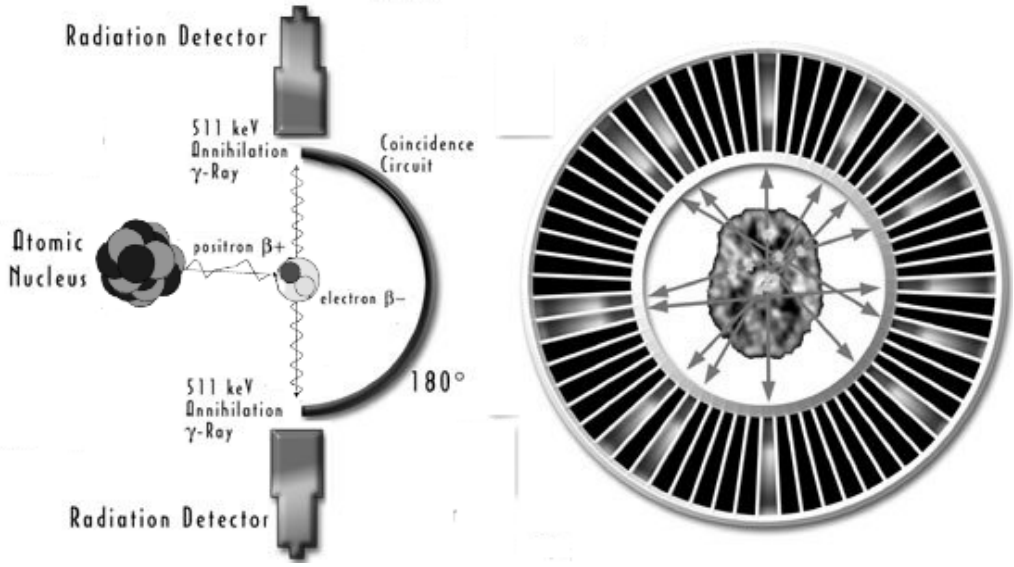


Figure 1.1: Principles of positron electron annihilation with coincidence measurement (left) and brain imaging with PET including ring of detectors (right)

The annihilation of the para-positronium and the resulting two body-penetrating photons provide the basis for PET (Figure 1.1). The PET device (PET camera) consists of circular arranged scintillation detectors. In these rings of detectors every pair of opposite detectors are connected for coincidence measurement. As a result, the two γ-rays of the annihilation process will be detected, if they hit both opposite detectors within a time window of a few nanoseconds (generally ~12 ns). Assuming that both detected photons result from one event, the positron emitter must be located on or nearby the connection line of the detector pair. Hereby, the spatial resolution depends on both the distance between origin and annihilation of the positron and the size of the detector crystals. As the distance of the positron from emission to annihilation is dependent on its β^+-energy, which is again specific for the decaying isotope, PET nuclides should emit positrons with an energy as low as possible to increase the spatial resolution and also to reduce the radiation dose. Besides, other uncertainties based on individual attenuation can be avoided by an attenuation factor, which is developed by an accurate independent transmission measurement. For this purpose a ^{68}Ge source is generally used to correct adsorption and scattering effects before the real tracer will be injected. Finally, the distribution of radioactivity quantity in the object tissues can be measured precisely [14].

Computer-aided image reconstruction of the data of several transversal measurement planes allows the output of 3D-images of regions of interest. These can be obtained with spatial resolutions down to 3-5 mm and accuracy in quantity down to nano- and picomolar

concentrations. Further on, physiological and pharmacological processes can be acquired in combination with a bio-mathematical model by dynamic studies with a longer span of time. With such methods and an accurate quantification, information about transport processes, metabolic rates and concentrations become accessible depending on the specific radiotracer used. Modern scanners combine PET and MRT/CT in one device, which leads to 3D-images with exact morphologic information as well as a physiological and biochemical representation. Those procedures are highly relevant in e.g. the clinical management of oncologic therapy [17].

Due to the fact that PET is a powerful tool in pharmacological and physiological research, special small animal PET scanners were developed in recent years [18]. Animal PET cameras make repeatable drug trials in one animal possible, without the need for vivisection and therefore costs and expenses for (radio)pharmaceutical development can be reduced [19, 20]. One of the latest innovations in this field is the so-called RatCAP, a small, head-mounted PET system, the main item of which is a 4 cm diameter ring consisting of 12 crystal detectors. Those systems allow PET measurements of the brain of an awake rat without the need of anesthesia, which actually make studies of behaviour or severely depressed brain functions impossible [21].

1.3 Radionuclides and -tracers for positron emission tomography

As mentioned before, PET presents an excellent imaging technique with its advantages in very high sensitivity, good spatial resolution and the ability to acquire (patho)physiological processes and functions and to quantify them accurately. Enhancements of the devices and combined scanner systems made strong contributions to the understanding of metabolic functions and processes of the brain and of brain diseases. But not only the progress of the technical equipment had achieved these acquisitions, also steady improvement and advanced development of suitable and high specific radiotracers were needed.

To find the right tracer molecule a close look into the designated processes and the related bio-chemistry is necessary, the following gives a short overview:

- metabolism and general biochemical function
- receptor-ligand biochemistry
- enzyme function and inhibition
- immune reaction and response
- pharmaceutical effects
- toxicology (carcinogen and mutagenic substances)

In terms of radiotracer development the choice of a biochemical or physiological concept is only the first step and more considerations are compulsory. One is the choice of the radionuclide with the suitable half-life (cf. Table 1.1), which is affected by the radiosynthesis as well as the characteristic of the finally studied biochemistry. Furthermore, a comprehensive pharmacological evaluation of the radiotracer including *in vitro*, *ex vivo* and *in vivo* metabolic investigations, dosimetry and toxicology studies is required. An inclusive quality management with automation and up-scaling (GBq range) of the radiosynthesis as well as validation of the bio-mathematical modelling for quantitation should be completed before the radiotracer is taken into routine practice.

Table 1.1: Important positron emitters used for PET and their nuclear data [from 6, 12]

Nuclide	Half-life		Decay mode (%)			$E_{\beta+,max}$ [keV]
organic						
^{11}C	20.4	min	β^+ (99.8)	EC (0.2)		960
^{13}N	9.96	min	β^+ (100)			1190
^{15}O	2.03	min	β^+ (99.9)	EC (0.1)		1720
^{30}P	2.5	min	β^+ (99.8)	EC (0.2)		3250
analogue						
^{18}F	109.6	min	β^+ (97)	EC (3)		635
^{75}Br	98	min	β^+ (75.5)	EC (24.5)		1740
^{76}Br	16.1	h	β^+ (57)	EC (43)		3900
^{73}Se	7.1	h	β^+ (65)	EC (35)		1320
^{120}I	1.35	h	β^+ (64)	EC (36)		4100
^{124}I	4.18	d	β^+ (25)	EC (75)		2140
metallic						
^{38}K	7.6	min	β^+ (100)			2680
^{62}Cu	9.7	min	β^+ (98)	EC (2)		2930
^{64}Cu	12.7	h	β^+ (18)	β^- (37)	EC (45)	655
^{68}Ga	68.3	min	β^+ (90)	EC (10)		1900
^{82}Rb	1.3	min	β^+ (96)	EC (4)		3350
^{86}Y	14.7	h	β^+ (34)	EC (66)		1300
^{94m}Tc	52	min	β^+ (72)	EC (28)		2470
^{72}As	26	h	β^+ (88)	EC (12)		2515

Biomolecules (e.g. glucose, amino acids, fatty acids, enzymes, etc.) and pharmaceuticals mainly consist of carbon, hydrogen, oxygen, nitrogen, sulfur and phosphorous. Due to that fact positron emitting, short-lived isotopes of these elements are in order to achieve the so-called authentic

labelling. The so-called “organic” PET nuclides ^{11}C, ^{15}O, ^{13}N and ^{30}P allow the authentic labelling without any changes in (bio)chemical and physiological behaviour or properties of the labelled compounds. However, extremely short half-lives of those isotopes from two to twenty minutes strongly limit their applicability. In case of ^{15}O ($T_{½}$ = 2 min) and ^{13}N ($T_{½}$ = 10 min) only fast accessible, simple compounds, such as [^{15}O]H_2O, [^{15}O]C_4H_9OH and [^{13}N]NH_3 as tracers for blood flow, [^{15}O]O_2 as indicator for oxygen metabolism and [^{15}O]glucose as indicator for glucose uptake, can be synthesised [22]. Only the half-life of ^{11}C ($T_{½}$ = 20.4 min) provides the possibility of multi-step radiosyntheses and allows PET measurements of slower physiological processes. From the production of carbon-11 the primary labelling precursor [^{11}C]CO_2 is available, which unfortunately is rarely useful for direct labelling reaction of organic molecules. Nonetheless, [^{11}C]carbondioxide can be easily transferred to many precursors, which offer versatile ^{11}C-labelling pathways [23]. The most important secondary ^{11}C-precursor is [^{11}C]CH_3I, which enables ^{11}C-methylations of organic compounds in high specific activity [24]. For those radiotracers rapid, automatised radiosyntheses were developed and the ^{11}C-labelled products, such as the amino acid L-[methyl-^{11}C]methionine [25] or the dopamine D_2 receptor ligand [^{11}C]raclopride [26] are routinely prepared as PET radiopharmaceuticals for nuclear medicine diagnosis.

With time-consuming radiosyntheses and in cases of slow physiological processes, the very short-lived organic isotopes do not meet the demands. Alternatively, the introduction of longer-lived radionuclides into the tracer molecules should avoid these problems. The so-called “analogue” radiotracers are commonly labelled with ^{18}F, $^{75,76}Br$, ^{73}Se and $^{120,124}I$. Their longer half-lives range from 1.35 h to 4.15 d and allow more extensive radiosyntheses as well as PET studies of slower biochemical processes. In general, analogue tracers make use of similarities in steric demand and/or in electronic character of the substituted atom or function. As a result, $^{75,76}Br$ and $^{120,124}I$ can be regarded as structural analogues for methyl groups [27, 28]. Due to the fact that ^{73}Se is the next homologue to sulfur, they have very similar steric and chemical properties. ^{73}Se is therefore used in the same manner as sulfur, e.g. in the labelling of *L*-[^{73}Se]selenomethionine [29] and *L*-homocysteine[$^{73,75}Se$]selenolactone [30].

In the majority of cases the foreign isotopes evoke only small insignificant structural differences, but the arising electronic changes and those of chemical reactivity can be important. Substitutions with radioisotopes of higher halogens often result in an increased lipophilicity, what again is related to a higher non-specific binding. In particular radioiodine labelled molecules show frequently strong deviations in specificity, and even end sometimes as completely unspecific compounds. The biochemical behaviour of analogous labelled molecules has to be tested for changes in characteristics in each individual case. In the recent years the number of new developed pharmaceuticals has increased rapidly, thus more and more compounds can be found originally carrying fluorine, bromine and iodine. Consequently, the advantages of authentic

labelling and longer half-life accrue and simplify the evaluation of the corresponding radiopharmaceuticals (e.g. [^{18}F]altanserin [31]).

The most common analogue isotope is ^{18}F, which is sterically replacing a hydrogen atom. While the Van der Waals radii of fluorine (1.35 Å) and hydrogen (1.20 Å) are almost the same, the differences in electronic character of both elements are so much bigger. Nevertheless, most of the ^{18}F-labelled compounds are based on the analogy in steric demands of fluorine and hydrogen. In case of *L*-2-[^{18}F]fluorotyrosine as analogue tracer for the amino acid tyrosine, the ^{18}F-radiotracer shows metabolic acceptance and is bound to tRNA and into proteins while the 3-isomer does not and is very toxic. L-2-[^{18}F]fluorotyrosine can be employed for quantitation of the local protein synthesis rate in brain [32]. A recent developed radiotracer for tumour imaging is *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine [33]. Although this amino acid is not incorporated into proteins, uptake by tumour cells is stereospecific and mediated by amino acid transporters [17, 34, 35]. Another example is 2-[^{18}F]fluorodeoxyglucose ([^{18}F]FDG), which is the most widely used PET radiopharmaceutical. For the first metabolic steps FDG is accepted as glucose analogue and taken up into cells by the glucose transporters. In cells it is metabolised by the enzyme hexokinase to 2-[^{18}F]fluorodeoxyglucose-6-phosphate, but the ^{18}F-for-H substitution of the original glucose leads to a interruption of the metabolism and leaves the phosphorylated FDG in the cell unaltered. This effect is known as metabolic trapping and PET images of the regional glucose uptake can be obtained. Furthermore, with the help of a bio-mathematical three-compartment-model the glucose metabolism can be quantified [36]. Besides, FDG helps to study brain and myocardial metabolism and function, it is also a powerful tracer for detection of tumours and metastases, whose cells exhibit an increased glucose uptake and metabolism [37, 38].

The success of fluorine-18 as routine PET nuclide and in diagnosis and pharmacological research is moreover based in its almost perfect chemical and nuclear properties. Fluorine-18 can be produced in good yields, even with low-energy cyclotrons. As mentioned above, the half-life of 109.7 min allows both time-consuming multi-step radiosyntheses up to a limit of 6 h and extended PET studies of slower biochemical processes. In addition, the half-life makes shipment within a range of at least 200 km possible, thus in a so-called satellite concept the supply of clinics without an on-site cyclotron can be ensured [39]. ^{18}F has a low β^+-energy of 635 keV, besides ^{64}Cu the minimum of the PET nuclides, that promises a very high resolution for the PET images and guarantees minor radiation doses to the patients. In terms of chemistry several facile labelling reactions and methods are known for ^{18}F-introduction in organic molecules.

A third group of suitable positron emitters for PET is represented by the metallic isotopes (cf. Table 1.1). In contrast to the “organic” and “analogue” PET nuclides, a few metallic isotopes are achievable by generator systems (e.g. ^{82}Rb, ^{62}Cu and ^{68}Ga) which make them available in places without an on-site cyclotron [40]. For *in vivo* studies they are applied as free cationic tracers or in a complexed form. For example, rubidium-82 has been evaluated as a myocardial perfusion

tracer because of its similarities to the potassium cation and it is routinely employed as its free cation [41]. Otherwise the cyclotron-produced positron emitters ^{86}Y and ^{94m}Tc are of interest. ^{94m}Tc offers the possibility to use PET for quantifying the uptake kinetics of γ-emitting ^{99m}Tc-labelled SPECT radiopharmaceuticals. In the same sense ^{86}Y is the quantitative access to the pharmacokinetics of therapeutic ^{90}Y-agents for palliative treatment [28].

Production pathways of important positron emitting radionuclides

PET requires neutron deficient nuclides, which are generally produced by bombardment of stable isotopes by small charged particles in accelerators. Here protons, deuterons and alphas are predominantly employed. For optimal results of production exact knowledge about the nuclear data, such as cross sections and excitation functions are required. The final chemical form of the product depends on the type of nuclear reaction and even more on the target, the aggregate state (e.g. gas, liquid, solid) and the chemical form of the target material.

For fluorine-18 more than twenty nuclear reactions are known as production pathways. The most common nuclear reactions for ^{18}F-production are listed in Table 1.2. The use of the $^{18}O(p,n)^{18}F$ ($E_p = 16 \rightarrow 3$ MeV) reaction on ^{18}O-enriched water is the most effective method for the production of [^{18}F]fluoride of high specific radioactivity. Thus, under optimised conditions high activities of [^{18}F]fluoride can be easily achieved from cyclotrons, even with low energy machines, within less than one hour irradiation time. In case of electrophilic radiolabelling reactions [^{18}F]F_2 is required. Accordingly, ^{20}Ne and ^{18}O gas targets are the first choice. The major problem of these latter methods is the deposition of the produced fluorine-18 on the target walls. An addition of elemental fluorine to the target gas is needed for isotopic exchange of the adsorbed fluorine-18. For electrophilic fluorine-18 the $^{20}Ne(d,\alpha)^{18}F$ reaction is well-established and the most common process [42, 43].

Table 1.2: Most common nuclear reactions for production of fluorine-18 [from 6, 42, 43, 44]

Reaction	$^{18}O(p,n)^{18}F$	$^{16}O(^3He,p)^{18}F$	$^{20}Ne(d,\alpha)^{18}F$	$^{18}O(p,n)^{18}F$ [c]
Target	$H_2{}^{18}O$ [a]	H_2O	Ne (0.1-0.2 % F_2) [b]	$^{18}O_2$, Kr (1 % F_2) [b]
Particle energy [MeV]	$16 \rightarrow 3$	$36 \rightarrow 0$	$14 \rightarrow 0$	$10 \rightarrow 0$
Main product form	$^{18}F^-_{aq}$	$^{18}F^-_{aq}$	[^{18}F]F_2	[^{18}F]F_2
Yield [GBq/μAh]	2.22	0.26	0.37 – 0.44	~0.37
Specific activity [Bq/mmol]	$\leq 3.7 \cdot 10^{15}$	$\leq 3.7 \cdot 10^{15}$	$3.7 \cdot 10^{10\text{-}11}$	$3.7 - 185 \cdot 10^{10}$

[a] Ti-target with Ti-window [b] passivated Ni-target [c] two step process

As a general production method for carbon-11 the $^{14}N(p,\alpha)^{11}C$ nuclear reaction is applied. The reaction is carried out with ^{14}N gas targets in the energy range of 15 → 7 MeV, which is feasible for low energy cyclotrons. Small portions of oxygen added to the target gas cause $[^{11}C]CO_2$ formation and in case of hydrogen addition, $[^{11}C]CH_4$ is the product form [45]. Routinely produced ^{13}N results from the $^{16}O(p,\alpha)^{13}N$ reaction on a natural water target [46]. ^{15}O is regularly achieved from a natural nitrogen target via the $^{14}N(d,n)^{15}O$ reaction [47].

Further analogue isotopes are iodine-124 and iodine-120. An advantageous reaction for the former is $^{124}Te(p,n)^{124}I$ on a TeO_2 (enriched tellurium) target. The formation of undesired long-lived side products such as $^{125,126}I$ is here reduced in contrast to alternative methods with natural antimony ($^{nat}Sb(^3He,xn)^{124}I$ or $^{nat}Sb(\alpha,xn)^{124}I$), $^{124}Te(d,2n)^{124}I$ or reactions with other tellurium isotopes ($^{126}Te(p,3n)^{124}I$). The $^{124}Te(p,n)^{124}I$ reaction requires only a range of 13 → 9 MeV proton energy and is practicable with small cyclotrons [48, 49]. A recent developed production route is the $^{125}Te(p,2n)^{124}I$ reaction, which gives ^{124}I yields about four times higher than the aforementioned $^{124}Te(p,n)^{124}I$ reaction. However, the energy range is too high for small cyclotrons but large quantities of ^{124}I can be produced with medium-sized machines [50]. In all cases the radioiodine is extracted from the target by dry distillation. For the production of iodine-120 either $^{122}Te(p,3n)^{120}I$ or $^{120}Te(p,n)^{120}I$ are available as appropriate nuclear reaction. Both require the adoption of enriched target material. In case of ^{122}Te the required energies are higher than 30 MeV, thus only high energy accelerators are applicable. The $^{120}Te(p,n)^{120}I$ reaction runs under better conditions, viz. energies of less than 15 MeV. Furthermore, the ^{120}Te based reaction leads to reduced isotopic impurities [49, 51]. However, the costs for highly enriched ^{120}Te targets are vast. Again, the radioiodine is obtained by dry distillation.

Several production methods for the bromine isotopes ^{75}Br and ^{76}Br are known. Besides the $^{75}As(^3He,3n)^{75}Br$ nuclear reaction with a particle energy range of 36 → 25 MeV, the most suitable production route for Bromine-75 is the $^{76}Se(p,2n)^{75}Br$ reaction (E = 34 → 18 MeV). The target materials consist normally of alloys such as Cu_3As, $[^{76}Se]Ag_2Se$, or $[^{76}Se]Cu_2Se$. However, the enriched material for selenium-76 targets is relatively expensive and the $^{75}As(^3He,3n)^{75}Br$ reaction using natural arsenic target material is therefore the preferred route [42]. The ^{75}Br activity is usually extracted from the solid target by dry distillation. ^{75}Br, however, can not be generated without impurities of ^{76}Br. In case of ^{76}Br, three direct methods are available: $^{76}Se(p,n)^{76}Br$ (E = 16 → 10 MeV), $^{77}Se(p,2n)^{76}Br$ (E = 25 → 16 MeV) and $^{75}As(^3He,2n)^{76}Br$ (E = 18 → 10 MeV). Both reactions using selenium targets give the highest yields, but with the drawback of enriched target material. Thus the $^{75}As(^3He,2n)^{76}Br$ process is the most suitable procedure. Bromine-76 is again recovered by dry distillation [52].

In case of Selenium-73 there are two major production pathways. The first production route uses natural or enriched germanium targets and ^3He- and α-particles in medium-sized cyclotrons, i.e. $^{nat}Ge(^3He,xn)^{73}Se$ (E = 36 → 13 MeV) [53] and $^{70}Ge(\alpha,n)^{73}Se$ (E = 28 → 13 MeV) [54]. The

second process, $^{75}As(p,3n)^{73}Se$ (E = 40 → 30 MeV) [55], is presently the method of choice for ^{73}Se. Although this reaction requires higher energies than the routes via germanium, the obvious advantage is a very high production rate of the arsenic reaction. Radioselenium can be isolated from the target by e.g. anion-exchange chromatography [55] or thermochromatography [56].

Within the group of metallic positron emitting radionuclides the before mentioned generator systems for ^{62}Cu, ^{68}Ga and ^{82}Rb are very convenient sources. Of course, the appropriate mother nuclides which are fixed on the generator material still have to be produced. The remaining metallic nuclides are generally produced at cyclotrons. A short overview of the present methods of choice for metallic nuclides are given in Table 1.3 [data from 6, 28].

Table 1.3: Common production pathways of important metallic positron emitter [from 6, 28]

Nuclide	Production route	particle energy [MeV]	Generator system
^{38}K	$^{35}Cl(\alpha,n)^{38}K$	27 → 12	
^{62}Zn (^{62}Cu)	$^{63}Cu(p,n)^{62}Zn$	27.5	^{62}Zn → ^{62}Cu ($T_{½}$ = 9.26 h)
^{64}Cu	$^{64}Ni(p,n)^{64}Cu$	12 → 9	
^{68}Ge (^{68}Ga)	RbBr(p,spall.)	800, 500	^{68}Ge → ^{68}Ga ($T_{½}$ = 271 d)
^{82}Sr (^{82}Rb)	Mo(p,spall.)	800	^{82}Sr → ^{82}Rb ($T_{½}$ = 25.6 d)
^{86}Y	$^{86}Sr(p,n)^{86}Y$	14 → 10	
^{94m}Tc	$^{94}Mo(p,n)^{94m}Tc$	< 17	
^{72}As	$^{72}Ge(p,n)^{72}As$	14	

1.4 Basic aspects of reactions under no-carrier-added conditions

One of the greatest advantages of short-lived radionuclides is their extremely high sensitivity of detection. Consequently, they are produced and employed in quantities at a subnanomolar range. What is a benefit for applications in nuclear medicine, because physiological, toxic or immunologic response can be excluded, causes big problems for the chemical handling and work.

The quantity of the material is only determinable by the number of decays, thus the activity of 55 GBq (average production at a small cyclotron) ^{18}F equals $8.8 \cdot 10^{-10}$ mol fluorine. Owing to the desired insignificant quantities, a fundamental criterion of the quality of a radiotracer is its specific activity (A_s), which depends on the amount of stable isotopes present (carrier). Carrier can be divided into isotopic carrier, isotopes of the same element as the radionuclide, and non-isotopic carrier, isotopes of other elements mostly with very similar properties to the radionuclide. On this

account, the mass related activity, the specific activity is chemically more relevant than the activity itself [57]:

$$A_s = \frac{A}{m} \left[\frac{Bq}{g}\right]$$

where A is the activity and m is the mass of radioactive material including all impurities and carrier, respectively. The specification related to the mass is inconvenient in chemistry; more informative and practicable is the use of molar activity, thus A_s is usually expressed on the molar basis:

$$A_s = \frac{A}{n} \left[\frac{Bq}{mol}\right]$$

here the mass m is replaced by n for the amount of substance in moles. In the absence of impurities or isotopic carrier, the theoretically attainable maximum molar activity $A_{s,max}$ equals to:

$$A_{s,max} = N_A \frac{\ln 2}{T_{½}} \left[\frac{Bq}{mol}\right]$$

where N_A is Avogadro's number and $T_{½}$ the half-life of the radionuclide. Most of the applications in molecular imaging call for high molar activities. Therefore it is useful to know the maximum achievable molar activities. For the most prevalently used PET nuclides ^{18}F and ^{11}C they amount to $6.3 \cdot 10^{10}$ GBq/mol and $3.4 \cdot 10^{11}$ GBq/mol, respectively. Due to the natural occurrence of stable isotopes of these radionuclides only a $10^3 – 10^5$-fold smaller A_s is attainable in practise. However, the quantity of material becomes higher by the natural isotopic carrier, but it is still in nano- to picomolar scale.

The ubiquity of stable elements reduce the molar activities, but in some cases, principally for increasing the yields or in case of electrophilic ^{18}F production it is unavoidable, to add carrier on purpose. Otherwise, PET investigations using labelled biomolecules with very low concentrations in the destined tissue (e.g. substrates of enzymes, receptor ligands and reuptake inhibitors) demand for radionuclides of very high specific activity. In general, for radiochemical practise the radiosyntheses can be classified as:

- carrier-free (c.f.)
- no-carrier-added (n.c.a.)
- carrier-added (c.a.)

Ideally carrier-free systems are only achieved when artificial radioelements (e.g. astatine) are used and the presence of longer-lived radioisotopes of the element can be excluded. Earlier, ^{99m}Tc was also mentioned as an example for almost carrier-free radiosyntheses providing nuclide, but in recent years the extensive use and consequently the production of this SPECT nuclide increased rapidly. Due to this fact its very long-lived isomer ^{99}Tc ($T_{½}$ = 2.1 · 10^5 a) become more and more the status of a “natural-occurring” isotope, which scales down the radiochemistry of ^{99m}Tc almost to n.c.a. level. However, the dimension of ^{99m}Tc abundance is much lower than those of stable isotopes of other radionuclides.

Nevertheless, in radiosyntheses with cyclotron-produced radionuclides of natural-occurring elements, traces of stable isotopes of these elements are omnipresent and act as isotopic carrier. Even the most accurate operation methods can not circumvent this effect. Sources of natural isotopic carrier are the air, target and reaction vessel materials, chemicals and solvents. Such contaminations in solvents and chemicals are below the normal chemical purification limits, but they are still in the quantity or even in excess of the radionuclides. As mentioned above, radiosyntheses under those conditions are referred to as no-carrier-added (n.c.a.) and correspond to a state of practically highest A_s attainable. In contrast, some circumstances require addition of weighable quantities of stable isotopes. Predominantly carrier addition is employed to increase radiochemical yields or to make certain labelling reactions possible, but also for other reasons such as for electrophilic ^{18}F, when n.c.a. [^{18}F]F_2 is too reactive to remove it from the walls of targets and tublines. These methods are termed as carrier-added (c.a.).

Labelling reactions and radiosyntheses on the n.c.a. scale mean to work at a subnanomolar level. Hence, the course of the reaction may differ strongly from that of a classical reaction at equimolar stoichiometric ratios. Such reactions under non-equilibrium conditions generally proceed according to pseudo-first-order kinetics, since the concentration of the precursor to be labelled is in very high excess to the n.c.a. radionuclide and can approximately be set as constant. For a reaction in form of A + B $\rightarrow$ C, where A is precursor, B the radionuclide and C the labelled product and the starting concentration of B is $[B]_0$, the concentration of C after the reaction time t can be presented as:

$$[C]_t = [B]_0 \left(1 - e^{-k't}\right) \left[\frac{mol}{l}\right]$$

where *k'* is the rate coefficient of pseudo-first-order type and contains [A] as constant factor [58].

The decay-corrected yield, i.e. the radiochemical yield (RCY), is related to the starting activity. So the RCY increases with proceeding reaction time t and increasing precursor concentration [A] and shows a hyperbolic character in a plot versus time. The final saturation yield ideally equals $[B]_0$ and is often achieved within a few minutes, due to the high excess of the precursor. Furthermore, the radionuclide and the labelled product both exist on the n.c.a. scale, thus a

consecutive labelling reaction or other interactions of the two radioactive species can statistically be excluded.

In contrast to classic equimolar chemistry, radiochemistry requires some special points to be considered. Firstly, slightest impurities in solvents or chemicals can easily reach the concentration level of the n.c.a. radionuclide; to that reason highest purity grade of solvents and substrates is obliged. Secondly, the introduction of the radionuclide into the designated molecule should occur in the latest possible step (so-called last-step labelling) to avoid multi-step syntheses with radioactive intermediates which will minimise the final yield of activity and increase the radiation burden. Finally, the whole preparation of a radiopharmaceutical including labelling reaction, purification, isolation and quality control should be finished within three half-lives of the radionuclide.

1.5 Radiolabelling with fluorine-18 and radioiodine

1.5.1 ^{18}F-Labelling methods

In principle general pathways for the fluorination of organic molecules are transferable from macroscopic organic chemistry to n.c.a. radiochemistry. The preparative organic chemistry usually uses the Wallach reaction [59] and the Balz-Schiemann reaction [60] for fluorine introduction into aromatic organic compounds. These are dediazoniation reactions, where the fluoride replaces a decomposing diazonium function. In case of the Wallach reaction diazonium piperidines of arenes are decomposed by treatment with hydrofluoric acid and heating, what leads to the corresponding fluoroarenes. Balz-Schiemann used diazonium tetrafluoroborates of the appropriate arenes which are decomposed by heating and give the fluoroarenes, but in much better purity and higher yields than the Wallach procedure. However, in n.c.a. labelling syntheses these reaction types only result in low radiochemical yields [61, 62]. For the Balz-Schiemann reaction this is an effect of the type of the counter ion to the diazonium cation, which is a tetrafluoroborate anion and leads axiomatically to a maximum RCY of only 25 %. In addition, the tetrafluoroborate ion causes in isotopic carrier and thus reduces the specific activity. Further on, both reactions' mechanisms are principally of the S_N1-type, thus reactive cations evoke and interact with any nucleophilic species close by. The statistical probability of the reactive intermediates to encounter a [^{18}F]fluoride ion under n.c.a. conditions is marginal and only carrier addition leads to satisfying results and RCY, respectively [63].

Depending on the production procedure of fluorine-18 (cf. above), its chemical form is given for the labelling reaction. Generally, the ^{18}F-labelling methods can be divided into:

- electrophilic substitutions
- nucleophilic substitutions

} direct methods

- ^{18}F-fluorination via prosthetic groups
- ^{18}F-fluorination via built-up procedures

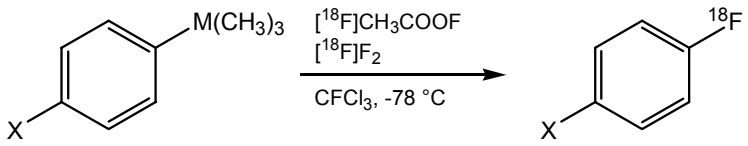
} indirect methods

where the former procedures represent direct methods and the latter indirect methods. In general, the indirect procedures are based on the direct methods for ^{18}F-labelling of the required prosthetic group or synthon.

Electrophilic substitution

For electrophilic ^{18}F-labelling reactions c.a. [^{18}F]F_2 is directly available directly from the target (cf. above), but only with specific activities of about 37 GBq/mmol [64]. In some cases [^{18}F]F_2 is transferred into somewhat less reactive and more selective fluorination agents such as acetylhypofluorite [^{18}F]CH_3COOF and xenon difluoride [^{18}F]XeF_2 [65, 66, 67]. These are options for the ^{18}F-fluorination of electron rich compounds (e.g. alkenes, aromatic molecules, carbanions, etc.), which are actually unavailable with nucleophilic ^{18}F-labelling methods. Due to the fact of necessary carrier-addition in the [^{18}F]F_2 production and the fact that every [^{18}F]F_2 molecule carries only one ^{18}F atom, the theoretical achievable maximum RCY in electrophilic ^{18}F-labelling is limited to 50 %. More recent attempts were made to reduce the amount of fluorine-19 carrier in the synthesis of the electrophilic ^{18}F-species in order to get higher specific activities of about 18 TBq/mmol, however, with the drawback of lower radiochemical yields [68]. As a result, the electrophilic ^{18}F-labelling routes are restricted to radiopharmaceuticals, where high specific activities are not compulsory. These particular cases occur when physiological processes are examined with endogenous tracers, which are naturally present in the investigated tissue area and the body. On the basis of the high reactivity of the electrophilic ^{18}F-labelling agents the selectivity is rather low and undesired radical side reactions and reactions with solvents take place. Therefore, electrophilic methods call for extensive purification procedures to meet the requirements of very high purity of radiopharmaceuticals. To increase the regioselectivity in arenes, demetallation reactions of organometallic precursors can be used (cf. Scheme 1.1). Suitable organometallic precursors are aryltrimethyltin, aryltrimethylgermanium and aryltrimethyl-silicium compounds, whereas the organotin moiety shows the best results [69, 70]. The substituent X deactivates the arene, but for the ^{18}F-fluorodemetallation reaction the effect is less

strong than in direct electrophilic ^{18}F-labelling reactions. Thus, side reactions and consecutive fluorination are decreased and simplify the purification.



Scheme 1.1: Regioselective ^{18}F-labelling via electrophilic demetallation reactions (M = Sn, Ge, Si; X = OCH_3, CH_3, H, F, CF_3, NO_2) [from 70]

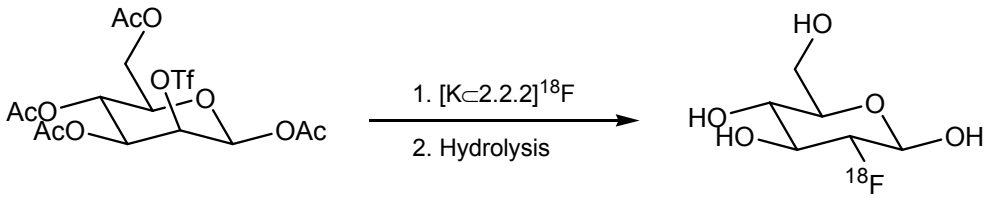
However, for complex molecules including sensitive functions, which have to be protected, further radiosynthesis steps become necessary for the deprotection. In case of 4-[^{18}F]fluoro-L-phenylalanine for example the ^{18}F-labelling via an organotin precursor leads to 25 % RCY [71]. One more relevant PET radiopharmaceutical produced via electrophilic substitution is 6-[^{18}F]fluoro-3,4-dihydroxy-L-phenylalanine (6-[^{18}F]fluoro-L-DOPA). 6-[^{18}F]fluoro-L-DOPA is a radiotracer for the dopamine anabolism in the brain and is employed for the diagnosis of patients with neurodegenerative diseases (Parkinson's disease) and recently also in oncology due to its high tumour uptake. In clinical routine 6-[^{18}F]fluoro-L-DOPA is produced via ^{18}F-fluorodestannylation, although the maximum RCY is only 30 % and the specific activities are low [72, 73]. The lack of an efficient and simple automate nucleophilic access to 6-[^{18}F]fluoro-L-DOPA requires the electrophilic pathway. The so far best nucleophilic method still encloses a multi-step radiosynthesis including chiral auxiliaries, and therefore complicates the automation and reduces the RCY [74].

Nucleophilic substitution

The most important route to get ^{18}F-labelled compounds is the nucleophilic ^{18}F-fluorination based on n.c.a. [^{18}F]fluoride, which is directly available from the target without any carrier addition. This is the only method to obtain n.c.a. ^{18}F-radiopharmaceuticals with high specific activity. This is required for investigations of e.g. binding-sites of neural receptor systems, which can then be studied without perturbation of the physiological equilibrium. The n.c.a. [^{18}F]fluoride is obtained in a water solution and due to its high electronegativity it is strongly hydrated ($\Delta_{hydrate}$ = 506 kJ/mol) and inactivated for nucleophilic reactions. In the presence of proton donors, the fluoride anion is very easily protonated and forms [^{18}F]hydrogen fluoride (E_B = 565 kJ/mol), thus it is unavailable for further reactions. Therefore the n.c.a. [^{18}F]fluoride must be activated and water removed

before radiolabelling. For this purpose water is replaced ideally by dipolar aprotic solvents such as acetonitrile (ACN), dimethyl sulphoxide (DMSO), *N*,*N*-dimethylformamide (DMF) and dimethylacetamide (DMAA) and anion activation phase transfer catalysts (PTC) like tetraakylammonium carbonates, hydroxides or mainly aminopolyethers such as Kryptofix© 2.2.2 in combination with potassium carbonate or oxalate as base are employed [63, 75, 76]. While the aminopolyether complexes the potassium ion and composes a $[K\subset 2.2.2]_2CO_3$ cryptate system, the [^{18}F]fluoride ion is non-hydrated and available with a high nucleophilicity. If the solubility product of the cryptate system is not exceeded in this procedure, the losses by wall-adsorption are negligibly small [77]. Further, the proper ^{18}F-labelling reaction must be carried out in absence of protons or e.g. metallic cations, which would also inactivate the naked [^{18}F]fluoride.

The direct nucleophilic ^{18}F-fluorination of aliphatic compounds proceeds according to a S_N2-mechanism, where halogens or sulphonic acid ester functions such as mesylate, tosylate and triflate act as leaving group [63]. Generally, triflate (trifluoromethane sulphonic acid ester) precursors give the best results [for an overview see: 78, 79].

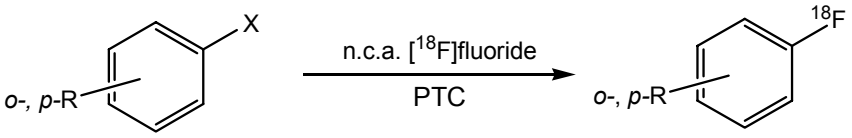


Scheme 1.2: Nucleophilic n.c.a. ^{18}F-fluorination and subsequent hydrolysis of acetylated mannose triflate for [^{18}F]FDG [80]

When the leaving group is replaced by the [^{18}F]fluoride the stereochemistry is changed by the concertedly proceeding Walden inversion according to the stereospecific S_N2-mechanism. In this way the most widespread radiopharmaceutical [^{18}F]FDG (2-[^{18}F]fluoro-2-deoxy-D-glucose) is synthesised starting from a completely acetylated mannose precursor by a ^{18}F-for-triflate exchange and a subsequent hydrolysis (cf. Scheme 1.2) [80]. Routinely RCY of more than 40 % are attained. Furthermore, the nucleophilic aromatic n.c.a. ^{18}F-fluorination is of great importance for the development of ^{18}F-labelled radiopharmaceuticals. Besides multiple possible aromatic radiotracers, the generally good metabolic stability of the resulting ^{18}F-labelled aromatic compounds is a major advantage. Nucleophilic aromatic ^{18}F-fluorinations call for activated aromatic molecules, consequently electron withdrawing substituents in *ortho*- or *para*-position to the leaving group are indispensable (cf. Scheme 1.3). Particularly function with high positive Hammett constants, such as nitro, cyano and carbonyl groups, are suitable for the activation [81]. As leaving group nitro, halogens and the trimethylammonium salts prove to be well adapted. For

example, several butyrophenone neuroleptics can be directly ^{18}F-labelled starting with the corresponding *para*-nitro precursor which is activated by a carbonyl function, e.g. [^{18}F]*N*-methyl-spiperone can be obtained in good RCY [82]. Additionally, fluorine as well is a very adequate leaving group, but its use introduces isotopic carrier. Within the trimethylammonium group, which shows the best quality as nucleofugic group, the counter ions give the following order of increasing RCY: iodide < perchlorate < tosylate < triflate. In cases of less activating substituents with low Hammett constants e.g. iodine and bromine (σ_p = 0.18 and 0.23 [83]) an aliphatic substitution results on the $N(CH_3)_3$-group and [^{18}F]fluoromethane formation competes to the aromatic ^{18}F-labelling. Nonetheless, RCY of about 12 % of 1-[^{18}F]fluoro-4-haloderivatives are attainable with the mentioned less activating substituents [84].

For nucleophilic ^{18}F-radiolabelling of non-activated aromatic compounds two general procedures are possible. In the first one, the deactivated arene is transferred to an activated species with the help of modified original by present moieties or introduction of additional activating groups. This procedure implies a multi-step radiosynthesis, where modification or removing steps of the activating groups are required after the ^{18}F-introduction [85].



Scheme 1.3: Nucleophilic aromatic ^{18}F-fluorination with activated arenes (X = NO_2, $N(CH_3)_3^+$ (counter ions: TfO^-, TsO^-, ClO_4^-, I^-), Br, Cl, I; R = NO_2, CN, CHO, RCO, COOR, Cl, Br, I; PTC = $[K\subset2.2.2]_2CO_3$, $[K\subset2.2.2]_2C_2O_4/CO_3$, $[K\subset2.2.2]HCO_3$, R_4N^+; Cs^+; Rb^+)

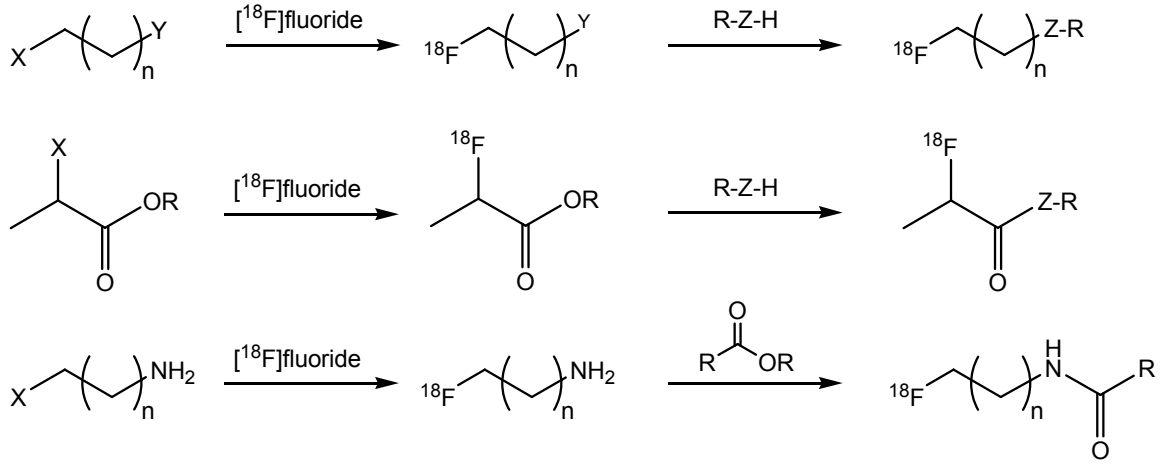
Secondly, the use of substituted diaryliodonium salts as precursors offers a more elegant route (see subchapter 1.6 for details). For the latter method the resulting product distribution after the nucleophilic attack of the n.c.a. [^{18}F]fluoride strongly depends on the electronic and steric character of each aryl ring and its substituents, respectively. Generally, the more electron deficient ring of the diaryliodonium salt is preferred for the ^{18}F-labelling. Furthermore, steric influences, especially for *ortho*-substituents, have an impact and increase usually the RCY.

^{18}F-Fluorination via prosthetic groups

As mentioned above, the ^{18}F-fluorination via prosthetic groups is an indirect method. This means a primary ^{18}F-fluorinated labelling group is coupled with a second molecule to form the product

molecule. Important procedures via prosthetic groups are the ^{18}F-fluoroalkylation [77, 86], the ^{18}F-fluoroacylation [87, 88], and the ^{18}F-fluoroamidation [89] (cf. Scheme 1.4).

Applications for these ^{18}F-labelling pathways via prosthetic groups are widespread and can be applied with almost every molecule carrying a protic function such as a thiol, amino or hydroxyl group. In practise, several bio-relevant molecules e.g. receptor ligands of the dopamine system [90] and the serotonin system [91], benzodiazepines [92], amino acids [33] and analogues for cocaine [93] are ^{18}F-labelled via ^{18}F-fluoroalkylation. In contrast, the ^{18}F-fluoroacylation and the ^{18}F-fluoroamidation are of great interest for the ^{18}F-labelling of proteins and peptides since they allow radiosyntheses under amide-bond formation in aqueous systems [94]. As a result, β-^{18}F-labelled esters were successfully coupled with e.g. biotin [95] and the protein octreotide, the first ^{18}F-labelled peptide [96].



