Nucleophilic Aromatic Substitution by [18F]Fluoride and its Applications to the Synthesis of Model Precursors for the Multi-step Synthesis of the PET-Tracer 6-[18F]Fluoro-L-DOPA

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Anwendung der nukleophilen aromatischen Substitution mit [18F]Fluorid an Modell-Substanzen für die Mehrstufensynthese des PET-Tracers 6-[18F]Fluoro-L-DOPA

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Im Namen Allahs,

des sich Erbarmenden, des Barmherzigen

In the Name of Allah,

the Most Beneficent, the Most Merciful

To the Memory of my Father

To my Wife and my Sons

To my Mother, Brothers and Sisters

To my Developing Country

Meinen Doktorvätern

Herrn Prof. Dr. K.-P. Zeller und Prof. Dr. H.-J. Machulla

danke ich herzlich für die Themenstellung,

für die Bereitstellung ausgezeichneter Arbeitsbedingungen,

für wertvolle Anregungen und Diskussionen,

für ihr stetes Interesse an dieser Arbeit,

sowie die finanzielle Unterstützung des PET-Zentrums.

Abbreviations:

Ar	Aryl
App.	Appendix
β^-	Beta particle, electron
β^+	Positron
Chpt	Chapter
Ci	Curie (radiation)
δ	Chemical shift
d	Day (time)
d	Doublet (NMR)
dd	Doublet of doublet (NMR)
dec.	Decomposition
DMAc	N,N-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
EAS	Electrophilic aromatic substitution
EDG	Electron donating group
EWG	Electron withdrawing group
FAB	Fast Atom Bombardment (mass spectrometry)
FD	Field desorption (mass spectrometry)
[^{18}F]FDG	2-Deoxy-2-[^{18}F]fluoro-D-glucose
[^{18}F]FDOPA	6-[^{18}F]Fluoro-L-dopa
[^{18}F]FTYR	[^{18}F]Fluorotyrosine
Fig.	Figure
h	Hour
g	Gram
GBq	Gigabecquerel
HPLC	High performance liquid chromatography
Hz	Hertz
IR	Infrared
k'	Rate constant
keV	Kilo electron volt
LG	Leaving group
Lit.	Literature
m	Multiplet (NMR)
min	Minute
mm	Millimeter

mp	Melting point (°C)
µs	Microsecond
MBq	Megabecquerel
Me	Methyl
meV	Milli-electron volt
MHz	Mega hertz
MPLC	Middle-pressure liquid chromatography
MS	Mass spectroscopy
MW	Microwave
nca	No-carrier-added (radiochemistry)
ns	Nanosecond
n	Neutron (s)
NAS	Nucleophilic aromatic substitution
NBS	N-Bromosuccinimid
NCS	N-Chlorosuccinimid
NFP	N-Formylpiperidine
NFM	N-Formylmorpholine
NMR	Nuclear Magnetic resonance
p	Proton (s)
Ph	Phenyl
PET	Positron Emission Tomography
ppm	Parts per million
RCY	Radiochemical yield
s	Singlet (NMR)
Sp. Ac.	Specific activity
t	Triplet (NMR)
$t_{1/2}$	Half life
Tab.	Table
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
vs	Versus

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List of Compounds

Comp. No	Code	Name
1	(**1**)	4,5-Dihydroxy-2-[^{18}F]fluoro-L-phenylalanine ([^{18}F]FDOPA)
2	(**2a**)	6-Nitroveratraldehyde
3	(**2b**)	Veratraldehyde-6-trimethylammoniumtriflate
4	(**2c**)	6-Fluoroveratraldehyde
5	(**2d**)	6-Bromoveratraldehyde
6	(**2e**)	6-Chloroveratraldehyde
7	(**3**)	6-[^{18}F]Fluoroveratraldehyde
8	(**4**)	Vanillin (4-hydroxy-3-methoxybenzaldehyde)
9	(**5**)	4-Acetoxy-3-methoxybenzaldehyde (vanillin acetate)
10	(**6**)	4-Acetoxy-2-Bromo-5-methoxybenzaldehyde
11	(**7**)	2-Bromo-4-hydroxy-5-methoxybenzaldehyde
12	(**8a**)	4-Benzoyloxy-2-bromo-5-methoxybenzaldehyde
13	(**8b**)	2-Bromo-5-methoxybenzaldehyde-4-benzenesulfonate
14	(**8c**)	3-Bromo-4,5-dimethoxybenzaldehyd
15	(**8d**)	4-Benzoyloxy-3-bromo-5-methoxybenzaldehyde
16	(**9a**)	6-Nitropiperonal
17	(**9b**)	6-Bromopiperonal
18	(**9c**)	6-Chloropiperonal
19	(**10**)	6-[^{18}F]Fluoropiperonal
20	(**11**)	*o*-Vanillin (2-hydroxy-3-methoxybenzaldehyde)
21	(**12**)	2-Acetoxy-3-methoxybenzaldehyde
22	(**13**)	2-Acetoxy-6-bromo-3-methoxybenzaldehyde
23	(**14**)	6-Bromo-2-hydroxy-3-methoxybenzaldehyde
24	(**15a**)	2-Benzoyloxy-6-bromo-3-methoxybenzaldehyde
25	(**15b**)	6-bromo-3-methoxybenzaldehyde-2-benzenesulfonate
26	(**16**)	*o*-Vanillin benzenesulfonate
27	(**17a**)	3-Methoxy-6-nitrobenzaldehyde-2-benzenesulfonate
28	(**17b**)	3-Methoxy-4-nitrobenzaldehyde-2-benzenesulfonate
29	(**18**)	2-Hydroxy-3-methoxy-6-nitrobenzaldehyde
30	(**19a**)	2,3-Dimethoxy-6-nitrobenzaldehyde
31	(**19b**)	2-Acetoxy-3-methoxy-6-nitrobenzaldehyde
32	(**19c**)	2-Benzoyloxy-3-methoxy-6-nitrobenzaldehyde
33	(**20**)	2-Hydroxy-3-methoxy-4-nitrobenzaldehyde
34	(**21**)	2,3-Dimethoxy-4-nitrobenzaldehyde
35	(**22**)	2,3-Dimethoxybenzaldehyde
36	(**23a**)	6-Bromo-2,3-dimethoxybenzaldehyd
37	(**23b**)	6-Chloro-2,3-Dimethoxybenzaldehyd
38	(**24a**)	5-Bromo-2,3-Dimethoxybenzaldehyd
39	(**24b**)	2,3-Dimethoxy-5-nitrobenzaldehyd
40	(**25**)	2,4-Dimethoxybenzaldehyde
41	(**26**)	5-Bromo-2,4-Dimethoxybenzaldehyd
42	(**27**)	2,5-Dimethoxybenzaldehyde
43	(**28**)	4-Bromo-2,5-Dimethoxybenzaldehyd
44	(**29**)	5,6-Dibromo-2-hydroxy-3-methoxybenzaldehyde
45	(**30a**)	5,6-Dibromo-2,3-dimethoxybenzaldehyde

46	(**30b**)	2-Acetoxy-5,6-dibromo-3-methoxybenzaldehyde
47	(**30c**)	2-Benzoyloxy-5,6-dibromo-3-methoxybenzaldehyde
48	(**30d**)	5,6-Dibromo-3-methoxybenzaldehyde-2-benzenesulfonate
49	(**31**)	3-Bromo-5,6-dimethoxy-2-nitrobenzaldehyde
50	(**32**)	6-Bromo-2,3-dihydroxybenzaldehyde
51	(**33**)	6-Bromo-2,3-methylenedioxybenzaldehyde
52	(**34**)	3,5-Dimethoxybenzaldehyde
53	(**35**)	3,5-Dimethoxy-2-nitrobenzaldehyde
54	(**36**)	3,4-Ethylenedioxybenzaldehyde
55	(**37a**)	4,5-Ethylenedioxy-2-nitrobenzaldehyde
56	(**37b**)	2-Bromo-4,5-ethylenedioxybenzaldehyde
57	(**38**)	4-Fluoroveratrole (4-fluoro-1,2-dimethoxybenzene)
58	(**39**)	6-Fluoro-2,3-dimethoxybenzaldehyde
59	(**40**)	6-Fluoro-2-hydroxy-3-methoxybenzaldehyde
60	(**41a**)	2-Acetoxy 6-Fluoro-3-methoxybenzaldehyde
61	(**41b**)	2-Benzoyloxy-6-Fluoro-3-methoxybenzaldehyde
62	(**41c**)	6-Fluoro-3-methoxybenzaldehyde-2-benzenesulfonate
63	(**42a**)	Phenyl benzenesulfonate
64	(**42b**)	Benzaldehyde-2-benzenesulfonate
65	(**42c**)	Benzaldehyde-4-benzenesulfonate
66	(**42d**)	Vanillin benzenesulfonate
67	(**42e**)	3-Methoxy-2-nitrobenzaldehyde-4-benzenesulfonate
68	(**42f**)	4-Nitrocatechol dibenzenesulfonate
69	(**42g**)	4-Methyl-5-nitrocatecholdibenzenesulfonate
70	(**42h**)	2-Nitro-3,4-dimethoxybenzaldehyde
71	(**43**)	Benzenesulfonyl[^{18}F]fluoride
72	(**44**)	3,4,5-Trimethoxybenzaldehyde
73	(**45**)	3,4,5-Trimethoxy-2-nitrobenzaldehyde
74	(**46**)	2-Bromo-3,4,5-trimethoxybenzaldehyde
75	(**47**)	2,3,4-Trimethoxybenzaldehyde
76	(**48**)	2,3,4-Trimethoxy-6-nitrobenzaldehyde
77	(**49**)	5-Bromo-2,3-dimethoxy-6-nitrobenzaldehyde ethyleneacetal
78	(**50**)	2,3-Dimethoxy-6-nitrobenzaldehyde ethyleneacetal
79	(**51**)	4-Nitrocatechol
80	(**52**)	4-Nitrocatechol dibenzoate
81	(**53**)	4-Methylcatechol
82	(**54**)	4-Methyl-5-nitrocatechol
83	(**55a**)	1,2-Dimethoxy-4-methyl-5-nitrobenzene
84	(**55b**)	4-Methyl-5-nitrocatechol dibenzoate
85	(**55c**)	4-Methyl-5-nitrocatechol diacetate
86	(**56**)	1,3-Benzodioxole
87	(**57**)	5-Nitro-1,3-benzodioxole
88	(**58**)	3,4-Methylenedioxytoluene
89	(**59**)	4,5-Methylenedioxy-2-nitrotoluene

1   INTRODUCTION

1.1   PET

1.1.1   Basics of PET

Positron Emission Tomography (PET) is one of the most important techniques for *in-vivo* studies by the radiotracer method. During the last two decades it has been under development as a biochemical research tool for studies in medicine. Now it attracts the interest of many scientists in the broad area of life sciences, particularly in the fields of diagnostic applications and therapy control as an excellent and very sensitive method for examination of physiological functions.

In the year 2000 PET had its international breakthrough as a method. This can clearly be illustrated by the broad applications of PET/CT, both in clinical research and healthcare. Moreover, during the last two years animal PET became available allowing to determine biochemical processes and biokinetics within small animals. In this particular international situation the radiopharmaceutical methods play the key role in PET applications since the spectrum of applications directly and, thus, strongly depends on the availability of compounds labelled with radionuclides appropriate for PET studies.

In radiopharmacy it is the aim to develop and supply compounds of metabolic relevance for PET applications. Those compounds are labelled with short-lived radionuclides of the biologically important elements. ^{15}O, ^{13}N, ^{11}C and ^{18}F are the PET radionuclides of choice. Their main properties are the emission of positrons and the short half lives. In combination with the coincidence measuring technique and the modus of tomographic imaging, the directly localized registration of such compounds ("tracers") is possible. Moreover, the PET technique allows both the qualitative imaging and quantification of the particular metabolic

process under study. The radioactive decay of the PET radionuclides gives rise to emission of a positron, a positively charged particle with the mass of an electron[1]. A positron is the anti-particle of an electron so that after loss of its kinetic energy it forms a positronium together with an electron. After a few microseconds the two electron masses end up in form of annihilation radiation as two gamma photons with an energy of 511 keV each. Those gamma photons are emitted in an angle of almost 180° (Fig. 1).
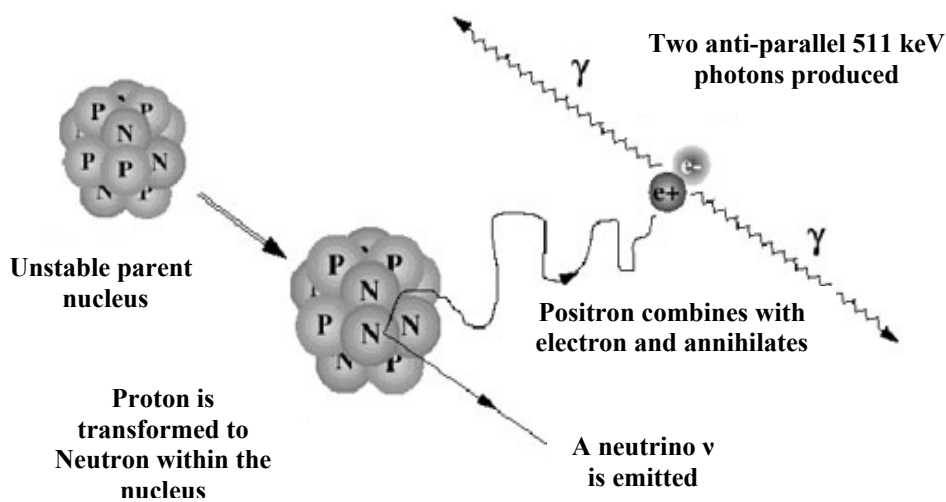
Fig. 1. Radioactive decay by positron emission[1]**.**

The production of two ϒ-quanta shortly after the positron emission allows the recording of this process by annihilation coincidence detection. Two detectors, oriented opposite to each other, are used to detect the two photons. The measuring system finally counts only those photons which are registered in coincidence within a pair of opposite detectors. The coincidence detector system also defines a volume between the two detectors as measured by two coincidence events[2].(Fig. 2). Events of this type are labelled as (A). Coincidence events outside this volume are not registered (B). However, coincidence events outside this volume involving scattering can also occur and are erroneously attached to the detection volume (C). The PET system is composed of a large number of coincidence detector pairs arranged in a ring. Each single detector is not only switched to coincidence with the diametrically

opposite detector but also with a greater number of detectors on the other side of the ring, forming a fan-shaped area of coincidence (Fig. 2). The visual field of the tomographic system is defined by the central area covered by all fan-shaped areas of coincidence. The body of the patient is placed in this visual field.
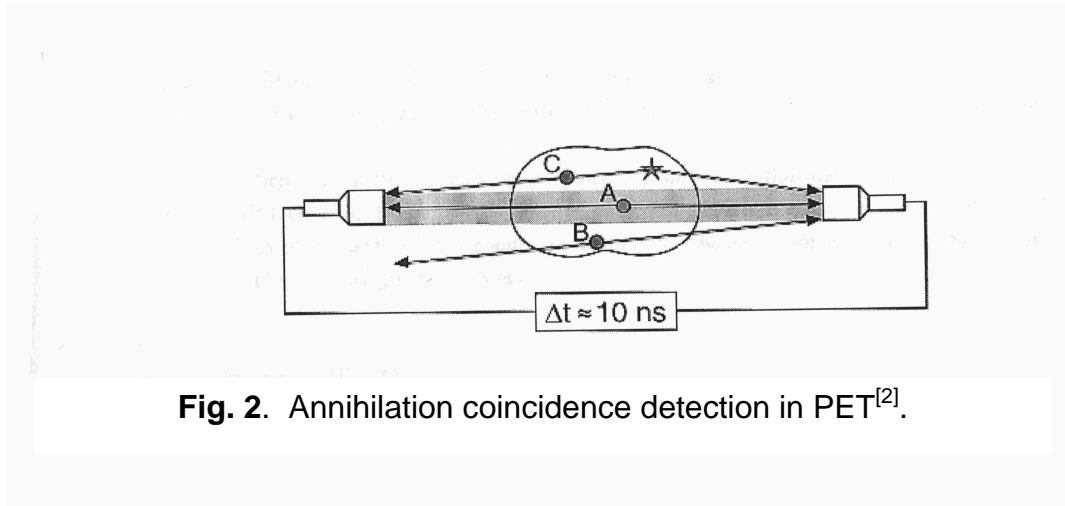
Fig. 2. Annihilation coincidence detection in PET[2].

If compounds labelled with positron emitting isotopes are accumulated in certain regions of the body, from the detected annihilation events an imaging of this region can be reconstructed to tomographic slices. Thus, the use of the PET technique is always combined with compounds labelled with PET radioisotopes (PET tracers). The most famous and most applied compound is 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG). This molecule is transported and phosphorylated like glucose, however, it does not take part in the succeeding metabolic processes. Therefore, [^{18}F]FDG accumulates in glucose demanding tissues. Active cancer tissue can thus be detected because of its elevated glucose metabolism. On the other hand, success of cancer chemotherapy results in the death of the cancer cells and, consequently, in low or no accumulation of [^{18}F]FDG. Another application is the investigation of the biodistribution of drugs in the body or the detection of receptors for certain biomolecules.

1.1.2 Radionuclides in PET

To perform any type of PET investigations, compounds labelled with positrons are essential. The short-lived positron emitting radionuclides that have the greatest importance in PET are carbon-11, nitrogen-13, oxygen-15 and fluorine-18. This is to be understood in view of the fact that the first three of these isotopes belong to the elements of life and can be substituted for their stable counterparts without influencing the bioactivity of the molecule. While fluorine-18 is not a significant element in living system, its half-life and properties make its use in labelling of considerable value. Most importantly, it is applied in the concept of "blocked metabolism" as explained in case of [^{18}F]FDG. Tab. 1 lists the physical properties of these radionuclides[3].

Tab. 1. Physical properties of some positron emitter radionuclides[3].

Isotope	Half-life (min)	Specific Activity[a] (GBq/mmol)	Maximum Energy (MeV)	Range (mm) in Water[b]	Decay Product
Fluorine-18	110	63.3×10^6	0.635	2.4	Oxygen-18
Carbon-11	20.4	341.1×10^6	0.96	4.1	Boron-11
Nitrogen-13	10	69.9×10^7	1.19	5.4	Carbon-13
Oxygen-15	2.1	336.0×10^7	1.72	8.2	Nitrogen-15

[a]) Theoretical maximal specific activity; in practice, specific activities are typically 5000 times lower because of unavoidable dilution with the non radioactive isotope.
[b]) Maximal linear range.

The development of any radiotracer begins with the selection of an appropriate radionuclide. This depends on several factors. The first is whether the physical half-life of the radioisotope matches the biological half-life of the process under investigation. The precursor's achievable

specific activity (sec. 1.2.2) is also very important. In addition, the time necessary to prepare the precursor, and manipulate it through the subsequent synthetic pathways, and/or purifications are important for the decision. Finally, the kind of information needed from the PET measurement is also important in the selection of the radioisotope. Finally, the spatial distribution and regional concentrations of a target substance or neurotransmitter binding or uptake site are also very important. Tab. 2 gives a list of some radiotracers and their applications[3].

Tab. 2. Some important radiotracers and their applications[3,4].

Tracer	Chemical name	Use
[^{15}O] Tracers		
[^{15}O]H$_2$O	[^{15}O]water	Blood flow
[^{15}O]CO	[^{15}O]carbon monoxide	Blood volume
[^{15}O]O$_2$	[^{15}O]oxygen	Oxygen consumption
[^{11}C] Tracers		
[^{11}C]Carfentanil	[methyl-^{11}C]-4-[(1-oxypropyl)phenyl-amino]-1-(2-phenylethyl)-4-piperidinecarboxylic acid methyl ester	Opiate receptors in brain
[^{11}C]CFT	[N-methyl-^{11}C]-2-β-carbomethoxy-3-β-(4-fluorophenyl)-tropane	Dopamine re-uptake sites in brain
[^{11}C]Choline	[N-methyl-^{11}C](2-hydroxyethyl) trimethylammonium	Choline metabolism, tumours
[^{11}C]CIT	[N-methyl-^{11}C]-2-β-carbomethoxy-3-β-(4-iodophenyl)-tropane	Dopamine re-uptake sites in brain
[^{11}C]FLB 457	[2-O-methyl-^{11}C]-(S)-N-(1-ethyl-2-pyrrolidinyl)-5-bromo-2,3-dimethoxybenzamide	Extrastriatal dopamine D2 receptors in Brain
[^{11}C]Flumazenil	8-Fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazipine-3-carboxylic acid ester	Benzodiazepine receptors in brain
[^{11}C]MeAIB	α-[^{11}C]methylamino-isobutyric acid	System A amino acid transport
[^{11}C]Methionine	(*S*)-2-amino-4-([^{11}C]methylsulfanyl)-butanoic acid	Amino acid transport, tumours
[^{11}C]Metomidate	O-[methyl-^{11}C]-(R)-1-(1-phenethyl)-1H-imidazole-5-carboxylic acid methyl ester	11β-hydroxylase activity in adrernal cortical tissue
[^{11}C]MP4A	N-[^{11}C]-methylpiperidine-4-yl acetate	Acetylcholine esterase activity in brain
[^{11}C]NMSP	N-[^{11}C]-methylspiperone	Dopamine D2 and serotonin 5HT2 receptors in brain
[^{11}C]NNC 756	[methyl-^{11}C]-(S)-(+)-8-chloro-5-(2,3-dihydro-benzofuran-7-yl)-7-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine	Dopamine D1 receptors in brain
[^{11}C]Raclopride	[6-O-methyl-^{11}C]-(S)-N-(1-ethyl-2-pyrrolidinyl)-3,5-dichloro-2-hydroxybenzamide	striatal dopamine D2 receptors in brain
[^{11}C]SCH 23390	[methyl-^{11}C]-(R)-(+)-8-chloro-5-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepin-7-ol	Dopamine D1 receptors in brain
[^{11}C]SCH 39166	[^{11}C]Ecopipam	Dopamine D1 receptors in brain
[^{18}F] Tracers		
[^{18}F]CFT	2β-carbomethoxy-3β-(4-[^{18}F]fluorophenyl)tropane	Dopamine re-uptake sites in brain
[^{18}F]FBPA	4-dihydroxyboryl-2-[^{18}F]fluoro-L-phenylalanine	Amino acid transport, boron carrier for BNCT
[^{18}F]FDG	2-[^{18}F]fluoro-2-deoxy-D-glucose	Glucose metabolism
[^{18}F]FDOPA	4,5-dihydroxy-2-[^{18}F]fluoro-L-phenylalanine	Pre-synaptic dopaminergic function in brain
[^{18}F]FETNIM	4-[^{18}F]fluoro-2,3-dihydroxy-1-(2-nitroimidazole-1-yl)-butanol	Tissue hypoxia
[^{18}F]Fluorodopamine	2-(4,5-dihydroxy-2-[^{18}F]fluorophenyl)ethylamine	Adrenergic innervation and tone in Heart
[^{18}F]Fluorometaraminol	(1R,2S)-2-amino-1-(4-[^{18}F]fluoro-3-hydroxyphenyl)-1-propanol	Adrenergic innervation in heart

1.1.3 Applications of PET

The PET method is a highly sensitive method for the investigation of biochemical reactions in the body with sensitivity reaching below 10^{-12} g. This enables scanning of the body without affecting at all biochemical reactions or introducing toxicity. Thus distribution and metabolism of drugs and necessary life compounds can be monitored. In many cases PET added valuable information to the existing methods of investigation and the whole case of study and therapy were changed. An example is the following case[5].
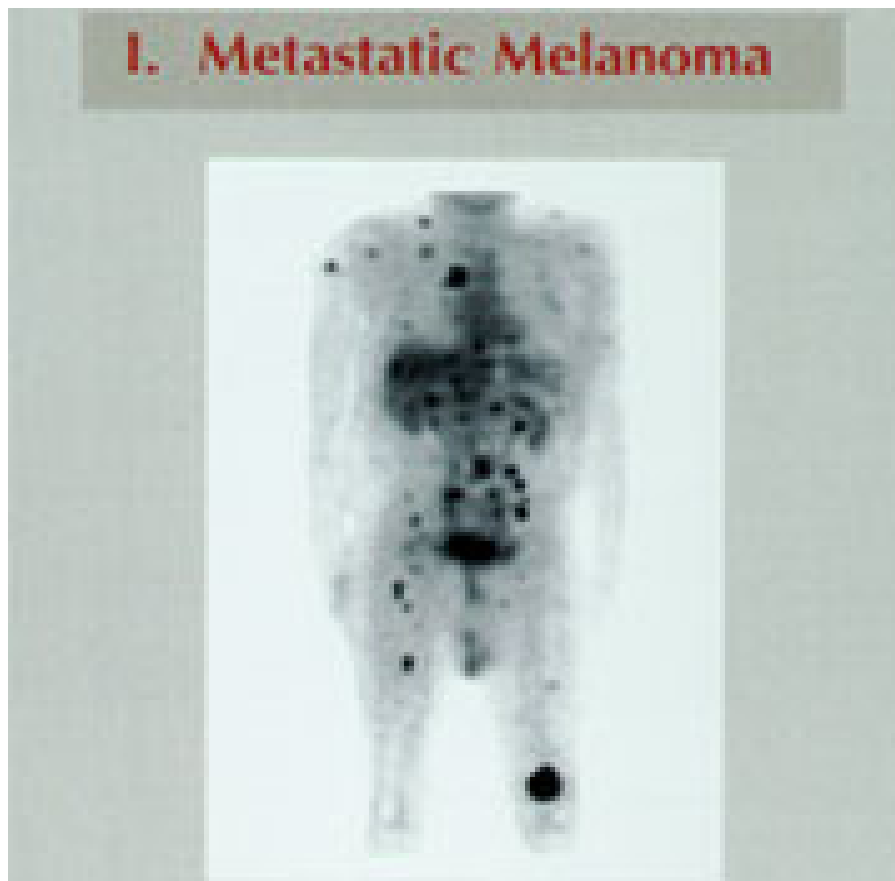
Fig. 3. [^{18}F]FDG PET scan of a patient with metastatic melanoma[5]

As Fig. 3 shows, a PET image of a 71 year old male with metastatic melanoma. The CT scan of the patient demonstrated a tumour of the distal femur and adjacent soft tissue with negative findings in the abdomen. A bone scan showed an abnormal femur and four spine lesions. Using the PET method, a whole-body [^{18}F]FDG PET scan demonstrated numerous lesions

throughout the body (Fig. 3). The patient was originally scheduled for an amputation based on CT and bone scan results. After the PET scan found multiple lesions, treatment was changed. The surgery was cancelled, avoiding both the cost and the trauma of an operation that would not have been effective.

1.2   Fluorine-18

1.2.1   Production of Fluorine-18

Fluorine-18 can be produced in a nucleophilic as well as an electrophilic form using various types of nuclear reactions. Tab. 3 shows the most important ones. Many labelling methods, based on both chemical forms of fluorine-18 (see 1.3), have been published in the last decade.

Tab. 3. Important production methods for fluorine-18[3].

Reaction	Target	Beam energy (MeV)	Product	Production Rate (MBq/µAh)
$^{18}O(p,n)$	$H_2^{18}O$	11 15	$[^{18}F^-]$ $[^{18}F^-]$	1500 2200
$^{16}O(^3H,p)$	H_2O	22	$[^{18}F^-]$	200-400
$^{16}O(\alpha, d)$	H_2O	30	$[^{18}F^-]$	40
$^{20}Ne(d, \alpha)$	F_2/Ne	11	$[^{18}F]F_2$	400
$^{20}Ne(d, \alpha)$	H_2/Ne	11	$H[^{18}F]$	400

Nowadays, mainly two target-systems are used to produce fluorine-18, the neon-20 target (Tab. 3, line 5 and 6) and the ^{18}O enriched water target (line 1). The use of an $[^{18}O]$water target is widely applied due to its reliability and the high yield of the nuclear reaction. In a neon target, fluorine-18 can be produced as an electrophilic ^{18}F reagent directly as $[^{18}F]F_2$ or in a chemically different form such as $[^{18}F]$acetylhypofluorite.

The use of a 1 % fluorine/neon gas mixture in the target leads to the formation of $[^{18}F]F_2$. The $[^{18}F]F_2$ that is formed in the target is highly reactive and interacts strongly with the target wall. The target has to be treated in advance with F_2 in order to coat the target wall with F_2: the target is "passivated". The fluorine acts as a kind of "carrier gas" by facilitating the transport of the radioactivity from the target to the laboratory. The addition of non-radioactive fluorine to the target results in a lower specific activity of the produced fluorine-18, so this production method is not applicable for the synthesis of receptor binding ligands which require a high specific activity. $[^{18}F]F_2$ can not be prepared as a no-carrier-added (nca) reagent.

The addition of hydrogen gas to the neon target leads to the *in-situ* formation of $H[^{18}F]$. The $[^{18}F]$fluoride can be isolated from the target as anhydrous $H[^{18}F]$ by a stream of hydrogen gas or as aqueous $[^{18}F]$fluoride by rinsing the target with a small volume of water.

In an $[^{18}O]$water target, $[^{18}F]$fluoride is produced efficiently in high yields and in short time and so it is used widely nowadays in most PET centres.

1.2.2 Specific Activity

The extent to which a compound labelled with a radionuclide is diluted with the non radioactive isotopic compound is referred as the *specific activity*. The specific activity is calculated from the ratio of the amount of radioactivity (Becquerel, Bq or Curie, Ci) and the molar concentration of the compound (mol) and is usually expressed in GBq/μmol or Ci/mmol[6]. The maximum theoretical specific activity of fluorine-18, with a half-life of 110 min, is 63,000 GBq/μmol (1.7 x 10^6 Ci/mmol). In practice much lower specific activities are obtained due to the unavoidable dilution with the non-radioactive stable element. The specific activity of a product is of importance, because many applications of PET (such as studying receptors in brain) require the administration of only a very small molar concentration of the

labelled biomolecule to the patient, hence a high specific activity is required which means also the no-carrier-added (nca) form.

1.2.3   Properties of Fluorine-18

Fluorine, as an element, is in many ways unique, both in chemical characteristics and usefulness in the pharmaceutical and chemical industries. Fluorine has a very small steric size and its bond with carbon exhibits very high bond energy. As fluorine is extremely electronegative, it can often produce significant and useful changes in physiochemical and biological properties of organic compounds[7]. In some cases, substitution with fluorine produces a derivative with improved pharmacological properties. Although sometimes considered as an isosteric replacement for hydrogen, the differences in electronegativity and hydrogen binding capability of fluorine make it more alike substituent for a hydroxyl group. Fluorine-18 (discovered as early as 1937) decays for 96.9 % by the emission of a positron (β^+) and a neutrino. This emission is the result of a transformation of a proton into a neutron in the nucleus. The nuclide which is formed in this process is oxygen-18. The remaining 3.1 % of fluorine-18 decays by electron capture.

$$^{18}F \rightarrow \ ^{18}O + \beta^+ + v$$
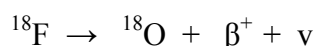
The moderate length half-life of 110 minutes allows enough time in the synthesis of radiopharmaceuticals. Usually, a synthesis time of no more than three half lives of a radionuclide is applied. In case of ^{18}F this means about 5.5 h. In practice lengthy procedures are rarely used. The relatively long half-life of fluorine-18 (in comparison, for example to carbon-11, oxygen-15 and nitrogen-13) permits large scale production of [^{18}F]fluorine labelled radiopharmaceuticals and distribution to distant locations (the satellite concept)[3]. In

case of carbon-11, and because of the short half-life, the distribution is mainly limited applications on site (in-house production).

1.2.4   Reactivity and Recovery of Fluorine-18

Fluorine is the most electronegative element of the periodic table and it is one of the three elements (N, O and F) which can act as a H-bond acceptor. The fluoride ion is therefore strongly solvated in protic solvents such as water or methanol. The use of protic solvents or even the presence of water in the reaction mixture leads to a serious decrease in the reactivity of [^{18}F]fluoride. Therefore, it is necessary to manipulate [^{18}F]fluoride in such a way that it is obtained in an unsolvated form and reactions must be performed in aprotic solvents, such as DMSO or DMF. Methods for the recovery of [^{18}O]water and the isolation of [^{18}F]fluoride include simple distillation techniques or other methods such as electrolysis and the use of ion-exchange resins[3]. However, one of the main problems in the recovery of fluorine-18, like any other radioactivity, is the adherence to vessels used. In this case, a percentage of fluorine-18 radioactivity is lost, depending on the type of material used for making a particular vessel. For [^{18}F]fluoride, washing with water as a solvent can recover most of radioactivity.

1.3   Electrophilic and Nucleophilic Aromatic Fluorination Reactions

1.3.1   Fluorination Reactions

Fluorine can be introduced into organic compounds using a variety of methods, such as the direct addition of fluorine, fluorine containing reagents to multiple bonds, or the substitution of a leaving group by electrophilic or nucleophilic fluorine or fluorine-containing reagents[7]. However, the number of fluorination methods is relatively limited when compared to other halogenations. This is because most fluorinating reagents are either very toxic, corrosive to glass and metals or very reactive. In most cases this limits the work of fluorination to solid or liquid non-volatile reagents[7]. The work with fluorine-18 (with good protection from

radiation) is safer because it is mostly performed automatically using commercially available modules. The number of reagents available for ^{19}F fluorinations is larger than that for ^{18}F reactions. The reason is related to the decay in case of the radioactive ^{18}F and the need to establish all of the work, including the synthesis of reagents *in-situ* and the fluorination reaction within limited time. Whereas in ^{19}F fluorination reactions it is easy to follow up the reaction by the usual spectroscopic techniques (^{1}H NMR, ^{13}C NMR, ^{19}F NMR, .. etc), it is difficult to follow up the [^{18}F]fluorination reactions unless the standard is available for quick comparison in TLC and HPLC[3,4]. Normally special radiochemical methods are needed. The large excess of the precursor relative to the ^{18}F label gives the nonstochiometric labelling process special characteristics. Many ^{18}F labelling reactions, therefore, are successful although they are difficult in the cold way, i.e. with ^{19}F. In electrophilic fluorination reactions, where most reagents are very highly reactive, usually several sites are susceptible for attack, and in this case several products are obtained. However, the regioselectivity in these reactions can be optimised by introducing a very good leaving group in the right place. This usually increases the number of steps in any synthesis. In nucleophilic fluorinations, the reagents are less reactive and the presence of leaving groups other than hydrogen is assumed previously, so the regioselectivity is very high (unless there are several different leaving groups or in case of the fluoride ion acting as a base instead of a nucleophile). Tab. 4 gives a summary of the main methods used in fluorinationreactions.

Tab. 4. General methods used for fluorination in lab or industrial scales[8].		
Method of fluorination	**Types of compounds or reactions**	**Common reagent**
A. Halogen exchange: C-X → C-F	1. Polychloroalkanes	AHF/SbCl$_5$ (liquid phase) AHF/Cr-based catalysts (vapour. Phase) SbF$_3$/SbCl$_5$ (lab. scale)
	2. Gem-dihalogeno-alkanes (or-cycloalkanes)	HgO/AHF or HgO$_2$; SbF$_3$; AgBF$_4$
	3. Monohalogenoalkanes	KF; AgF; CuF; TBAF
	4. Allylic or benzylic "activated" positions	AHF; SbF$_3$; AHF/SbCl$_5$; SbF$_3$/SbCl$_5$;
	5. Carbonyl compounds	KF; AgF; AHF/Cr-based catalysts
	6. "Activated" nuclear halogeno-aromatics	KF; [^{18}F]KF ; HF; NaF
B. Oxygen replacement: C-OX → C-F [OX= OH, OSO$_2$R, OC(O)F, OC (epoxide components)] C=O → CF$_2$ C(=O)OH → CF$_3$	1. Fluorodehydroxylation	AHF/pyridine/NaF; SF$_4$; SF$_4$/AHF (C$_2$H$_5$)$_2$NSF$_3$ (DAST); (C$_2$H$_5$)$_2$NCF$_2$CHFX
	2. Ester fluorolysis (Ts = 4-CH$_3$C$_6$H$_4$SO$_2$; Tf = CF$_3$SO$_2$)	KF; CsF; TBAF; TMAF
	3. Thermal fluorodecarboxylation of halogenoformates	CaF$_2$; COFCl; KF; AHF/pyridine BF$_3$O(C$_2$H$_5$)$_2$; AHF/AlF$_3$
	4. Ring-opening of epoxides	AHF/pyridine; AHF/ BF$_3$O(C$_2$H$_5$)$_2$ (i-C$_3$H$_7$)$_2$NH·3HF
	5. Replacement of oxygen in aldehydes, ketones and carboxylic acids	SF$_4$(+HF or BF$_3$); DAST
C. Nitrogen replacement: C-NH$_2$ → C-N$_2^+$ → C-F; C-N-C → CF-N-C	1. Deaminative fluorination of α–amino acids	AHF/pyridine/NaNO$_2$
	2. Fluorodediazonisation of aromatic diazonium salts	AHF/NaNO$_2$; HBF$_4$ aq or NaBF$_4$
	3. Ring-opening of azirine and aziridines	AHF/pyridine

D. Replacement of hydrogen:
 	
C-H → C-F
	1.Electrophilic fluorination with fluorine
	  a. Directly in aliphatic systems
	  b. Directly in aromatic systems
		F$_2$/N$_2$
		[^{18}F]F$_2$/Ne

	2. Electrophilic fluorination with "fluorine carriers (prepared from F$_2$)	CF$_3$OF; XeF$_2$/HF, (C$_6$H$_5$SO$_2$)$_2$NF FClO$_3$; (CF$_3$SO$_2$)$_2$NF; (C$_6$H$_5$SO$_2$)$_2$NF
	3.Anodic fluorination of aromatic hydrocarbons (Knunyants-Rozkhov ECF)	TEAF; (C$_2$H$_5$)$_3$N·HF
E. Addition to C=C or C≡C bonds		AHF/pyridine; AHF/pyridine/NBA or NBS AHF/pyridine/ NBS then AgF/AHF/ pyridine HF/SbCl$_5$; KF/H$_2$NCONH$_2$; IF$_5$/I$_2$ BrF$_3$/Br$_2$; XeF$_2$

Tab. 4 shows that substitution methods are more important than addition methods in fluorination reactions. Moreover, methods for aliphatic fluorination are more numerous and variant than those for aromatic fluorination. Owing to the importance of this field of research, there has been extensive research and developments in the last decades, and numerous reviews and books were edited[7-10,15-17]. Since the development of PET and the need for new radiopharmaceuticals with new structures and new applications, fluorination reactions have been widely studied with the hope to find more suitable reagents and methods to facilitate the introduction of the fluorine atom into organic compounds. The introduction of a fluorine atom into an aromatic ring is still limited to a small number of reactions and remains always an active area of research. In this work the focus is limited only to the nucleophilic aromatic substitution by [^{18}F]fluoride.

1.3.2   Electrophilic Aromatic [^{18}F]Fluorination Reactions

These methods rely on fluorine [^{18}F]F$_2$ or reagents that can supply electrophilic fluorine[9]. These reagents create a chemical environment in which the fluorine atom is highly polarized with a partial positive charge[3]. Hence, it is possible to fluorinate a variety of electron-rich substrates like the aromatic compounds. Although electrophilic fluorination reactions are fast and efficient, labelling reactions with fluorine-18 can only provide low specific activity of fluorine-18 radiopharmaceuticals because they rely mostly on [^{18}F]F$_2$ (or reagents derived from it) which is always produced in the carrier-added mode. Thus, all electrophilic ^{18}F-fluorinations are necessarily carrier-added and result finally in radiotracers with low to at-best moderate specific activities. Unless there is a good leaving group in place of the incoming fluorine-18, most of these reactions are also non-regioselective, producing a mixture of [^{18}F]fluorinated products. This has limited the usefulness of electrophilic fluorinations to the synthesis of radiopharmaceuticals for which there is no need of high specific activity, and

where the chemical species in question are not toxic. The following is a brief list of some electrophilic fluorination reagents[3]:

1- **Elemental fluorine, [^{18}F]F$_2$:** This is the simplest reagent in this class. It is produced through the deuteron bombardment of a high-pressure neon gas target containing 0.1 % to 2 % of carrier added F$_2$ according to the following reaction:

$$^{20}Ne(d, \alpha)^{18}F$$
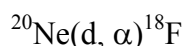
The reagent is actually ^{18}F–^{19}F diluted in normal fluorine gas, i.e. ^{19}F–^{19}F. Several modifications were introduced into this method to improve the final specific activity.

2- **[^{18}F]Trifluoromethyl hypofluorite, [^{18}F]F-CF$_2$O[^{18}F]F:** This reagent is produced by caesium fluoride mediated reaction between [^{18}F]F$_2$ and carbonylfluoride.

$$[^{18}F]F_2 \; + \; F_2C{=}O \quad \rightarrow \quad [^{18}F]F\text{-}CF_2O[^{18}F]F$$
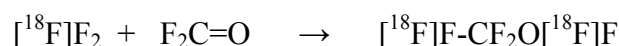
Optimal conditions are obtained within 15 minutes of reaction at 110 °C producing yields up to 33 % of CF$_3$O[^{18}F].

3- **[^{18}F]Acetyl hypofluorite, [^{18}F]CH$_3$COOF:** This reagent is produced by a well-known method according to the following reaction:

$$[^{18}F]F_2 \; + \; CH_3COONH_4 \quad \rightarrow \quad CH_3COO^{18}F \; (40\,\%) \; + \; NH_4{}^{18}F$$
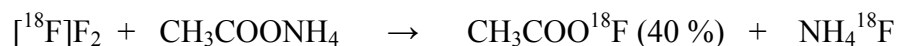
this method was later improved by the following gas-solid reaction:

$$[^{18}F]F_2 \; + \; AcOH^.AcOK \quad \rightarrow \quad CH_3COO^{18}F \; + \; [^{18}F]HF^.AcOK$$

4- **[^{18}F]Perchloryl fluoride, [^{18}F]FClO$_3$:** The method for producing this reagent involves passing [^{18}F]F$_2$ through a column containing KClO$_3$ maintained at 90 °C.

$$[^{18}F]F_2 \; + KClO_3 \quad \rightarrow \quad ^{18}FClO_3 \; + \; K^{18}F$$
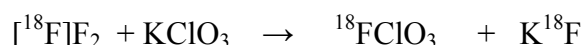
1.3.3   Nucleophilic [^{18}F]Fluorination Reactions

[^{18}F]Fluoride is mainly obtained as an aqueous solution, most often as a product of direct irradiation of [^{18}O]H$_2$O target. In aqueous form [^{18}F]fluoride is unreactive, and requires some simple but very important manipulations to provide a reactive nucleophilic reagent. The steps in preparing reactive [^{18}F]fluoride are the following[3]:

Addition of a cation: After irradiation of [^{18}O]H$_2$O target, the [^{18}F]fluoride must be accompanied by a positively charged counterion. This is mainly solved by the addition of a cationic counterion (mostly potassium complexed by a cryptand such as Kryptofix 222®, or tetraalkylammonium salts) prior to the evaporation of the water. Many syntheses now utilize the potassium/Kryptofix® system, although examples of the use of tetraalkylammonium salts are frequently encountered in the literature. The carbonate ion CO_3^{-2} is mostly used as the counterion because it has low nucleophilicity and moderate basicity.

Water evaporation: Aqueous [^{18}F]fluoride is quite unreactive. Hence, water is evaporated first by application of heat (130-160 °C) and second the use of a relatively volatile solvent such as acetonitrile (azeotropic distillation) under a mild stream of an inert gas like argon. This method provides practically anhydrous and reactive [^{18}F]fluoride.

Addition of the precursor solution: The residue from the last step contains [^{18}F]fluoride in an excellent dry and "naked" form, suitable for the substitution reaction. The precursor is usually added to this residue as a solution. In general, dipolar aprotic solvents are used, because many organic compounds used as precursors dissolve only in them and they readily solubilize [^{18}F]fluoride (particularly the K$^+$/Kryptofix® pair). In addition, nucleophilic substitution reactions are favourable in dipolar aprotic solvents. Solvents such as DMSO and DMF are inert towards [^{18}F]fluoride. In addition to being a strong nucleophile, [^{18}F]fluoride is also a strong base, therefore all reactions performed in polar protic solvents (such as methanol and ethanol) fail. The majority of [^{18}F]fluorination reactions using fluoride ion are done in solvents such as DMSO, DMF, DMAc or acetonitrile.

In these dipolar aprotic solvents, the nucleophilicities of halide ions in S_NAr reactions follow the order[10]: $F^- \gg Cl^- > Br^- > I^-$. However, nucleophilic [^{18}F]fluorination reactions can be less frequently performed in other solvents such as THF and dichloromethane. The choice of solvent is predicted on the solubility of other reagents, the type of chemical reaction being performed, or simplification of the subsequent work-up and product isolation procedure. In the last few years, ionic liquids were applied successfully[11] as a media to carry out nucleophilic fluorination. These solvents can be recycled (they have practically no vapour pressure, hence they are safe for the environment). Another very important advantage is the fact that they tolerate the presence of water up to 20 % in solution. This is very important in fluorination reactions where traces of water can reduce the yield drastically. The use of ionic liquids as a media for [^{18}F]fluorinations[12-14] is being extended now to other important tracers like [^{18}F]FDG and [^{18}F]FLT.

1.3.4   Nucleophilic Aromatic [^{18}F]Fluorination Reactions

Aromatic nucleophilic substitution is an important reaction for introducing fluorine to a ring. This reaction is activated by electron withdrawing groups ortho and/or para to the leaving group. The mechanism is generally the S_NAr. The leaving groups are usually NO_2^-, F^-, Cl^-, Br^-, OTs^-, NR_3^+ and others. The nucleophilic ways for putting a fluorine atom into the aromatic ring are generally less than for the other halogens, and normally involve one of the following:

1- Fluorodenitration reactions (Ar-NO$_2$ + F^- → Ar-F)[15-16].

2- Fluorodehalogenation reactions (Ar-X + F^- → Ar-F), X= Cl, Br, I and F (fluorine isotopic exchange)[15-16].

3- Fluorodediazonation reactions (ArN$_2^+$ + BF$_4^-$ → Ar-F + N$_2$ + BF$_3$)[17].