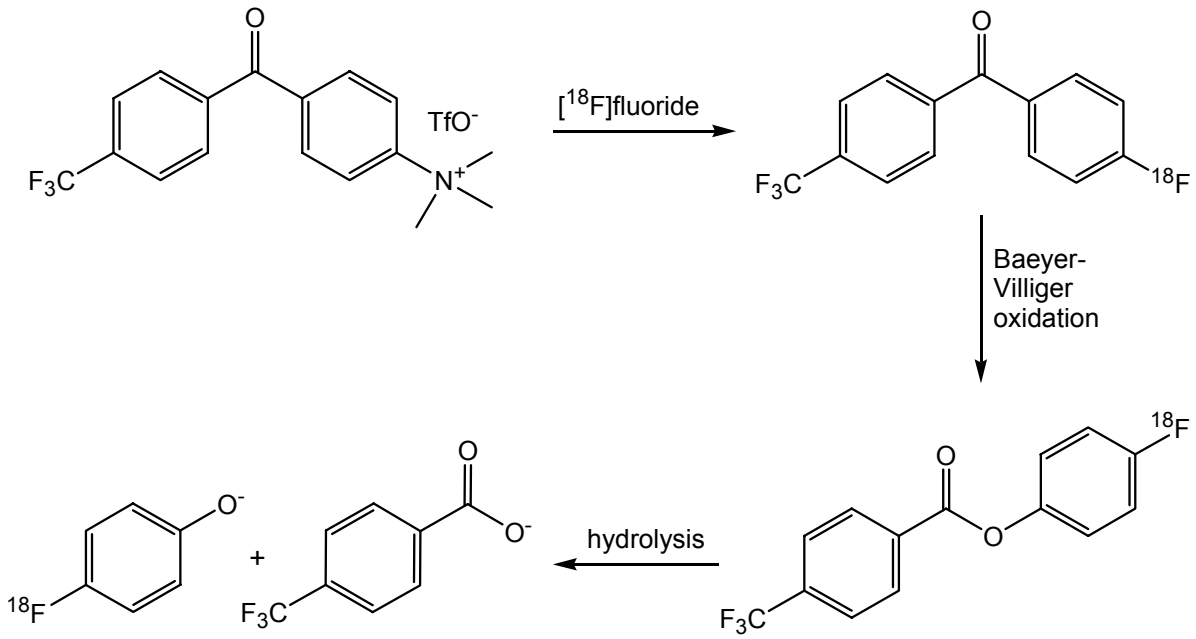
Scheme 1.4: ^{18}F-fluorination via prosthetic groups; top: ^{18}F-fluoroalkylation; middle: ^{18}F-fluoroacylation; bottom: ^{18}F-fluoroamidation (X, Y = Br, I, OTs, OTf; Z = N, O, S; R = alkyl, aryl)

^{18}F-labelling synthons for built-up radiosyntheses

A further, recent developed built-up ^{18}F-labelling method is the ^{18}F-fluoroarylation. This procedure is based on metallorganic molecules like 4-[^{18}F]fluorophenyl lithium as versatile metallorganic compound for general coupling reactions or on synthons like 1-[^{18}F]fluoro-4-haloarenes as reagents for palladium-(0)-catalysed reactions such as the Stille [97], the Hartwig-Buchwald [98] and the Sonogashira reaction [99]. 4-[^{18}F]Fluorophenyl lithium can be synthesised from 1-[^{18}F]fluoro-4-haloarenes, which in turn are obtainable from the appropriate symmetrical

diaryliodonium salts in good RCY of about 50 – 60 % [99, 100]. The wide applicability of ^{18}F-fluoroarylation was demonstrated with several different model compounds [101].

Beside 1-[^{18}F]fluoro-4-haloarenes, further primary ^{18}F-labelling synthons are known and commonly used in multi-step radiosyntheses of radiopharmaceuticals. Thus 4-cyano-1-[^{18}F]fluorobenzene was employed in the built-up ^{18}F-labelling procedure of several ^{18}F-labelled butyrophenone neuroleptics, e.g. [^{18}F]haloperidol, [^{18}F]benperidol, etc. [102]. More versatile synthons are given by molecules such as 4-[^{18}F]fluorobenzaldehyde, 4-[^{18}F]fluoro-1-nitrobenzene or 4-[^{18}F]fluoroaniline, e.g. in recent studies 4-[^{18}F]fluorobenzaldehyde was employed in a two-step ^{18}F-labelling procedure of peptides [103].

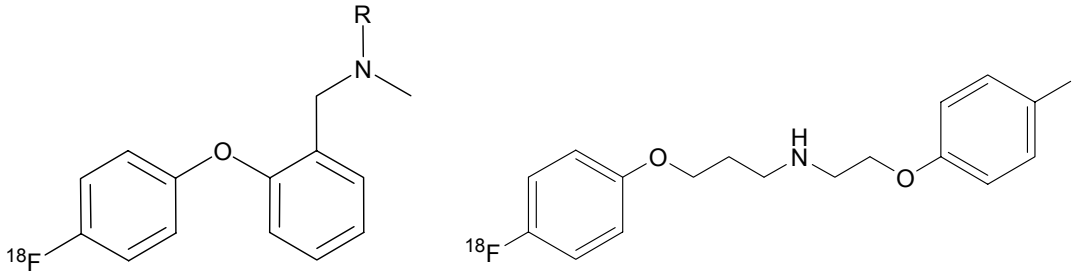


Scheme 1.5: Improved radiosynthesis of n.c.a. 4-[^{18}F]fluorophenol via Baeyer-Villiger oxidation [108]

Another useful primary synthon for ^{18}F-fluorinations is represented by 4-[^{18}F]fluorophenol, which is part of several bioactive substrates [104, 105]. In the last decade various attempts have been made to improve the synthesis and the availability of 4-[^{18}F]fluorophenol. The first practicable radiosynthesis of n.c.a. 4-[^{18}F]fluorophenol proceeded via hydrolysis of a 4-[^{18}F]fluorophenyl-diazonium salt, but reached only 15 – 33 % RCY after 60 min [106]. An enhancement was the radiosynthesis via Baeyer-Villiger oxidation of ^{18}F-labelled benzaldehydes, acetophenones and benzophenones. As oxidant *m*-chloroperbenzoic acid proved useful in the presence of trifluoroacetic acid and gave a RCY of about 25 % within 40 – 50 min [107]. An optimisation of this route included detailed studies of effects of various substituents and led to (4-(trifluoro-

methyl)phenyl)-benzoyl-4'-N,N,N-trimethylammonium triflate as ideal precursor for the labelling reaction, the hydrolysis and purification. The cationic precursor as well as polar impurities are easily removed in an intermediate C18-cartridge purification. An optimised product ratio in the final hydrolysis resulted in 60 % RCY of 4-[^{18}F]fluorophenol within 60 min (cf. Scheme 1.5) [108].

Due to the improved radiosynthesis of n.c.a. 4-[^{18}F]fluorophenol and a subsequent coupling with alkylhalides various 4-[^{18}F]fluoroarylalkylethers became available [108]. Further on, n.c.a. 4-[^{18}F]fluorophenol was used for ^{18}F-labelling of the dopamine D_4 receptor antagonist (3-(4-fluorophenoxy)propyl)-(2-(4-tolyloxy)ethyl)amine (FPTEA) (cf. Scheme 1.6) [109].



Scheme 1.6: Structures of the 4-[^{18}F]fluorophenoxy moiety containing compounds 2-(4-[^{18}F]fluorophenoxy)-*N*-dimethylbenzylamine (R = CH_3) and 2-(4-[^{18}F]fluorophenoxy)-*N*-methylbenzylamine (R = H) (left). [^{18}F]FPTEA (right)

In a recent study radiosyntheses of n.c.a. 2-(4-[^{18}F]fluorophenoxy)-*N*-dimethylbenzylamine and n.c.a. 2-(4-[^{18}F]fluorophenoxy)-*N*-methylbenzylamine were realized. An Ullmann ether coupling of the corresponding 2-bromobenzoic acid amides using tetrakis(acetonitrile)copper(I)hexafluorophosphate as catalyst and a subsequent reduction of the amides leads to the products (cf. Scheme 1.6) [110]. Both compounds are structural analogues of known radiotracers for serotonin reuptake transporter sites (SERT) [111].

1.5.2 Radiolabelling with radioiodine

From more than thirty radioactive isotopes of iodine only iodine-120 and iodine-124 bring along suitable properties for PET. However, their low abundance of positron emission (56 % for ^{120}I and 22 % for ^{124}I), their high positron energies (4.1 MeV for ^{120}I and 2.1 MeV for ^{124}I) and an extensive production route make them less attractive. Significantly more importance for life sciences have iodine-123 (100 % EC, 159 keV γ-line (main)) as SPECT nuclide, iodine-125 (100 % EC, 35 keV γ-line (main)) for long-term *in vitro* studies and radioimmunoassays and the β^--emitter iodine-131

as nuclide in therapy of thyroid gland and other tumours. Because of the convenient longer half-life ($T_{½}$ = 8.02 d), the well-detectable γ-line of 364 keV (85.5 %) and the good availability, ^{131}I lends itself as model isotope for radiotracer development. The main pathways for radioiodine labelling can be classified in four general procedures [for an overview see: 112, 113]:

- direct electrophilic radioiodination
- electrophilic demetallation
- non-isotopic exchange
- prosthetic group labelling (indirect method)

Direct electrophilic radioiodination

The direct electrophilic substitution is the most commonly used radioiodination method. A lot of various techniques are available, which lead to high RCY in uncomplicated labelling reactions, which can be often carried out at room temperature. Due to its high volatility, low reactivity and the need of carrier addition, molecular iodine (I_2) is excluded for the n.c.a. scale. These problems to achieve reactive electrophilic species are easily circumvented by an *in situ* oxidation of iodide, which is obtained straight from the target. The generally used oxidants are Chloramine-T (CAT; *para*-tosylchloramide sodium), Iodogen™ (1,3,4,6-tetrachloro-3α,6α-diphenylglycouril) and *N*-halogensuccinimides. The exact chemical nature and oxidation state of the iodinating species is not fully clarified so far. In case of aqueous solutions with strong acidic conditions a hypoiodite, and for neutral and alkaline conditions an iodine-analogue of e.g. CAT are postulated [114]. Due to the insignificant differences in their redox potentials the choice of the proper oxidant is depended on the reaction conditions and the character of the iodine substrate. CAT allows oxidations in homogeneous aqueous solutions, whereas Iodogen™ is insoluble in water and thus it is the proper substance for a heterogenic reaction route, which is advantageous for oxidation sensible precursors. In the group of *N*-halogensuccinimides *N*-chlorotetrafluorosuccinimide (NCTFS), *N*-chlorosuccinimide (NCS) and rarely *N*-bromosuccinimide (NBS) are applied for *in situ* oxidation [115, 116]. When using NCS in trifluoromethane sulphonic acid, even deactivated aromatic compounds can be labelled with radioiodine in acceptable RCY [117]. Besides these oxidants, conventional oxidising reagents are in use, such as hydrogen peroxide, respectively peracids [118] and metal cations (Ag^+, Tl^{3+}, Pb^{4+} and Ce^{4+}) [119]. Rather unconventional, but also utilisable are enzymatic [120] or electrochemical [121] methods for oxidation. As a disadvantage the electrophilic radioiodination may raise the problem of a regio-unselective attack, as a result isomeric derivatives may occur.

Electrophilic demetallation

Contrary to the direct electrophilic procedure, the electrophilic demetallation provides an almost regiospecific radioiodination. Especially for automated syntheses it offers simple purification and isolation of the radiotracer and is therefore the first choice. Nonetheless, the syntheses of the organometallic precursors may become complex and extensive [122]. Suitable precursors for demetallation radioiodine-labelling are organometallic compounds of thallium [123], boron [124], mercury [125] and particularly the organometallics of the elements of the group IVb. An exceptional position of these takes the organotins, which show in many times excellent RCY in very short reaction time (few minutes), generally the RCY increases with Si < Ge < Sn [126]. Presently, the radioiodo-destannylation is the most suitable radioiodination procedure and thus it is the most commonly employed method.

Non-isotopic exchange

Another labelling procedure for regiospecific radioiodine introduction is the non-isotopic exchange. Non-isotopic exchange is generally Cu(I)-catalysed and is suitable for electron-rich as well as for electron-deficient aromatic molecules [127]. In case of iodine-for-bromine exchange high specific activities are available. In Cu(I)-promoted reactions the readiness of the displacement follows the nucleofugality of the halogens ($I^- > Br^- > Cl^-$). In the Cu(I)-mediated substitution mechanism a quadratic-planar complex was suggested, including Cu(I) as coordinated central atom, whereby the activation energy for the substitution process is reduced and the iodine can be introduced [128]. In variations the Cu(I)-salts are *in situ* synthesised by a mild reduction of Cu(II)-salts (reducing agent: ascorbic acid, bisulfite or Sn(II)-compounds). Hereby Cu_2SO_4 is more applicable than the use of copper halides, because the formation of halogenated side-products is excluded [129]. One of the important advantages is the much easier precursor preparation and their high stability. Moreover, it is again a highly regiospecific labelling route for radioiodine. In comparison to the electrophilic radioiodination disadvantages are relatively high reaction temperatures up to 180 °C and vastly longer reaction times up to hours. In given cases the separation and isolation of the radiotracer provokes difficulties due to its chemical and physical similarities to the bromine precursor.

Prosthetic group labelling

If molecules are sensitive to oxidative reagents or functional groups for iodination are lacking, the above mentioned direct radioiodination methods fail. As alternative, small molecules can be radioiodinated as labelling synthons and subsequently coupled with the desired compound. This

is principally the same procedure as for the ^{18}F-labelling via prosthetic groups (cf. subchapter 1.5.1). The first approach on prosthetic groups for radioiodination was the so-called Bolton-Hunter reagent, *N*-succinimidyl-3-(4-hydroxyphenyl)propionate (SHPP), an activated ester as labelling synthon for proteins via coupling with a free amino function, normally of the amino acid lysine [130, 131]. It is still widely used for radioiodination of proteins and macromolecules, thus a ^{124}I-labelled VEGF antibody (VEGF = vascular endothelial growth factor, a number of genes associated with angiogenesis; a process necessary for tumours) was e.g. recently radioiodinated via a derivative of the Bolton-Hunter reagent [132]. The Bolton-Hunter principle for radioiodination of proteins led to further developments of prosthetic groups such as methyl-*p*-hydroxybenzimidate (Wood reagent) which is an activated imidate ester and also a versatile and convenient radioiodination synthon [133]. In addition, aldehydes, isothiocyanates [134] and activated □-carbonyl halides [135] are further prosthetic groups for labelling via free amino functions. In case of aldehydes, the radioiodo-tyramine-cellobiose is an important compound which, for example, was used for labelling monoclonal antibodies [136]. Several other coupling methods of prosthetic groups with functional groups of proteins or large molecules are known. Another common example for suitable functions is the thiol group of cysteine, where appropriate prosthetic groups are malimide derivatives [137].

1.6 Use of diaryliodonium salts in (radio-)chemistry

Since C. Willgerodt first synthesised an iodine(III)-compound containing an organic moiety, (dichloroiodo)benzene, in 1886 [138] and in 1892 another one, (diacetoxyiodo)benzene [139], an uncountable number of organic iodonium compounds have been developed until today [for an overview see: 140]. All theses iodonium salts are employed in widespread fields of chemistry and related sciences. Besides their advantageous properties as photopolymerisation initiators [141, 142] and as chemical amplifications in imaging systems, microlithography and nanopatterning [143, 144], they display biological, antimicrobial and antifungal activities [145, 146]. Furthermore, iodonium reagents resemble in their reactivity characteristics mercury(II), thallium(III) and lead(IV) compounds and can serve as substitutes without the toxic and environmental problems associated with these heavy metal species. In organic chemistry diaryliodonium compounds are applied for direct arylation reactions, cross coupling reactions (Suzuki [147], Stille [148], Heck [149]) and mild chemoselective oxidations [150]. [for an overview see: 151, 152]

Relatively recent iodine(III) species are the alkenyliodonium and the alkynyliodonium salts. The former undergo reactions with a wide variety of nucleophiles and are excellent reagents in metal-catalysed cross-coupling reactions, the latter serve as electrophilic acetylene equivalents in

reactions with nucleophiles as well as superb cycloaddition partners, e.g. for Diels-Alder-reactions [for an overview see: 153, 154].

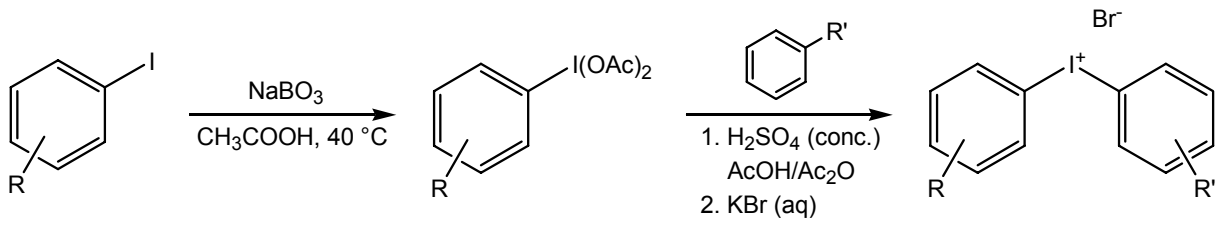
The radiochemical interest in iodonium salts is based on their use as precursors for direct nucleophilic ^{18}F-fluorination, especially since even electron rich arenes can be ^{18}F-labelled in one-step. The first nucleophilic ^{18}F-labelling reaction via diaryliodonium salts was carried out by Pike and Aigbirhio in 1995 [155].

1.6.1 Production routes for diaryliodonium salts

Diaryliodonium salts can be synthesised by a variety of ways [for an overview see: 151, 152, 156]. Several methods involve the use of a strong acid medium while other methods require neutral organic solvents. The commonly employed procedures occur according a typical electrophilic aromatic substitution. Generally, these acid-catalysed methods require an iodoaryl species containing iodine(III), which is coupled with an arene or a proper derivative. Alternative routes are available from treatment of organometallic aryl compounds with Koser's reagent ([hydroxy(tosyloxy)iodo]benzene) or its derivatives [157]. These molecules undergo an *ipso*-demetallation and lead to the iodonium tosylates or in variations (only for symmetric diaryliodonium salts) with $CF_3SO_3I{=}O$ and $FSO_3I{=}O$ to triflates or fluorosulfonates, respectively. Another access to diaryliodonium salts is offered by the coupling of *trans*-β-functionalised vinyl(aryl)iodonium salts with aryllithiums, whereby electron withdrawing groups (good leaving groups) are necessary in the *trans*-β-position.

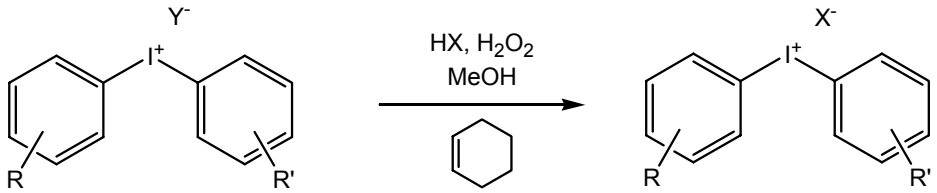
Electrophilic aromatic substitution

In most cases the necessary iodo(III)arene can be oxidised either *in situ* or by an individual oxidation procedure. The resulting iodonium compounds are generally iodosoarenes or (diacetoxyiodo)arenes. Both are suitable substrates for synthesis of diaryliodonium salts. One disadvantage of the iodosoarenes is, that they may suffer reduction to the corresponding iodoarenes instead of coupling with aromatic substrates [158]. Consequently, (diacetoxyiodo)-arenes are the more successful compounds in these syntheses and they are widely employed. Over the years several oxidants have shown their suitability for selective mild oxidation of iodine(0) to iodine(III). Examples are chromium(VI) oxide [159], peracetic acid [150, 160], sodium perborate [161 , 162], sodium periodate [163], sodium percarbonate [164] and even electrochemical procedures [165].



Scheme 1.7: General synthesis of a diaryliodonium bromide via oxidation to the (diacetoxyiodo)arene and subsequent electrophilic aromatic substitution catalysed by sulphuric acid

In a typical reaction the iodoarene is converted by the oxidant (e.g. sodium perborate) in acetic acid into its diacetoxyiodo analogue. For subsequent formation of the desired diaryliodonium hydrogensulfate the (diacetoxyiodo)arene and the appropriate aromatic compound is treated with concentrated sulphuric acid in a mixture of acetic acid and acetic anhydride. Finally, by an addition of aqueous chloride, bromide or iodide solution the desired diaryliodonium halide precipitates (cf. Scheme 1.7). Numerous symmetric (R = R') and asymmetric (R ≠ R') diaryliodonium salts have been synthesised by this method. In case of the iodoarene and the aromatic coupling reagents various substituted and non-substituted aromatic, heteroaromatic and bicyclic molecules can be adopted.



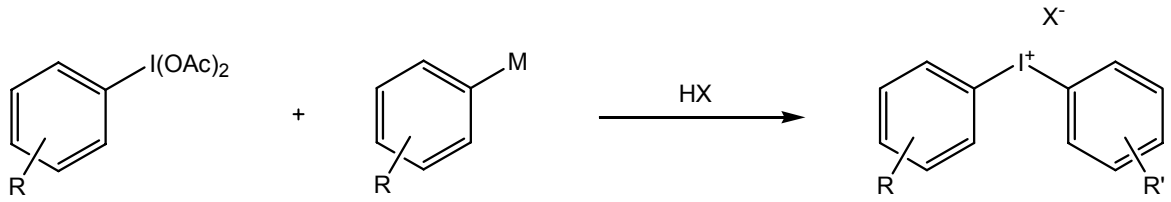
Scheme 1.8: Oxidative anion metathesis of diaryliodonium bromides and chlorides (Y = Br, Cl; X = HSO_4, Cl, NO_2, BF_4, TsO, CF_3SO_3, CF_3CO_2) with cyclohexene as "*halogen scavenger*"

The resulting diaryliodonium chlorides, bromides and iodides can easily be transferred into various iodonium salts differing in counter ions by an oxidative anion metathesis in very high yields [166, 167]. In practice, the diaryliodonium halide, the acid corresponding to the intended anion and hydrogen peroxide are heated to reflux in methanol (rarely: ethanol or propanol) for a short reaction time (~10 min) [noteworthy is, that diaryliodonium halides are thermally unstable

on prolonged heating]. Suitable anions are hydrogensulfates, bromides (only from iodides), chlorides, nitrates, tetrafluoroborates, triflates, tosylates and trifluoroacetates. For halide-halide transfers their reduction potential tendency has to be taken into account, thus those metatheses are only feasible according this order: iodide → bromide → chloride. In case of bromides and chlorides as starting materials any liberated bromine or chlorine evolving in the oxidative reaction can be trapped by cyclohexene (cf. Scheme 1.8).

Ipso-demetallation

An inherent weakness of arenes as coupling partners in electrophilic substitutions is that regio-isomers may be formed. This drawback can be avoided by using organometallic compounds for a regiospecific demetallation (*ipso*-demetallation). Typical regiospecific coupling of diaryliodonium salts is carried out with [hydroxy(tosyloxy)iodo]benzene (Koser's reagent) and various substituted aryltrimethylsilanes in acetonitrile what gives the corresponding diaryliodonium tosylates in absolute isomeric purity [157]. Since this method offers a general, mild and regiospecific synthesis of diaryliodonium salts, diverse *ipso*-demetallation reactions have been developed. Commonly employed organometallics for these are silanes [157], mercurials [168], stannanes [169] and boronic acids [170] (Scheme 1.9).



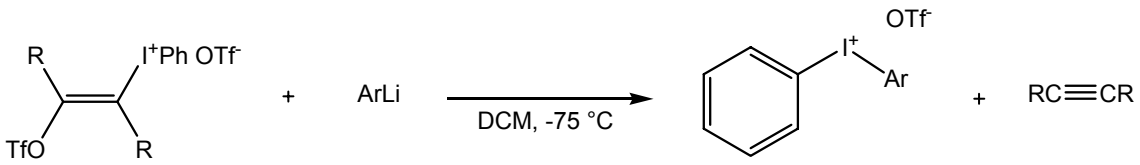
Scheme 1.9: General principle of diaryliodonium salts syntheses via *ipso*-demetallation reactions (M = $Si(alkyl)_3$, $Sn(alkyl)_3$, Hg(OAc), $B(OH)_2$; X = TsO, CF_3SO_3, CF_3CO_2)

However, the electrophilicity of Koser's reagent and its derivatives is somewhat attenuated in comparison to (diacetoxyiodo)arenes and iodosoarenes. Those compounds react most readily with weaker bonds, thus the reaction conditions need to become stronger in the order of the C_{aryl}-metal bond strengths (C-Hg < C-Sn < C-Si < C-B) [171]. Otherwise these nuances offer a selection of demetallation precursors differing in reactivity. Thus, a choice can be made according to the sensitivity of the aromatic coupling substrate. For example electron rich aromatic

compounds (e.g. heteroaryls) show high amounts of by-products during the procedure using heteroaryltrialkystannanes and make an isolation of the product salts from the highly coloured reaction mixture very complicate or even impossible. Using electron rich arylboronic acids reduce such problems due to their decreased sensitivity. Furthermore, the reactivity of the iodine(III) component has also to be taken into consideration. In this way 2-thienyl(phenyl)iodonium triflate could not be obtained in analytical purity via the 2-thiopheneboronic acid and trifluorosulphonic acid; a change to the Koser's reagent made the 2-thienyl(phenyl)iodonium available as its tosylate [170]. In addition, the arylboronic acids help to avoid toxic substrates such as the heavy metal organometallics, what is very important with regard to the production of radiotracers for human application in PET studies.

trans-β-Functionalised vinyl(aryl)iodonium salts

Ligand exchange reactions are well-known for iodonium salts and build the basis for their ability as arylation substrates. In case of vinyliodonium salts this can be used for the synthesis of symmetric and asymmetric diaryliodonium salts [151, 156]. Accordingly, the coupling of *trans*-*β*-functionalised vinyl(aryl)iodonium salts with aryllithium compounds leads to the diaryliodonium salts. In the *trans*-*β*-position a highly nucleofugic group is required to cause an elimination at the stage of the ligand exchange.

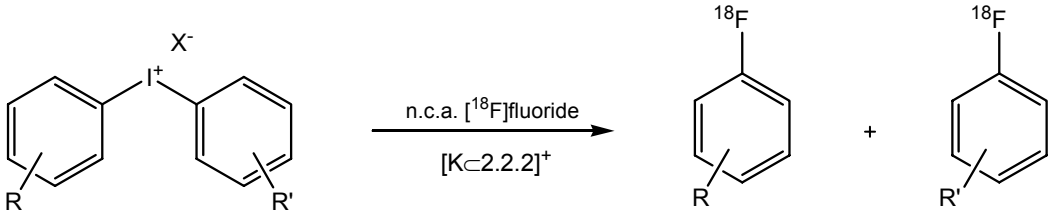


Scheme 1.10: Synthesis of various aryl(phenyl)iodonium triflates via ligand exchange of *trans*-*β*-trifyloxyvinyl(phenyl)iodonium triflates (R = *n*-propyl; Ar = 2-benzothienyl, 2-thienyl, 2-tolyl, 2-anisyl, 3-anisyl) [from 172]

The reaction proceeds via an initial formation of a tricovalent iodine(III) intermediate (diaryl(vinyl)-iodane) which subsequently decomposes to the diaryliodonium salt and via a coeval elimination to the corresponding acetylene derivative [151]. By using *trans*-*β*-trifyloxyvinyl(phenyl)iodonium triflates and aryllithium reagents, various diaryliodonium triflates were synthesised in good yields (cf. Scheme 1.10) [172]. *Trans*-*β*-functionalised vinyl(aryl)iodonium salts are attainable by several reactions of *β*-functionalised acetylene derivatives and reactive iodine(III) species such as Koser's reagent and derivatives [153, 154, 173].

1.6.2 ^{18}F-Radiofluorination via diaryliodonium salts

It is well-known that diaryliodonium salts react with a wide range of nucleophiles and give the substituted arenes and the corresponding iodoarenes [151]. The first use of fluoride as nucleophile and the fluorination via diaryliodonium salt was performed by Grushin et al. in 1983 [174]. A reaction of diphenyliodonium fluoroborate and potassium fluoride in the presence of a crown ether led to fluorobenzene in high yields. Based on this, Pike and Aigbirhio made the first attempt for nucleophilic ^{18}F-labelling with diaryliodonium salts in 1995 [155]. They used diaryliodonium salts with diverse substituents and counter ions to label them in acetonitrile with n.c.a. [^{18}F]fluoride, activated by the Kryptofix© 2.2.2/K_2CO_3-system. Since that time a variety of arenes has been ^{18}F-labelled via diaryliodonium salts. Further, it has been demonstrated that via diaryliodonium salts even ^{18}F-labelled electron rich arenes become available by using nucleophilic n.c.a. [^{18}F]fluoride. The nucleophilic way has distinct advantages over alternative electrophilic procedures, which employ molecular [^{18}F]F_2 or reagents derived thereof, since n.c.a. [^{18}F]fluoride can be produced in higher amounts and particularly with higher specific activity which is of great importance for *in vivo* radiotracers. [99, 100, 155, 175-178]



Scheme 1.11: General principle of ^{18}F-labelling via diaryliodonium salts (X = Cl, Br, I, TsO, CF_3SO_3, CF_3CO_2; R, R' = H, Cl, Br, I, NO_2, CH_3, OCH_3, …)

During the ^{18}F-labelling the reaction proceeds via a S_N-Ar-mechanism and leads to the n.c.a. [^{18}F]fluoroarenes and the non-radioactive iodoarenes as by-products (cf. Scheme 1.11). According to the reactions of the S_N-Ar type, in an asymmetric diaryliodonium salt the electron deficient ring is preferably attacked by the [^{18}F]fluoride. As a consequence, this is reflected in the product ratios of the [^{18}F]fluoroarenes formed. In case of *para*-substituted aryl(phenyl)iodonium salts the electronic influence of the substituent lead to expected product yields as follows 70 % (bromo), 60 % (chloro), 40 % (methyl), and 0 % (methoxy); the corresponding percentages of the [^{18}F]fluorobenzene increased with the same sequence [100, 155, 177]. As a result, the outcome of the substitution process can be predicted or controlled by the electronic character of substituents. Under this consideration, a subsequent methylation of one arylring should lead to a clear ratio in favour of [^{18}F]fluorobenzene. However, experiments show that an increasing

number of methyl groups at one aromatic ring of up to four is accompanied by a decreasing percentage of [^{18}F]fluorobenzene (cf. Figure 1.2) [176]. In spite of an increasing steric hindrance and electronic deactivation of the *multi*-methylated arylrest in the diaryliodonium salt the very same shows a higher probability for the nucleophilic attack.

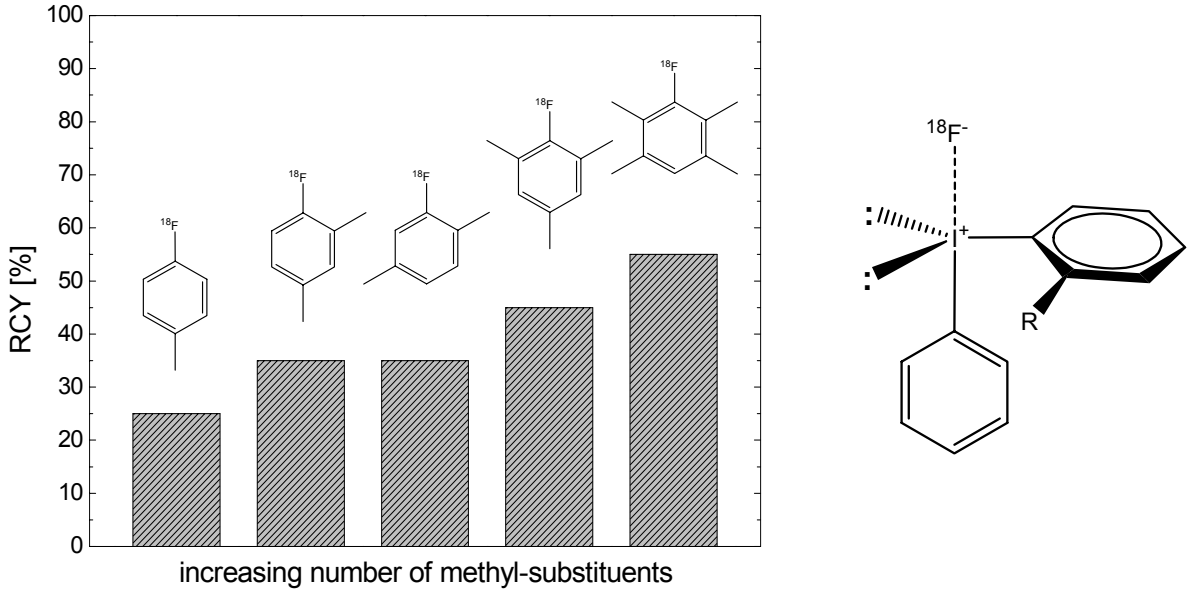


Figure 1.2: Increasing number of methyl-substituents leads to higher RCY [from 176]; trigonal bipyramidal geometry of the intermediate [^{18}F]fluoride complex of the nucleophilic attack

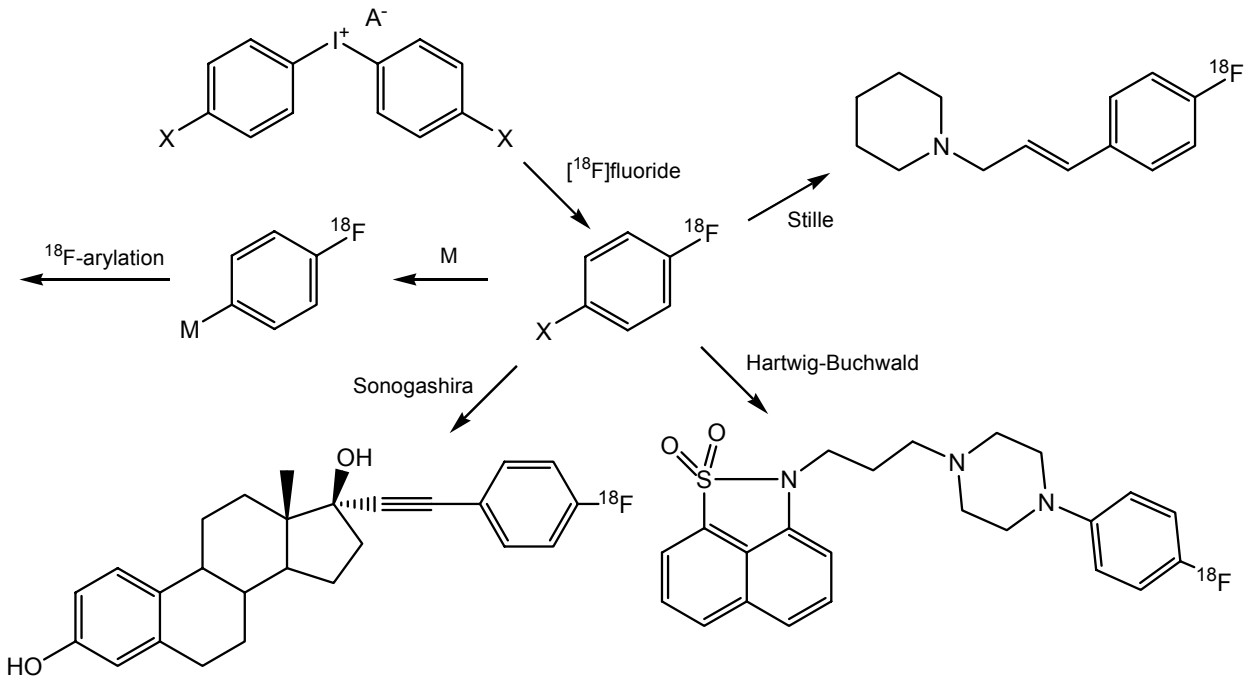
This fact is explainable by trigonal bipyramidal geometry of an iodine(III) intermediate formed upon the nucleophilic attack of [^{18}F]fluoride (cf. Figure 1.2). First indications for the so-called "*ortho*-effect" in these reactions were mentioned in 1967 by Le Count et al. [179]. The phenomenon was confirmed and the trigonal bipyramidal geometry incipiently postulated as explanation by Yamada et al. in 1972 [180]. Furthermore, the same interpretation was used to explain similar results in corresponding radiofluorination reactions via diaryliodonium salts [176, 181, 182]. It has been proposed that the intermediate is fluxional and the "reactive" ring is occupying the equatorial position *syn* to the nucleophile [183, 182].

Hence, in addition to the electron density the substitution pattern and its steric influence, especially with *ortho*-substituents, determine the regioselectivity of the nucleophilic attack. With regard to the electronic influence highly electron rich moieties such as heteroaromatic rings come into consideration. Consequently, various reactions of non-radioactive nucleophiles including fluoride as caesium or potassium fluoride have been carried out and show very high regioselectivity up to regiospecificity [180, 182, 184]. However, only non-radioactive nucleophiles

have been reacted with aryl(heteroaryl)iodonium salts so far and studies with n.c.a. [^{18}F]fluoride are still open.

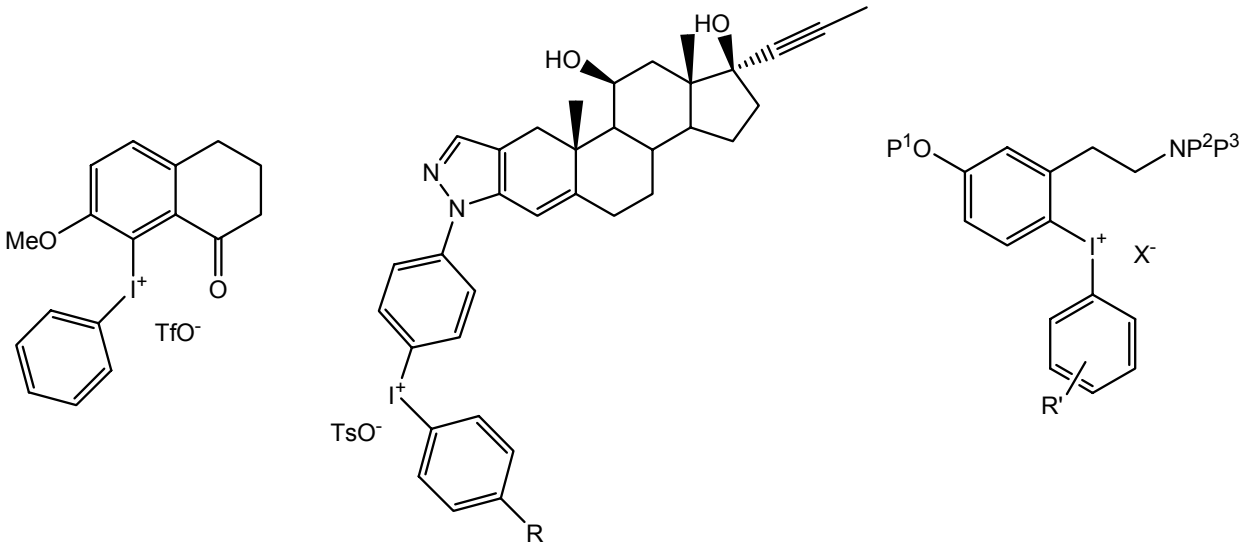
1.6.3 ^{18}F-Labelled radiotracers via diaryliodonium salts

In fluorine-18 radiochemistry the diaryliodonium method established their applicability especially for smaller aromatic compounds as primary ^{18}F-labelling synthons. A very versatile synthon is n.c.a. 4-halo[^{18}F]fluorobenzene (cf. Scheme 1.12), which was used as iodine and bromine derivative. Both can be obtained from the appropriate symmetric di-(4-halophenyl)iodonium salts in RCY of 60 – 70 % [99, 100], which is a much improved procedure than the earlier used method with *N*,*N*,*N*,-trimethylammonium precursors [84, 177]. The former was successfully coupled in a Sonogashira reaction to ^{18}F-label two estradiol derivatives, which were the first approaches of Sonogashira-coupling in ^{18}F-chemistry [99]. The latter proved its routine applicability in Stille [97] and Hartwig-Buchwald [98] reactions as well as in various ^{18}F-fluoroarylations after a subsequent transfer into its lithium or manganese organometallic derivative [101]. Also in cases of Stille and Hartwig-Buchwald reactions the diaryliodonium route is more convenient, leads to higher RCY and saves reaction time and steps.



Scheme 1.12: Versatile application of 4-halo-[^{18}F]fluorobenzene (X = Br, I; M = Li, MgX): Stille-[97]; Hartwig-Buchwald- [98]; Sonogashira- [99] coupling and ^{18}F-arylation [101]

In recent years the diaryliodonium salts became more and more popular due to all the above mentioned advantages. Anyway, in case of complex molecules a limiting factor is indicated by molecule size and complexity. Approaches to label a complex molecule in one step with [^{18}F]fluoride via its iodonium salt often led to low RCY or failed completely. Thus the triflate precursor 7-methoxy-8-phenyliodotriflate tetralone (cf. Scheme 1.13) was chosen as model compound for 2-[^{18}F]fluoroestradiol, but only the starting material, 7-methoxytertalone, and iodobenzene were recovered from the reaction mixture [181].



Scheme 1.13: Iodonium precursors of complex radiotracer for PET; left: model compound for ^{18}F-labelling of estradiol (no ^{18}F-labelling!); middle: precursor for an ^{18}F-labelled steroid (RCY = 0.2 % (R = H); 2.0 % (R = CH_3)); right: precursor for 6-[^{18}F]fluoro-*m*-tyramine as model for 6-*L*-[^{18}F]fluoroDOPA (P^{1-3} = protecting group; ^{18}F-labelling successful; RCY = ?)

Another attempt to label a relevant biomolecule via its iodonium salt was made for a corticosteroid as potential PET ligand for imaging brain glucocorticoid receptors (cf. Scheme 1.13). For this purpose, the iodonium precursor was synthesised as tosylate with both phenyl and tolyl counter rings. The RCY were very low, but an increase from the phenyl (RCY = 0.2 %) to the tolyl (RCY = 2.0 %) group was observable, accordingly to the assumption of directing the regiochemical outcome by electronic effects [185].

Recent investigations using iodonium salts report on the preparation of 6-[^{18}F]fluoro-*m*-tyramine as model compound for 6-*L*-[^{18}F]fluoroDOPA. Initial studies should lead to a nucleophilic access of this important radiotracer. The protected iodonium precursor (cf. Scheme 1.13) was successfully ^{18}F-labelled and influences of protection groups, substituents in the non-intended

ring and counter ions were examined. The data are not yet published in detail and only a symposium abstract gives an idea of the expected results [186].

1.7 The role of AMPA receptors

1.7.1 Basic neurophysiology of cerebral synapses

The central nervous system (CNS) consists of a highly complex aggregation of cells, part of which is a communication network and another part a supportive and structural matrix (glial cells) [for an overview see: 187, 188, 189]. Neurons forming the communication network consist of a cell body (soma) with extensions (dendrites and an axon). The axon and dendrites make connections to the other neurons and they intercommunicate by means of specialised junctional complexes (synapses). In a synapse the presynaptic and the postsynaptic site are separated by the synaptic cleft, which is a gap of 15 – 20 nm. Almost all synapses involved in signal transmission in CNS are chemical synapses. However, only a very small number are electric synapses whose membranes are fused and the neurons are directly connected by ion channels.