4- Fluorination via substitution of trimethyammonium group (Ar-NMe$_3^+$ + F^- → Ar-F)[18].

5- Dialkyltriazine substrates (Ar-N=N-NR$_2$ + F^- → Ar-F + N$_2$ + R$_2$N$^-$) [19].

6- Diaryliodonium substrates (Ar-I$^+$-Ar' + F$^-$ → Ar-F + Ar'-F) [20].

7- Fluorination via substitution of dimethylsulfonium group (Ar-SMe$_2^+$ + F$^-$ → Ar-F)[21].

Fluorination of aryl rings by nucleophilic displacement forms one example of significant differences between organic chemistry and radiochemistry. Nucleophilic aromatic substitution performed in the organic/medicinal laboratory often requires high temperatures and long reaction times with low-moderate yields. However, the reaction proceeds very rapidly, at moderate temperatures and in high yields when done at the nca level using [^{18}F]fluoride. Nucleophilic aromatic substitution has thus become a method used widely in fluorine-18 chemistry, and there are some common characteristics of all applications, noted in the following sections.

(a) A good leaving group on the aromatic ring is needed. The nitro (-NO$_2$) and the trimethylammoniumtriflate [-NMe$_3$OTf] groups are the most widely utilized leaving groups in aromatic substitutions with [^{18}F]fluoride. Less frequently halogens are used. The recent groups, such as diphenyliodonium (Ar-I$^+$-Ar'), have the advantage of not needing activating groups on the ring but they have problems associated with specific activity limitations. Simple isotopic substitution, ^{18}F for ^{19}F, is also a very good method for the synthesis of radiotracers. However, the low specific activity from these isotopic substitutions make this process unsuitable and limits its use only to low-specific activity applications.

(b) The aromatic ring needs to be activated, for the aromatic nucleophilic substitution to proceed efficiently, by the presence of one or more electron-withdrawing groups (EWG), preferably *ortho* or *para* to the leaving group (sometimes with the *meta* position, good results are obtained). A wide variety of substituents can function as electron-withdrawing groups, including nitro, ketone, aldehyde, nitrile, ester, amide, halogens and groups derived from them (CX$_3$). Studies[38,44] utilizing ^{13}C NMR have shown a direct correlation between withdrawing power of a substituent and yields in nucleophilic aromatic substitutions by

[^{18}F]fluoride. The choice of activating group often depends on the structure of the desired final product, or the sequence of synthetic steps to be followed after the introduction of [^{18}F]fluoride. For example, the activating group may form a part of the desired product, and this is a very good case because it does not need further steps for removal. The activating group can also be conveniently transformed into the needed structural component. For example:

$$CN \quad \rightarrow \quad CH_2NH_2$$

$$CN \quad \rightarrow \quad CONH_2$$

$$CN \quad \rightarrow \quad COOH$$

$$CHO \quad \rightarrow \quad CH_2OH$$

$$CONH_2 \quad \rightarrow \quad CH_2NH_2$$
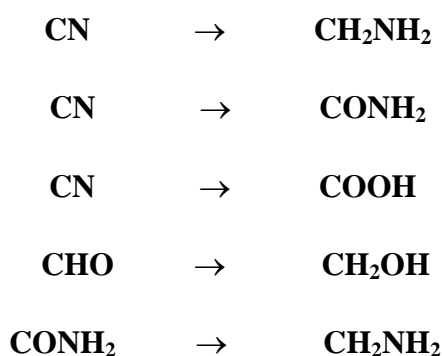
In some cases, activating groups can be temporarily placed on the aryl ring and subsequently completely removed. This process is necessary for the placement of [^{18}F]fluoride at positions of a ring that cannot be activated towards substitution. An example here is the aldehyde group which can be removed by catalytic deformylation[22] (using Rh[PPh$_3$]$_3$Cl) or the carboxyl group which can also be removed by decarboxylation.

1.4 Dopamine and Related Compounds

1.4.1 Catecholamines

Dopa (3,4-dihydroxyphenylalanine) is a precursor of a family of biological compounds called catecholamines. The principal catecholamines are norepinephrine, epinephrine and dopamine. These compounds are formed initially from phenylalanine and tyrosine. Tyrosine is produced in the liver from phenylalanine through the action of phenylalanine hydroxylase. Tyrosine is then transported to catecholamine-secreting neurons where a series of reactions convert it to

Dopa, dopamine, norepinephrine and finally to epinephrine. These transformations are explained in Fig. 4.
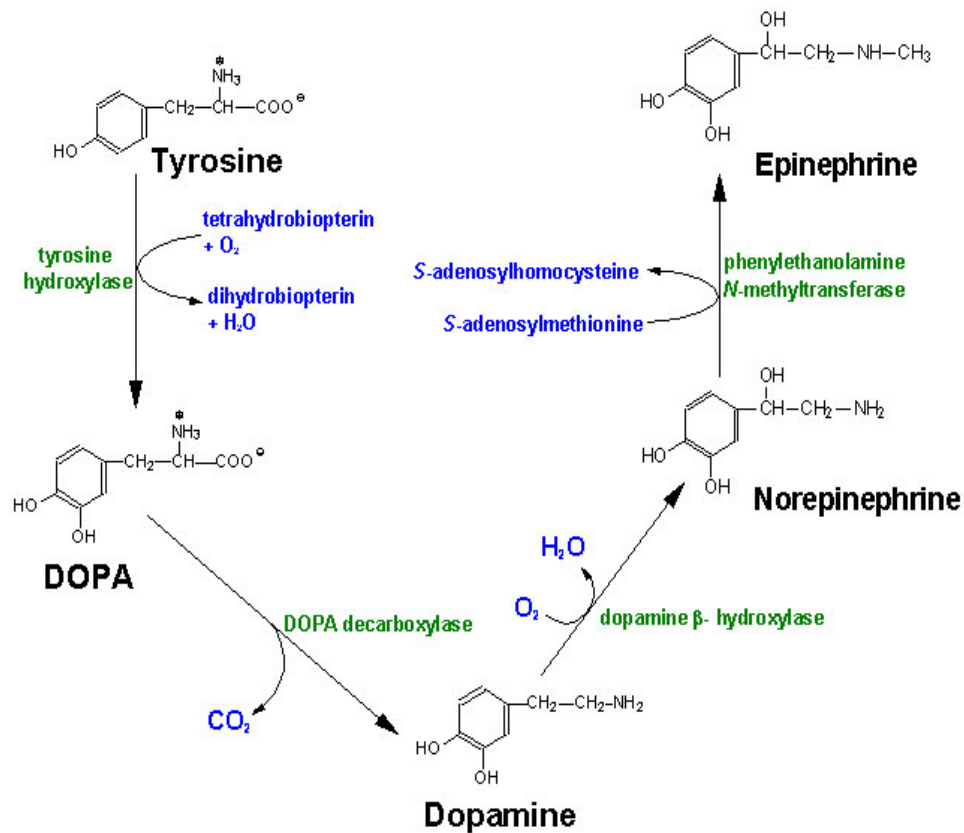
Fig. 4. Scheme for the synthesis of catecholamines from tyrosine.

1.4.2   The Dopaminergic System and Dopamine

In brain several bodies of nerves containing dopamine are concentrated in the substantia nigra and project to the caudate nucleus (neostriatum): this is the nigrostriatal pathway. Dopamine systems with cell bodies dorsal to the interpeduncular nucleus (midbrain area) and with terminals in the nucleus accumbens and olfactory tubercle (forebrain areas) have also been identified: this is the mesolimbic system. This dopaminergic system is shown in the Fig. 5.
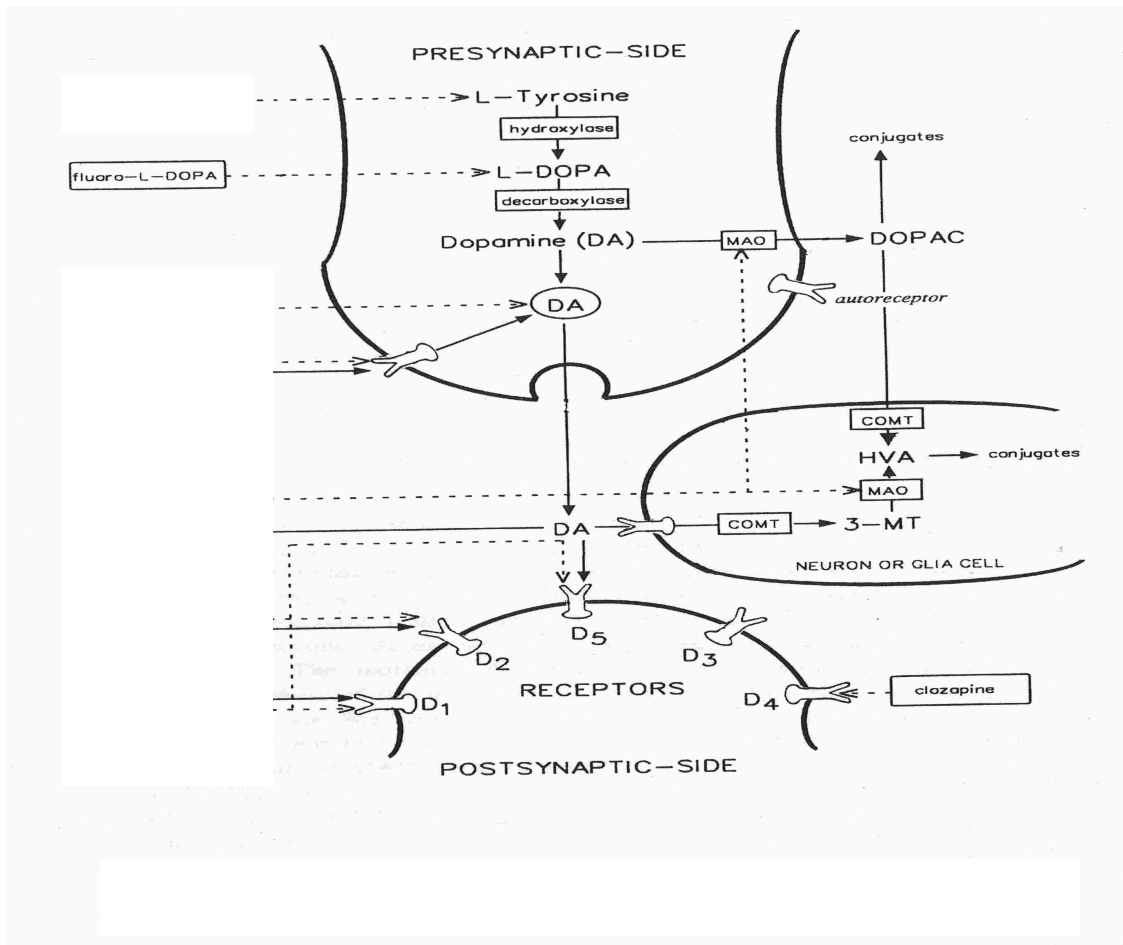
Fig 5. The dopaminergic system[23].

Communication between neurons takes place through the release of several compounds such as dopamine, a neurotransmitter stored in presynaptic vesicles, which binds postsynaptic receptors. Dopamine, present in a free state or outside the presynaptic terminal, can be metabolized via distinct pathways. In the noradrenaline containing neurons, benzylic hydroxylation of dopamine, catalyzed by the enzyme dopamine-β-hydroxylase (DBH), produces the neurotransmitter norepinephrine. In dopaminergic neurons, dopamine can be degraded to homovanillic acid (HVA) and conjugates. The oxidative deamination to HVA proceeds via two steps. Most of the dopamine is converted to 3,4-dihydroxyphenylacetic acid (DOPAC) via the enzymes monoamine oxidase (MAO) and aldehyde reductase. There are two types of MAO: MAO-A and MAO-B. Most MAO is present outside the dopaminergic neuron. DOPAC is converted to HVA, catalyzed by the enzyme catechol-O-methyltransferase

(COMT). As the third pathway, dopamine can also be directly inactivated by the enzyme COMT, giving 3-methoxytyramine (3-MT) which is subsequently deaminated by MAO to give HVA. COMT is an enzyme, which is predominantly localized outside the catecholamine neurons. Fig. 6 illustrates these transformations[23].
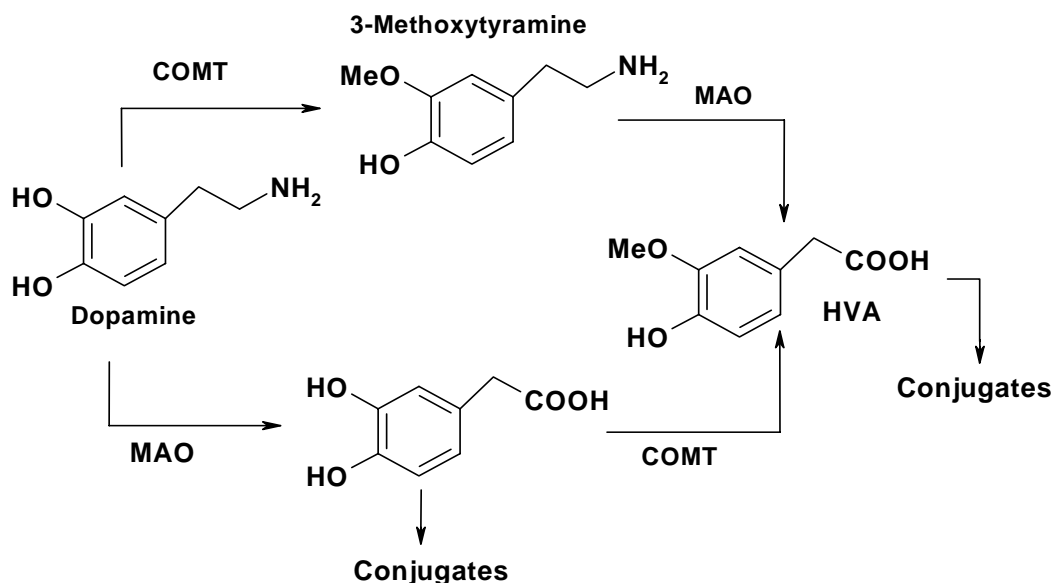
Fig. 6. Scheme for the metabolic pathways of dopamine[23].

1.4.3 Biological Role of Dopamine and Dopa: Applications in Medicine and Pharmacy

Parkinson's disease, which is caused by a shortage of dopamine production in the nerve cells, is normally treated by giving patients L-dopa to supply the dopamine that is missing. The predominant neuropathologic feature in Parkinson's disease is a degeneration of the dopaminergic cells in the substantia nigra. This results in a marked loss of cerebral, especially striatal dopamine. The severity of neuronal loss correlates with the clinical severity of Parkinson's disease. Therefore, the most common therapeutic strategy has been directed along the metabolic pathways of dopamine, therefore L-dopa is currently the most effective therapy for Parkinson's disease. However, L-dopa only helps with symptoms and does not prevent the disease from progressing.

1.4.4   Dopa and Dopamine: Applications in PET

For PET studies several ^{18}F and ^{11}C tracers, related to the structure of dopa and dopamine, were developed and were found to be very useful for studying dopamine production, transport and metabolism. Examples of such tracers include [^{18}F]FDOPA and [^{18}F]FTYR (*m*eta and *p*ara). These internationally well-established tracers are used mostly for clinical investigations of cerebral disorders such as the Parkinson's disease. Therefore, research is directed towards developing commercial production methods which can be applied for large scale production suitable for multi analyses.

2   THE PROBLEM

Among the several known neurotransmitter systems, special interest has been directed towards the study of the dopamine receptor system which is linked to a number of disorders such as Parkinson's disease, Huntington's Chorea, Tardive dyskinea and schizophrenia. Effects of variability in dopamine receptor density and information on the status of those receptors are of great interest for the study of pathogenesis as well as therapeutic interventions. Positron emission tomography (PET) provides direct access to the *in-vivo* biochemistry of those disorders and, consequently, to brain receptors. This scanning technique is a method for direct *in-vivo* quantification of the regional receptor distribution in the brain and other organs. For instance, PET imaging with a radiolabelled D_2 receptor ligand allows *in-vivo* visualisation of the postsynaptic receptors.
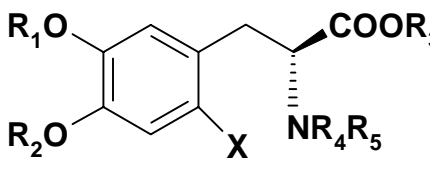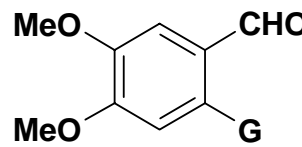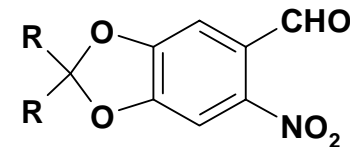
Since 1985, [^{18}F]FDOPA (**1**) is an internationally well accepted and applied radiotracer for the evaluation of the presynaptic dopaminergic functions by means of PET. It is converted to 6-[^{18}F]fluorodopamine and subsequently metabolized similarly to the nonfluoro analogue. Thus, [^{18}F]FDOPA is applied in patients with hemiparkinsonian symptoms and in Parkinson's disease.
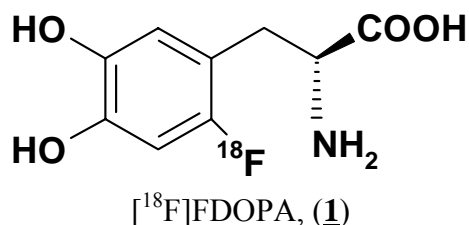
[^{18}F]FDOPA, (**1**)

The production of [^{18}F]FDOPA is still limited to a low scale. The labelling is mainly performed in the electrophilic way and that gives rise to serious problem of general importance: the specific activity is low because the product is obtained in the carrier added

form. In the nucleophilic way of labelling, however, the problem is how to optimize the structure and the conditions of the reaction in order to obtain both a high yield and a high specific activity. Tab. 5 gives a summary of some results obtained in the last twenty years. Syntheses reported in literature are not satisfactory (3-11 %), however, in the last few years the yields were improved (15-25 %) together with a high chemical, radiochemical and enantiomeric purity. Yet, data available until now are insufficient for applying the route of nucleophilic substitution in case of $[^{18}F]$FDOPA.

Tab. 5. Reported synthetic routes of [^{18}F]FDOPA						

Type of reaction	No	Labelling reagents	Labelling precursors	Leaving groups	RCY (%)	Synthesis time (min)	Ref.
Electrophilic Aromatic substitution	1	[^{18}F]F$_2$	(a)	H	3	120	24
	2	[^{18}F]AcOF	(b)	H	4	100	25
	3		(c)	HgOCOCF$_3$	8	50	26
	4		(d)	H	10-14	60	27
	5	[^{18}F]F$_2$	(e)	SiMe$_3$	8	60	28
	6		(f)	SnMe$_3$	26	45-50	29
Nucleophilic Aromatic substitution	7	[^{18}F]F$^-$	(j)	NMe$_3$OTf	25-30	100	30
	8		(g)	NO$_2$	16 ± 5	110-120	31
	9		(g)	NO$_2$	5	100	32
	10		(h)	NO$_2$	5	100-110	33
	11		(g)/(h)	NO$_2$	5	110	34
	12		(j)	NMe$_3$OTf	11-15	90	35
	13		(g)	NO$_2$	6-13	85	33
	14		(g)	NO$_2$	1	125	36
	15		(j)	NMe$_3$OTf	4-9	80-85	37
	16		(h), (i)	NO$_2$	12	110	38
	17		(g)/(h)	NO$_2$	3-5	120	39

Comp.	R$_1$	R$_2$	R$_3$	R$_4$	R$_5$	X
(a)	H	H	H	H	H	H
(b)	Me	MeCO	Me	H	MeO	H
(c)	Me	Me	Et	H	COCF$_3$	HgOCOCF$_3$
(d)	H/Me$_3$CCO	Me$_3$CCO	H	H	H	H
(e)	Me	Me	Et		CArH	SiMe$_3$
(f)	BOC	BOC	ET	H	BOC/CHO	SnMe$_3$

(a)- (f)

(g) G= NO$_2$
(j) G= NMe$_3$OTf

(h) R= H
(i) R= CH$_3$

For the electrophilic production commercial modules are available. The precursors can also be obtained commercially. However, for the nucleophilic production of [^{18}F]FDOPA there are no such commercial modules and the process still needs a considerable effort for development. Although yields up to 30 % were reported in the last few years, the commercial application and the large scale production suitable for PET centers is still a challenge. To solve this problem, a systematic study for choosing the appropriate precursor including a better understanding of the theoretical background this is highly demanding. Therefore, the nucleophilic aromatic substitution is to be studied systematically with the focus on developing and/or finding new structures, new protection groups and new reaction conditions. In this work the development has to follow one of two parallel ways:

1- **Path A**: improvement of the old, existing method (Fig. 7) which builds the tracer step by step starting from 6-substituted derivatives of veratraldehyde or piperonal (Tab. 5) by labelling in the first reaction, then building the side chain with the amino acid function and finally hydrolysing of all protected groups. These steps are to be optimized.
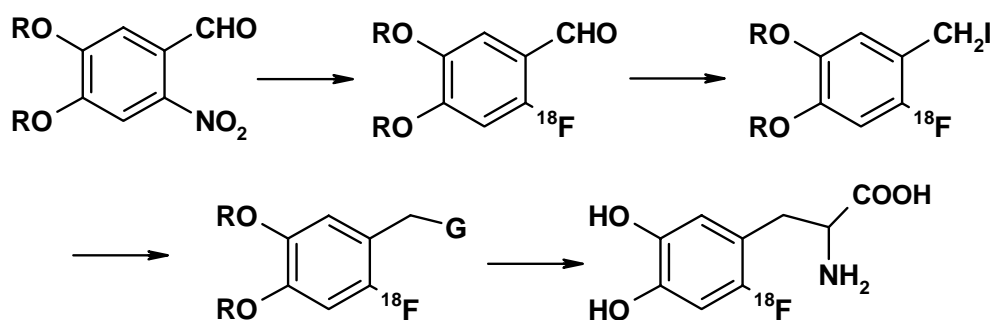
Fig. 7. Scheme for reported synthetic pathway of [^{18}F]FDOPA (path A) starting from 6-nitroveratraldehyde (R= CH$_3$).

2- **Path B**: developing completely new precursors with different structures (Fig. 8). In this way, the precursor already contains the amino acid function and, thus, is ready for labelling by nucleophilic substitution (^{18}F $\rightarrow$ ^{19}F) followed by removal of the assisting electron withdrawing group (EWG) and hydrolysing of the protecting groups.
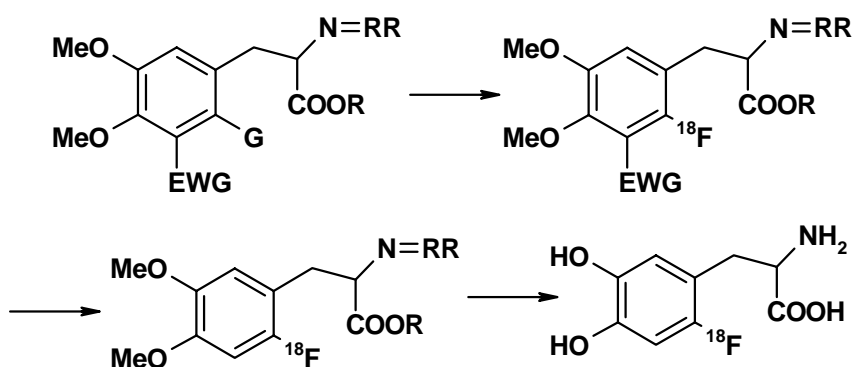
Fig. 8. Scheme for the suggested new synthetic pathway of [^{18}F]FDOPA (path B).

In order to get basically important information for solving the problem, in this work model precursors for the two pathways are to be examined and evaluated with respect to nucleophilic aromatic substitution by [^{18}F]fluoride. For this approach aromatic substrates in which up to three different groups are present at the benzene ring. Most importantly, the substituents can be both electron donating such as the methoxy group or electron withdrawing such as the nitro group and it is to be found out if and how much the electron donating effect of even two groups can be compensated that labelling by nucleophilic substitution can be realised in good radiochemical yields. The data are important for the development in path A and B and for theoretical and mechanistic studies of these types of reactions.

3 RESULTS AND DISCUSSION

3.1 Introduction

In this study the radiochemical yields (RCY) are determined on the basis of the measurement by means of a gamma counter or bio imager and the data are calculated as the amount of radioactivity of the product related to the total activity present in solution. If necessary, the measurements are always corrected in a way to compensate the decay of the radionuclide. The dependencies of the RCY on temperature, concentration of precursor and on solvent were studied in detail at time periods of 5, 10, 20, 30 and 60 minutes for precursors of path A. For precursors of path B (see Chpt 3.6) and the aryl systems, usually one value for the RCY is determined at a fixed temperature and in one solvent within a reaction time of 10, 20 or 30 minutes.

The two main types of reactions studied here are:

1- Fluorodenitration reactions: **Ar-NO$_2$** $\rightarrow$ **Ar-^{18}F**

2- Fluorodehalogenation reactions: **Ar-X** $\rightarrow$ **Ar-^{18}F**   (X= F, Br, Cl)

The mechanism is generally the S$_N$Ar (Fig. 9) which involves two intermediate steps for the labelling with [^{18}F]fluoride[40].
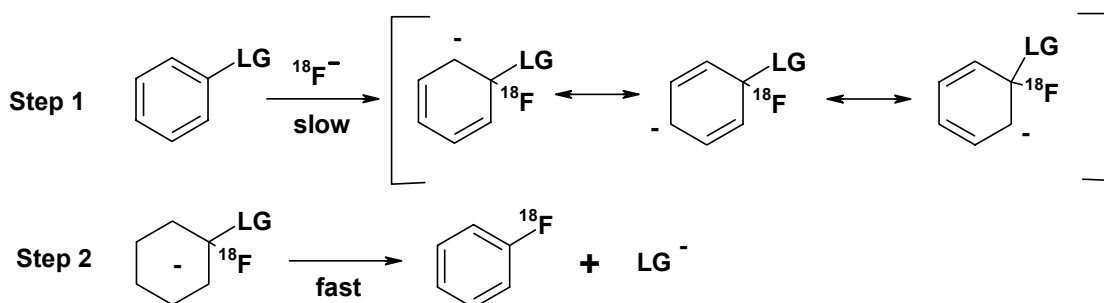
Fig. 9. Scheme for S$_N$Ar the mechanism of the nucleophilic aromatic substitution by [^{18}F]fluoride. LG is a leaving group.

The protection of the hydroxyl groups is necessary in order to avoid the solvation of the fluoride-ion and to retain the activity of [^{18}F]fluoride for the labelling reactions. For this purpose, methyl ethers (-OCH$_3$), carboxylic esters (-OCOCH$_3$, -OCOPh) and sulfonic esters (-OSO$_2$Ph) were used. The results of the ^{18}F labelling of aryl systems are presented, followed by the results of [^{18}F]FDOPA precursors (path A) and finally the results of [^{18}F]FDOPA precursors (path B). A general discussion following the results will summarise all data for comparison.

3.2 Aromatic Nucleophilic Substitution by [^{18}F]Fluoride on Aryl Systems

3.2.1 Aryl Halides

In general the labelling of mono substituted aryl halides gave very low yields because there are no S$_N$Ar enhancing groups and because the ability to act as a leaving group is less pronounced than in case of other groups. Bromobenzene gave yields in the range between 0.4 % and 1.8 %. In case of disubstituted arylhalides the yields were improved to 5.6-15.7 % for the three dibromobenzenes but to a smaller extent for the three dichlorobenzenes (0.8-7.3 %). With trisubstituted arylhalides the activation is good enough and the yields were higher. Hence, two tribromobenzenes, i.e. the 1,2,4- and the 1,3,5- isomers gave RCYs in the range of 33.3-64.3 % within 20 min. These results are shown in Fig. 10 and 11.
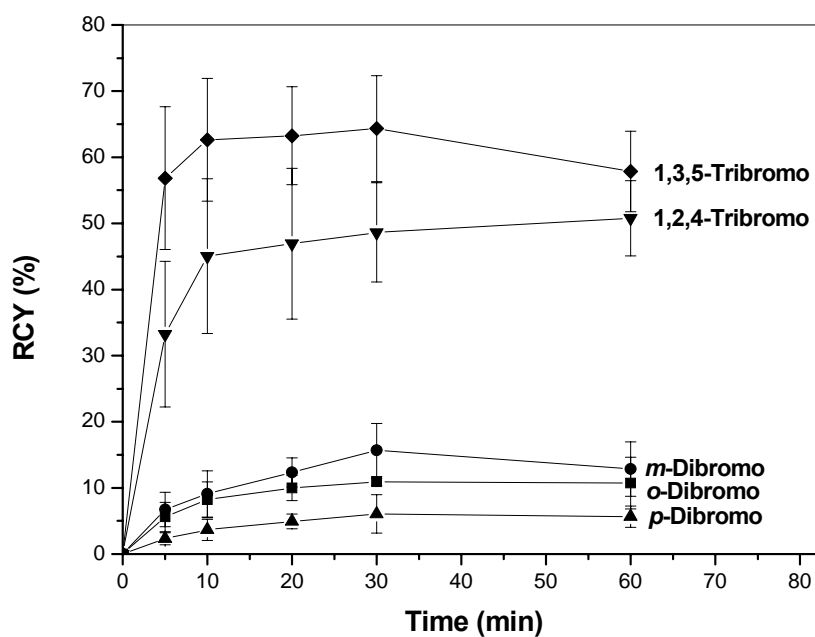
Fig. 10. [^{18}F] Labelling of bromobenzene derivatives (10 mg/mL) in DMF at 150 °C in dependence on time (Tab. 33 , App. 1).
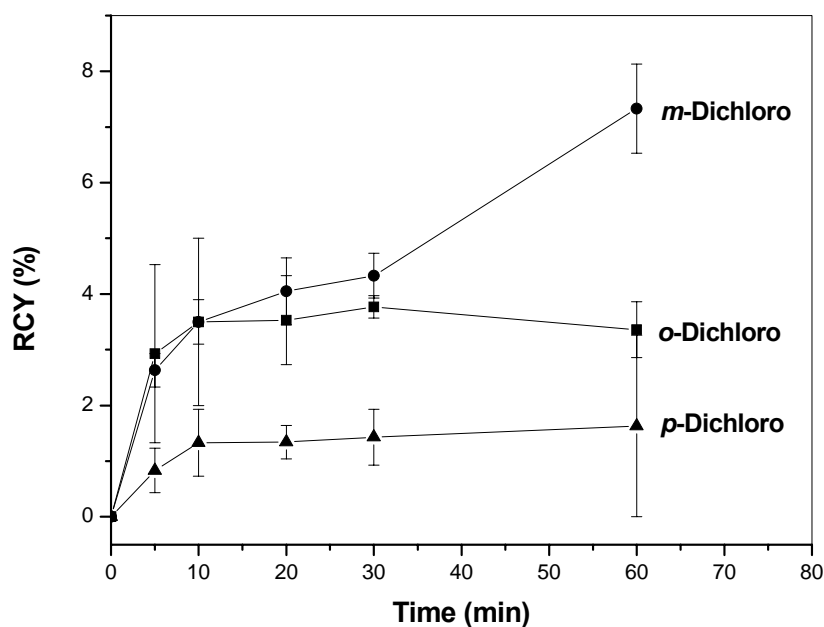
Fig. 11. [^{18}F] Labelling of three dichlorobenzene derivatives (10 mg/mL) in DMF at 150 °C in dependence on time (Tab. 34 , App. 1).

3.2.2   Nitroaryl Derivatives

Dinitrobenzenes (*o*-, *m*-, and *p*-) are particularly well activated for S_NAr and the ^{18}F labelling yields were expected to be high. In the case of the ortho isomer, this was observed previously. The labelling in DMF gave yields in the range of 78 % to 84 % within 20 min at temperatures between 80 °C and 120 °C. At higher temperatures the yields were smaller, so at 140 °C it started at 60 % within 5 min but decreased to only 15.2 % within 1 h. In acetonitrile, yields between 77 % and 84 % could be obtained within 20 min at temperatures between 60 °C and 80 °C. Fig. 12 and Fig. 13 illustrate the results.
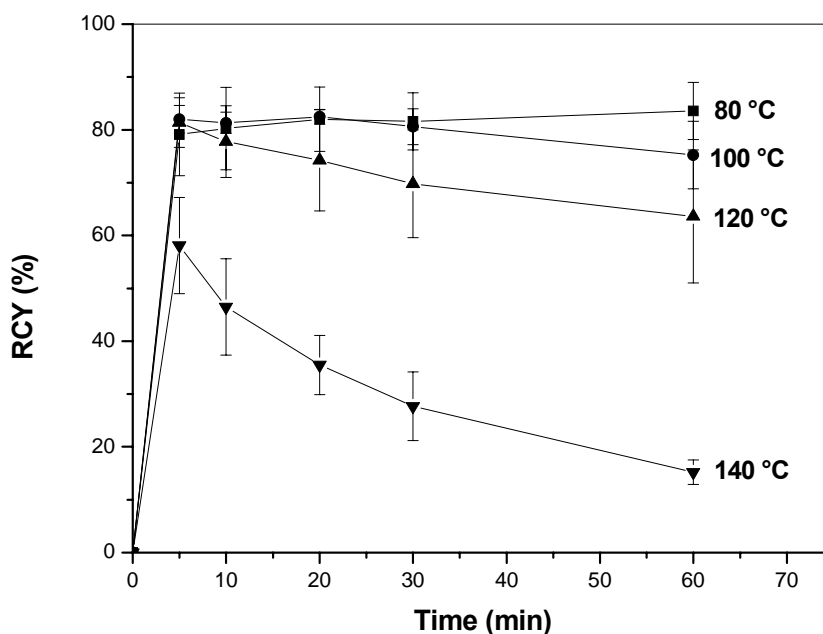
Fig. 12. [^{18}F] Labelling of *o*-dinitrobenzene (10 mg/mL) in DMF. Dependence of the RCY on temperature (Tab. 35, App. 1).
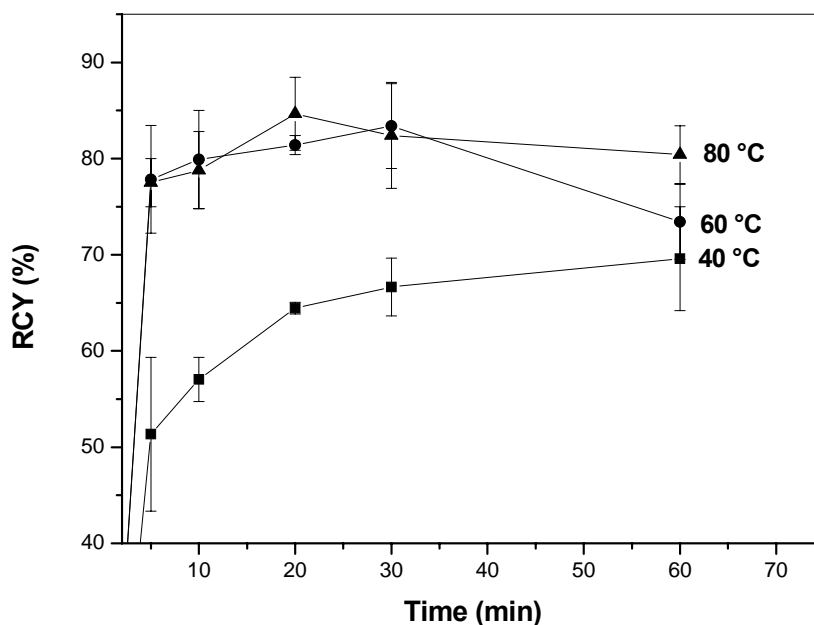
Fig. 13. [^{18}F] Labelling of *o*-dinitrobenzene (10 mg/mL) in acetonitrile. Dependence of the RCY on temperature (Tab. 35, App. 1).

Halonitrobenzene derivatives are less activated than dinitrobenzene and they are expected to give lower yields. Moreover, the leaving group is also thought to be the most activated one, i.e. the halogen. In case of the three bromonitrobenzenes, the RCYs of the [^{18}F]fluoronitrobenzene (conditions: DMF, 10 mg/ml, 150 °C, 10 min) followed the order:

(65.6 %)	(46.5 %)	(30.0 %)
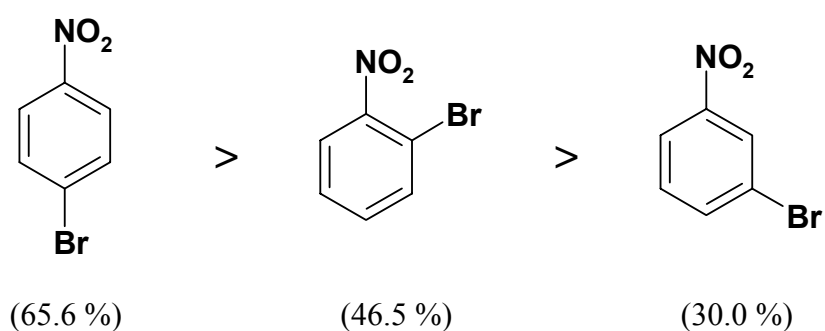
The results are shown in Fig. 14.
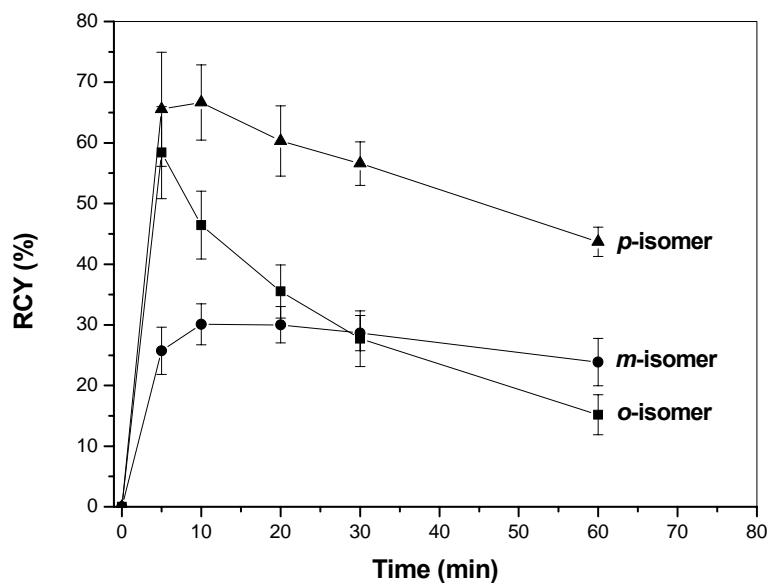
Fig. 14. [^{18}F] Labelling of three bromonitrobenzene isomers (10 mg/mL) in DMF at 150 °C in dependence on time (Tab. 36, App. 1).

3.2.3   Benzaldehyde Systems

The aldehyde is a good electron withdrawing group, hence with a good leaving group the labelling yields are expected to be high. In fact, at high temperatures (> 100 °C) the labelling yields using o-nitrobenzaldehyde were in the range of 60-70 % within 20 min and increased slightly to 79 % within 1 h (Fig. 15).
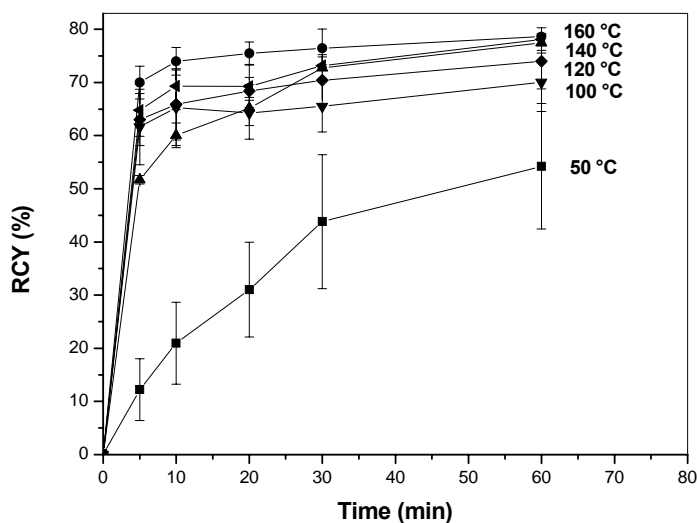
Fig. 15. [^{18}F] Labelling of *o*-nitrobenzaldehyde (10 mg/mL) in DMF. Dependence of the RCY on temperature. (Tab. 37, App. 1).

For the other derivatives of benzaldehyde, Tab. 6 gives a summary of the labelling results together with those reported in literature. It can be seen that all the RCYs are between 65 % and 82 %. Moreover, the highest yields obtained are those compounds with the best leaving groups, i.e. with the nitro and the fluoro substituents. The yields using the *para* isomers are always higher than those of the *ortho* isomer. Compared to the literature, where only DMSO was used for labelling of all benzaldehyde precursors, it can be noticed that the yields are almost the same with respect to the 2-nitro derivative, and only improved a little bit in case of the 4-nitro isomer. The labelling yields of the halogeno precursors were highly improved when using DMF as a solvent. Hence, RCYs in the range 65-83 % could be obtained using DMF instead of 3-7 % using DMSO. Among halogens the ability to act as a leaving group was the following:

$$F \approx Br > Cl$$

Tab. 6. [18F] Labelling yields of *ortho* and *para* derivatives of benzaldehyde. (Conditions of this study: DMF(1 /mL), 10 mg/mL, 140-150 °C, 20 min).

| Precursor | This work | | Literature | | |
| | RCY (%) | | | | |
	TLC	HPLC	RCY (%)	Conditions	Ref.
2-Nitro	73.2 ± 0.2 (n=3)	74.4	55.0 ± 10	DMSO (0.5 ml), 120-130 °C, 15 min	41
			78.0	DMSO (0.3 ml), 120 °C, 10 min	38
			65.0	DMSO (1 ml), 130-140 °C, 20 min	42
			53.0	DMSO (1 ml), 114 °C, 25 min	44
			50-60	DMSO (0.3 ml), MW, 4 min	45
			65.0	DMSO (1 ml), MW, 2 min	22
			76.0	DMSO (0.2 ml), MW, 0,25 min	46
2-Fluoro	75.0 ± 1.6 (n=1)	73.0 ± 2.5	-	-	-
2-Bromo	73.0 ± 0.2 (n=3)	75.0 ± 3.2	-	-	-
2-Chloro	65.0 ± 1.1 (n=3)	62.7 ± 4.6	-	-	-
4-Nitro	81.5 ± 5.9 (n=3)	82.8 ± 5.0	55 ± 10	DMSO (0.5 ml), 120-130 °C, 5 min	41
			70.0	DMSO (1.5 ml), 85-110 °C, 20 min	43
			65.0	DMSO (1 ml), 130-140 °C, 20 min	42
			53.0	DMSO (1 ml), 114 °C, 25 min	44
			65.0	DMSO (1 ml), 145 °C, 20 min	22
			50-60	DMSO (0.3 ml), MW, 4 min	45
			65.0	DMSO (1 ml), MW, 2 min	22
			75.0	DMSO (0.2 ml), MW, 0,5 min	46
4-Fluoro	78.3 ± 0.5 (n=3)	80.0 ± 3.7	-	-	-
4-Bromo	75.7 ± 0.5 (n=3)	82.0 ± 1.2	3.0	DMSO (1.5 ml), 85-110 °C, 20 min	43
			7.0	DMSO (0.2 ml), MW, 0,5 min	46
4-Chloro	65.7 ± 3.3 (n=3)	69.7 ± 2.0	1.0	DMSO (1.5 ml), 85-110 °C, 20 min	43
			6.0	DMSO (0.2 ml), MW, 0,5 min	46

3.2.4   Acetophenone and Benzophenone Systems

A different good electron withdrawing substituent is the ketone group (COR, COAr). With

a nitro group as a good leaving substituent the labelling yields are expected to be high. So the

labelling of 4-nitroacetophenone was studied in detail using DMF and DMSO, respectively

(Fig. 16 and 17). A clear dependence on temperature was observed in both cases. In both

solvents the yields within 30 min were comparable to those at temperatures 50-140 °C and

increased at 160 °C to be 60-73 % in DMF and 50-60 % in DMSO.
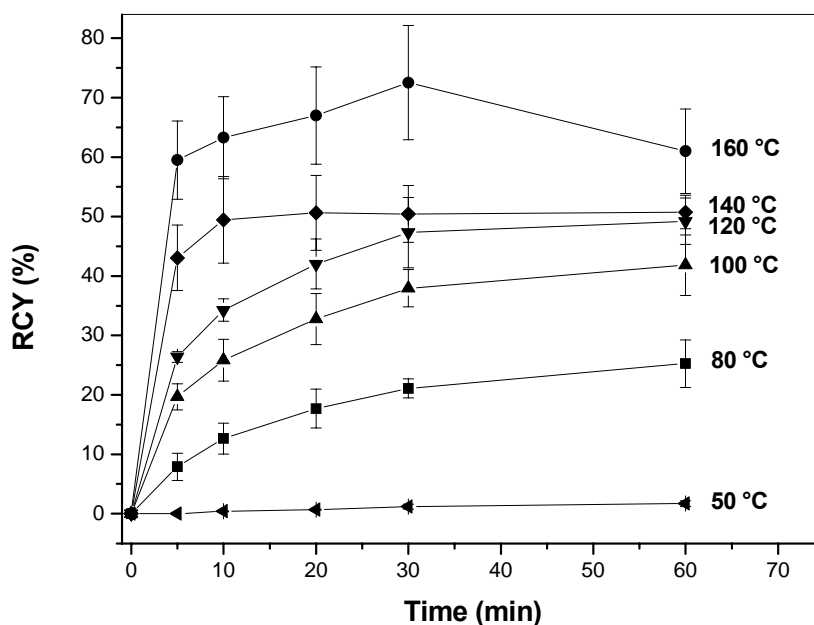
Fig. 16. [^{18}F] Labelling of *p*-nitroacetophenone (10 mg/mL) in DMF. Dependence of the RCY on temperature (Tab. 39, App. 1).
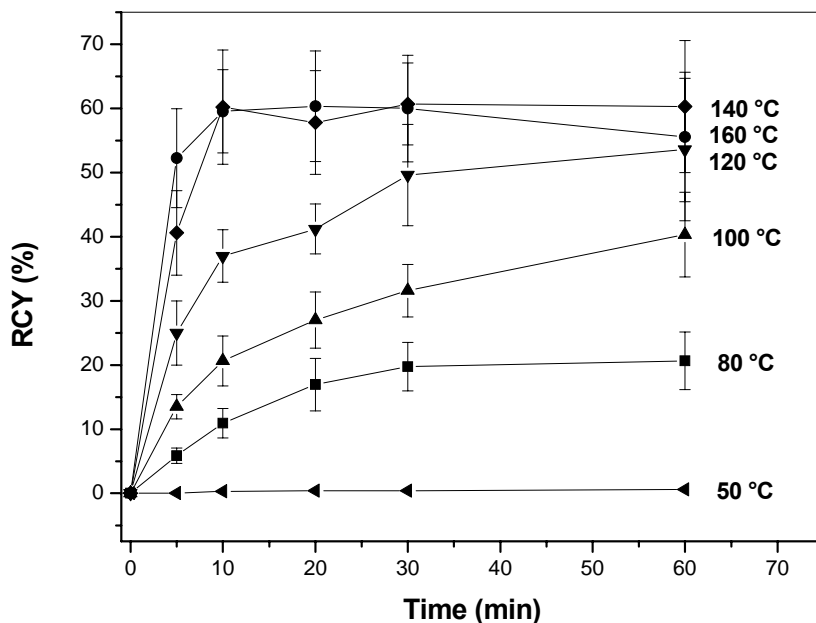
Fig 17. [^{18}F] Labelling of *p*-nitroacetophenone (10 mg/mL) in DMSO. Dependence of the RCY on temperature. (Tab. 39, App. 1).