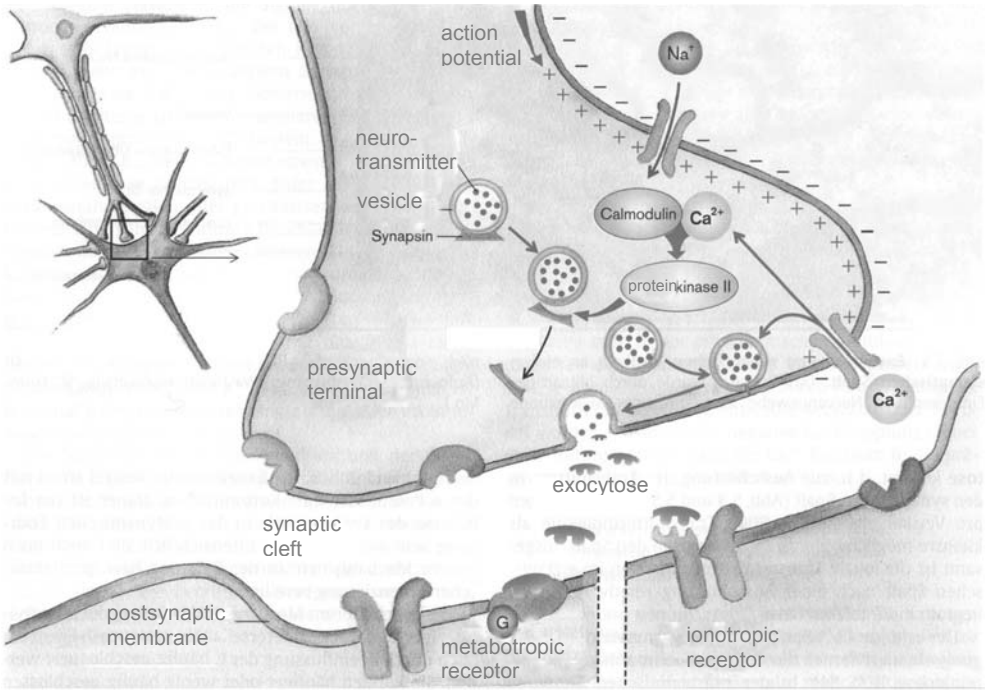


Figure 1.3: Principle of Ca^{2+} mediated neurotransmitter release (exocytose) into the synaptic cleft in a synaptic junction [modified from 188]

Along a neuron, information is transmitted by conduction of an electrical signal (action potential) from the soma or the dendrites to a synaptic ending, where a chemical neurotransmitter transfers the signal from the presynaptic to the postsynaptic site of the synapse (cf. Figure 1.1).

For the synthesis of the neurotransmitter in the soma of presynaptic cells appropriate precursor molecules are taken up into the neuron. The resulting neurotransmitter is stored in vesicles in the presynaptic terminal. One part of the vesicles is linked to the presynaptic membrane and is intended for the exocytic release (exocytose) into the synaptic cleft. The remaining main part of the vesicles is bound to the protein synapsin as a reservoir. While an action potential moves along the axon and reaches the axon tip, voltage-gated Ca^{2+} channels open and allow Ca^{2+} entry into the presynaptic neuron. The increase of the internal Ca^{2+} concentration triggers the exocytic release of the neurotransmitter into the synaptic cleft. Beside the exocytose, Ca^{2+} activates the calmodulin-dependent protein kinase II, which phosphorylates synapsin for the release of stored vesicles for the next exocytose. Within approximately 0.1 ms the released neurotransmitter diffuses through the synaptic cleft to the postsynaptic site, where it is recognised and bound by postsynaptic receptor proteins to form a receptor-ligand complex. The receptor sites are classified in two types, the ionotropic and the metabotropic receptors. In ionotropic receptors the ion channel is part of the receptor protein and is gated or closed directly by changes of the receptor conformation. In case of ionotropic receptors, the binding by receptor-ligand complex formation cause a change in the conformation of ligand-gated ion channel proteins in the membrane. Resulting ion flux (Na^+, K^+ or Cl^-) though the opened channel provoke a depolarisation of the membrane and a new electric signal arises (postsynaptic potential) and moves along the cell body and the axon to the next neuron. Depending on the type of receptors and synapses, different ion channels are opened. Thus inward flows of Cl^- activate and stabilise the resting potential (hyperpolarisation) and inhibit the excitation, in the same way efflux of positive ions (K^+, Na^+) hyperpolarises the membrane (inhibitory postsynaptic potential). Conversely, efflux of Cl^- or influx of positive ions depolarise the membrane and produce an excitatory postsynaptic potential, which amplifies the forwarded signal.

Metabotropic receptors are coupled with so-called G proteins (guanosine nucleotide-binding protein). The G protein, stimulated by the activated receptor, triggers nearby ion channels or generates an intracellular second messenger by interaction with enzymes. To stop the synaptic transmission and regenerate the post synaptic membrane for new processes, the neurotransmitters need to be deactivated from the synaptic cleft. Therefore they are metabolised by enzymes, taken up into the presynaptic terminal (re-uptake) or removed from the cleft and metabolised by the glial cells.

In addition to the specific neurotransmitter (e.g. acetylcholine, amino acids (glutamate, glycine, and γ-aminobutyric acid (GABA), monoamines (serotonin, histamine, dopamine, noradrenaline (norepinephrine) adrenalin (epinephrine)) and some oligopeptides (neuropeptides)) several

natural substances (e.g. hormones, antibodies and -genes) and even NO are known to be active on specific receptors as agonists. Furthermore, foreign molecules such as pharmaceuticals show high specific affinities to neuronal receptors as agonists and antagonists, respectively. Thus, agonism and antagonism generally divide all possible receptor ligands in two classes. Agonists cause the same effect as the natural neurotransmitter, and antagonists block the binding site and generally inhibit any response. Within the agonists, full agonists and partial agonist are known. The former is able to produce the full tissue response whereas the latter provokes a response, but the response is less than the maximum to a full agonist. Antagonism is divided in competitive, non-competitive, chemical and functional one. In principle, competitive antagonism provokes a (ir)reversible blocking at the binding site, whereas non-competitive antagonists cause an (ir)reversible blocking by binding to another location at the receptor molecule. In contrast, functional antagonism is based on an indirect effect provoked at the neuron of the receptor or even at different neuronal cells.

Many synapses have further receptors for regulatory functions in both the postsynaptic and the presynaptic membrane. Presynaptic autoreceptors (specific for the own transmitter) and heteroreceptors (specific for other substances) generate secondary messenger compounds to regulate the exocytose. Accessorily, heteroreceptors can affect preliminary mechanisms like neurotransmitter synthesis and storage (neuromodulation). In the postsynaptic membrane the heteroreceptors normally provoke a neuromodulation of the G protein processes or in case of ionotropic synapses they act directly of the ion channels. Artificial ligands for these receptors are referred to as neuromodulators and show agonistic and antagonistic function; several such substances are known and they are commonly used as pharmaceuticals.

1.7.2 Ionotropic glutamate receptors

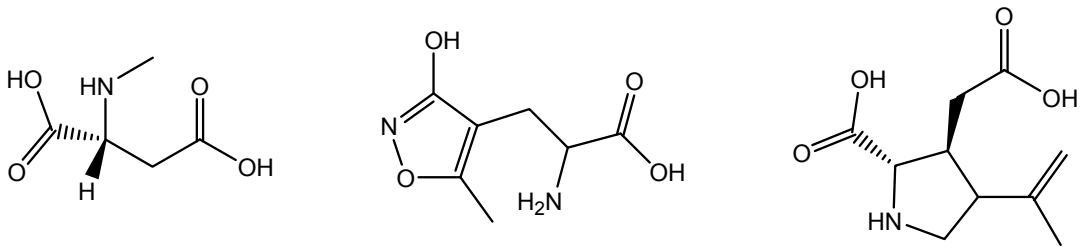
The structure and function of glutamate receptors were recently reviewed in several reports, the following gives a short overview [from 190].

Glutamate receptors can be found in the cerebellum and the hippocampus and convey most of the fast excitatory transmission in the CNS. In addition, they appear to be crucially involved in memory functions and formation. Furthermore, the glutamate receptor system is assumed to play an important role in several degenerative neuronal dysfunctions and diseases, e.g. ischaemia and seizures, epilepsy, schizophrenia, Alzheimer's, Huntington's, and Parkinson's disease [191, 192]. Glutamate receptors generally subdivide into ionotropic and metabotropic receptors, which are classified into further subunits depending on the mechanism of their signal transduction (cf. Table 1.4). In case of the ionotropic glutamate receptors (iGluRs) there are three major types, which are named after the agonists that were originally identified to activate them selectively.

Thus they are called *N*-methyl-D-aspartate (NDMA), α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA) and 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine (kainic acid / kainate (KA)) receptors (cf. Scheme 1.14).

Table 1.4: Overview of the glutamate receptor system, classification into ionotropic and metabotropic receptors as well as their subunits and the corresponding signal transduction mechanisms ($G_{q/11/i/o}$ = classes of the coupled G protein; $G_{q/11}$ proteins activate the enzyme phospholipase C (PLC); $G_{i/o}$ proteins inhibit the enzyme adenylate cyclase (AC)) [from 190]

Glutamate Receptors					
Ionotropic (iGluRs)			**Metabotropic (mGluRs)**		
NDMA	**AMPA**	**Kainate**	**Group I**	**Group II**	**Group III**
NR1	GluR1	GluR5	mGluR1	mGluR2	mGluR4
NR2A	GluR2	GluR6	mGluR5	mGluR3	mGluR6
NR2B	GluR3	GluR7	↘	↙	mGluR7
NR2C	GluR4	KA-1			mGluR8
NR2D		KA-2	↘	↙	↓
NR3A			G_q / G_{11}		G_i / G_o
NR3B					
↓	↓	↓	↓		↓
Ca^{2+} Na^+	Na^+ (Ca^{2+})	Na^+ (Ca^{2+})	↑ PLC		↓ AC



Scheme 1.14: Chemical structures of the original agonists naming the ionotropic glutamate receptors: NDMA (left), AMPA (middle) and kainic acid (KA) (right)

The structure of ionotropic glutamate receptors is assumed to be tetrameric, which is similar to that of voltage-gated potassium channels. Although the amino acid sequences of the large number of glutamate receptor subunits are not identified completely (only ~20-30 % are

identified), they share common structural features, which place them into a single large superfamily.

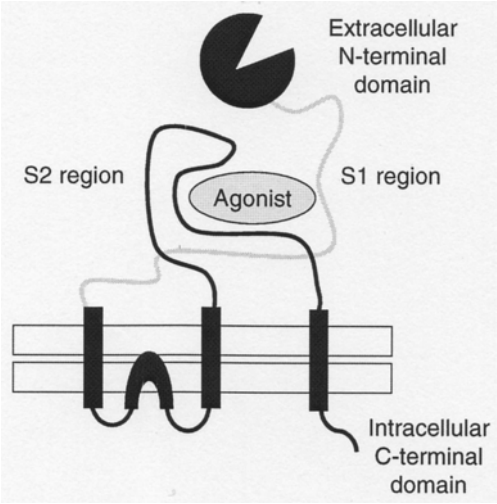


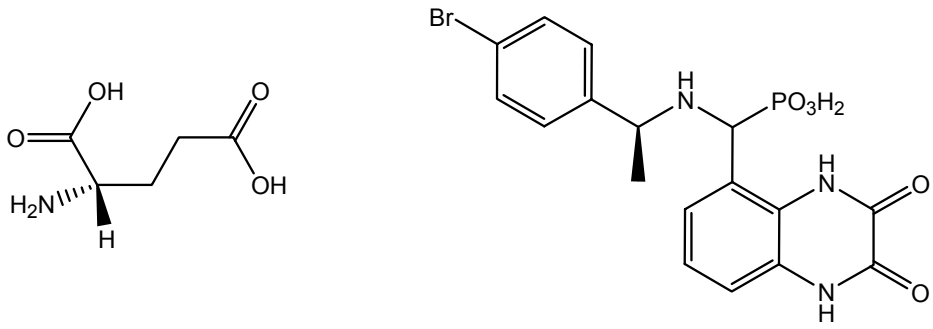
Figure 1.4: Schematic depiction of an ionotropic glutamate receptor (iGluR) family member [from 190]

Whereas the topology of classic metabotropic receptors usually correspond to a four transmembrane domain model of the nicotinic acetylcholine receptors, the ionotropic glutamate receptors show only three transmembrane domains and one pore forming domain in the intracellular membrane surface (cf. Figure 1.4). The classic transmembrane domain exhibits the amino and the carboxy termini extracellularly and a large intracellular loop between the third and the fourth transmembrane domains. In contrast, the ionotropic glutamate receptors possess an intracellular carboxy terminus and an extracellular amino terminus (N-terminal domain). That amino terminus is followed by a polypeptide and the first transmembrane domain (S1 region in Figure 1.4). Then one domain forms an intracellular pore in the surface of the membrane. The second and third transmembrane domains are linked by a large extracellular loop (S2 region in Figure 1.4)) and finally it ends with an intracellular carboxy terminal domain (C-terminus). The agonist binding domain is located in a pocket formed between the N-terminal region and the extracellular loop between the second and third transmembrane domain (cf. Figure 1.4).

NDMA receptors

The NDMA receptor family is composed of seven subunits, NR1, NR2A to D and NR3A and B. Functional NDMA receptors appear to be comprised of NR1 and at least one NR2 subunit, or NR1 and both, NR2 and NR3 subunits. Accordingly, in NR1, NR2 and NR3 receptors the NR3 unit likely substitutes one of the NR2 subunits. The NDMA receptor is unique amongst ligand-

gated ion channels due to its requirement for two obligatory co-agonists binding on two different binding sites, the NR1 glycine site and the NR2 glutamate site. For receptor activation the occupation of two independent glycine sites and two independent glutamate sites are necessary. Thus the minimum need for a functional NDMA receptor seems to be a tetramer composed of two NR1 and two NR2 subunits, what is likely achieved by pairs or dimers of dimers (e.g. an NR1 dimer in combination with an NR2A-D dimer).



Scheme 1.15: Structures of the NDMA receptor full agonist *L*-glutamic acid (left) and the very high affine and selective competitive NDMA receptor antagonist (1*RS*,1'*S*)-PEAQX (right)

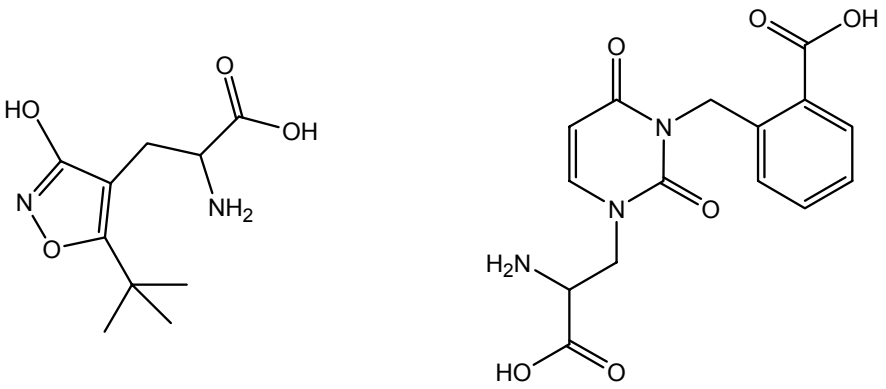
Besides NDMA as most commonly used agonist, glutamate (cf. Scheme 1.15) represents a full agonist for the NDMA receptor system. NDMA is not affected by the glutamate metabolism, therefore it is much more effective, although it is not quite a full agonist and of lower potence than glutamate. Furthermore, the ligand NDMA shows very good selectivity over non-NMDA ionotropic and metabotropic glutamate receptor families, but little selectivity between the NDMA receptor subtypes.

A large number of competitive and non-competitive antagonists for the glutamate recognition site of the NDMA receptor have been synthesised. Competitive antagonists are usually α-amino carboxylic acids containing a ω-phosphonic acid group. They penetrate the blood-brain barrier (BBB) relatively poorly due to their high charged nature and equilibrate slowly in the brain. In general, they show only modest NDMA receptor subtype selectivity, although there are exceptions. One is (1*RS*,1'*S*)-PEAQX (cf. Scheme 1.15), which has an affinity in the nanomolar range at human NR1/NR2A receptors and > 100-fold selectivity over NR1/NR2B receptors. One of the potentially most important recent developments in NDMA receptor pharmacology has been the identification of highly subtype selective antagonists, which act allosterically though an interaction with the extracellular N-terminal domain of the NR2 subunits. Most of these compounds are selective to the NR2B subunits. A large number of substrates with high NR2B

affinity and selectivity over other NDMA receptor subtypes have been developed, which readily penetrate the brain and are systemically active.

Kainate receptors

Kainate receptors are subdivided in two subunit families, GluR5 to 7 and KA-1 and -2. They show again structural features of tetrameric combinations, where both, homomeric and heteromeric combinations are possible. Concerning KA-1 and -2 subunits, no homomeric combination can be found, thus they only occur in heteromeric combinations with one or more members of GluR5 to 7 subunits. At first the lack of selective agonists for kainate receptors has hampered the discovery of the kainate receptor physiology. Since then several selective agonists with different selectivity across the GluR5 to 7 subfamily have been developed, including the substituted AMPA-analogue 5-tert-butyl-4-isoxazolepropionic acid (ATPA) (cf. Scheme 1.16), which shows selectivity for GluR5 receptors and only low affinity to GluR6 and 7 receptor subtypes.



Scheme 1.16: Structures of the kainate receptor agonist ATPA (left) and the very potent non-competitive antagonist UBP296 (right)

In addition, several competitive and non-competitive antagonists have been developed as ligands for the kainate receptor family. Especially, the further development of the non-competitive antagonists, selective at the GluR5 subtype, lead to the recent most potent member of this group, (*R*,*S*)-3-(2-carboxybenzyl)willardiine (UBP296) (cf. Scheme 1.16). UBP296 exhibits selectivity for GluR5 containing receptors over GluR6 and AMPA receptors, whereby the activity is residing in the S enantiomer. Another class of kainate receptors affecting compounds is represented by the positive allosteric modulators. Only the lectin concanavalin A has been identified thus far. Although it has been proven to be a valuable tool for the study of kainate receptors, it shows also activity at AMPA and NDMA receptor sites.

AMPA receptors

The AMPA receptor family is composed of four subunits, GluR1 to 4, and functional AMPA receptors are assumed to assemble as tetramers. Like NDMA receptors, AMPA receptors occur likely in heteromeric combinations. The GluR2 subunit plays a critical role in the permeability of the heteromeric receptors to Ca^{2+}. So AMPA receptors that do not contain the GluR2 subunit are Ca^{2+}-permeable, what is a result of a voltage-dependent block of the ion channel by intracellular polyamines. In contrast, the Ca^{2+} impermeability of GluR2 containing receptors is based on a molecular modification, which is identified as an arginine (R) at a critical site in the pore loop (2m domain), which is a glutamine (Q) at the corresponding position in the other subunits. Further complexity is introduced in all AMPA subunits by alternative splicing in the extracellular S2 domain. Two alternatively spliced forms are present, known as Flip and Flop. Flip variants are predominant prenatally, whereas Flop variants become expressed postnatally and reach equivalent levels to those of Flip in the adult. These splice variations have effects on the rate and extent of desensitisation of heteromeric AMPA receptors and also influence their sensitivity to allosteric modulators. In the same way GluR2 and 4 have further C-terminal splice variants, which likely play roles in intracellular protein-protein interactions and receptor clustering.

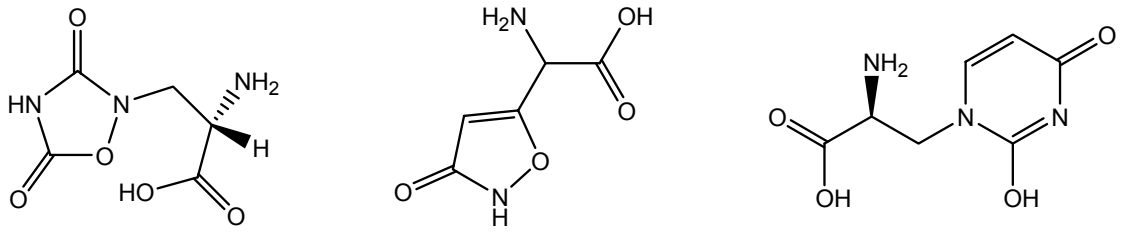
Indications speak for AMPA receptors, lacking the GluR2 and with high Ca^{2+} permeability located in hippocampus and amygdala. They predominate in inhibitory interneurones, whereas pyramidal cells have AMPA receptors containing GluR2 subunits and thus largely Ca^{2+}-impermeability. There is also evidence that in stellate cells activity-induced Ca^{2+} influx through AMPA GluR2-lacking receptors controls the designing of GluR2-containing AMPA receptors, implying a self-regulating mechanism of the Ca^{2+} permeability of synapses.

1.7.3 Ligands of AMPA receptors

AMPA receptor agonists

A large number of AMPA receptor agonists have been described and many of them, like AMPA itself, are derived from classic structure-activity-relationship (SAR) studies using ibotenic acid, quisqualic acid and willardiine as lead structures (cf. Scheme 1.17). One of the interesting aspects of AMPA receptor agonists is that they can vary dramatically in the amount of receptor desensitisation that they induce. The receptor desensitisation effect can be described as a self-control or –protection mechanism against too high signal frequencies, signal overdose and receptor or neuron damage. While a neurotransmitter binds to the receptor it also induces generally a specific receptor desensitisation, which affects the recovery rate of the receptor and its binding sites, respectively. In some cases a strong desensitisation can lead to temporarily

complete deactivation of the receptor. Desensitisation depends on particular agonist structures; for example, glutamate and AMPA act as full agonists and induce a rapid desensitisation response at the AMPA receptors, while kainate acts as partial agonist and induces only little desensitisation response [193].



Scheme 1.17: Lead structures used for the development of AMPA agonists; ibotenic acid (left); *L*-quisqualic acid (middle); willardiine (right)

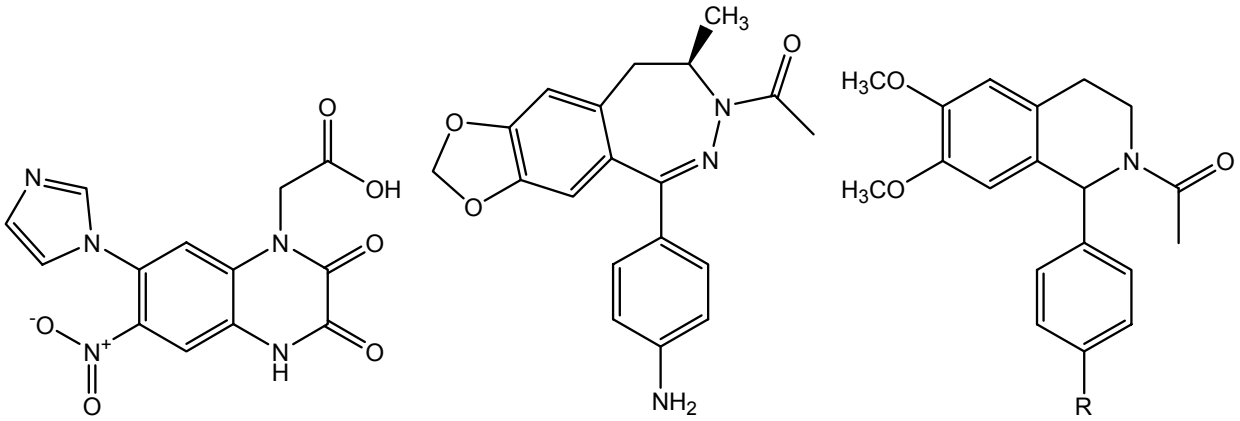
The degree of partial agonism is correlated with the extent of domain closure of the bi-lobed agonist binding (cf. Figure 1.4), thus partial agonists induce domain closure, but not the closed state induced by full agonists. The degree of desensitisation appears to be directly correlated with the degree of dimerisation between the pairs of subunits within the tetrameric receptor.

AMPA receptor antagonists

AMPA receptor subtypes are involved in learning and memory but can also mediate neuronal degeneration and even cell death [for an overview see: 190, 194, 195]. For this reason particular attention has been devoted to selective AMPA receptor antagonists as potential neuroprotective agents. Several AMPA receptor antagonists inhibit glutamatergic transmission in a competitive way, whereas only a few classes of selective, non-competitive AMPA receptor ligands (e.g. 2,3-benzodiazepines, phthalazines, quinazolines and more recently tetrahydroisoquinolines) have been developed.

However, the first compounds identified as competitive AMPA antagonists shows also activity at the glycine sites of NDMA receptors and therefore insufficient selectivity to be useful agents. Furthermore, most of them were quinoxaline derivatives and have a limited, or even poor water solubility, that causes nephrotoxicity in some cases and the compounds have failed the clinical trials. One promising member of the quinoxalines is [2,3-dioxo-7-(1*H*-imidazol-1-yl)-6-nitro-1,2,3,4-tetrahydro-1-quinoxalinyl]-acetic acid (YM872 / zonampanel) (cf. Scheme 1.18), which succeeded in clinical trials for the treatment of acute ischaemic stroke. The trial phase II has been completed, but, so far, no further information is available [196].

The main advantage of non-competitive AMPA receptor antagonists is that they use different binding sites than those of glutamate and therefore the normal glutamatergic activity is not influenced after prolonged use. Hence, they are also referred to as negative allosteric modulators. With 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (GYKI 52466) as first prototype of non-competitive AMPA receptor antagonists and lead structure, several 2,3 benzodiazepines have been identified as selective ligands for AMPA receptors. Although they exhibit relatively little selectivity between AMPA receptor subtypes, they are selective for AMPA over kainate and NDMA receptors. (*R*)-7-Acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7*H*-1,3-dioxolo(4,5-*h*)-2,3-benzodiazepine ((-)-GYKI 53773/(*R*)-LY300164 / talampanel) (cf. Scheme 1.18) has entered in clinical trials for indications including epilepsy and shows positive results in patients with severe epilepsy not responsive to other drugs and so it is selected as antiepileptic drug candidate [197, 198].

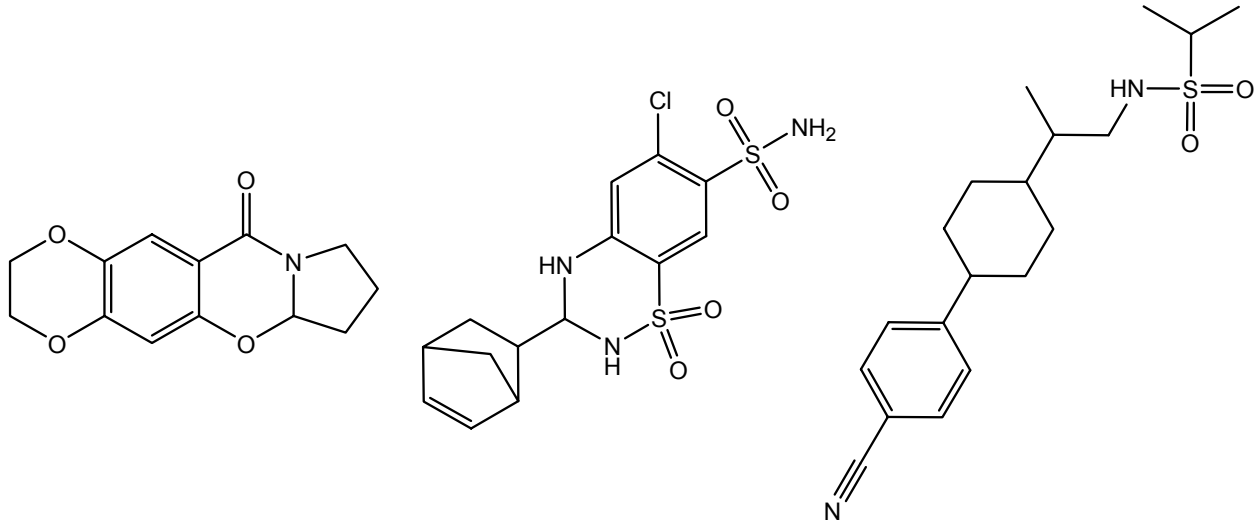


Scheme 1.18: Structures of AMPA receptor antagonists; left: competitive antagonist zonampanel (YM872); middle: non-competitive antagonist talampanel ((-)-GYKI 53773); right: series of tetrahydroisoquinoline derivatives as non-competitive antagonists (R = H, Br, Cl, F, NO_2, NH_2)

Tetrahydroisoquinolines were recently identified as highly potent non-competitive AMPA receptor antagonists (cf. Scheme 1.18) and demonstrated anticonvulsant effects. The 2-acetyl-1-(4'-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (R = Cl) proved to be more potent than other known AMPA antagonists, which require a 100-fold higher dose to show similar effects. In addition, the fluoro-substituted compound 2-acetyl-6,7-dimethoxy-1-(4'-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline also showed a potence in the range of GYKI 52466 and it is very interesting for ^{18}F-labelling in the original position of the fluorine with regard to get a AMPA radiotracer for PET.

Positive allosteric modulators (potentiators)

The desensitisation and deactivation of AMPA receptors can be controlled by positive allosteric modulators. Thus, these so-called potentiators regulate the magnitude and kinetics of AMPA receptor-mediated synaptic currents. A number of positive allosteric modulators have been identified which modulate receptor desensitisation and / or deactivation but do not activate the receptor when applied alone. Only a few chemical classes have been reported to show effects as AMPA receptor modulators, benzamides (AMPAkines), benzothiadiazides and biarylpropylsulfonamides (cf. Scheme 1.19). Such compounds demonstrated mediated synaptic activity in various *in vitro* and *in vivo* studies, most notably in models of cognition.



Scheme 1.19: Structures of AMPA receptor potentiators of different chemical classes; left: CX614, a benzamide (AMPAkines); middle: cyclothiazide, a benzothiadiazide; right: LY404187, a biarylpropylsulfonamide)

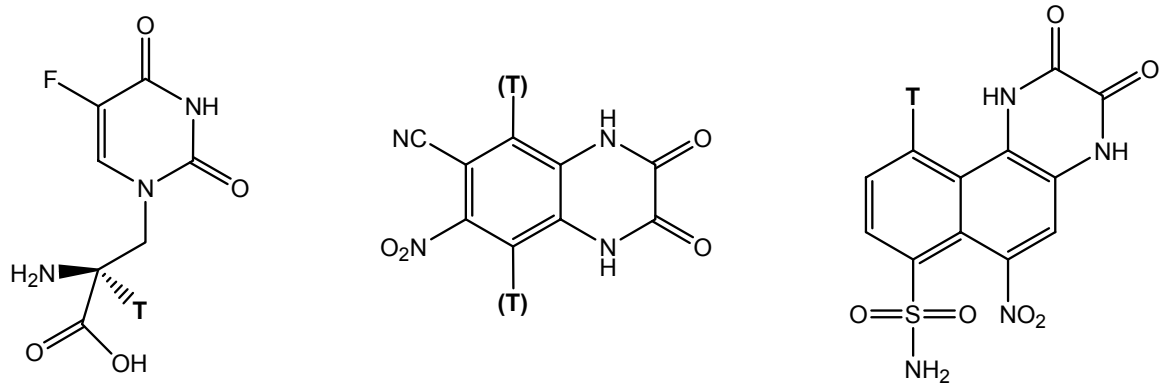
Moreover, known and commonly used drugs for diseases affecting memory and learning appear likely to act as AMPA receptor modulators. The positive modulators exhibit discrete mechanistic profiles and selectivity for individual AMPA receptor subunits and their isoforms (splice variants). As a result, the AMPAkine 2*H*,3*H*,6*aH*-pyrrolidino[2'',1''-3'2']1,3-oxazino[6'5'-5,4]benzo[*e*]1,4-dioxan-10-one (CX614) enhances the AMPA receptor-mediated currents by blocking the desensitisation and slowing the deactivation (cf. Scheme 1.19), whereas the benzothiadiazide 6-chloro-3,4-dihydro-3-(5-norbornen-2-yl)-2*H*-1,2,4-benzothiazidiazine-7-sulfonamide-1,1-dioxide (cyclothiazide) inhibits the receptor desensitisation but has only little effect on receptor deactivation (cf. Scheme 1.19).

However, also the biarylpropylsulfonamide *N*-2-[4-(4-cyanophenyl)phenyl]propyl 2-propanesulfonamid (LY404187) suppresses receptor desensitisation but with a distinct time dependence in

the presence of an agonist. The AMPAkines exhibit somewhat higher potencies at flop than flip isoforms of recombinant homomeric receptors and have only little selectivity between the subfamily members of AMPA receptors. In contrast, cyclothiazide and LY404187 show higher potencies at flip than flop isoforms and increased potencies at flip isoforms of GluR2 and 4 vs. GluR1 and 3. The binding site of cyclothiazide was identified at the dimer interface between AMPA receptor subunits. There is evidence within the benzamides for different binding sites of some members, thus there are likely multiple binding sites for positive allosteric modulators, even for compounds of the same chemical class. These differences in the mechanism of action and receptor subunit / isoforms selectivity provide the potential for special *in vivo* profiles for the different positive allosteric modulators for AMPA receptors.

1.7.4 Radioligands of AMPA receptors

There is a lack of suitable radiotracers for *in vivo* investigations of the AMPA receptor family. So far, only a few specific substances have been labelled, but only with tritium, which is only suitable for *in vitro* or *ex vivo* applications. Thus, there is enormous demand for PET or SPECT tracers for the AMPA receptor system.



Scheme 1.20: ^{3}H-labelled radiotracers for the AMPA receptor system; left: (*S*)-[^{3}H]-5-fluorowillardiine; middle: [^{3}H]CNQX; right: [^{3}H]NBQX

Besides [^{3}H]glutamate and [^{3}H]AMPA as labelled agonists, which offered the first insight into the AMPA receptor family, only (*S*)-5-[^{3}H]fluorowillardiine ([^{3}H]FW) as agonist and 6-cyano-7-[^{3}H]nitroquinoxaline-2,3-dione ([^{3}H]CNQX) as well as 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-[^{3}H]benzo(*F*)quinoxaline-7-sulfonamide ([^{3}H]NBQX) as antagonists are available for further investigations (cf. Scheme 1.20).

Aims and Scope

Especially *in vivo* studies using positron emission tomography (PET) call for very high standards in purity and specific activity of ^{18}F-labelled compounds. However, for the positron emitter fluorine-18 a high specific activity is only achievable with n.c.a. [^{18}F]fluoride. This implies a ^{18}F-radiochemistry almost reduced to nucleophilic substitution reactions. Whereas electron deficient arenes can directly be labelled with no-carrier-added [^{18}F]fluoride in one step, electron rich ^{18}F-labelled aromatic molecules are only available by electrophilic methods with [^{18}F]F_2 or via multi-step radiosyntheses using accessory activating groups. Both accesses are accompanied by severe drawbacks; the former leads to low specific activities due to necessary carrier addition and the latter requires additional radiosynthetic steps for converting or removing the activating groups. Here, diaryliodonium salts represent an alternative, since they have been proven as potent precursors for direct nucleophilic ^{18}F-labelling of arenes including even relatively electron rich derivatives. Furthermore, the 2-thienyl group represents a highly electron rich moiety and is known to induce a high regioselectivity in reactions of aryl(2-thienyl)iodonium salts with nucleophiles. However, the 2-thienyl group so far has only been employed in non-radioactive studies.

The aim of this work was to develop a new direct nucleophilic n.c.a. ^{18}F-labelling method for arenes based on aryl(2-thienyl)iodonium salts as precursors, where particularly non-activated molecules were of interest. As model electron rich molecules n.c.a. [^{18}F]fluoroanisoles should be radiofluorinated by using this new method.

As first approach, a reliable synthesis route for the employed aryl(2-thienyl)iodonium salts had to be elaborated. Since different methods are described in the literature, especially for electron rich molecules, a reliable and convenient synthesis was of importance.

In order to optimise the general conditions of the ^{18}F-substitution procedure with the 2-thienyl-iodonium leaving group, the focus was particularly on the solvent system, precursor concentration, and reaction temperature.

A major concern was the influence of the highly electron rich 2-thienyl group on a very high induced regioselectivity. Therefore influences of counter anions of the precursor salts on RCY and reaction rate had to be systematically examined. For a comparison between organic and inorganic counter anions, the iodonium precursors were employed as bromides, iodides, tosylates and triflates. In addition, the influence of the substitution pattern was of interest as determining factor. Especially, the so-called *ortho*-effect was expected to show distinct impact on the orientation of the ^{18}F-labelling reactions.

One important focus should be on the influence of the electronic character of the precursor molecules on the RCY and reaction rate of the ^{18}F-substitution reaction. Therefore the study was extended to a series of substituted aryl(2-thienyl)iodonium salts with systematically varying electron density. Thus, the aryl(2-thienyl)iodonium salts ranged from highly activated (electron deficient) to deactivated (electron rich) precursors.

Since the empirical Hammett relation is the most commonly used *linear-free-energy* relationship for studying and investigating organic reactions and their mechanisms, the reaction rates of the n.c.a. ^{18}F-exchange reactions should be correlated with the appropriate Hammett constants of the aryl substituents in the precursors.

In order to demonstrate the applicability and versatility of the new method by direct no-carrier-added ^{18}F-labelling via aryl(2-thienyl)iodonium salts, two deactivated molecules relevant for radiopharmaceutical chemistry should be ^{18}F-labelled.

First, the primary ^{18}F-labelling synthon n.c.a. 4-[^{18}F]fluorophenol, which has proven its applicability in various radiosyntheses of radiopharmaceuticals, should be prepared via an appropriate aryl(2-thienyl)iodonium precursor. Thus, a more convenient and time-saving procedure would be attained in comparison to the so far alternative five-step radiosynthesis.

Second, a more complex molecule should be ^{18}F-labelled via aryl(2-thienyl)iodonium salts. Thus far, only a few complex molecules were ^{18}F-labelled via diaryliodonium salts and all showed a very small RCY of 3 % and below. Radioligands for *in vivo* studies of the AMPA neuroreceptor system are lacking and in great demand. 2-Acetyl-6,7-dimethoxy-1-(4‘-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (F-ADTQ) was characterised as a non-competitive AMPA receptor antagonist, which is not available as ^{18}F-labelled radioligand so far. Accordingly, F-ADTQ should be synthesised by a direct ^{18}F-labelling procedure using (2-thienyl)iodonium salts.

For the synthesis of precursor molecules for the ^{18}F-labelling of F-ADTQ the iodine derivative 2-acetyl-6,7-dimethoxy-1-(4‘-iodophenyl)-1,2,3,4-tetrahydroisoquinoline (I-ADTQ) had to be prepared as well as its corresponding trimethyltin compound. Since I-ADTQ, unlike other 4’-substituted analogues, has not yet been characterised as AMPA receptor antagonist, it should be labelled for comparison with radioiodine in order to make preliminary radiopharmacological evaluation studies possible and possibly enlarging the very low number of radiolabelled AMPA ligands.

In terms of radioanalytical methods, suitable systems and conditions for radio thin layer chromatography and radio high performance liquid chromatography needed to be developed for identification and quantitation of the ^{18}F- and ^{131}I-labelled compounds. Finally, reference compounds and standards had to be synthesised for this purpose.

Results and Discussion

Diaryliodonium salts are well-known as stable and well-manageable compounds which are light-sensitive. In chemistry they show widespread applications [151, 152]. Furthermore, diaryl-iodonium salts have earlier been proven as potent precursors for nucleophilic ^{18}F-labelling reactions (see subchapter 1.6). A wide range of symmetric and asymmetric diaryliodonium salts were employed with n.c.a. [^{18}F]fluoride for direct nucleophilic ^{18}F-labelling reactions. Of particular interest is their ability to serve as precursors for a direct nucleophilic ^{18}F-introduction into electron rich aromatic compounds [155, 175-178]. Such nucleophilically deactivated aromatic molecules can generally be labelled only with electrophilic reactions or with the help of accessory activating groups, which decrease the electron density in the arenes and enable a nucleophilic ^{18}F-labelling approach. However, additional activating groups have to be removed or converted after the ^{18}F-intoduction process. In terms of [^{18}F]fluorotracers for nuclear medicine diagnosis two important facts call for high specific activity. Firstly, toxic and pharmacological effects or responses can be excluded in the n.c.a. range and secondly, special applications such as brain imaging and determination of receptor occupancy and density become available. For ^{18}F-labelled compounds with high specific activity, labelling reactions have to be carried out at n.c.a. scale, which is only accessible for nucleophilic fluoride-18.

Nucleophilic reactions with diaryliodonium salts are well investigated and they proceed according to a classic S_NAr-mechanism. As a result, the more electron deficient ring in the diaryliodonium salt is preferably attacked by the nucleophile and thus, the regiochemical outcome of the reaction can be directed or controlled by the electronic character of the arylrests, i.e. their substituents. Besides electronic properties, the steric hindrance of attached groups must be considered. Based on a trigonal bipyramidal intermediate during the substitution process, the "*ortho*-effect" causes a favoured attack of *ortho*-substituted compounds in the nucleophilic reaction even in case of deactivated rings.

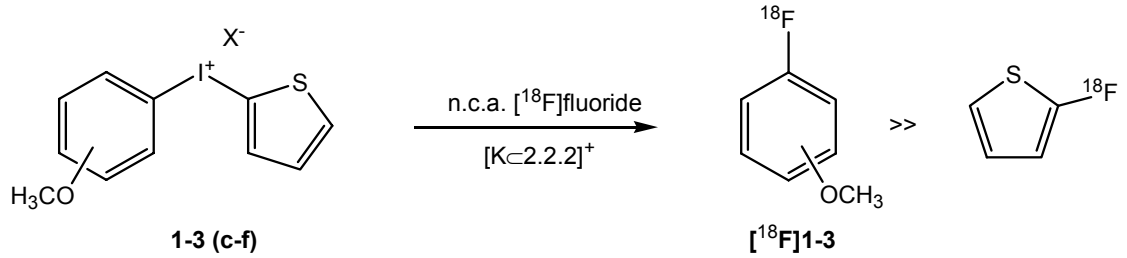
Concerning the dependence on electronic influences the direct nucleophilic n.c.a. ^{18}F-labelling of electron rich aromatic molecules receives major interest. For the development of radiopharma-ceuticals via diaryliodonium salt precursors it is much more practicable in most cases to modify the undesired aromatic ring electronically for better product ratios, faster kinetics and thus higher RCY, than finding an object molecule carrying originally an *ortho*-substituent.

In principle, product ratios of ^{18}F-labelling reactions with asymmetric diaryliodonium precursors mirror the difference between the relative electron densities of the aryl-moieties, when steric influences are negligible. Thus the more the undesired ring becomes deactivated the more the preference of ^{18}F-labelled electron rich molecules increases. Considering this, heteroaromatic

rings with a high electron density as intended moieties not for labelling offer the way to a variety of electron rich ^{18}F-compounds, where generally a direct nucleophilic access is lacking or inefficient.

Based on auspicious reports of reactions with aryl(2-thienyl)iodonium salts and non-radioactive nucleophiles [182, 184], this class of precursors is investigated in this work. In detail, they are tested for their suitability and practicability in direct nucleophilic n.c.a. ^{18}F-labelling chemistry of electron rich arenes.

For a systematic approach, a group of precursors for ^{18}F-labelling of the electron rich [^{18}F]fluoroanisoles (*ortho* **[^{18}F]1**, *meta* **[^{18}F]2** and *para* **[^{18}F]3**) was employed. This group includes all structural isomers for investigation of the influence of substitution pattern. Furthermore, the highly electron rich 2-thienyl moiety was expected to direct the product ratio in favour of the [^{18}F]fluoroanisoles (cf. Scheme 3.1).