Tab. 7 shows the results of [^{18}F]labelling of *ortho* and *para* acetophenones. 2-Nitroacetophenone gave unexpectedly very low yield in accordance with the values reported in the literature. A possible explanation is the existence of *o*-nitroacetophenone mainly in the form of an ***enol***. In the enol form, the hydroxy group can easily form hydrogen bonding with the nitro group only if it is in the *ortho* position. This is a general structural feature observed with acetophenones having an *ortho* group that can form hydrogen bonding with the enol form of acetophenone. Examples of such groups include -OH, -NH$_2$ and -NO$_2$. For example *o*-hydroxyacetophenone exists predominantly in the enol form[105] (Fig. 18).
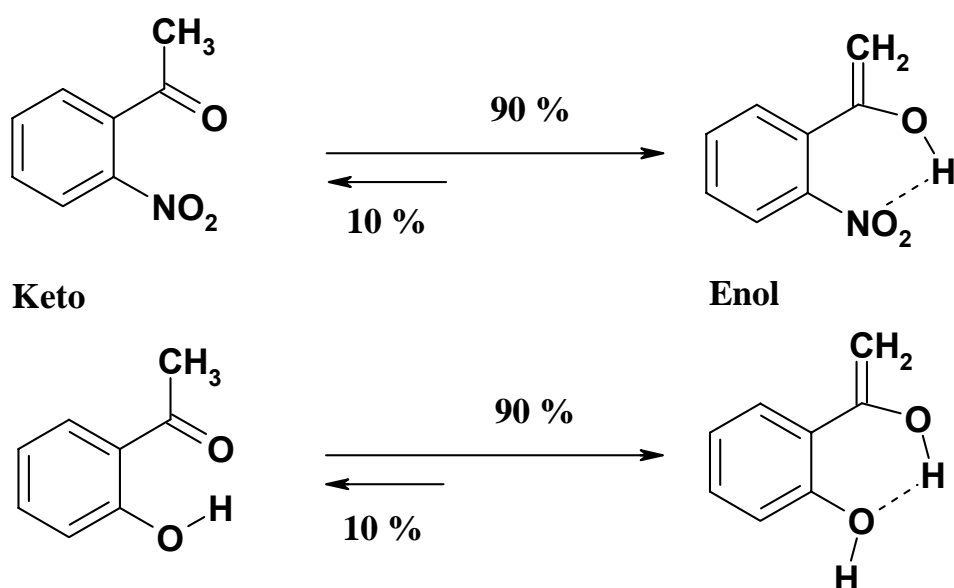
Fig. 18. Scheme for the keto-enol tautomerism in 2-hydroxy and 2-nitro acetophenone (data from X-ray studies)[105].

The existence of the enol form with its free hydroxyl group (even up to 10 %) diminishes the reactivity of [18F]fluoride hence low yields are expected to be obtained with *o*-nitroacetophenone. This reasoning is also supported by the fact that other structures, which can not form stable enol forms, gave high yields in the nucleophilic aromatic substitution by [18F]fluoride. Examples include *p*-nitroacetophenone, *o*- and *p*-nitrobenzophenone. The highest labelling yields were obtained from the fluoro derivative (75 %). The labelling yields of the 2-bromo, 2-chloro and 4-bromo derivatives were comparable and they were in the range 35-40 %. The labelling yields of the 4-nitro and the 4-chloro derivatives were very close to each other (59-61 %) but smaller than those of the fluoro analogue.

Tab. 7. [^{18}F] Labelling yields of ortho and para derivatives of acetophenone. (Conditions in this study: DMF, 10 mg/mL, 150 °C, 20 min).

Precursor	This study		Literature		
	RCY (%)				
	TLC	HPLC	RCY (%)	Conditions	Ref.
2-Nitro	13.3 ± 0.9 (n=3)	13.3 ± 1.7 (n=3)	15.0 ± 5	DMSO (0.5 ml), 120-130 °C, 15 min	41
			10-22	DMSO (1 ml), MW, 2.5-5 min	46
			11.0	DMSO (0.2 ml), MW, 0,4 min	47
2-Fluoro	70.1 ± 1.3 (n=3)	75.0 ± 0.8 (n=3)	-	-	-
2-Bromo	39.3 ± 2.9 (n=4)	34.3 ± 2.6 (n=4)	-	-	-
2-Chloro	37.7 ± 5.4 (n=34	37.0 ± 5.9 (n=4)	-	-	-
4-Nitro	61.7 ± 3.9 (n=4)	60.8 ± 2.5 (n=4)	61 ± 10	DMSO (0.5 ml), 120-130 °C, 20 min	41
			34.0	DMSO (0.5 ml), 160 °C, 20 min	48
			40-50	DMSO (1 ml), MW, 5 min	45
			63.5	DMSO (1 ml), MW, 2.5 min	49
			71.0	DMSO , MW, 0,5 min	48
4-Fluoro	74.7 ± 1.2 (n=2)	75.0 (n=1)	75	DMSO (0.5 ml), 160 °C, 20 min	48
4-Bromo	35.3 ± 1.7 (n=4	31.5 ± 3.2 (n=4)	6.0	DMSO (0.5 ml), 160 °C, 20 min	48
4-Chloro	59.0 ± 3.6 (n=4)	58.7 ± 3.8 (n=4)	28.0	DMSO (0.5 ml), 160 °C, 20 min	48

Tab. 8. [^{18}F] Labelling yields of *ortho* and *para* derivatives of benzophenone. (Conditions in this study: DMF(1 mL), 10 mg/ mL, 140-150 °C, 20 min).

| Precursor | This study | | Literature | | |
| | RCY (%) | | | | |
	TLC	HPLC	RCY (%)	Conditions	Ref.
2-Nitro	78.7 ± 1.9 (n=5)	78.4 ± 4.3 (n=5)	-	-	-
2-Fluoro	91.2 ± 1.0 (n=4)	92.3 ± 0.6 (n=4)	-	-	-
2-Chloro	6.6 ± 2.2 (n=7)	6.2 ± 0.9 (n=7)	-	-	-
4-Nitro	86.8 ± 4.8 (n=4)	88.6 ± 3.3 (n=4)	93 ± 2	DMSO, 130 °C, 5 min	41
			52	DMSO, 160 °C, 20 min	50
4-Fluoro	83.3 ± 3.0 (n=4)	83.0 ± 1.9 (n=4)	-	-	-
4-Bromo	76.0 ± 2.6 (n=4)	76.5 ± 3.7 (n=4)	-	-	-
4-Chloro	70.7 ± 3.6 (n=4)	71.7 ± 4.5 (n=4)	-	-	-

With regard to the benzophenone derivatives the results are illustrated in Tab. 8. With benzophenones the labelling yields were higher than those with acetophenones. That means that the -COPh group is better than the corresponding -COCH$_3$ group for enhancing S$_N$Ar. Furthermore, the highest labelling yields (83-92 %) were obtained with the fluoro and the nitro derivatives. With the exception of the fluoro derivative, the *para* isomers gave higher yields than the *ortho* isomers. This can be explained by the steric hindrance provided by the second ring in the *ortho* position (because the fluorine atom is small, the steric hindrance in case of the 2-fluoro derivative is small, hence the yield still is high).

An order of the leaving group ability can be written here as:

$$F > NO_2 > Br > Cl \qquad (\textit{ortho} \text{ derivatives of benzophenone})$$

$$NO_2 > F > Br > Cl \qquad (\textit{para} \text{ derivatives of benzophenone})$$

Unfortunately no literature data exist for most of these precursors for the purposes of comparison.

3.3 The Calculation of Activation Energy by Means of the Arrhenius Equation

From the curves showing the dependency of the RCY on temperature it is possible to determine the rate constants and the activation energy of these reactions. A labelling reaction is assumed to follow pseudo-first-order kinetics[44] since the organic substrates were present in extremely large excess over the nca [^{18}F]fluoride. The equation for the speed of such a reaction is equivalent to the following differential equation:

$$-d\,[^{18}F^-]\,/\,dt = k'[^{18}F^-]$$

where k' is the rate constant. Separating the variables gives:

$$-d\,[^{18}F^-]\,/\,[^{18}F^-] = k'dt$$

integrating this equation (boundary conditions $C_o \rightarrow C$ and $0 \rightarrow t$) gives:

$$-\ln\,([^{18}F^-]_t\,/\,[^{18}F^-]_o) = k't$$

$$-\,(\ln\,([^{18}F^-]_t - \ln\,[^{18}F^-]_o) = k't$$

$$\ln\,[^{18}F^-]_o - \ln\,[^{18}F^-]_t = k't$$

$$\ln\,([^{18}F^-]_o\,/\,[^{18}F^-]_t) = k't$$

introducing $\quad [^{18}F^-]_t = [^{18}F^-]_o - RCY \quad$ we get the following:

$$\ln\,([^{18}F^-]_o\,/\,[^{18}F^-]_o - RCY) = k't \qquad \text{or} \qquad \ln\,(1 - RCY/[^{18}F^-]_o) = k't$$

which is equivalent to: $\qquad \textbf{ln (1 – RCY) = k't}$

hence a graph of ln (1-RCY) versus reaction time gives a linear function with the slope of $-k'$.

The temperature dependency of the labelling reactions is given by the temperature dependency of the rate constant[51]. The rate constant increases exponentially with increasing temperature. This is expressed usually by the following equation:

$$k = A \, e^{-b/T}$$

where A and b are empirically determined constants.

According to Arrhenius, the constant b can be replaced by $-E_{act}/R$, where E_{act} is the activation energy and R is the gas constant (R = 8.314 J/K mol). Therefore we can write this equation as:

$$K = A \, e^{-E_{act} / (RT)}$$

which may be written in natural logarithmic way as:

$$\ln k = \ln A - E_{act} / (RT)$$

Hence, a plot of ln k against 1/T (K) gives a linear function with the slope of $-E_{act}/R$. The activation energy can be determined graphically in this way. With at least two rate constants for one reaction, measured at different temperatures, the activation energy can be determined also mathematically by the following formulae:

for T_1: $\ln k_1 = \ln A - E_{act}/(RT_1)$

for T_2: $\ln k_2 = \ln A - E_{act}/(RT_2)$

subtraction of T_2 from T_1 leads to:

$$\ln (k_1/k_2) = E_A/R \, (1/T_2 - 1/T_1)$$

from this the activation energy is equivalent to:

$$E_{act} = R[T_1 T_2/(T_1 - T_2)] \ln (k_1/k_2)$$

In dealing with the labelling reactions, and for purposes of calculating the Arrhenius constants, part of the graph of RCY versus time is chosen where the RCY is increasing. This gives reliable values and avoid the problems of meaningless negative values. The labelling process was noticed to be mainly in the first 5-10 min. After this, decomposition started which competes with the labelling reaction. Therefore, for purposes of simplifying the calculations, the first stage of the labelling reaction, i. e. 0-10 min is applied in calculating the rate constant and the activation energy graphically. The linearity of all graphs is evaluated by the correlation coefficient r. A reliable linear graph would be assumed to have r in the range 0.85-1.00 or the same values in the negative region.

3.4   Applications of the Arrhenius Calculations

Applying the Arrhenius calculations, the following results were obtained for *o*-nitrobenzaldehyde and *p*-nitroacetophenone.

3.4.1   *o*-Nitrobenzaldehyde

This system is highly activated in nucleophilic aromatic substitution. The best linear range for Arrhenius calculations was found to be 0-10 min at temperatures 80-140 °C. By drawing the graph of ln (1-RCY) versus time, the rate constants as shown in Tab. 9 were obtained and an activation energy of 24 kJ/mol was calculated (Fig. 19).

Tab. 9. Rate constants (min^{-1}) for the labelling of *o*-nitrobenzaldehyde at temperatures 80-140 °C.	
Temp. (°C)	k' (min^{-1})
80	0.0919
100	0.1058
120	0.1076
140	0.1181
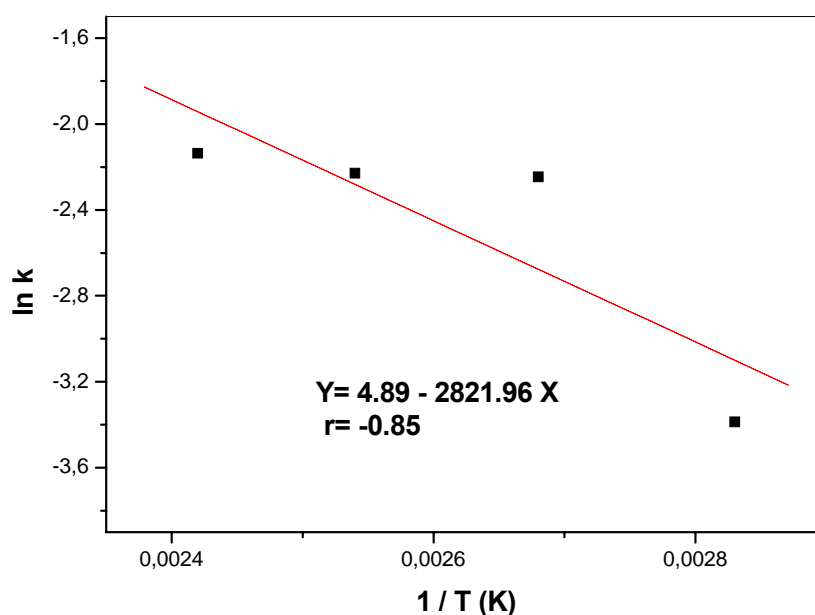
Fig. 19. Plot of ln k versus 1/ T (K) for *o*-nitrobenzaldehyde. (Conditions: 0-10 min, 80-140 °C) (Tab. 38, App. 1).

3.4.2   *p*-Nitroacetophenone

This system is also highly activated in nucleophilic aromatic substitution. The best linear range for Arrhenius calculations was found to be 0-10 min at temperatures 80-140 °C. By drawing the graph of ln (1-RCY) vs time, the rate constants as shown in Tab. 10 were obtained and an activation energy of 32 kJ/mol was calculated (Fig. 20)

Tab. 10. Rate constants (min^{-1}) for the labelling of *p*-nitroacetophenone at temperatures 80-140 °C.

Temp (°C)	k' (min^{-1})
80	0.0136
100	0.0298
120	0.0420
140	0.0683
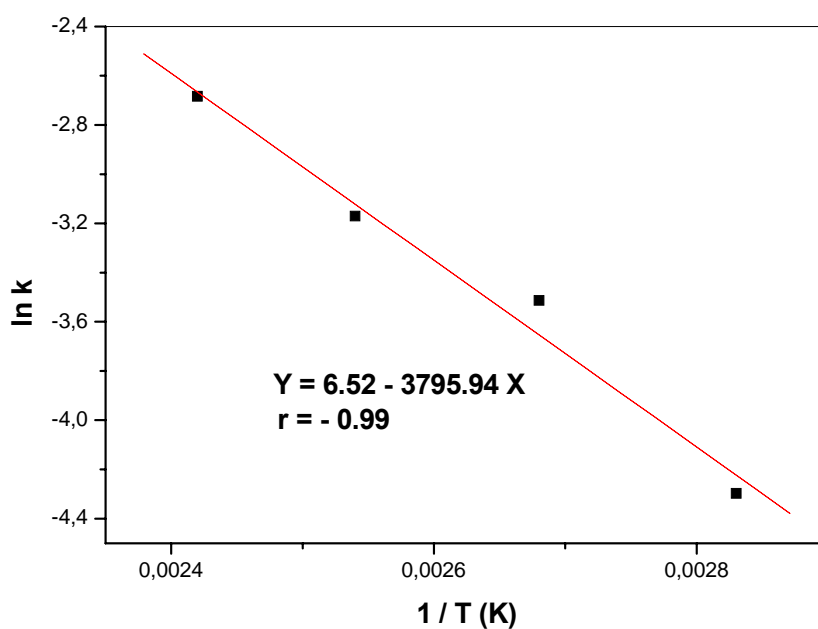
Fig. 20. Plot of ln k versus 1/ T (K) for *p*-nitroacetophenone. (Conditions: 0-10 min, 80-140 °C) (Tab. 40, App. 1).

3.5 Aromatic Nucleophilic Substitution by [^{18}F]Fluoride on Precursors for Path A of [^{18}F]FDOPA

3.5.1 Introduction

The total synthesis of [^{18}F]FDOPA via path A (see Chpt. 2) is well known in the literature and until now more than ten different approaches have been applied, depending on the type of starting precursor, type of protection of the hydroxyl groups and the amino acid function and on the reagents used to achieve the intermediate transformations. Tab. 5 shows the results. However, except for the latest syntheses (RCY 16-30 %), yields always were low (3-11 %). There principally are two main types of compounds used frequently for the labelling step (first step) in the total synthesis of [^{18}F]FDOPA. Those are the 6-substituted veratraldehydes (**2**) and the 6-substituted piperonals (**9**). Two leaving groups used frequently are the nitro group and the trimethylammonium triflate. The nitro precursors are commercially available while the trimethylammonium triflates are not, and they generally have to be prepared relatively short before use. Therefore, a choice was made to investigate the commercially available precursors since one needs high quantities in high purity. Tab. 11 summarises the results for the labelling of [^{18}F]FDOPA precursors for path A depending on 6-substituted veratraldehyde (i.e. synthesis of 6-[^{18}F]fluoroveratraldehyde, **3**)

(**2a**)	G= NO$_2$
(**2b**)	G= NMe$_3$OTf
(**2c**)	G= F
(**2d**)	G= Br
(**2e**)	G= Cl
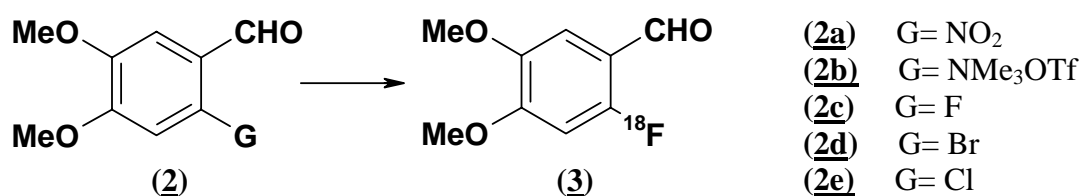
Fig. 21. Scheme for the synthesis of 6-[^{18}F]fluoroveratraldehyde by nucleophilic aromatic substitution.

Precursor	Leaving group	Conditions [a]	RCY (%)	Ref.
2a	NO$_2$	120 °C, 10 min	23	38
		20 min, 130 °C Microwave (300 W), 2 min	50	46
		25 min, 114 °C	52	44
		130 °C	50	52
		20 min, 130 °C	50-55	32
		20 min, 135 °C	25-35	39
		20 min, 130 °C	55	36
		20 min, 145 °C	27	53
		20 min, 145 °C Microwave (300 W), 2 min	50	22
		Microwave (300 W), 2 min	45-50	34
		20 min, 130-140 °C	50	42
2b	NMe$_3$OTf	110 °C	45-50	54
		20 min, 160 °C	30-35	37
		140 °C, 10 min Microwave (300 W), 1 min	45 ± 5	36
2c	F	New precursors (this work)		
2d	Br			
2e	Cl			

Tab. 11. Literature syntheses of 6-[^{18}F]fluoroveratraldehyde (**3**).

[a]) Other reagents: K$^{(18)}$F, DMSO, K$_2$CO$_3$, kryptofix [2.2.2].

3.5.2 6-Nitroveratraldehyde: Reaction Parameters and Activation Energy Calculation for the ^{18}F labelling

(**2a**)
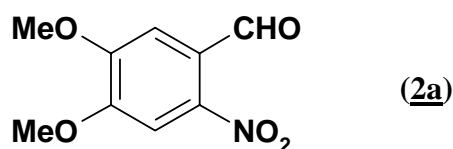
This compound is the most important precursor for [^{18}F]FDOPA and it is used widely since it

is commercially available, inexpensive and stable for long time. The literature yields

(Tab. 11) for the ^{18}F labelling were between 20 % and 55 % in DMSO within 10-20 min at

temperatures between 110 °C and 140 °C. A more investigation of the kinetics of ^{18}F labelling

of this precursor shows the results reported below.

The reaction of nca [^{18}F]fluoride with 6-nitroveratraldehyde was performed in DMF, DMAc,

DMSO, sulfolane and 1,2-dimethoxyethane at 140 °C with 20.0 mg/mL of precursor (Fig. 22).
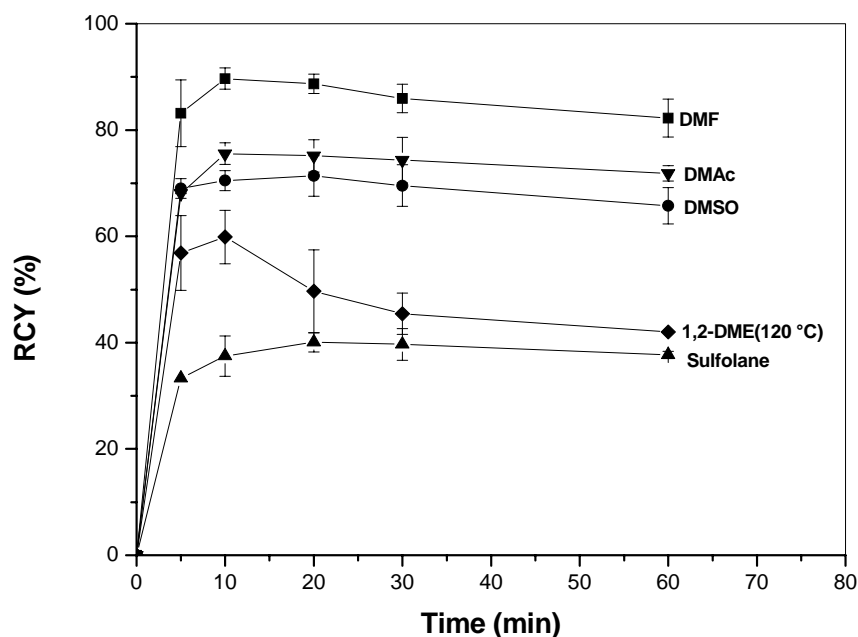
Fig. 22. [^{18}F] Labelling of 6-nitroveratraldehyde (20 mg/mL) at 140 °C. Dependence
of the RCY on the type of solvent (Tab. 41, App. 2)

DMF proved to be the best solvent for the labelling process. The labelling yield was 89 ± 2 %

(n=15) after a reaction time of 10 min. Relatively fast kinetics were observed, i.e. within the

first period of 10 min yields reached highest values or were already close to the maximum.

While in DMSO and DMAc the labelling yields were slightly above 70 %, in sulfolane and

1,2-dimethoxyethane the amount of labelled product was clearly lower. In the literature (see

Tab. 11), where DMSO was used as the solvent of choice, the radiochemical yields were not

higher than 55 % at reaction temperatures of 120-150 °C. Although at 140 °C higher yields

(70 %) were also observed in DMSO, the labelling process appears to be clearly improved

when performed in DMF.

Sulfolane is a solvent less frequently used for nucleophilic fluorinations, yet it was chosen for this work because it has the advantage of allowing the applications of high reaction temperatures up to 300 ºC. However, the lowest yields in this series of experiments (40 % after 20 min) were observed.

As expected because of the lower polarity, 1,2-dimethoxyethane did also not give high yields which were in the range of 55 % to 60 % within 10 min at 120 ºC and dropped afterwards to 42 % at 60 min.

Other aprotic solvents were tested without success. In acetonitrile (at 100 ºC) and benzonitrile the labelling reactions failed. Nitromethane and nitroethane could also be applied principally but these solvents appeared to react fast with the aldehyde group (Knoevenagel condensation), resulting in labelled products of other than desired structure.

All labelling experiments were repeated at least 4 to 10 times and the standard deviations calculated were in the range from 3 to 15 % of the reported values.

Furthermore, nine reactions were performed under the best labelling conditions (140 °C, DMF, 20 mg) for 10 min in order to analyse the product by HPLC. The labelling yields were 89 ± 3 %. Thus , it was clearly proven that the product was analysed without any impurities and the TLC data reported above are reliable.

Since best labelling results were obtained in DMF, the effect of precursor concentration was studied in this solvent. The concentrations were varied from 0.5 mg/mL up to 50 mg/mL, the results are shown in Fig. 23.
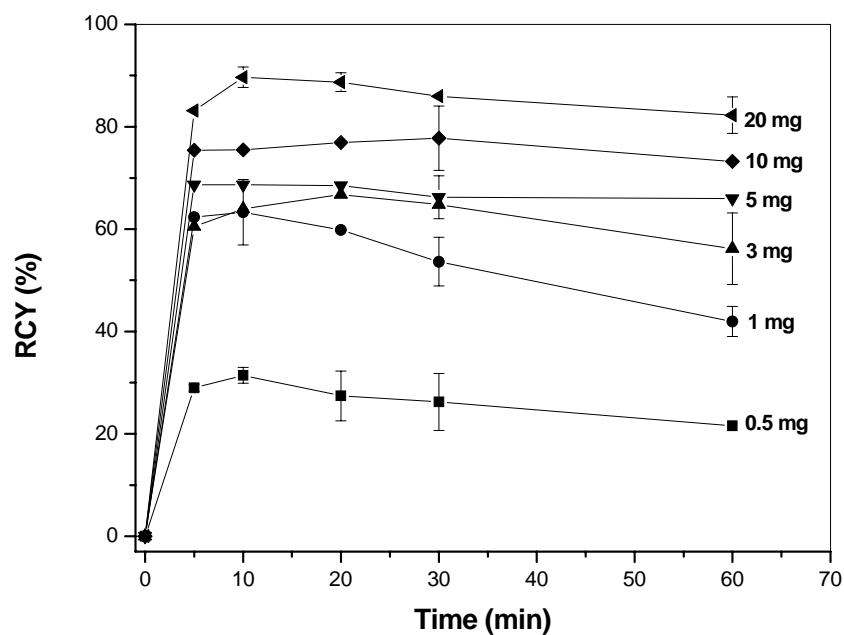
Fig. 23. [^{18}F] Labelling of 6-nitroveratraldehyde in 1 mL DMF at 140 °C. Dependence of the RCY on the concentration of the precursor (Tab. 41, App. 2).

At 0.5 mg/mL the yields remained below 35 %, but at 1 mg/mL and higher concentrations yields were above 60 % within 10 min. The amount of labelled product was between 80 % and 90 % when using a concentration of 20 mg/mL also within 10 min. Interestingly, higher concentrations did not end up in a really quantitative reaction. Therefore, 20 mg/mL was the concentration to perform the fluorination with best yields.

The dependencies of the labelling yields on temperature are shown in Fig. 24 at concentrations of 20 mg/mL using DMF as the solvent.
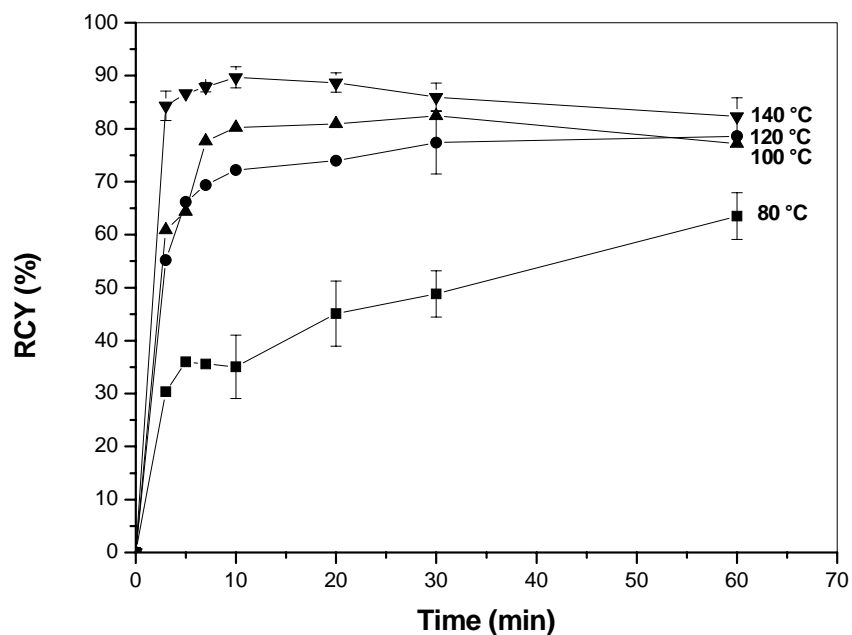
Fig. 24. [^{18}F] Labelling of 6-nitroveratraldehyde (20 mg/mL) in DMF. Dependence of the RCY on temperature (Tab. 41, App. 2).

For purposes of improving visibility of the graph the 150 °C data are not shown because they were close to those at 140 °C exhibiting similar standard deviations. It was found that the best temperature for the [^{18}F]labelling in different solvents was 140 °C. The RCY increased rapidly when going from 80 °C to 150 °C. At high temperatures (120-150 °C) very fast kinetics were observed. In this case it was necessary to study the reaction yields at very short time intervals (3, 5, 7 and 10 min).

Like in case of many other precursors, the best linear range for Arrhenius calculations was found to be 0-10 min at temperatures of 80-140 °C. By drawing the graph of ln (1-RCY) *vs* time, the rate constants as shown in Tab. 12 were obtained and an activation energy of 33 kJ/mol was calculated (Fig. 25).

Tab. 12. Rate constants (min^{-1}) for the labelling of 6-nitroveratraldehyde at temperatures 80-140 °C.

Temp. (°C)	k' (min^{-1})
80	0.0432
100	0.1114
120	0.1621
140	0.2271
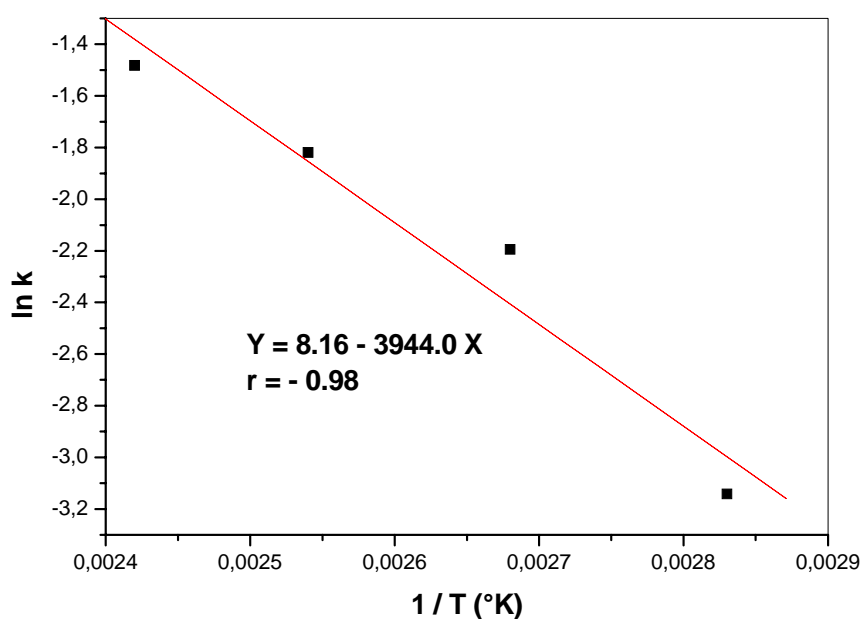
Fig. 25. Plot of ln k versus 1/ T (K) for 6-nitroveratraldehyde. (Conditions: 0-10 min, 80-140 °C) (Tab. 42, App. 2).

3.5.3 6-Fluoroveratraldehyde: Reaction Parameters and Activation Energy Calculation for the [18]F Labelling

(**2c**)
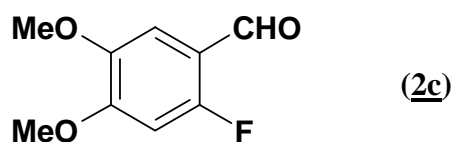
Until now this precursor was not described in literature. In general, the aromatic fluorodenitration reactions are much more common than the fluorodehalogenation, because the nitro as a leaving group is better than the halogens (Br, Cl, I). However, in case of the fluorine atom as a leaving group the situation is different since the substitution proceeds as an

isotope exchange reaction as the results showed. So the ability to act as a leaving group is more or less the same as the nitro group. More investigation of the kinetics of labelling this precursor shows the following results.

The reaction of [^{18}F]fluoride with 6-fluoroveratraldehyde (^{18}F for ^{19}F exchange) was performed in four solvents: DMF, DMSO, DMAc and sulfolane (Fig 26).
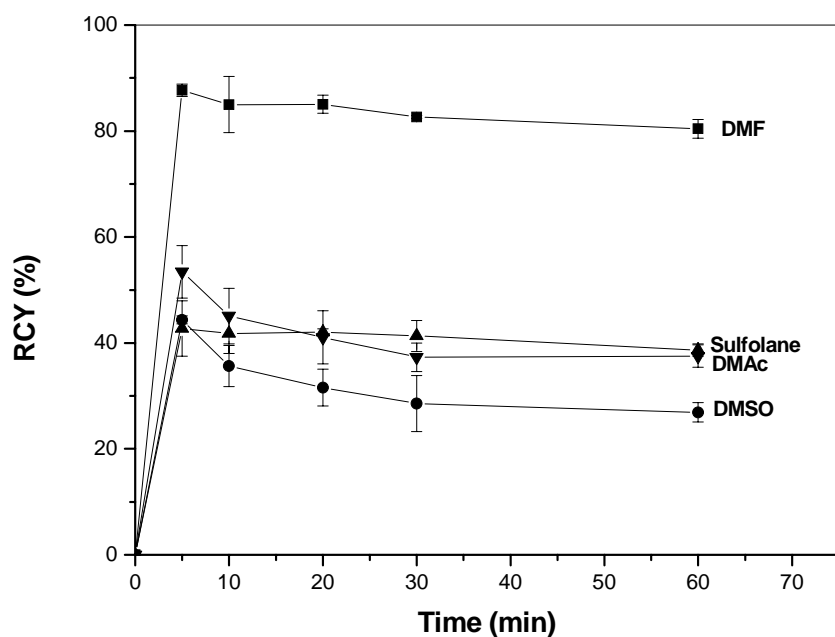
Fig. 26. [^{18}F] Labelling of 6-fluoroveratraldehyde (20 mg/mL) at 140 °C. Dependence of the RCY on the type of solvent (Tab. 43, App: 3).

In DMF, which was the best solvent for carrying the labelling reaction, a maximum RCY of 87.7 ± 1.2 % (n= 4) could be obtained within 5 min at 140 °C using 20 mg/mL of the ^{19}F precursor. This was almost double the yield obtained in other solvents. Within 60 min the yield was always higher than 80 % in DMF but dropped to 27 % to 38 % for the other solvents with the lowest yield being in DMSO.

For the ^{18}F for ^{19}F exchange in 6-fluoroveratraldehyde, the labelling highly depended on the precursor concentration at low concentrations, i. e. 0.5 -1.0 mg/mL, with yields ranging between 65 to 75 % in 5 min at 140 °C. At higher concentrations the yields were high and

almost very near in the range between 85 % and 87.7 % at the same conditions. The yields remained always high even after 30 min with 60.4 % for the concentration of 0.5 mg/mL and almost high as 87.4 % for the 50 mg/mL. This is shown in Fig 27.
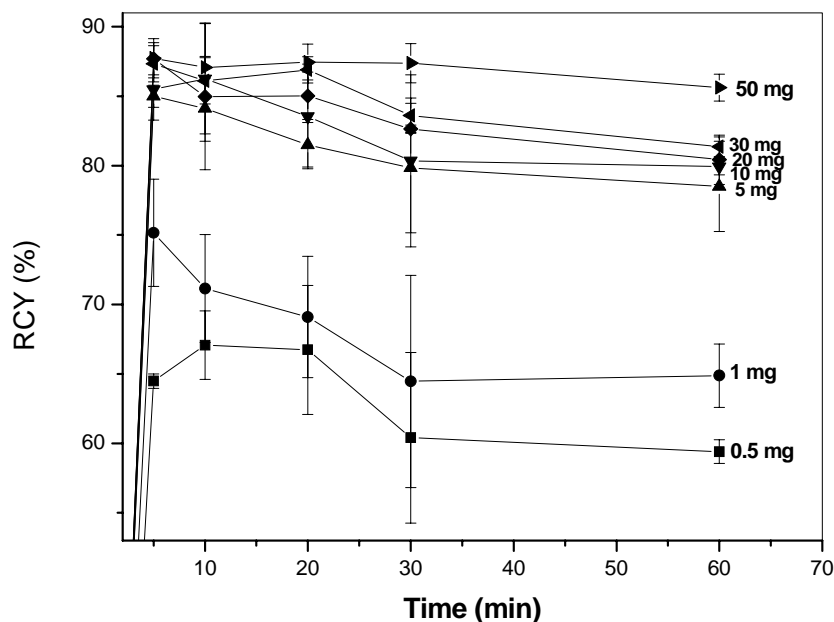
Fig. 27. [^{18}F] Labelling of 6-fluoroveratraldehyde in DMF (1 mL) at 140 °C. Dependence of the RCY on the concentration of the precursor (Tab. 43, App. 3).
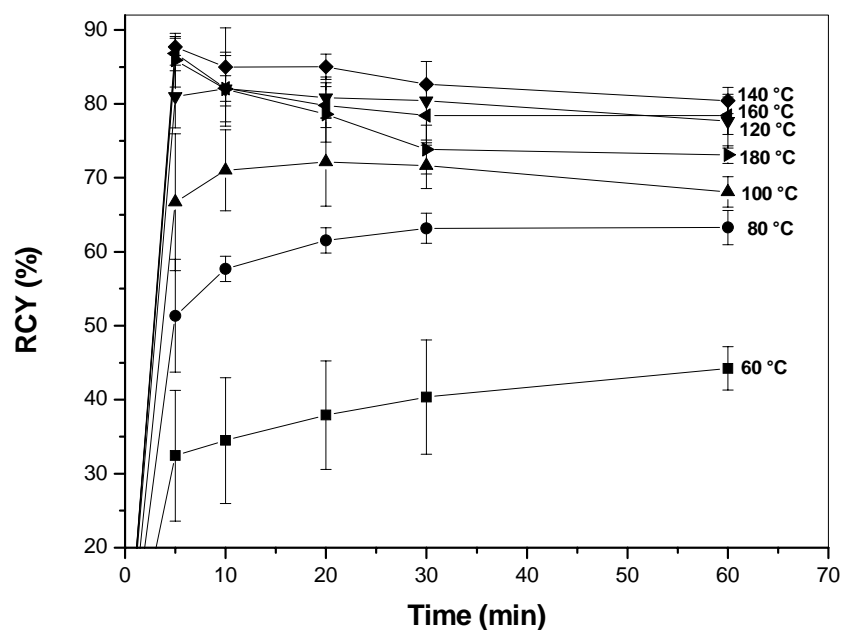
Fig. 28. [^{18}F] Labelling of 6-fluoroveratraldehyde (20 mg/mL) in DMF. Dependence of the RCY on temperature (Tab. 43, App. 3).

The ^{18}F labelling of 6-fluoroveratraldehyde showed strong dependence on temperature (Fig 28). Within 10 min using a concentration of 20 mg/mL precursor in DMF, the minimum yield was 34.5 ± 5.5 % at 60 °C while at 140 °C it was as high as 85.0 ± 5.3 %. Surprisingly, the yields tended to be close to each other (78.4-82.6 %) for the three temperatures 120, 140 and 160 °C but dropped for the 180 °C to 73 %.

Using the best linear range for Arrhenius calculations (0-10 min at temperatures 80-140 °C), and by drawing the graph of ln (1-RCY) vs time, the rate constants (see Tab. 13) were obtained and an activation energy of 17 kJ/mol was calculated (Fig. 29).

Tab. 13. Rate constants (min^{-1}) for the ^{18}F labelling of 6-fluoroveratraldehyde at temperatures 80-140 °C.	
Temp. (°C)	**k' (min^{-1})**
80	0.0860
100	0.1238
120	0.1720
140	0.1897

Fig. 29. Plot of ln k versus 1/ T (K) for 6-fluoroveratraldehyde. (Conditions: 0-10 min, 80-140 °C) (Tab. 44, App. 3).

3.5.4 6-Bromoveratraldehyde: Reaction Parameters and Activation Energy Calculation for the ^{18}F Labelling

(**2d**)
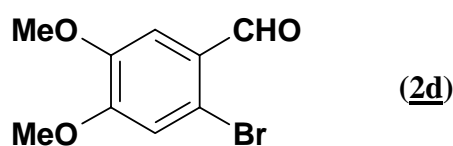
Until now this precursor was not described in literature. The detailed investigation of the kinetics of ^{18}F labelling of this precursor shows the following results.

The reaction of nca [^{18}F]fluoride with 6-bromoveratraldehyde was performed in different solvents i.e. DMF, DMAc, DMSO and sulfolane at 160 ºC with 20 mg/mL of precursor (Fig. 30).
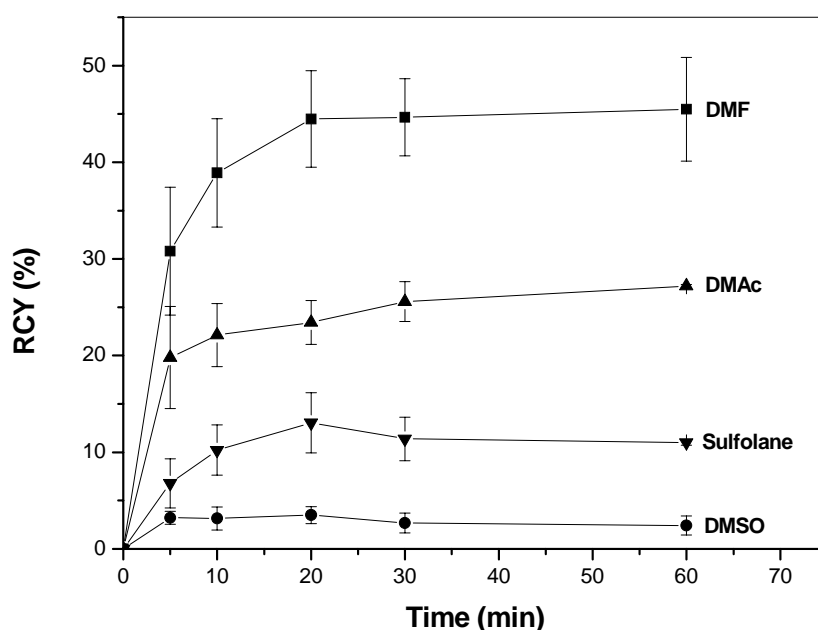
Fig. 30. [^{18}F] Labelling of 6-bromoveratraldehyde (20 mg/mL) at 160 °C. Dependence of the RCY on the type of solvent (Tab. 45, App. 4).

Again DMF proved to be the best solvent for the labelling process. The labelling yields were 44.5 ± 4.2 % (n=5) within 20 min. Fast kinetics were observed, i.e. within the first period of 10 min yields reached highest values or were close to the maximum. While the yields were between 39 % and 45 % after 10 min in DMF, they were lower (22-27 %) in DMAc. In

sulfolane, the yields were very low in the first 5 min, but almost doubled (13.0 %) at 20 min. DMSO gave the lowest yields among all the solvents used (less than 4 %). The yields even did not improve with time in DMSO and they were in all cases by a factor of ten or more lower than the yields in DMF. The labelling started in DMSO only at temperatures higher than 140 °C whereas in other solvents it started at temperatures after 100 °C. The labelling in an equal mixture of DMF (0.5 mL) and DMSO (0.5 mL) did not improve at all and yields remained in the range 1-5 % indicating the great suppressing effect of DMSO as a solvent on the labelling of these halogenated precursors. Other aprotic solvents were tried without success either because of low boiling points (acetonitrile and 1,2-dimethoxyethane) or because solvents such as nitromethane and nitroethane give unwanted by-products by reacting fast with the aldehyde group (Knoevenagel condensation).

Since best labelling results were obtained in DMF the effect of precursor concentration was studied in this solvent. The concentrations were varied from 0.5 up to 50 mg/mL at 160 °C. The results are shown in Fig. 31.
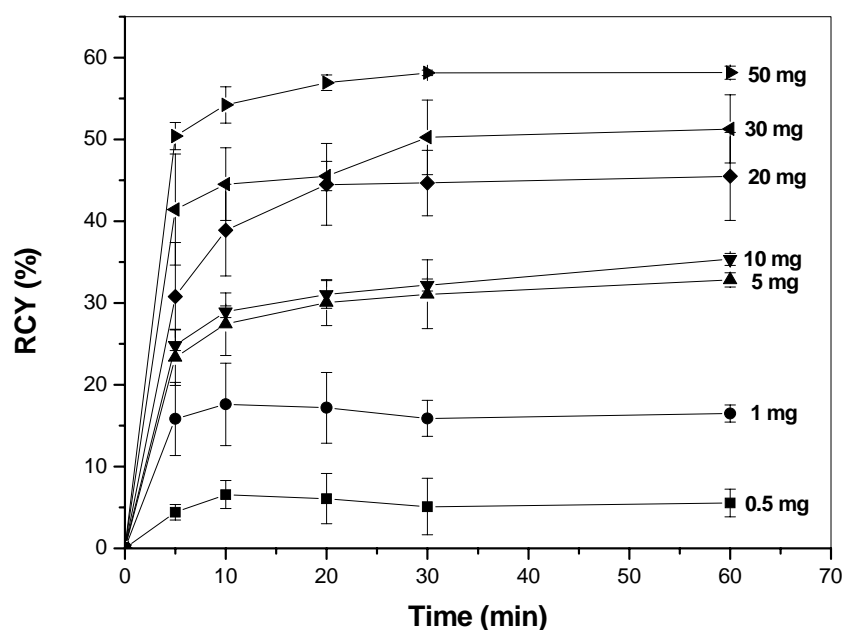
Fig. 31. [^{18}F] Labelling of 6-bromoveratraldehyde in DMF at 160 °C. Dependence of the RCY on the concentration of the precursor (Tab. 45, App. 4).

At 0.5 mg/mL the yields remained below 7 % but almost doubled in going from 0.5 to 1 mg/mL and from 1 up to 5 mg/mL. The increase was then not uniform at 10 mg/mL and it was very close to the 5 mg/mL. At high concentrations (20, 30 and 50 mg/mL) yields were between 40 % and 55 % and increased always with increasing the precursor concentration, to reach maximum of 58.1 % with 50 mg/mL within 30 min

The study of the dependence of RCY on temperature was performed in DMF using a concentration of 20 mg/ mL. This is shown in Fig. 32. The RCY increased slowly at short times (5-20 min) when going from 80 to 120 °C but more rapidly after that (140 to 180 °C). At high temperatures (140-180 °C) very fast kinetics were observed and a RCY of 45.7 ± 5.5 % could be obtained in 5 min at 180 °C. After 1 h the highest yield was 49.9 % at 180 °C.
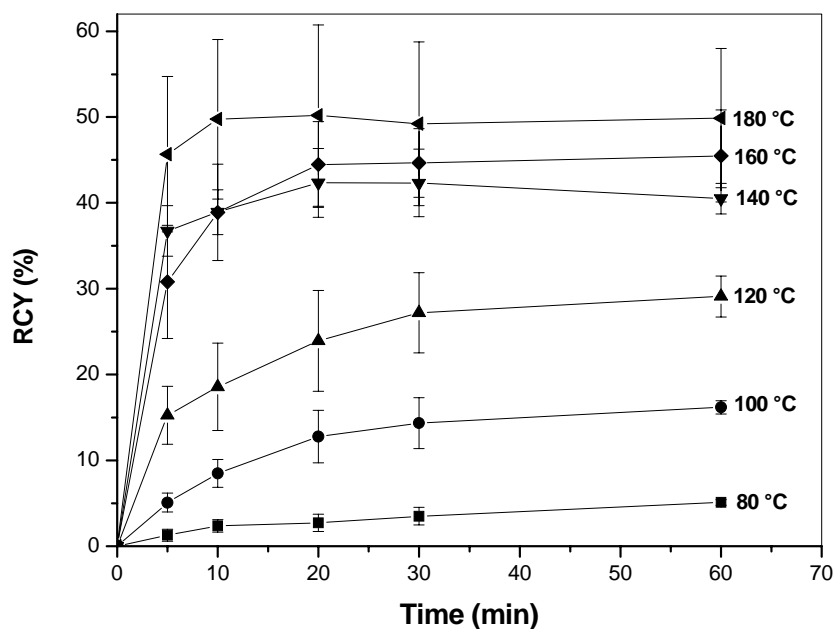
Fig. 32. [^{18}F] Labelling of 6-bromoveratraldehyde (20 mg/mL) in DMF. Dependence of the RCY on temperature (Tab. 45, App. 4).

As with the fluoro analogue, and using the best linear range for Arrhenius calculations (0-10 min at temperatures 80-140 °C), the graph of ln (1-RCY) vs time gave the rate constants shown in Tab. 14. Hence, an activation energy of 60 kJ/mol was calculated (Fig. 33).

Tab. 14. Rate constants (min^{-1}) for the labelling of 6-bromoveratraldehyde at temperatures 80-140 °C.

Temp. (°C)	k' (min^{-1})
80	0.0024
100	0.0089
120	0.0206
140	0.0493
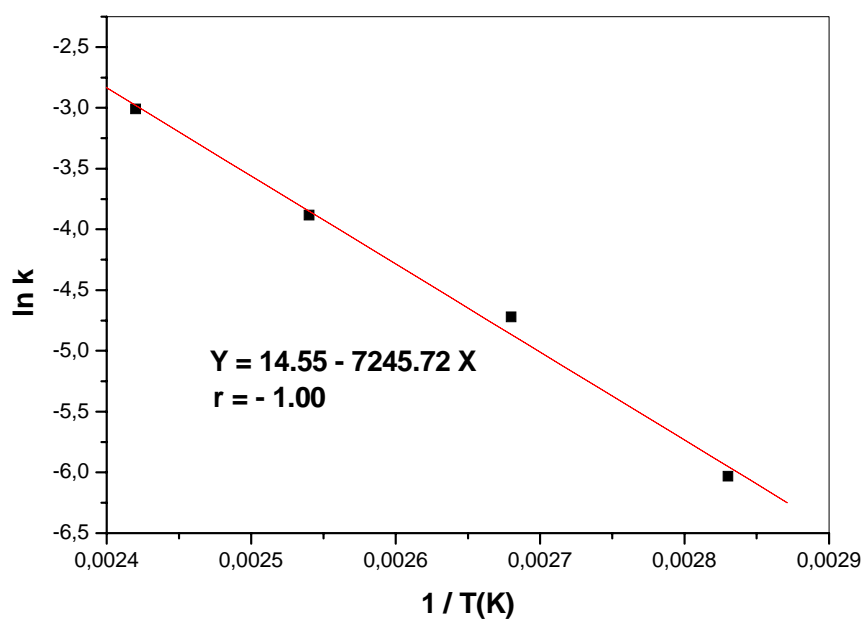
Fig. 33. Plot of ln k versus 1/ T (K) for 6-bromoveratraldehyde. (Conditions: 0-10 min, 80-140 °C) (Tab. 46, App. 4).

3.5.5 6-Chloroveratraldehyde: Reaction Parameters and Activation Energy Calculation for the [18]F Labelling

(**2e**)
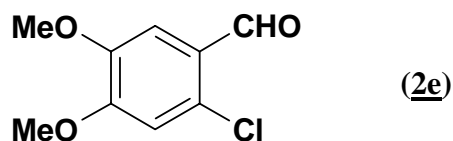
Until now this precursor was not described in literature. The detailed investigation of the kinetics of ^{18}F labelling of this precursor showed the results as presented below.

The reaction of [^{18}F]fluoride with 6-chloroveratraldehyde was performed in the following solvents: DMF, DMAc, DMSO and sulfolane at 160 °C with 20.0 mg/mL of precursor (Fig. 34). DMF proved to be the best solvent for the labelling process. The labelling yields were 57 % $\pm$ 5.1 % (n=5) which means it is slightly higher than in the case of the bromo precursor. Fast kinetics were observed also here, and in the period of the first 10 min yields reached highest values or were close to the maximum. Very strange here is the wide gab between the yields after 10 min in DMF (52-58 %) and in other solvents (3-12 %), which was not observed in case of the precursor. Hence in sulfolane the yields were very low and in the range between 7-9 % but were slightly higher in DMAc (9-12 %).
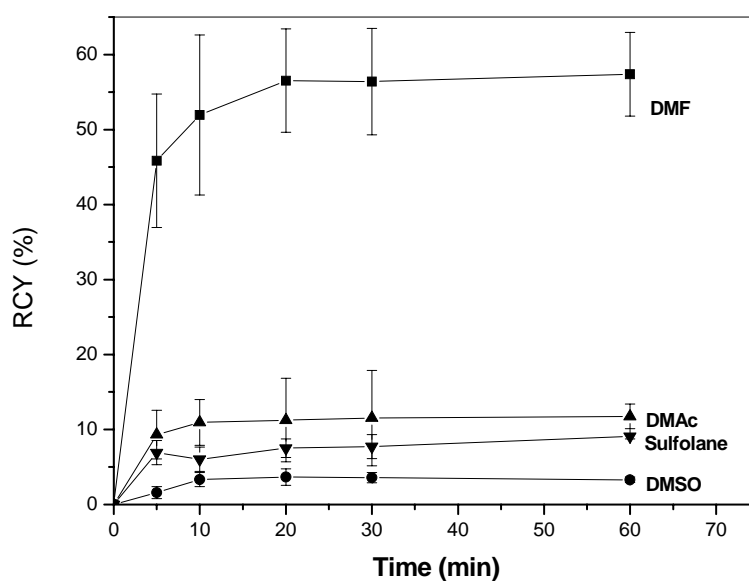
Fig. 34. [^{18}F] Labelling of 6-chloroveratraldehyde (20 mg/mL) at 160 °C. Dependence of the RCY on the type of solvent (Tab. 47, App. 5).

Again DMSO gave the lowest yields among all the solvents used (1-4 %). The yields even did not improve with time in DMSO and they were in all times less then the yields in DMF by a factor of tenth or more.

Since best labelling results were obtained in DMF the effect of precursor concentration was studied in this solvent. The concentrations were varied from 0.5 mg/mL up to 50 mg/mL and the results are shown in Fig. 35.
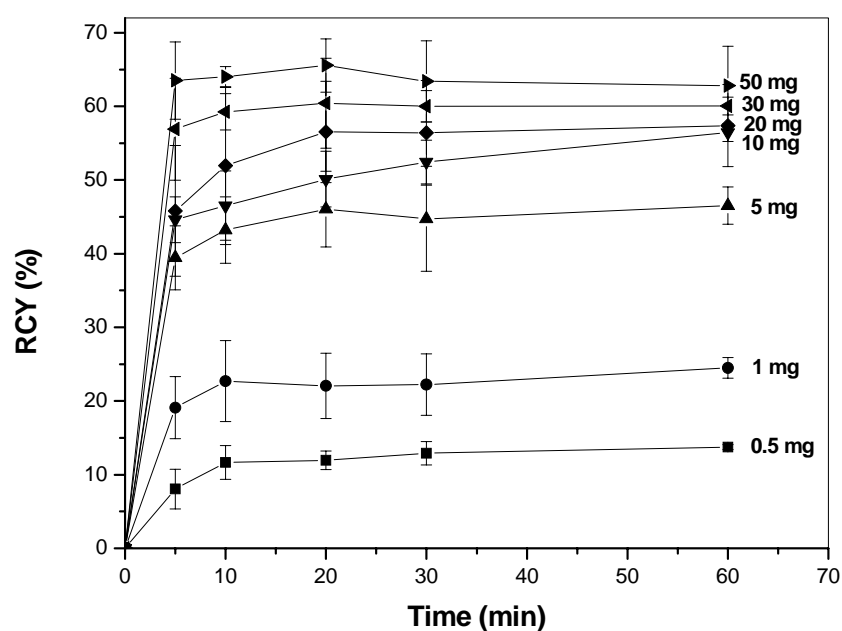
Fig. 35. [^{18}F] Labelling of 6-chloroveratraldehyde (20 mg/mL) in DMF at 160 °C. Dependence of the RCY on the concentration of the precursor (Tab. 47, App. 5).

At 0.5 mg/mL the yields remained below 14 % but almost doubled in going from 0.5 to 1 mg/mL and from 1 to 5 mg/mL. The increase was then not uniform at 10, 20, 30 and 50 mg/mL (high concentrations). At these concentrations the amount of labelled product was between 45 % and 66 %. The highest concentrations gave the highest yields in all times (63-66 %).

The study of the dependence of RCY on temperature was carried out in DMF using a concentration of 20 mg/mL. This is shown in Fig 36.
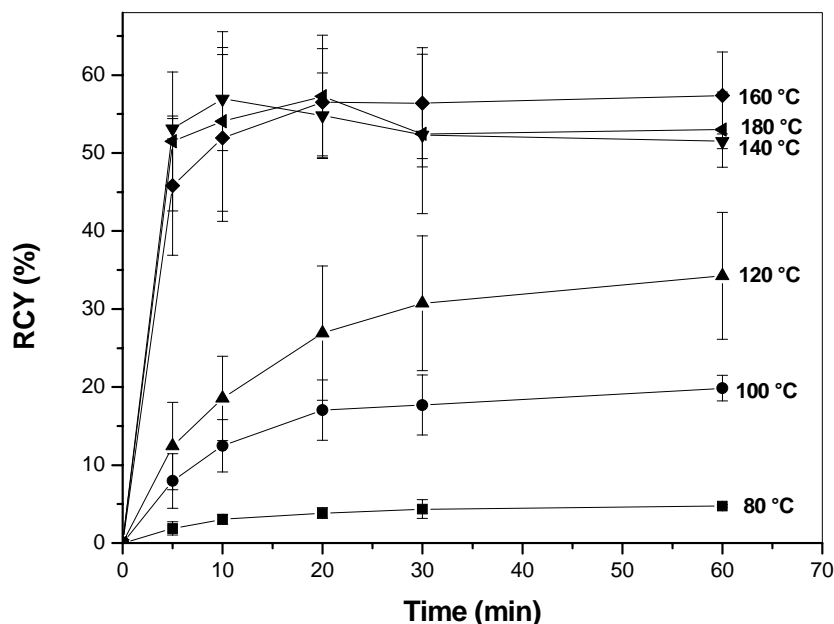
Fig. 36. [^{18}F] Labelling of 6-chloroveratraldehyde (20 mg/mL) in DMF. Dependence of the RCY on temperature (Tab. 47, App. 5).

The RCY slowly increased at short times (5 min up to 20 min) when going from 80 °C to 120 °C but rapidly after that (120 °C to 180 °C) for the chloro precursor. At high temperatures (120-180 °C) very fast kinetics were observed and a RCY of 51.5 ± 4.4 % can be obtained in 5 min at 180 °C. Unlike the behaviour of the bromo precursor, the highest yield for the chloro precursor after 1 h was obtained at 160 °C instead of 180 °C.

The graph of ln (1-RCY) vs time gave the rate constants shown in Tab. 15. Hence, an activation energy of 63 kJ/mol was calculated (Fig. 37).

Tab. 15. Rate constants (min^{-1}) for the labelling of 6-chloroveratraldehyde at temperatures 80-140 °C.

Temp. (°C)	k' (min^{-1})
80	0.0031
100	0.0134
120	0.0206
140	0.0842
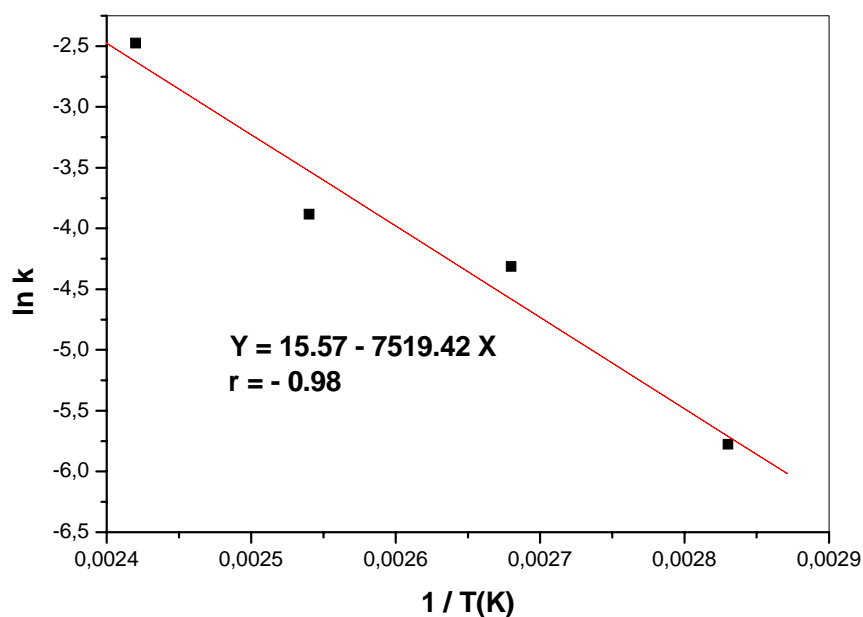
Fig. 37. Plot of ln k versus 1/ T (K) for 6-chloroveratraldehyde. (Conditions: 0-10 min, 80-140 °C) (Tab. 48, App. 5).

3.5.6   6-Nitropiperonal: Reaction Parameters and Activation Energy Calculation for the [18]F Labelling

(**9a**)
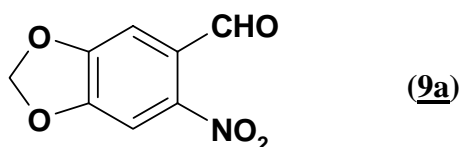
The derivatives of piperonal are the second of the most important precursors for the total synthesis of [^{18}F]FDOPA. Tab. 16 gives a summary of the results for the labelling of

[18F]FDOPA precursors for path A (see Chpt. 2) depending on 6-substituted piperonal (**9**). The reason for using these compounds is the desired smooth and milder deprotection at the end of synthesis of [18F]FDOPA as suggested in literature [36].
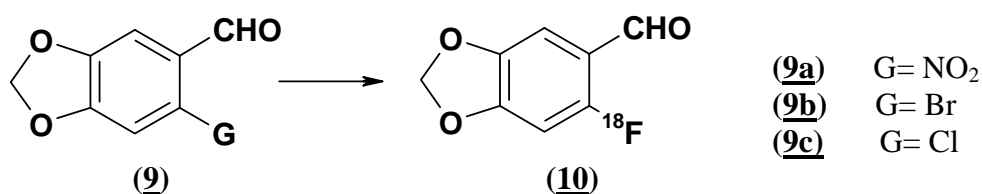
Fig. 38. Scheme for the synthesis of 6-[18F]fluoropiperonal by nucleophilic aromatic substitution.

Tab. 16. Literature syntheses of 6-[18F]fluoropiperonal (**10**).				
Precursor	**Leaving group**	**Conditions [a]**	**RCY (%)**	**Ref.**
9a	NO$_2$	5 min, 180 °C	53	31
		10 min, 120 °C	68	54
		20 min, 135 °C	50	39
		25 min, 114 °C	44	44
		10 min, 120 °C	51	38
		20 min, 130 °C	55	36
		20 min, 130 °C	50-55	32
		MW (300 W), 0.5 min	53	46
9b	Br	New precursors (this work)		
9c	Cl			

[a]) Other conditions: K(18)F, DMSO, K$_2$CO$_3$, Kryptofix 222.

The detailed investigation of the kinetics of 18F labelling of this precursor showed the following results .

The reaction of [18F]fluoride with 6-nitropiperonal was performed in the following solvents: DMF, DMAc, DMSO, sulfolane and 1,2-DME at 140 ºC with 20 mg/mL of precursor. The results are illustrated in Fig. 39. Unlike other [18F]FDOPA precursors, the labelling of this precursor showed the highest yields not in DMF but in DMAc. These two solvents are closely structurally related. The labelling yield was 75.3 ± 1.6 % after 10 min in DMAc, while in

DMF it was 67 ± 4.6 %. Surprisingly, in the other two solvents the yields were also very good. After 10 min in DMSO the yield was 56.4 3 $\pm$ 2.6 % and in sulfolane slightly higher (59 ± 3.1%). The lowest yields (14.4 ± 4.4 %) were obtained in the least polar solvent, i. e. in 1,2-DME. Very fast kinetics were observed within 5 min. Except for 1,2-DME, the yields reached highest values in 5-10 min but in all cases a plateau is reached with slightly lower yields at 60 min.
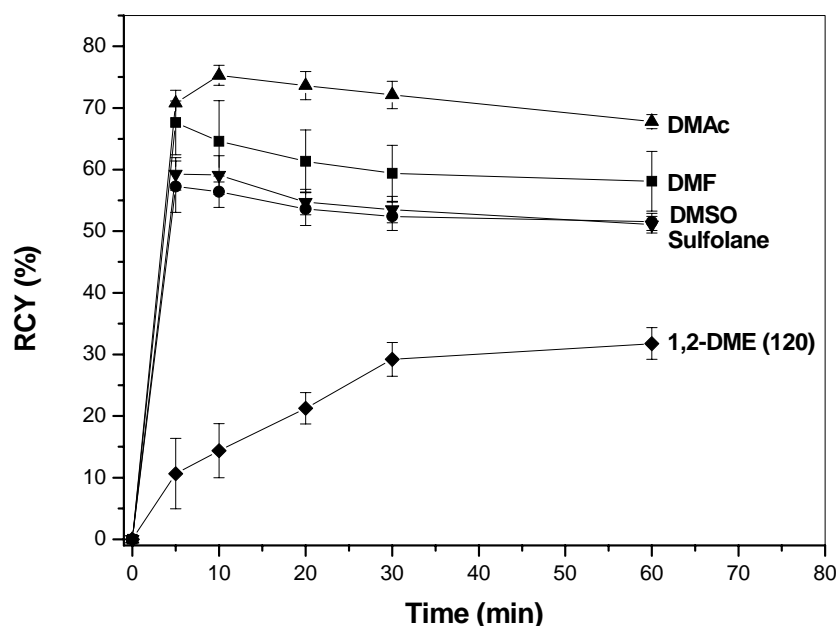
Fig. 39. [^{18}F] Labelling of 6-nitropiperonal (20 mg/mL) at 140 $^\circ$C. Dependence of the RCY on the type of solvent (Tab. 49, App. 6).

The effect of precursor concentration was studied in DMF at 140 °C. The concentrations were varied from 0.5 up to 50 mg/mL. The results are shown in Fig. 40. In all cases fast kinetics and thus highest yields were observed within 5 min. In the case 0.5 mg/mL the yield in 5 min was 36.3 ± 7 % but dropped within 1 h to 9.0 ± 0.9 %. The yields with the concentration of 1 mg/mL and above were all in the range between 58.9 and 67.6 %. The decrease of yield within 1 h was also observed with the low concentrations of 1 mg/mL (from 58.9 ± 7.7 % to 13.5 ± 1.3 %) and with the 5 mg/mL (from 62.0 ± 4.3 % to 35.3 ± 1.1 %). At high

concentrations (10-50 mg/mL) the yields did not drop sharply within 1 h. The dependence of

the RCY on the concentration was not strong hence with 10 and 20 mg/mL almost the same

highest yields were observed. In addition, with 30 and 50 mg/mL almost the same yields were

also observed, but they were generally less than with the 10 or the 20 mg/mL. Hence the

20 mg/mL was the optimum concentration to do the labelling.
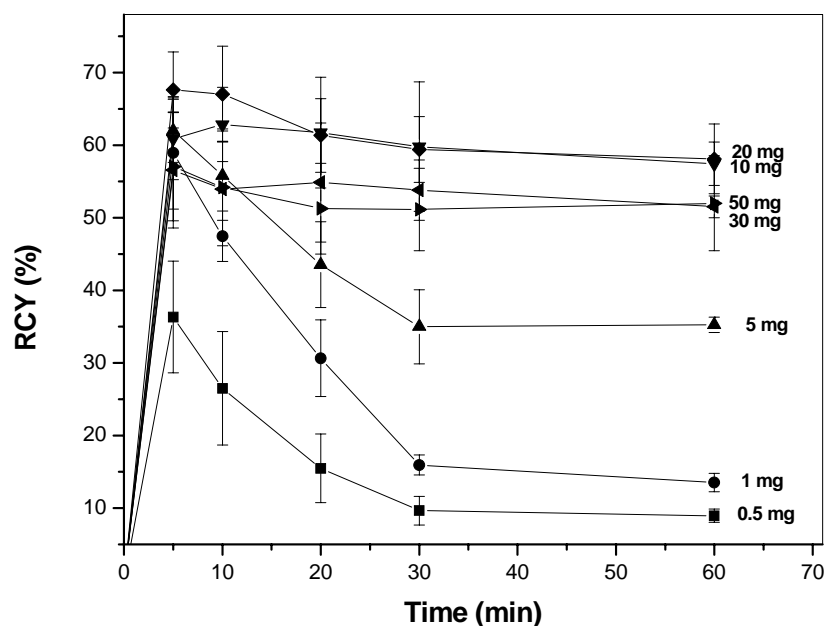
Fig. 40. [^{18}F] Labelling of 6-nitropiperonal in 1 mL DMF at 140 °C. Dependence of the
RCY on the concentration of the precursor (Tab. 49, App. 6).

The investigation of the effect of temperature (DMF, 20 mg/mL) also showed discrepancies

among the results shown here in Fig. 41. At the temperatures between 80 and 180 °C the

yields were in the range between 60 % and 70 % within 10 min and between 56 % and 64 %

within 1h. For the labelling process the best temperature seemed to be at 120 °C. For better

illustration of the effect of temperature, Fig. 42 showed the RCY dependence on temperature

at all times. By changing temperatures between 80 °C and 100 °C the yield was almost

constant, but when changing from 100 °C to 120 °C a maximum RCY is reached at all times,

followed by descending to a valley at 140-160 °C and climbing again to reach another

maximum at 180 °C. It is noticed also that the yields are directly proportional to the time

before 110 °C but inversely proportional after this temperature. Hence, at 110°C the yield is

independent of the reaction time.
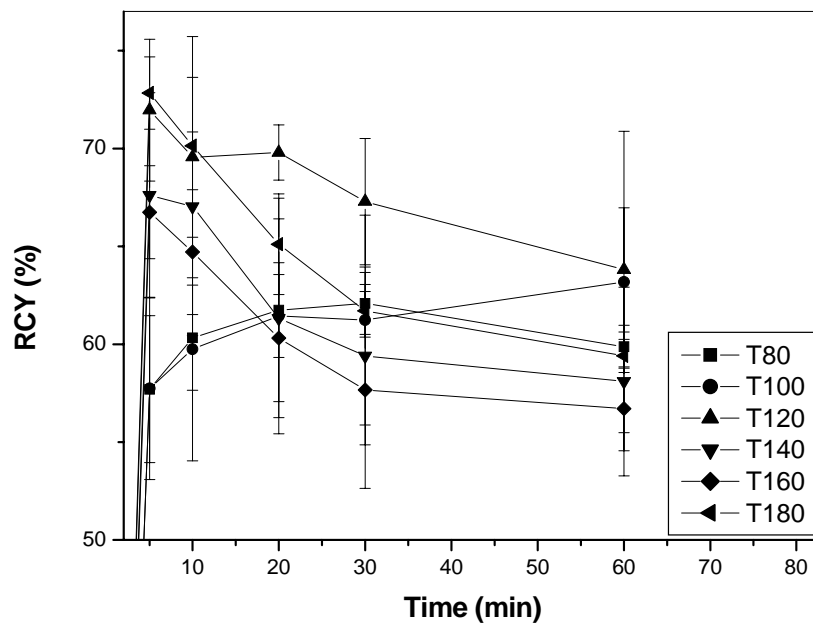
Fig. 41. [^{18}F] Labelling of 6-nitropiperonal (20 mg/mL) in DMF. Dependence of the RCY on temperature (Tab. 49, App. 6).

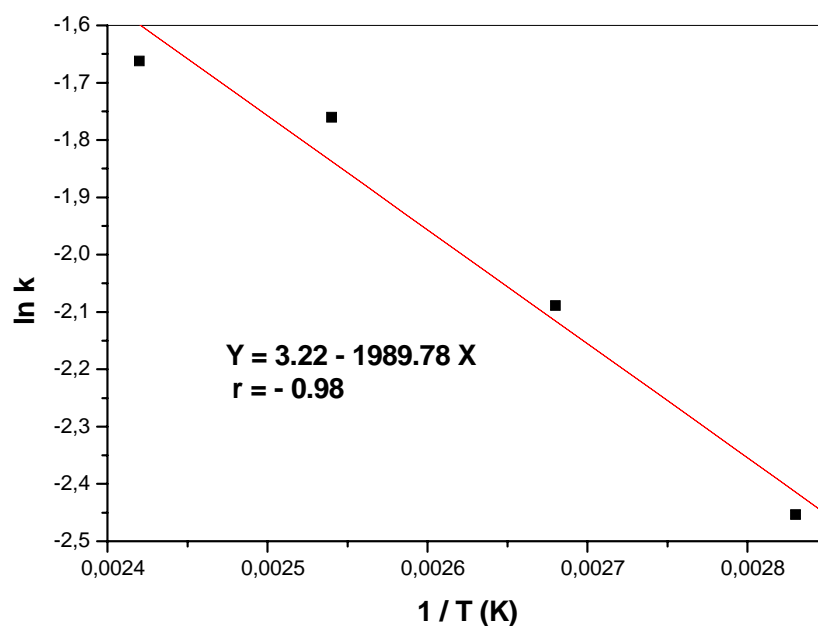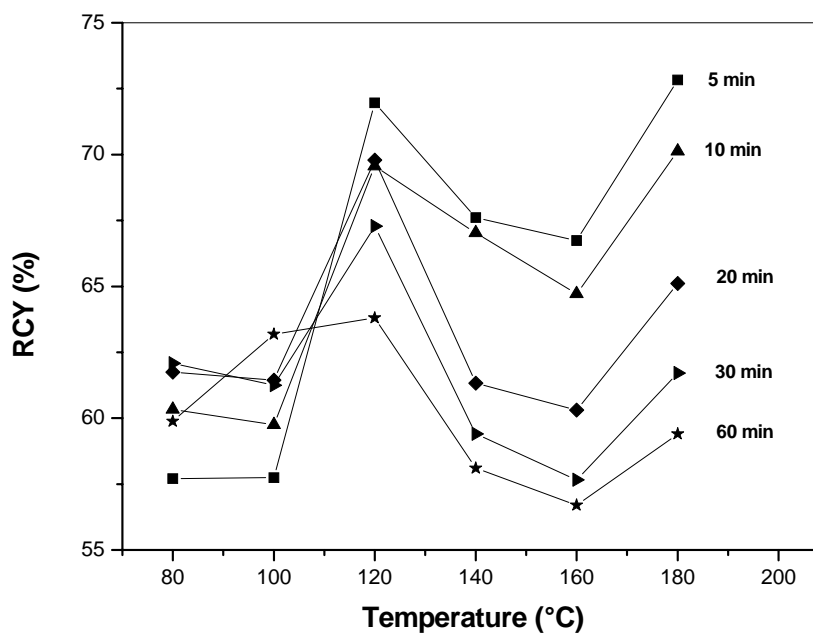**Fig. 42.** [^{18}F] Labelling of 6-nitropiperonal (20 mg/mL) in DMF. Dependence of the RCY on temperature (Tab. 49, App. 6).

The graph of ln (1-RCY) versus time gave the following rate constants (see Tab. 17) from

which the graph of ln k versus 1/T (K) gave an activation energy of 5 kJ/mol (Fig. 43).

Tab. 17. Rate constants (min^{-1}) for the labelling of 6-nitropiperonal at temperatures 80-140 °C.

Temp. (°C)	k' (min^{-1})
80	0.0924
100	0.0911
120	0.1191
140	0.1109

$$Y = -0.70 - 601.66\ X$$
$$r = -0.8$$
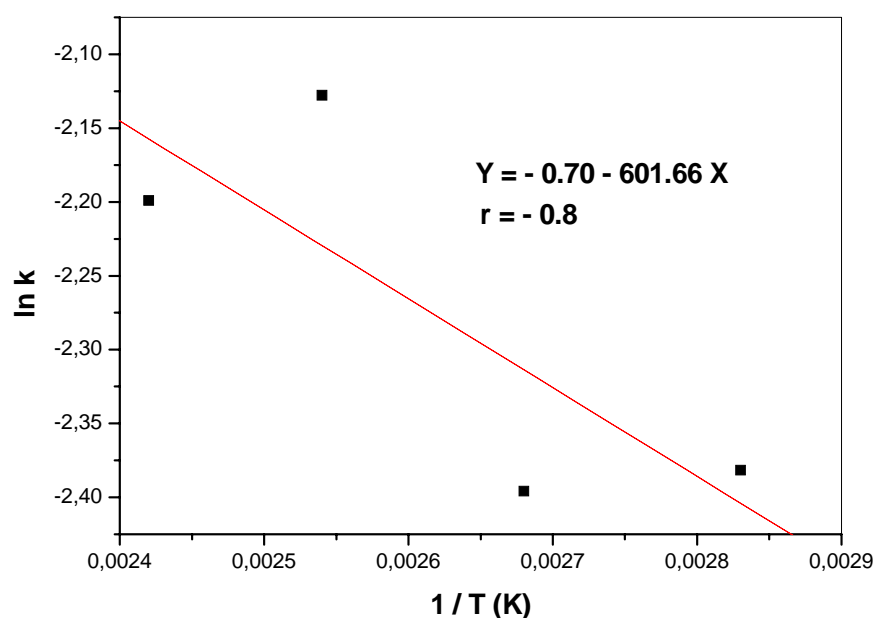
Fig. 43. Plot of ln k versus 1/ T (K) for 6-nitropiperonal. (Conditions: 0-10 min, 80-140 °C). (Tab. 50, App. 6).

3.5.7 6-Bromopiperonal: Reaction Parameters for the ^{18}F Labelling
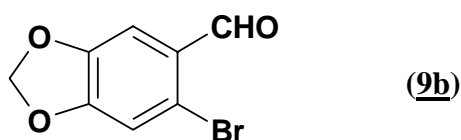
(**9b**)

Until now this precursor was not described in literature. In general, labelling of this precursor

gave by-product which decreased the yields significantly. The yield of the by-product was

twice that of the labelled precursor. This by-product could have the ring-opened structure. The investigation of ^{18}F labelling of this precursor in DMF (the best solvent) at temperatures 80-180 °C is shown in Fig 44. The labelling yields were generally in the range between 6 % and 12 %. A general increase of yield was noticed with increasing temperatures up to 140 °C. After that the yields did not improve. In most cases the yields reached a maximum within 30 min after which we got a plateau.
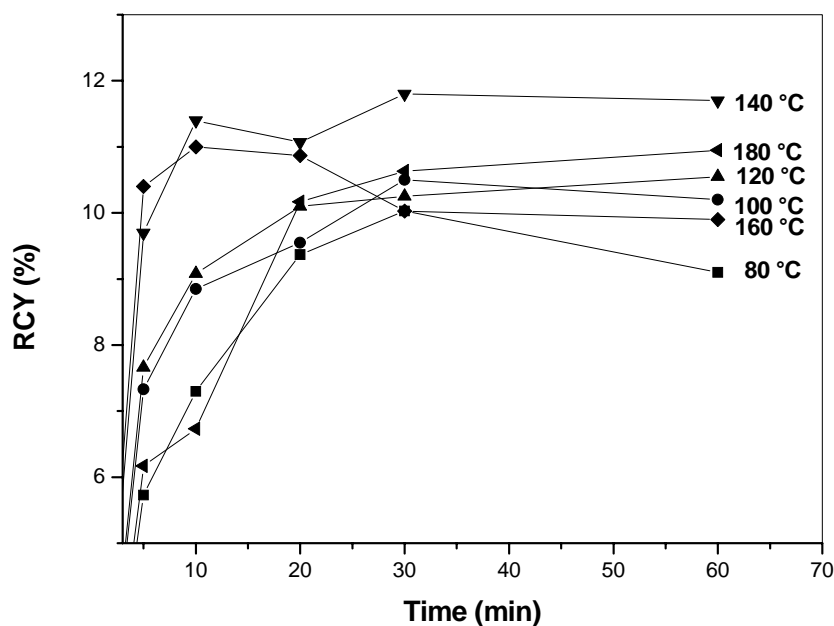
Fig. 44. [18F] Labelling of 6-Bromopiperonal (20 mg/mL) in DMF. Dependence of the RCY on temperature (Tab. 51, App. 7)

3.5.8   6-Chloropiperonal: Reaction Parameters for the [18]F Labelling
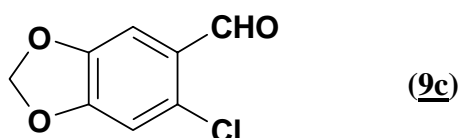
(**9c**)

Until now this precursor was not described in literature. In general, labelling of this precursor gave in all cases a by-product which decreased the yield. The yield of the by-product was in most cases double that of the labelled precursor. The investigation of ^{18}F labelling of this

precursor in DMF (in this work usually a very good solvent for labelling) at different temperatures is shown in Fig. 45. The labelling yields were low, generally between 4 % and 12 % and they increased with increasing temperature. In most cases the yields reached a maximum within 10 min and did not change significantly thereafter.
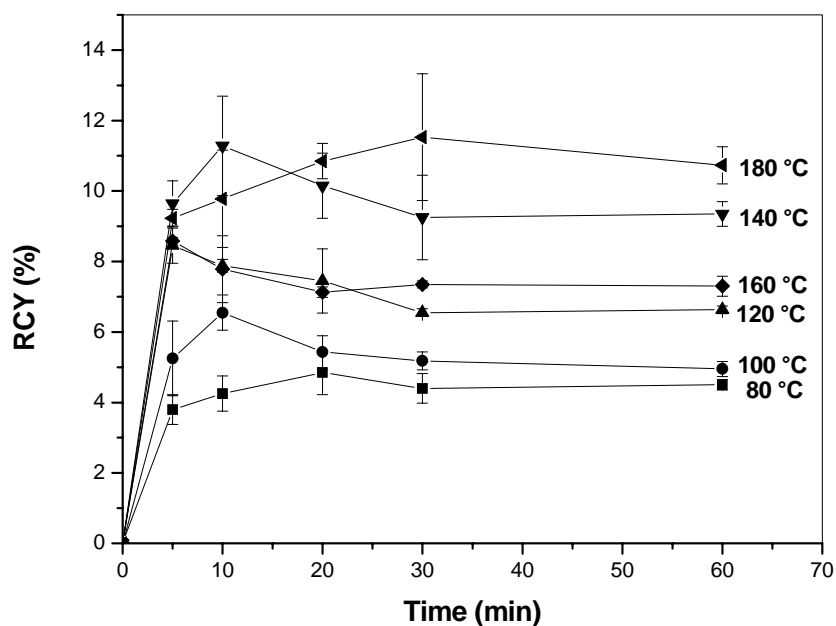
Fig. 45. [^{18}F] Labelling of 6-chloropiperonal (20 mg/mL) in DMF. Dependence of the RCY on temperature (Tab. 52, App. 8).

3.6   Aromatic Nucleophilic Substitution by [18F]Fluoride on Precursors for Path B of [18F]FDOPA

3.6.1   Synthesis of Precursors and Standards

To overcome some disadvantages encountered in path (A) (see Chpt. 2), like many steps involved (4-5) and the high enantiomeric purity required, a second path (B) is proposed, which utilizes a ready-to-label and protected [18F]FDOPA precursor (Chpt. 2, Fig. 8). In order to study this path systematically and to evaluate it, simple model precursors were chosen. These were mainly derivatives of the following four structures or their different isomers, as shown in Fig. 46.

Fig. 46. General structure of model compounds used to study and evaluate the production of [18F]FDOPA via path (B).

X, Y, Z: NO_2, Br, Cl, F, H
R', R'': protection of the hydroxyl group [ethers (open or cyclic), carbonic esters (open), sulfonic esters (open)]
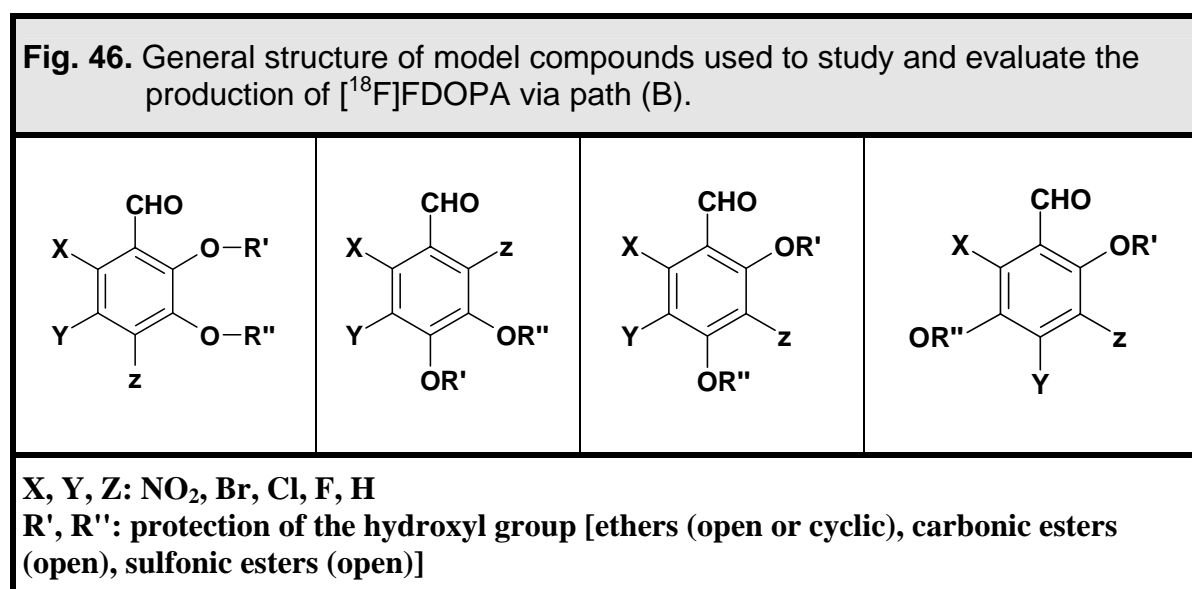
Most of these precursors were synthesised directly from substituted benzaldehydes by halogenation or nitration. They however, can be prepared by the appropriate protection of substituted bromo or nitro phenols. The most important commercially available starting compounds are vanillin, *o*-vanillin, 2,3-dimethoxybenzaldehyde, 2,4-dimethoxybenzaldehyde, 2,5-dimethoxybenzaldehyde, 3,5-dimethoxybenzaldehyde and 4-fluoroveratrole. The following figures show general schemes used for the synthesis of precursors. For details of experimental procedures see chapter 4.

The three compounds 4-acetoxy-2-bromo-5-methoxybenzaldehyde (**6**), 4-benzoyloxy-2-bromo-5-methoxybenzaldehyde (**8a**) and 2-bromo-5-methoxybenzaldehyde-4-benzene sulfonate (**8b**) were prepared by acetylation of vanillin (**4**), bromination (**5**) then subsequent hydrolysis of the acetoxy group (**6**). This is followed by protection with the desired group. On the other hand, bromination of vanillin gave the 5-bromo derivative (**7b**) from which two precursors were prepared (**8c**, **8d**) (Fig. 47).
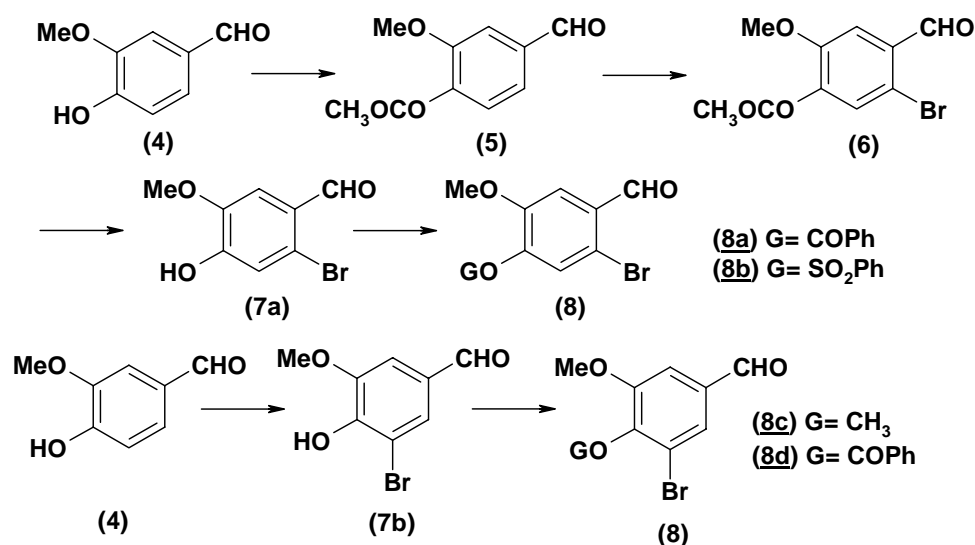
Fig. 47. Scheme for the synthesis of derivatives of 2- and 3-bromo-4,5-dihydroxybenzaldehyde as precursors for path A of [^{18}F]FDOPA.