1-3 (c-f) **[^{18}F]1-3**

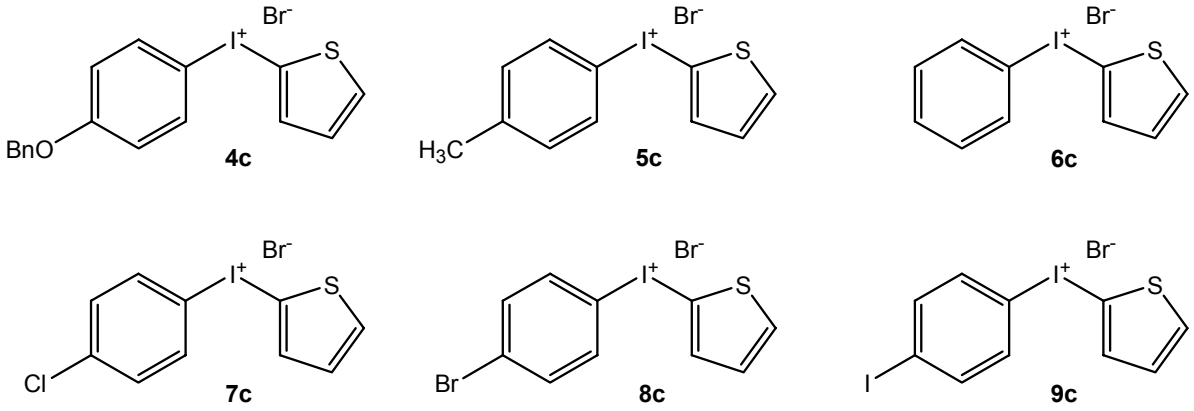
Scheme 3.1: Expected results of the nucleophilic n.c.a. ^{18}F-labelling of methoxyphenyl-(2-thienyl)iodonium salts **1** to **3** (X = Br (**c**), I (**d**), OTs (**e**), OTf (**f**); position of OCH_3: *ortho* **1**, *meta* **2** and *para* **3**)

The molecules investigated in this work are numbered systematically as described in the following, where still numbers indicate the fluoroarenes, added letters define the corresponding iodoarenes as **a**, the (diacetoxyiodo)arenes as **b**, the aryl(2-thienyl)Iodonium bromides as **c**, iodides as **d**, tosylates as **e** and triflates as **f** (cf. Scheme 3.1, Scheme 3.2 and Scheme 3.3).

Each methoxyphenyl(2-thienyl)iodonium salt **1** to **3** is employed as its bromide (**c**), iodide (**d**), tosylate (**e**), and triflate (**f**) in order to cover different counter anion effects. Especially the differences between organic and inorganic ions are here of primary interest.

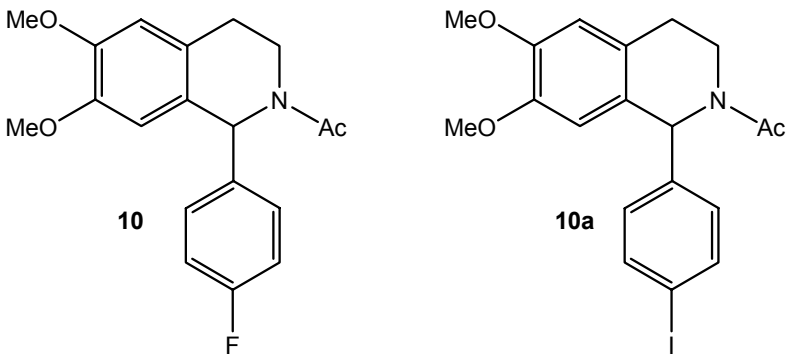
In view of a systematic examination of this method, a second group of *para*-substituted aryl-(2-thienyl)iodonium bromides **4c** to **9c** is used in this work (cf. Scheme 3.2) in order to study the effect of electronic influences. Within this group of molecules, the products show a decreasing tendency of electron density. A main focus for these precursors is on a complete correlation between the electronic character of the intendeds and the ^{18}F-substitution kinetics.

Since the precursor 4-benzyloxyphenyl(2-thienyl)iodonium bromide **4c** represents a benzyl-protected 4-[^{18}F]fluorophenol as ^{18}F-labelling product, a new convenient two-step (^{18}F-labelling and deprotection) radiosynthesis of the versatile synthon n.c.a. 4-[^{18}F]fluorophenol is offered by this method.



Scheme 3.2: *Para*-substituted precursor molecules **4c** to **9c** with different electron density in the homoaryl group (X = Br)

Further, the appropriate iodonium precursors for the preparation of a complex, ^{18}F-labelled radiopharmaceutical are synthesised to show the efficiency of the method. The molecule 2-*N*-acetyl-6,7-dimethoxy-1-(4'-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline [F-ADTQ] **10** (cf. Scheme 3.3) was identified as non-competitive AMPA receptor antagonist, but not yet really pharmacologically evaluated (cf. subchapter 1.7.3). Thus, the radioligand [^{18}F]F-ADTQ **[^{18}F]10** should enable further pharmacological evaluation studies of this AMPA receptor ligand.



Scheme 3.3: Structures of non-competitive AMPA receptor antagonist F-ADTQ (**10**) and potential non-competitive AMPA receptor antagonist I-ADTQ (**10a**)

In addition, the iodine analogue 2-*N*-acetyl-6,7-dimethoxy-1-(4'-iodophenyl)-1,2,3,4-tetrahydroisoquinoline [I-ADTQ] **10a** (cf. Scheme 3.3) has not been pharmacologically evaluated, either. In order to make pharmacological evaluation studies of **10a** possible, **10a** was labelled with radioiodine ([^{131}I]I-ADTQ **[^{131}I]10a**).

Both radioligands formed can be compared and their pharmacological evaluation should give more detailed information of the potence of this category of molecules as non-competitive AMPA receptor ligands. Furthermore, the iodine derivative was not included in the original study, where only the fluorine, chlorine and bromine derivatives were examined. These show good but very diverse results and thus the potence of I-ADTQ as AMPA receptor antagonist is of interest [194].

3.1 Syntheses of precursors

3.1.1 Syntheses of (diacetoxyiodo)arenes and oxidation methods

For the synthesis of diaryliodonium salts various procedures are described in the literature, three of which were shortlisted for this work as shown in Scheme 3.4. All those routes need a preliminarily oxidised iodine(III) species for the formation of the diaryliodonium salt as pointed out before (cf. subchapter 1.6.1). This can be done *in situ* or in an individual oxidation step. Due to the fact that the choice of the suitable method for the diaryliodonium salt synthesis is depended on the desired type and character of the salt, it is more practicable to use an individual oxidation step and the resulting iodine(III) compound can be employed for different further syntheses. According to the various production pathways of diaryliodonium salts, the (diacetoxyiodo)arenes are very stable and versatile iodine(III) reagents.

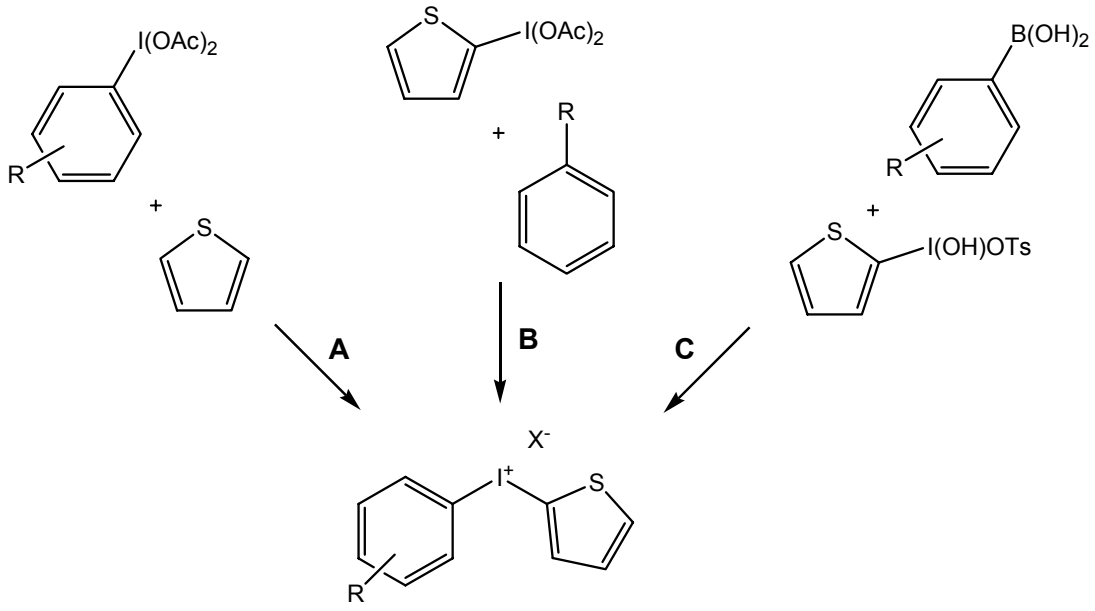
Hence, in the first step all iodoarenes were oxidised to their diacetoxyiodo derivatives. For this procedure the oxidation with sodium perborate [161, 162] and with sodium periodate [163] were tested. The main differences are harsher conditions (reflux in acetic acid/acetic anhydride) and shorter reaction times (~2h) with the periodate oxidation. In case of sodium perborate a much more gentle procedure was used. Here, the reaction was carried out at 40 °C in pure acetic acid, but it took up to 24 hours for completion. However, the major advantage is the purity of the obtained (diacetoxyiodo)arenes; they are formed with very little side-products and less impurities by the milder perborate method. An important fact here is to keep the temperature strictly below 45 °C, because at higher temperatures the oxidation proceeds further to the iodine(V) species (iodylarenes). These are very sensitive substrates and tend to explosive decomposition. The perborate oxidation was suitable for the most iodoarenes employed and gave good yields of 42 - 74 % of the (diacetoxyiodo)arenes in 20 – 24 h. Only two exceptions need a different treatment. First, the 4-benzyloxy-1-iodobenzene **4a**, which could not be oxidised by the perborate

method and where only starting material was recovered, even after extended reaction times of up to 48 h. Therefore in this case, it was necessary to use the periodate system, which led to a yield of 66 % after 2 h, but this implied the above mentioned additional effort of a purification process. Second, the 1,4-diiodobenzene **9a**, which poses the challenge to oxidise only one iodine in order to assure an unaltered iodine-function in the final iodonium precursor. Both oxidation methods described, work with large excesses of oxidant and lead always to *bis*-1,4-(diacetoxyiodo)-benzene as product. The reverse approach via 2-(diacetoxyiodo)thiophene and iodobenzene always led to an isomeric mixture of the *ortho* and *para* derivative (ratio: ~5:95), which are hard to separate by re-crystallisation. Thus, the selective oxidation of only one iodine group was necessary. This became possible by the equimolar use of peracetic acid as oxidant [99]. 4-Iodo-1-(diacetoxyiodo)benzene **9b** was obtained in yields of up to 42 % after ~1 h reflux, but the yields strongly differ. Too fast addition of the peracetic acid as well as too long reaction times can decrease the yield due to probable consecutive oxidation of the second iodine function and/or redox processes between the different iodine species (e.g. via disproportionation). Most of the (diacetoxyiodo)arenes here synthesised are known compounds and were only characterised by comparison of their melting points. However, some melting points disagree to those reported in the literature. In these cases the identity was additionally confirmed by mass spectrometry. Even in the literature diverse melting points with huge differences are found for some (diacetoxyiodo)-arenes. Only 4-benzyloxy-1-(diacetoxyiodo)benzene **4b** was characterised by ^{1}H- and ^{13}C-NMR spectroscopy, mass spectrometry and elemental analysis, due to the fact that **4b** was not described in the literature so far.

3.1.2 Syntheses of aryl(2-thienyl)iodonium salts

As mentioned above (cf. Scheme 3.4), three reaction routes were considered for the preparation of the aryl(2-thienyl)iodonium salts. In the first one, the (diacetoxyiodo)arene and thiophene react in form of a classic electrophilic aromatic substitution in presence of concentrated sulphuric acid as catalyst to the aryl(2-thienyl)iodonium hydrogensulfate, which is subsequently precipitated as the bromide or iodide (path **A** in Scheme 3.4).

Path **B** described the same reaction, but the functional groups of the heteroaromatic and aromatic compound are exchanged, i.e. 2-(diacetoxyiodo)thiophene is coupled with appropriate arenes. The compounds resulting via path **A** and **B** seem to be identical (cf. Scheme 3.4). However, due to the highly activated 2-position of thiophene, path **A** led exclusively to one aryl-(2-thienyl)iodonium salt, while via path **B** generally an isomeric mixture of *ortho*- and *para*-derivatives was obtained.



Scheme 3.4: Examined pathways to aryl(2-thienyl)iodonium salts (X = Br, I, OTs)

As a third route, the regiospecific *ipso*-demetallation of boronic acid derivatives was examined (path **C** in Scheme 3.4). Especially for the electron rich molecules this way caused problems due to impurities and side-products, which are assumed to originate from internal redox processes and other side-reactions of the highly reactive 2-(hydroxy(tosyloxy)iodo)thiophene. Several crystallisation steps had to be performed and diminished the moderate yields. Furthermore, this procedure led only to tosylate counter ions and was not applicable to prepare bromides or iodides. Moreover, the Koser's derivative of 2-iodothiophene is very reactive and has to be handled and stored under inert gas, what makes its application more inconvenient.

Consequently, path **A** proved to be the most suitable method. This route had the advantage to achieve reliable and good yields even with electron rich molecules. The aryl(2-thienyl)iodonium bromides **1c** to **8c** are obtained in yields of 36 – 67 %, while the yield of 4-iodophenyl(2-thienyl)iodonium bromide **9c** of 18 % was an exception. This outlier was the most complicate precursor to be synthesised. The difficulties of the 4-iodo-1-(diacetoxyiodo)benzene **9b** preparation were continued with the preparation of **9c**. A lot of side-products evolved during the synthesis and also starting iodoarene from reductive processes and deiodinated arene was found. As a consequence, several purification and re-crystallisation steps for **9c** were necessary.

All other bromides were obtainable in good yields and with high purity. Generally, one re-crystallisation step from methanol/ether mixtures gave analytically pure samples. The methoxyphenyl-(2-thienyl)iodonium iodides **1d** to **3d** showed similar results. They were obtained in yields of 36 – 60 %. In some cases they needed more re-crystallisation steps and showed a higher sensitivity to light and air.

Due to the disadvantageous effects of path **C** mentioned before, the triflates and tosylates were received from the bromides **1c** to **3c** by an oxidative anion metathesis [167]. The bromide was oxidised by hydrogen peroxide and free molecular bromine was trapped by addition of cyclohexene in excess. The appropriate acids of the organic anions, *para*-toluenesulphonic acid or triflic acid, were added and the corresponding salts precipitated. Only the 4-methoxyphenyl(2-thienyl)iodonium triflate **3f** was hard to crystallise; several work-up methods with extractions by dichloromethane, re-crystallisations and long storing times at -25 °C led at last to pure crystalline samples in 37 % yield. Derivatives **1e** and **2e** are easily obtained in very high yields of 98 % and 81 %, respectively. The triflates are the most sensitive salts and darken quickly in contact with air. The conversion to the tosylates resulted in similar high yields of 76 % for **1e**, 93 % for **2e** and 93 % for **3e**. They were obtained as very pure samples of white crystals. Tosylates are much more stable and can be stored at room temperature in the dark, whereas the triflates have to be stored under inert gas or in an exsiccator at 4 °C. Concerning their application for n.c.a. ^{18}F-labelling reactions, all precursors are stored in an exsiccator at 4 °C. All synthesised aryl(2-thienyl)-iodonium salts were analytically characterised by their ^{1}H- and ^{13}C-NMR spectra, mass spectra and elemental analyses.

3.2 N.c.a. ^{18}F-radiofluorination of arenes via aryl(2-thienyl)iodonium salts

3.2.1 Optimisation of reaction conditions using 2-methoxyphenyl(2-thienyl)-iodonium bromide

In a first attempt an investigation of the general reaction conditions of the n.c.a. ^{18}F-labelling of arenes via aryl(2-thienyl)iodonium salts was carried out. Since **1c** represents an electron rich model compound and it includes an *ortho*-substituent, it was employed for these optimisation studies. In addition, the *ortho*-effect of **1c** was generally expected to lead to higher RCY than reactions with the precursors **2c** or **3c**; thus small influences of general reaction conditions become better visible.

Earlier studies showed that the Kryptofix© 2.2.2/K_2CO_3-System for activation of the n.c.a. [^{18}F]fluoride is suitable for ^{18}F-labelling reactions with diaryliodonium salts. Therefore, it was used to activate the n.c.a. [^{18}F]fluoride as nucleophile after the aqueous [^{18}F]fluoride solution was dried by an azeotropic distillation with acetonitrile. For the ^{18}F-labelling **1c** together with the solvent of choice was given to the dry cryptate complex. During the labelling process a slight overpressure

of 1100 mbar argon was necessary to avoid losses of the volatile product 2-[^{18}F]fluoroanisole **[^{18}F]1**.

It is well-known that the kind of the solvent has a strong influence on nucleophilic aromatic substitution reactions. Generally, S_NAr-reactions call for polar solvents and particularly in n.c.a. ^{18}F-labelling reactions diplor-aprotic solvents are highly demanded. Accordingly, acetonitrile (ACN), dimethylacetamide (DMAA), dimethylformamide (DMF) and dimethyl sulphoxide (DMSO) were used to examine the solvent effect on this reaction (cf. Figure 3.1). The reactions were carried out at 130 °C, only for acetonitrile a lower bath temperature of 90 °C (closed vessel) was chosen to avoid problems with too high pressure due to its low boiling point of 81 - 82 °C.

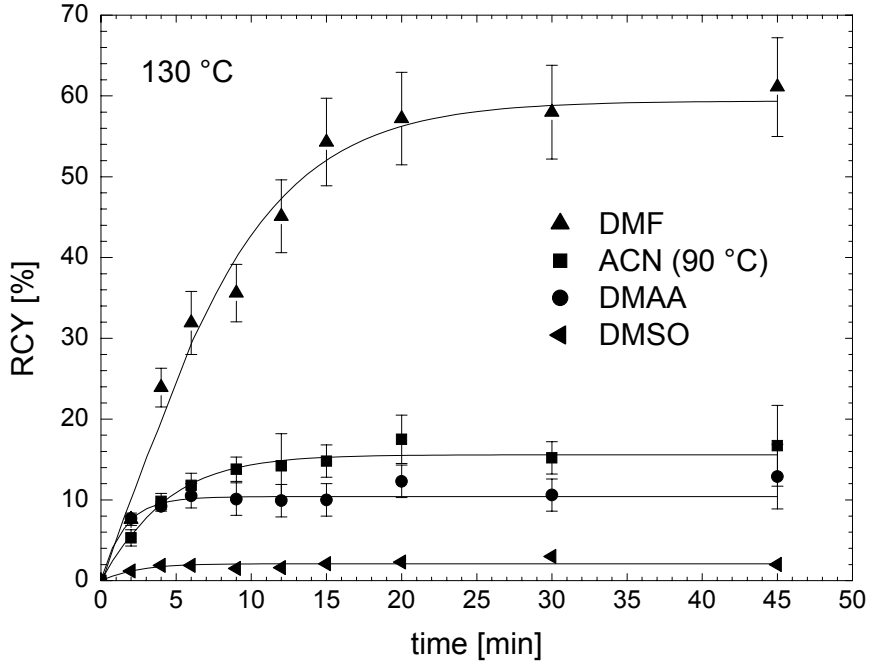


Figure 3.1: Radiochemical yield of n.c.a. 2-[^{18}F]fluoroanisole via 2-methoxyphenyl(2-thienyl)-iodonium bromide as a function of reaction time in different solvents; [37 MBq n.c.a. [^{18}F]fluoride, c(**1c**) = 25 mmol/l, 1 ml solvent, 1100 mbar, 130 °C (90 °C in case of ACN)]

The best results were achieved in DMF, where a RCY of **[^{18}F]1** of up to 60 % could be obtained. ACN and DMAA gave only a low RCY of 10 - 15 %. Although DMSO is one of the most suitable aprotic dipolar solvents and a highly effective medium for nucleophilic ^{18}F-labelling reactions, it did not work for this reaction and led only to a RCY of ~1 – 2 %. This order of dependence on solvents in the nucleophilic ^{18}F-fluorination of **1c** was also found in other studies of n.c.a. ^{18}F-labelling with diaryliodonium salts.

Furthermore, the unfavourable use of DMSO in cases of diaryliodonium salts was also earlier reported in literature [99, 100, 176]. There are two assumable explanations for this outcome. On one hand, the low reduction potential of DMSO presumably causes redox processes between iodine(III) species and DMSO molecules. On the other hand, the S-O binding in DMSO has a semipolar character in favour of a S^+-O^- binding and shows distinct nucleophilicity and a strong solvation of cations [199], what would lower or even prevent their reactivity. Furthermore, there is evidence that DMSO affects diaryliodonium cations in a special way, in which the oriented oxygen atom partially neutralises the positive charge. Such a neutralisation process was also assumed with proton magnetic resonance studies of diphenyliodonium cations in deuterated water [200]. Additionally, Fraenkel *et al.* showed that DMSO neutralises the positive charge in *p*-chloroanilinium chloride by ion-pair formation, so that the chemical shifts of ring protons correspond to those of chlorobenzene [201]. Likely a combination of both processes with a preliminary strong solvation and subsequent redox processes was assumed to explain the inappropriateness of DMSO in ^{18}F-labelling reactions with diaryliodonium salts which is obvious from the time dependence depicted in Figure 3.1.

In the case of DMAA, only a RCY of 10 % was obtained. Due to the $E_T(30)$ based polarity of DMAA of 42.9 kcal/mol (cf. Table 3.1), which is only slightly lower than that of DMF of 43.2 kcal/mol, probably additional effects as discussed for DMSO appear to contribute to the total solvent effect of DMAA. As a result, analogue solvation effects as with DMSO presumably occur, thus the nucleophilic attack is hindered by a partial charge neutralisation and sterically by a strong solvation shell. The low RCY obtained in ACN is mainly due to the low reaction temperature of 90 °C. The course of the time dependence of the radiofluorination in ACN in Figure 3.1 shows the expected slow rate for low temperatures, but even extended reaction times did not increase the RCY and the maximum of ~15 % was reached within 15 – 20 min. However, in literature contradicting reports exist about the utility of ACN in ^{18}F-labelling reactions with diaryliodonium salts. Whereas Shah *et al.* reported high RCY by using ACN at lower temperatures (80 – 100 °C) and long reaction times up to 40 min [155], other studies could not reproduce these results and show similar observations as those of this work [99, 100].

Table 3.1: Polarity of important solvents as derived from measurements of the longest waved UV/Vis/NIR absorption band of the pryridinium *N*-phenolate betaine dye $E_T(30)$ at 25 °C and 1 bar [from 202]

Solvent	benzene	acetone	DMAA	DMF	DMSO	ACN	H_2O
$E_T(30)$-Value [kcal/mol]	34.3	42.2	42.9	43.2	45.1	45.6	63.1
			→				
			increase of polarity				

The E_T (30) scale represents an empirical scale of solvent polarity by means of UV/Vis/near-IR spectroscopic measurements of the negatively solvatochromic pyridinium *N*-phenolate betaine dye $E_T(30)$ [202]. The corresponding values of the solvents employed in this work are listed in Table 3.1 along with some $E_T(30)$ polarities of benzene and water; higher values comply with increasing polarities.

As a further important reaction parameter the concentration of the precursor was optimised in the range from 6 mmol/l to 75 mmol/l (DMF). Whereas in case of 6 mmol/l only 1 to 3 % RCY of **[^{18}F]1** was found, more than 25 mmol/l did not notably improve the RCY. As a result, a concentration of 25 mmol/l was kept as optimal. Further, higher concentrations involved problems in solubility and led to suspensions, which in turn cleared within seconds when adding the mixture to the warm reaction vial.

Raising the concentration of the aminopolyether complex $[K\subset2.2.2]_2CO_3$ to more than 13 mmol/l did not affect the RCY nor the reaction rate. However, less than 13 mmol/l considerably reduced the RCY. Very high concentrations of 26 mmol/l and above surprisingly led to traces of an unidentified radioactive side-product (< 5 %) with higher polarity. Consequently, the use of 13 mmol/l $[K\subset2.2.2]_2CO_3$ as 1 M solution was not changed and is obviously optimal for these ^{18}F-labelling reactions. This is in agreement with earlier studies on n.c.a ^{18}F-labelling using diaryliodonium salt precursors [84, 100].

An increase of the reaction temperature leads generally to higher yields and faster rates in case of S_NAr-reactions. In terms of kinetics this can be confirmed for the nucleophilic n.c.a. ^{18}F-fluorination of **1c**. Hence, the reaction rate of the ^{18}F-introduction becomes faster along with the increase of temperature from 90 to 150 °C (cf. Figure 3.2).

Accordingly, the RCY shows the same trend in the range of 90 to 130 °C. Unexpectedly, at higher temperatures the initial exchange rate is still going faster whereas the maximum RCY descends. This may be a result of the thermal instability of the diaryliodonium salt precursor, so its decomposition competes with the ^{18}F-substitution. Diaryliodonium halides are known to decompose under heating in polar solvents by an internal attack of the counter ion [203, 204]. This cleavage proceeds according the S_NAr-mechanism and leads here to 2-bromoanisole and 2-iodothiophene. Since the decomposition process is caused by the internal nucleophilic attack, it is strongly influenced by the reactivity of the diaryliodonium cation, the solvent used and the nucleophilicity of the counter anion. Hence, it appears necessary to determine the thermal decomposition sensitivity of new diaryliodonium salts individually, especially for complex diaryliodonium salts.

In order to find the optimal range of temperature, where the ^{18}F-introduction proceeds effectively while the decomposition of the precursor does not become the crucial factor yet, the RCY of **[^{18}F]1** was plotted against the temperature as shown in Figure 3.3.

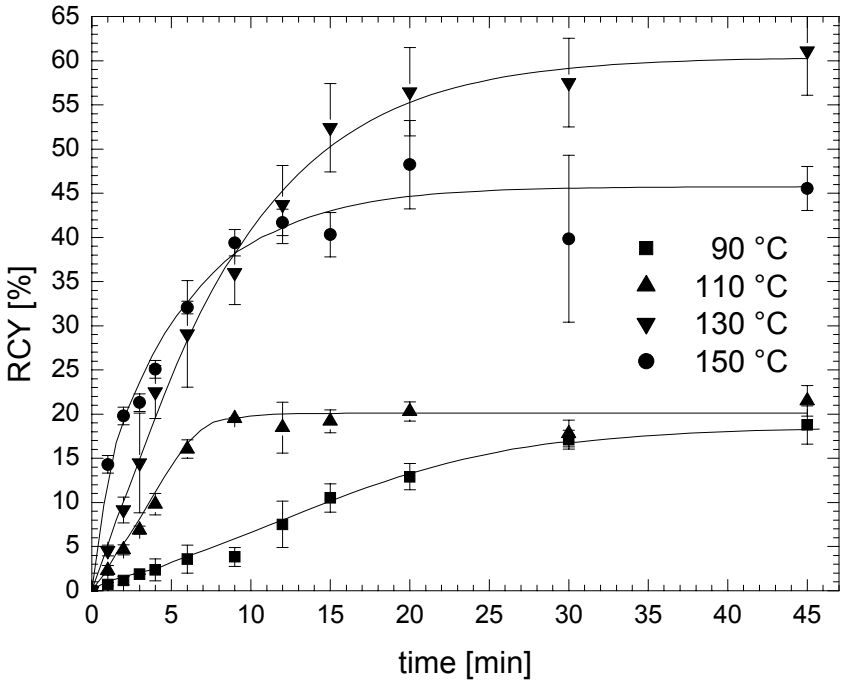


Figure 3.2: RCY of **[^{18}F]1** via **1c** as a function of temperature and time
[37 MBq n.c.a. [^{18}F]fluoride, c(**1c**) = 25 mmol/l, 1 ml DMF, 1100 mbar argon]

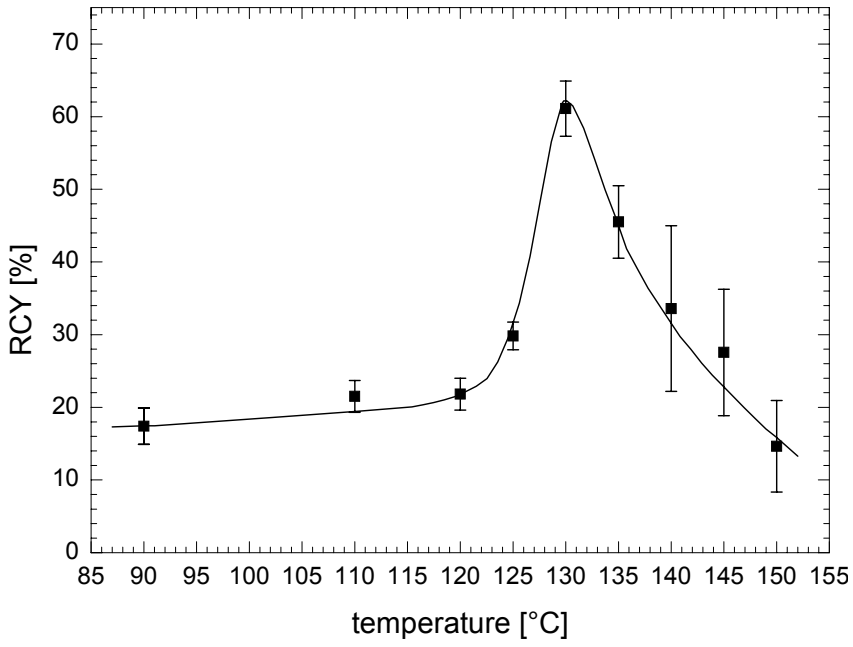
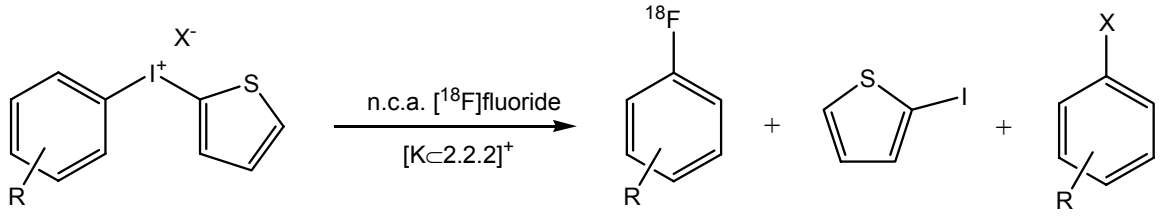


Figure 3.3: Temperature dependence of the nucleophilic ^{18}F-substitution on **1c**
[c(**1c**) = 25 mmol/l, 1 ml DMF, 30 min reaction time, 1100 mbar argon]

The function confirms the distinct dependence of the RCY on the temperature. Until 120 °C the RCY rises slightly and than rapidly from 120 to 130 °C. At temperatures higher than about 130 °C the reaction shows a strong decrease in RCY. As a consequence, the highest RCY of **[^{18}F]1** can be obtained in a narrow range of 130 ± 3 °C and 130 °C was selected as the most suitable reaction temperature. The same range of temperature was found as optimal for the radio-fluorination via **1d**. Despite of the different nucleophilicity of iodide and bromide, the temperature range is not significantly influenced by this change; presumably the reactivity of the diaryliodonium cation is here a more crucial factor.

In all reactions described so far, the ^{18}F-labelling with **1c** led to n.c.a. **[^{18}F]1** as an electron rich ^{18}F-labelled product with regiospecific purity without any radioactive side-products (cf. Scheme 3.5). Since **1** represents the highest electron density in the arene moiety of the group of precursors examined in this study, the strong electronic influence of the 2-thienyl group is expected to induce regiospecificity for all n.c.a. ^{18}F-labelling reactions using aryl(2-thienyl)-iodonium salts investigated. According to this expectation, in fact in all ^{18}F-labelling reactions the 2-thienyl group led always to the desired regiospecific ^{18}F-introduction into the aromatic ring as graphically depicted in Scheme 3.5. Only non-radioactive side-products were detected, thus the 2-iodothiophene as well as in case of the bromide and iodide precursors the appropriate bromo- and iodoarenes were found. The latter confirm the internal decomposition mechanism as discussed before. Tosylates and triflates led only to 2-iodothiophene as major non-radioactive side-product, probably their decomposition processes has more radical character rather than a nucleophilic one. The radical decomposition process becomes very likely, since diaryliodonium salts are known as photopolymerisation initiators in radical reactions [141, 142].



Scheme 3.5: Regiospecific ^{18}F-labelling reactions on aryl(2-thienyl)iodonium salts **1a** to **9f** results to the desired compounds **[^{18}F]1** to **[^{18}F]9** and to 2-iodothiophene and X-substituted arenes as non-radioactive side-product
(R = 2-OCH_3 (**1**), 3-OCH_3 (**2**), 4-OCH_3 (**3**), 4-OBn (**4**), 4-CH_3 (**5**), H (**6**), 4-Cl (**7**), 4-Br (**8**), 4-I (**9**))

The analysis of the specific activity was carried out exemplarily with **[^{18}F]4** via HPLC. No UV-signal corresponding to **4** was detected, thus only a lower limit of the specific activity of $\geq$ 58 TBq/mmol could be determined. This confirmed that the ^{18}F-labelling reactions proceeded under n.c.a. conditions.

3.2.2 Influence of counter anions of iodonium precursors

Different counter anions of diaryliodonium salts are known to effect strongly the reaction of the latter with nucleophiles. Earlier studies show slightly differing results and characteristics for the influence of counter ions on the RCY of ^{18}F-labelling via iodonium salts [100, 175], but the highest RCY were found by using an inorganic counter ion and preferably with bromide. An advantage of an inorganic counter ions is the effective ion pair separation of diaryliodonium salts in polar solvents [204, 205]; although there are also indications for partially dimeric and trimeric structures of the iodonium salt with inorganic counter ions, even in polar solvents [206, 207]. However, these species are more relevant for non-polar solvents, wherein iodonium salts can also be present as quadrupole complexes [203, 208].

On one side, the nucleophilic attack of [^{18}F]fluoride is favoured by a dissociated diaryliodonium salt and hence a “naked” diaryliodonium cation. On the other side, ions with a high nucleophilicity compete with [^{18}F]fluoride for the substitution reaction and induce the decomposition of the precursor. Considering their low nucleophilicity, organic counter ions can be ruled out for this aspect. Otherwise their bond to iodine has a more covalent character and they form not well separated ion pairs. Thus they cause a steric and electronic hindrance of the direct nucleophilic attack of [^{18}F]fluoride. This entails a two step synthesis of the ^{18}F-fluorination in which the [^{18}F]fluoride at first has to replace the organic counter anion and to form an ion pair including a reactive diaryliodonium cation, which is then attacked by the [^{18}F]fluoride [206, 207].

The effects of different counter ions were therefore examined with the bromides, iodides, tosylates and triflates of methoxyphenyl(2-thienyl)iodonium precursors in DMF at 130 °C on the yield of [^{18}F]fluoroanisoles **[^{18}F]1** to **[^{18}F]3**. The following dependence on the type of counter anion in the order of increasing RCY was obtained: tosylates < iodides < triflates < bromides. For n.c.a. ^{18}F-labelling reactions with **1c** to **1f** the RCY of **[^{18}F]1** is exemplarily graphically depicted in Figure 3.4 as a function of the counter anion and the reaction time. The radiofluorinations with the salts of the *meta*- and *para*-derivative show the same dependence on the type of counter anions as the *ortho*-substances. However, the obtained RCY were generally lower than those of the *ortho*-derivatives and the differences for each anion were much better noticeable for the latter. The bromides prove the assumptions and reports mentioned before for inorganic counter anions just as the tosylates do for the organic counter anions. Only the triflates stand out and

show a slightly higher RCY than iodides, that may be caused by their very high reactivity as leaving group [209, 210, 211]. Nevertheless, this sequence is in agreement with previous studies of nucleophilic ^{18}F-fluorination of arenes via dihomoaryliodonium salt precursors [175].

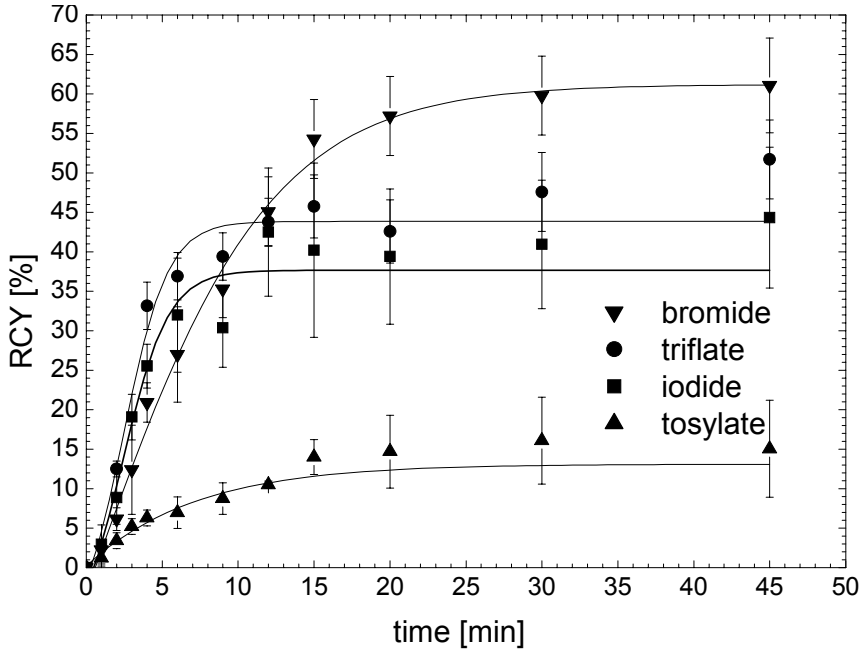


Figure 3.4: Dependence of radiochemical yield of the nucleophilic ^{18}F-substitution on 2-methoxyphenyl(2-thienyl)Iodonium bromide on the type of counter anion [c (**1c**) = 25 mmol/l, 130 °C, 1 ml DMF, 1100 mbar argon)]

In terms of kinetics the triflates and iodides give the highest initial reaction rates and from this point of view a different series of increasing rates can be listed: tosylates < bromides < iodides < triflates (cf. Figure 3.4). The tosylates show the lowest rates as well as the lowest yields, this may be attributed to the above mentioned fact that their electronic deactivation by a rather covalent bond combines with a major steric demand. However, the triflates give the fastest rate, which correlates with their high reactivity as leaving group. The iodides show a slightly higher rate than the bromides, although bromides are the better leaving group considering highest RCY obtainable [212, 213].

The strong influence of the character of counter anions argues for incomplete dissociated diaryliodonium salts, even with iodides and bromides.

Evidence for the grade of dissociation of diaryliodonium salts in different solvents can be received from investigations of the nuclear magnetic resonance (NMR) spectra of these solutions. Particularly the proton shifts of the arylrests are of interest. In case of fully dissociated

iodonium salts the proton shifts of the cations would be identical, regardless of the nature of the anion. This was confirmed by studies of various diphenyliodonium salts varying in counter anions, which show all the same proton shifts in protic, polar solvents such as methanol and deuterated water, whereas the signals in dipolar aprotic dichloromethane and DMSO differ. The grade of dissociation was also confirmed by cryoscopic, conductance and osmometric measurements [200, 205, 214]. Consequently, the NMR spectra of **1c** to **1f** were measured in d_6-DMF as DMF proved the best solvent for the ^{18}F-exchange. Although the ^{18}F-fluorination was examined in DMF at 130 °C and a higher grade of dissociation can be expected at higher temperatures, the NMR spectra measured at room temperature should give an indication on the relative degree of dissociation in different solutions.

Table 3.2.: Proton shifts δ [ppm] of the diaryliodonium cations of **1c** to **1f** in d_6-DMF

counter ion	δ [ppm]							
		2-methoxyphenyl-ring				2-thienyl-ring		
	OCH_3	H3	H4	H5	H6	H3	H4	H5
bromide (non-dissociated, 92 %)	4.166	7.437	7.736	7.169	8.432	7.973[(i)]	7.209	7.973[(i)]
bromide (dissociated, 8 %)	4.014	[(ii)]	7.522	6.901	[(ii)]	[(ii)]	[(ii)]	7.939
iodide (non-dissociated, 87 %)	4.104	7.451	7.770	7.198	8.466	8.036[(i)]	7.242	8.036[(i)]
iodide (dissociated, 13 %)	4.016	7.280	7.525	6.903	[(ii)]	7.829	7.039	7.939
tosylate	4.199	7.521	7.820	7.242[(iii)]	8.513	8.142	7.313	8.184
triflate	4.223	7.549	7.846	7.267	8.531	8.172	7.342	8.214

[(i)] Signals are overlaid and show a multiplet [(ii)] Signals are too small or overlaid completely
[(iii)] Signals show a multiplet with tosylates' H2 + H6

As expected, the proton shifts in the NMR spectra of **1c** to **1f**, measured in d_6-DMF at room temperature, diverge (cf. Table 3.2). Clear differences between the proton shifts disprove the presence of fully dissociated iodonium salts. Even between the inorganic **1c**,**d** and organic anions **1e**,**f** deviations are well notable. Especially the spectra of the bromide and the iodide show both proton shifts of non-dissociated salt and proton shifts of free aryl(2-thienyl)iodonium cations. The signals of the latter are identical with signals obtained from spectra in d_6-DMSO (cf. subchapter 4.2.3), where almost identical signals, even with the organic counter anions, were observed and thus can be attributed to originate from dissociated salts. Although the signals of the latter are very small and some are largely overlaid, they are significant for the free cation and

similar with both counter anions, expectedly. The grade of dissociation was determined for **1c** and **1d** by integration of the peak-areas, the results are given in Table 3.2. The tosylate and the triflate present more similarities in their proton shifts, but small differences can be noticed. Their proton spectra show only one set of signals which are in favour of non-dissociated salts **1e** and **1f**. Despite of the concluded partial covalent binding, the differences in proton shifts of **1e** and **1f** are unexpectedly small. It can be assumed that the inductive effects of both counter anions on the proton shifts are nearly the same, due to the fact that the anions are both sulphonic acids and consequently the immediate vicinity of the iodine(III) in **1e** and **1f** is similar.

Both, the variation in the proton shifts and the outcome of the nucleophilic ^{18}F-fluorination reactions are in favour of non-fully dissociated aryl(2-thienyl)iodonium salts. In case of the iodide and the bromide, a disagreement between maximum obtainable RCY and initial reaction rates occurs. Presumably, this is an effect of the mentioned thermal instability and the tendency of the precursors to decompose, which depends on the nucleophilicity of the counter anion. As a result, the iodide is more reactive to both, the ^{18}F-introduction and the decomposition, which causes a faster loss of reactive precursor and leads to lower RCY. This is also confirmed by a slightly higher grade of dissociation of the iodide. The proton spectra of **1e** and **1f** as well as the strong influence of the organic counter anions on the ^{18}F-radiofluorination reaction confirm the partial covalent binding expected for organic anions. However, both, **1e** and **1f** differ in RCY and initial reaction rates, thus it appears that the iodine-triflate binding is more polar and causes a faster release of the triflate than it can be assumed for the tosylate which favours for a highly covalent character of the binding to the iodine.

3.2.3 Influence of the substitution pattern of iodonium precursors

In general, the influence of the substitution pattern in S_NAr-reactions is well predictable for common arenes. By making a rough estimate the reactivity of the *ortho*- and *para*-position is approximately comparable and differs from that of the *meta*-position. This dependence from the position of the substituent is explainable by the resonance stabilisation of a negative charge in the transition state, where a *meta*-substituent offers no such resonance stabilisation. While a nucleophile attacks the *ipso*-carbon of an aromatic compound a so-called Meisenheimer complex is formed as transition state which includes a negative charge. Subsequent removing of the leaving group carrying the negative charge forms the product. Whereas the Meisenheimer complex can be stabilised by resonance with electron withdrawing groups in *ortho*- and *para*-position, electron donating group, regardless of their position, can obviously not conjugate with the negative reaction centre and stabilise it.

Considering diaryliodonium salts, the nucleophilic attack on is strongly affected by the substitution pattern. Especially a huge difference between *ortho*- and *para*- and *meta*-substituted rings, is not explainable by the regular character of the S_NAr-mechanism as described above and is due to the influence of the *ortho*-effect mentioned before (cf. Figure 1.2).

The precursors **1c** to **3c** were labelled under the optimised conditions, viz 130°C, 25 mmol/l precursor in DMF and 1100 mbar argon. In Figure 3.5 the RCY of **[^{18}F]1** to **[^{18}F]3** are plotted as functions of the position of the methoxy group and reaction time. The results correspond to the expectations and indeed a strong *ortho*-effect was observed. The *para*-derivative showed a moderate RCY of 25 to 30 % and the *meta*-derivative only reached a RCY of ~20 %. The *ortho*-derivative gave a twofold higher RCY of ~60 % than the *para*-derivative after a reaction time of 35 min. Obviously, this results originates from the *ortho*-effect alone.

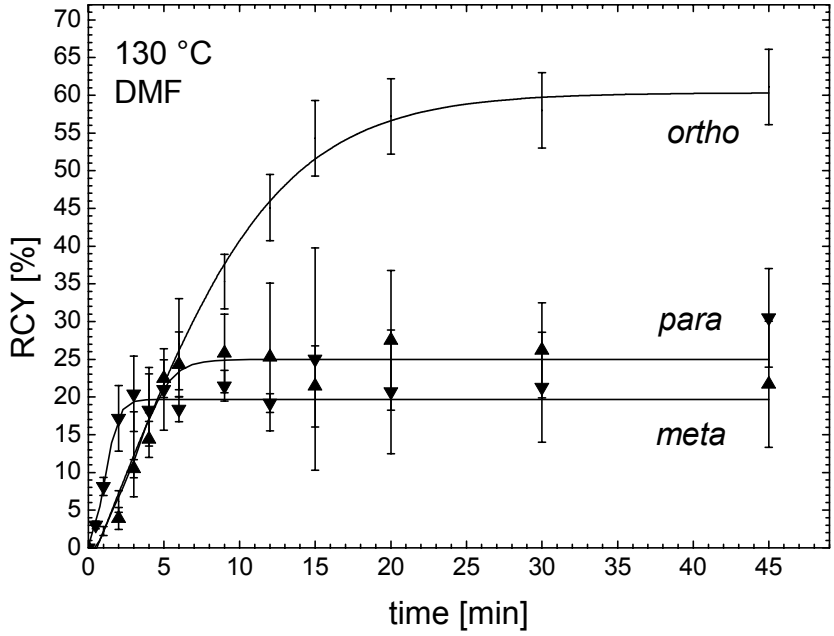
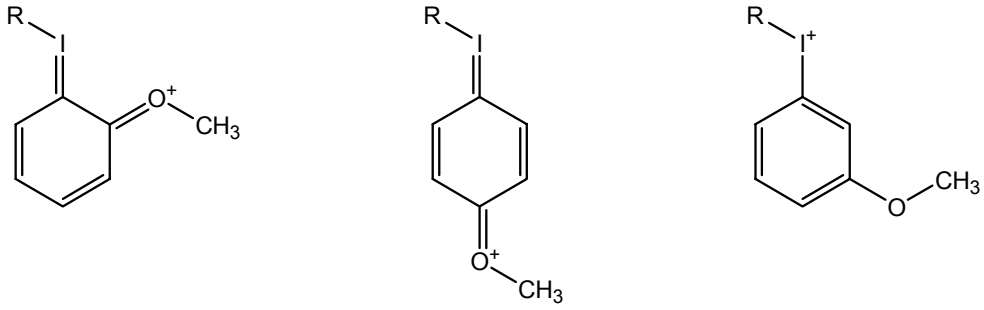


Figure 3.5: Dependence of the radiochemical yield of **[^{18}F]1** to **[^{18}F]3** on the substitution pattern of **1c** to **3c**
[c (**1c-3c**) = 25 mmol/l, 130 °C, 1 ml DMF, 1100 mbar argon)]

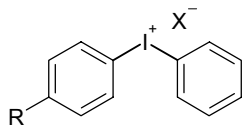
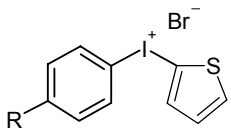
In terms of kinetics, all precursors showed relatively fast reaction rates. The *meta*-derivative shows even a slightly higher initial reaction rate than the *ortho*- and *para*-derivative with identical rates, but ends at lower optimum RCY. Hence, the *meta*-derivative is relatively activated for substitution but also for the decomposition by an *ipso*-attack of the counter anion, which reduces the amount of the precursor and eventually results in low RCY.

As described above, the methoxy group is not able to stabilise a negative charge in the transition state of the S_NAr-reaction due to its electron-donating character. However, the aryl(2-thienyl)-iodonium cation represents a positive charged initial state and can be stabilised by conjugation with methoxy substituents in *ortho*- and *para*-position, whereas in the *meta*-position of course no such resonance stabilisation can occur (cf. Scheme 3.6). By a resonance stabilisation of the initial state the C-I-bond is strengthened, this reduces the initial rate of both the ^{18}F-introduction and the *ipso*-attack of the counter anion which leads to the decomposition. Therefore **1c** and **3c** show nearly the same reaction rate which is much slower than that of **2c**. No stabilisation of the aryl(2-thienyl)iodonium cation in **2c** leads to faster rates of both reactions, accordingly the radiofluorination proceeds much faster in the same way as the decomposition causes earlier loss of precursor and leads in turn to lower RCY.



Scheme 3.6: Relevant resonance forms of the diaryliodonium cation in dependence of the position of a methoxy group; the *meta*-position offers no resonance stabilisation

Table 3.3.: Comparison of RCY and product ratios of ^{18}F-substitutions of *para*-substituted aryl(phenyl)iodonium salts from literature data with results of this work

						This work
						
	Product ratio					
Ref.	[^{18}F]Fluoro-arene	[^{18}F]Fluoro-benzene	RCY [%]	X	R	RCY [%] [^{18}F]Fluoroarene
[176]	75	25	51	OTf	I	60
[100]	70	30	50	OTf	Br	70
[176]	60	40	51	OTf	Cl	62
[176]	36	64	64	OTf	CH_3	32
[155]	0	100	88	Br	OCH_3	29

In comparison of the here developed method with previously described ^{18}F-substitution methods via diaryliodonium salts, one principal drawback of the latter is that the radiofluorination leads mostly to both ^{18}F-labelled arenes in different product ratios (cf. Table 3.3). This problem can now be avoided by using aryl(2-thienyl)iodonium precursors due to the regiospecificity of the ^{18}F-introduction induced by the 2-thienyl group. Particularly for electron rich molecules this is of major interest. Furthermore, also the electron deficient n.c.a. 4-halo-[^{18}F]fluoroarenes can be prepared in higher RCY by this new method and obviously without any radioactive side-products.

3.2.4 Influence of the homoarene substituent of aryl(2-thienyl)iodonium bromides

As described in the introduction (cf. subchapter 1.6.2), the attack of the n.c.a. [^{18}F]fluoride on diaryliodonium salts depends on the electronic character of the aromatic rings. If differences in electron density are present, the outcome will generally be a product ratio with preference of the fluorination of the more electron deficient group. For a detailed insight in the influence of the electronic character on the nucleophilic ^{18}F-fluorination a comparison of the aryl(2-thienyl)-iodonium bromides was carried out with substituted phenyl rings systematically differing in electron density.

1c to **9c** were labelled under the optimised conditions as elaborated above with the precursor **1c**. The obtained RCY of **[^{18}F]1** to **[^{18}F]9** are listed in Table 3.4. Expectedly, the RCY generally increased with a decrease of the electron density in the designated molecule; the *ortho*-methoxy derivative **1c** being an exception, which reached a RCY of 61 $\pm$ 5 %. This could be explained by a strong *ortho*-effect. Based on increasing RCY the following series of substituent-activation was obtained:

$$4\text{-Br} > \text{H} > 4\text{-Cl} > 2\text{-OCH}_3 > 4\text{-I} > 4\text{-OBn} > 4\text{-CH}_3 > 4\text{-OCH}_3 > 3\text{-OCH}_3$$

Indeed, for all investigated aryl(2-thienyl)iodonium bromides **1c** to **9c** it can be reemphasised that the highly electron rich 2-thienyl group induced a regiospecific ^{18}F-introduction in the homoaryl ring and led only to the desired n.c.a. [^{18}F]fluoroarenes **[^{18}F]1** to **[^{18}F]9** (cf. Scheme 3.5).

The n.c.a. ^{18}F-labelling of arenes via diaryl(2-thienyl)iodonium salts represents reactions proceeding according to pseudo-first order kinetics due to the high excess of precursor. Thus the reaction A + B $\rightarrow$ C can be written as (cf. subchapter 1.4):

$$[C]_t = [B]_0 \left(1 - e^{-k't}\right) \left[\frac{mol}{l}\right]$$

where k' is the rate coefficient of pseudo-first-order type, $[B]_0$ is the decay corrected starting activity of n.c.a. [^{18}F]fluoride and $[C]_t$ the decay corrected activity of the ^{18}F-labelled products **[^{18}F]1** to **[^{18}F]9** after the reaction time t. Here the activities of the substances instead of concentrations are employed, because the radioactivity is proportional to the concentration of the corresponding substance. In order to determine the rate constant *k'* this equation can be converted to:

$$\ln \frac{[B]_0}{[B]_0 - [B]_t} = k' \, t$$

The corresponding plots of this term as a function of time for the molecules **[^{18}F]1** to **[^{18}F]9** are shown in Figure 3.6. By linear regression the rate constant *k'* is obtained from the slopes of least square fits (LSF). The obtained rate constants *k'* are listed in Table 3.4.

In this kinetic approach the differences of electronic substituents' effect on the substitution reaction are better visible. The *k'*-values show a distinct dependence on the electronic character of the substituents. As a result, the following order of decreasing reaction rate *k'* was obtained (cf. Figure 3.6):

4-Br > 4-I > 4-Cl > 3-OCH_3 > H > 4-CH_3 > 2-OCH_3 > 4-OBn > 4-OCH_3

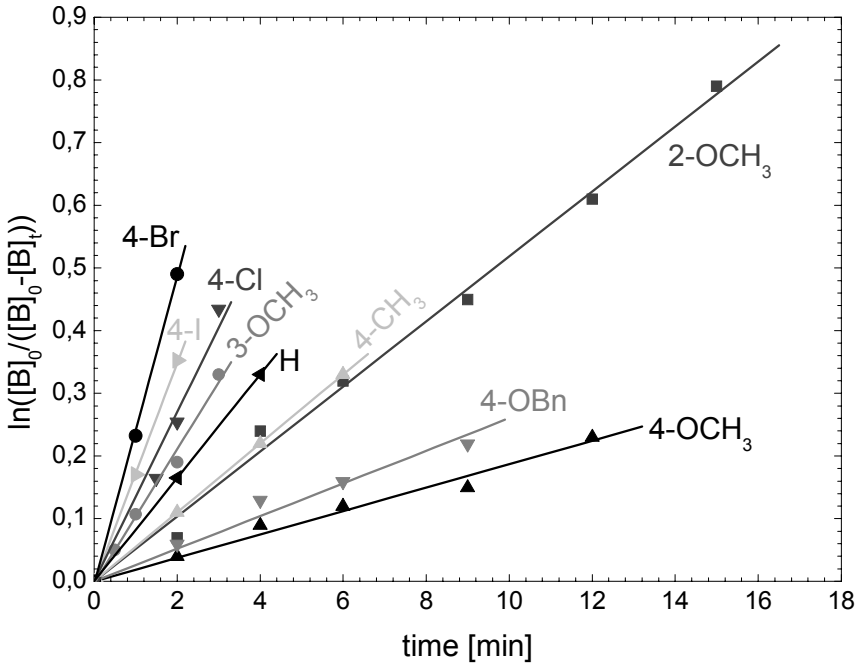


Figure 3.6: Term $\ln([B]_0/([B]_0-[B]_t)$ as function of reaction time for **[^{18}F]1** to **[^{18}F]9** for determination of rate constants *k'* from slopes of linear square fits

This series corresponds to the expectations and mirrors the effects of the substituents on the reaction rate. In case of activated 4-halo derivatives **[^{18}F]7** to **[^{18}F]9** the fastest rates were obtained. Again the high reactivity of the *meta*-derivative **2c** is prevalent, which is presumably entailed by the lack of resonance stabilisation of the aryl(2-thienyl)iodonium cation (cf. Scheme 3.6). As anticipated, the other electron rich radiofluorinated products **[^{18}F]1**, **[^{18}F]3** and **[^{18}F]4** show the slowest rates, where the *ortho*-effect of **1c** causes a faster rate than the ^{18}F-labelling of **3c** and **4c**.

Table 3.4: RCY and *k'*-values (rate constants) for the ^{18}F-radiosyntheses of **[^{18}F]1** to **[^{18}F]9**

R	RCY [%]	*k'* [min^{-1}]
4-Br	70	0.2325 ± 0.045
4-I	60	0.1750 ± 0.020
4-Cl	62	0.1437 ± 0.017
3-OCH_3	20	0.1072 ± 0.006
H	64	0.0865 ± 0.009
4-CH_3	32	0.0625 ± 0.013
2-OCH_3	61	0.0518 ± 0.002
4-OBn	38	0.0305 ± 0.004
4-OCH_3	29	0.0187 ± 0.001

Generally, systematic treatments of quantitative effects on organic reactions are accomplished by analyses of empiric correlations of linear relations between logarithms of rate constants and/or equilibrium constants of the appropriate reactions. Those relations are referred to as linear free energy relationships (LFER), which is reflected by the following equations:

$$\lg K = - \frac{\Delta G^0}{2.303 \cdot RT}$$

$$\lg k = - \frac{\Delta G^{\ddagger}}{2.303 \cdot RT} + \lg \frac{RT}{N_A \cdot h}$$

where K is the reaction equilibrium constant; ΔG^0 is the Gibbs free energy (standard free energy), R is the gas constant (8.31441 J · K^{-1} · mol^{-1}); T is the temperature in Kelvin; *k* is the reaction rate constant; $\Delta G^{\ddagger}$ is the Gibbs activation energy (standard activation energy); N_A is the Avogadro

constant ($6.023 \cdot 10^{23}$ mol^{-1}); and *h* is the Planck constant ($6.626 \cdot 10^{-34}$ J · s). Accordingly, the aforementioned correlations of lg *k* and/or lg K at constant temperatures are in fact relations of Gibbs energies [215].

In 1937, Hammett found empirically a linear relation between the effects of *meta*- and *para*-arylsubstituents on equilibrium constants of a reaction, in which the reaction takes place in a attached side chain of the benzene ring, and the electronic character of the substituents [216]. As a result, the Hammett equation was formulated as:

$$\frac{\lg k_i}{\lg k_0} = \rho\,\sigma$$

here k_i and k_0 are the rate constants for the reaction of the substituted and the unsubstituted (R = H) compound, respectively; σ is the individual substituent constant which depends solely on the nature and position of the substituent R; and ρ is the reaction constant for the given reaction under a given set of conditions. The validity of the Hammett equation is restricted to substituents in *meta*- and *para*-position of the benzene ring, since no steric interactions as occurring in case of *ortho*-substituents were considered. The Hammett equation is one of the best-known LFER and has been one of the most widely used means for the study and interpretation of organic reactions and their mechanisms [83, 217].

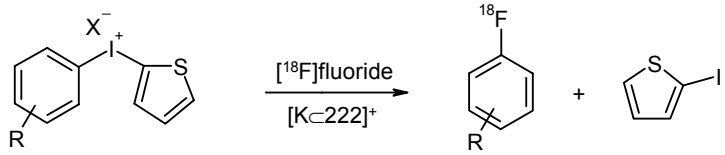
The empirical Hammett correlation is always related to a reference compound which is normally the unsubstituted benzene derivative (R = H). From linear regression of the graphical depiction of lg (k_i/k_0) as a function of Hammett constants σ, ρ results as the slope of the LSF. With $\rho > 0$ stabilisation effects of substituents on a positively charged reaction centre are confirmed; in the same manner $\rho < 0$ proves the stabilisation of a negatively charged reaction centre. The absolute value of ρ indicates the sensitivity (susceptibility) of the reaction to polar substituent effects. Also it gives information about the relative changes of the charge density at the reaction centre during the formation of the transition state. The substituent constants σ represent the total electronic effects, which can be summarised as inductive/field and resonance effects. Deviations from the Hammett equation and its correlation can be found for certain substituents (e.g. *p*-NO_2, *p*-CN, *p*-OCH_3), which are able to conjugate with the reaction centre (charged intermediate state) in a similar way as described in Scheme 3.6. This problem was solved by an extension of the Hammett constants σ with a set of σ^- and σ^+ constants which generally result from reactions of phenols and anilines. σ^- parameters describe the effects of substituents conjugating an electron rich reaction centre (nucleophilic substitution reactions) and σ^+ values derive from substituents which are able to delocalise a positive charge of the reaction centre (electrophilic substitution reactions). The σ^- and σ^+ constants have amplified the applicability of the Hammett equation.

Since σ, σ^- and σ^+ constants are only suitable for *meta*- and *para*-substituents further investigations, also for the *ortho*-position as well as for di-substituted compounds, have been carried out [for overviews see: 83, 215, 217].

In general, for a wide range of substituents the Hammett equation leads to well-fitting linear relations in combination with σ and $\sigma^{+/-}$ constants, respectively. A good linear regression/relation provides important mechanistic information and confirms a consistent reaction mechanism for all investigated substituents. Furthermore, an occasional failure of the Hammett equation and a non-linear function point to a more complex mechanism, which can be examined by that way in greater detail [218].

The pseudo-first order reaction rates k'_i of the syntheses of **[^{18}F]1** to **[^{18}F]9** resulting from the linear regressions in Figure 3.6 were taken and correlated with the Hammett constants σ of the substituents (R) (cf. Table 3.5). The general Hammett constants σ were used from Hansch *et al.* [83] and only for **4c** from Jaffé [217] as listed in Table 3.5. However, both show almost no difference in the σ constants, but Hansch's data are more current and the values are based on more studies and investigations. Subsequently the lg k'/k_0 values were plotted against the Hammett substituent constants (cf. Figure 3.7).

Table 3.5: The lg k_i'/k_0 values of the n.c.a. ^{18}F-fluorination of aryl(2-thienyl)iodonium bromides in dependence on *para*-substituents (R) and their Hammett constants σ and σ_p^-, respectively



R	σ [83]	σ_p^- [83]	lg k_i'/k_0
4-OBn	- 0.415[217]	-	- 0.4527 ± 0.1043
4-OCH_3	- 0.268	- 0.26	- 0.5172 ± 0.0230
4-CH_3	- 0.170	- 0.17	- 0.1411 ± 0.0586
H	0.000	0.00	0.0000 ± 0.0507
3-OCH_3	0.115	-	0.0933 ± 0.0238
4-Cl	0.227	0.19	0.2205 ± 0.0205
4-Br	0.232	0.25	0.4294 ± 0.0440
4-I	0.276	0.27	0.3060 ± 0.0265
2-OCH_3	-	-	0.2224 ± 0.0185

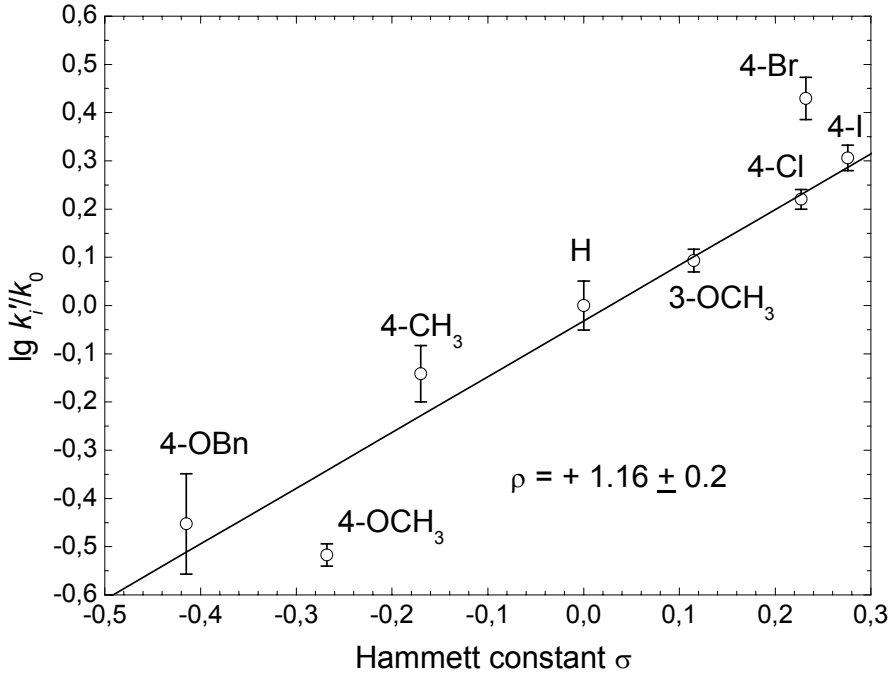


Figure 3.7: Hammett diagram (lg $k_i'/k_0 = \rho \cdot \sigma$) for the n.c.a. ^{18}F-substitution on the aryl-(2-thienyl)iodonium bromides **2c** to **9c**; k_i'- and k_0-values are determined by linear regression (cf. Figure 3.6), σ constants are taken from Hansch *et al.* and Jaffé [83, 217];
[25 mmol/l precursor, 130 °C, DMF, 1100 mbar argon]

The relationship in the Hammett diagram shows a reasonable good linear fit, which leads to the implication of the expected S_NAr-mechanism of the ^{18}F-substitution on aryl(2-thienyl)iodonium salts. The determined slope of $\rho = + 1.16 \pm 0.2$ confirms the nucleophilic mechanism and a consistent mechanism over the range of investigated substituents, even for electron donating groups. Since the reaction parameter of the nucleophilic ^{18}F-substitution on substituted aryl-(2-thienyl)iodonium bromides is $\rho > 1$, the reaction is positively influenced by electron withdrawing groups, which can stabilise the negatively charged transition state. As mentioned above, the absolute value of ρ indicates the sensitivity of the reaction to substituent effects. For example, the reference reaction for the Hammett equation, the hydrolysis of *meta*- and *para*-substituted benzoic acid derivatives has a reaction parameter of $\rho = +1.00$ as consequence of the definition of the Hammett equation. For comparison some ρ-values of various reactions are listed in Table 3.6. The reaction parameter $\rho = + 1.16 \pm 0.2$ implies a mechanism with strong changes in the charge density of the reaction centre. Although the ρ-value is not in the range of the “extreme” reactions, its high reactivity indicates a relatively low sensitivity of the reaction to substituent effects.

Table 3.6: Reaction parameters (ρ) of various reactions in comparison to that of the nucleophilic ^{18}F-substitution on substituted aryl(2-thienyl)iodonium bromides (Ar = aryl)

Reaction	Solvent (T [°C])	ρ	Ref.
$ArX + Hg(CH_3COO)_2$	Acetic acid (25)	- 4.00	[219]
$ArO^- + C_2H_5I$	Ethanol (25)	- 0.99	[220]
$ArCH_2Cl + I^-$	Acetone (20)	+ 0.79	[220]
$ArCOOH + OH^-$	H_2O (25)	+ 1.00	[218]
$Ar(2\text{-thienyl})I^+ + {}^{18}F^-$	DMF (130)	+ 1.16	This work
$ArBr + C_6H_5Li$	Ether (25)	+ 4.00	[218]
$ArF + CH_3O^-$	Methanol (0)	+ 7.55	[218]

Besides the 4-OCH_3 group the 4-Br group give the widest deviations. The former is known for its strong resonance effects which presumably cause this difference, although there is no ability of 4-OCH_3 to conjugate the electron rich intermediate state, only the initial state. Therefore the σ and σ_p^- values of the *para*-methoxy group are identical, whereas its constant $\sigma_p^+ = 0.78$ [83] proves its strong resonance stabilisation of electron deficient reaction centres as electron donating group. The deviation of 4-Br can not be completely clarified. Due to the ability of the *para*-bromine group to stabilise an electron rich reaction centre by resonance, a conjunction effect could be assumed. However, the σ and σ_p^- constants of the *para*-bromine group also show only little differences and point out the moderate resonance effect of the *para*-bromine substituent (cf. Table 3.5). The use of σ_p^- instead of σ values here leads to no significant improvements. In all other cases, the σ and σ_p^- values of the substituents differ hardly. Thus, the employment of σ_p^- instead σ constants gives no better relation and furthermore, σ_p^- data exist only for a few of the examined substituents.

Due to the high activation of the *ipso*-arylcarbon in aryl(2-thienyl)iodonium salts, the nucleophilic radiofluorination shows high reactivity. In spite of this, positional specificity can be observed which is due to the activated *ipso*-arylcarbon where exclusively ^{18}F-substitution takes place. This is also supported by the strong electronic influence of the highly electron rich 2-thienyliodonium leaving group.

3.3 ^{18}F-Labelling of pharmaceutically relevant molecules

3.3.1 N.c.a. 4-[^{18}F]fluorophenol via 4-benzyloxyphenyl(2-thienyl)iodonium bromide

The versatile primary ^{18}F-labelling synthon n.c.a. 4-[^{18}F]fluorophenol has proved its applicability in various radiosyntheses of biological relevant molecules or radiopharmaceuticals and several attempts have been made in the last decade to improve the access to n.c.a. 4-[^{18}F]fluorophenol (cf. subchapter 1.5.1).

With regard to the commonly used complex multi-step radiosynthesis of n.c.a. 4-[^{18}F]fluorophenol via Baeyer-Villiger oxidation using benzophenones as precursors, a more direct and convenient pathway via aryl(2-thienyl)iodonium salts was anticipated in this work; also in order to save losses of radioactivity by shortening preparation times.

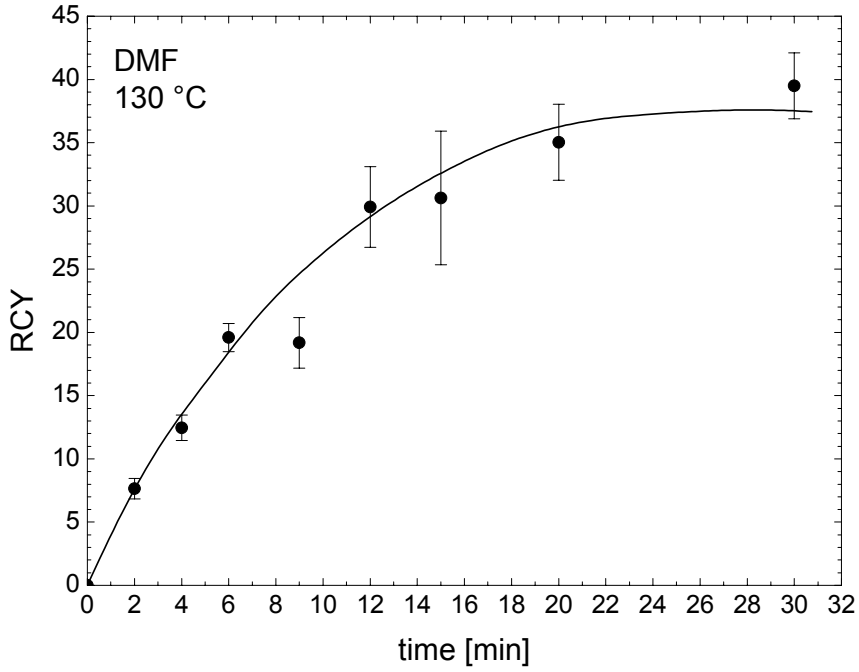


Figure 3.8: Radiochemical yield of n.c.a. 4-benzyloxy-1-[^{18}F]fluorobenzene **[^{18}F]4** as function of reaction time
[c(**4c**) = 25mmol/l, 130 °C, DMF, 1100 mbar argon]

The need of aprotic systems in the n.c.a ^{18}F-labelling step excludes a direct ^{18}F-introduction into an unprotected phenol-substituted iodonium compound. Since the benzyl-protection group offers

an easy and gentle protection procedure via condensation with benzyl bromide and also various ways of deprotection, it is very suitable for this attempt. Thus the 4-benzyloxyphenyl(2-thienyl)-iodonium bromide **4c** was employed as precursor. **4c** was prepared according to the mentioned before general methods for aryl(2-thienyl)iodonium bromides. The precursor was synthesised in good and reliable yields of 55 % by pathway **A** (cf. subchapter 3.1).

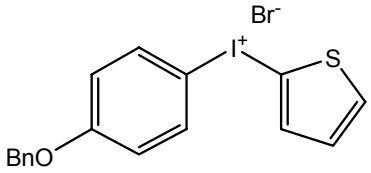
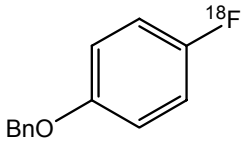
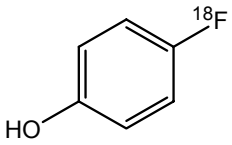
Starting from the dry and activated n.c.a. [^{18}F]fluoride-cryptate complex, **4c** was added to the reaction vial using DMF. The n.c.a. ^{18}F-labelling reaction was carried out under the optimised conditions as described above (c (**4c**) = 25mmol/l, 130 °C, DMF, 1100 mbar argon).

The RCY of the benzyl protected 4-[^{18}F]fluorophenol as function of time is graphically depicted in Figure 3.8. Due to no activating but rather deactivating effects of the *para*-benzyloxy group (σ = 0.415), the reaction rate is expectedly moderate. However, the ^{18}F-labelling reaction led regiospecifically to a good RCY of 38 $\pm$ 4% of n.c.a. **[^{18}F]4** within 20 - 30 min as only radioactive product.

For the preparation of the deprotection procedure, a short purification via Sep-Pak© Plus C18 and ALOX cartridges followed. Consequently, a solvent change to methanol was possible and the system was free of polar substances and particularly free of water which had been added to enable the fixation of **[^{18}F]4** on the reversed phase cartridge and to remove DMF. As eluent methanol is suitable and moreover, also used as solvent in the following deprotection step. For the subsequent displacement of the benzyl-protection group a reductive deprotection via ammonium formate and palladium black as catalyst in methanol was elaborated. First attempts with ammonium formate and palladium on activated charcoal led to the desired n.c.a. 4-[^{18}F]fluorophenol, but showed problems in removing fine particles of the charcoal via a subsequent filtration. In addition, the system with palladium on activated charcoal gave a RCY of the deprotection step of 75 – 80 % within 15 min at 100 °C, whereas the palladium black system yielded in 90 – 95 % RCY of n.c.a. 4-[^{18}F]fluorophenol under the same conditions. By filtration of the reaction suspension via a LiChrolut© glass column containing a PTFE frit, n.c.a. 4-[^{18}F]fluoro-phenol was obtained in an anhydrous methanol system. A flow chart of the radiosynthesis is depicted in Scheme 3.7.

In comparison to the so far best alternative procedure for n.c.a. 4-[^{18}F]fluorophenol preparation from Ludwig et al. [108] the route via **4c** points out two major improvements. First, the radiosynthesis is more convenient, since instead of a 3 + 2 step procedure (3 synthesis steps; 2 purification steps), the developed process via **4c** provides an easier 2 + 1 radiosynthesis. This bears great advantages for automation or remode controlled radiosynthesis. Second, the new route saves 20 min of total synthesis time which is one of the primary concerns in ^{18}F-radio-syntheses. Additionally, the resulting 4-[^{18}F]fluorophenol is obtained in an anhydrous methanol system which allows further radiosynthesis steps including compounds susceptible to moisture without time-consuming drying procedures. However, a weakness is the lower RCY of 35 $\pm$ 1 %

compared to that of 55 % with the benzophenone method which is only partly compensated by the shorter synthesis time. In contrast, the synthesis of the precursor **4c** is easier, faster and finally less expensive than the preparation of (4-(trifluoromethyl)phenyl)benzoyl-4'-*N*,*N*,*N*-trimethylammonium triflate as precursor. In conclusion, the n.c.a. 4-[^{18}F]fluorophenol preparation via 4-benzyloxyphenyl(2-thienyl)iodonium bromide (**4c**) presents an improved radiosynthesis of this primary ^{18}F-labelling synthon, especially in terms of practicability of labelling.

time	**radiosynthesis**		**RCY**
0 min		**4c**	
		[K⊂2.2.2]^{18}F; c(**4c**) = 25mmol/l DMF; 130 °C; 1100 mbar Ar	
20 min		**[^{18}F]4**	34 - 38 %
		cartridge purification eluent: MeOH (2 ml)	
		$HCOONH_4$; Pd (black) MeOH; 100 °C; filtration	
40 min		**4-[^{18}F]fluorophenol**	32 – 36 % (90 – 95 %)[1]

[1] RCY related to deprotection step

Scheme 3.7: Radiosynthesis of n.c.a. 4-[^{18}F]fluorophenol via the *O*-benzyl-protected 4-phenol-(2-thienyl)iodonium precursor **4c**

3.3.2 Radiosynthesis of [^{18}F]F-ADTQ

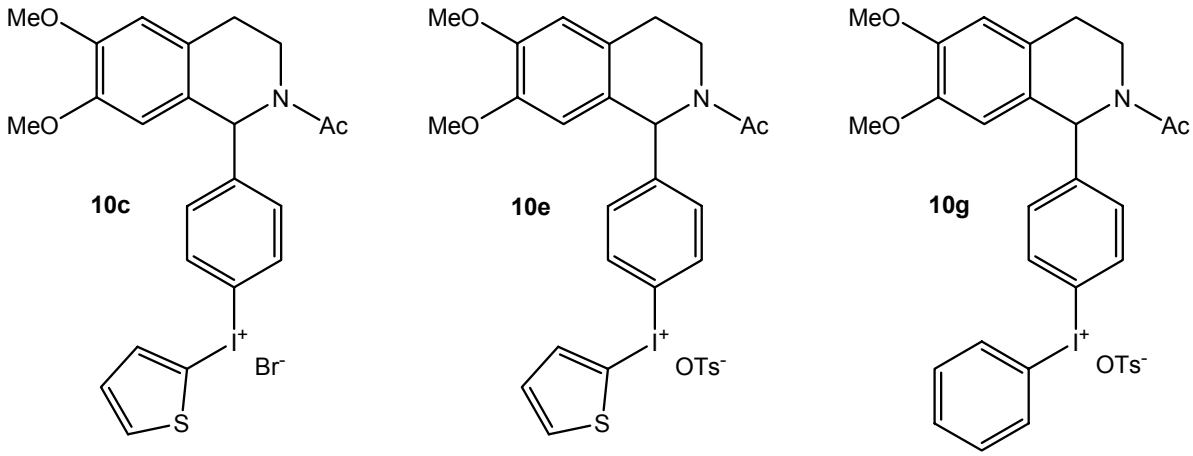
As outlined in the introduction (cf. subchapter 1.7), radioactive labelled AMPA receptor ligands are in great demand for studying this receptor family. Particularly, the labelling with positron- and single-photon-emitting nuclides for PET and SPET is of major interest; primarily in order to allow human studies.

F-ADTQ (**10**) was classified as non-competitive AMPA receptor antagonist, but only the ED_{50}-value (ED = effective dose) of anticonvulsant effects was determined which gives no concrete information about the direct interaction with the AMPA receptor [194] (cf. Scheme 3.3). Thus, pharmacological data and information about the AMPA receptor system would become available by *in vitro* and *in vivo* investigations using **[^{18}F]10**.

The synthesis route for **10** from the literature via a Pictet-Spengler reaction was adopted for preparation of the standard compound and led to an overall yield of 10 % within three synthesis steps. Two intermediate products which were not completely described thus far were isolated, purified and characterised by ^{1}H-, ^{13}C- and ^{19}F-NMR spectroscopy, mass spectrometry and elemental analysis (CHN). Moreover, the iodoanalogue I-ADTQ (**10a**), which is not known from the literature, was also successfully synthesised following the Pictet-Spengler approach and was obtained in an overall yield of 27 % (3 steps). The trimethyltin compound **11** was attained from the iodine compound **10a**, hexamethyldistannane and tetrakis(triphenylphosphine) palladium as catalyst in a standard procedure which led to good yields of **11** of 68 %. **11** was employed for *ipso*-demetallation reactions to **10e** and **10g** as well as for the ^{131}I-labelling to **[^{131}I]10a** as described later.

For the synthesis of an iodonium precursor for the ^{18}F-labelling of **10** first the diacetoxyiodo compound route was tested. The oxidation of **10a** was not successful using the sodium perborate system and even after extended reaction times of 48 h mostly starting material was recovered. Consequently, the sodium periodate system was tested next. This method led in several attempts to elemental iodine formation after 1 to 1.5 h reaction time and under milder conditions or shorter reaction times no oxidation could be observed. When stopping the reaction at the begin of elemental iodine formation (~1.5 h), only 6 % of the desired diacetoxyiodo derivative **10c** was obtained. However, this result was only attained once and could not be repeated. Thus, an alternative one-pot procedure was applied for the precursor synthesis. Probably due to a necessary preliminary *in situ* oxidation step in this method, the one-pot procedure was not successful, either, and only 3 % (36 mg) of the iodonium bromide precursor **10c** could be obtained. In two ^{18}F-labelling experiments (cf. Scheme 3.8) only some unidentified radioactive and non-radioactive side-products were observed and were assumed to be a result of impurities of the precursor which had not been purified due to the small amount of substance. In addition, for the same reason no analytics of **10c** were carried out.

In another attempt, *ipso*-demetallation of **11** was used to get iodonium precursors for the ^{18}F-labelling of **10**. For an *ipso*-demetallations iodine(III) reagent compounds like Koser's reagent ([hydroxy(tosyloxy)iodo]benzene) are needed and the appropriate 2-iodothiophene derivative 2-[hydroxy(tosyloxy)iodo]thiophene was synthesised according to the literature. The oxidation of 2-iodothiophene to 2-(diacetoxyiodo)thiophene gives 55 % yield and the subsequent conversion to 2-[hydroxy(tosyloxy)iodo]thiophene succeeds nearly quantitative with 98 % yield and is very fast within 5 min. This Koser derivative was used for the preparation of **10e** by the *ipso*-demetallation of **11** and gave very high yields of 80 % of **10e** (cf. Scheme 3.8). In the same procedure using [hydroxy(tosyloxy)iodo]benzene good yields of **10g** of 50 % were obtained (cf. Scheme 3.8).



Scheme 3.8: Molecule structure of the iodonium precursors for the ^{18}F-labelling of the non-competitive AMPA receptor antagonist F-ADTQ; yields: 3 % (**10c**), 80 % (**10e**) and 50 % (**10g**)

For the ^{18}F-labelling the appropriate precursor was dissolved in DMF (25 mmol/l) and given to the reaction vial containing the dry and activated n.c.a. [^{18}F]fluoride-cryptate complex. The ^{18}F-labelling reaction was carried out under the optimised conditions of 1100 mbar argon at 130 °C. Aliquots were taken and analysed via radio-TLC and/or radio-HPLC, respectively. The RCY of **[^{18}F]10** is shown in Figure 3.9 as a function of the time and the type of precursor. Due to the above mentioned problems in the synthesis of **10c**, these results are presented as dashed line in grey.

The results from reactions with **10c** show the best RCY of **[^{18}F]10** of about 3.6 %. However, this was anticipated for the bromide precursor with regard to the above discussed results of the ^{18}F-labelling studies on [^{18}F]fluoroarenes via aryl(2-thienyl)iodonium salts. Comparing the precursors **10e** and **10g**, the RCY and reaction rate show an increase from the phenyliodonium

group to the 2-thienyliodonium group, as expected for the electronic differences between these both iodonium leaving groups, thus the 2-thienyliodonium group leads to higher a RCY (**10g**: 1.2 %, **10e**: 2.9 %) and a faster reaction rate. In contrast, in the ^{18}F-labelling reactions with **10g** the formation of [^{18}F]fluorobenzene with high yields of up to 96 % was observed, whereas **10e** regiospecifically only yields **[^{18}F]10**.

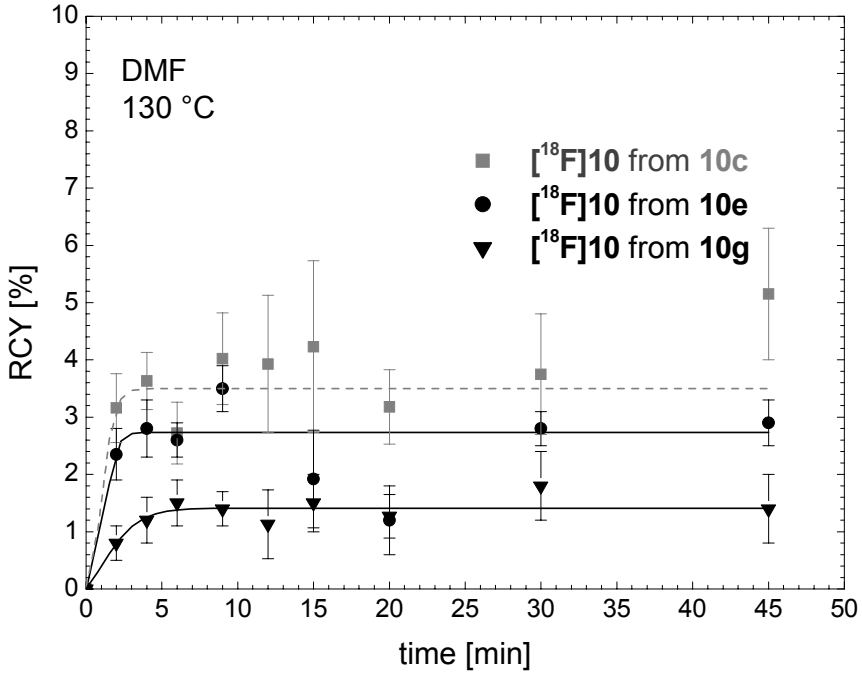


Figure 3.9: Radiochemical yield of **[^{18}F]10** as a function of the reaction time and the type of precursor (cf. Scheme 3.8)
[c(precursor) = 25mmol/l, 130 °C, DMF]

Unfortunately, however, all radiofluorination reactions of the complex molecule **[^{18}F]10** exhibit a very low RCY and therefore the product was not isolated or prepared for pharmacological evaluation studies so far.

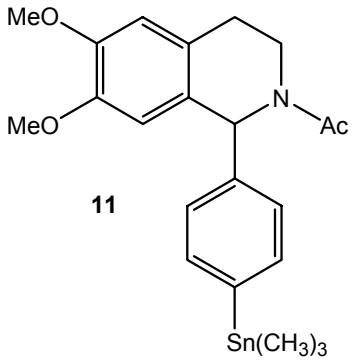
Earlier studies reported about similar effects, where the ^{18}F-labelling via iodonium precursors of complex structures or molecules of larger size gave only very low yields or were completely unsuccessful [181, 185]. It is assumed that the ^{18}F-labelling via iodonium precursors is somehow limited by the molecule size and complexity of the structure. The effect is not clearly understood but appears to be based mainly on steric influences. In addition, the problems in the oxidation procedure of **10a** and the synthesis of **10c** presumably originate from the same reason.

Considering the problems occurred in the synthesis of **10c** and the low RCY of the ^{18}F-labelling reactions, further optimisation studies in order to make one step nucleophilic radiofluorination of complex molecules via iodonium precursor possible, seem to be necessary.

3.3.3 Radiosynthesis of [^{131}I]I-ADTQ

The lead structure of *N*-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (ADTQ) (cf. Scheme 1.18) was identified as non-competitive AMPA receptor antagonist [194]. So far, the iodine derivative I-ADTQ was not examined/prepared, but could also be expected to show activity as non-competitive AMPA receptor antagonist and therefore it was ^{131}I-labelled for a preliminary pharmacological evaluation.

Since the synthesis of I-ADTQ as well as the trimethyltin analogue Sn-ADTQ (**11**) became necessary for the precursor syntheses for the ^{18}F-labelling of F-ADTQ, they offered conveniently the radioiodination of **10a**. The standards and the precursor for the radiosynthesis of **[^{131}I]10a** were synthesised as described in the above paragraph. The structure of the trimethyltin precursor Sn-ADTQ is shown in Scheme 3.9.



11

Scheme 3.9: Structure of the trimethyltin precursor Sn-ADTQ for the preparation of **[^{131}I]10a**

For the ^{131}I-labelling procedure **11** was treated in ethanol with [^{131}I-]iodide and chloramine T as oxidant. After 2 min reaction time at room temperature, a very high RCY of 97 + 2 % of **[^{131}I]10a** was obtained. Hence, no further optimisation for this procedure seemed necessary.