Fig. 48 shows the scheme for the preparation of the derivatives of 6-bromo-2-hydroxy-3-methoxybenzaldehyde (compounds **13**, **15a** and **15b**) [55].
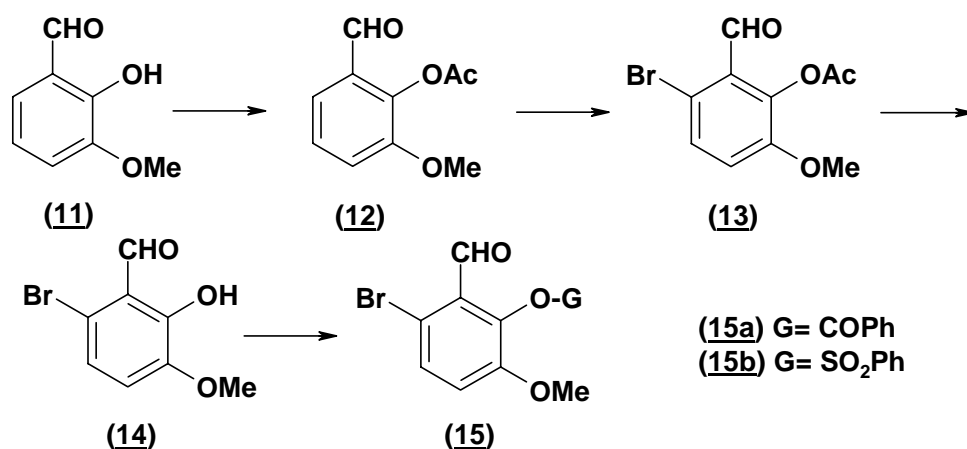
Fig. 48. Scheme for the synthesis of derivatives of 6-bromo-2-hydroxy-3-methoxy benzaldehyde as precursors for path B of [^{18}F]FDOPA

Fig. 49 shows the scheme for the preparation of the derivatives of 4 and 6-nitro-2-hydroxy-3-methoxybenzaldehyde (**17a**), (**17b**), (**19a**), (**19b**) and (**19c**)[56].
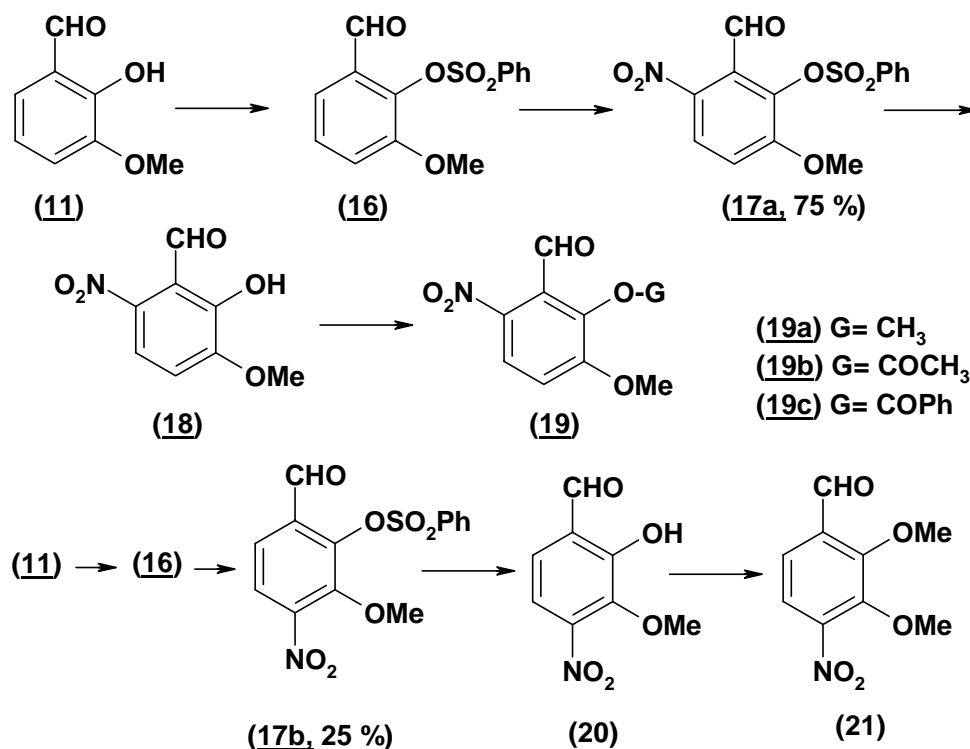
Fig. 49. Scheme for the synthesis of derivatives of 4- and 6-nitro-2-hydroxy-3-methoxybenzaldehyde as precursors for path B of [^{18}F]FDOPA

The reaction of 2,3-dimethoxybenzaldehyde (**22**) with NBS and NCS afforded the 6-bromo (**23a**) and 6-chloro (**23b**) derivatives, respectively, while the direct bromination or nitration gave the 5-bromo (**24a**) and the 5-nitro (**24b**)derivatives, respectively (Fig. 50).
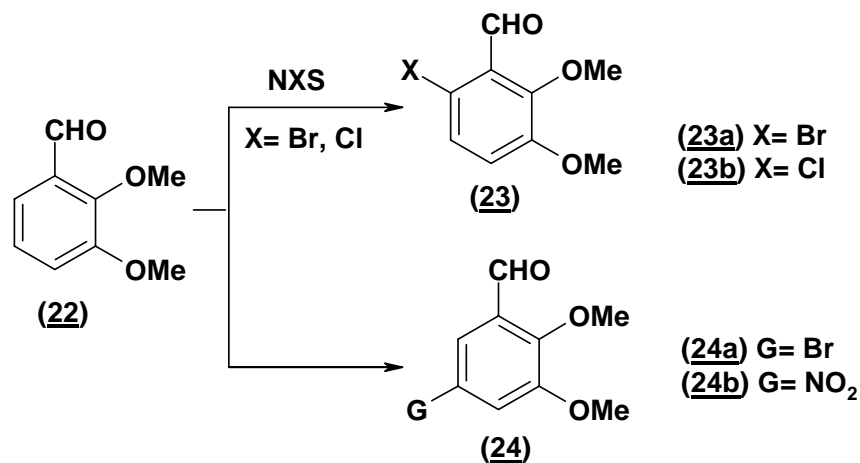
Fig. 50. Scheme for the synthesis of 5- and 6-substituted derivatives of 2,3-dimethoxybenzaldehyde as precursors for path B of [^{18}F]FDOPA.

Direct bromination of 2,4-dimethoxybenzaldehyde (**25**) gave the 5-bromo derivative (**26**) while for 2,5-dimethoxybenzaldehyde (**27**) it gave the 4-bromo derivative (**28**) (Fig. 51)
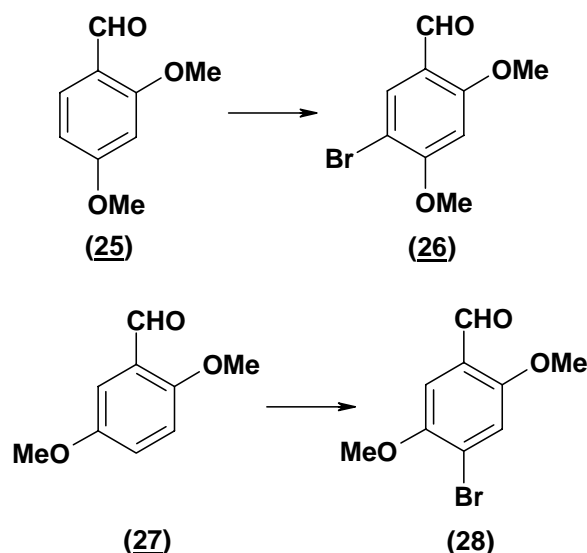
Fig. 51. Scheme for the synthesis of 5-bromo-2,4-dimethoxybenzaldehyde and 4-bromo-2,5-dimethoxybenzaldehyde as precursors for path B of [^{18}F]FDOPA.

For derivatives with substituents at positions 5 and 6 the starting is either 2-acetoxy-3-methoxy benzaldehyde (**12**) or 2,3-dimethoxybenzaldehyde (**22**). Harsh bromination of (**12**) gave directly 2,3-dibromo-6-hydroxy-5-methoxybenzaldehyde (**29**) from which a number of OH-protected derivatives (**30**) were prepared (Fig. 52).

(**30a**) G= CH3
(**30b**) G= COCH$_3$
(**30c**) G= COPh
(**30d**) G= SO$_2$Ph
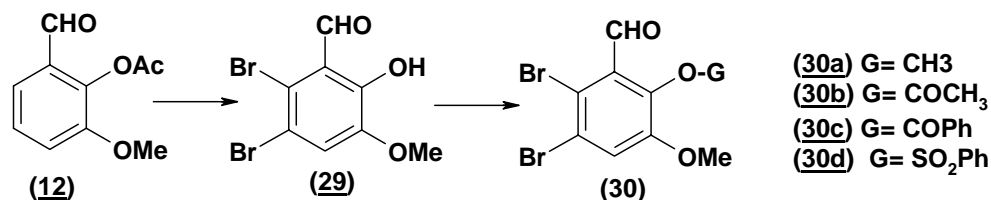
Fig. 52. Scheme for the synthesis of derivatives of 2,3-dibromo-6-hydroxy -5-methoxybenzaldehyde as precursors for path B of [^{18}F]FDOPA.

Bromination (bromine in acetic acid) of 2,3-dimethoxybenzaldehyde afforded the 5-bromo derivative (**24a**), which upon nitration gave 3-bromo-5,6-dimethoxy-2-nitrobenzaldehyde (**31**) (Fig. 53).
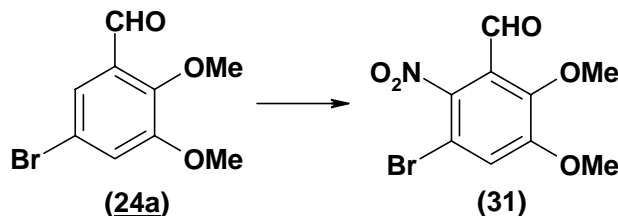
Fig. 53. Scheme for the synthesis of 3-bromo-5,6-dimethoxy-2-nitrobenzaldehyde as precursor for path B of [^{18}F]FDOPA.

The reaction of (**14**) with BBr$_3$ gave the dihydroxy compound (**32**) which upon protection with dibromomethane gave the 2,3-methylenedioxybenzaldehyde precursor (**33**) (the isomer of 6-bromopiepronal) (Fig. 54):
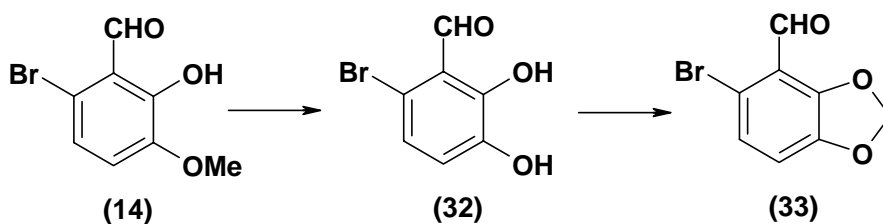
Fig. 54. Scheme for the synthesis of 6-bromo-2,3-methylenedioxybenzaldehyde as precursor for path B of [^{18}F]FDOPA.

Nitration of 3,5-dimethoxybenzaldehyde (**34**) gave the corresponding 2-nitro derivative (**35**) (Fig. 55)
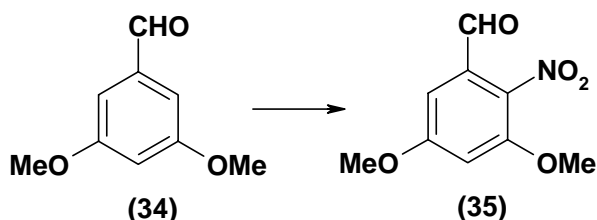
Fig. 55. Scheme for the synthesis of 3,5-dimethoxy-2-nitrobenzaldehyde as precursor for path B of [^{18}F]FDOPA.

Nitration or bromination (NBS) of 3,4-ethylenedioxybenzaldehyde (**36**) gave the 2-nitro (**37a**)

and the 2-bromo (**37b**)derivatives (Fig. 56).
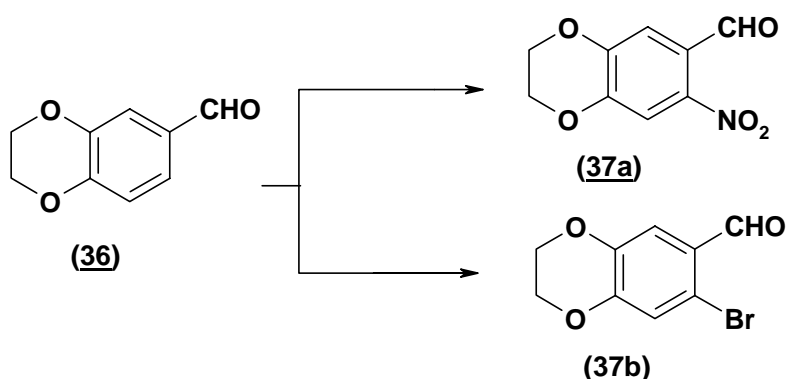
Fig. 56. Scheme for the synthesis of 2-nitro- and 2-bromo-4,5-ethylenedioxy benzaldehyde as precursors for path B of [^{18}F]FDOPA.

Because of the difficulty in obtaining all the fluorine standards for this path, some of these

standards are only prepared. The main pathway for the synthesis of these standards (Fig. 57)

starts from 4-fluoroveratraole (**38**) [57]. After lithiation and formylation, the standard (**39**) is

obtained. Other standards (**41a-c**) are obtained following deprotection of the methoxy ortho to

the aldehyde and then the proper protection of the hydroxyl is introduced.
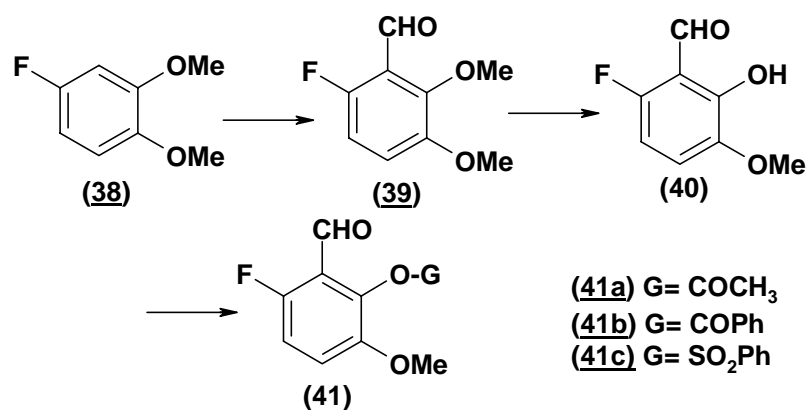
Fig. 57. Scheme for the synthesis of 6-fluoro-2-hydroxy-3-methoxybenzaldehyde and derivatives as standards for path B of [^{18}F]FDOPA.

3.6.2 2,3-Dimethoxy-6-nitrobenzaldehyde as an Important Model Precursor for Path B of [^{18}F]FDOPA: Reaction Parameters and Activation Energy Calculation for the ^{18}F Labelling

This precursor was chosen for full investigation of the kinetics of labelling with ^{18}F because of the stability of the protection of the hydroxyl groups as ethers and also because the nitro group is much better than halogens as a leaving group in fluorination reactions. The detailed investigation of the kinetics of ^{18}F labelling of this precursor showed the following results. The ^{18}F labelling was performed in DMF, DMAc, DMSO, benzonitrile and sulfolane (Fig. 58). In general the labelling of most precursors here was best achieved in DMF. A maximum RCY of 28-30 % can be obtained using 20 mg/ml within 30 min at 140-150 °C. The labelling yields in DMAc, DMSO, and benzonitrile were in the range 15-20 % and in sulfolane less than 10 %. The results are shown in Fig. 38. A second by-product was always observed which had an R_f value close to that of the product. Thus, the activity was always distributed between the standard [^{18}F]fluoro product and the second compound. The yield of the second unknown compound was between 10 % and 20 %, hence the total incorporation of the activity was 30 % to 50 %.
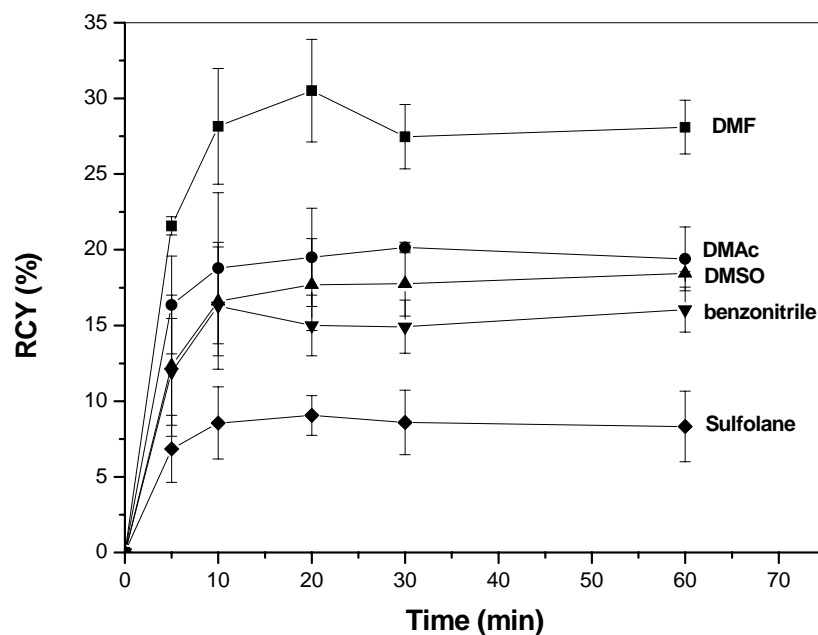
Fig. 58. [^{18}F] Labelling of 2,3-dimethoxy-6-nitrobenzaldehyde (20 mg/mL) at 140 °C. Dependence of the RCY on the type of solvent (Tab. 53, App. 9).

The temperature dependence for the [^{18}F] labelling of this precursor was studied in DMF at temperatures 80-150 °C. The results are shown in Fig. 59. A strong dependence on temperature was observed. Thus with higher temperatures higher yields were obtained. It was observed that the by-product was dominating in low temperatures but at higher temperatures it was relatively unstable and gave lower yields.
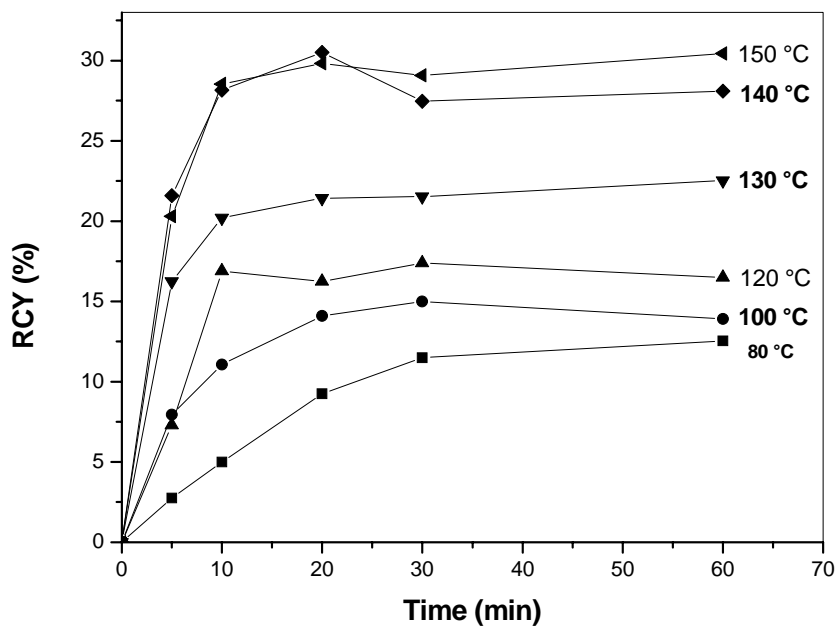
Fig. 59. [^{18}F] Labelling of 2,3-dimethoxy-6-nitrobenzaldehyde (20 mg/mL) in DMF. Dependence of the RCY on temperature (Tab. 53, App. 9).

By drawing the graph of ln (1-RCY) *vs* time, the rate constants as shown in Tab. 18 were obtained and an activation energy of 34 kJ/mol was calculated (Fig. 60).

Tab. 18. Rate constants (min^{-1}) for the labelling of 2,3-dimethoxy-6-nitro benzaldehyde at temperatures 80-150 °C.	
Temp. (°C)	**k' (min^{-1})**
80	0.0051
100	0.0118
120	0.0185
130	0.0226
140	0.0331
150	0.0336
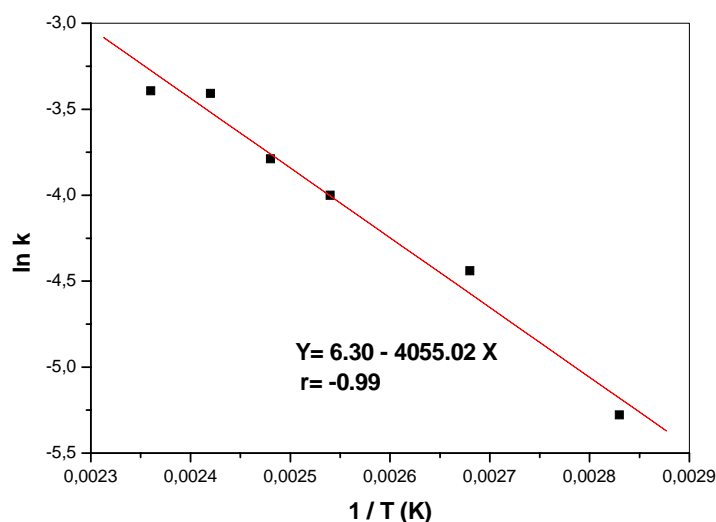
Fig. 60. Plot of ln k versus 1/T (K) for 2,3-dimethoxy-6-nitrobenzaldehyde (Conditions: 0-10 min, 80-150 °C) (Tab. 54, App. 9).

3.6.3   Precursors with Halogens as Leaving Groups

Tab. 19 shows the results of [^{18}F] labelling of haloaryl precursors and their isomers for path B

of [^{18}F]FDOPA. These precursors were prepared by reactions illustrated in schemes shown in

Fig. 5, 7, 8, 9, 11 and 12. Bromine was used mainly because it is easily introduced into the

aromatic ring by a variety of ways. Experimental procedures described in details are found in

chapter 4.
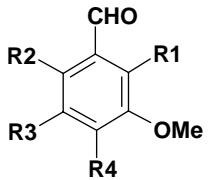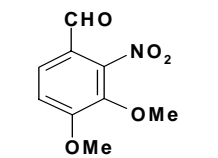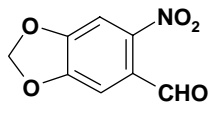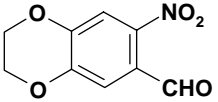
The labelling reactions were performed at the usual optimum conditions found for other

precursors of [^{18}F]FDOPA. In general, the labelling yields ranged from 1 % up to 56 %. The

reason is that the halogens (except for F) have less ability as leaving groups than others like

NO_2 or NMe_3OTf. The stability of the protection group of the hydroxyl plays also important

role. In case of protection as ethers such as the methoxy groups, the protection is very stable

against the labelling conditions, hence the highest yields were found between 11 % and 56 %.

The stability is lower for other types of protection like the esters and the yields tend to be

lower (2.5-12 %). Bromine was better as a leaving group than chlorine which is the reverse

case in the 6-haloveratraldehydes.

Tab. 19. [^{18}F] Labelling of haloaryl systems for path (B) of [^{18}F]FDOPA. (Unless otherwise stated, the conditions are: DMF, 150 °C, 10 mg/mL, 30 min).

No	Structure	Comp.	R1	R2	R3	RCY (%)	Notes
1	CHO, R2, O–R1, R3, OMe	(**39**)	CH$_3$	F	H	71.6	with standard
2		(**23a**)	CH$_3$	Br	H	18.9	with standard
3		(**30a**)	CH$_3$	Br	Br	13.0	assigned product
4		(**23b**)	CH$_3$	Cl	H	11.0	10 min, with standard
5		(**13**)	COCH$_3$	Br	H	2.5	120 °C, assigned product
6		(**15a**)	COPh	Br	H	4.6	assigned product
7		(**30b**)	COCH$_3$	Br	Br	10.6	assigned product
8		(**30c**)	COPh	Br	Br	13.7	assigned product
9		(**24a**)	CH$_3$	H	Br	1.9	assigned product
10	CHO, R2, OMe, O–R1	(**2d**)	CH$_3$	Br	-	42.3	with standard
11		(**6**)	COCH$_3$	Br	-	2.5	assigned product
12		(**8a**)	COPh	Br	-	0	assigned product
13	CHO, R2, OMe, O–R1	(**8c**)	CH$_3$	Br		2.2	assigned product
14		(**8d**)	COPh	Br		7.9	assigned product
15	CHO, OMe, MeO, Br	(**28**)	-			22.2	assigned product
16	CHO, OMe, Br, OMe	(**26**)	-			1.0	assigned product
17	O, CHO, O, Br	(**37b**)	-			9.4 ± 0.7	assigned product
18	CHO, O, Br, O	(**33**)	-			33.5 ± 2.8	assigned product

3.6.4 Precursors with Nitro as A leaving Group

Using the nitro derivatives, the yields were better as shown in Tab. 20 . In general, the yields

were in the range 25-90 % when the aldehyde is the only group ortho to the nitro. When two

groups are both ortho to the aldehyde group, the yields are not high. Also when the aldehyde

group is meta to the nitro, the yields were very low (< 5 %).

Tab. 20. [^{18}F] Labelling of nitro-aryl systems for path B of [^{18}F]FDOPA. (Unless otherwise stated, the conditions are: DMF, 150 °C, 10 mg/mL, 30 min)

No	Structure	Comp.	R1	R2	R3	R4	RCY (%)	Notes
1		(**19a**)	OCH_3	NO_2	H	H	30.5	with standard
2		(**31**)	OCH_3	NO_2	Br	H	18.4	assigned product
3		(**19b**)	$OCOCH_3$	NO_2	H	H	24.5	30 min, 150 °C, assigned product
4		(**19c**)	$OCOPh$	NO_2	H	H	28.0	5 min
5		(**24b**)	OCH_3	H	NO_2	H	4.5	with standard
6		(**21**)	OCH_3	H	H	NO_2	60.4	assigned product
7		(**42h**)			-			89.8	prepared by nitration of (**42d**)
8		(**9a**)			-			67.0	results in section 3.5.7
9		(**37a**)			-			66.4 [lit.[38] 0]	prepared by nitration of (**36**)

3.6.5 Benzenesulfonate Systems

The common protections of phenols include carbonic ethers (ROR), carboxylic esters

(ROCOR', ROCOAr) and sulfonic asters (ROSO$_2$R, ROSO$_2$Ar). An attempt to carry out [^{18}F]

labelling of phenolic precursors protected with the benzenesulfonate group, i. e. OSO$_2$Ph

resulted in an attack on the sulphur atom instead of the carbon holding the leaving group. The result was most likely always [^{18}F]benzenesulfonylfluoride which is reported for the first time in this study. The fast attack of the strong ^{18}F$^-$ nucleophile on the protection group (which is unstable in basic conditions) cleaves it readily. Within 5 min the RCY is 81-89 %. In the following, Tab. 21 gives the results of ^{18}F labelling of some benzenesulfonates.
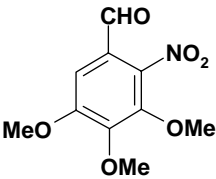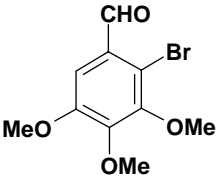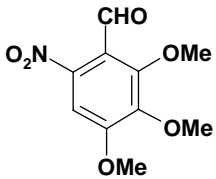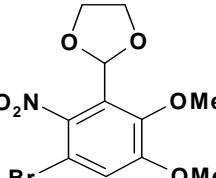
Tab. 21. [^{18}F] Labelling of benzenesulfonate systems for path B of [^{18}F]FDOPA. (conditions: DMF, 150 °C, 10 mg/mL, 5 min).
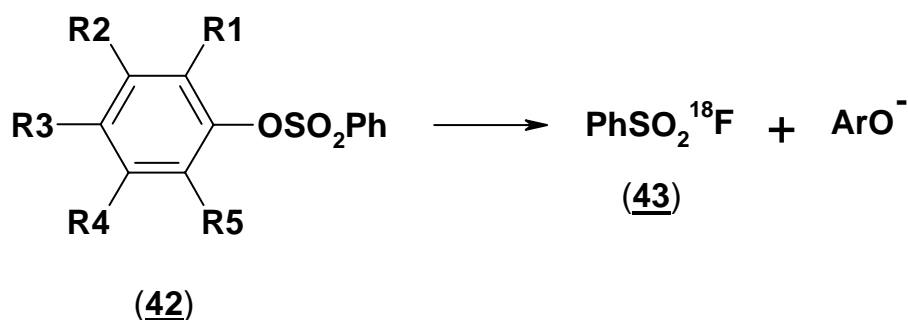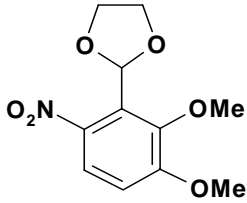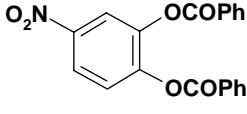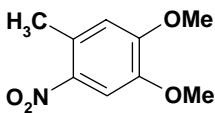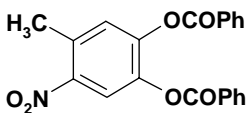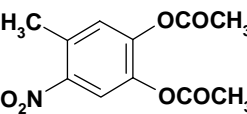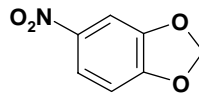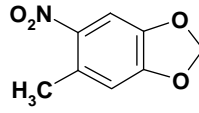
No	code	R1	R2	R3	R4	R5	RCY (%) PhSO$_2$^{18}F	Notes
1	(**42a**)	H	H	H	H	H	81.0	
2	(**42b**)	CHO	H	H	H	H	84.7	
3	(**42c**)	H	H	CHO	H	H	85.2	Standard product is
4	(**16**)	CHO	H	H	H	OCH$_3$	82.1	detected by
5	(**42d**)	OCH$_3$	H	CHO	H	H	83.2	comparison in TLC
6	(**8b**)	OCH$_3$	H	CHO	Br	H	87.3	and HPLC with
7	(**42e**)	OCH$_3$	NO$_2$	CHO	H	H	88.6	authentic ^{19}F sample.
8	(**15b**)	CHO	Br	H	H	OCH$_3$	86.2	No detection of
9	(**30d**)	CHO	Br	Br	H	OCH$_3$	84.6	halogen or nitro
10	(**17a**)	CHO	NO$_2$	H	H	OCH$_3$	85.0	substitution by
11	(**17b**)	CHO	H	H	NO$_2$	OCH$_3$	82.0	[^{18}F]fluoride
12	(**42f**)	OSO$_2$Ph	H	NO$_2$	H	H	87.0	
13	(**42g**)	OSO$_2$Ph	H	NO$_2$	CH$_3$	H	81.0	

3.6.6   Miscellaneous (Other Systems)

In the following, Tab. 22 gives the results of the [^{18}F] labelling of other aryl systems. (see chapter 4 for experimental details). Most of these are classified as electron rich aromatic compounds. As the results show, the RCY are high for those systems with a very good leaving group (like the nitro) and with very stable protection of the hydroxy groups (like the methyl ethers). Systems with no activation at all (toward S_NAr) and with methyl group on the ring or protection of the hydroxyl groups as esters gave very bad yields and sometimes gave no yield at all.

Tab. 22. [^{18}F] Labelling of other aryl systems. (Assigned product. Unless otherwise stated, the conditions are: DMF, 150 °C, 10 mg/mL, 20 min, TLC results)

No	Structure	Comp.	RCY (%)	Notes on preparation
1		(**45**)	68.6 ± 4.5	prepared by direct nitration of 3,4,5-trimethoxybenzaldehyde (**44**)
2		(**46**)	8.6 ± 0.8	prepared by direct bromination of 3,4,5-trimethoxybenzaldehyde (**44**)
3		(**48**)	66.2 ± 4.2	prepared by nitration of 2,3,4-trimethoxybenzaldehyde (**47**)
4		(**49**)	22.1 ± 0.2	prepared by the protection of the aldehyde group in compound (**31**)

Tab. 22. Continued

5	O_2N ... OMe / OMe	(**50**)	3.0	prepared by the protection of the aldehyde group in compound (**19a**)
6	O_2N ... OCOPh / OCOPh	(**52**)	1.0	prepared by protection of the two OH's in of 4-nitrocatechol (**51**) as benzoate esters
7	H_3C ... OMe / O_2N ... OMe	(**55a**)	0	prepared by nitration of 4-methylcatechol (**53**) **.** The product (**54**) is then protected (the two OH's) as arylmethyl ether (**55a**), benzoate (**55b**) or acetate (**55c**) esters
8	H_3C ... OCOPh / O_2N ... OCOPh	(**55b**)	0	
9	H_3C ... $OCOCH_3$ / O_2N ... $OCOCH_3$	(**55c**)	0	
10	O_2N ... O / O	(**57**)	0	prepared by nitration of 1,3-benzodioxole (**56**)
11	O_2N ... O / H_3C ... O	(**59**)	0	prepared by nitration of 3,4-methylenedioxytoluene (**59**)

3.7 General Discussion

3.7.1 Structural Effects

The discussion of the structural effects in the labelling by [^{18}F]fluoride can be divided into **four** main categories according to the types and positions of the groups on the aromatic ring (whether these are electron donating, electron withdrawing, leaving or protecting groups). In the following sections, these types of structural effects are discussed in detail depending on the experimental results. It is assumed that the factor under investigation is the only one operating in every case and that all other factors or variables are constant (whether controlled such as temperature and concentration or uncontrolled such as quality of fluoride or impurities up to 5 % in the precursor sample). To overcome the problem of uncertainty, each value reported here is assumed to be repeated at least 4 times (n > 3).

3.7.1.1 Positions of Different Groups on the Aromatic Ring

One can get a better idea about this factor if we consider different isomers of the same compound labelled with [^{18}F]fluoride under the same conditions. In the following, Tab. 23 gives an idea of how the different positions of the same groups on the ring can affect the RCY. As it is expected, the labelling yields will be high if a good electron withdrawing group (EWG) is *ortho* or *para* to a good leaving group (LG) (in some cases where only two *meta* EWGs existed on the ring, the RCY also was good)[40]. The intermediate Meisenheimer complex is highly stabilised in this case by several resonance structures in which the particular EWG present can stabilise the negative charge.

In case of the existence of one or two more EDGs on the ring the RCYs can still be very good if again a good EWG is *ortho* or *para* to a good LG. The *ortho* effect here is much more effective than the *para*. For entry 1 in Tab. 23 we see the lowest yield (4.5 %) in case of compound (1-a). The activation towards nucleophilic aromatic substitution (S$_N$Ar) is very

week here because the aldehyde is *meta* to the nitro, while two methoxy groups are present, one of them is *para* to the nitro.

In compound (1-b) the yield is improved up to 16.6 % although the methoxy groups are now both *ortho* and *para* to the nitro. The reason for this is that the aldehyde is *ortho* to the nitro which means strong activation.

A much better situation is present in case of compound (1-c) where we also have strong activation by an *ortho* aldehyde group. Only one methoxy group is *para* to the nitro (weak deactivation). A possible explanation is that the aldehyde group adopt a conformation in which it is perpendicular to the plane of the aromatic ring, i.e. the dihedral angle = 90°[96]. This was confirmed by X-ray structure analysis (Fig. 61, App. 9). This means the aldehyde group is less effective in stabilising the negative charge of the Meisenheimer complex, hence the yield would be low[93].
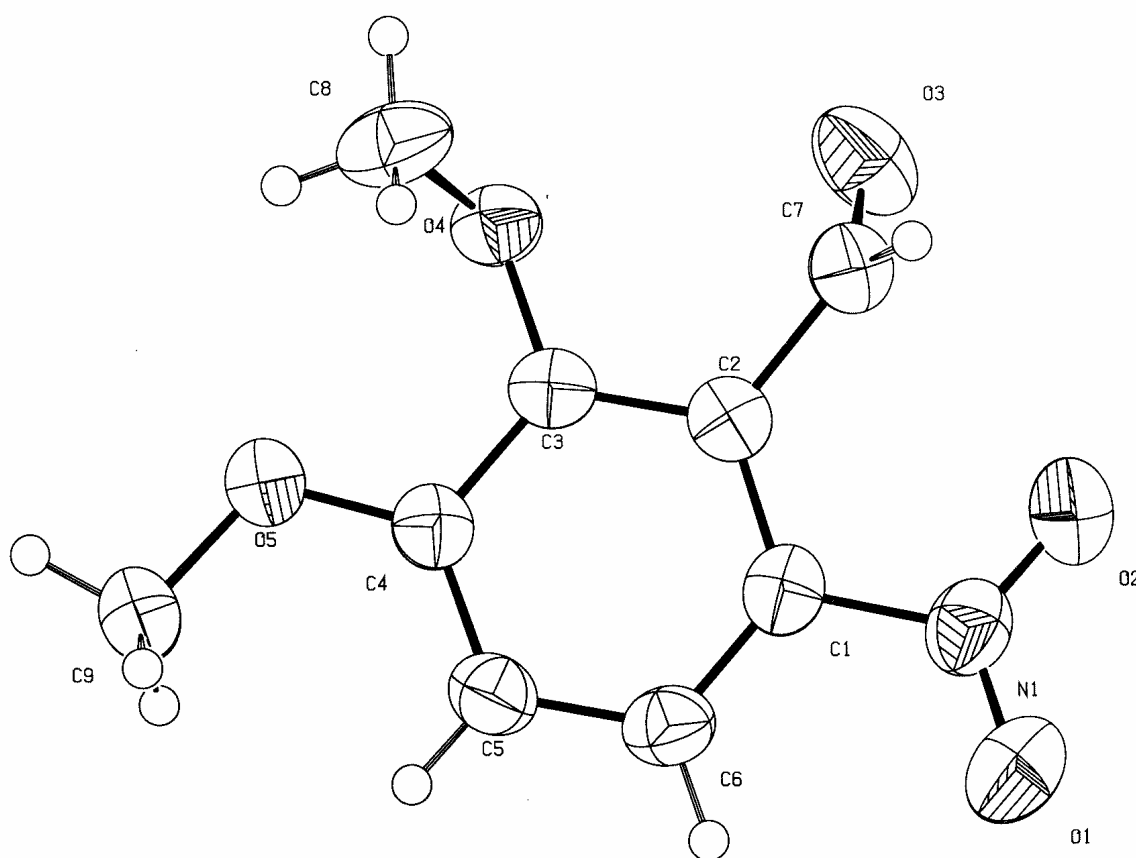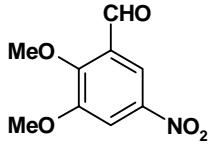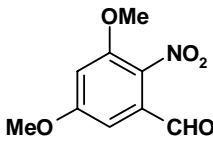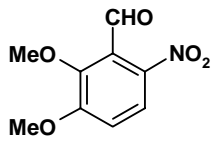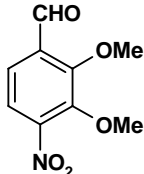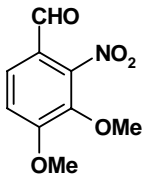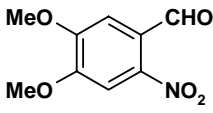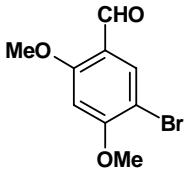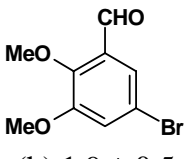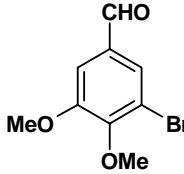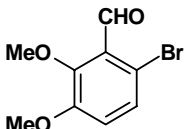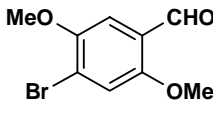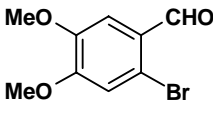
Fig. 61. X-ray structure of 2,3-dimethoxy-6-nitrobenzaldehyde.

In case of compound (1-d) no sterical hindrance exists as in (1-c) and yields are higher. Yet, the activation by a *para* aldehyde group towards the nitro is less effective than in case of the *ortho* isomer. Therefore, the yield is higher than (1-c) but not as high as in (1-e) and (1-f). Consequently, the highest yields were obtained with compounds (1-e) and (1-f). In these precursors, which gave almost the same RCY, the activation is strong (an aldehyde is *ortho* to the nitro group). In addition, one methoxy is either *ortho* or *para* to the leaving group and another one is *meta* which render it inactive. A very important note here is that the aldehyde activates very well as the case in the last two compounds if it is not *ortho* to two other groups simultaneously (this means no sterical hindrance).

A similar discussion also holds for the bromo precursors (Tab. 23, entry 2). Compounds (2-g), (2-h) and (2-i) are not activated at all (they gave the lowest yields between 1.0 % and 2.2 %) because the aldehyde here is *meta* to the bromine while strong EDGs (two methoxy groups) are either *ortho* or *para*. In compound (2-j) the activation is better (an aldehyde is *ortho* to the bromine) and the yields (19 %) are better (although still low because the two methoxy groups are *ortho* and *para* to the bromine) . In compound (2-k) the yields (22.2 %) were still better (but still not very high because the aldehyde is *ortho* to two other groups (the same case as in the nitro analogue). Again the highest yields were obtained with structure (2-l) where the aldehyde is *ortho* to the leaving group (high activation) and only one methoxy is *para* (low deactivation) to the leaving group.

Tab. 23. Structural effects in the labelling by [^{18}F]fluoride. (**A**) Effect of different positions of the same groups (isomeric precursors) on the aromatic ring listed in order of increasing RCY. (Conditions: DMF, 20 mg/mL, 140-150 °C, 20 min, results of TLC analyses).

No	Isomers / RCY (%) ± Sdv		
1	 (a) 4.5 ± 0.8	 (b) 16.6 ± 1.3	 (c) 30.5 ± 3.4
	 (d) 60.4 ± 2.0	 (e) 89.8 ± 0.7	 (f) 89.7 ± 2.0
2	 (g) 1.0 ± 0.3	 (h) 1.9 ± 0.5	 (i) 2.2 ± 0.4
	 (j) 19 ± 2.6	 (k) 22.2 ± 3.4	 (l) 42.3 ± 4.0

3.7.1.2   Type of Leaving Group

In this work four types of leaving groups were used to investigate the labelling by
[^{18}F]fluoride. Those are NO_2^-, F^-, Br^- and Cl^-. Except for some cases the order of leaving
group ability followed the expected order[40] , i.e.

$$NO_2 \approx F > Br > Cl$$
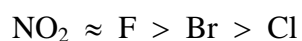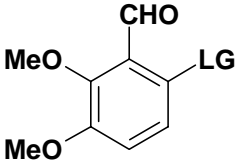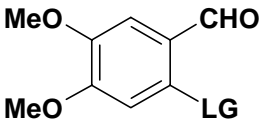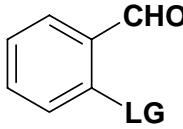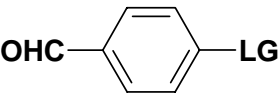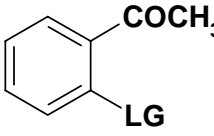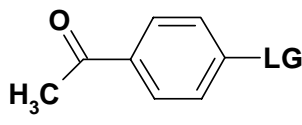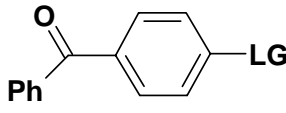
[^{18}F]fluorodenitration reactions and the fluorine isotopic exchange (^{18}F for ^{19}F) gave the
highest yields (all other variables are the same) indicating that the two groups NO_2^- and F^-
are among the best leaving groups for the nucleophilic aromatic substitution by [^{18}F]fluoride.
To a smaller extent, the other halogens were used as leaving groups. The yields of Cl^- or Br^-
substitution were lower than in case of NO_2 or F. The relative order of the leaving group
ability of the bromine or the chlorine was not always the same. In most cases bromine was
better leaving group. Tab. 24 illustrates the effect of the leaving group on the RCY by
[^{18}F]fluoride.

Tab. 24. Structural effects in the labelling by [^{18}F]fluoride.
(**B**) Type of leaving group (LG)
(conditions: DMF, 150 °C, 20 mg/mL, 30 min, results of TLC analyses)

No	Structure	LG / RCY (%) ± Sdv			
		NO$_2$	F	Br	Cl
1	CHO, MeO, LG, MeO	30.5 ± 2.3	73.6 ± 4.6	19.3 ± 3.1	12.1 ± 2.0
2	MeO, CHO, MeO, LG	89.6 ± 1.4	87.7 ± 1.2	42.3 ± 3.9	56.4 ± 7.1
3	CHO, LG	73.2 ± 0.2	75.0 ± 1.6	73.0 ± 0.2	65.0 ± 1.1
4	OHC—LG	81.5 ± 5.9	78.3 ± 0.5	75.7 ± 0.5	65.7 ± 3.3
5	COCH$_3$, LG	13.3 ± 0.9	70.1 ± 1.3	39.3 ± 2.9	37.7 ± 5.4
6	O, H$_3$C—LG	61.7 ± 3.9	74.7 ± 4.5	35.3 ± 1.7	59.0 ± 3.6
7	O, Ph—LG	86.8 ± 4.8	83.3 ± 3.0	76.0 ± 2.6	70.7 ± 4.5

3.7.1.3   Type of Activation (Type of Electron Withdrawing Group EWG)

The type of the EWG has a great effect on the RCY in the labelling by [^{18}F]fluoride as in other types of nucleophilic substitutions. This effect can be studied systematically by changing the EWG in a defined aromatic system. This group should not contain free OH groups (as the case in COOH) in order to avoid solvation effects on the [^{18}F]fluoride ion. Tab. 25 compares the results. The compounds are nitro or bromo derivatives of benzene, benzaldehyde, acetophenone and benzophenone (*ortho* or *para*). The RCYs indicated that the approximate order of electron withdrawing ability of different groups in the nucleophilic aromatic substitution by [^{18}F]fluoride is the following:

$$COPh \approx NO_2 > CHO > COCH_3 \qquad \textbf{(solvent: DMF, leaving group: NO_2)}$$
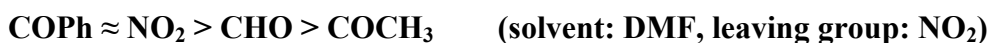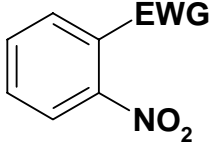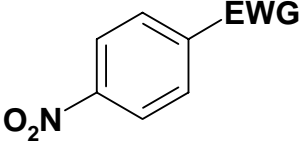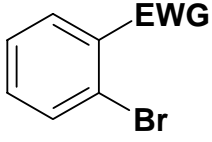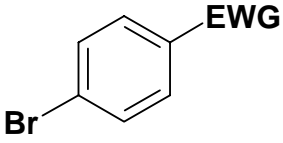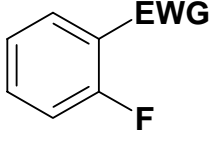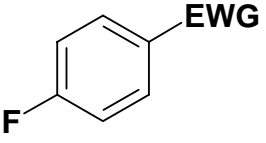
The results showed that the groups COPh and NO$_2$ are powerful in the electron withdrawal effect (RCY were in the range 76-87 % in case of NO$_2$ also as a leaving group). Smaller effect was found for the aldehyde group (RCY= 73-81 %), and it was smaller for the COCH$_3$ group (RCY= 13-61 %). Using fluorine or bromine as leaving groups the situation is changed, and the order is:

$$COPh \approx CHO > NO_2 > COCH_3 > Br \qquad \textbf{(solvent: DMF, leaving groups: F, Br)}$$
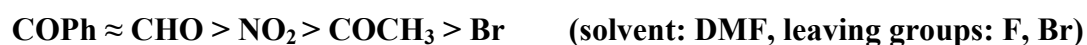
In both cases the *para* effect of the EWG was more powerful than the *ortho* effect, and this was the reverse case with the electron-rich [^{18}F]DOPA precursors. One group, which has the ability to act as a temporary EWG on the ring then can be removed afterwards, is the aldehyde. Hence, it is used in some applications to enhance the nucleophilic aromatic substitution by [^{18}F]fluoride. It is removed afterwards catalytically [using the complex Rh(PPh$_3$)$_3$Cl].

Tab. 25. Structural effects in the labelling by [^{18}F]fluoride.
(**C**) Type of activation by EWGs (EWG and not a leaving group). (Unless otherwise stated, the conditions are: DMF, 150 °C, 20 mg/mL, 20 min. Results of TLC analyses).

Structure	EWG / RCY (%) ± Sdv				
	Br	**NO$_2$**	**CHO**	**COCH$_3$**	**COPh**
EWG ortho to NO$_2$	-	81.6 ± 5.4	73.2 ± 0.2	13.3 ± 1.0	78.7 ± 1.9
EWG para to O$_2$N	-	87.0 ± 2.1	81.5 ± 5.9	61.7 ± 3.9	86.8 ± 4.8
EWG ortho to Br	10.9 ± 0.5	58.4 ± 9.1	73.0 ± 0.2	39.3 ± 2.9	-
EWG para to Br	6.1 ± 2.9	66.7 ± 5.7	75.7 ± 0.5	35.3 ± 1.7	76.0 ± 2.6
EWG ortho to F	-	-	75 ± 1.6	70.1 ± 1.3	91.2 ± 1.0
EWG para to F	-	-	78.3 ± 0.5	74.7 ± 1.2	83.3 ± 3.0

3.7.1.4   Type of Protection of the Hydroxyl Group[58].

Protection of the hydroxyl group is necessary in the labelling by [^{18}F]fluoride. If strong hydrogen bonding is formed between free OH or NH$_2$ groups (present in the precursor, in traces of water in the solvent, in the solvent itself or even impurities present in the solution) and the fluoride ion, the nucleophilicity of the fluoride is reduced very much. In this case it becomes inactive in the nucleophilic fluorination reactions. This effect is a serious problem in case of ^{18}F relative to ^{19}F because in case of ^{18}F this radiotracer is present in very small concentration in the solution.

The protection of the hydroxyl group must be very stable against the labelling conditions (temperature:100-180 °C, pH: 8-10). In addition it should be stable against the conditions and reagents used in others steps if it is to be employed in the total synthesis of [^{18}F]FDOPA. However, very few OH-protecting groups exist which sustain the labelling conditions. In choosing the specific protecting group there is a compromise. The protection should sustain the labelling and the subsequent conditions but it should be relatively easy to deprotect at the last step. Protection as ethers is very practical because it is relatively stable in all steps however, the deprotection needs drastic conditions (HI conc., 150 °C). On the other hand the protection as esters (carbonic, sulfonic, ...etc) is relatively easy and the deprotection is also easy, but they are relatively unstable towards the labelling and most of the subsequent steps. This is variable among different groups. Table 26 shows the effect of the labelling conditions on some common protection groups of the phenolic OH groups. We notice that the methyl ethers, aryl methanesulfonates and methylenedioxy derivatives are stable against all conditions. The acetates were unstable in most cases except in neutral conditions and high temperatures. The benzoates are stable in most cases but shows marginal stability against high pH and the use of K$_2$CO$_3$ / X$^-$.

In this study the acetates were the least stable groups, providing several spots after labelling. The benzoates were more stable. The benzene sulfonates were the least stable and the sulfonate group is rapidly attacked by the strong nucleophile $^{18}F^-$ to provide the unwanted product $PhSO_2{}^{18}F$. This finding is surprising because Tab. 26 shows the methanesulfonates to be stable under most conditions. However, in case of the benzene sulfonates the presence of the aromatic ring on both sides of the protecting group provides stability of the intermediates by conjugation with the ring, hence the attack of the fluoride on the protecting group is favoured (unlike in case of the methanesulfonates).

Tab. 26. Stability of some phenolic OH groups against common labelling conditions by [^{18}F]fluoride[58].

Type of OH protection	pH 8.5-10	pH 10-12	Nucleophilic * X$^-$	Temp. ** 100-250 °C	K$_2$CO$_3$ MeI
Methyl ethers	S	S	S	S	S
Acetates	US	US	S	S	US
Benzoates	S	MS	S	S	MS
Aryl methanesulfonates	S	S	S	S	S
Methylenedioxy derivatives	S	S	S	S	S

Notes:
1- **S**: protective group is **stable** under the reaction conditions.
2- **US**: protective group is **unstable under** the reaction conditions and it is removed to yield the original OH group.
3- **MS**: **marginal stability**. Depends on the exact other conditions of the reaction.
4- *) Nature of X$^-$ is not specified.
5- **) Neutral conditions: pH ≈ 7

Tab 27 shows the structural effect played by protection of the OH group on the RCY by [^{18}F]fluoride. In most the results cases fit generally with the expectations. The highest yields were obtained with the methyl ethers since they are the most stable. With respect to the esters, the benzoates gave higher yields than the acetates (in most cases the benzoates gave one or two spots, unlike the acetates which gave always several spots). In case of two *ortho* OH

groups the protection can be open or cyclic (Tab. 26, entry 5). It was found that best results were obtained with the open protection. The difference in the RCY from 89 % in the open structure to 66-68 % in the cyclic structures (five and six membered rings) suggests possibly that side reactions involving opening of the protection ring occurred with the labelling reaction which lowered the yields finally. The stability of open ethers is higher than cyclic ethers and this is supported by the fact that the deprotection occurs much faster and smoother in cyclic ethers than in open ethers. Finally, the protection of the catechols as five or six membered rings (cyclic ethers) seems not to affect the fluorodenitration or the fluorodehalogenation reactions on the aromatic ring. This can be seen in table 27, entries 6 and 7. The RCYs are very close (67.6 and 66.4 %) in case of fluorodenitration reactions on five and the six membered rings, respectively. The same holds for the fluorodehalogenation reactions where we got a RCY of 10.7 % and 9.4 % in case of the five and six membered rings, respectively. An exception was the results obtained from 6-bromo-2,3-dimethoxy benzaldehyde (entry 2, open protection) and 6-bromo-2,3-methylenedioxybenzaldehyde (entry 6, cyclic 5 membered ring protection) where we have better results from the cyclic structure. From this we can conclude that catecholic (2 *o*-OHs) precursors protected as cyclic ethers (five or six membered rings) will mostly give lower RCYs in the labelling by [18F]fluoride than open ethers. Moreover, the size of the protection ring has practically no effect on the RCY. Only five or six membered rings were tested because they are the easiest to prepare and deprotect back to the OH function.
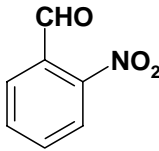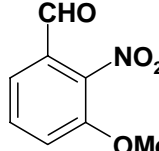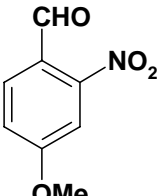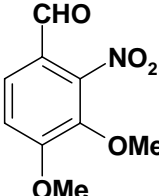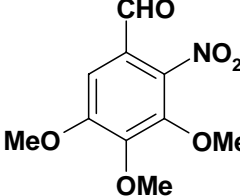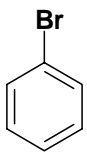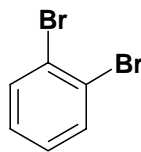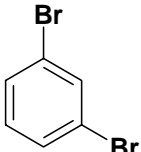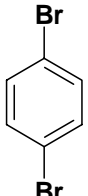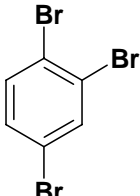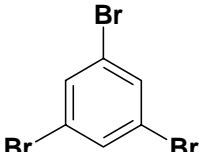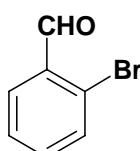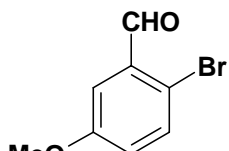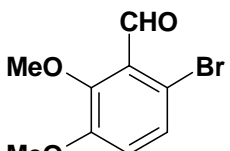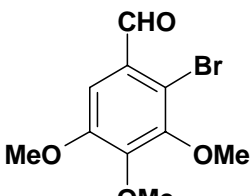
Tab. 27. Structural effects in the labelling by [^{18}F]fluoride.
        (**D**) Protection of two ortho OH groups (G is a protective group).
        (conditions: DMF, 150 °C, 20 mg/mL, 20 min, results of TLC analyses)

Open similar or different protection of two OH groups

No.	Precursor structure	Type of protective group G / RCY (%) ± Sdv		
		CH$_3$ (methyl ethers)	COCH$_3$ (acetates)	COPh (benzoates)
1		30.5 ± 3.4	24.5 ± 2.4	28.0 ± 2.9
2		18.9 ± 2.6	2.5 ± 0.8	4.6 ± 1.2
3		13.0 ± 3.2	10.6 ± 2.8	13.7 ± 4.6
4		42.3 ± 4.0	2.5 ± 0.6	0
5		89.7 ± 2.0	-	-

Cyclic (5 or 6 membered ring) protection of the two OH groups

6	Precursor structure			
	RCY (%)	67.6 ± 5.2	10.9 ± 1.1	33.5 ± 2.7
7	Precursor structure			
	RCY (%)	7.1 ± 0.2	66.4 ± 4.7	9.4 ± 0.7

3.7.1.5 Other Structural Effects

One structural effect that can be discussed but carefully is the total number of groups on the ring and whether these groups are EDGs or EWGs. Because the total net effect of the presence of many groups can not be estimated easily, the results can not always be generalised. Tab 28 shows the results. In case of successive increase of EWGs (bromobenzene derivatives, entry 2) the effect is high activation towards the nucleophilic aromatic substitution as it is expected. In case, however, of successive increase of EDGs (mono-, di- and trimethoxylated 2-nitrobenzaldehyde, entry 1) the total effect is surprising and it seems that the presence of the methoxy groups has no affect at all or has positive effect. Unlike methoxy, the presence of methyl groups on the ring has a negative effect on the labelling by [^{18}F]fluoride. This was explained in methyl substituted nitrobenzaldehyde by formation of unreactive complex with the [^{18}F]fluoride (perhaps relatively stable Meisenheimer complex)[44]. This would transform most of the [^{18}F]fluoride into an unwanted product or intermediate. The high RCYs obtained with methoxylated nitrobenzaldehyde is one difference between the chemistry of ^{19}F and that of ^{18}F. Beside being very fast and giving high yields within few minutes, labelling by [^{18}F]fluoride shows tolerance for the presence of even strong EDGs that would otherwise reduce the yields dramatically in ^{19}F nucleophilic fluorinations or stop the reaction completely. It should be emphasised that the previous discussion holds for precursors with excellent leaving groups such as -NO$_2$. For other precursors involving groups with a weaker ability to act as leaving groups, the predicted RCYs match with the experimental values (Tab. 28, entry 3). The highest yield (73 %) was obtained from *o*-bromobenzaldehyde. The successive addition of methoxy groups to the ring lowers the yields, and this also depends on the number of these groups.

Tab. 28. Structural effects in the labelling by [^{18}F]fluoride.
(**E**) Total number of groups on the ring. (Unless otherwise stated, the conditions are: DMF, 150 °C, 20 mg/mL, 20 min. Results of TLC analyses)

No.	Structure / RCY (%) ± Sdv
1	
	73.2 ± 0.2 66.7 ± 2.3 87.0 ± 1.0 89.8 ± 0.7 69.1 ± 4.5
2	
	0.5 ± 0.1 10.9 ± 0.5 13.3 ± 6.7 4.3 ± 2.8 48.6 ± 10 64.3 ± 6.9
3	
	73.0 ± 0.2 31.7 ± 2.5 19.0 ± 0.1 8.6 ± 0.7

3.7.2 Solvent Effects

Solvents have generally great effects on most reactions and effects on the aromatic fluorination reactions are to be expected[59, 60] . In this study several solvents were used. Those mostly are dipolar aprotic solvents in which the fluoride is very soluble and free (not bonded to the solvent, which means increased nucleophilicity and basicity). In addition, those solvents stabilise the reaction intermediates. Examples are DMF, DMSO, DMAc, sulfolane, 1,2-DME, NFP, NFM, pyridine, benzonitrile, acetonitrile, dioxane and nitromethane. Tab. 29 shows the labelling of 6-nitroveratraldehyde (**2a**) in different solvents:

Tab. 29. [^{18}F] labelling of 6-nitroveratraldehyde in different solvents. (conditions: 140 °C, 20 mg/mL, highest yields within 10-20 min, results of TLC analyses)

Solvent	DMF	DMSO	DMAc	1,2-DME	Sulfolane	Pyridine	NFP	Dioxane
RCY (%)	89.7 ± 2.0	71.4 ± 3.8	75.6 ± 2.0	59.9 ± 5.0	40.1 ± 1.8	56.1 ± 7.5	59.2 ± 5.5	18.7 ± 3.1

 Most of those solvents have high boiling points and good thermal stabilities. DMF was mainly used in this study and it showed to be an excellent solvent for carrying out the labelling reactions. In all cases the less polar solvents such as 1,2-DME, dioxane or acetonitrile gave very poor results (note: maximum achievable temperature from these solvents is ≈110 °C, which appear to be low for the nucleophilic aromatic substitution). The choice of solvent depends also on the boiling point. However, for most nucleophilic aromatic labelling reactions by [^{18}F]fluoride the range of 120-160 °C was found to be the best. Higher temperatures can be used but a general note is that solvent decomposition starts significantly around 200 °C (except for sulfolane which has a boiling point of 285 °C). The use of solvents with the amide function proved to be the best in this study, especially in two cases: the first is the fluorodehalogenation reactions which gave very good yields in DMF but poor results in other solvents. The other case is the electron-rich aromatic rings which again gave high yields

of labelling in DMF or DMAc but instead much lower yields in the case of DMSO or sulfolane. The reaction with the solvent molecules was noticed in the case of nitro methane and nitro ethane (Knoevenagel condensation). It should be mentioned that in nucleophilic labelling with [18F]fluoride, in literature two solvents used mostly are acetonitrile (for low temperatures up to 90 °C) and DMSO (for high temperatures up to 180 °C).

3.7.3   Concentration Effects

Generally in this work, where the concentration effects are studied in detail, the following concentrations were used: 0.5, 1, 5, 10, 20, 30 and 50 mg/mL (a concentration of 20 mg/mL was used in case of non-detailed studies). The dependence of the RCY on the precursor-concentration was strong and investigation of the results showed that the concentration range 20-30 mg/mL was the optimum range for the optimum RCY[32]. Another note is that at lower concentrations, i.e. 0.5-1 mg/mL the RCY tends to decrease rapidly after 20 min but at higher concentrations (> 5 mg/mL) the RCY reaches a plateau which is not much different than the maximum yield obtained. In case of fluorodehalogenation reactions were the leaving groups are weaker (when related to NO_2) the increase of precursor concentration was accompanied by increase in the RCY even up to 50 mg/mL. In fluorodenitration and fluorine isotopic exchange reactions, where high RCY can be obtained in short time and with low concentrations, the effect of increasing the concentrations on the RCY is not high, especially after 10 mg/mL.

3.7.4   Temperature Effects

The dependency of all types of reactions on temperature is well known and expected from the Arrhenius equations. In this study the temperature range used mainly is 80-180 °C for most compounds but also lower temperatures were used for very activated systems like

o-dinitrobenzene. At higher temperatures high amount of decomposition was observed either from the precursors and even from the solvent. In general, the optimum temperature range found to be the best for the labelling with [^{18}F]fluoride was 140-150 °C although as in fluorodehalogenation reactions higher temperatures resulted also in an increase in the RCY. For very activated systems like *o*-dinitrobenzene, higher temperatures (> 120 °C) were found to have negatively lowering effect on the RCY.

3.7.5   Energy of Activation and Mechanistic Implications
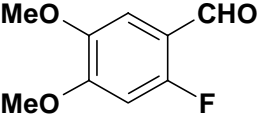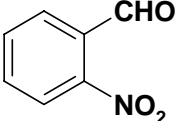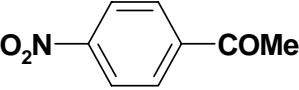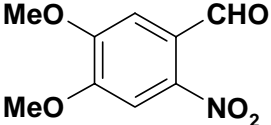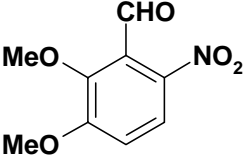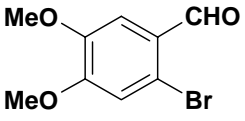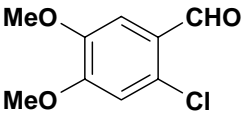
Calculations of the energy of activation [E_{act}(kJ/mol)] for selected aryl systems revealed the following sequence in general:

fluorine isotopic exchange < fluorodenitration reactions < fluorodehalogenation reactions

This is in agreement with the order of leaving group ability. The fluorine isotopic exchange should have the least E_{act} since the exchange here is for isotopes of the same element. Fluorodenitration reactions proceed with a lower E_{act} than fluorodehalogenation reactions because the nitro group is much more better than the halogens as a leaving group. The results are shown in Tab. 30.

Tab. 30. E_{act} values (kJ/mol) of selected aryl systems used in this work.

Precursor	E_{act} (kJ/mol)	Reaction type
MeO, CHO, MeO, F	17	**Fluorine isotopic exchange**
CHO, NO₂	24	**Fluorodenitration**
O₂N, COMe	32	
MeO, CHO, MeO, NO₂	33	
CHO, MeO, NO₂, MeO	36	
MeO, CHO, MeO, Br	60	**Fluorodehalogenation**
MeO, CHO, MeO, Cl	63	

Tab. 31. E_{act} (kJ/mol) of selected nucleophilic aromatic substitution reactions. (X is substituted by the nucleophile. For details of reactions, see literature).

No	Substrate	X	Nucleophile	E_{act} (kJ/mol)	Lit.
1	1-(X)anthraquinones	F	Piperidine	*50.6*	97
2		Cl		*53.1*	
3		Br		*56.4*	
4		I		*53.5*	
5	2-(X)anthraquinones	F		*58.9*	
6		Cl		*55.6*	
7		Br		*63.5*	
8		I		*78.2*	
9	1-(X)-2,4-dintrobenzene	PhSO		*45.1*	98
10		Br		*49.3*	
11		Cl		*48.5*	
12		PhSO$_2$		*50.2*	
13		p-NO$_2$-C$_6$H$_4$O		*43.9*	
14		I		*50.2*	
	6-(G)-2,4-di-NO$_2$-chlorobenzene				
15	G= Cl	Cl	OMe$^-$	*71.9*	99
16	Ph			*76.9*	
17	H			*75.2*	
18	Me			*84.0*	
19	MeO			*94.9*	
	4-(G)-2-NO$_2$-chlorobenzene				
20	G= NO$_2$	Cl	OMe$^-$	*70.2*	99
21	MeSO$_2$			*77.8*	
22	Me$_3$N$^+$			*84.9*	
23	CH$_3$CO			*79.8*	
24	CF$_3$			*85.3*	
25	PhN=N			*79.8*	
26	**1-Chloro-2,4-dintrobenzene** (catalysed, under solid-solid-liquid phase transfer conditions)	Cl	F$^-$	*40.0*	100
27	**Fluorobenzene**	F	OMe$^-$	*152.2*	101
28	**2-Nitrofluorobenzene**			*120.8*	
29	**3-Nitrofluorobenzene**			*83.2*	
30	**4-Nitrofluorobenzene**			*84.0*	
31	**2,4-Dinitrofluorobenzene**			*51.4*	
32	**3,5-Dinitrofluorobenzene**			*90.7*	
	4-(G)-2-NO$_2$-chlorobenzene				
33	G= H	Cl	OMe$^-$	*96.2*	102
34	SMe$_2$. SO$_4$			*24.0*	
35	Sme			*74.0*	
36	NMe$_3^+$			*92.8*	
37	**Bromobenzene**	Br	EtO$^-$	*237.0*	103

Tab. 31 gives selected literature values for the activation energies (nucleophilic aromatic substitution reactions) using different substrates and nucleophiles. The activation energies are in the range between 40 kJ/mol and 240 kJ/mol with an average value of 75 kJ/mol. In this work, all E_{act} values (which are in the range of 16-62 kJ/mol) are in the low range or partly even lower than reported in literature for the nucleophilic aromatic substitution. The reason is that those reactions are very fast reactions[95]. The maximum yields are often obtained within 10 min. Very activated systems like *o*-dinitrobenzene gave very low E_{act} (2 kJ/mol), which is expected since in these systems the reaction is very fast even at low temperatures. Other systems that gave very low E_{act} was 6-nitropiperonal (**9a**). For this compound, calculation of E_{act} revealed a value of exactly 5 kJ/mol, which is too low for fluorodenitration reactions.

The low values of E_{act} obtained here for the nucleophilic reaction of [^{18}F]fluoride can well be understood when compared to literature. An example is the investigation of the gas phase reaction between the fluoride ion and nitro benzene[95]. That was studied by FTICR mass spectrometry and DFT calculation. The displacement of the nitro group proceeds as an unusually fast reaction with a bimolecular rate constant of $k = 3 \times 10^{-9}$ cm^{3}molecule^{-1}sec^{-1}, the reaction was the following:

$$\mathbf{F^-} \quad + \quad \mathbf{C_6H_5NO_2} \quad \longrightarrow \quad \mathbf{NO_2^-} \quad + \quad \mathbf{C_6H_5F}$$
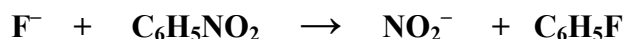
According to the DFT calculations the most stable complex between the fluoride ion and the nitrobenzene (structure 1) results from a fluoride ion bound loosely to the aromatic hydrogens in the *para* position.

(1)
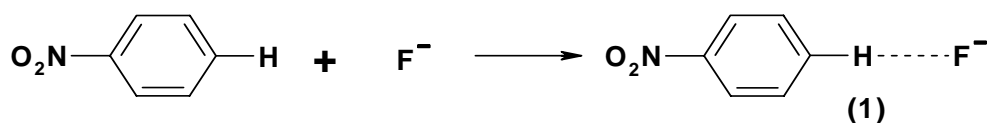
Similar complexes were also formed as local minima for fluoride ions loosely bound to the *meta* and *ortho* aromatic hydrogens. Furthermore, two different stable complexes could be

identified by out-of-plane attack of the fluoride ion to the *para* and *ipso* carbon atoms (structures 2, 3).

(2)   **(3)**   **(4)**   **(5)**
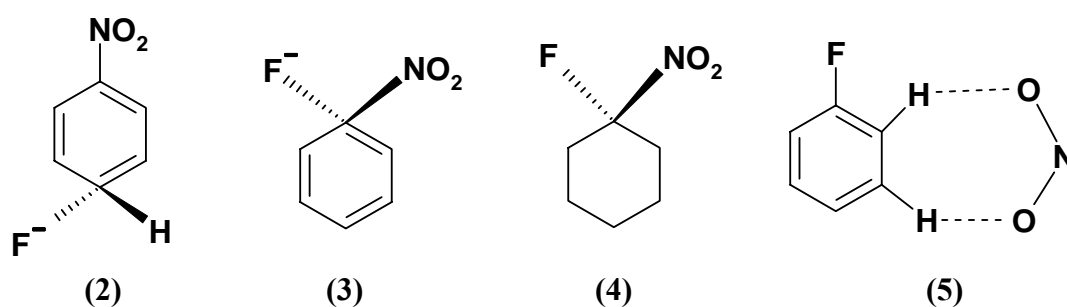
The stable ion molecule adduct (3) with a C-F bond length of 2.24 Å and an outside covalent bond proceeds then through a local transition state (4). Finally before the products, an ion molecule complex between fluorobenzene and the nitrite ion (5) is obtained. According to these calculations the prototype Meisenheimer complex (5) is a transition state and not a local minimum (in the gas phase). The energy of this transition state is 52.7 kJ/mol below the energy of the reactants (Fig. 62).
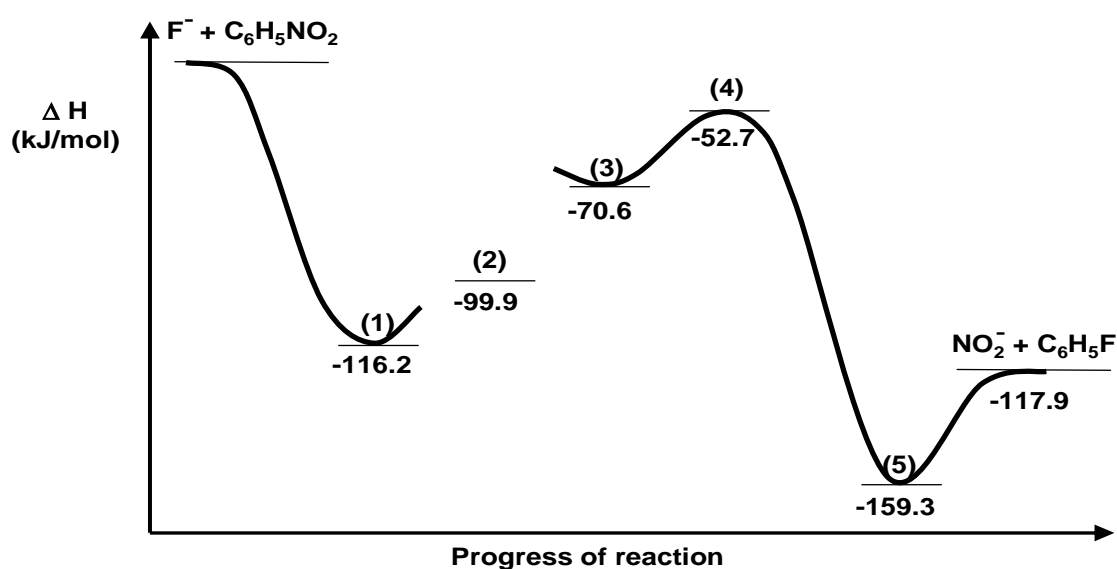
Fig. 62. Energy profile for the gas phase reaction of fluoride ion with nitrobenzene[95].

The gas phase investigation clearly demonstrates that reaction of fluoride ion with nitrobenzene is intrinsically very fast. The fraction of collisions that yields products has been estimated to be 69 % which is far more than in most known reactions.

In contrast to nitrobenzene the Meisenheimer complex between fluorobenzene and fluoride ion (**4'**) is found to be a local minimum by theoretical calculations[104]. Again an ion molecule complex (**1'**) was found to be lowest in energy. In this case the ion molecule complex (**3'**) (where fluoride ion is loosely bound to the ipso carbon) is a transition state. The energy profile for the reaction between fluorobenzene and fluoride ion is illustrated in Fig. 63.
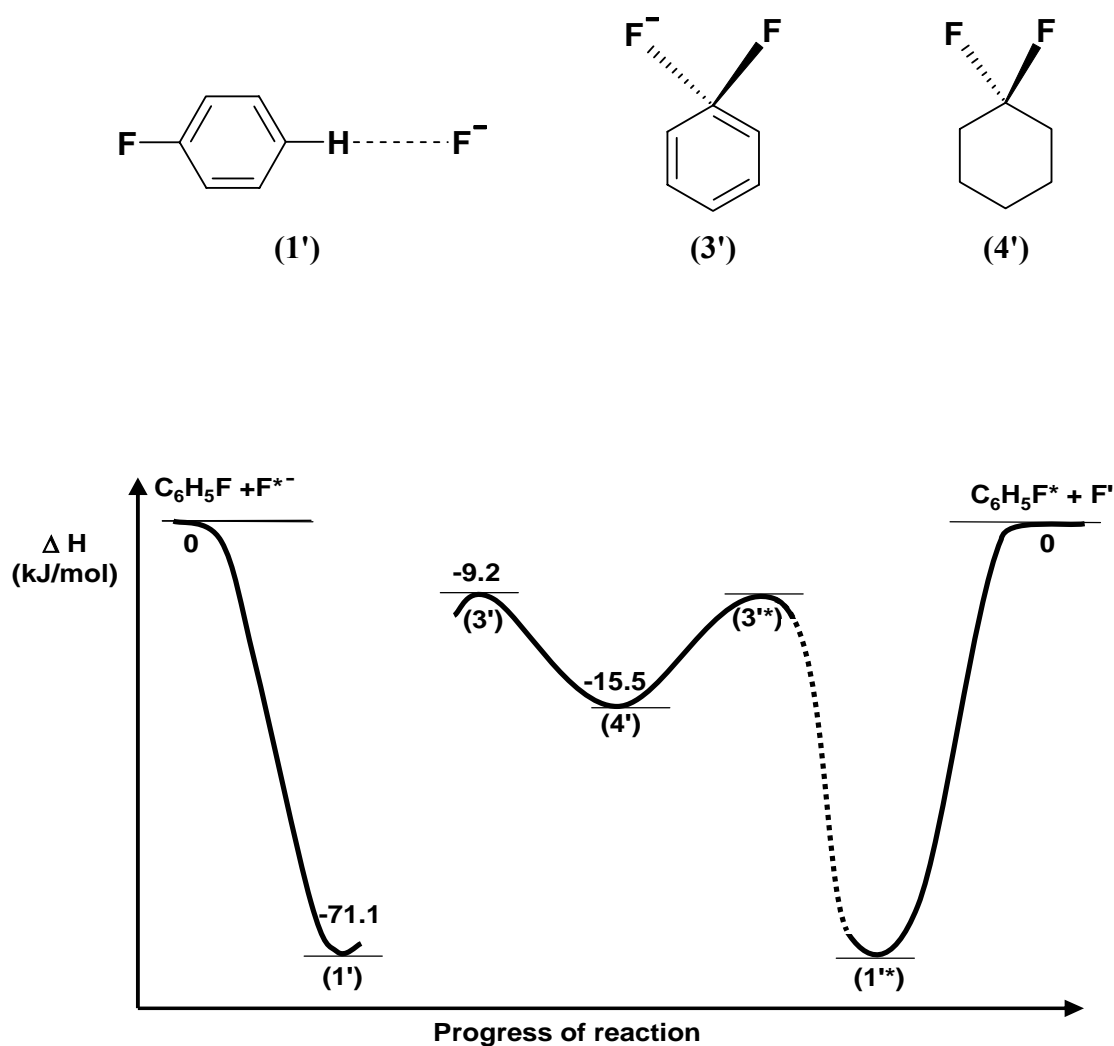
Fig. 63. Energy profile for the reaction of fluoride ion with fluorobenzene[104].

The minimum energy barrier between the ion molecule complex $F^{-\cdots}C_6H_5F$ and the transition state is 61.9 kJ/mol. For the substitution reaction of nitrobenzene and fluoride ion this value is 63.5 kJ/mol. With respect to the starting compounds $C_6H_5NO_2$ and C_6H_5F negative barriers for the overall reaction result (i.e. for $C_6H_5NO_2$: –52.7 kJ/mol and for C_6H_5F: –9.2 kJ/mol).

A negative overall barrier seems to be a paradox at first glance. The solution of this paradox is that an ion molecule complex is formed from C_6H_5X and the fluoride ion which is 71.1 kJ/mol (X= F) and 116.2 kJ/mol (X= NO_2), respectively more stable than the isolated reactants C_6H_5X + F^-. The replacement of X^- by F^- starts from this ion molecule complex. Overall, the transition state of the substitution process is placed below the sum of the energies for C_6H_5X and F^-., With respect to C_6H_5X and F^- apparently "negative" energies of activation results. However, this term should be avoided because the negative barrier for the overall process is the result of the exothermic formation of stable ion molecule complex in the gas phase prior to the substitution process.

In solution the PES profile may be modified to some extent. The major changes to be expected are strong ion-dipole interactions between the small F^- ion and the dipolar solvents such as DMF. It seems possible that this stabilises the starting material more than the formation of the ion molecule complexes (**1**, **1'**). Thus, it seems unlikely that in aprotic dipolar solvents the overall barrier for substitution will be negative (see Fig 64).
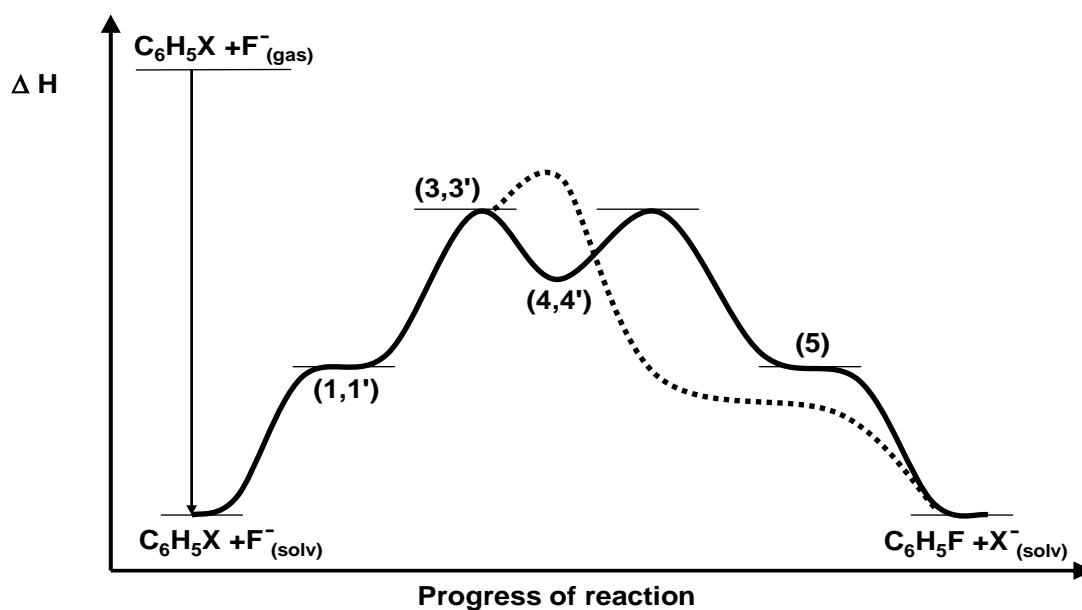
Fig. 64. Hypothetically PES for the reaction $C_6H_5X + F^-$ in aprotic dipolar solvents. (Continuos line: X= F, dotted line: X= NO_2. For structures of intermediates, see the text).

The high efficiency of the overall process and, thus, the discussed gas-phase mechanism may still be valid. The labelling reactions with [18F]fluoride are performed using potassium as a counter ion and phase transfer catalysts thus assuming to deal with "naked" [18F]fluoride ions. That hypothesis could explain the small E_{act} values experimentally determined in this work when DMF was used as a solvent.

4   EXPERIMENTAL SECTION

4.1   Chemicals

Chemicals for synthesis and labelling of precursors were obtained from the following companies: Aldrich (Germany), Sigma (Germany), Riedel-de Haën (Germany), Fluka (Germany), Merck (Germany), Lancaster (England), ABCR (England). Tab. 32 gives the commercial source and the purity of these chemicals.

Tab. 32. Chemicals used in this study and their commercial sources. (CS: Commercial Source, A: Aldrich, B: ABCR, F: Fluka, L: Lancaster, M: Merck, R: Riedel-de Haën)

Substance	CS	Purity (%)	Substance	CS	Purity (%)
o-Vanillin	F	> 99	6-Nitropiperonal	A	97
Potassium bromide	F	> 99	6-Nitroveratraldehyde	B	96
Dimethylsulfate	F	> 99	6-Choroveratraldehyde	L	98
Benzoylchloride	F	> 98	6-Bromoveratraldehyde	B	98
Benzenesulfonyl chloride	F	> 97	Potassium carbonate	M	99
Acetic acid	F	> 99	Kryptofix [2.2.2]®	M	99
Acetic acid anhydride	F	100	N-Formyl piperidine	A	99
2,3-Dimethoxy benzaldehyde	F	> 97	2,4-Dimethoxy benzaldehyde	F	> 97
2,5-Dimethoxy benzaldehyde	F	98	3,5-Dimethoxy benzaldehyde	F	97
Bromine	F	> 99	4-Fluoroveratrole	L	97
Ethyleneglycol	R	> 99	Butyllithium (2.5 M solution in hexane)	F	97
Toluene-4-sulfonic acid monohydrate	F	~99	Lithium chloride	F	> 99
DMF (dry)	F	100	THF (dry)	F	100
DMSO (dry)	F	100	Methanol (dry)	F	100
DMAc (dry)	F	100	Sulfolane (dry)	A	100
6-Bromopiperonal	B	98	6-Chloropiperonal	L	98
NBS	F	> 97	Potassium hydroxide	M	98

4.2 Analyses

Mass spectra were obtained by using the following devices: EI-MS: Finnigan TSQ 70 e.V. (200 °C), FAB-MS: Finnigan 711A 8(kV), modified by AMD. Unless otherwise stated, the method is always EI. Unless it is the molecular ion peak, important peaks (more than 10 %) are only reported.

IR spectra were carried out on Perkin-Elmer spectrum-one FT-IR spectrometer. Important peaks are only reported in cm^{-1}.

^{1}H NMR, ^{13}C NMR and ^{19}F NMR were carried out on Bruker DRX-250 spectrometer operating at 250 MHz. ^{1}H NMR and ^{13}C NMR chemical shifts (δ) were calibrated against the deuterated solvent (CDCl$_3$ unless otherwise stated) multiplet and referenced to TMS. ^{19}F NMR were measured also in CDCl$_3$ and the data (δ) are reported relative to the standard CFCl$_3$.

Melting points (°C) were measured using Gallenkamp device and were uncorrected.

Chromatography i.e. TLC was performed on silica gel plates (Polygram® Silica G/UV$_{254}$, 8 X 4 cm, Macherey Nagel, Germany) and eluted with 1:1 or 1:2, ethylacetate / petroleum ether (v/v). HPLC was carried out by use of a Hewlet Packard Model 1050 equipped with a NaI(Tl)-scintillation detector and a UV detector (254 nm) .

4.3 Production of [^{18}F]Fluoride

No-carrier-added (nca) [^{18}F]Fluoride was produced at the cyclotron (PETtrace, GE Medical Systems, Uppsala) in the PET-Center, Tübingen, via the ^{18}O(p,n)^{18}F reaction by irradiating 1.60 ml of >95 % enriched [^{18}O]water with 16.5 MeV protons. Activities were in the range between 10 and 20 GBq out of which 10 to 100 MBq were used for each labelling process. No kind of quality control was made for the resulting [^{18}F]fluoride solution.

4.4 Labelling with [^{18}F]Fluoride

The activity was transferred into a 5.0 mL sealed vial containing 50 µL of 0.50 M K$_2$CO$_3$ and 15 mg Kryptofix 222$^®$. The ^{18}F-fluoride solution was dried for 20 min under a mild stream of argon (ca. 2 mL/min) at 140 ^{o}C by azeotropic distillation with acetonitrile (2 x 1mL) and finally a dry residue of the complex [K/222]$^{+18}$F$^-$ remained as a white solid.

The required quantity of the precursor in 1.0 mL (< 0.05 % H$_2$O) solvent was added as a solution into the vial with the [K/222]$^{+18}$F$^-$ complex. Then the vial, equipped with a screw cap and a silicone septum, was tightly closed and kept heated at the required temperature. TLC samples were withdrawn (1-5 µL) for the determination of the RCY at the required time (5, 10, 20, 30 and 60 min for some precursors and only at fixed time for others).

4.5 Analytical Assay

Product solutions were analyzed by thin layer chromatography (TLC) using the silica gel plates described above. The non-radioactive fluoro-compound was used as a standard on the same TLC plate, and the spot was marked within light of 254 nm UV lamp. The radioactive spots were assessed quantitatively by means of an InstantImager (Canberra Packard, electronic autoradiography). Size of the TLC plate was made visible by radioactivity spotes, thus correlation between radioactive and nonradioactive spots was assured.

High performance liquid chromatography (HPLC) was used for additional identification of the labelled product (in case of availability of standards). HPLC was carried out by means of a Hewlet Packard Model 1050 equipped with a NaI(Tl)-scintillation detector and a UV detector (254 nm) for identification and purity control. A Phenomenex, Luna (5µ C 18, 250 mm x 10 mm) column with a flow rate of 2 mL/min was used. The eluent mixture was acetonitrile/water (30/70, v/v). In some cases a gradient was used starting from 97 % water up to 3 %.

4.6   Synthesis of Phenols and Catechols

4.6.1   6-Bromo-2-hydroxy-3-methoxybenzaldehyde (**14**)

2-Acetoxy-3-methoxybenzaldehyde (12)

Prepared according to literature[55]. A solution of 50.0 g (0.33 mol) of *o*-vanillin (**11**) in 50 mL pyridine and 35 mL (0.34 mmol) of acetic anhydride was stirred at room temperature for 24 h to give a white precipitate. The mixture was transferred to a flask containing 300 mL of 6 N HCl solution. The solid product was collected by filtration and washed with additional (500 mL) 6 N HCl solution followed by distilled water. Recrystallization from methanol gave white crystals : 63 g (98 %), mp 73-75 °C [lit[65] 75 °C].

^{1}H NMR: 10.12 (s, 1 H), 7.28-7.55 (m, 3 H), 3.89 (s, 3 H), 2.39 (s, 3 H).
^{13}C NMR: 19.2, 55.2, 117.0, 120.3, 125.9, 128.4, 140.7, 167.8, 187.8.
Ms (m/z): 152 (M$^+$, 100 %), 136, 122, 106, 81, 52, 43 .
IR: 1763, 1694, 1680, 1580, 1484, 1441, 1404, 1372, 1319, 1275, 1253, 1211, 1201, 1149, 1082, 1064, 1046, 1013, 901, 826, 780, 767, 669.

2-Acetoxy-6-bromo-3-methoxybenzaldehyde (13)

Prepared according to literature[55]. Compound (**12**) (50.0 g, 0.26 mol) was added in small portions to a solution of 100 g of KBr and 15 mL of bromine in 1.0 L of distilled water. The mixture was stirred for 3 h and the resulting precipitate collected by filtration. The crude product (pinkish solid) was recrystallized from diisopropyl ether to give white crystals.

Yield: 57.5 g (96%), mp 121 °C [lit.[66] 119-120 °C].

^{1}H NMR: 10.23 (s, 1 H), 7.00 (d, 1 H), 7.45 (d, 1 H), 3.82 (s, 3 H), 2.34 (s, 3 H).
^{13}C NMR: 190.3, 168.7, 151.9, 141.0, 131.5, 126.6, 117.8, 116.4, 55.5, 20.5.
Ms (m/z): 272/274 (M$^+$, 4 %), 230/232 (100 %), 201/203, 184/186, 105, 107, 94, 79, 51, 43.
IR: 1760, 1693, 1570, 1465, 1439, 1399, 1371, 1296, 1266, 1175, 1077, 1013, 942, 915, 814, 755, 718, 663.

6-Bromo-2-hydroxy-3-methoxybenzaldehyde (14)

Prepared according to literature[55]. Compound (13) (50.0 g, 0.18 mol) was suspended in 1.5 L

of 6 N HCl and stirred for 6 h at 50 °C. The yellow precipitate obtained was collected by

filtration and recrystallized from isopropyl ether to give yellow crystals.

Yield: 34 g (80 %), mp 104-106 °C [lit.[66] 105-106 °C].

^{1}H NMR: 12.19 (s, 1 H), 10.19 (1 H), 6.99 (d, 1 H), 6.84 (d, 1 H), 3.81 (s, 3 H).
^{13}C NMR: 198.8, 154.8, 148.8, 123.8, 118.5, 117.6, 116.8, 56.7.
Ms (m/z): 230/232 ([M]$^+$/[M+2]$^+$, 100 %), 201, 184/186, 152, 133, 107, 94, 79, 51, 43.
IR: 1634, 1579, 1460, 1423, 1299, 1246, 1080, 948, 886, 809.

4.6.2   2,3-Dibromo-6-hydroxy-5-methoxybenzaldehyde (29)

Prepared according to literature[75]. To a stirred solution of compound (12) (5 g, 25.7 mmol)

in glacial acetic acid (30 mL) containing a small amount of iron powder (0.25 g) was added

bromine (3.0 mL) in glacial acetic acid (30 mL) dropwise. It was stirred further for 5 h at

room temperature, allowed to stand overnight, diluted with water (150 mL), and extracted

with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ layer was washed with 5% sodium thiosulfate, dried (MgSO$_4$) and

evaporated to yield a yellow solid which was recrystallized from isopropyl ether to give

yellow crystals.

Yield: 7.1 g (89 %), mp 144-146 °C [lit.[75] Reported without mp].

^{1}H NMR: 12.47 (s, 1 H), 10.32 (m, 1 H), 7.16 (s, 1 H), 3.89 (s, 3 H).
^{13}C NMR: 199.2, 154.0, 148.8, 121.5, 118.6, 118.4, 115.1, 56.6
Ms (m/z): 308/310/312 ([M]$^+$/([M+2]$^+$/([M+4]$^+$, 100 %), 279, 262/264/266, 230/232, 214/216, 185/187, 157/159, 129/131, 107, 77, 79.
IR: 1643, 1570, 1453, 1433, 1399, 1294, 1270, 1245, 955, 873, 766.

4.6.3   6-Bromo-2,3-dihydroxybenzaldehyde (32)

Prepared according to literature[77]. To a stirred solution of BBr$_3$ (1.87 g, 7.5 mmol) in CH$_2$Cl$_2$

(15 mL) under nitrogen there was added a solution of compound (14) (1.22 gm, 5 mmol) in

CH$_2$Cl$_2$ (5 mL) dropwise at 25 °C over 30 min. The mixture was stirred for 5 h and left to

stand in open air for 24 h. Water (25 mL) was then added and the organic layer then

separated, washed with water, dried (MgSO₄) and evaporated to yield a yellow solid which

was recrystallized from toluene to give yellow needles (1 g, 87 %), mp 143-145 °C [lit [77]

142-145 °C].