[^{131}I]10a was isolated by radio-HPLC (cf. Figure 3.10) and was employed in pharmacological studies for preliminary evaluation. The radio-HPL chromatogram shows a very good separation of **[^{131}I]10a** and the precursor **11**. Furthermore, no radioactive side-product could be detected and only a few minor unidentified non-radioactive compounds can be observed, which are separated by HPLC.

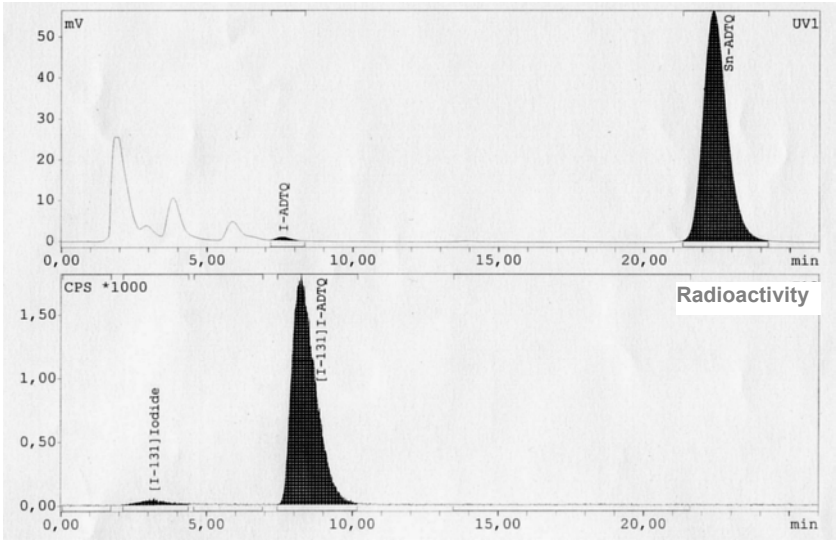


Figure 3.10: Radio-HPL chromatogram after radiosynthesis of **[^{131}I]10a** (Column: Luna 5µ (Phenomenex®), eluent: methanol/water (70/30))

The analysis of specific activity of **[^{131}I]10a** was carried out via HPLC. The applied amount of non-radioactive references is proportional to the integral of the UV-signals obtained by the UV/Vis-detector (cf. Figure 4.2). In the radiosynthesis of **[^{131}I]10a**, with a starting activity of ~7.5 MBq, an average specific activity of **[^{131}I]10a** of 681 GBq/mmol (18.4 Ci/mmol) could be obtained.

3.3.4 Preliminary evaluation studies of [^{131}I]I-ADTQ

The pharmacological evaluation studies were carried out by the Pharmacology Group of the Institute of Nuclear Chemistry (Forschungszentrum Jülich GmbH).

Two studies were elaborated. First an *ex vivo* study was performed to investigate the ability of **[^{131}I]10a** to pass the blood-brain barrier (BBB). For this test, **[^{131}I]10a** was injected into the tail vein of female NMRI mice. After 10 min and 60 min the brains were removed, blotted dry, and measured with a γ-counter for radioactivity. In addition, the brains were cut into slides (horizontal) and measured autoradiographically.

[^{131}I]10a penetrated the blood-brain barrier, accumulating in the whole brain to an extent of 2.1 % ID/g 10 min after injection and wash-out to 0.2 % ID/g after 60 min. The *ex vivo* autoradiography showed uniformly distributed radioactivity, both, 10 min and 60 min after injection.

Second, *in vitro* autoradiography was carried out. Frozen brain section of Wistar rats were employed and preincubated with Tris-HCl buffer. After incubation with **[^{131}I]10a** alone, in combination with non-radioactive **10a**, and in combination with the AMPA receptor antagonist CNQX (cf. Scheme 1.20), the sections were analysed via autoradiography.

Image scanning again revealed a uniform distribution of **[^{131}I]10a** and no influence of the unlabelled substances on the binding, assuming that the uptake of the radioligand represents a remarkable part of non-specific binding. The depletion in the buffer was 13 % (7.5 nM) and 21 % (0.5 nM).

The preliminary pharmacological evaluation studies of **[^{131}I]10a** show evidence for a too high non-specific binding which is often noticed with iodinated compounds (cf. subchapter 1.3). Although the brain uptake is excellent no specific distribution is observed when **[^{131}I]10a** is washed out. Nevertheless, this results point out that the investigated structure is able to pass the BBB and it can be assumed that analogous molecules like F-ADTQ show similar or identical behaviour, however, possibly without such high non-specific binding.

Experimental

4.1 General

All chemicals and solvents were purchased from Aldrich (Germany), Fluka (Switzerland), KMF (Germany), Acros Organics (Belgium), or Merck (Germany). They were reagent grade or better and were used without further purification. Sep-Pak© Plus C18 and ALOX cartridges were obtained from Waters (USA) and LiChrolut© glass columns and appropriate PTFE frits (porosity 10 µm) from Merck (Germany). Column chromatography was performed with Merck silica gel 60 (0.063 – 0.200 mm) and *flash*-chromatography with Fluka silica gel 60 (mesh 220 – 440). The eluent mixtures are given as v:v ratios. Thin-layer chromatography (TLC) was carried out with Macherey-Nagel (Germany) precoated silica gel plates (PolyGram SIL G/UV254, 40 x 80 mm) visualised under an UV-lamp (254 nm). The employed high performance liquid chromatography (HPLC) system consists of a Knauer WellChrom Mini-Star K-500 HPLC pump, a Rheodyne-Injector block 7125 and a Merck/Hitachi UV/Vis photometer L4000. HPLC was performed on a Phenomenex© Luna 5µ C18 column (3 x 250 mm) and various eluent mixtures of methanol/water or acetonitrile/water all given as v:v ratios.

Melting points (mp) were determined on a Mettler FP-61 or a BÜCHI Melting Point B-540 apparatus. They are uncorrected. Analytical gas chromatography was performed with a HP 6890 Series GC System, G1530A gas chromatograph using a cross-linked 5% PHME siloxane HP-5 capillary column (30 m x 0.32 mm) and a flame ionisation detector (FID). Mass spectra (MS) were obtained on a Thermoquest Automass Multi III mass spectrometer. ^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were recorded at 200 or 400, 50 and 188 MHz, respectively, on a Bruker DPX Avance 200 spectrometer (Institut für Nuklearchemie, Forschungszentrum Jülich) or a Varian Inova 400 MHz NMR spectrometer (Zentralabteilung für Chemische Analysen, Forschungszentrum Jülich). For NMR measurements substances were dissolved in $CDCl_3$, d_6-DMSO or d_6-DMF and the measured chemical shifts are specified in δ ppm related to the tetramethylsilane (TMS) standard using the signals of the solvents as references. CHN-elemental analyses (EA, microanalyses) were performed on a Leco CHNS-932 CHNS analyser (ZCH, Forschungszentrum Jülich). The samples were burned at a temperature of 1000 °C in flowing oxygen for the analysis. C and H were measured by selective IR absorption of their combustion gases CO_2 and H_2O. The combustion gas NO_x of N was converted to N_2 by reduction which was determined by thermal conductivity detection.

4.2 Syntheses of standards and precursors of n.c.a. [^{18}F]fluoroarenes

In the majority of cases the syntheses described below were carried out as modified versions of corresponding original literature. In few cases the syntheses were taken directly from literature without any changes and in some cases completely new syntheses were elaborated.

4.2.1 Syntheses of fluoro- and iodoarenes

Most of the fluoro- and iodoarenes employed are commercially available compounds and were purchased by the above mentioned companies. Only the following compounds had to be synthesised:

*4-Benzyloxy-1-fluorobenzene (**4**)*

Benzyl bromide (15 mmol), 4-fluorophenol (10 mmol) and potassium carbonate (15 mmol) were suspended in 50 ml acetone. The reaction mixture was heated to reflux until no 4-fluorophenol was left as checked by TLC or GC control. The solvent was removed by distillation and the residue was taken up in 50 ml water and the aqueous solution extracted with ether. The ether layer was dried over sodium sulfate and reduced to the crude product. *Flash*-chromatography on silica gel using pure petrol ether gave the purified 1-benzyloxy-4-fluorobenzene (R_f = 0.26).

Yield: 1.0 g (33 %).

Melting point: 55.5 °C.

^{1}H-NMR ($DMSO_{d6}$): δ = 5.00 (s, 2H, CH_2), 6.94 (m, 2H, H3 + H5), 7.05 (m, 2H, H2 + H6), 7.28 (m, 1H, H11), 7.32 (m, 2H, H10 + H12), 7.38 (m, 5H, H9 + H13).

^{13}C-NMR ($DMSO_{d6}$): δ = 70.08 (CH_2), 116.2 (2C, CH, C2 + C6), 116.5 (2C, CH, C3 + C5), 128.1 (2C, CH, C9 + C13), 128.3 (CH, C11), 128.8 (2C, CH, C10 + C12), 137.3 (C, C8), 155.0 (C, C1), 158.2 (C, C4).

^{19}F-NMR ($DMSO_{d6}$): δ = -124.12 (CF).

MS: m/e 202 [M^+, 100].

EA: $C_{13}H_{11}FO$, calculated: C 77.2, H 5.48; found: C 77.4, H 5.61.

*4-Benzyloxy-1-iodobenzene (**4a**)*

Benzyl bromide (15 mmol), 4-iodophenol (10 mmol) and potassium carbonate (15 mmol) were suspended in 50 ml acetone. The reaction mixture was heated to reflux until no 4-iodophenol was left as checked by TLC or GC control. The solvent was removed and the residue was taken up in

50 ml water and this solution was extracted with ether. The ether layer was dried over sodium sulfate and reduced to the crude product. Column chromatography on silica gel using *n*-hexane/ether (9:1) gave the purified 1-benzyloxy-4-iodobenzene (R_f = 0.67).

Yield: 2.05 g (66 %).

Melting point: 68.1 °C.

^{1}H-NMR ($CDCl_3$): δ = 5.08 (s, 2H, CH_2), 6.82 (m, 2H, H3 + H5), 7.46 (m, 5H, H9 – H13), 7.62 (m, 2H, H2 + H6).

^{13}C-NMR ($CDCl_3$): δ = 70.50 (CH_2), 83.57 (C, C1), 117.8 (2C, CH, C3 + C5), 127.9 (2C, CH, C9 + C13), 128.6 (CH, C11), 129.1 (2C, CH, C10 + C12), 136.9 (C, C8), 138.7 (2C, CH, C2 + C6), 159.1 (C, C4).

MS: m/e 312 [M^+, 100].

EA: $C_{13}H_{11}IO$, calculated: C 50.4, H 3.58; found: C 50.7, H 3.57.

4.2.2 Syntheses of (diacetoxyiodo)arenes

(Diacetoxyiodo)benzene **6b** was purchased from Aldrich (Germany). The compounds **1b to 3b**, **5b**, **7b** and **8b** were all synthesised according a general procedure as described below. All these (diacetoxyiodo)arenes are known from the literature and were only identified by their melting points. Some melting points differ strongly from the literature data, in those cases the identity was confirmed by mass spectrometry. The general procedure was not suitable for **4b** and **9b**, which consequently were prepared by different methods as explained.

*General procedure for the synthesis of **1 to 3b** and **5-8b** [following 161]*

The appropriate iodoarene (10 mmol) was dissolved in 90 ml of acetic acid and warmed up to 40 °C. Over a period of 20 min sodium perborate tetrahydrate (110 mmol) was added in several portions. The mixture was stirred at 40 °C until no starting material was left or stopped after 24 h. Half of the solvent was distilled off under reduced pressure and 100 ml water were added. After 1 to 2 h of cooling in the refrigerator, the precipitates were collected, washed with water and dried at the air in the dark.

*2-(Diacetoxyiodo)anisole (**1b**)*

Yield: 2.0 g (57 %).

Melting point: 171-173 °C (mp (Lit.) 147-149 °C [163]).

MS: m/e 293 [100]

*3-(Diacetoxyiodo)anisole (**2b**)*

Yield: 2.6 g (74 %).

Melting point: 177-178 °C (mp (Lit.) 133-135 °C [163]).

MS: m/e 293 [100]

*4-(Diacetoxyiodo)anisole (**3b**)*

Yield: 2.2 g (62 %).

Melting point: 85-87 °C (mp (Lit.) 88-90 °C [163]).

*4-(Diacetoxyiodo)toluene (**5b**)*

Yield 1.5 g (45 %).

Melting point: 106-108 °C (mp (Lit.) 108-110 °C [163]).

*4-Chloro-1-(diacetoxyiodo)benzene (**7b**)*

Yield: 2.3 g (63 %).

Melting point: 175°C (mp (Lit.) 114-116 °C [163]).

MS: m/e 297 [100]

*4-Bromo-1-(diacetoxyiodo)benzene (**8b**)*

Yield: 1.8 g (45 %).

Melting point: 180-185 °C (mp (Lit.) 120-122 °C [163]).

MS: m/e 341 [100]

*Synthesis of 4-iodo-1-(diacetoxyiodo)benzene (**9b**) [from 99]*

1,4-Diiodobezene (10 mmol) was suspended in 19 ml peracetic acid (40 % in water) under stirring. The mixture was carefully warmed up to 40 °C and subsequently heated until reflux. During 1 h at reflux a yellow precipitate was formed. After cooling the precipitate was filtered and washed with acetic acid. The product was re-crystallised from acetic acid/acetic anhydride (4:1).

Yield 1.9 g (42 %).

Melting point: 175 °C (mp (Lit.) 170-172 °C).

*Synthesis of 4-benzyloxy-1-(diacetoxyiodo)benzene (**4b**) [following 163]*

Sodium periodate (13 mmol) and sodium acetate (26 mmol) were suspended in 20 ml of a mixture of acetic acid/acetic anhydride (9:1). 4-Benzyloxy-1-iodobenzene (10 mmol) was added

and the mixture was heated at reflux for 4 h. After cooling down to room temperature the mixture was poured into 60 ml of ice-water. The product was extracted with dichloromethane. The organic layers were collected and dried over Mg_2SO_4. The solvent was removed under reduced pressure and the oily residue treated with ether for crystallisation. The product was re-crystallised from ethyl acetate/acetic anhydride (9:1).

Yield: 2.83 g (66 %).

Melting point: 113 °C.

^{1}H-NMR ($CDCl_3$): δ = 2.03 (s, 6H, CH_3), 5.15 (s, 2H, CH_2), 7.07 (d, 2H, H2 + H6), 7.39 – 7.47 (m, 5H, CH_{Ph}, H9 – H13), 8.03 (d, 2H, H3 + H5).

^{13}C-NMR ($CDCl_3$): δ = 20.8 (2C, CH_3), 70.8 (CH_2), 112.3 (C, C1), 117.9 (2C, CH, C3 + C5), 127.9 (2C, CH, C9 + C13), 128.9 (CH, C11), 129.2 (2C, CH, C10 + C12), 136.2 (C, C8), 137.6 (2C, CH, C2 + C6), 161.8 (C, C4), 176.8 (2C, CO).

MS: m/e 369 [M^+, 100].

$C_{17}H_{17}IO_5$ calculated: C 47.7, H 4.00; found: C 45.6, H 3.71.

4.2.3 Syntheses of aryl(2-thienyl)iodonium bromides and iodides

The corresponding (diacetoxyiodo)arene (2 mmol) and thiophene (6 mmol) were stirred in 10 ml acetic anhydride at –30 °C. Concentrated sulphuric acid (0.5 ml) was added dropwise over 1 h. The mixture was allowed to warm up to 5 °C and was further stirred at this temperature for 3 to 5 h. The dark solution was poured into 15 ml ice-water. The organic compounds were extracted with ether and discarded. The aqueous layers were treated with activated coal for 10 min at 40 °C to become a clear solution. To the filtered, clear solution 10 ml of a potassium bromide or a potassium iodide solution (25 %), respectively, was added. After 1h storage in the refrigerator, precipitates were collected, washed with a small portion of acetone and ether. The product was dried and stored in an exsiccator. The freshly produced precursors could be used for the n.c.a. ^{18}F-labelling without any further purification. For eventual re-crystallisation the compounds were dissolved in hot methanol and precipitated with ether.

*2-Methoxyphenyl(2-thienyl)iodonium bromide (**1c**)*

Yield: 0.31 g (39 %).

Melting point: 174 °C.

^{1}H-NMR ($DMSO_{d6}$): δ = 3.91 (s, 3H, OCH_3), 6.99 (t, 1H, $H5_{Ar}$), 7.03 (t, 1H, $H4_{Th}$), 7.23 (d, 1H, $H3_{Ar}$), 7.55 (t, 1H, $H4_{Ar}$), 7.78 (d, 1H, $H5_{Th}$), 7.80 (d, 1H, $H3_{Th}$), 8.21 (d, 1H, $H6_{Ar}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 57.3 (CH_3, OCH_3), 104.9 (C, $C2_{Th}$), 112.3 (C, $C1_{Ar}$), 113.2 (CH, $C3_{Ar}$), 123.6 (CH, $C5_{Ar}$), 129.4 (CH, $C4_{Th}$), 134.8 (CH, $C4_{Ar}$), 136.0 (CH, $C3_{Th}$), 137.2 (CH, $C6_{Ar}$), 139.1 (CH, $C5_{Th}$), 156.1 (C, $C2_{Ar}$).

MS: m/e 317 [M^+, 100].

EA: $C_{11}H_{10}BrIOS$, calculated: C 33.3, H 2.54; found: C 32.9, H 2.46.

*2-Methoxyphenyl(2-thienyl)iodonium iodide (**1d**)*

Yield: 0.51 g (58 %).

Melting point: 183 °C.

^{1}H-NMR ($DMSO_{d6}$): δ = 3.93 (s, 3H, OCH_3), 7.01 (t, 1H, $H5_{Ar}$), 7.06 (t, 1H, $H4_{Th}$), 7.25 (d, 1H, $H3_{Ar}$), 7.58 (t, 1H, $H4_{Ar}$), 7.84 (d, 1H, $H3_{Th}$), 7.84 (d, 1H, $H5_{Th}$), 8.24 (d, 1H, $H6_{Ar}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 57.4 (CH_3, OCH_3), 102.6 (C, $C2_{Th}$), 111.1 (C, $C1_{Ar}$), 113.3 (CH, $C3_{Ar}$), 123.7 (CH, $C5_{Ar}$), 129.6 (CH, $C4_{Th}$), 135.1 (CH, $C4_{Ar}$), 136.5 (CH, $C3_{Th}$), 137.2 (CH, $C6_{Ar}$), 139.7 (CH, $C5_{Th}$), 156.2 (C, $C2_{Ar}$).

MS: m/e 317 [M^+, 100].

EA: $C_{11}H_{10}I_2OS$, calculated: C 29.8, H 2.27; found: C 29.5, H 2.21.

*3-Methoxyphenyl(2-thienyl)iodonium bromide (**2c**)*

Yield: 0.54 g (67 %).

Melting point: 161 °C.

^{1}H-NMR ($DMSO_{d6}$): δ = 3.79 (s, 3H, OCH_3), 7.11 (t, 1H, $H4_{Th}$), 7.16 (d, 1H, $H4_{Ar}$), 7.39 (t, 1H, $H5_{Ar}$), 7.74 (d, 1H, $H2_{Ar}$), 7.88 (d, 1H, $H5_{Th}$), 7.89 (d, 1H, $H3_{Th}$), 7.96 (d, 1H, $H6_{Ar}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 56.7 (OCH_3), 107.7 (C, $C2_{Th}$), 117.8 (C, $C1_{Ar}$), 121.0 (CH, $C4_{Ar}$), 123.2 (CH, $C2_{Ar}$), 127.3 (CH, $C5_{Ar}$), 130.0 ($H4_{Th}$), 132.8 (CH, $C6_{Ar}$), 136.6 (CH, $C3_{Th}$), 139.7 (CH, $C5_{Th}$), 160.9 (C, $C3_{Ar}$).

MS: m/e 317 [M^+, 100].

EA: $C_{11}H_{10}BrIOS$, calculated: C 33.3, H 2.54; found: C 33.6, H 2.47.

*3-Methoxyphenyl(2-thienyl)iodonium iodide (**2d**)*

Yield: 0.32 g (36 %).

Melting point: 155 °C.

^{1}H-NMR ($DMSO_{d6}$): δ = 3.79 (s, 3H, OCH_3), 7.11 (t, 1H, $H4_{Th}$), 7.17 (d, 1H, $H4_{Ar}$), 7.39 (t, 1H, $H5_{Ar}$), 7.74 (d, 1H, $H2_{Ar}$), 7.87 (d, 1H, $H5_{Th}$), 7.89 (d, 1H, $H3_{Th}$), 7.96 (d, 1H, $H6_{Ar}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 56.7 (OCH_3), 107.6 (C, $C2_{Th}$), 117.8 (C, $C1_{Ar}$), 121.0 (CH, $C4_{Ar}$), 123.2 (CH, $C2_{Ar}$), 127.3 (CH, $C5_{Ar}$), 129.4 (CH, $C4_{Th}$), 132.2 (CH, $C6_{Ar}$), 136.6 (CH, $C3_{Th}$), 139.7 (CH, $C5_{Th}$), 160.9 (C, $C3_{Ar}$).

MS: m/e 317 [M^+, 100].

EA: $C_{11}H_{10}I_2OS$, calculated: C 29.8, H 2.27; found: C 30.2, H 2.56.

*4-Methoxyphenyl(2-thienyl)iodonium bromide (**3c**)*

Yield: 0.50 g (62 %).

Melting point: 196 °C (mp (Lit.) 180-185 °C [184]).

^{1}H-NMR ($DMSO_{d6}$): δ = 3.79 (s, 3H, OCH_3), 7.03 (d, 2H, $H3_{Ar}$ + $H5_{Ar}$), 7.11 (t, 1H, $H4_{Th}$), 7.87 (d, 1H, $H3_{Th}$), 7.92 (d, 1H, $H5_{Th}$), 8.14 (d, 2H, $H2_{Ar}$ + $H6_{Ar}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 56.5 (OCH_3), 107.3 (C, $C2_{Th}$), 111.8 (C, $C1_{Ar}$), 117.8 (2C, CH, $C2_{Ar}$ + $C6_{Ar}$), 129.9 (CH, $C4_{Th}$), 136.4 (CH, $C3_{Th}$), 137.4 (CH, $C3_{Ar}$), 139.3 (CH, $C5_{Th}$), 162.2 (C, $C4_{Ar}$).

MS: m/e 317 [M^+, 100].

EA: $C_{11}H_{10}BrIOS$, calculated: C 33.3, H 2.54; found: C 33.3, H 2.39.

*4-Methoxyphenyl(2-thienyl)iodonium iodide (**3d**)*

Yield: 0.53 g (60 %).

Melting point: 155 °C (mp (Lit.) 150-155 °C [184]).

^{1}H-NMR ($DMSO_{d6}$): δ = 3.71 (s, 3H, OCH_3), 6.96 (d, 2H, $H3_{Ar}$ + $H5_{Ar}$), 7.05 (t, 1H, $H4_{Th}$), 7.82 (d, 1H, $H3_{Th}$), 7.88 (d, 1H, $H5_{Th}$), 8.08 (d, 2H, $H2_{Ar}$ + $H6_{Ar}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 56.1 (OCH_3), 104.0 (C, $C2_{Th}$), 110.0 (C, $C1_{Ar}$), 117.6 (2C, CH, $C3_{Ar}$ + $C5_{Ar}$), 129.6 (CH, $C4_{Th}$), 136.6 (CH, $C3_{Th}$), 137.1 (2C, CH, $C2_{Ar}$ + $C6_{Ar}$), 139.4 (CH, $C5_{Th}$), 162.0 (C, $C4_{Ar}$).

MS: m/e 317 [M^+, 100].

EA: $C_{11}H_{10}I_2OS$, calculated: C 29.8, H 2.27; found: C 29.4, H 2.18.

*4-Benzyloxyphenyl(2-thienyl)iodonium bromide (**4c**)*

Yield: 0.52 g (55 %).

Melting point: 202 °C.

^{1}H-NMR ($DMSO_{d6}$): δ = 5.08 (s, 2H, CH_2), 7.05 (2H, $H3_{Ar}$ + $H5_{Ar}$), 7.06 (1H, $H4_{Th}$), 7.25 – 7.40 (m, 5H, CH_{Ph}), 7.83 (d, 1H, $H3_{Th}$), 7.89 (d, 1H, $H5_{Th}$), 8.01 (d, 2H, $H2_{Ar}$ + $H6_{Ar}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 70.07 (CH_2), 104.6 (C, $C2_{Th}$), 110.4 (C, $C1_{Ar}$), 118.3 (2C, CH, $C3_{Ar}$ + $C5_{Ar}$), 128.3 (2C, CH, $C9_{Ar}$ + $C13_{Ar}$), 128.6 (CH, $C11_{Ar}$), 128.9 (2C, CH, $C10_{Ar}$ + $C12_{Ar}$), 129.7

(CH, $C4_{Th}$), 136.5 (C, $C8_{Ar}$), 136.7 (CH, $C3_{Th}$), 137.0 (2C, CH, $C2_{Ar}$ + $C6_{Ar}$), 139.6 (CH, $C5_{Th}$), 161.1 (C, $C4_{Ar}$).

MS: m/e 393 [M^+, 100].

EA: $C_{17}H_{14}BrIOS$, calculated: C 43.2, H 2.98; found: C 43.2, H 2.93.

*4-Methylphenyl(2-thienyl)iodonium bromide (**5c**)*

Yield: 0.27 g (35 %).

Melting point: 195 °C (mp (Lit.) 180-185 °C [184]).

^{1}H-NMR ($DMSO_{d6}$): δ = 2.23 (s, 3H, CH_3), 7.10 (1H, $H4_{Th}$), 7.27 (d, 2H, $H2_{Ar}$ + $H6_{Ar}$), 7.81 (d, 1H, $H3_{Th}$), 7.85 (d, 1H, $H5_{Th}$), 8.08 (d, 2H, $H3_{Ar}$ + $H5_{Ar}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 21.7 (CH_3), 107.8 (C, $C2_{Th}$), 119.6 (C, $C1_{Ar}$), 129.9 (CH, $C4_{Th}$), 132.8 (2C, CH, $C2_{Ar}$ + $C6_{Ar}$), 135.4 (2C, CH, $C3_{Ar}$ + $C5_{Ar}$), 136.5 (CH, $C3_{Th}$), 139.4 (CH, $C5_{Th}$), 142.5 (C, $C4_{Ar}$).

MS: m/e 301 [M^+, 100].

EA: $C_{11}H_{10}BrIS$, calculated: C 34.7, H 2.65; found: C 34.8, H 2.58.

*Phenyl(2-thienyl)iodonium bromide (**6c**)*

Yield: 0,48 g (65 %).

Melting point: 173 °C (mp (Lit.) 170-174 °C [221], 200-205 °C [184], 180 °C [166]).

^{1}H-NMR ($DMSO_{d6}$): δ = 7.05 (d, 1H, $H4_{Th}$), 7.41 (t, 2H, $H3_{Ar}$ + $H5_{Ar}$), 7.55 (t, 1H, $H4_{Ar}$), 7.82 (d, 1H, $H3_{Th}$), 7.89 (d, 1H, $H5_{Th}$), 8.13 (d, 2H, $H2_{Ar}$ + $H6_{Ar}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 105.1 (C, $C2_{Th}$), 121.6 (C, $C1_{Ar}$), 129.7 (CH, $C4_{Th}$), 131.9 (2C, CH, $C3_{Ar}$ + $C5_{Ar}$), 132.0 (CH, $C4_{Ar}$), 134.9 (2C, CH, $C2_{Ar}$ + $C6_{Ar}$), 136.7 (CH, $C3_{Th}$), 139.7 (CH, $C5_{Th}$).

MS: m/e 287 [M^+, 100].

EA: $C_{10}H_8BrIS$, calculated: C 32.7, H 2.20; found: C 33.1, H 2.26.

*4-Chlorophenyl(2-thienyl)iodonium bromide (**7c**)*

Yield: 0.34 g (42 %).

Melting point: 186 °C (mp (Lit.) 180-185 °C [184]).

^{1}H-NMR ($DMSO_{d6}$): δ = 7.05 (t, 1H, $H4_{Th}$), 7.48 (d, 2H, $H3_{Ar}$ + $H5_{Ar}$), 7.82 (d, 1H, $H3_{Th}$), 7.89 (d, 1H, $H5_{Th}$), 8.15 (d, 2H, $H2_{Ar}$ + $H6_{Ar}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 106.4 (C, $C2_{Th}$), 120.2 (C, $C1_{Ar}$), 129.7 (CH, $C4_{Th}$), 131.7 (2C, CH, $C3_{Ar}$ + $C5_{Ar}$), 136.5 (CH, $C3_{Th}$), 136.7 (2C, CH, $C2_{Ar}$ + $C6_{Ar}$), 137.0 (C, $C4_{Ar}$), 139.5 (CH, $C5_{Th}$).

MS: m/e 321 [M^+, 100], 323 [M^+, 56].

EA: $C_{10}H_7BrClIS$, calculated: C 29.9, H 1.76; found: C 29.5, H 1.74.

*4-Bromophenyl(2-thienyl)iodonium bromide (**8c**)*

Yield: 0.33 g (36 %).

Melting point: 165 °C.

^{1}H-NMR ($DMSO_{d6}$): δ = 7.05 (t, 1H, $H4_{Th}$), 7.61 (d, 2H, $H3_{Ar}$ + $H5_{Ar}$), 7.81 (d, 1H, $H3_{Th}$), 7.88 (d, 1H, $H5_{Th}$), 8.06 (d, 2H, $H2_{Ar}$ + $H6_{Ar}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 106.3 (C, $C2_{Th}$), 120.9 (C, $C1_{Ar}$), 125.9 (C, $C4_{Ar}$), 129.7 (CH, $C4_{Th}$), 134.6 (2C, CH, $C3_{Ar}$ + $C5_{Ar}$), 136.6 (CH, $C3_{Th}$), 136.9 (2C, CH, $C2_{Ar}$ + $C6_{Ar}$), 139.6 (CH, $C5_{Th}$).

MS: m/e 366 [M^+, 100], 365 (97).

EA: $C_{10}H_7Br_2IS$ calculated: C 26.9, H 1.58; found: C 26.7, H 1.65.

*4-Iodophenyl(2-thienyl)iodonium bromide (**9c**)*

Yield: 0.17 g (18 %).

Melting point: 161.9 °C.

^{1}H-NMR ($DMSO_{d6}$): δ = 7.04 (t, 1H, $H4_{Th}$), 7.56 (d, 2H, $H3_{Ar}$ + $H5_{Ar}$), 7.81 (d, 1H, $H3_{Th}$), 7.88 (d, 1H, $H5_{Th}$), 8.14 (d, 2H, $H2_{Ar}$ + $H6_{Ar}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 97.1 (C, $C4_{ar}$), 106.3 (C, $C2_{Th}$), 120.8 (C, $C1_{ar}$), 129.7 (CH, $C4_{Th}$), 136.0 (2C, CH, $C3_{ar}$ + $C5_{ar}$), 136.4 (CH, $C3_{th}$), 137.2 (2C, CH, $C2_{ar}$ + $C6_{ar}$), 139.6 (CH, $C5_{th}$).

MS 413 [M^+, 100].

$C_{10}H_7BrI_2S$, calculated: C 24.4, H 1.43; found: C 24.1, H 1.38.

4.2.4 Syntheses of methoxyphenyl(2-thienyl)iodonium tosylates and triflates

The corresponding methoxyphenyl(2-thienyl)iodonium bromide (2.5 mmol) and cyclohexene (2.5 mmol) were suspended in 8 ml pure methanol. *p*-Toluenesulphonic acid monohydrate (3 mmol) or trifluoromethane sulphonic acid (3 mmol), respectively, was added while stirring. Finally, 30 % aqueous hydrogen peroxide solution (3.4 mmol) was added. The mixture was heated to reflux until complete dissolution. The reflux was continued for further 15 min. Under reduced pressure the solvent and most of the water were removed. The crude product was dissolved in methanol at 60 °C and the solution quickly cooled down. The product was precipitated with addition of ether and *n*-hexane (v:v = 3:1) in excess.

*2-Methoxyphenyl(2-thienyl)iodonium tosylate (**1e**)*

Yield: 0.9 g (76 %).

Melting point: 140 °C.

^{1}H-NMR ($DMSO_{d6}$): δ = 2.24 (s, 3H, $(CH_3)_{Ts}$), 3.94 (s, 3H, OCH_3), 7.03 (t, 1H, $H5_{Ar}$), 7.10 (d, 2H, $H2_{Ts}$ + $H6_{Ts}$), 7.11 (1H, $H4_{Th}$), 7.28 (d, 1H, $H3_{Ar}$), 7.44 (d, 2H, $H3_{Ts}$ + $H5_{Ts}$), 7.60 (t, 1H, $H4_{Ar}$), 7.89 (d, 1H, $H3_{Th}$), 7.90 (d, 1H, $H5_{Th}$), 8.27 (d, 1H, $H6_{Ar}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 21.2 ($(CH_3)_{Ts}$), 57.5 (OCH_3), 100.5 (C, $C2_{Th}$), 109.7 (C, $C1_{Ar}$), 113.4 (CH, $C3_{Ar}$), 123.8 (CH, $C5_{Ar}$), 125.9 (2C, CH, $C2_{Ts}$ + $C6_{Ts}$), 128.6 (2C, CH, $C3_{Ts}$ + $C5_{Ts}$), 129.8 (CH, $C4_{Th}$), 135.5 (CH, $C4_{Ar}$), 137.2 (CH, $C6_{Ar}$), 137.3 (CH, $C3_{Th}$), 138.3 (C, $C4_{Ts}$), 140.5 (CH, $C5_{Th}$), 145.8 (C, $C1_{Ts}$), 156.3 (C, $C2_{Ar}$).

MS: m/e 317 [M^+, 100].

EA: $C_{18}H_{17}IO_4S_2$, calculated: C 44.3, H 3.51; found: C 43.6, H 3.39.

*2-Methoxyphenyl(2-thienyl)iodonium triflate (**1f**)*

Yield: 2.03 g (98 %).

Melting point: 170-175 °C.

^{1}H-NMR ($DMSO_{d6}$): δ = 3.95 (s, 3H, OCH_3), 7.04 (t, 1H, $H5_{Ar}$), 7.10 (1H, $H4_{Th}$), 7.28 (d, 1H, $H3_{Ar}$), 7.61 (t, 1H, $H4_{Ar}$), 7.89 (d, 1H, $H3_{Th}$), 7.90 (d, 1H, $H5_{Th}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 57.4 (OCH_3), 100.4 (C, $C2_{Th}$), 109.6 (C, $C1_{Ar}$), 113.4 (CH, $C3_{Ar}$), 121.1 (C, CF_3), 123.8 (CH, $C5_{Ar}$), 129.8 (CH, $C4_{Th}$), 135.5 (CH, $C4_{Ar}$), 137.17 (CH, $C6_{Ar}$), 137.23 (CH, $C3_{Th}$), 140.5 (CH, $C5_{Th}$), 156.3 (C, $C2_{Ar}$).

^{19}F-NMR ($DMSO_{d6}$): δ = -78.4 (CF_3)

MS: m/e 317 [M^+, 100].

EA: $C_{12}H_{10}F_3IO_4S_2$, calculated: C 30.9, H 2.16; found: C 30.7, H 2.13.

*3-Methoxyphenyl(2-thienyl)iodonium tosylate (**2e**)*

Yield: 1.1 g (93 %).

Melting point: 161.0 °C.

^{1}H-NMR ($DMSO_{d6}$): δ = 2.07 (s, 3H, $(CH_3)_{Ts}$), 3.57 (s, 3H, OCH_3), 7.01 (d, 2H, $C3_{Ts}$ + $C5_{Ts}$), 7.06 (t, 1H, $H4_{Th}$), 7.09 (t, 1H, $H4_{Ar}$), 7.33 (t, 1H, $H5_{Ar}$), 7.38 (d, 2H, $C2_{Ts}$ + $C6_{Ts}$), 7.68 (d, 1H, $H6_{Ar}$), 7.81 (s, 1H, $H2_{Ar}$), 7.85 (d, 1H, $H3_{Th}$), 7.96 (d, 1H, $H5_{Th}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 20.7 ($(CH_3)_{Ts}$), 55.8 (OCH_3), 100.7 (C, $C2_{Th}$), 117.7 (CH, $C4_{Ar}$), 119.2 (C, $C1_{Ar}$), 120.0 (CH, $C2_{Ar}$), 125.4 (2C, CH, $C2_{Ts}$ + $C6_{Ts}$), 126.5 (CH, $C6_{Ar}$), 128.1 (2C, CH,

$C3_{Ts}$ + $C5_{Ts}$), 129.5 (CH, $C4_{Th}$), 132.3 (CH, $C5_{Ar}$), 137.1 (CH, $C3_{Th}$), 137.8 (C, $C4_{Ts}$), 140.3 (CH, $C5_{Th}$), 145.1 (C, $C1_{Ts}$), 160.2 (C, $C3_{Ar}$).

MS: m/e 317 [M^+, 100].

EA: $C_{18}H_{17}IO_4S_2$, calculated: C 44.3, H 3.51; found: C 44,6, H 3.61.

*3-Methoxyphenyl(2-thienyl)iodonium triflate (**2f**)*

Yield: 0.94 g (81 %).

Melting point: 88.0 °C.

^{1}H-NMR ($DMSO_{d6}$): δ = 3.73 (s, 3H, OCH_3), 7.11 (t, 1H, $H4_{Th}$), 7.14 (t, 1H, $H4_{Ar}$), 7.38 (t, 1H, $H5_{Ar}$), 7.72 (d, 1H, $H6_{Ar}$), 7.85 (s, 1H, $H2_{Ar}$), 7.89 (d, 1H, $H3_{Th}$), 7.99 (d, 1H, $H5_{Th}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 56.3 (OCH_3), 101.1 (C, $C2_{Th}$), 118.3 (CH, $C4_{Ar}$), 119.5 (C, $C1_{Ar}$), 120.5 (C, CF_3), 126.9 (CH, $C6_{Ar}$), 130.0 (CH, $C4_{Th}$), 132.8 (CH, $C5_{Ar}$), 137.7 (CH, $C3_{Th}$), 140.8 (CH, $C5_{Th}$), 160.7 (C, $C3_{Ar}$).

^{19}F-NMR ($DMSO_{d6}$): δ = -77.9 (CF_3)

MS: m/e 317 [M^+, 100].

EA: $C_{12}H_{10}F_3IO_4S_2$, calculated: C 30.9, H 2.16; found: C 30.6, H 2.21.

*4-Methoxyphenyl(2-thienyl)iodonium tosylate (**3e**)*

Yield: 1.01 g (93 %).

Melting point: 185.4 °C.

^{1}H-NMR ($DMSO_{d6}$): δ = 2.21 (s, 3H, $(CH_3)_{Ts}$), 3.72 (s, 3H, OCH_3), 6.98 (d, 2H, $H3_{Ar}$ + $H5_{Ar}$), 7.04 (d, 2H, $C3_{Ts}$ + $C5_{Ts}$), 7.08 (t, 1H, $H4_{Th}$), 7.41 (d, 2H, $C2_{Ts}$ + $C6_{Ts}$), 7.87 (d, 1H, $H3_{Th}$), 7.94 (d, 1H, $H5_{Th}$), 8.10 (d, 2H, $H2_{Ar}$ + $H6_{Ar}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 21.2 ($(CH_3)_{Ts}$), 56.1 (OCH_3), 101.8 (C, $C2_{Th}$), 108.7 (C, $C1_{Ar}$), 117.7 (2C, CH, $C3_{Ar}$ + $C5_{Ar}$), 125.9 (2C, CH, $C2_{Ts}$ + $C6_{Ts}$), 128.5 (2C, CH, $C3_{Ts}$ + $C5_{Ts}$), 129.9 (CH, $C4_{Th}$), 137.2 (2C, CH, $C2_{Ar}$ + $C6_{Ar}$), 137.3 (CH, $C3_{Th}$), 138.1 (C, $C4_{Ts}$), 140.2 (CH, $C5_{Th}$), 145.1 (C, $C1_{Ts}$), 162.3 (C, $C4_{Ar}$).

MS: m/e 317 [M^+, 100].

EA: $C_{18}H_{17}IO_4S_2$ calculated: C 44.3, H 3.51; found: C 43.8, H 3.50.

*4-Methoxyphenyl(2-thienyl)iodonium triflate (**3f**)*

Yield: 0.44 g (37 %).

Melting point: 92.5 °C.

^{1}H-NMR ($DMSO_{d6}$): δ = 3.72 (s, 3H, OCH_3), 7.00 (d, 2H, $H3_{Ar}$ + $H5_{Ar}$), 7.10 (t, 1H, $H4_{Th}$), 7.86 (d, 1H, $H3_{Th}$), 7.93 (d, 1H, $H5_{Th}$), 8.10 (d, 2H, $H2_{Ar}$ + $H6_{Ar}$).

^{13}C-NMR ($DMSO_{d6}$): δ = 56.1 (OCH_3), 101.6 (C, $C2_{Th}$), 108.6 (C, $C1_{Ar}$), 117.8 (2C, CH, $C3_{Ar}$ + $C5_{Ar}$), 121.0 (C, CF_3), 129.9 (CH, $C4_{Th}$), 137.2 (2C, CH, $C2_{Ar}$ + $C6_{Ar}$), 137.3 (CH, $C3_{Th}$), 140.2 (CH, $C5_{Th}$), 162.4 (C, $C4_{Ar}$).

^{19}F-NMR ($DMSO_{d6}$): δ = -78.2 (CF_3)

MS: m/e 317 [M^+, 100].

EA: $C_{12}H_{10}F_3IO_4S_2$ calculated: C 30.9, H 2.16; found: C 31.1, H 2.26.

4.3 Syntheses of standards and precursors for [^{18}F]F-ADTQ and [^{131}I]I-ADTQ

As mentioned earlier, the here synthesised potential non-competitive AMPA receptor antagonists are derived from the lead structure of *N*-acetyl-1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. The fluorine derivative is described in the literature and characterised as non-competitive AMPA receptor antagonist and was synthesised as described earlier via the Pictet-Spengler approach. The analytical data in the literature are only known for the final product and have not been reported for the intermediates so far. In contrast, the iodine derivative is not described in the literature, but the same approach of synthesis was suitable.

4.3.1 Syntheses of fluorine, iodine and trimethyltin derivatives of ADTQ

*2-Acetyl-6,7-dimethoxy-1-(4'-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (**10**) [from 194]*

A mixture of 2-(3',4'-dimethoxyphenyl)ethylamine (homoveratrylamine) (10 mmol) and 4-fluorobenzaldehyde (12 mmol) were heated at reflux for 3 h in anhydrous toluene (50 ml). Afterwards the solvent was evaporated under reduced pressure. The oily residue was treated with ether to give a solid product, which was re-crystallised from methanol to afford 4-fluorobenzyl[2-(3',4'-dimethoxyphenyl)ethyl]imine as a white solid.

Yield: 1.09 g (38 %).

Melting point: 101.2 °C.

^{1}H-NMR ($CDCl_3$): δ = 2.91 (d, 2H, $H2_{Et}$), 3.75 (s, 3H, C4'-OCH_3), 3.80 (s, 3H, C3'-OCH_3), 3.78 (d, 2H, $H1_{Et}$), 6.74 (s, 1H, H5'), 6.68 (s, 1H, H2'), 7.04 (d, 2H, H2 + H6), 6.72 (d, 1H, H6'), 7.64 (d, 2H, H3 + H5), 8.04 (s, 1H, H5).

^{13}C-NMR ($CDCl_3$): δ = 36.9 (CH_2, $C2_{Et}$), 55.7 (C4'-OCH_3), 55.8 (C3'-OCH_3), 63.2 (CH_2, $C1_{Et}$), 111.1 (CH, C5'), 112.4 (CH, C2'), 115.6 (2C, CH, C2 + C6), 120.8 (CH, C6'), 129.8 (2C, CH,

C3 + C5), 132.4 (C, C1'), 132.4 (C, C4), 147.3 (C, C3'), 148.5 (C, C4'), 160.0 (CH, C5), 164.2 (C, C1).