¹H NMR (DMSO, d6): 11.76 (s, 1 H), 10.29 (s, 1 H), 10.0 (s, 1H), 7.11, 7.09 (dd, dd, 2 H).
¹³C NMR (DMSO, d6): 197.1, 152.2, 146.1, 123.8, 122.5, 117.7, 113.6.
Ms (m/z): 216/218 ([M]⁺/([M+2]⁺, 100 %), 198/200, 184/186170/172, 159/161, 107, 91, 79.
IR: 3382, 1632, 1432, 1379, 1267, 1192, 1012, 891, 814, 715.

4.6.4   2-Hydroxy-3-methoxy-6-nitrobenzaldehyde (18)

3-Methoxybenzaldehyde-2-benzenesulfonate (16)

Prepared according to literature[56]. A solution of *o*-vanillin (5.0 g, 32.9 mmol) in distilled

water (33.5 mL) containing potassium hydroxide (2.0 g, 33.3 mmol) was treated with

benzenesulfonyl chloride (5 mL, 39.3 mmol) dropwise over a period of 30 min. CH₂Cl₂

(1 mL) was then added and the mixture was stirred overnight. The resultant solid was

extracted with CH₂Cl₂ (3 x 50 mL) and the organic layer washed with water (200 mL) and

with 5 % KOH (100 mL). The solvent was dried *in vacuo* to give a brown solid which needed

no further purification and was suitable for the next step.

Yield: 11.5 g (94 %). Mp 117-119 °C [lit.[67] 119-120 °C].

¹H NMR: 10.12 (s, 1 H), 7.07-7.91 (m, 8 H), 3.53 (s, 3 H).
¹³C NMR: 187.9, 152.5, 140.6, 135.9, 134.4, 131.3, 129.1, 128.6, 128.0, 119.6, 118.0, 55.9.
Ms (m/z): 292 (M⁺, 15 %), 167, 151 (100%), 141, 123, 108, 93, 77.
IR: 1697, 1578, 1479, 1446, 1371, 1277, 1246, 1197, 1190, 1151, 1064, 905, 853, 162, 753.

3-Methoxy-6-nitrobenzaldehyde-2-benzenesulfonate (17a)

Prepared according to literature[56]. Aldehyde (16) (20 g, 68.5 mole) was added to 90 % nitric

acid (44 mL) with temperature maintained between −10 and 0° over a period of 30 min. The

reaction mixture was stirred an additional hour, poured cautiously on ice-water mixture (250

mL) and stirred for further 2 h. The white solid was collected by filtration and washed with

water (200 mL). It was refluxed in acetone (150 mL) for 30 min, concentrated to 20 mL and

cooled to 0 °C. The resultant solid was collected by filtration and washed with cold acetone

(10 mL) to give pure product as white crystals.

Yield: 16.2 g (70 %), mp 144-146 °C [lit.[68] 145 °C].

^{1}H NMR (acetone d6): 10.12 (s, 1 H), 8.17 (d, 1 H), 8.13 (d, 1 H), 7.55-7.94 (m, 5 H), 3.72 (s, 3 H).
^{13}C NMR (acetone d6): 188.8, 158.3, 147.5, 136.3, 135.8, 134.7, 132.3, 129.3, 128.5, 118.8, 114.0, 57.2.
Ms (FAB, m/z): 338 ([M+1]$^+$, 42 %), 80, 179, 141, 123, 106, 77.
IR: 1697, 1578, 1516, 1479, 1448, 1431, 1375, 1346, 1322, 1289, 1193, 1169, 1088, 1067, 993, 952, 914, 834, 822, 775, 757, 737, 691.

3-Methoxy-4-nitrobenzaldehyde-2-benzenesulfonate (17b)

Prepared as a by-product with compound (17a) in not more than 25 %. Colorless crystals.

Mp 93-95 °C.

^{1}H NMR: 10.13 (s, 1 H), 7.78 (d, 1 H), 7.66 (d, 1 H), 7.56-7.75 (m, 7 H), 3.72 (s, 3 H).
^{13}C NMR: 192.9, 148.0, 147.7, 146.0, 135.4, 134.9, 134.3, 129.6, 128.5, 123.2, 122.9, 62.7.
Ms (m/z): 337 (M$^+$, 5 %), 320, 196, 141 (100 %), 125, 107, 77.
IR: 1703, 1583, 1532, 1446, 1418, 1388, 1364, 1266, 1201, 1184, 1169, 1090, 1024, 997, 906, 820, 769, 745, 732, 702, 686.

2-Hydroxy-3-methoxy-6-nitrobenzaldehyde (18)

Prepared according to literature[56]. Compound (17a) (12.1 g, 30.6 mmol) was added to

methanol (160 mL) and the mixture was heated with vigorous stirring. NaOH (6 g) in distilled

water (6 mL) was added dropwise maintaining reflux temperature. An orange precipitate

formed which interfered with stirring. The reaction was heated to reflux for an additional 1 h.

The solid was collected by filtration, washed with methanol and acetone and air dried. The

solid was dissolved in distilled water and treated with concentrated hydrochloric acid

dropwise until a yellow solid is formed (pH 3-5). Mp 104-106 °C [lit.[68] 104 °C].

^{1}H NMR: 12.55 (s, 1 H), 10.47 (s, 1 H), 7.70 (dd, 1 H), 7.04 (dd, 1 H), 3.99 (s, 3 H).
^{13}C NMR: 194.9, 153.6, 142.5, 117.9, 113.6, 113.1, 112.9, 56.7
Ms (m/z): 197 (M$^+$, 56 %), 167, 152, 135, 123, 121, 106, 96, 81, 65, 51.
IR: 1646, 1573, 1509, 1473, 1429, 1393, 1321, 1250, 1199, 1182, 1071, 972, 935, 840, 813, 765, 727, 676.

4.6.5   6-Fluoro-2-hydroxy-3-methoxybenzaldehyde (**40**)

6-Fluoro-2,3-dimethoxybenzaldehyde (39)

Prepared according to literature[57]. Butyl lithium (2.5 M) in hexane (27.2 ml, 68.1 mmol) was added slowly (20 min) to a solution of 4-fluorovertratole (**38**) (10.8 g, 61.9 mmol) in 220 mL of dry THF at –65 °C under nitrogen. The solution was stirred at –65 °C for 30 min. DMF (5.3 mL, 68.1 mmol) was added dropwise to the solution . The mixture was allowed to warm up to room temperature, poured onto ice (500 mL) and extracted with ether. It was washed with saturated NaCl solution, dried (MgSO$_4$) and evaporated to give a colorless oil which solidify on standing in the refrigerator for several days.

Yield: 74 %. Mp 48-50 °C [lit.[57] reported without mp].

^{1}H NMR: 10.26 (s, 1 H), 6.42-7.01 (m, 2 H), 3.85 (s, 3 H), 3.70 (s, 3 H).
^{13}C NMR: 187.3, 157.9, 153.8, 149.3, 118.2, 110.5, 61.9, 56.2.
^{19}F NMR (400 MHz, CDCl$_3$): -126.3 (s, 1 F).
Ms (m/z): 184 ([M]$^+$, 100 %), 169, 166, 154, 141, 138, 126, 123, 113, 95, 83, 77, 65.
IR: 1687, 1604, 1582, 1488, 1450, 1392, 1273, 1255, 1236, 1195, 1081, 1046, 961, 870, 817.

6-Fluoro-2-hydroxy-3-methoxybenzaldehyde (40)

Compound (**39**) (1 g, 5.4 mmol) and LiCl (0.76g, 18 mmol) were heated in boiling DMF (10 mL) and the reaction was continued for 24 h. After this, 10 % NaOH (30 mL) was added. The mixture is washed with ether (2 x 25 mL) and then acidified with 10 % HCl (50 mL) and extracted with ether (2 x 25 mL). The solvent was evaporated and the residue purified through a silica column with the mobile phase as 10 % ethyl acetate in petroleum ether.

Yield: 74 %. Yellow solid. Mp 143-145 °C.

^{1}H NMR: 11.67 (s, 1 H), 10.20 (s, 1 H), 7.00 (d, 1 H), 6.55 (d, 1 H), 3.84 (s, 3 H).
^{13}C NMR: 192.6, 160.0., 156.0, 152.7, 144.8, 119.3, 110.7, 104.4, 56.8.
Ms (m/z): 170 (M$^+$, 100 %).
IR: 1644, 1586, 1466, 1409, 1326, 1275, 1226, 1187, 1114, 1001, 955, 843, 632.

4.6.6   2-Bromo-4-hydroxy-5-methoxybenzaldehyde (7a)

4-Acetoxy-3-methoxybenzaldehyde (5)

Prepared similarly to (12) starting from vanillin (4). Recrystallization from diisopropylether

gave white crystals: 63 g (98 %), mp 77-78 °C [lit.[61] 77-78 °C].

^{1}H NMR: 9.91 (s, 1 H), 7.46 (dd, 1 H), 7.21 (dd, 1 H), 3.88 (s, 3 H), 2.31 (s, 3 H).
^{13}C NMR: 191.0, 168.3, 152.0, 145.0, 135.3, 124.7, 123.5, 111.0, 56.1, 20.6.
M (m/z): 152 ([M]$^+$, 100 %), 151, 137, 123, 109, 95, 81, 65, 51, 43.
IR: 1747, 1687, 1677, 1597, 1505, 1470, 1425, 1393, 1374, 1331, 1277, 1204, 1153, 1123, 1032, 1013, 905, 1013, 905, 861, 829, 796, 737, 680.

4-Acetoxy-2-bromo-3-methoxybenzaldehyde (6)

Prepared similarly to (13) starting from vanillin acetate (5). Recrystallization from

diisopropylether gave white crystals. Yield: 90 %, mp 109-110 °C [lit.[62] 109-110 °C].

^{1}H NMR: 10.25 (s, 1 H), 7.50 (s, 1 H), 7.34 (s, 1 H), 3.87 (s, 3 H), 2.31 (s, 3H).
^{13}C NMR: 190.8, 167.9, 151.4, 145.1, 131.7, 128.0, 117.9, 112.2, 56.3, 20.5.
Ms (m/z): 272/274 ([M]$^+$/[M +2]$^+$, 8 %), 230/232 (100 %), 201/203, 187/189, 159/161, 152, 151, 123, 122, 107, 79, 63, 51.
IR: 1755, 1686, 1593, 1482, 1383, 1364, 1311, 1271, 1212, 1200, 1152, 1040, 1009, 979, 916, 878, 862, 827, 742, 716.

2-Bromo-4-hydroxy-5-methoxybenzaldehyde (7a)

Prepared similarly to (14) starting from compound (6). Recrystallization from

diisopropylether gave white crystals: yield: 77 %. Mp 104-106 °C [lit.[62] 104-104.5 °C].

^{1}H NMR: 10.05 (s, 1 H), 7.34 (s, 1H), 7.08 (s, 1H), 3.86 (s, 3H).
^{13}C NMR: 189.3, 153.0, 147.3, 125.0, 119.2, 119.0, 110.5, 55.2.
Ms (m/z): 230/232 ([M]$^+$/[M+2]$^+$, 100 %), 215/217, 201/203, 187/189, 159/161, 152, 151, 123, 122, 107, 94, 79, 63, 51.
IR: 3149, 1655, 1595, 1566, 1507, 1401, 1266, 1202, 1149, 1042, 981, 866, 733, 691.

4.6.7   3-Bromo-4-hydroxy-5-methoxybenzaldehyde (7b)

Prepared similar to (29) starting from vanillin (4). White solid, yield: 75 %, mp 166-168 °C

[lit.[63] 166-169 °C].

^{1}H NMR: 9.82 (s, 1 H), 7.55 (s, 1 H), 7.33 (s, 1 H), 3.88 (s, 3 H).
^{13}C NMR: 189.4, 154.2, 148.3, 132.0, 128.6, 115.1, 109.3, 56.0
M (m/z): 230/232 ([M]$^+$/[M+2]$^+$, 100 %), 215/217, 201/203, 187/189, 159/161, 15, 122, 79.
IR: 32701672, 1579, 1499, 1462, 1447, 1422, 1404, 1352, 1288, 1145, 1044, 970, 853, 830.

4.6.8   4-Methyl-5-nitrocatechol (<u>54</u>)

Prepared according to literature[89]. 4-Methylcatechol (<u>53</u>) (2.0 g) and NaNO$_2$ (3.0 g) were dissolved in water (100 mL). The solution was cooled down to - 10 °C. H$_2$SO$_4$ (25 mL, 20 %) was then added very slowly to the mixture with good stirring. The solution was stirred for 4 h at 0 °C. The resulting solid was then collected by filtration and washed thoroughly with water. Recrystallization from methanol gave brown crystals.

Yield: 65 %, mp 180-183 °C [lit[89] 180-182 °C].

^{1}H NMR (acetone d6): 7.61 (s, 1 H), 6.91 (s, 1 H), 2.44 (s, 3 H).
^{13}C NMR (acetone d6): 151.3, 144.0, 144.9, 128.2, 119.0, 112.7, 20.5.
Ms (m/z): 169 ([M]$^+$, 48 %), 152 (100 %), 138, 124, 106, 96, 83, 77, 68, 51, 39.
IR: 3435, 3186, 1638, 1587, 1523, 1493, 1429, 1361, 1318, 1277, 1227, 1184, 1144, 1045.

4.7   Synthesis of Haloaryl Precursors

4.7.1   General Method for Halogenation with NBS or NCS

Halogenations with NXS (X= Br, Cl) are successful only for electron-rich (activated) aromatic rings. A general procedure for bromination with NBS involves the following. To a solution of the proper compound (15 mmol) in DMF (73 mL) is added dropwise NBS (3.92 g, 22 mmol) in DMF (100 mL) within 30 min. After 48 h, the solution is poured onto ice and water (500 mL). The resulting precipitate is collected by filtration and washed thoroughly with water. The same procedure is used for chlorination with NCS using 2.94 g (22 mmol).

4.7.2   Haloaryl Precursors by Halogenation with NBS or NCS

4.7.2.1   6-Bromo-2,3-dimethoxybenzaldehyde (<u>23a</u>)

Prepared from 2,3-dimethoxybenzaldehyxde (<u>22</u>) and recrystallized from diisopropylether.

White crystals. Yield: 78 %, mp 77-78 °C [lit.[71] 77-78 °C].

^{1}H NMR: 10.24 (s, 1 H), 7.23 (d, 1 H), 7.9 (d, 1 H), 3.80 (s, 3 H), 3.78 (s, 3 H).
^{13}C NMR: 190.4, 152.7, 152.0, 129.2, 128.4, 117.5, 112.5,. 62.2, 56.1.
Ms (m/z): 244/246 ([M]$^+$/([M+2]$^+$, 100 %), 229/231, 214/216, 198/200, 166, 148, 122.
IR: 1685, 1570, 1468, 1432, 1388, 1296, 1264, 1234, 1056, 990, 922, 813, 770, 665.

4.7.2.2   6-Chloro-2,3-dimethoxybenzaldehyde (<u>23b</u>)

Prepared from 2,3-dimethoxybenzaldehyxde (<u>22</u>) and recrystallized from diisopropylether.

White crystals, yield: 69 %, mp 72-74 °C.

^{1}H NMR: 10.43 (s, 1 H), 7.12 (d, 1 H), 7.04 (d, 1 H), 3.93 (s, 3 H), 3.84 (s, 3 H).

^{13}C NMR: 189.5, 152.2, 127.5, 126,1, 125.8, 117.8, 117.3, 62.3, 56.5.

Ms (m/z): 200/202 ([M]$^+$/([M+2]$^+$, 100 %).

IR: 1689, 1574, 1470, 1434, 1393, 1298, 1267, 1236, 1177, 1060, 995, 931, 816, 772, 666.

4.7.2.3   2-Bromo-4,5-ethylenedioxybenzaldehyde (<u>37b</u>)

Prepared from 3,4-ethylenedioxybenzaldehyxde (<u>36</u>) and purified by MPLC. White solid,

yield: 78 %, mp 146-149 °C [lit.[79] 149-150 °C].

^{1}H NMR: 10.43 (s, 1 H), 7.42 (s, 1 H), 7.06 (s, 1 H), 4.20 (t, 2 H), 4.08 (t, 2 H).
^{13}C NMR: 191.0, 153.1, 144.6, 128.4, 121.1, 119.3, 114.4, 63.6, 62.
Ms (m/z): 242/244 ([M]$^+$/([M+2]$^+$, 100 %).
IR: 1686, 1580, 1550, 1483, 1455, 1437, 1415, 1367, 1353, 1290, 1242, 1174, 1065, 935, 912, 892, 852, 826, 700.

4.7.2.4   2-Bromo-3,4,5-trimethoxybenzaldehyde (<u>46</u>)

Prepared from 3,4,5-trimethoxybenzaldehyde (<u>44</u>) and purified by MPLC. White-pinkish

crystals, yield: 83 %, mp 68- 71°C [lit [85] 67-69].

^{1}H NMR: 10.38 (s, 1 H), 7.21 (s, 1 H), 4.05 (s, 3 H), 3.84 (s, 3 H), 3.80 (s, 3 H).
^{13}C NMR: 189.5, 153.2, 150.1, 147, 9, 130.8, 111.5, 110.1, 61.4, 60.6, 56.9.
Ms (m/z): 274/276 ([M]$^{+}$, 100 %), 259/261, 231/233, 203/205, 188/190, 180, 165, 152, 147, 124, 109, 103, 77, 50, 40.
IR: 1683, 1577, 1563, 1470, 1449, 1383, 1314, 1197, 1164, 1103, 1044, 1000, 980, 920, 859.

4.7.3   General Method for Bromination with Br$_2$/CH$_3$COOH

A general procedure for bromination with this reagent involves the following. The proper compound (18 mmol) is dissolved in glacial acetic acid (20 mL). To this solution there is slowly added a solution of bromine (3 g) in glacial acetic acid (4 mL) with good stirring. The temperature is maintained at 20 °C for 2 d. The solution is then poured onto water (100 mL) and the precipitate collected by filtration and washed thoroughly with water and with 5 % Na$_2$S$_2$O$_3$ solution.

4.7.4   Haloaryl Precursors by Bromination with Br$_2$/CH$_3$COOH

4.7.4.1   5-Bromo-2,3-dimethoxybenzaldehyde (24a)

Prepared from 2,3-dimethoxybenzaldehyxde (22) and recrystallized from methanol. White crystals. Yield: 80 %, mp 80-82 °C [lit.[72] 81 °C].

^{1}H NMR: 10.22 (s, 1 H), 7.23 (s, 1 H), 7.43 (s, 1 H), 3.91 (s, 3 H), 3.89 (s, 3 H).
^{13}C NMR: 190.1, 152.2, 149.8, 126.4, 128.6, 119.2, 117.5, 60.6, 56.3.
Ms (m/z): 244/246 ([M]$^{+}$/([M+2]$^{+}$, 100 %), 226/228, 215/217, 198/200, 185, 170, 148, 135, 121, 107, 94, 79, 77, 51.
IR: 1677, 1576, 1479, 1444, 1394, 1316, 1264, 1239, 1218, 1191, 1073, 987, 929, 852, 775.

4.7.4.2   5-Bromo-2,4-dimethoxybenzaldehyde (26)

Prepared from 2,5-dimethoxybenzaldehyxde (25). White solid. Yield: 73 %, mp 135-136 °C [lit.[73] 134-138 °C].

^{1}H NMR: 10.00 (s, 1 H), 7.80 (s, 1 H), 6.49 (s, 1 H), 3.95 (s, 3 H), 3.80 (s, 3H).
^{13}C NMR: 189.4, 154.8, 150.0, 133.2, 122.3, 104.6, 99.1, 57.2, 55.6.
Ms (m/z): 244/246 ([M]$^{+}$/([M+2]$^{+}$, 100 %), 229/231, 214/216, 198/200, 166.
IR: 1663, 1593, 1487, 1463, 1434, 1397, 1369, 1320, 1275, 1209, 1165, 1149, 1051, 1018, 912, 878, 850, 813, 714, 685.

4.7.4.3   4-Bromo-2,5-dimethoxybenzaldehyde (**28**)

Prepared from 2,5-dimethoxybenzaldehyxde (**27**) and recrystallized from methanol. White crystals. Yield: 80 %, mp 121-122 °C [lit.[74] 122-124 °C].

^{1}H NMR: 10.41 (s, 1 H), 7.30 (s, 1 H), 7.01 (s, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H).
^{13}C NMR: 190.3, 152.44, 154.0, 1247.1, 117.2, 116, 57.7, 56.3.
Ms (m/z): 244/246 ([M]$^+$/([M+2]$^+$, 100 %), 229/231, 198/200, 186, 174, 157, 148, 135, 107.
IR: 1676, 1598, 1483, 1448, 1392, 1272, 1250, 1211, 1183, 1018, 968, 880, 717.

4.8   Synthesis of Nitroaryl Precursors

4.8.1   General method for nitration with HNO$_3$

Direct nitration with HNO$_3$ (50-60 %) was successful for most activated (S$_N$Ar) precursors in cold (0 °C) within short time (30-60 min). A general procedure for nitration with this reagent involves the following. One part of the compound is dissolved slowly in 20 parts of nitric acid (50-60 %) at 0 °C under good stirring. The temperature is kept at 0 °C for 30 min then at RT for another 30 min. The solution is poured then cautiously onto ice and water. The resulting precipitate is collected by filtration and thoroughly washed with water and 5 % K$_2$CO$_3$ to remove traces of the acid.

4.8.2   Nitroaryl Precursors by Nitration with HNO$_3$

4.8.2.1   2,3-Dimethoxy-5-nitrobenzaldehyde (**24b**)

Prepared from 2,3-dimethoxybenzaldehyxde (**22**) and recrystallized from diisopropylether. White crystals, yield: 76 %, mp 115-117 °C [lit.[72] 115 °C].

^{1}H NMR: 10.09 (s, 1 H), 8.21 (s, 1 H), 8.10 (s, 1 H), 4.00 (s, 3 H), 3.71 (s, 3 H).
^{13}C NMR: 187.9, 155.7, 151.8, 146.4, 125.3, 120.4, 113.3, 60.6, 56.2.
Ms (m/z): 211 ([M]$^+$, 100 %), 193 (95 %), 182, 165 (50 %), 150, 135, 121, 107, 99, 79, 77.
IR: 1685, 1583, 1515, 1481, 1433, 1352, 1334, 1276, 1243, 1183, 1089, 1066, 978, 950, 927, 895, 797, 776, 758, 742, 704.

4.8.2.2   3-Bromo-5,6-dimethoxy-2-nitrobenzaldehyde (**31**)

Prepared from 5-bromo-2,3-dimethoxybenzaldehyxde (**24a**) and recrystallized from aqueous

ethanol. White crystals, yield: 69 %, mp 141 °C [lit.[75] 141 °C].

^{1}H NMR: 10.25 (s, 1 H), 7.29 (s, 1 H), 4.02 (s, 3 H), 3.97 (s, 3 H).
^{13}C NMR: 189.5, 154.4, 147.8, 144.6, 131.6, 121.9, 120.2, 62.8, 56.4.
Ms (m/z): 289/291 ([M]$^{+}$/[M+2]$^{+}$, 40 %), 272/274 (100 %), 259/261, 244/246, 218, 216, 203, 179, 165, 157, 137, 121, 93, 77.
IR: 1695, 1574, 1541, 1478, 1429, 1387, 1361, 1317, 1266, 1238, 1182, 1077, 1018, 957, 893, 854, 808, 765, 729, 670.

4.8.2.3   3,5-Dimethoxy-2-nitrobenzaldehyde (**35**)

Prepared from 3,5-dimethoxybenzaldehyxde (**34**) and recrystallized from methanol. Yellow

crystals: (yield: 69 %), mp 108-110 °C [lit.[78] 109-110 °C].

^{1}H NMR: 10.49 (s, 1 H), 7.06 (s, 1 H), 6.92 (s, 1 H), 4.06 (s, 1 H), 3.83 (s, 1 H).
^{13}C NMR: 188.8, 157.9, 147.2, 132.4, 121.4, 114.1, 106.9, 56.6, 55.5.
Ms (m/z): 211 ([M]$^{+}$, 50 %), 194, 179, 164, 151, 136, 123, 105, 95, 77, 69.
IR: 1700, 1590, 1529, 1492, 1430, 1386, 1369, 1334, 1311, 1231, 1198, 1185, 1166, 1118, 1112, 852, 831, 775, 735, 695.

4.8.2.4   4,5-Ethylenedioxy-2-nitrobenzaldehyde (**37a**)

Prepared from 3,4-ethylenedioxybenzaldehyde (**36**) and purified by MPLC. Yellow crystals,

yield: 91 %, mp 164-166 °C (dec.) [lit.[38] reported without mp].

^{1}H NMR: 10.41 (s, 1 H), 7.63 (s, 1 H), 7.32 (s, 1 H), 4.45 (t, 2 H), 4.41 (t, 2 H).
^{13}C NMR: 188.8, 150.0, 148.3, 145.0, 126.5, 111.1, 108.5, 64.1, 63.7.
Ms (m/z): 209 ([M]$^{+}$, 9 %), 181, (100 %), 179, 151, 135, 107, 105, 79, 51.
IR: 1679, 1612, 1577, 1512, 1456, 1416, 1237, 1287, 1194, 1153, 1053, 1004, 918, 900, 848.

4.8.2.5   3-Methoxy-2-nitrobenzaldehyde-4-benzenesulfonate (**42e**)

Prepared from vanillinbenzenesulfonate (**42d**) and recrystallized from diisopropylether.

Colorless crystals. Yield: 84 %, mp 133 °C.

^{1}H NMR: 10.12 (s, 1 H), 7.55-7.75 (m, 5 H), 7.84 (d, 1 H), 7.44 (d, 1 H), 3.86 (s, 3 H).
^{13}C NMR: 189.1, 144.1, 141.2, 143.3, 125.7, 128.8, 122.6, 129.6, 129.2-135.0 (5 C), 61.4
Ms(m/z): 337 ([M]$^{+}$, 4 %), 196, 141 (84 %), 125, 107, 77 (100 %).
IR: 1705, 1623, 1566, 1510, 1469, 1433, 1401, 1355, 1316, 1279, 1182, 1099, 994, 933, 845, 822, 776, 747, 666.

4.8.2.6 3,4,5-Trimethoxy-2-nitrobenzaldehyde (**45**)

Prepared from 3,4,5-trimethoxybenzaldehyde (**45**) and purified by MPLC. Yellow solid.

Yield: 45 %, mp 78-80 °C [lit.[84] 80-82 °C].

^{1}H NMR: 9.88 (s, 1 H), 7.02 (s, 1 H), 3.98 (m, 3 H), 3.81 (s, 3 H), 3.79 (s, 3 H).
^{13}C NMR: 188.9, 153.2, 151.6 150.6, 131.0, 127.5, 121.6, 120.0, 116.6, 106.5, 103.5, 90.1, 63.0, 62.7, 56.6.
Ms (m/z): 241 ([M$^+$], 100 %), 211, 196, 181, 153, 137, 125, 109.
IR: 1702, 1583, 1539, 1489, 1458, 1366, 1325, 1307, 1253, 1197, 1114, 1018, 961, 933, 920, 879, 751, 681.

4.8.2.7 2,3,4-Trimethoxy-6-nitrobenzaldehyde (**48**)

Prepared from 2,3,4-trimethoxybenzaldehyde (**47**) and purified by MPLC. Yellow crystals,

yield: 74 %, mp 80-82 °C [lit.[86] 80-82 °C].

^{1}H NMR: 10.24 (s, 1 H), 7.30 (s, 1 H), 3.98 (s, 3 H), 3.97 (s, 3 H), 3.92 (s, 3 H).
^{13}C NMR: 187.0, 103.7, 62.9, 61.3, 56.7.
Ms (m/z): 241 ([M$^+$], 40 %), 211 (98 %), 196 (100 %), 181, 168 (70 %), 153 (73 %), 137, 125, 109, 93, 77, 66, 53.
IR: 1703, 1607, 1560, 1520, 1485, 1389, 1301, 1253, 1207, 1119, 1048, 1030, 963, 919, 885, 799, 767, 731, 675.

4.8.2.8 5-Nitro-1,3-benzodioxole (**57**)

Prepared from 1,3-benzodioxole (**57**) and recrystallized from diisopropylether. Dark brown

crystals, yield: 81 %, mp 147-148 °C [lit.[91] 146-149 °C]

^{1}H NMR: 8.22 (s, 1 H), 8.01 (d, 1 H), 7.23 (d, 1 H), 6.14 (s, 2 H).
^{3}C NMR: 150.2, 145.5, 142.0, 118.7, 108.3, 104.1, 101.6.
Ms (m/z): 167 ([M]$^+$, 100 %), 151, 137, 121, 107, 91, 79, 65, 63, 45.
IR: 1500, 1485, 1434, 1379, 1333, 1266, 1236, 1171, 1113, 1030, 917, 869, 823, 808, 741, 718.

4.8.2.9 4,5-Methylenedioxy-2-nitrotoluene (**59**)

Prepared from 3,4-methylenedioxytoluene (**59**) and recrystallized from diisopropylether. Dark

yellow crystals, yield: 71 %, mp 80-82 °C [lit.[92] 82 °C]

^{1}H NMR: 7.55 (s, 1 H), 6.81 (s, 1 H), 6.11 (s, 2 H), 2.69 (s, 3 H).
^{13}C NMR: 150.1, 144.9, 142.2, 125.6, 112.9, 104.2, 102.3, 20.9.
Ms (m/z): 181([M]$^+$, 100 %), 166, 152, 136, 121, 107, 93, 77, 65, 39.
IR: 1616, 1520, 1498, 1466, 1452, 1350, 1324, 1264, 1223, 1188, 1170, 1059, 1033, 1015, 981, 869, 795, 755.

4.9   Synthesis of Ester-Protected Phenolic or Catecholic Precursors

4.9.1   General Procedure

A general procedure for protection of phenols as esters (acetates or benzoates) involves the following procedure. The proper phenol (10 mmol) in pyridine (50 mL) is treated slowly under good stirring with a solution of acetic acid anhydride (13 mmol) in pyridine (10 mL). After addition is completed, the solution is stirred further for 2 h. The solution is then poured onto ice and water (200 mL) and the precipitate is collected by filtration and washed thoroughly with water. The same procedure is used for the benzoates using 13 mmol of benzoylchloride.

4.9.2   Ester-Protected Phenolic or Catecholic Precursors

4.9.2.1   4-Benzoyloxy-2-bromo-5-methoxybenzaldehyde (**8a**)

Prepared from 2-bromo-4-hydroxy-5-methoxybenzaldehyde (**7a**) and recrystallized from diisopropylether. White crystals, yield: 71 %, mp 119-121 °C.

^{1}H NMR: 10.22, 7.47 (s, 1 H), 7.28 (s, 1 H), 7.44-7.81 (m, 5 H), 3.96 (s, 3 H)
^{13}C NMR: 190.6, 165.5, 149.0, 145.1, 134.4, 131.3, 128.1-133.6 (5 C), 117.2, 114.1, 56.0
Ms (m/z): 334/336 ([M]$^+$/[M+2]$^+$, < 1 %),
IR: 1737, 1682, 1594, 1488, 1466, 1449, 1381, 1312, 1263, 1248, 1194, 1166, 1150, 1052, 1020, 980, 914, 859, 798, 736, 706, 677.

4.9.2.2   2-Benzoyloxy-6-bromo-3-methoxybenzaldehyde (**15a**)

Prepared from 6-bromo-2-hydroxy-3-methoxybenzaldehyde (**14**) and recrystallized from diisopropylether. Colorless crystals, yield: 79 %, mp 158-160 °C.

^{1}H NMR: 10.27 (s, 1 H), 8.17 (d, 1 H), 7.08 (d, 1 H), 7.47-7.66 (m, 5 H), 3.82 (s, 3 H), 2.34.
^{13}C NMR: 190.6, 164.0, 152.4, 141.0, 134.2, 132.0, 130.9, 129.1, 129.0, 118.1, 116.3, 56.9.
Ms (m/z): 334/336 ([M]$^+$/[M+2]$^+$, < 1 %), 230/232 (100 %), 201/203, 189,184/186, 159/161, 132, 105/107, 79, 63, 51.
IR: 1732, 1690, 1585, 1570, 1491, 1470, 1438, 1404, 1301, 1273, 1207, 1173, 1161, 1148, 1075, 1058, 1022, 1161, 1075, 1058, 1022, 943, 825, 796, 744, 696.

4.9.2.3 2-Acetoxy-3-methoxy-6-nitrobenzaldehyde (**19b**)

Prepared from 2-hydroxy-3-methoxy-6-nitrobenzaldehyde (**18**) and recrystallized from diisopropylether. Brown crystals, yield: 85 %, mp 131-132 °C [lit.[69] 134 °C].

^{1}H NMR: 10.22 (s, 1 H), 7.83 (d, 1 H), 7.60 (d, 1 H), 3.96 (s, 3 H), 2.34 (s, 3 H).
^{13}C NMR: 189.0, 167.1, 153.1, 145.6, 141.3, 121.6, 120.9, 120.3, 56.3, 20.7.
Ms (m/z): 239 ([M]$^+$, 5 %).
IR: 1774, 1700, 1578, 1515, 1479, 1433, 1370, 1341, 1277, 1177, 1070, 1015, 925, 875, 834, 818, 758, 725, 671.

4.9.2.4 2-Benzoyloxy-3-methoxy-6-nitrobenzaldehyde (**19c**)

Prepared from 2-hydroxy-3-methoxy-6-nitrobenzaldehyde (**18**) and recrystallized from diisopropylether. Brown crystals, yield: 66 %, mp 125-127 °C.

^{1}H NMR: 10.26 (s, 1 H), 7.80 (d, 1 H), 7.33 (d, 1 H), 7.51-7.89 (m, 5 H), 3.99 (s, 3 H).
^{13}C NMR: 190.1, 163.3, 153.0, 146.6, 141.2, 129.5, 134.2, 131.9, 128.6, 122.0, 56.2.
Ms (m/z): 301([M]$^+$, < 1 %), 243, 271, 196, 105 (100 %), 77, 58, 43.
IR: 1743, 1703, 1579, 1509, 1480, 1387, 1334, 1287, 1251, 1201, 1188, 1075, 1056, 1025, 989, 955, 911, 818, 709, 663.

4.9.2.5 2-Acetoxy-5,6-dibromo-3-methoxybenzaldehyde (**30b**)

Prepared from 5,6-dibromo-2-hydroxy-3-methoxybenzaldehyde (**29**) and recrystallized from diisopropylether. White crystals, yield: 70 %, mp 138 °C (dec.).

^{1}H NMR: 10.12 (s, 1 H), 7.28 (m, 1 H), 3.86 (s, 3 H), 2.39 (s, 3 H).
^{13}C NMR: 189.1, 167.8, 151.9, 147.2, 134.6, 128.5, 121.1, 117.7, 56.6, 20.6
Ms (m/z): 350/352/354 ([M]$^+$/[M+2]$^+$/[M+4]$^+$, < 1 %), 308/310/312 (100 %), 262/264/266 (60 %), 230/232, 214, 185, 159, 157, 129/131, 105/107, 79, 50, 43.
IR: 1768, 1693, 1642, 1570, 1453, 1433, 1398, 1372, 1336, 1294, 1271, 1245, 1171, 1088, 1011, 952, 873, 765, 725.

4.9.2.6 2-Benzoyloxy-5,6-dibromo-3-methoxybenzaldehyde (**30c**)

Prepared from 5,6-dibromo-2-hydroxy-3-methoxybenzaldehyde (**29**). White solid, yield: 68 %, mp 147-149 °C.

^{1}H NMR: 10.12 (s, 1 H), 7.36 (s, 1 H), 7.42-7.63 (m, 5 H), 3.86 (s, 3 H).
^{13}C NMR: 189.4, 162.9, 151.0, 146.4, 132.9, 131.9, 131.0, 128.8, 128.1, 126.6, 120.4, 56.6.
Ms (m/z): 412/414/416 ([M]$^+$/[M+2]$^+$/[M+4]$^+$, < 1 %), 333/335, 307/309/311, 266, 228, 185, 181, 157, 143, 122, 130, 105 (100 %), 77.
IR: 1739, 1692, 1600, 1577, 1463, 1434, 1392, 1362, 1301, 1258, 1204, 1176, 1088, 1076, 1058, 1021, 996, 947, 879, 779, 705.

4.9.2.7 2-Acetoxy-6-fluoro-3-methoxybenzaldehyde (<u>41a</u>)

Prepared from 6-fluoro-2-hydroxy-3-methoxybenzaldehyde (<u>40</u>). White solid, yield: 66 %, mp 102 °C.

^{1}H NMR: 10.12 (s, 1 H), 7.24 (d, 1 H), 7.08 (d, 1 H), 3.99 (s, 3 H), 2.42 (s, 3 H).
^{13}C NMR: 188.1, 167.7, 158.5, 145.5, 144.0, 118.3, 117.7, 116.6, 56.4, 20.4.
IR: 1757, 1681, 1600, 1571, 1477, 1436, 1371, 1277, 1234, 1155, 1019, 945, 830.

4.9.2.8 2-Benzoyloxy-6-fluoro-3-methoxybenzaldehyde (<u>41b</u>)

Prepared from 6-fluoro-2-hydroxy-3-methoxybenzaldehyde (<u>40</u>). Colorless crystals, yield: 73 %, mp 117 °C.

^{1}H NMR: 10.22 (s, 1 H), 7.44-7.86 (m, 5 H), 7.33 (d, 1 H), 7.02 (d, 1 H), 3.98 (s, 3 H).
^{13}C NMR: 186.9, 163.0, 157.7, 146.6, 145.2, 134.1, 131.9, 130.0, 118.6, 117.0, 116.1, 56.5.
Ms (m/z): 274 ([M]$^+$, 1 %).
IR: 1738, 1688, 1571, 1480, 1433, 1306, 1267, 1211, 1136, 1076, 964, 904, 855.

4.9.2.9 4-Benzoyloxy-3-bromo-5-methoxybenzaldehyde (<u>8d</u>)

Prepared from 3-bromo-4-hydroxy-5-methoxybenzaldehyde (<u>7b</u>).

White solid, yield: 68 %, mp 131-132 °C.

^{1}H NMR: 10.36 (s, 1 H), 7.40-7.80 (m, 5 H), 7.38 (s, 1 H), 7.12 (s, 1 H), 3.86 (s, 3 H).
^{13}C NMR: 189.6, 164.0, 151.0, 145.7, 134.4, 132.1, 129.6, 128.6, 127.4, 113.6, 109.1, 56.0.
Ms (m/z): 334/336 ([M]$^+$/[M+2]$^+$, < 1 %).
IR: 1736, 1691, 1580, 1473, 1462, 1450, 1420, 1389, 1317, 1280, 1259, 1215, 1193, 1132, 1051,. 1037, 1021, 967, 870, 852, 833, 799, 722, 702, 689.

4.9.2.10 4-Nitrocatechol dibenzoate (<u>52</u>)

Prepared from 4-Nitrocatechol (<u>51</u>) and recrystallized from diisopropylether. White crystals:, yield: 66 %, mp 150 °C.

^{1}H NMR: 7.37-8.33 (m, 13 H).
^{13}C NMR: 163.7, 163.4, 148.1, 145.6, 142.9, 134.3, 130.3, 128.7, 128.0, 124.1, 122.0, 119.8

4.9.2.11 4-Methyl-5-nitrocatechol dibenzoate (**55b**)

Prepared from 4-methyl-5-nitrocatechol (**54**). Brown solid, yield: 47 %, mp 133-136 °C.

^{1}H NMR: 7.39-7.96 (m, 12 H), 2.79 (s, 3 H).
^{13}C NMR: 164.1, 163.4, 150.0, 146.9, 139.9, 126-134 (10 C), 124.4, 20.8.
Ms (m/z): 377 ([M]$^+$, < 1 %), 181 , 136, 105 (100 %), 77, 51.
IR: 1741, 1597, 1482, 1524, 1495, 1448, 1386, 1347, 1301, 1240, 1171, 1146, 1050, 901, 843, 810, 757, 740, 703, 690, 669.

4.9.2.12 4-Methyl-5-nitrocatechol diacetate (**55c**)

Prepared from 4-methyl-5-nitrocatechol (**54**). Brown solid, yield: 54 %, mp 100 °C [lit.[88] 103-105 °C].

^{1}H NMR: 7.92 (s, 1 H), 7.19 (s, 1 H), 2.60 (s, 3 H), 2.56 (s, 3 H), 20.3 (s, 3 H).
^{13}C NMR: 167.7, 167.4, 145.9, 145.6, 140.3, 133.0, 127.2, 120.7, 20.6, 20.5.
Ms (m/z): 253 ([M]$^+$, < 1 %).

4.10   Synthesis of Ether-Protected Phenolic or Catecholic Precursors

4.10.1   Open Ethers: General Procedures

A general procedure for protection of phenols as arylmethyl ethers involves the following: anhydrous K_2CO_3 (3.2 g) is cautiously added to a stirred solution of the proper phenol (13.4 mmol) in DMF (50 mL) at 60 °C. The mixture is kept at 110-120 °C during the portionwise addition of dimethyl sulfate (2.7 mL, 21.4 mmol). The mixture is stirred at 110-120 ° for 5 h, cooled down to room temperature and poured onto ice-water (400 mL). The precipitate is collected by filtration and washed thoroughly with water. For two OH groups (protection of catechols as open ethers) the quantities are simply doubled.

4.10.2   Ether-Protected Phenolic or Catecholic Precursors

4.10.2.1   3-Bromo-4,5-dimethoxybenzaldehyde (<u>8c</u>)

Prepared from 3-bromo-4-hydroxy-5-methoxybenzaldehyde (<u>7b</u>). Recrystallization from diisopropyl ether gave white crystals. Yield: 86 %, mp 65-66 °C [lit.[64] 64-66 °C].

^{1}H NMR: 9.96 (s, 1 H), 7.58 (s, 1 H), 7.50 (s, 1 H), 3.86 (s, 3 H), 3.82 (s, 3 H).
^{13}C NMR: 190.0, 153.0, 149.2, 133.3, 128.4, 112.0, 110.0, 61.2, 56.0.
Ms (m/z): 244/246 ([M]$^+$/[M+2]$^+$, 100 %).
IR: 1686, 1586, 1563, 1484, 1449, 1419, 1392, 1379, 1310, 1278, 1238, 1128, 1044, 986, 855, 837, 817, 786, 750, 742, 696, 665.

4.10.2.2   2,3-Dimethoxy-6-nitrobenzaldehyde (<u>19a</u>)

Prepared from 2-hydroxy-3-methoxy-6-nitrobenzaldehyde (<u>18</u>). Recrystallization from acetone gave white crystals. Yield: 70 %, mp 108-110 °C [lit.[68] 108-110 °C].

^{1}H NMR: 10.35 (s, 1 H), 7.96 (d, 1 H), 7.05, (d, 1 H), 4.00 (s, 3 H), 3.96 (s, 3 H).
^{13}C NMR: 188.3, 158.6, 148.0, 130.4, 121.5, 112.6, 62.7, 56.6.
Ms (m/z): 211 ([M]$^+$, 20 %), 194, 181, 166 (100 %), 152, 138, 123, 107, 95, 77, 65, 51.
IR: 1694, 1572, 1511, 1477, 1405, 1325, 1275, 1240, 1195, 1072, 1027, 988, 947, 897, 824.

4.10.2.3   3,4-Dimethoxy-2-nitrobenzaldehyde (<u>42h</u>)

Prepared from 3-methoxy-2-nitrobenzaldehyde-4-benzenesulfonate (<u>42e</u>). White powder. Yield: 58 %, mp 63-65 °C [lit.[80] 63.5-64 °C].

^{1}H NMR: 10.0 (s, 1 H), 7.66 (d, 1 H), 7.12, (d, 1 H), 3.84 (s, 3 H), 3.80 (s, 3 H).
^{13}C NMR: 187.0, 144.2, 141.4, 156.6, 128.6, 122.1, 62.0, 56.7.
Ms (m/z): 211 ([M]$^+$, 40 %), 194, 181, 166, 152, 138, 123.
IR: 1685, 1566, 1501, 1434, 1409, 1336, 1270, 1249, 1179, 1070, 1033, 984, 941, 900, 813.

4.10.2.4   2,3-Dibromo-5,6-dimethoxybenzaldehyde (<u>30a</u>)

Prepared from 2,3-dibromo-6-hydroxy-5-methoxybenzaldehyde (<u>29</u>). Light yellow solid. Yield: 70 %, mp 144 °C.

^{1}H NMR: 10.32 (s, 1 H), 7.25 (s, 1 H), 3.89 (s, 3 H), 3.86 (s, 3 H).
^{13}C NMR: 190.2, 152.9, 150.3, 131.4, 121.3, 120.6, 119.6, 114.7, 62.6, 60.5.
Ms (m/z): 322/324/326 ([M]$^+$/[M+2]$^+$/[M+4]$^+$, 100 %), .
IR: 1694, 1569, 1556, 1456, 1429, 1397, 1298, 1258, 1232, 1202, 1179, 1069, 996, 975, 937, 866, 813, 749, 699.

4.10.2.5   1,2-Dimethoxy-4-methyl-5-nitrobenzene (**55a**)

Prepared from 4-methyl-5-nitrocatechol (**54**) and recrystallized from diisopropylether. Yellow solid. Yield: 69 %, mp 116-120 °C [lit.[90] 119-120 °C].

^{1}H NMR: 7.65 (s, 1 H), 6.72 (s, 1 H), 3.96 (s, 3 H), 3.93 (s, 3 H), 2.62 (s, 3H).
^{13}C NMR: 153.0, 147.1, 129.0, 114.0, 108.2, 56.3, 21.3.
Ms (m/z): 197 ([M]$^+$, 100 %).
IR: 1616, 1581, 1520, 1466, 1452, 1350, 1324, 1264, 1223, 1188, 1170, 1059, 981, 869, 795.