^{19}F-NMR ($CDCl_3$): δ = -115.5.

MS: m/e 288 [M^+, 100].

EA: $C_{17}H_{18}FNO_2$ calculated: C 71.1, H 6.31, N 4.87; found: C 71.9, H 6.18, N 5.06.

4-Fluorobenzyl[2-(3',4'-dimethoxyphenyl)ethyl]imine (3.8 mmol) was given into 10 ml trifluoro-acetic acid and the mixture was refluxed for 90 min. The reaction was quenched by adding water (~20 ml) and basified (pH ~8 – 9) with aqueous sodium hydroxide solution (50 %). The product 6,7-dimethoxy-1-(4'-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline precipitated and was filtered off. Re-crystallisation from methanol gave the purified product.

Yield: 0.43 g (39 %).

Melting point: 82.8 °C.

^{1}H-NMR ($CDCl_3$): δ = 2.69 (d, 1H, H4 pseudo eq.), 2.88 (d, 1H, H4 pseudo ax.), 3.00 (d, 1H, H3 pseudo ax.), 3.15 (d, 1H, H3 pseudo eq.), 3.59 (s, 3H, C6-OCH_3), 3.82 (s, 3H, C7-OCH_3), 4.98 (s, 1H, H1), 6.15 (s, 1H, H8), 6.58 (s, 1H, H5), 6.95 (d, 2H, H3'), 7.18 (d, 2H, H2').

^{13}C-NMR ($CDCl_3$): δ = 29.2 (CH_2, C4), 41.9 (CH_2, C3), , 55.8 (2C, OCH_3), 60.7 (CH, C1), 110.7 (CH, C8), 111.4 (CH, C5), 115.1 (2C, CH, C3' + C5'), 127.6 (C, C4a), 129.6 (C, C8a), 130.4 (2C, CH, C2' + C6'), 140.6 (C, C1'), 147.0 (C, C7), 147.6 (C, C6), 162.0 (C, C4').

^{19}F-NMR ($CDCl_3$): δ = -115.3.

MS: m/e 288 [M^+, 100].

EA: $C_{17}H_{18}FNO_2$ calculated: C 71.1, H 6.31, N 4.87; found: C 70.3, H 5.80, N 4.39.

6,7-Dimethoxy-1-(4'-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (1.5 mmol) was dissolved in acetic anhydride (10 ml) and heated until reflux for 90 min. The mixture was cooled and the reaction quenched by adding water (~10 ml). The organic layer was extracted with dichloro-methane (3 x 10 ml), which was dried over Mg_2SO_4. The solvent was removed under reduced pressure until dryness. The oily residue was treated with ether for crystallisation and washed with ether. *Flash*-chromatography on silica gel using petrol ether/acetone (2:1) gave the purified 2-acetyl-6,7-dimethoxy-1-(4'-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (F-ADTQ, **10**) (R_f = 0.35).

Yield: 0.36 g (74 %).

Melting point: 160 °C (mp (Lit.) 158-160 °C [*194*]).

^{1}H-NMR ($CDCl_3$): δ = 2.13 (s, 3H, CH_3), 2.75 (d, 1H, H4 pseudo eq.), 2.92 (d, 1H, H4 pseudo ax.), 3.30 (d, 1H, H3 pseudo ax.), 3.72 (d, 1H, H3 pseudo eq.), 3.73 (s, 3H, OCH_3), 3.83 (s, 3H,

OCH_3), 6.47 (s, 1H, H8), 6.64 (s, 1H, H5), 6.81 (s, 1H, H1), 6.91 (d, 2H, H3' + H5'), 7.18 (d, 2H, H2' + H6').

^{13}C-NMR ($CDCl_3$): δ = 21.5 (CH_3), 28.5 (CH_2, C4), 40.1 (CH_2, C3), 53.8 (CH, C1), 56.0 (2C, OCH_3), 111.5 (2C, CH, C5 + C8), 115.0 (2C, CH, C3' + C5'), 126.4 (C, C8a), 127.0 (C, C4a), 130.3 (2C, CH, C2' + C6'), 138.5 (C, C1'), 148.0 (C, C6), 148.5 (C, C7), 162.1 (C, C4'), 168.8 (CO).

^{19}F-NMR ($CDCl_3$): δ = -115.5.

MS: m/e 330.2 [M^+, 100].

EA: $C_{19}H_{20}FNO_3$ calculated: C 69.3, H 6.12, N 4.25; found: C 70.3, H 6.12, N 4.37.

*2-Acetyl-6,7-dimethoxy-1-(4'-iodophenyl)-1,2,3,4-tetrahydroisoquinoline (**10a**) [following 194]*

A mixture of 2-(3',4'-dimethoxyphenyl)ethylamine (homoveratrylamine) (10 mmol) and 4-iodo-benzaldehyde (12 mmol) were heated to 100 °C for 3 h in anhydrous toluene (50 ml). Afterward the solvent was evaporated under reduced pressure. The oily residue was treated with ether to give a solid product which was re-crystallised from methanol to afford 4-iodobenzyl-[2-(3',4'-dimethoxyphenyl)ethyl]imine as a white solid.

Yield: 2.45 g (62 %).

Melting point: 89.3 °C.

^{1}H-NMR ($CDCl_3$): δ = 2.90 (d, 2H, $H2_{Et}$), 3.76 (s, 3H, C3'-OCH_3), 3.80 (s, 3H, C4'-OCH_3), 3.78 (d, 2H, $H1_{Et}$), 6.73 (s, 1H, H5'), 6.68 (s, 1H, H2'), 6.71 (d, 1H, H6'), 7.38 (d, 2H, H3 +H5), 7.70 (d, 2H, H2+ H6), 8.0 (s, 1H, H5).

^{13}C-NMR ($CDCl_3$): δ = 36.8 (CH_2, $C2_{Et}$), 55.7 (C4'-OCH_3), 55.8 (C4'-OCH_3), 63.3 (CH_2, $C1_{Et}$), 97.1 (C, C1), 111.1 (CH, C5'), 112.4 (CH, C2'), 120.8 (CH, C6'), 129.5 (2C, CH, C3 + C5), 132.3 (C, C1'), 135.6 (C, C4), 137.7 (2C, CH, C2 + C6), 147.3 (C, C3'), 148.6 (C, C4'), 160.4 (CH, C5).

MS: m/e 330 [M^+, 100].

EA: $C_{17}H_{18}INO_2$ calculated: C 51.7, H 4.59, N 3.54; found: C 52.2, H 4.63, N 3.76.

4-Iodobenzyl[2-(3',4'-dimethoxyphenyl)ethyl]imine (6.2 mmol) was given into 10 ml trifluoroacetic acid and the mixture was refluxed for 90 min. The reaction was quenched by adding water (~10 ml) and basified (pH ~8 – 9) with aqueous sodium hydroxide solution (50 %). The product 6,7-dimethoxy-1-(4'-iodophenyl)-1,2,3,4-tetrahydroisoquinoline precipitated and was filtered off. Re-crystallisation from methanol gave the purified product.

Yield: 1.33 g (54 %).

Melting point: 152.7 °C.

^{1}H-NMR ($CDCl_3$): δ = 2.67 (d, 1H, H4 pseudo eq.), 2.84 (d, 1H, H4 pseudo ax.), 2.96 (d, 1H, H3 pseudo ax.), 3.11 (d, 1H, H3 pseudo eq.), 3.59 (s, 3H, C7-OCH_3), 3.80 (s, 3H, C6-OCH_3), 4.92 (s, 1H, H1), 5.04 (s, 1H, NH), 6.13 (s, 1H, H8), 6.56 (s, 1H, H5), 6.94 (d, 2H, H2' + H6'), 7.58 (d, 2H, H3' + H5').

^{13}C-NMR ($CDCl_3$): δ = 29.1 (CH_2, C4), 41.6 (CH_2, C3), 55.7 (CH_3, C6-OCH_3), 55.8 (CH_3, C7-OCH_3), 60.8 (CH, C1), 92.9 (C, C4'), 110.6 (CH, C8), 111.4 (CH, C5), 127.6 (C, C4a), 129.0 (C, C8a), 130.9 (2C, CH, C2' + C6'), 137.4 (2C, CH, C3' + C5'), 144.5 (C, C1'), 147.1 (C, C7), 147.7 (C, C6).

MS: m/e 396 [M^+, 100].

EA: $C_{17}H_{18}INO_2$ calculated: C 51.7, H 4.59, N 3.54; found: C 52.2, H 4.44, N 3.75.

6,7-Dimethoxy-1-(4'-iodophenyl)-1,2,3,4-tetrahydroisoquinoline (3.4 mmol) was dissolved in acetic anhydride (10 ml) and heated to reflux for 90 min. The mixture was cooled and the reaction quenched by adding water (~10 ml). The organic layer was extracted with dichloromethane (3 x 10 ml), dried over Mg_2SO_4 and the solvent was removed under reduced pressure until dryness. The oily residue was treated with ether for crystallisation and washed with ether. *Flash*-chromatography on silica gel using *n*-hexane/acetone (5:2) gave the purified 2-acetyl-6,7-dimethoxy-1-(4'-iodophenyl)-1,2,3,4-tetrahydroisoquinoline (I-ADTQ, **10a**) (R_f = 0.23).

Yield: 1.20 g (81 %).

Melting point: 141.3 °C.

^{1}H-NMR ($CDCl_3$): δ = 2.20 (s, 3H, CH_3), 2.76 (d, 1H, H4 pseudo eq.), 2.94 (d, 1H, H4 pseudo ax.), 3.33 (d, 1H, H3 pseudo ax.), 3.43 (d, 1H, H3 pseudo eq.), 3.79 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.51 (s, 1H, H8), 6.70 (s, 1H, H5), 6.84 (s, 1H, H1), 6.99 (d, 2H, H3' + H5'), 7.63 (d, 2H, H2' + H6').

^{13}C-NMR ($CDCl_3$): δ = 22.1 (CH_3), 28.9 (CH_2, C4), 40.6 (CH_2, C3), 54.4 (CH, C1), 56.3 (2C, OCH_3), 93.6 (2C, CH, C3'+ C5'),111.5 (2C, CH, C5 + C8), 126.7 (C, C8a), 126.8 (C, C4a), 131.2 (2C, CH, C2' + C6'), 137.7 (C, C1'), 142.7 (C, C4'), 148.2 (C, C6), 148.7 (C, C7), 169.4 (CO).

MS: m/e 438 [M^+, 100].

EA: $C_{19}H_{20}INO_3$ calculated: C 52.2, H 4.61, N 3.20; found: C 52.7, H 4.70, N 3.41.

*2-Acetyl-6,7-dimethoxy-1-(4'-trimethylstannylphenyl)-1,2,3,4-tetrahydroisoquinoline (**11**)*

A solution of I-ADTQ **10a** (2 mmol), hexamethyldistannane (5.3 mmol) and tetrakis(triphenylphosphine) palladium (30 µmol) in 50 ml toluene was heated until reflux for 3 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography

using silica gel and n-hexane/ethyl acetate (1:10) to give 2-acetyl-6,7-dimethoxy-1-(4'-trimethyl-stannylphenyl)-1,2,3,4-tetrahydroisoquinoline (Sn-ADTQ) (**11**) (R_f = 0.69).

Yield: 0.65 g (68 %).

Melting point: 117.2 °C.

^{1}H-NMR ($CDCl_3$): δ = 0.21 (s, 9H, $(CH_3)_3$), 2.11 (s, 3H, CH_3), 2.70 (d, 1H, H4 pseudo eq.), 2.89 (d, 1H, H4 pseudo ax.), 3.34 (d, 1H, H3 pseudo ax.), 3.64 (d, 1H, H3 pseudo eq.), 3.71 (s, 3H, C7-OCH_3), 3.84 (s, 3H, C6-OCH_3), 6.48 (s, 1H, H8), 6.61 (s, 1H, H5), 6.82 (s, 1H, H1), 6.95 (d, 2H, H3' + H5'), 7.14 (d, 2H, H2' + H6').

^{13}C-NMR ($CDCl_3$): δ = -9.6 (3C, $(CH_3)_3$), 21.6 (CH_3), 28.5 (CH_2, C4), 40.1 (CH_2, C3), 54.3 (CH, C1), 55.8 (C6-OCH_3), 55.9 (C7-OCH_3), 111.0 (CH, C5), 111.2 (CH, C8), 126.3 (C, C4a), 126.9 (C, C8a), 128.4 (2C, CH, C3'+ C5'), 135.7 (2C, CH, C2' + C6'), 141.3 (C, C4'), 142.4 (C, C1'), 147.6 (C, C7), 148.0 (C, C6), 168.8 (CO).

MS: m/e 476 [M^+, 100], 474 [76], 472 [39], 480 [16].

EA: $C_{22}H_{29}NO_3Sn$ calculated: C 55.7, H 6.16, N 2.95; found: C 55.4, H 6.19, N 3.09.

4.3.2 Synthesis of the diacetoxyiodo compound of ADTQ

Sodium periodate (5.1 mmol) and sodium acetate (11 mmol) were suspended in 8 ml of a mixture of acetic acid/acetic anhydride (9:1). I-ADTQ (**10a**) (5 mmol) was added and the mixture was heated to reflux, but it was stopped after 1.5 h due to I_2-formation in the solution. After the mixture was allowed to cool down to room temperature, it was poured into 25 ml ice-water. The crude product was extracted with dichloromethane and iodine was removed by washing with sodium thiosulfate solution (10 %). The organic layers were collected and dried over Mg_2SO_4. The solvent was removed under reduced pressure and the oily residue treated with ether for crystallisation. A small amount of 2-acetyl-6,7-dimethoxy-1-(4'-(diacetoxyiodo)phenyl)-1,2,3,4-tetrahydroisoquinoline (**10b**) as a yellow solid could be obtained [following 163].

Yield: 0.166 g (6 %).

Melting point: 201 °C.

MS: m/e 496 [M^+, 100].

Due to the small amount of product no NMR analytics were carried out.

EA: $C_{23}H_{26}INO_7$ calculated: C 49.7, H 4.72, N 2.52; found: C 49.5, H 4.49, N 3.23.

4.3.3 Syntheses of precursors for ^{18}F-labelling of [^{18}F]F-ADTQ

The below described *ipso*-demetallation calls for compounds like Koser's reagent ([hydroxy-(tosyloxy)iodo]benzene), thus the appropriate 2-iodothiophene derivative 2-[hydroxy(tosyloxy)-iodo]thiophene was synthesised according to the literature and is described in the following [222]. The [hydroxy(tosyloxy)iodo]benzene was purchased from Aldrich (Germany).

*1'-[2-Acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline]-4'-phenyl(2-thienyl)iodonium bromide (**10c**) [following 162]*

Sodium perborate monohydrate (6 mmol) was suspended in 10 ml acetic anhydride and stirred at 30 °C for 90 min. **10a** (2 mmol) was then given to the mixture and it was stirred at 40 °C for 90 min. Thiophene (10 mmol) was added and the mixture was cooled to -15 °C. Concentrated sulphuric acid (0.5 ml) was added dropwise, under stirring and keeping the temperature below -10 °C. After addition was completed the mixture was allowed to warm up to 0 to 5 °C and stirred at this temperature for 5 h. The final reaction mixture was poured into 100 ml ice-water and stirred for 30 min. The non-reacted organic compounds were extracted by ether (2 x 10 ml) and discarded. The aqueous layer was treated with activated coal at 40 °C for 10 min. After filtration and cooling, 10 ml aqueous potassium bromide solution (25 %) was added and the mixture was stirred for 1 to 2 h for precipitation. The precipitates were collected, washed well with water, acetone and ether. For re-crystallisation the crude product was quickly dissolved in hot methanol and after cooling ether was added in excess.

Yield: 0.036 g (3 %)

Due to the very small yield, all the amount was used for preliminary ^{18}F-labelling reactions, so analytical data could not determined.

*1'-[2-Acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline]-4'-phenyl(2-thienyl)Iodonium tosylate (**10e**) [following 171]*

2-Iodothiophene (10 mmol) was oxidised by sodium perborate according to the above mentioned procedure for **1b** to **3b** and **5b** to **8b**.

Yield: 1.82 g (55 %).

Melting point (decomp.): 143 °C.

A suspension of 2-(diacetoxyiodo)thiophene (2 mmol) in 4 ml acetonitrile was added to a solution of *p*-toluenesulphonic acid monohydrate (4 mmol) in 4 ml acetonitrile under an argon atmosphere and stirred for 15 to 20 min at 0 °C. The reaction mixture was filtered quickly and the yellow solid product washed with ether. 2-[Hydroxy(tosyloxy)iodo]thiophene was dried for 5 min under vacuum and then stored under argon at -30 °C in the dark.

Yield: 1.56 g (98 %).

Melting point (decomp.): 64.8 °C (mp (Lit.) 65-68 °C [222]).

Sn-ADTQ **11** (1 mmol) and 2-[hydroxy(tosyloxy)iodo]thiophene (1 mmol) were suspended in 15 ml dichloromethane. The mixture was stirred under argon at room temperature for 2 h. The solvent was removed under a constant argon flow and reduced pressure (~750 mbar). The residue was treated with ether to crystallise. The crude product was filtered off and washed with ether. *1'-[2-Acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline]-4'-phenyl(2-thienyl)Iodonium tosylate* (**10e**) was dried under vacuum and stored in an exsiccator in the dark.

Yield: 0.55 g (80 %).

Melting point: 141.9 °C.

^{1}H-NMR ($CDCl_3$): δ = 2.00 (s, 3H, CO-CH_3), 2.19 (s, 3H, $C1_{Ts}$-CH_3), 2.53 (2H, H4), 3.31 (2H, H3), 3.50 (s, 3H, C7-OCH_3), 3.60 (s, 3H, C6-OCH_3), 6.46 (s, 1H, H1), 6.68 (s, 1H, H5), 6.71 (s, 1H, H8), 7.04 (d, 2H, CH, $H2_{Ts}$ + $H6_{Ts}$), 7.19 (1H, CH, $H4_{Th}$), 7.37 (d, 2H, CH, $H3_{Ts}$ + $H5_{Ts}$), 7.39 (d, 2H, CH, H2' + H6'), 7.56 (d, 2H, CH, H3' + H5'), 8.04 (1H, CH, $H3_{Th}$), 8.13 (1H, CH, $H5_{Th}$).

^{13}C-NMR ($CDCl_3$): δ = 21.1 (CH_3, $C1_{Ts}$-CH_3), 21.9 (CH_3, CO-CH_3), 27.8 (CH_2, C4), 41.4 (CH_2, C3), 54.5 (CH, C1), 55.8 (C6, OCH_3), 55.9 (C7, OCH_3), 111.8 (CH, C8), 112.0 (CH, C5), 114.7 (C, $C2_{Th}$), 116.6 (C, C4'), 125.9 (2C, CH, $C3_{Ts}$ + $C5_{Ts}$), 126.5 (C, C8a), 127.4 (C, C4a), 128.6 (2C, CH, $C2_{Ts}$ + $C6_{Ts}$), 131.1 (CH, $C4_{Th}$), 132.2 (2C, CH, C2' + C6'), 132.5 (CH, $C3_{Th}$), 135.4 (2C, CH, C3' + C5'), 135.6 (CH, $C5_{Th}$), 138.5 (C, $C1_{Ts}$), 145.3 (C, $C4_{Ts}$), 147.5 (C, C1'), 147.7 (C, C7), 148.4 (C, C6), 169.9 (CO).

MS: m/e 520 [M^+, 100]

EA: $C_{30}H_{30}INO_6S_2$ calculated: C 52.1, H 4.37, N 2.03; found: C 51.6, H 4.46, N 1.21.

*1'-[2-Acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline]-4'-phenyl(phenyl)Iodonium tosylate (**10g**) [following 171]*

Sn-ADTQ **11** (1 mmol) and [hydroxy(tosyloxy)iodo]benzene (1 mmol) were suspended in 15 ml dichloromethane. The mixture was stirred under argon at room temperature for 2 h. The solvent was removed under a constant argon flow and reduced pressure (~750 mbar). The residue was treated with ether to crystallise. The crude product was filtered off and washed with ether. **10g** was dried under vacuum and stored in an exsiccator in the dark.

Yield: 0.34 g (50 %).

Melting point: 141 °C.

^{1}H-NMR ($CDCl_3$): δ = 1.88 (s, 3H, CO-CH_3), 2.07 (s, 3H, $C1_{Ts}$-CH_3), 2.42 (d, 1H, H4 pseudo eq.), 2.62 (d, 1H, H4 pseudo ax.), 3.18 (d, 1H, H3 pseudo ax.), 3.41 (s, 3H, C7-OCH_3), 3.42 (d, 1H, H3

pseudo eq.), 3.49 (s, 3H, C6-OCH_3), 6.32 (s, 1H, H1), 6.57 (s, 1H, H5), 6.59 (s, 1H, H8), 6.92 (d, 2H, CH, $H2_{Ts}$ + $H6_{Ts}$), 6.93 (1H, CH, $H4_{Ph}$), 7.07 (d, 2H, CH, H2' + H6'), 7.26 (d, 2H, CH, $H3_{Ts}$ + $H5_{Ts}$), 7.71 (d, 2H, CH, $H3_{Ph}$ + $H5_{Ph}$), 7.81 (d, 2H, CH, $H2_{Ph}$ + $H6_{Ph}$), 7.91 (d, 2H, CH, H3' + H5').

^{13}C-NMR ($CDCl_3$): δ = 21.1 (CH_3, $C1_{Ts}$-CH_3), 21.9 (CH_3, CO-CH_3), 27.8 (CH_2, C4), 41.4 (CH_2, C3), 54.4 (CH, C1), 55.8 (C6, OCH_3), 56.0 (C7, OCH_3), 100.7 (C, $C1_{Ph}$), 111.8 (CH, C8), 112.0 (CH, C5), 117.5 (C, C4'), 125.8 (2C, CH, $C3_{Ts}$ + $C5_{Ts}$), 126.5 (C, C8a), 127.4 (C, C4a), 128.6 (2C, CH, $C2_{Ts}$ + $C6_{Ts}$), 130.1 (CH, $C4_{Ph}$), 131.0 (2C, CH, C2' + C6'), 134.9 (2C, CH, C3' + C5'), 137.7 (2C, CH, $C3_{Ph}$ + $C5_{Ph}$), 138.6 (C, $C1_{Ts}$), 140.9 (2C, CH, $C2_{Ph}$ + $C6_{Ph}$), 145.1 (C, $C4_{Ts}$), 147.5 (C, C1'), 147.7 (C, C7), 148.4 (C, C6), 169.9 (CO).

MS: m/e 514 [M^+, 100]

EA: $C_{32}H_{32}INO_6S$ calculated: C 56.1, H 4.70, N 2.04; found: C 55.7, H 4.82, N 1.71.

4.4 Radiosyntheses

4.4.1 Production of n.c.a. [^{18}F]fluoride

The production of n.c.a. [^{18}F]fluoride is routinely carried out at the JSW BC 1710 Cyclotron (Forschungszentrum Jülich). N.c.a. [^{18}F]fluoride is obtained via bombardment of an isotopically enriched [^{18}O]water target (1.3 ml) with a 17 MeV proton beam using the $^{18}O(p,n)^{18}F$ nuclear reaction. The n.c.a. [^{18}F]fluoride is separated from the enriched [^{18}O]water by an electrochemical cell [223]. By this method, up to 55 GBq n.c.a. [^{18}F]fluoride can be produced within 1 h at a nominal beam current of 25 µA.

4.4.2 Preparation of the n.c.a. [^{18}F]fluoride-cryptate complex

A 5 ml Wheaton© glass vial equipped with a triangle stirring bar and a silicone septum sealed lid, into which two needles are stuck, connecting the vacuum line and the argon gas line, is evacuated and flushed with argon three times. From the aqueous n.c.a. [^{18}F]fluoride solution, 30 to 50 MBq (10 - 50 µl) were given to Kryptofix© 2.2.2 (26 µmol) and 13 µl of a 1 M potassium carbonate solution. This mixture is taken with 0.8 ml anhydrous acetonitrile and given through the septum into the prepared vial by a 1 ml syringe. For an azeotropic distillation the vial is heated in an oil bath to 80 to 82 °C and a constant argon flow at 750 to 850 mbar is adjusted. When no acetonitrile/water mixture is left, again 1 ml acetonitrile is added to the vial. This step is repeated

two times and subsequent by 5 min of full vacuum (~10 mbar) follow. After argon flushing and pressure balancing the resulting dry n.c.a. [^{18}F]fluoride-cryptate complex is ready for nucleophilic ^{18}F-labelling reactions.

4.4.3 Radiosyntheses of n.c.a. [^{18}F]fluoroarenes

The appropriate aryl(2-thienyl)iodonium salt (25 µmol) was dissolved in 1.0 ml anhydrous DMF. This solution was added by a syringe through the silicone septum to the vial containing the dry n.c.a. [^{18}F]fluoride-cryptate complex and was stirred under 1100 mbar argon at 130 °C. The slight overpressure was necessary to avoid losses of volatile products, such as [^{18}F]fluoroanisoles and [^{18}F]fluorobenzene. At appropriate times aliquots of 10 µl were taken with a Hamilton© syringe via the septum and given to 50 µl cold acetonitrile. These samples were closed quickly and stored in liquid nitrogen until they were analysed by radio-HPLC and/or radio-TLC.

4.4.4 Radiosynthesis of n.c.a. 4-[^{18}F]fluorophenol

4-Benzyloxyphenyl(2-thienyl)iodonium bromide (25 µmol) was used as precursor following the before mentioned procedure to give n.c.a. 4-benzyloxy-[^{18}F]fluorobenzene. After 15 to 20 min the whole reaction mixture was given into 10 ml water by a 20 ml syringe. This mixture was passed though SepPak© C18 plus cartridge pre-washed with 3 ml ethanol and 5 ml water. The cartridge was washed with 3 ml water and dried by an argon flow for 5 min. Before elution, the cartridge was connected to a dry SepPak© ALOX cartridge. The product absorbed on the solid C18 phase was eluted with 3 ml of methanol and given through both cartridges into a new reaction vial. 4-Benzyloxy-[^{18}F]fluorobenzene was analysed by radio-TLC and radio-HPLC.

Ammonium formate (~5 mmol) and palladium black (~0.15 mmol) were added to the solution. For debenzylation the mixture was stirred at 80 C for 15 -20 min. The whole reaction mixture was taken and filtered through a Merck LiChrolut© glass column (65 x 10 mm) containing only a PTFE frit (porosity 10 µm) which was washed with 0.5 ml methanol. The obtained n.c.a. 4-[^{18}F]fluorophenol was analysed by radio-TLC and radio-HPLC.

4.4.5 Radiosynthesis of n.c.a. [^{18}F]F-ADTQ

The precursor **10c**, **10e** or **10g** was dissolved in 1 ml anhydrous DMF and given to the activated [^{18}F]fluoride-cryptate complex. This mixture was stirred at the appropriate temperature for the

desired reaction time. Aliquots of 10 µl were taken, added to 50 µl methanol and analysed by radio-TLC and/or radio-HPLC.

4.4.6 Radiosynthesis of [^{131}I]I-ADTQ

For radioiodination the isotope iodine-131 was purchased from Amersham Buchler (Germany) and was obtained as sodium [^{131}I]iodide solution (sodium hydroxide solution pH 7 to 11) with ~1.48 GBq/ml specific volume activity.

To 50 µl of a **11** solution in ethanol (c = 0.2 µmol/ml) and 5 µl of an aqueous chloramine T solution (1 M) 5 µl (~7.5 MBq) of [^{131}I]iodine solution is added. After addition of 5 µl hydrochloric acid solution (1 M) the reaction vial was shaken for 2 min at room temperature.

To stop the reaction about 100 µl of the HPLC eluent was added. **[^{131}I]10a** was analysed and separated by radio-HPLC.

4.5 Radioanalytical methods

For identification and determination of the radiochemical yields (RCY) both radio high performance liquid chromatography (radio-HPLC) and radio thin layer chromatography (radio-TLC) were used. All ^{18}F-labelled compounds were identified by their non-radioactive reference compounds via comparison of the UV-signals with the radioactive signals. **[^{18}F]1** to **[^{18}F]3**, **[^{18}F]5** and **[^{18}F]6** are volatile products and not suitable for radio-TLC, thus these [^{18}F]fluoroarenes were only analysed by radio-HPLC.

4.5.1 Radio thin layer chromatography

Analytical radio thin layer chromatography (radio-TLC) was carried out to determine the RCY and to verify that no further especially very polar radioactive species than those detected by radio-HPLC were present. Radio-TLC was performed on Macherey-Nagel (Germany) precoated silica gel plates (PolyGram SIL G/UV254, 40 x 80 mm) with different solvent systems. In practice, ~1.5 µl of the sample solution was given on the TLC plates and developed in the appropriate solvent mixtures. The developed radio-TL-chromatograms were measured on an Instant Imager^{TM} (Packard, USA) for radioactivity. Individual R_f-values of standards are listed in Table 4.1 along with solvent systems (given as v:v ratios).

Table 4.1: R_f-Values and solvent systems (given in v:v ratios) of the relevant fluorine reference compounds for radio-TLC on silica gel plates

Compound	Solvent system (v:v)	R_f
4-benzyloxy-1-fluorobenzene (**4**)	*n*-hexane/ether (2:1)	0.79
	n-hexane/ethyl acetate (3:1)	0.91
1-chloro-4-fluorobenzene (**7**)	*n*-hexane	0.52
1-bromo-4-fluorobenzene (**8**)	*n*-hexane/ether (1:1)	0.85
1-fluoro-4-iodobenzene (**9**)	*n*-hexane/ether (1:1)	0.78
F-ADTQ (**10**)	petrol ether/acetone (2:1)	0.35
4-fluorophenol	*n*-hexane/ethyl acetate (3:1)	0.59

4.5.2 Radio high performance liquid chromatography

Analytical radio high performance chromatography (radio-HPLC) was performed on the same system as described in chapter 4.1 (*General*) for the non-radioactive HPLC. For measurement of radioactivity the outlet of the UV/Vis detector is connected to a NaI(Tl) well-type scintillation detector (EG&G ACE Mate™). The aliquots of the labelled compounds were analysed by reversed-phase radio-HPLC using a Phenomenex© Luna 5µ C18 column (3 x 250 mm) and as mobile phase acetonitrile/water or methanol/water systems in various concentration ratios. The flow rate was varied from 0.6 to 1.0 ml/min. All measurements were performed at room temperature. Individual k'-values of the reference compounds, mobile phase systems (given in v:v ratios) and the flow rate are given in Table 4.2.

An analysis of the specific activity obtained after labelling was carried out for **[^{18}F]3** and **[^{131}I]10a** via HPLC. The integral of the UV-signals obtained by the UV/Vis-detector is proportional to the applied amount of non-radioactive reference material. The measured peak-areas were fitted by linear regression as functions of the amount of reference compound and led to straight lines, which were used for calibration (cf. Figure 4.1 and Figure 4.2).
In the determination of the specific activity of **[^{18}F]3** no UV-signal corresponding to **3** was detected, thus only a lower limit of the specific activity of $\geq$ 58 TBq/mmol was estimated.

From ^{131}I-labelling reactions of **11** with starting activities of ~7.5 MBq an average specific activity of **[^{131}I]10a** of 681 GBq/mmol (18.4 Ci/mmol) was determined.

Table 4.2: k'-values, solvent systems (in v:v ratios) and flow rates of the relevant fluorine reference compounds for radio-HPLC (Phenomenex© Luna 5µ C18 column)

Compound	Solvent system (v:v); flow [ml/min]	k'
2-fluoroanisole (**1**)	acetonitrile/water (40:60); 0.7	2.44
3-fluoroanisole (**2**)	acetonitrile/water (40:60); 0.7	3.82
4-fluoroanisole (**3**)	acetonitrile/water (40:60); 0.7	3.32
4-benzyloxy-1-fluorobenzene (**4**)	acetonitrile/water (60:40); 1.0	3.39
4-methyl-1-fluorobenzene (**5**)	acetonitrile/water (40:60); 0.7	4.81
fluorobenzene (**6**)	acetonitrile/water (40:60); 0.7	3.00
1-chloro-4-fluorobenzene (**7**)	acetonitrile/water (40:60); 0.7	5.30
1-bromo-4-fluorobenzene (**8**)	acetonitrile/water (40:60); 0.7	6.65
4-iodo-1-fluorobenzene (**9**)	acetonitrile/water (40:60); 0.7	8.84
F-ADTQ (**10**)	methanol/water (70:30); 0.6	1.23
I-ADTQ (**10a**)	methanol/water (70:30); 0.8	2.53

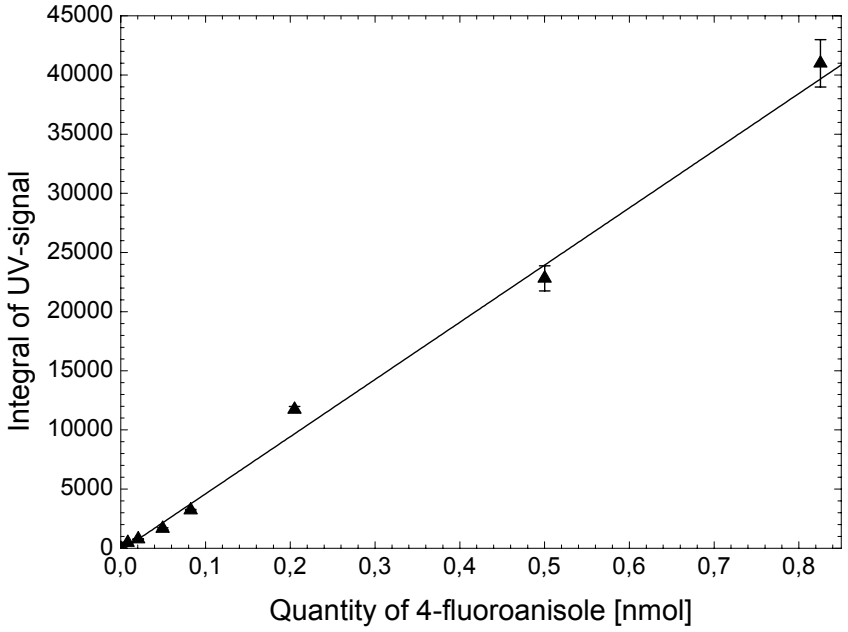


Figure 4.1: Integral of the UV-peak as a function of the quantity of **3**

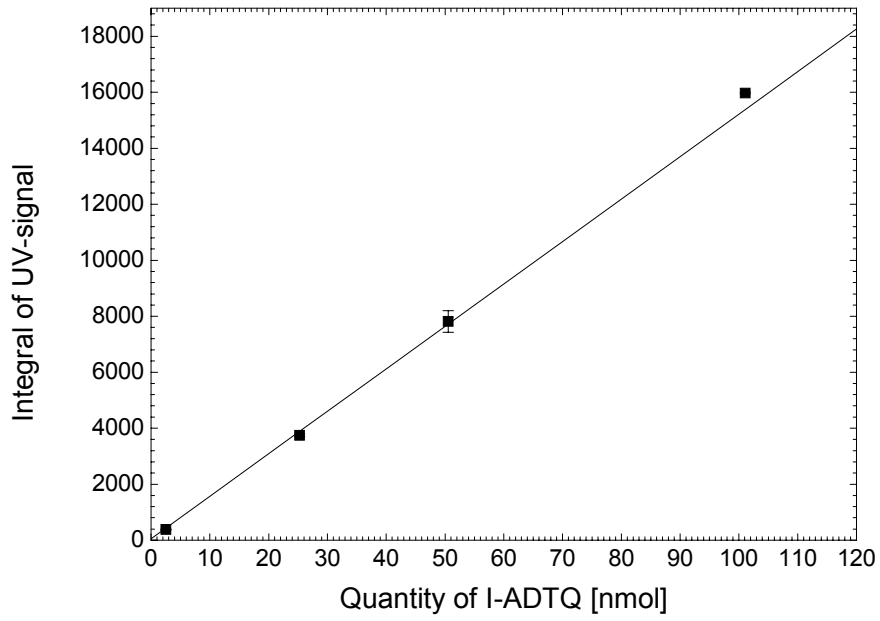


Figure 4.2: Integral of the UV-peak as a function of the quantity of **10a**

4.6 Pharmacological evaluation of [^{131}I]I-ADTQ

Pharmacology evaluation studies were carried out by the Pharmacology Group of the Institute of Nuclear Chemistry (Forschungszentrum Jülich GmbH).

4.6.1 *Ex vivo* study

To investigate if [^{131}I]I-ADTQ **[^{131}I]10a** passes the blood-brain barrier, female NMRI mice weighing 25 ± 2 g received about 4 µCi **[^{131}I]10a** by tail vein injection. The animals were sacrificed 10 min and 60 min after tracer injection, the brains removed, weighed and the radioactivity measured with a gamma-counter. For *ex vivo* autoradiography the brains were frozen, cut into 40 µm thick horizontal slices and exposed to a phosphor imaging plate (Fuji). After exposure for 90 min, a laser phosphor imager (BAS 5000, Fuji) controlled with software by the vendor (Version 3.14, Raytest, Germany) scanned the images.

4.6.2 *In vitro* autoradiography

For autoradiography, frozen brains of Wistar rats were cut horizontal at -18 °C into 20 µm thick sections (Leica AG Microsystems, Germany), mounted onto gelatine-coated object glasses (LO-Laboroptik GmbH) and stored at -80 °C until use.

For the assay, the brain sections were thawed and dried at room temperature. After preincubation for 15 min at 4 °C in 50 mM Tris-HCl containing 0.5 mM $CaCl_2$, the cryosections were incubated with additionally 50 mM KSCN and about 0.5 nM or 7.5 nM of **[^{131}I]10a** (A_S = 21.45 Ci/mmol) in the buffer for 45 min at 4 °C. Adjacent sections were incubated in the presence of 15 µM unlabeled I-ADTQ **10a** or the AMPA antagonist CNQX. After treatment the sections were washed twice for 15 sec in buffer without KSCN at 4 °C, dipped in deionised water, dried and exposed for 45 min to a phosphor imaging plate (Fuji).

Summary

Diaryliodonium salts have been proven as potent precursors for direct nucleophilic n.c.a. ^{18}F-labelling even of electron rich aromatic compounds. In addition, it is known that the 2-thienyl group represents a highly electron rich moiety and that it induces a high regioselectivity in reactions of aryl(2-thienyl)iodonium salts with nucleophiles. However, the 2-thienyl group has only been employed in non-radioactive studies thus far.

In this work, the nucleophilic ^{18}F-labelling methods using diaryliodonium salts were extended by the development of aryl(2-thienyl)iodonium salts as precursors for the nucleophilic ^{18}F-intoduction into arenes, even of electron rich nature. In a systematic approach, a broad investigation of eighteen aryl(2-thienyl)iodonium salts was accomplished in order to study the suitability and applicability of this class of compounds for direct nucleophilic ^{18}F-labelling chemistry.

As first precursors the electron rich *ortho*-, *meta*- and *para*-methoxyphenyl(2-thienyl)iodonium salts were synthesised as their bromide, iodide, tosylate and triflate. Further, *para*-substituted (R = BnO, CH_3, H, Cl, Br, I) aryl(2-thienyl)iodonium bromides were prepared as precursors with a systematically varying electron density.

Three methods for the preparation of aryl(2-thienyl)iodonium salts were compared and tested in this work. One, an *ipso*-demetallation using boronic acids and the Koser's reagent analogue of 2-iodothiophene has the advantage of a regiospecific reaction, but led to many impurities and side-products, especially with electron rich molecules. The other approaches are based on an electrophilic aromatic substitution reaction, where a (diacetoxyiodo)arene reacts with a corresponding aromatic component in presence of concentrated sulphuric acid as catalyst. Both differ by the location of diacetoxyiodo substituent which is either on the thiophene or homoarene component. In case 2-(diacetoxyiodo)thiophene was one reagent, the formed aryl(2-thienyl)-iodonium salt was always obtained as an isomeric mixture of *ortho*- and *para*-derivatives. In the reversed order, using (diacetoxyiodo)arenes and thiophene, the highly activated 2-position of thiophene led regiospecifically to the desired 2-thienyl derivative. Therefore the appropriate iodoarenes were oxidised to their diacetoxyiodo analogue by a gentle procedure using sodium perborate. Only the 4-benzyloxyiodobenzene and 1,4-diiodobenzene required different treatments and were oxidised via sodium periodate and peracetic acid, respectively.

Using these, the corresponding iodonium bromides and iodides were directly formed in yields of 18 to 67 % and 30 to 60%, respectively. The methoxyphenyl(2-thienyl)iodonium tosylates and triflates were prepared by an oxidative anion metathesis of the bromide salts using hydrogen peroxide. The tosylates were obtained in yields of 76 to 93 % and the triflates in yields of

37 to 98 %. All precursors were obtained as pure samples and only for a few re-crystallisation was necessary. Most of the aryl(2-thienyl)iodonium salts were here prepared for the first time.

At first, the general reaction conditions of the n.c.a. ^{18}F-labelling procedure were optimised. This was carried out with 2-methoxyphenyl(2-thienyl)iodonium bromide which led to n.c.a. 2-[^{18}F]fluoroanisole. The activation of n.c.a. [^{18}F]fluoride was performed with the [K⊂2.2.2]$_2$CO$_3$-system at an optimum concentration of 26 mmol/l. Varying the concentration of the precursor from 6 mmol/l to 75 mmol/l in DMF showed the best result with 25 mmol/l. In order to prove the n.c.a. scale an analysis of the high specific activity (A_S) was carried out exemplarily with 4-[^{18}F]fluoroanisole via HPLC. Since no corresponding UV-signal was detected, only a lower limit of $A_S \geq 58$ TBq/mmol could be determined.

The ^{18}F-introduction into diaryliodonium salts proceeds via a S_NAr-mechanism where aprotic polar solvents being the best suitable medium. Therefore acetonitrile (ACN), dimethylacetamide (DMAA), dimethylformamide (DMF) and dimethyl sulphoxide (DMSO) were compared and their effects on the RCY of n.c.a. 2-[^{18}F]fluoroanisole were examined. DMF led to best result with a RCY of 60 % at 130 °C. ACN (90 °C) and DMAA (130 °C) gave only 10 to 15 % RCY. In DMSO the ^{18}F-labelling did not work and only a RCY of ~1 to 2 % was observed. Thus, strong influence of solvents on the n.c.a. ^{18}F-substitution reactions on aryl(2-thienyl)iodonium salts was observed, whereby DMF represents the optimal reaction medium.

In general, higher temperatures lead to an increase of RCY and reaction rates in n.c.a. ^{18}F-for-iodonium exchange procedures. Consequently, the reaction temperature was varied from 90 to 150 °C. Expectedly, the reaction rate increased with higher temperature. Above 130 °C, however, the thermal decomposition of the precursor molecules enters into competition to the ^{18}F-introduction. The optimal temperature where the ^{18}F-exchange still succeeded and the decomposition did not become the crucial factor was found at 130 ± 3 °C.

Different counter anions of iodonium salts strongly influence the ^{18}F-labelling reaction but literature data differ in this factor. An advantage of inorganic counter anions is an effective ion pair separation of diaryliodonium salts in polar solvents. On one hand, dissociated diaryliodonium salts provide a “naked” diaryliodonium cation which is in favour for the attack of [^{18}F]fluoride. On the other hand, counter anions with high nucleophilicity compete for the substitution. Organic counter anions can be ruled out for this problem, but due to a more covalent binding to iodine, they cause a steric and electronic hindrance. The effects of bromides, iodides, tosylates and triflates as counter anions were investigated and, based on the RCY, the following order was obtained: tosylate < iodide < triflate < bromide. However, in terms of kinetics a different order based on the initial reaction rates was observed: tosylate < bromide < iodide < triflate. To explain the disagreement in RCY and kinetics, effects of different dissociation grade and the decomposition tendency of the precursor molecules are assumed.

Evidence for the grade of dissociation of diaryliodonium salts in various solvents can be received by NMR spectra. The proton shifts of 2-methoxyphenyl(2-thienyl)iodonium bromide in d_6-DMF showed a fraction of 92 % in the non-dissociated versus 8 % in the dissociated form; for the iodide the fraction were 87 % and 13 %, respectively. Tosylates and triflates show no dissociation according to their NMR spectra. Thus, the proton shifts / NMR data as well as the RCY obtained favour the presence of non-fully dissociated aryl(2-thienyl)iodonium salts.

Using *ortho*-, *meta*- and *para*-methoxyphenyl(2-thienyl)iodonium bromide in the ^{18}F-exchange reaction gave information about the dependence of the ^{18}F-labelling reaction on the substituent position. Nucleophilic ^{18}F-labelling reactions with diaryliodonium salts are strongly affected by the substitution pattern. Furthermore, a so-called *ortho*-effect as result of the trigonal-bipyramidal intermediate during the ^{18}F-substitution causes generally a preferred attack on *ortho*-substituted rings. Expectedly, the *ortho*-derivative gave a much higher RCY with 60 % of n.c.a. [^{18}F]fluoro-anisole than the *para*-derivative with a RCY of 25 to 30 % and the *meta*-derivative with a RCY of ~20 %. With regard to kinetics, the *meta*-derivative showed a faster initial reaction rate than the *ortho*- and *para*-derivative with almost similar rates.

In view of a systematic examination, the reaction rates *k'* of the ^{18}F-substitution on substituted aryl(2-thienyl)iodonium bromides were compared. Pseudo-first order kinetics were determined by linear regression as a function of the reaction time. The *k'*-values showed a distinct dependence on the electronic character of the substituents and the following order in decreasing reaction rate *k'* was obtained: 4-Br > 4-I > 4-Cl > 3-OCH_3 > H > 4-CH_3 > 2-OCH_3 > 4-OBn > 4-OCH_3. As expected, the electron rich molecules 2- and 4-[^{18}F]fluoroanisole and 4-benzyloxy-1-[^{18}F]fluorobenzene showed the slowest rates, where the *ortho*-effect of 2-methoxyphenyl(2-thienyl)iodonium bromide caused a slightly faster rate. All precursors showed increasing rates along with stronger activation up to the fastest rates with the highly activated *para*-halides.

The *k'*-values were correlated in a Hammett relationship with the appropriate Hammett constants of the substituents. It showed a good linear fit which confirmed the expected S_NAr-mechanism of the ^{18}F-substitution on aryl(2-thienyl)iodonium salts. Furthermore, the reaction parameter ρ was determined with $\rho = + 1.16 \pm 0.2$ and confirmed the nucleophilic mechanism and a consistent mechanism over the range of investigated substituents. A deviation of the *para*-methoxy derivative from the linear relation is accounted on a strong resonance effect of this electron donating group on the iodonium group. Also the *para*-bromo derivative showed also a larger deviation from the linear correlation which was not completely understood.

In all ^{18}F-substitution reactions on aryl(2-thienyl)iodonium salts the high electron density of the 2-thienyl group induced a regiospecific ^{18}F-introduction; i.e. [^{18}F]fluorothiophene was not formed in any reaction. Thus, the one-step nucleophilic n.c.a. ^{18}F-labelling procedure of electron rich molecules via aryl(2-thienyl)iodonium salts developed in this work has proven to be a very potent and fast access to ^{18}F-labelled arenes.

In order to demonstrate the versatility and applicability of this method in practice, the radiosyntheses of two pharmacological relevant molecules were carried out. First, the well-known primary ^{18}F-labelling synthon 4-[^{18}F]fluorophenol was synthesised via 4-benzyloxyphenyl(2-thienyl)iodonium bromide. Within 40 min the desired n.c.a. 4-[^{18}F]fluorophenol was obtained with an overall RCY of 34 to 36 % by ^{18}F-labelling under the optimised conditions, described above, and subsequent reductive debenzylation using ammonium formate and palladium. The new elaborated approach presents a more convenient and faster radiosynthesis for this versatile ^{18}F-labelling synthon. Moreover, 4-[^{18}F]fluorophenol is obtained in anhydrous methanol which allows further radiosynthetic steps including compounds susceptible to moisture without time-consuming drying procedures.

Second, the complex molecule 2-acetyl-6,7-dimethoxy-1-(4'-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (F-ADTQ), earlier characterised as non-competitive AMPA receptor antagonist, was ^{18}F-labelled via three different iodonium precursors. *Ipso*-demetallation of the trimethyltin derivative (Sn-ADTQ) was used to prepare two tosylate precursors containing the 2-thienyl group with good yields of 80 % and 50 %, respectively. However, the n.c.a. ^{18}F-labelling of these three precursors only led to very low RCY of 1.2 to 3.6 %. The bromide precursor gave the best result, when relying on two ^{18}F-labelling attempts. The tosylates showed a small increase in RCY from 1.2 % (phenyl) to 2.9 % (2-thienyl).

The reference F-ADTQ was synthesised via a Pictet-Spengler approach as described in the literature. Similarly, 2-acetyl-6,7-dimethoxy-1-(4'-iodophenyl)-1,2,3,4-tetrahydroisoquinoline (I-ADTQ) was prepared for the first time. As mentioned above, F-ADTQ is known as AMPA receptor antagonist whereas the iodine derivative was not described or pharmacologically characterised so far. Therefore I-ADTQ was labelled with iodine-131 via the trimethyltin precursor using [^{131}I]iodide in ethanol and chloramine T as oxidant. After 2 min reaction time at room temperature, a very high RCY of 97 $\pm$ 2 % of 2-acetyl-6,7-dimethoxy-1-(4'-[^{131}I]iodophenyl)-1,2,3,4-tetrahydroisoquinoline ([^{131}I]I-ADTQ) was obtained without any radioactive side-product formed. The radio-HPL chromatogram showed a very good separation of [^{131}I]I-ADTQ from the trimethyltin precursor Sn-ADTQ. The [^{131}I]I-ADTQ was isolated with a specific activity of ca. 680 GBq/mmol and could be used for preliminary pharmacological evaluation studies. [^{131}I]I-ADTQ passes the blood-brain-barrier with an excellent brain uptake, but no specific accumulation was observed, thus a too high non-specific binding can be assumed.

For proof of identity and determination of radiochemical yields and specific activities radio-HPLC and radio-TLC methods and systems were developed for all radioactive compounds. Furthermore, compounds synthesised for the first time were characterised by NMR-spectroscopy, mass spectrometry and elemental analysis (CHN).

References

[1] Choppin, G. R.; Rydberg, J. in Nuclear Chemistry: Theory and Applications; Pergamon Press, Oxford 1980

[2] Hevesy, G. de; Biochem. J. 17, 439-445 (1923)

[3] Stöcklin, G. in Ullmanns Enzyclopädie der technischen Chemie, Bd. 20: Erzeugung künstlicher Radionuklide; VCH Weinheim 1981, 25-42

[4] Stöcklin, G.; Qaim, S. M.; Rösch, F.; Radiochim. Acta 70/71, 249-272 (1995)

[5] Schicha, H.; Schober, O.; Nuklearmedizin (Compact Lehrbuch), 3. Aufl., Schattenauer Verlag, Stuttgart 1997

[6] Qaim, S. M.; Radiochim. Acta 89, 223-232 (2001)

[7] Qaim, S. M.; Radiochim. Acta 89, 297-302 (2001)

[8] Bremer, K. H. in Ullmanns Enzyclopädie der technischen Chemie, Bd. 20: Anwendung von Radionukliden in der Medizin, VCH Weinheim 1981, 59-64

[9] Wüstenberg, T.; Jordan, K.; Giesel, F. L.; Villringer, A.; Der Radiologe 7, 552-557 (2003)

[10] Stöcklin, G.; Nachr. Chem. Tech. Lab. 34, 1057-1064 (1986)

[11] Wienhard, K.; Wagner, R.; Heiss, W. D. in PET – Grundlagen und Anwendung der Positronen Emissions Tomographie, Springer Verlag Heidelberg 1989

[12] Coenen, H. H.; Der Nuklearmediziner 17, 203-214 (1994)

[13] Coenen, H. H. in Clinical Molecular Anatomic Imaging: PET, PET/CT and SPECT/CT, Ch. 16, PET-radiopharmaceuticals: fluorinated compounds; Lippincott Williams & Wilkins 2003

[14] Herzog, H.; Radiochim. Acta 89, 203-214 (2001)

[15] Henrich, E.; Ebert, K. H.; Angew. Chem. 104, 1310-1324 (1992)

[16] Ache H. J.; Angew. Chem. 84, 234-254 (1972)

[17] Pauleit, D.; Floeth, F., Hamacher, K.; Riemenschneider, M. J.; Reifenberger, G.; Müller, H.-W.; Zilles, K.; Coenen, H. H.; Langen, K.-J.; Brain 128, 678-687 (2005)

[18] Weber S.; Herzog, A.; Cremer, M.; Engels, R.; Hamacher, K.; Kehren, F.; Mühlensiepen, H.; Ploux, L.; Reinartz, R.; Reinhart, P.; Rongen, F.; Sonnenberg, F.; Coenen, H. H.; Halling, H.; IEEE Trans. Nucl. Sci. 46, 1177-1183 (1999)

[19] Weber S.; Bauer, A.; Herzog, A.; Kehren, F.; Mühlensiepen, H.; Vogelbruch, J.; Coenen, H. H.; Zilles, K.; Halling, H.; IEEE Trans. Nucl. Sci. 47, 1665-1669 (2000)

[20] Missimer, J.; Madi, Z.; Honer, M.; Keller, C.; Schubiger, P. A.; Ametamey, S. M.; Phys. Med. Biol. 49, 2069-2081 (2004)

[21] Woody, C.; Kriplani, A.; O'Connor, P.; Pratte, J.-F.; Radeka, V.; Rescia, S.; Schlyer, D.; Shokouhi, S.; Stoll, S.; Vaska, P.; Villaneuva, A.; Volkow, N.; Yu, B.; Nuc. Inst. and Meth. A 527, 166-170 (2004)

[22] Fowler, J. S.; Wolf, A. P.; Nuclear Science Series (NAS-NS-3201) 1982

[23] Långström, B.; Andersson, Y.; Antoni, G.; Axelson, S.; Bjurling, P.; Fasth, K. J.; Gee, A.; Kihlberg, T.; Ulin, J.; Watanabe, Y.; Acta. Radiol. Suppl. 376, 31-35 (1991)

[24] Holschbach, M.; Schirrmacher, R.; Solbach, C.; Hamkens, W.; Coenen, H. H.; J. Label. Compds. Radiopharm. 40, 762 (1997)

[25] Långström, B.; Antoni, G.; Gullberg, P.; Halldin, C.; Malmborg, P.; Någren, K.; Rimland, A.; Svärd, H.; J. Nucl. Med. 28, 1037-1040 (1987)

[26] Ehrin, E.; Gawell, L.; Högberg, T.; de Paulis, T.; Ström, P.; J. Label. Compds. Radiopharm. 24, 931-940 (1987)

[27] Coenen, H. H.; Moerlein, S. M.; Stöcklin, G.; Radiochim. Acta 34, 47-68 (1983)

[28] Pagani, M.; Stone-Elander, S.; Larsson, S. A.; Eur. J. Nucl. Med. 24, 1302-1327 (1997)

[29] Plenevaux, A.; Guillaume, M.; Brihaye, C.; Lemaire, C.; Cantineau, R.; Appl. Radiat. Isot. 41, 829-838 (1990)

[30] Emert, J.; Blum, T.; Hamacher, K.; Coenen, H. H.; Radiochim. Acta 89, 863-866 (2001)

[31] Lemaire, C.; Cantineau, R.; Guillaume, M.; Plenevaux, A.; Christiaens, L.; J. Nucl. Med. 32, 2266-2272 (1991)

[32] Coenen, H. H.; Kling, P., Stöcklin, G.; J. Nucl. Med. 41, 829-838 (1989)

[33] Wester, H. J.; Herz, M.; Weber, W.; Heiss, P.; Senekowitsch-Schmidtke, R.; Schwaiger, M.; Stöcklin, G.; J. Nucl. Med. 40, 205-212 (1999)

[34] Pauleit, D.; Stoffels, G.; Schaden, W.; Hamacher, K.; Bauer, D.; Tellmann, L.; Herzog, H.; Bröer, S.; Coenen, H. H.; Langen, K.-J.;J. Nucl. Med. 46, 411-416 (2005)

[35] Weckesser, M.; Langen, K.-J.; Rickert, C. H.; Kloska, S.; Straeter, R.; Hamacher, K.; Kurlemann, G.; Wassmann, H.; Coenen, H. H.; Schober, O.; Eur. J. Nucl. Med. Mol. Imaging 32, 422-429 (2005)

[36] Reivich, M.; Kuhl, D.; Wolf, A.; Greenberg, J., Phelps, M., Ido, T.; Casella, V.; Fowler, J.; Hoffman, E.; Alavi, A.; Som, P.; Sokoloff, L.; Circ. Res. 44, 127-137 (1979)

[37] Gallagher, B.M.; Fowler, J. S.; Gutterson, N. I.; McGregor, R. R.; Wan, C. N.; Wolf, A. P.; J. Nucl. Med. 19, 1154-1161 (1978)

[38] Coleman, R. E., Nucl. Med. Biol. 27, 689-690 (2000)

[39] Stöcklin, G.; Eur. J. Nucl. Med. 19, 527-551 (1992)

[40] Knapp, F. F.; Mirzadeh, S., Eur. J. Nucl. Med. 21, 1151-1165 (1994)

[41] Gould, K. L.; Goldstein, R. A.; Mullani, N. A.; Kirkeeide, R. L.; Wong, W. H.; Tweson, T. J.; Berridge, M. S.; Bolomey, L. A.; Hartz, R. K.; Smalling, R. W.; Facc, F. F.; Nishikawa, A.; J. Am. Coll. Cardiol. 7, 775-789 (1986)

[42] Qaim, S. M.; Stöcklin, G.; Radiochim. Acta 34, 25-40 (1983)

[43] Guillaume, M.; Luxen, A.; Nebeling, B.; Argentini, M.; Clark, J. C.; Pike, V. W.; Appl. Radiat. Isot. 42, 749-762 (1991)

[44] Hess, E.; Takács, S.; Scholten, B., Tárkányi, F.; Coenen, H. H.; Qaim, S. M.; Radiochim. Acta 89, 357-362 (2001)

[45] Casella, V.; Christman, D. R.; Ido, T., Wolf, A. P.; Radiochim. Acta 25, 17-20 (1978)

[46] Tilbury, R. S.; Dahl, J. R.; Radiat. Res. 79, 22-23 (1979)

[47] Retz-Schmidt, T., Weil, J. L.; Phys. Rev. 119, 1079-1084 (1960)

[48] Bastian, Th.; Coenen, H. H.; Qaim, S. M.; Appl. Radiat. Isot. 55, 303-308 (2001)

[49] Qaim, S. M.; Hohn, A.; Bastian, Th.; El-Azony, K. M.; Blessing, G.; Spellerberg, S.; Scholten, B.; Coenen, H. H.; Appl. Radiat. Isot. 58, 69-78 (2003)

[50] Hohn, A.; Nortier, F. M.; Scholten, B.; van der Walt, T. N.; Coenen, H. H.; Qaim, S. M.; Appl. Radiat. Isot. 55, 149-156 (2001)

[51] Hohn, A.; Dissertation Universität zu Köln, Berichte des Forschungszentrum Jülich, JÜL 3838 (2000)

[52] Qaim, S. M.; Appl.Radiat. Isot. 37, 803-810 (1986)

[53] Mushtaq, A.; Qaim, S. M.; Radiochim. Acta 50, 27-31 (1990)

[54] Blessing, G.; Lavi, N.; Qaim, S. M.; Appl. Radiat. Isot. 43, 455-461 (1992)

[55] Mushtaq, A.; Qaim, S. M.; Stöcklin, G.; Appl. Radiat. Isot. 39, 1085-1091 (1988)

[56] Blessing, G.; Lavi, N.; Hashimoto, K.; Qaim, S. M.; Radiochim. Acta 65, 93-98 (1994)

[57] Lieser, K. H.; Einführung in die Kernchemie, Verlag Chemie, Weinheim 1980

[58] Atkins, P. W.; Physikalische Chemie, VCH, Weinheim 1990

[59] Wallach, O.; Justus Liebigs Ann. Chem. 235, 242-255 (1886)

[60] Balz, G.; Schiemann, G., Chem. Ber. 60, 1186-1190 (1927)

[61] Atkins, H. L.; Christmann, D. R.; Fowler, J. S.; Hauser, W.; Hoyte, R. M.; Kloper, J. F.; Lin, S. S.; Wolfe, A. P.; J. Nucl. Med. 13, 713-719 (1972)

[62] Tewson, T. J.; Welch, M. J.; J. Chem. Soc. Chem. Comm., 1149-1150 (1979)

[63] Coenen, H. H. in Synthesis and Application of Isotopically Labelled Compounds (Baille, T. A.; Jones, J. R. (eds.)), No-carrier-added 18F-chemistry of Radiopharmaceuticals, Elsevier Publ., Amsterdam 1989, 433-448

[64] Hess, E.; Blessing, G.; Coenen, H. H.; Qaim, S. M.; Appl. Radiat. Isot. 52, 1431-1440 (2000)

[65] Visser, G. W. M.; Bakker, C. N. M., Herscheid, J. D. M.; Brinkman, G.; Hoekstra, A.; J. Label. Compds. Radiopharm. 21, 1226 (1984)

[66] Chirakal, R.; Firnau, G.; Schrobilgen, G. J.; McKay, J.; Garnett, E. S.; Appl. Radiat. Isot. 35, 401-404 (1984)

[67] Constantinou, M.; Aigbirhio, F. I.; Smith, R. G.; Ramsden, C. A.; Pike, V. W.; J. Am. Chem. Soc. 123, 1780-1781 (2001)

[68] Bergman, J.; Solin, O.; Nucl. Med. Biol. 24, 677-683 (1997)

[69] Adam, M. J.; Abeysekaera, B. F.; Ruth, T. J.; J. Label. Compds. Radiopharm. 21, 1227 (1984)

[70] Coenen, H. H.; Moerlein, S. M.; J. Fluorine Chem. 36, 63-75 (1987)

[71] Coenen, H. H.; Franken, K.; Kling, P.; Stöcklin, G.; Appl. Radiat. Isot. 39, 1243-1250 (1988)

[72] Namavari, M.; Bishop, A.; Satyamurthy, N.; Bisa, G.; Barrio, J. R.; Appl. Radiat. Isot. 43, 989-996 (1992)

[73] de Vries, E. F. J.; Luurtsema, G.; Brüssermann, M.; Elsinga, P. H.; Vaalburg, W.; Appl. Radiat. Isot. 51, 389-394 (1999)

[74] Lemaire, C.; Damhaut, P.; Plenevaux, A.; Comar, D.; J. Nucl. Med. 35, 1996-2002 (1994)

[75] Coenen, H. H.; Klatte, B.; Knöchel, A.; Schüller, M.; Stöcklin, G.; J. Label. Compds. Radiopharm. 23, 455-467 (1986)

[76] Block, D.; Klatte, B.; Knöchel, A.; Beckmann, R.; Holm, U.; J. Label. Compds. Radiopharm. 23, 468-477 (1986)

[77] Block, D.; Coenen, H. H.; Stöcklin, G.; J. Label. Compds. Radiopharm. 24, 1029-1042 (1987)

[78] Coenen, H. H. in Progress in Radiopharmacy Development in Nuclear Medicine 10 (Cox, Mather, Sambson, Lazarus, eds.), New radiohalogenation methods: An overview, Martinus Nijhoff Publishers, Dordrecht, 196-220 (1986)

[79] Kilbourn, M. R.; Fluorine-18 Labelling of Radiopharmaceuticals, Nuclear Science Series NAS-NS-3203, National Academy Press Washington D.C. (1990)

[80] Hamacher, K.; Coenen, H. H.; Stöcklin, G.; J. Nucl. Med. 27, 235-238 (1986)

[81] Angelini, G.; Speranza, M.; Wolf, A. P.; Shiue, C. Y.; Fowler, J. S.; J. Label. Compds. Radiopharm. 21, 1223-1226 (1984)

[82] Hamacher, K.; Hamkens, W.; Appl. Radiat. Isot. 46, 911-916 (1995)

[83] Hansch, C.; Leo A.; Taft, R. W.; Chem. Rev. 91, 165-195 (1991)

[84] Gail, R.; Coenen, H. H.; Appl. Radiat. Isot. 45, 105-111 (1993)

[85] Plenevaux, A.; Lemaire, C.; Palmer, A. J.; Damhaut, P.; Comar, D.; Appl. Radiat. Isot. 43, 1035-1040 (1992)

[86] Block, D.; Coenen, H. H.; Stöcklin, G.; J. Label. Compds. Radiopharm. 25, 201-216 (1988)

[87] Kilbourn, M. R. ; Dence, C. S.; Welch, M. J.; Mathias, C. J.; J. Nucl. Med. 28, 462–470 (1987)

[88] Block, D.; Coenen, H. H.; Stöcklin, G.; J. Label. Compds. Radiopharm. 25, 185–200 (1988)

[89] Shai, Y.; Kirk, K. L.; Channing, M. A.; Dunn, B. B.; Lesniak, M. A.; Eastman, R. C.; Finn, R. D.; Roth, J.; Jacobson, K. A.; Biochem. 28, 4801–4806 (1989)

[90] Coenen, H. H.; Laufer, P.; Stöcklin, G.; Wienhard, K.; Pawlik, G.; Böcker-Schwarz, H. G.; Heiss, W. D.; Life Sciences 40; 81–88 (1987)

[91] Moerlein, S. M.; Perlmutter, J. S.; Neurosci. Lett. 123; 23–26 (1991)

[92] Moerlein, S. M.; Perlmutter, J. S.; Eur. J. Pharmacol. 218; 109–115 (1992)

[93] Wilson, A. A.; Dasilva, J. N.; Houle, S.; Appl. Radiat. Isot. 46; 765–770 (1995)

[94] Jelinski, M.; Dissertation Universität zu Köln, Berichte des Forschungszentrum Jülich, JÜL 4044 (2003)

[95] Guhlke, S.; Coenen, H. H.; Stöcklin, G.; J. Nucl. Med. 32; 1009–1016 (1991)

[96] Guhlke, S.; Wester, H. J.; Bruns, C.; Stöcklin, G.; Nucl. Med. Biol. 21, 819-825 (1994)

[97] Allain Barbier, L.; Lasne, M. C.; Perrio Huard, C.; Moreau, B.; Barré, L.; Acta Chem. Scand. 52, 480-489 (1998)

[98] Marriére, E.; Rouden, J.; Tadino, V.; Lasne, M.-C.; Org. Lett. 2, 1121-1124 (2000)

[99] Wüst, F. R.; Kniess, T.; J. Label. Compds. Radiopharm. 46, 699–713 (2003)

[100] Ermert, J.; Hocke, C.; Ludwig, T.; Gail, R.; Coenen, H. H.; J. Label. Compd. Radiopharm. 47, 429-441 (2004)

[101] Ludwig, T.; Gail, R.; Coenen, H. H.; J. Nucl. Med. 39, 21P (1998)

[102] Shiue, C. Y.; Fowler, J. S.; Wolf, A. P.; Watanabe, M.; Arnett, C. D.; J. Nucl. Med. 26, 181-186 (1985)

[103] Poethko, T.; Schottelius, M.; Thumshirn, G.; Hersel, U.; Herz, M.; Henriksen, G.; Kessler, H.; Schwaiger, M.; Wester, H. J.; J. Nucl. Med. 45, 892-902 (2004)

[104] Kirk, K. L.; Creveling, C. R.; Med. Res. Rev. 4, 189-220 (1984)

[105] Kirk, K. L.; Olubajo, O.; Buchhold, K.; Lewandowski, G. A.; Gusovsky, F.; McCulloh, D.; Daly, J. W.; Creveling, C. R.; J. Med. Chem. 29, 1982-1988 (1986)

[106] Barre, L.; Barbier, L.; Lasne, M. C.; J. Label. Compds. Radiopharm. 35, 167 (1993)

[107] Ekaeva, I.; Barre, L.; Lasne, M. C.; Gourand, F.; Appl. Radiat. Isot. 46, 777-782 (1995)

[108] Ludwig, T.; Ermert, J.; Coenen, H. H.; Nucl. Med. Biol. 29, 255–262 (2002)

[109] Ludwig, T.; Ermert, J.; Coenen, H. H.; J. Label. Compds.. Radiopharm. 44 (Suppl. 1), S1 (2001)

[110] Stoll, T.; Ermert, J.; Oya, S.; Kung, H. F.; Coenen, H. H.; J. Label. Compds. Radiopharm. 47, 443-455 (2004)

[111] Oya, S.; Kung, M.-P.; Acton, P. D.; Mu, M.; Hou, C.; Kung, H. F.; J. Med. Chem. 42, 333-335 (1999)

[112] Seevers, R. H.; Counsell, R. E.; Chem. Rev. 82, 575-590 (1982)

[113] Coenen, H. H.; Mertens, J.; Mazière, B.; Compemdium on Radioiodination Reactions for Radiopharmaceuticals, not yet published

[114] Jirousek, L.; J. Radioanal. Chem. 65, 139-154 (1981)

[115] Coenen, H. H.; El-Wetery, A. S.; Stöcklin, G.; J. Label. Compds. Radiopharm. 18, 114-115 (1981)

[116] Youfeng, H.; Coenen, H. H.; Petzold, G.; Stöcklin, G.; J. Label. Compds. Radiopharm. 19, 807-819 (1982)

[117] Mennicke, E.; Holschbach, M.; Coenen, H. H.; J. Label. Compds. Radiopharm. 43, 721-737 (2000)

[118] Moerlein, S. M.; Mathis, C. A.; Yano, Y.; Appl. Radiat. Isot. 38, 85-90 (1987)

[119] Mennicke, E.; Hennecken, H.; Holschbach, M., Coenen, H. H.; Eur. J. Nucl. Med. 25, 843-845 (1998)

[120] Morrison, M.; Bayse, G. S.; Biochem. 9, 2995-3000 (1970)

[121] Moore, D. H.; Wolf, W.; J. Label. Compds. Radiopharm. 15, 443-450 (1978)

[122] Moerlein, S. M.; Beyer, W.; Stöcklin, G.; J. Chem. Soc. Perkin Trans. 1, 779-786 (1988)

[123] McKillop, A.; Taylor, E. C.; Fowler, J. S.; Zelesko, M. J.; Hunt, J. D.; McGillivray, G.; Tetrahedron Lett. 10, 2427-2430 (1969)

[124] Kabalka, G. W.; Varma, R. S.; Tetrahedron 45, 6601-6621 (1989)

[125] Flanagan, R. J. in New Trends in Radiopharmaceutical Synthesis, Quality Assurance and Regulatory Control (Emran, A. M., ed.), The Synthesis of Halogenated Radiopharmaceuticals Using Organomercurials, Plenum Press, New York 1991, 279-288

[126] Moerlein, S. M.; Coenen, H. H.; J. Chem. Soc. Perkin Trans. 1, 1941-1947 (1985)

[127] Lindley, J.; Tetrahedron 40, 1433-1456 (1984)

[128] Clark, J. H.; Jones, C. W.; J. Chem. Soc., Chem. Commun., 1409-1411 (1987)

[129] Henneken, H.; Dissertation Universität zu Köln, Berichte der Kernforschungsanlage Jülich JÜL 3162 (1995)

[130] Bolton, A. E.; Hunter, W. M.; Biochem. J. 133, 529-533 (1973)

[131] Rudinger, J.; Ruegg, U.; Biochem. J. 133, 538-539 (1973)

[132] Glaser, M.; Carroll, V. A.; Collinbridge, D. R.; Aboagye, E. O.; Price, P.; Bicknell, R.; Harris, A. L.; Luthra, S. K.; Brady, F.; J. Label. Compd. Radiopharm. 45, 1077-1090 (2002)

[133] Wood, F. T.; Wu, M. M.; Gerhart, J. J.; Anal. Biochem. 69, 339-349 (1975)

[134] Ram, S.; Fleming, E.; Buchsbaum, D. J.; J. Nucl. Med. 33,1029-1029 (1992)

[135] Khawli, L. A.; Chen, F. M.; Alaudin, M. M.; Stein, A. L.; Antibody Immunoconj. Radiophar. 4, 163-182 (1991)

[136] Ali, S. A.; Eary, J. F.; Warren, S. D.; Krohn, K. A.; Nucl. Med. Biol. 15, 557-561(1988)

[137] Khawli, L. A.; van de Abeele, A. D.; Kassis, A. I.; Nucl. Med. Biol. 19, 289-295 (1992)

[138] Willgerodt, C.; J. Prakt. Chem. 33, 154-160 (1886)

[139] Willgerodt, C.; Chem. Ber. 25, 3494-3502 (1892)

[140] Zhdankin, V. V.; Stang, P. J.; Chem. Rev. 102, 2523-2584 (2002)

[141] Crivello, J. V.; Sangermano, M.; J. Polym. Sci. Part A: Polym. Chem. 39, 343-356 (2001)

[142] Yagci, Y; Yilmaz,F.; Kiralp, S.; Toppare, L.; Macromol. Chem. Phys. 206, 1178–1182 (2005)

[143] Dentinger, P. M.; Hunter, L. L.; O'Connell, D. J.; Gunn, S.; Goods, D.; Fedynyshyn, T. H.; Goodman, R. B.; Astolfi, D. K.; J. Vac. Sci. Technol. B 20, 2962-2967 (2002)

[144] Murakami, Y.; Coenjarts, C. A.; Ober, C. K.; J. Photopolym. Sci. Technol. 17, 115-118 (2004)

[145] Gallop, P. M.; Paz, M. A.; Flückiger, R.; Stang, P. J.; Zhdankin, V. V.; Tykwinski, R. R.; J. Am. Chem. Soc. 115, 11702-11704 (1993)

[146] Holland, P. C.; Clark, M. G.; Bloxham, D. P.; Lardy, H. A.; J. Biol. Chem. 248, 6050-6056 (1973)

[147] Kang, S.-K.; Yamaguchi, T.; Kim, T.-H.; Ho, P.-S.; J. Org. Chem. 61, 9082–9083 (1996)

[148] Kang, S.-K.; Lim, K.-H.; Ho, P.-S.; Yoon, S.-K.; Son, H.-Y.; Synth. Commun. 28, 1481-1489 (1998)

[149] Kang, S.-K.; Kim, J.-S.; Choi, S.-C.; Lim, K.-H.; Synthesis, 1249-1251 (1998)

[150] Wang, G.-P.; Chen, D.-J.; Synth. Commun. 29, 2859-2866 (1999)

[151] Koser, G. F. in The Chemistry of Functional Groups, Suppl. D, Ch. 25 (Patai, S and Rappaport, Z.; eds.), Halonium Ions, Wiley 1983, 1265-1351

[152] Stang, P. J.; J. Org. Chem. 68, 2997-3008 (2003)

[153] Stang, P. J.; Angew. Chem. 104, 281-292 (1992)

[154] Zhdankin, V. V.; Stang, P. J.; Tetrahedron 54, 10927-10966 (1998)

[155] Pike, V. W.; Aigbirhio, F. I.; J. Chem. Soc. Chem. Commun. 21, 2215-2216 (1995)

[156] Varvoglis, A. in Topics of Current Chemistry Vol. 224, Preparation of Hypervalent Iodine Compounds, Springer-Verlag, Heidelberg 2003, 70-98

[157] Koser, G. F.; Wettach, R. H.; J. Org. Chem. 45, 1542-1543 (1980)

[158] Beringer, F. M.; Drexler, M.; Gindler, E. M.; Lumpkin, C. C.; J. Am. Chem. Soc. 75, 2705-2712 (1953)

[159] Kazmierczak, P.; Skulski, L.; Synthesis, 1721-1723 (1998)

[160] Shah, A.; Pike, V. W.; Widdowson, D. A.; J. Chem. Soc, Perkin Trans. 1, 2463-2465 (1997)

[161] Mc Killop, A.; Kemp, D.; Tetrahedron 45, 3299-3306 (1989)

[162] Kryska, A.; Skulski, L.; Molecules 6, 875-880 (2001)

[163] Kazmierczak, P.; Skulski, L.; Kraszkiewicz, L.; Molecules 6, 881-891 (2001)

[164] Kazmierczak, P.; Skulski, L.; Molecules 8, 810-812 (2002)

[165] Peacock, M. J.; Pletcher, D.; Tetrahedron Lett. 41, 8995-8998 (2000)

[166] Kazmierczak, P.; Skulski, L.; Synthesis, 1027-1032 (1995)

[167] Kazmierczak, P.; Skulski, L.; Bull. Chem. Soc. Jpn. 70, 219-224 (1997)

[168] Skulski, L.; Wroczynski, P.; Bull. Polish Acad. Sci. Chem. 47, 231-238 (1999)

[169] Kitamura, T.; Matsuyuki, J.; Taniguchi, H.; Synthesis, 147-148 (1994)

[170] Carroll, M. A.; Pike, V. W.; Widdowson, D. A.; Tetrahedron Lett. 41, 5393-5396 (2000)

[171] Pike, V. W.; Butt, F.; Shah, A.; Widdowson, D. A.; J. Chem. Soc. Perkin Trans. 1, 245-248 (1999)

[172] Kitamura, T.; Kotani, M.; Fujiwara, Y.; Tetrahedron Lett. 37, 3721-3722 (1996)

[173] Kasumov, T. M.; Pirguliyev, N. Sh.; Brel, V. K.; Grishin, Y. K.; Zefirov, N. S.; Stang, P. J.; Tetrahedron 53, 13139-13148 (1997)

[174] Grushin, V. V.; Tolstaya, T. P.; Lisichkina, I. N.; Bull. Acad. Sci. USSR, Div. Chem. 33, 1957-1960 (1983)

[175] Pike, V. W.; Aigbirhio, F. I.; J. Label. Compd. Radiopharm. 37, 120-122 (1995)

[176] Gail, R.; Hocke, C.; Coenen, H. H.; J. Label. Compd. Radiopharm. 40, 50-52 (1997)

[177] Gail, R.; Hocke, C.; Coenen, H. H.; J. Nucl. Med. 38, 43P (Suppl.) (1997)

[178] Shah, A.; Pike, V. W.; Widdowson, D. A.; J. Chem. Soc, Perkin Trans. 1, 2043-2046 (1998)

[179] Count Le, D. J.; Reid, J. A. W.; J. Chem. Soc. (C), 1298-1301 (1967)

[180] Yamada, Y.; Okawara, M.; Bull. Chem. Soc. Jap. 45, 1860-1863 (1972)

[181] Hostetler, E. D.; Jonson, S. D.; Welch, M. J.; Katzenellenbogen, J. A.; J. Org. Chem. 64, 178-185 (1999)

[182] Martin-Santamaria, S.; Carroll, M. A.; Carroll, C. M.; Carter, C. D.; Pike, V. W.; Rzepa, H. S.; Widdowson, D. A.; Chem. Commun., 649-650 (2000)

[183] Grushin, V. V.; Demkina, I. I.; Tolstaya, T. P.; J. Chem. Soc., Perkin Trans 2, 505-511 (1992)

[184] Yamada, Y.; Okawara, M.; Bull. Chem. Soc. Jap. 45, 2515-2519 (1972)

[185] Wüst, F.; Carlson, K. E.; Katzenellenbogen, J. A.; Steroids 68, 177-191 (2003)

[186] Carroll, M. A.; Kamara, L. M.; Widdowson, D. A.; Pike, V. V.; J. Label. Compds. Radiopharm. 48, 519-520 (2005)

[187] Siegel, G. J.; Agranoff, B. W.; Albers, R. W.; Molinoff, P. B. (eds.); Basic Neurochemistry, Raven Press New York 1994

[188] Klinke, R.; Silbernagel, S.; Lehrbuch der Physiologie, 2. Aufl., GeorgThieme Verlag, Stuttgart 1996

[189] Nelson, D. L.; Cox, M. M.; Principles of Biochemistry (Lehniger), 4th ed., W. H. Freeman and Company, New York 2005

[190] Kew, J. N. C.; Kemp, J. A.; Psychopharmacology 179, 4-29 (2005)

[191] Less, G. J.; Drugs 59, 33-78 (2000)

[192] Bräuner-Osborne, H.; Egebjerg, J.; Nielsen, E. Ø.; Madsen, U.; Krogsgaard-Larsen, P.; J. Med. Chem. 43, 2609-2645 (2000)

[193] Dingledine, R.; Borges, K.; Bowie, D.; Traynelis, S. F.; Pharmacol. Rev. 51, 7-61 (1999)

[194] Gitto, R.; Barreca, M. L.; De Luca, L.; De Sarro, G.; Ferreri, G.; Quartarone, S.; Russo, E.; Constanti, A.; Chimirri, A.; J. Med. Chem. 46, 197-200 (2003)

[195] Gitto, R.; Barreca, M. L.; De Luca, L.; Chimirri, A.; Expert Opin. Ther. Patents 14, 1199-1213 (2004)

[196] http://www.clinicaltrials.gov

[197] Chappell, A. S.; Sander J. W.; Brodie, M. J.; Chadwick, D.; Lledo, A.; Zhang, D.; Bjerke, J.; Kiesler, G. M.; Arroyo, S.; Neurology 58, 1680-1682 (2002)

[198] Langan, Y. M.; Lucas, R.; Jewell, H.; Toublanc, N.; Schaefer, H.; Sander, J. W. A. S.; Patsalos, P. N.; Epilepsia 44, 46-53 (2003)

[199] Walter, W.; Francke, W.; Beyer Walter – Lehrbuch der Organischen Chemie, 23. Aufl., S. Hirzel Verlag Stuttgart 1998

[200] Beringer, F. M.; Galton, S. A.; J. Org. Chem. 31, 1648-1651 (1966)

[201] Fraenkel, G.; J. Chem. Phys. 39, 1614-1615 (1963)

[202] Reichardt, C.; Chem. Rev. 94, 2319-2358 (1994)

[203] Beringer, F. M.; Geering, E. J.; Kuntz, I.; Mausner, M.; J. Phys. Chem. 60, 141-150 (1956)

[204] Beringer, F. M.; Mausner, M.; J. Am. Chem. Soc. 80, 4535-4536 (1958)

[205] Ochiai, M.; Kida, M.; Sato, K., Takino, T.; Goto, S.; Donkai, N.; Okuyama, T.; Tetrahedron Lett. 40, 1559-1562 (1999)

[206] Carroll, M. A.; Martín-Santamaría, S.; Pike, V. W.; Rzepa, H. S.; Widdowson, D. A.; J. Chem. Soc., Perkin Trans. 2, 2707-2714 (1999)

[207] Martín-Santamaría, S.; Carroll, M. A.; Pike, V. W.; Rzepa, H. S.; Widdowson, D. A.; J. Chem. Soc., Perkin Trans. 2, 2158-2161 (2000)

[208] Beringer, F. M.; Gindler, E. M.; J. Am. Chem. Soc. 77, 3200-3203 (1955)

[209] Streitwieser Jr., A.; Wilkins, C. L.; Kiehlmann, E.; J. Am. Chem. Soc. 90, 1598-1601 (1968)

[210] Whitesides, G. M.; Mitchell, H. L.; J. Am. Chem. Soc. 91, 5386-5388 (1969)

[211] Howells, R. D.; Mc Cown, J. D.; Chem. Rev. 77, 69-92 (1977)

[212] Ayers, P. W.; Anderson, J. S. M.; Rodriguez, J. I.; Jawed, Z.; Phys. Chem. Chem. Phys. 7, 1918-1925 (2005)

[213] Suhr, H.; Chem. Ber. 97, 3268-3276 (1964)

[214] Petrosyan, V. S.; Reutov, O. A.; Chem. Abstr. 68; 7940u (1968)

[215] Shorter, J.; Chem. unserer Zeit 19, 197-208 (1985)

[216] Hammett, L. P.; J. Am. Chem. Soc. 59, 96-102 (1937)

[217] Jaffé, H. H.; Chem. Rev. 53, 191-261 (1953)

[218] Exner, O. in Advances in Linear Free Relationships (Chapman, N. B.; Shorter, J. (eds.)), Ch. 1, Plenum London 1972

[219] Stock, L. M.; Brown, H. C.; *Adv. Phys. Org. Chem.* **1**, 35-154 (1935)

[220] Sykes, P.; Reaktionsmechanismen der Organischen Chemie, 9. Aufl., VCH Weinheim 1988

[221] Beringer, F. M.; Bachofner, E. H.; Falk, R. A.; Leff, M.; J. Am. Chem. Soc. 80, 4279-4281 (1958)

[222] Nabana, T.; Togo, H.; J. Org. Chem. 67, 4362-4365 (2002)

[223] Hamacher, K.; Hirschfelder, Th.; Coenen, H. H.; Appl. Radiat. Isot. 56, 519-523 (2002)

Abbreviations

ACN	acetonitrile
ADTQ	2-Acetyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline
AMPA	α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid
A_s	specific activity
b.p.	boiling point
BBB	blood-brain barrier
Bn	benzyl group ($-CH_2C_6H_5$)
Bq	Becquerel
c.a.	carrier-added
c.f.	carrier-free
CAT	chloramine T
cf.	confer
Ci	Curie (1 Ci = $3.7 \cdot 10^{10}$ Bq)
CNS	central nervous system
CT	computed tomography
d	days (half-life), duplet (NMR), deuterium (nuclear reactions)
DCM	dichloromethane
DMAA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethyl sulphoxide
DNA	deoxyribonucleic acid
DOPA	3,4-dihydroxy-L-phenylalanine
e.g.	for example (lat. *exempli gratia*)
EC	electron capture
eq.	equivalent
EtOH	ethanol
eV	electronvolt
F-ADTQ	2-acetyl-6,7-dimethoxy-1-(4'-fluorophenyl)-1,2,3,4-tetrahydro-isoquinoline
FDG	2-fluoro-2-deoxy-D-glucose
GABA	γ-aminobutyric acid
GC	gas chromatography
HPLC	high performance liquid chromatography
i.e.	that is (lat. *id est*)
I-ADTQ	2-acetyl-6,7-dimethoxy-1-(4'-iodophenyl)-1,2,3,4-tetrahydro-isoquinoline
iGluR(s)	ionotropic glutamate receptor(s)
IR	infrared
k	reaction rate constant

K	reaction equilibrium constant
KA	kainic acid / kainate
LET	linear energy transfer
LFER	linear free energy relationship
LSF	least square fit
m	multiplet
m.p.	melting point
MeOH	methanol
mGluR(s)	metabotropic glutamate receptor(s)
(f)MRI	(functional) magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MRT	magnetic resonance tomography
n.c.a.	no-carrier-added
N_A	Avogadro's number
NDMA	*N*-methyl-D-aspartate
NMR	nuclear magnetic resonance
NR(s)	NDMA receptor(s)
ns	nanoseconds
p	proton
PET	positron emission tomography
PLC	phospholipase C
ppm	parts per million
PTC	phase transfer catalyst
q	quartet
RCY	radiochemical yield
RIA	radioimmunoassay
s	singlet
Sn-ADTQ	2-Acetyl-6,7-dimethoxy-1-(4'-trimethylstannylphenyl)-1,2,3,4-tetrahydroisoquinoline
S_NAr	nucleophilic aromatic substitution
spall.	spallation
SPE(C)T	single photon emission (computed) tomography
t	triplet
$T_{½}$	half-life
TLC	thin layer chromatography
UV	ultraviolet
VEGF	vascular endothelial growth factor
vs.	versus
ρ	reaction parameter (Hammett equation)
σ	substituent constant (Hammett equation)

Erklärung

Ich versichere, dass die von mir vorgelegte Dissertation selbständig angefertigt, die benutzten Quellen und Hilfsmittel vollständig angegeben und die Stellen der Arbeit einschließlich Tabellen, Karten und Abbildungen, die anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, in jedem Einzelfall als Entlehnung kenntlich gemacht habe; dass diese Dissertation noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie nicht veröffentlicht worden ist sowie, dass ich eine solche Veröffentlichung vor Abschluss des Promotionsverfahrens nicht vornehmen werde.
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