4.10.3   Cyclic Ethers: General Procedure for five Membered Rings

A general procedure for protection of catechols as cyclic five membered rings involves the following. A solution of the proper catechol (25 mmol) and freshly distilled acetone (30 mmol) in dry toluene (50 mL) is treated with good stirring under nitrogen over a period of 30 min with PCl$_3$ (40 mmol). Stirring is continued for another 30 until TLC shows the disappearance of the starting catechol. The solution is then treated with NaOH before being extracted with CH$_2$Cl$_2$.

4.10.4   Five Membered Ring Ether-Protected Catecholic Precursors

4.10.4.1   6-Bromo-2,3-methylenedioxybenzaldehyde (**33**)

Prepared from 6-Bromo-2,3-dihydroxybenzaldehyde (**32**). Colorless solid. Yield: 55 %, mp 156-159 °C [lit.[77] 158-160 °C].

^{1}H NMR: 10.28 (s, 1 H), 7.12 (d, 1 H), 6.87 (d, 1 H), 6.16 (s, 2 H).
^{13}C NMR: 190.4, 149.5, 148.8, 126.2, 117.2, 115.6, 113.6, 103.4.
Ms (m/z): 228/230 ([M]$^+$/[M+2]$^+$, 100 %), 199/201, 185/187, 171, 157/159, 143/145, 121.
IR: 1677, 1617, 1586, 1505, 1450, 1396, 1348, 1240, 1210, 1115, 1048, 1017, 920, 876, 806, 758, 701.

4.11 Synthesis of Phenolic or Catecholic Precursors Protected as Open Sulfonate Esters

4.11.1   General Procedure

A general procedure for the preparation of these precursors from the phenols (or catechols) involves the following. The proper phenol (10 mmol) in water (50 mL) is treated with KOH (12 mmol, 0.72 g). To this mixture there is added dropwise benzenesulfonyl chloride (10 mmol, 1.77 g, 1.3 mL) within 20-30 min. Stirring is continued over 24 h. The resulting solid is filtered, washed thoroughly with water (500 mL) and with 5 % KOH solution (100 mL). If the product is still oily, it is extracted first with CH_2Cl_2 (3 X 50 mL). The organic phase is washed with water and 5 % KOH and dried ($MgSO_4$). The solvent is removed under vacuum at a rotational evaporator.

4.11.2   Phenolic or Catecholic Precursors Protected as Open Sulfonate Esters

4.11.2.1   2-Bromo-5-methoxybenzaldehyde-4-benzenesulfonate (**8b**)

Prepared from 2-Bromo-4-hydroxy-5-methoxybenzaldehyde (**7**) and recrystallized from diisopropylether. White crystals: (yield: 85 %), mp 135-137 °C.

^{1}H NMR: 10.18 (s, 1 H), 7.28 (d, 1 H), 7.55 (d, 1 H), 3.86 (s, 3 H).
^{13}C NMR: 189.0, 152.9, 144.3,136.3, 134.4, 133.1, 129.0, 128.5, 117.5, 113.0, 56.2.
Ms (m/z): 370/372 ([M]$^+$/[M+2]$^+$,80 %) 229/231 (85 %), 201/2032, 173/175, 141 (100 %).
IR: 1691, 1589, 1481, 1448, 1370, 1304, 1267, 1190, 1140, 1089, 1037, 978, 882, 856, 764, 750, 720, 700.

4.11.2.2   6-Bromo-3-methoxybenzaldehyde-2-benzenesulfonate (**15b**)

Prepared from 6-Bromo-2-hydroxy-3-methoxybenzaldehyde (**14**) and recrystallized from diisopropylether. White crystals: (yield: 93 %), mp 122-124 °C.

^{1}H NMR: 10.11 (s, 1 H), 7.92 (d, 1 H), 6.88 (d, 1 H), 7.27-7.70 (m, 5 H), 3.53 (s, 3 H).
^{13}C NMR: 188.3, 152.4, 136.3, 134.4, 133.1, 129.0, 128.5, 117.5, 113.0, 56.2.
Ms (m/z): 370/372 ([M]$^+$/[M+2]$^+$, 30 %), 245/247, 229/231 (100 %), 214/216, 200/202, 186/188, 173/175, 141, 121, 107, 94, 77.
IR (cm^{-1}): 1698, 1584, 1566, 1465, 1399, 1372, 1300, 1273, 1195, 1183, 1168, 1090, 1077, 938, 896, 822, 775, 748, 682.

4.11.2.3   2,3-Dibromo-5-methoxybenzaldehyde-6-benzenesulfonate (30d)

Prepared from 2,3-dibromo-6-hydroxy-5-methoxybenzaldehyde (29).

White solid. yield: 81 %, mp 155 °C.

^{1}H NMR: 10.23 (s, 1 H), 7.49 (s, 3 H), 7.51-7.82 (m, 5 H), 3.91 (s, 3 H).
^{13}C NMR: 191.0, 147.4, 140.1, 139.7, 135.5, 127.5-133.0 (7 C), 122.9, 120.4, 56.0
Ms (m/z): 448/450/452 ([M]$^+$/[M+2]$^+$[M+4]$^+$, 10 %), 369/371, 323/325/327, 307/309/311 (100 %), 292/294/296, 291, 266, 253, 185/187, 157/159, 141, 77, 51.
IR: 1708, 1581, 1553, 1451, 1427, 1378, 1292, 1259, 1174, 1165, 1086, 998, 942, 904, 843, 788, 768, 753, 730, 677.

4.11.2.4   6-Fluoro-3-methoxybenzaldehyde-2-benzenesulfonate (41c)

Prepared from 6-fluoro-2-hydroxy-3-methoxybenzaldehyde (40).

White solid. Yield 76 %, mp 133 °C.

^{1}H NMR: 10.66 (s, 1 H), 7.28 (d, 1 H), 7.02 (d, 1 H), 7.39-7.73 (m, 5 H), 4.02 (s, 3 H).
Ms (m/z): 310 ([M]$^+$, 15 %), 203, 185, 169 (100 %), 154,. 141, 125, 98, 77, 70, 51.

4.11.2.5   Phenylbenzenesulfonate (42a)

Prepared from phenol. Identified by comparison of its melting point with the reported value.

Oily material which solidify on standing in refrigerator for several days. Yield 87 %, mp

35-39 °C [lit.[81] 36-37 °C].

4.11.2.6   Benzaldehyde-2-benzenesulfonate (42b)

Prepared from 2-hydroxybenzaldehyde. Identified by comparison of its melting point with the

reported value. Pink solid. Yield 76 %, mp 57-59 °C [lit.[81] 56-58.5 °C].

4.11.2.7   Benzaldehyde-4-benzenesulfonate (42c)

Prepared from 4-hydroxybenzaldehyde. Identified by comparison of its melting point with the

reported value. Pink solid. Yield 80 %, mp 80-82 °C [lit. [82] 81-82].

4.11.2.8   3-Methoxybenzaldehyde-4-benzenesulfonate (42d)

Prepared from 3-methoxy-4-hydroxybenzaldehyde (4).

White solid. Yield 76 %, mp 69-70 °C [lit.[67] 69-70 °C].

^{1}H NMR: 10.12 (s, 1 H), 7.10-7.85 (m, 8 H), 3.55 (s, 3 H).
^{13}C NMR: 191.3, 154.5, 142.3, 135.9, 133.6, 131.3, 129.4, 128.9, 127.5, 112.6, 118.0, 55.9.
Ms (m/z): 292 ([M]$^+$, 15 %), 176, 152, 151 (100 %), 141, 123, 109, 95, 81, 77.

IR: 1683, 1597, 1497, 1463, 1450, 1398, 1382, 1321, 1274, 1192, 1202, 1175, 1143, 1118, 1086, 1025, 960, 857, 844, 833, 754, 726, 691.

4.11.2.9   4-Nitrocatechol dibenzenesulfonate (**42f**)

Prepared from 4-nitrocatechol (**51**). White solid. Yield 76 %, mp 135-139 °C [lit.[83]

136-137 °C].

^{1}H NMR: 8.42 (s, 1 H), 8.05 (d, 1 H), 7.76 (d, 1 H), 7.61-7.85 (m, 10 H).
^{13}C NMR: 144.47, 142.9, 139.8, 122.6, 118.9, 115.4, 129-134 (12 C).
Ms (FAB, m/z): 371 ([M+1]$^+$, 33 %).
IR: 1591, 1529, 1489, 1376, 1361, 1300, 1255, 1244, 1129, 1055, 970, 854, 780, 722, 671.

4.11.2.10   4-Methyl-5-nitrocatechol dibenzenesulfonate (**42g**)

Prepared from 4-methyl-5-nitrocatechol (**54**). White solid. Yield 76 %, mp 155 °C.

^{1}H NMR: 8.26 (s, 1 H), 7.28 (s, 1 H), 7.55-7.84 (m, 10 H), 2.69 (s, 3 H).
^{13}C NMR: 147.5, 141.3, 138.0, 129.3-135.2 (12 C), 128.0, 122.0, 114.2, 20.9.
Ms (FAB, m/z): 386 ([M+1]$^+$, 20 %).
IR: 1585, 1535, 1498, 1360, 1348, 1279, 1213, 1172, 1155, 1129, 1034, 967, 883, 831, 799, 761, 701, 677.

4.12 Miscellaneous

4.12.1   Aldehydic Precursors Protected as Cyclic Acetals: General Procedure

The protection of the aldehyde group as cyclic acetals can be achieved by the following

general procedure. The proper aldehyde (7.5 mmol), ethylene glycol (6.4 g, 10.3 mmol) and

p-toluenesulfonic acid monohydrate (200 mg) are dissolved in toluene (75 mL) and the

mixture is refluxed in the Dean-Stark apparatus for 2.5 d. The solution is then poured on

water (100 mL). The organic phase is separated, washed with water and saturated NaHCO$_3$

and dried (MgSO$_4$). It is then removed *in vacuo*.

4.12.2 Aldehydic Precursors Protected as Cyclic Acetals

4.12.2.1 3-Bromo-5,6-dimethoxy-2-nitrobenzaldehyde ethyleneacetal (<u>49</u>)

Prepared from 3-Bromo-5,6-dimethoxy-2-nitrobenzaldehyde (<u>31</u>) and purified by MPLC.

White solid. Yield 68 %, mp 79.5-80.5 °C.

^{1}H NMR: 7.14 (s, 1 H), 6.17 (s, 1 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 4.02 (t, 2 H), 4.00 (t, 2 H).
Ms (FD, m/z): 3357336 ([M]$^+$/[M+2]$^+$).
IR: 1577, 1534, 1477, 1430, 1382, 1357, 1310, 1268, 1229, 1172, 1128, 1060, 1018, 956, 939, 835, 800, 771, 745, 660.

4.12.2.2 2,3-Dimethoxy-6-nitrobenzaldehyde ethyleneacetal (<u>50</u>)

Prepared from 2,3-dimethoxy-6-nitrobenzaldehyde (<u>19a</u>) and purified by MPLC. White solid.

Yield 75 %, mp 74-76°C [lit.[87] 74-76 °C].

^{1}H NMR: 7.26 (d, 1 H), 7.13 (d, 1 H), 6.18 (s, 1 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 4.10 (t, 2 H), 3.99 (t, 2 H).
Ms (m/z): 256 ([M+1]$^+$, 25 %), 255 ([M]$^+$, 8 %), 205, 180, 163, 150, 136, 122, 107, 93, 73.
IR: 1583, 1538, 1483, 1440, 1374, 1363, 1309, 1275, 1238, 1178, 1112, 1016, 971, 938, 860, 821, 810, 773, 735, 655.

5   SUMMARY

The objective of this work was to investigate the nucleophilic aromatic substitution using [^{18}F]fluoride as nucleophile. Therefore, structures ranging from simple monosubstituted aromatic systems to complicated multi-substituted aromatic systems were tested, and several effects were studied in detail, including the following:

1- Structural effects (positions and number of groups on the ring, type of activation or deactivation, type of possible leaving groups and type of protection of OH groups).

2- Solvent effects (was studied using a variety of dipolar aprotic solvents)

3- Concentration effects (was studied using concentrations 1-50 mg/mL).

4- Temperature effects (was studied using temperatures 60-180 °C).

Two types of reactions were studied. Those are:

1- Fluorodenitration reactions: **Ar-NO$_2$ $\rightarrow$ Ar-^{18}F**

2- Fluorodehalogenation reactions: **Ar-X $\rightarrow$ Ar-^{18}F**   (X= F, Br, Cl)

The study was divided into 3 parts. In the first part, aryl systems (including haloaryls, nitroaryls, benzaldehydes, acetophenones and benzophenones) were tested. In the second part, the focus was on optimising the conditions for the production of [^{18}F]FDOPA precursors for path A (chapter 2). In the last part, model systems for producing [^{18}F]FDOPA via path B (chapter 2) were tested in the nucleophilic aromatic substitution by [^{18}F]fluoride. The radiochemical yields (RCYs) obtained from some precursors were used further to calculate the rate constants and the energy of activation for this process.

The main results can be summarised in the following points:

1- Fluorodenitration reactions can be used efficiently to produce nca [^{18}F]arylfluorides. DMF is the best solvent but DMSO and DMAc can be used also. For very activated systems, acetonitrile can be used at lower temperatures. The optimum temperature range is 120-150 °C, although lower temperatures can be used for very activated systems. The optimum concentration range is 15-30 mg/mL and optimum time is 10-20 min.

2- Fluorodehalogenation (X= F) reactions can also be a good alternative for the synthesis of [^{18}F]arylfluorides. DMF is the best solvent and most other solvents proved to be less efficient for carrying out this process. Optimum conditions being nearly the same as in fluorodenitration reactions.

3- Fluorodehalogenation (X= Br, Cl) reactions can also be used for the synthesis of nca [^{18}F]arylfluorides when the conditions are well optimised. For this, DMF is the best solvent and most other solvents proved to be not useful. Aromatic systems with electron withdrawing groups only on the ring gave yields which were almost comparable to those from fluorodenitration reactions. However, with the increasing introduction of electron donating groups on the aromatic ring, the yield tend to be much lower compared to similar nitro systems. The RCYs were always directly proportional both to concentrations up to 50 mg/mL and temperatures as high as 180 °C.

Calculations of the activation energy for the previous processes reveals low values in the range 16-63 kJ/mole for most compounds but even lower values were obtained for very highly activated compounds towards S_NAr. These values indicate very fast reactions between the fluoride ion and the substituted nitro or halo benzene derivatives. In all cases the yields from the nitro derivatives were better than the halo derivatives. Within the halogens, the fluoro precursors gave always the highest yields.

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7   APPENDICIES

6.1   Appendix 1: Data for Aryl Systems

Tab. 33. [^{18}F] Labelling data for mono, di and tribromobenzenes.

Precursor	n	RCY (%)									
		5 min		10 min		20 min		30 min		60 min	
		Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv
Mono	2	1.4	0.4	1.1	0.2	1.4	0.2	1.8	0.4	0.5	0.2
o-dibromo	3	5.6	2.2	8.2	2.7	10.0	1.9	10.9	0.5	10.7	3.9
m-dibromo	4	6.7	2.6	9.1	3.5	12.2	2.2	15.7	4.0	12.9	4.1
p-dibromo	4	2.3	0.9	3.7	1.6	4.9	1.1	6.1	2.9	5.7	1.6
1,2,4-tribromo	5	33.3	11.0	45.1	11.7	46.9	11.4	48.6	3.3	50.8	5.7
1,3,5-tribromo	4	56.9	10.8	62.6	9.3	63.3	7.4	64.3	8.0	57.9	6.1

Tab. 34. [^{18}F] Labelling data for dichlorobenzenes.

Precursor	n	RCY (%)									
		5 min		10 min		20 min		30 min		60 min	
		Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv
o-dichloro	3	2.9	1.6	3.5	1.5	3.5	0.8	3.8	0.2	3.4	0.5
m-dichloro	3	2.6	0.3	3.5	0.4	4.1	0.6	4.3	0.4	7.3	0.8
p-dichloro	3	0.8	0.4	1.3	0.6	1.3	0.3	1.4	0.5	1.6	0.2

Tab. 35. [^{18}F] Labelling data for *o*-dinitrobenzene in DMF and CH$_3$CN

Solvent	Temp. (°C)	n	RCY (%)									
			5 min		10 min		20 min		30 min		60 min	
			Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv
DMF	80	4	79.1	7.8	80.3	7.8	82.0	6.1	81.6	5.4	83.6	5.4
	100	4	82.0	2.6	81.3	2.0	82.5	1.4	80.6	3.4	75.2	6.4
	120	4	81.4	4.7	77.8	6.8	74.2	9.6	69.8	10.2	63.6	12.6
	140	4	58.4	9.1	46.5	9.1	35.5	5.6	27.7	6.5	15.2	2.3
CH$_3$CN	40	3	51.4	8.0	57.1	2.3	64.5	0.6	66.7	3.0	69.6	5.4
	60	3	77.8	5.6	79.9	5.1	81.4	1.0	83.4	4.4	73.4	3.9
	80	5	77.5	2.5	78.8	4.0	84.7	3.8	82.4	5.5	80.4	3.0

Tab. 36. [^18F] Labelling data for the three bromonitrobenzene isomers

Precursor	n	RCY (%)									
		5 min		10 min		20 min		30 min		60 min	
		Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv
o-isomer	4	58.4	9.1	46.5	9.0	35.5	5.6	27.7	6.5	15.2	2.3
m-isomer-	4	25.7	3.3	30.1	2.7	30.0	3.1	28.6	2.1	23.9	3.2
p-isomer	3	65.6	8.8	66.7	5.7	60.3	5.	56.6	8.8	43.7	9.9

Tab. 37. [^18F] Labelling data for *o*-nitrobenzaldehyde in DMF.

Temp. (°C)	n	RCY (%)									
		5 min		10 min		20 min		30 min		60 min	
		Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv
50	3	12.2	5.8	21.0	7.7	31.0	8.9	43.8	12.6	54.3	11.8
80	4	51.7	0.8	60.1	2.3	65.2	5.8	72.7	2.1	77.5	1.4
100	3	61.6	7.1	65.3	7.1	64.3	2.4	65.5	4.8	70.0	5.5
120	4	63.0	4.9	65.9	6.7	68.4	1.2	70.5	4.8	74.0	5.2
140	4	64.8	4.9	69.3	4.4	69.3	4.0	73.2	0.2	78.1	0.9
160	1	70.0	3.1	74.0	2.6	75.5	2.1	76.5	3.6	78.6	1.7

Tab. 38. Calculations of activation energy and rate constants for *o*-nitrobenzaldehyde in DMF.

Temp. (°C)	ln (1-RCY)				
	5 min	10 min	20 min	30 min	60 min
80	-0.7277	-0.9188	-1.0556	-1.2983	-1.4917
100	-0.9571	-1.0584	-1.0300	-1.0642	-1.2040
120	-0.9943	-1.0759	-1.1520	-1.2208	-1.3471
140	-1.0441	-1.1809	-1.1809	-1.3168	-1.5187

Temp. (°C)	Best linear graph for ln (1-RCY) vs time	Correlation coefficient	k' (min^{-1})	ln k'
80	Y= - 0.0894 – 0.0919 X	-0.95	0.0919	-3.3871
100	Y= - 0.1426 – 0.1058 X	-0.91	0.1058	-2.2462
120	Y= - 0.1521 – 0.1076 X	-0.90	0.1076	-2.2293
140	Y= - 0.1521 – 0.1181X	-0.91	0.1181	-2.1362

Tab. 39. [^{18}F] Labelling data for *p*-nitroacetophenone in DMF and DMSO

Solvent	Temp. (°C)	n	RCY (%)									
			5 min		10 min		20 min		30 min		60 min	
			Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv
DMF	50	2	0	0	0.4	0.1	0.7	0.1	1.2	0.4	1.7	0.5
	80	2	7.9	2,3	12.7	2,6	17.7	3,3	21.1	1,6	25.3	4.0
	100	2	19.7	1.7	25.8	2.0	32.8	0.3	38.0	5.6	41.8	7.0
	120	2	26.4	6.5	34.3	7.7	42.0	8.2	47.3	9.5	49.2	9.8
	140	2	43.1	13.2	49.5	8.4	50.7	3.3	50.5	4.5	50.8	5.6
	160	2	59.5	1.4	63.3	1.7	67.0	11.7	72.5	13.7	61.0	8.1
DMSO	50	3	0	0	0.3	0	0.4	0	0.4	0	0.6	0
	80	3	5.9	1.2	11.0	2.3	17.0	4.1	19.8	3.8	20.7	4.5
	100	3	13.5	1.9	20.7	3.9	27.0	4.4	31.6	4.1	40.4	6.6
	120	4	25.0	5.0	37.0	4.1	41.2	3.9	49.6	7.9	53.6	11.1
	140	4	40.6	6.6	50.2	8.9	57.8	8.1	60.7	6.4	60.3	10.3
	160	4	52.3	7.7	59.6	6.5	60.4	8.6	60	8.3	48.8	10.1

Tab. 40. Calculations of activation energy and rate constants for *p*-nitroacetophenone in DMF.

Temp. (°C)	ln (1-RCY)				
	5 min	10 min	20 min	30 min	60 min
80	-0.0823	-0.1358	-0.1948	-0.2370	-0.2917
100	-0.2194	-0.2984	-0.3975	-0.4780	-0.5413
120	-0.3065	-0.4201	-0.5447	-0.6401	-0.6773
140	-0.5639	-0.6832	-0.7072	-0.7032	-0.7093

Temp. (°C)	Best linear graph for ln (1-RCY) vs time	Correlation coefficient	k' (min^{-1})	ln k'
80	Y= - 0.0048 – 0.0136 X	- 0.99	0.0136	-4.2977
100	Y= - 0.0234 – 0.0298X	-0.97	0.0298	-3.5132
120	Y= - 0.0322 – 0.0420X	-0.97	0.0420	-3.1701
140	Y= - 0.0741 – 0.0683 X	-0.93	0.0683	-2.6838

6.2 Appendix 2: Data for 6-Nitroveratraldehyde

Tab. 41. [^{18}F] Labelling data for 6-nitroveratraldehyde. Conditions: [a]) 20 mg/mL, 140 °C. [b]) DMF (1 mL), 140 °C. [c]) 20 mg/mL, DMF (1 mL).

Variable		RCY (%) ± Sdv				
		5 min	10 min	20 min	30 min	60 min
Solvent [a]	DMF	83.2 ± 6.3	89.7 ± 2.0	88.7 ± 1.8	85.9 ± 2.7	82.3 ± 3.6
	DMAc	68.1 ± 0.1	75.6 ± 2.0	75.1 ± 3.0	74.4 ± 4.3	71.9 ± 1.5
	DMSO	69.0 ± 1.9	70.5 ± 1.9	71.4 ± 3.8	69.6 ± 3.9	65.8 ± 3.4
	Sulfolane	33.3 ± 0.1	37.5 ± 3.8	40.1 ± 1.8	39.7 ± 3.0	37.7 ± 0.7
	1,2-DME	56.9 ± 7.0	59.9 ± 5.0	49.7 ± 7.8	45.5 ± 3.9	42.0 ± 0.1
Concentration [b] (mg/mL)	0.5	29.0 ± 0.7	31.4 ± 1.6	27.4 ± 4.9	26.2 ± 5.6	21.6 ± 2.6
	1	62.4 ± 8.0	63.3 ± 6.4	59.9 ± 6.1	53.6 ± 4.8	41.9 ± 2.9
	3	60.5 ± 1.3	63.9 ± 0.7	66.8 ± 3.5	64.8 ± 1.1	56.2 ± 7.0
	6	68.7 ± 4.3	68.7 ± 3.7	68.5 ± 4.4	66.2 ± 4.2	66.0 ± 0.1
	10	75.5 ± 6.0	75.5 ± 5.3	76.9 ± 6.0	77.8 ± 6.3	73.2 ± 9.8
	20	83.2 ± 6.3	89.7 ± 2.0	88.7 ± 1.8	85.9 ± 2.7	82.3 ± 3.6
	30	85.9 ± 2.3	85.5 ± 2.1	82.6 ± 0.1	81.6 ± 0.8	80.9 ± 0.1
	50	85.5 ± 1.6	84.7 ± 1.1	81.9 ± 0.8	82.6 ± 0.2	81.0 ± 0.1
Temperatur [c] (°C)	80	36.0 ± 0.1	35.1 ± 6.0	45.1 ± 6.2	48.8 ± 4.4	63.5 ± 4.4
	100	60.6 ± 7.6	67.2 ± 9.9	70.1 ± 10.1	72.3 ± 5.9	78.6 ± 10.9
	120	64.4 ± 0.1	80.2 ± 12.7	80.9 ± 9.4	82.4 ± 8.8	77.2 ± 9.6
	140	83.2 ± 6.3	89.7 ± 2.0	88.7 ± 1.8	85.9 ± 2.7	82.3 ± 3.6
	150	85.4 ± 5.3	87.0 ± 3.2	89.6 ± 1.4	87.2 ± 3.7	85.4 ± 3.3

Tab. 42. Calculations of activation energy and rate constants for
6-nitroveratraldehyde.

Time (min)	ln (1-RCY)				
	80 °C	**100 °C**	**120 °C**	**140 °C**	**150 °C**
5	-0.4463	-0.9314	-1.0328	-1.7838	-1.9241
10	-0.4323	-1.1147	-1.6210	-2.2711	-2.0379
20	-0.5997	-1.2073	-1.6570	-2.1813	-2.2672
30	-0.6694	-1.2837	-1.7390	-1.9618	-2.0557
60	-1.0079	-1.5418	-1.4784	-1.7293	-1.9262

Temp. (°C)	Best linear graph for ln (1-RCY) vs time	Correlation coefficient	k' (min^{-1})	ln k'
80	Y= - 0.0768 – 0.0432 X	-0.85	0.0432	-3.1419
100	Y= - 0.1247 – 0.1114 X	-0.93	0.1114	-2.1946
120	Y= - 0.0741 – 0.1621 X	-0.99	0.1621	-1.8195
140	Y= - 0.2161 – 0.2271 X	-0.95	0.2271	-1.4824

6.3   Appendix 3: Data for 6-Fluoroveratraldehyde

Tab. 43. [^{18}F] Labelling data for 6-fluoroveratraldehyde. Conditions:
    ^{a}) 20 mg/mL,140 °C. ^{b}) DMF (1 mL), 140 °C. ^{c}) 20 mg/mL, DMF (1 mL).

Variable		RCY (%) ± Sdv				
		5 min	10 min	20 min	30 min	60 min
Solvent ^{a}	**DMF**	87.7 ± 1.2	85.0 ± 5.3	85.0 ± 1.7	82.7 ± 0.3	80.4 ± 1.8
	DMAc	53.4 ± 4.9	45.1 ± 5.3	41.5 ± 5.0	37.3 ± 2.7	37.5 ± 2.1
	DMSO	44.4 ± 0.8	35.6 ± 3.9	31.6 ± 3.5	28.6 ± 5.3	26.9 ± 1.8
	Sulfolane	42.7 ± 5.2	41.8 ± 3.8	42.0 ± 0.6	41.3 ± 2.9	38.7 ± 1.1
Concentration ^{b} **(mg/mL)**	**0.5**	64.5 ± 0.5	67.1 ± 2.5	66.7 ± 4.7	60.4 ± 6.2	59.4 ± 0.9
	1	75.2 ± 3.9	71.2 ± 3.9	69.1 ± 4.4	64.5 ± 7.7	64.5 ± 2.3
	5	85.0 ± 0.8	84.1 ± 2.4	81.5 ± 1.6	79.9 ± 4.7	78.5 ± 3.3
	10	85.5 ± 2.2	86.3 ± 4.0	83.6 ± 3.8	80.4 ± 6.2	79.9 ± 0.6
	20	87.7 ± 1.2	85.0 ± 5.3	85.0 ± 1.7	82.6 ± 0.3	80.4 ± 1.8
	30	87.4 ± 1.3	86.1 ± 1.7	86.9 ± 1.0	83.6 ± 1.3	81.4 ± 0.7
	50	87.7 ± 1.4	87.1 ± 0.8	87.5 ± 1.3	87.4 ± 1.4	85.6 ± 1.0
Temperatur ^{c} **(°C)**	**60**	32.5 ± 8.8	34.5 ± 8.5	37.9 ± 7.4	40.4 ± 7.7	44.2 ± 2.9
	80	51.4 ± 7.6	57.7 ± 1.7	61.6 ± 1.7	63.2 ± 2.0	63.3 ± 2.3
	100	66.7 ± 9.3	71.0 ± 5.5	72.2 ± 6.0	71.7 ± 3.1	68.1 ± 2.0
	120	81.0 ± 4.3	82.1 ± 4.5	80.9 ± 2.8	80.4 ± 5.3	77.7 ± 3.7
	140	87.7 ± 1.2	85.0 ± 5.3	85.0 ± 1.7	82.7 ± 0.3	80.4 ± 1.8
	160	86.8 ± 2.3	82.1 ± 1.7	79.8 ± 3.0	78.4 ± 4.0	78.4 ± 2.5
	180	85.9 ± 3.6	82.0 ± 5.0	78.6 ± 3.8	73.8 ± 3.3	73.1 ± 1.2

Tab. 44. Calculations of activation energy and rate constants for 6-fluoroveratraldehyde.

Time (min)	ln (1-RCY)						
	60 °C	**80 °C**	**100 °C**	**120 °C**	**140 °C**	**160 °C**	**180 °C**
5	-0.3930	-0.7215	-1.0996	-1.6607	-2.0956	-2.0249	-1.9590
10	-0.4231	-0.8604	-1.2379	-1.7204	-1.8971	-1.7204	-1.7148
20	-0.4764	-0.9571	-1.2801	-1.6555	-1.8971	-1.5995	-1.5418
30	-0.5175	-0.9996	-1.2623	-1.6296	-1.7545	-1.5325	-1.3394
60	-0.5834	-1.0024	-1.1426	-1.5006	-1.6296	-1.5325	-1.3130

Temp. (°C)	Best linear graph for ln (1-RCY) vs time	Correlation coefficient	k' (min⁻¹)	ln k'
80	Y= - 0.0971 – 0.0860 X	-0.93	0.0860	-2.4534
100	Y= - 0.1602 – 0.1238 X	-0.91	0.1238	-2.0891
120	Y= - 0.2668 – 0.1720 X	-0.88	0.1720	-1.7603
140	Y= - 0.3824 – 0.1897 X	-0.82	0.1897	-1.6623

6.4   Appendix 4: Data for 6-Bromoveratraldehyde

Tab. 45. [^{18}F] Labelling data for 6-bromoveratraldehyde. Conditions: ^{a}) 20 mg/mL,160 °C. ^{b}) DMF (1 mL), 160 °C. ^{c}) 20 mg/mL, DMF (1 mL).

Variable		RCY (%) ± Sdv				
		5 min	10 min	20 min	30 min	60 min
Solvent [a]	DMF	30.8 ± 6.6	38.9 ± 5.6	44.5 ± 5.0	44.7 ± 4.0	45.5 ± 5.4
	DMAc	19.8 ± 5.3	22.1 ± 3.3	23.4 ± 2.3	25.6 ± 2.1	27.2 ± 0.2
	DMSO	3.2 ± 0.7	3.2 ± 1.2	3.5 ± 0.9	2.7 ± 1.0	2.4 ± 1.0
	Sulfolane	6.8 ± 2.5	10.2 ± 2.6	13.0 ± 3.1	11.4 ± 2.3	11.4 ± 0.3
Concentration [b] (mg/mL)	0.5	4.4 ± 0.9	6.6 ± 1.7	6.1 ± 3.1	5.1 ± 3.5	5.6 ± 1.7
	1	15.9 ± 4.5	17.6 ± 5.1	17.2 ± 4.3	15.9 ± 2.2	16.5 ± 1.1
	5	23.4 ± 3.4	27.4 ± 3.8	30.1 ± 2.8	31.1 ± 4.2	32.8 ± 0.9
	10	24.8 ± 1.9	28.9 ± 0.7	31.1 ± 1.7	32.2 ± 0.7	35.3 ± 0.7
	20	30.8 ± 6.6	38.9 ± 5.6	44.5 ± 5.0	44.7 ± 4.0	45.5 ± 5.4
	30	41.4 ± 6.8	44.5 ± 4.4	45.5 ± 1.8	50.3 ± 4.6	51.3 ± 4.2
	50	50.4 ± 1.7	54.2 ± 2.2	56.9 ± 0.9	58.1 ± 0.4	58.1 ± 0.8
Temperatur [c] (°C)	80	1.3 ± 0.7	2.4 ± 0.7	2.7 ± 1.0	3.5 ± 1.0	5.1 ± 0.3
	100	5.1 ± 1.1	8.5 ± 1.6	12.8 ± 3.1	14.3 ± 2.9	16.2 ± 0.8
	120	15.3 ± 3.4	18.6 ± 5.1	23.9 ± 5.9	27.2 ± 4.7	29.1 ± 2.4
	140	36.7 ± 2.9	38.9 ± 2.6	42.3 ± 4.0	4.3 ± 3.9	40.5 ± 1.8
	160	30.8 ± 6.6	38.9 ± 5.6	44.5 ± 5.0	44.7 ± 4.0	45.5 ± 5.4
	180	45.7 ± 9.0	49.8 ± 9.3	50.2 ± 9.6	49.2 ± 8.5	49.9 ± 11.1

Tab. 46. Calculations of activation energy and rate constants for 6-bromoveratraldehyde.

Time (min)	ln (1-RCY)					
	80 °C	**100 °C**	**120 °C**	**140 °C**	**160 °C**	**180 °C**
5	-0.0131	-0.0523	-0.1661	-0.4573	-0.3682	-0.6106
10	-0.0243	-0.0888	-0.2058	-0.4927	-0.4927	-0.6892
20	-0.0274	-0.1370	-0.2731	-0.5499	-0.5888	-0.6972
30	-0.0356	-0.1543	-0.3175	-0.5499	-0.5924	-0.6773
60	-0.0523	-0.1767	-0.3439	-0.5192	-0.6070	-0.6911

Temp. (°C)	Best linear graph for ln (1-RCY) vs time	Correlation coefficient	k' (min⁻¹)	ln k'
80	Y= - 3.1667E⁻⁴ – 0.0024 X	-1.00	0.0024	-6.0323
100	Y= - 0.0026 – 0.0089 X	-0.99	0.0089	-4.7217
120	Y= - 0.0211 – 0.0206 X	-094	0.0206	-3.8825
140	Y= - 0.0703 – 0.0493 X	-0.90	0.0493	-3.0098

6.5   Appendix 5: Data for 6-Chloroveratraldehyde

Tab. 47. [^{18}F] Labelling data for 6-chloroveratraldehyde. Conditions: ^{a}) 20 mg/mL,160 °C. ^{b}) DMF (1 mL), 160 °C. ^{c}) 20 mg/mL, DMF (1 mL).

Variable		RCY (%) ± Sdv				
		5 min	**10 min**	**20 min**	**30 min**	**60 min**
Solvent [a]	**DMF**	45.8 ± 8.9	52.0 ± 9.7	56.5 ± 6.7	56.4 ± 7.1	57.4 ± 5.6
	DMAc	9.3 ± 3.2	10.9 ± 3.1	11.3 ± 4.6	11.5 ± 4.4	11.8 ± 1.6
	DMSO	1.6 ± 0.8	3.3 ± 0.9	3.7 ± 1.1	3.6 ± 0.7	3.3 ± 0.4
	Sulfolane	6.9 ± 1.6	6.1 ± 1.6	7.5 ± 1.3	7.7 ± 1.6	9.1 ± 0.3
Concentration [b] **(mg/mL)**	**0.5**	8.1 ± 2.7	11.7 ± 2.3	12.0 ± 1.3	12.9 ± 1.6	13.8 ± 0.4
	1	19.1 ± 4.2	22.7 ± 5.5	22.1 ± 4.4	22.2 ± 4.2	24.5 ± 1.4
	5	39.5 ± 4.4	43.2 ± 4.5	46.0 ± 5.1	44.7 ± 9.1	46.5 ± 2.5
	10	44.6 ± 3.1	46.5 ± 4.7	50.1 ± 3.8	52.4 ± 3.0	56.5 ± 1.2
	20	45.8 ± 8.9	52.0 ± 9.7	56.5 ± 6.7	56.4 ± 7.1	57.4 ± 5.6
	30	56.9 ± 6.9	59.3 ± 4.5	60.4 ± 6.1	60.0 ± 2.1	60.1 ± 1.2
	50	63.5 ± 5.2	64.0 ± 1.4	65.6 ± 3.6	63.4 ± 5.5	52.8 ± 5.4
Temperatur [c] **(°C)**	**80**	1.9 ± 0.9	3.0 ± 0.6	3.9 ± 0.7	4.4 ± 1.2	4.8 ± 0.2
	100	8.0 ± 3.5	12.5 ± 3.4	17.1 ± 3.9	17.7 ± 3.8	19.9 ± 1.6
	120	12.4 ± 5.6	18.6 ± 5.4	26.9 ± 8.6	30.8 ± 8.6	34.3 ± 8.1
	140	53.1 ± 1.3	56.9 ± 6.6	54.8 ± 5.5	52.3 ± 4.1	51.5 ± 1.0
	160	45.8 ± 8.9	52.0 ± 9.7	56.5 ± 6.7	56.4 ± 7.1	57.4 ± 5.6
	180	51.5 ± 10.9	54.1 ± 9.5	57.3 ± 7.8	52.5 ± 10.2	53.0 ± 4.8

Tab. 48.	Calculations of activation energy and rate constants for 6-chloroveratraldehyde.

Time (min)	ln (1-RCY)					
	80 °C	100 °C	120 °C	140 °C	160 °C	180 °C
5	-0.0192	-0.0834	-0.1324	-0.7572	-0.6125	-0.7236
10	-0.0305	-0.1335	-0.2058	-0.8416	-0.7340	-0.7787
20	-0.0398	-0.1875	-0.3133	-0.7941	-0.8324	-0.8510
30	-0.0450	-0.1948	-0.3682	-0.7402	-0.8301	-0.7444
60	-0.0492	-0.2219	-0.4201	-0.7236	-0.7444	-0.7550

Temp. (°C)	Best linear graph for ln (1-RCY) vs time	Correlation coefficient	k' (min^{-1})	ln k'
80	Y= - 0.0013 – 0.0031 X	-0.99	0.0031	-5.7764
100	Y= - 0.0056 – 0.0134 X	-0.99	0.0134	-4.3125
120	Y= - 0.0098 – 0.0206 X	.0.99	0.0206	-3.8825
140	Y= - 0.1121 – 0.0842 X	-0.91	0.0842	-2.4746
160	Y= - 0.0818 – 0.0734 X	-0.93	0.0734	-2.6118
180	Y= - 0.1114 – 0.0779 X	-0.90	0.0779	-2.5523

6.6 Appendix 6: Data for 6-Nitropiperonal

Tab. 49. [^{18}F] Labelling data for 6-nitropiperonal. Conditions: [a]) 20 mg/mL, 140 °C. [b]) DMF (1 mL), 140 °C. [c]) 20 mg/mL, DMF (1 mL).

Variable		RCY (%) ± Sdv				
		5 min	10 min	20 min	30 min	60 min
Solvent [a]	DMF	67.6 ± 5.2	67.0 ± 6.6	61.3 ± 5.1	59.4 ± 4.6	58.1 ± 4.8
	DMAc	70.8 ± 0.4	75.3 ± 1.6	73.6 ± 2.3	72.1 ± 2.2	67.8 ± 1.2
	DMSO	57.2 ± 4.2	56.4 ± 2.6	53.6 ± 2.7	52.4 ± 2.3	51.5 ± 1.4
	Sulfolane	59.3 ± 2.6	59.1 ± 3.1	54.7 ± 2.1	53.5 ± 2.2	51.1 ± 1.3
	1,2-DME	10.7 ± 5.7	14.4 ± 4.4	21.3 ± 2.5	29.2 ± 2.8	31.8 ± 2.6
Concentration [b] (mg/mL)	0.5	36.3 ± 7.7	26.5 ± 6.8	15.5 ± 4.7	9.7 ± 1.9	9.0 ± 0.9
	1	58.9 ± 7.7	47.5 ± 3.5	30.7 ± 5.3	16.0 ± 1.4	13.5 ± 1.3
	5	62.0 ± 4.3	55.8 ± 6.1	43.5 ± 5.9	35.0 ± 5.1	35.3 ± 1.1
	10	60.9 ± 5.7	62.9 ± 5.1	61.7 ± 7.6	59.8 ± 8.9	57.4 ± 3.0
	20	67.6 ± 5.2	67.0 ± 6.6	61.3 ± 5.1	59.4 ± 4.6	58.1 ± 4.8
	30	56.6 ± 7.0	54.0 ± 6.6	54.9 ± 8.0	53.8 ± 4.2	51.58 ± 1.5
	50	57.0 ± 7.4	54.2 ± 8.0	51.3 ± 6.3	51.1 ± 5.7	52.0 ± 6.6
Temperatur [c] (°C)	80	57.7 ± 3.8	60.3 ± 2.7	61.7 ± 2.4	62.1 ± 1.6	59.9 ± 1.1
	100	57.7 ± 4.7	59.8 ± 5.7	61.4 ± 6.0	61.2 ± 5.4	63.2 ± 7.7
	120	72.0 ± 3.6	69.6 ± 6.1	69.8 ± 1.4	67.3 ± 3.2	63.8 ± 3.2
	140	67.6 ± 5.2	67.0 ± 6.6	61.3 ± 5.1	59.4 ± 4.6	58.1 ± 4.8
	160	66.7 ± 2.4	64.7 ± 3.2	60.3 ± 3.3	57.7 ± 5.0	56.7 ± 2.1
	180	72.8 ± 1.9	70.1 ± 0.7	65.1 ± 2.6	61.7 ± 1.4	59.4 ± 0.9

Tab. 50. Calculations of activation energy and rate constants for 6-nitropiperonal.

Time (min)	ln (1-RCY)					
	80 °C	**100 °C**	**120 °C**	**140 °C**	**160 °C**	**180 °C**
5	-0.8604	-0.8604	-1.2730	-1.1270	-1.0996	-1.3020
10	-0.9238	-0.9113	-1.1907	-1.1087	-1.0413	-1.2073
20	-0.9597	-0.9519	-1.1973	-0.9493	-0.9238	-1.0527
30	-0.9702	-0.9467	-1.1178	-0.9014	-0.8604	-0.9597
60	-0.9138	-0,9997	-1.0161	-0.8700	-0.8370	-0.9014

Temp. (°C)	Best linear graph for ln (1-RCY) vs time	Correlation coefficient	k' (min⁻¹)	ln k'
80	Y= - 0.1328 – 0.0924 X	-0.90	0.0924	-2.3816
100	Y= - 0.1349 – 0.0911 X	-0.89	0.0911	-2.3958
120	Y= - 0.2256 – 0.1191 X	-0.84	0.1191	-2.1278
140	Y= - 0.1909 – 0.1109 X	-0.86	0.1109	-2.1991

6.7 Appendix 7: Data for 6-Bromopiperonal

Tab. 51. [^{18}F] Labelling data for 6-bromopiperonal

Temp. (°C)	n	RCY (%)									
		5 min		10 min		20 min		30 min		60 min	
		Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv
80	4	5.7	0.3	7.3	0.6	9.4	0.9	10.0	0.8	9.1	0.5
100	5	7.3	0.9	8.9	0.7	9.6	0.9	10.5	0.5	10.2	0.5
120	4	7.7	0.6	9.1	1.0	10.1	0.8	10.3	0.6	10.6	0.4
140	5	9.7	0.5	11.4	1.1	11.1	1.0	11.8	1.1	11.7	1.0
160	5	10.4	0.3	11.0	1.3	10.9	1.1	10.0	0.7	9.9	1.1
180	4	6.2	0.2	6.7	1.3	10.2	0.6	10.6	0.8	11.0	1.2

6.8 Appendix 8: Data for 6-Chloropiperonal

Tab. 52. [^{18}F] Labelling data for 6-chloropiperonal

Temp. (°C)	n	RCY (%)									
		5 min		10 min		20 min		30 min		60 min	
		Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv	Mean	Sdv
80	4	3.8	0.4	4.3	0.5	4.9	0.6	4.4	0.4	4.5	0.2
100	5	5.3	1.1	6.6	0.5	5.4	0.5	5.2	0.3	5.0	0.2
120	4	8.5	0.5	7.9	0.2	7.5	0.9	6.6	0.1	6.6	0.1
140	10	9.7	0.6	11.3	1.4	10.2	0.9	9.3	1.2	9.4	0.4
160	5	8.6	0.1	7.8	1.0	7.1	0.2	7.4	0.1	7.3	0.3
180	3	9.2	0.3	9.8	1.4	10.9	0.5	11.5	1.8	10.7	05

6.9   Appendix 9: Data for 2,3-Dimethoxy-6-nitrobenzaldehyde

Tab. 53. [^{18}F] Labelling data for 2,3-dimethoxy-6-nitrobenzaldehyde. Conditions: [a]) 20 mg/mL,140 °C . [b]) DMF (1 mL), 140 °C. [c]) 20 mg/mL, DMF (1 mL).						
Variable		**RCY (%) ± Sdv**				
		5 min	**10 min**	**20 min**	**30 min**	**60 min**
Solvent [a]	**DMF**	21.6 ± 0.6	28.2 ± 3.8	30.5 ± 3.4	27.5 ± 2.1	28.1 ± 1.8
	DMAc	12.3 ± 4.6	16.6 ± 3.6	17.7 ± 3.0	17.8 ± 2.1	8.5 ± 0.2
	DMSO	16.4 ± 3.2	18.8 ± 5.0	19.5 ± 3.3	20.2 ± 0.4	19.4 ± 2.1
	Sulfolane	6.9 ± 2.2	8.6 ± 2.4	9.1 ± 1.3	8.6 ± 2.2	8.3 ± 2.3
	benzonitrile	11.9 ± 3.5	16.3 ± 4.2	15.0 ± 2.0	14.9 ± 1.8	16.1 ± 1.5
Concentration [b] **(mg/mL)**	**10**	19.8 ± 2.1	23.9 ± 3.1	28.3 ± 3.6	25.7 ± 1.8	26.2 ± 2.2
	20	21.6 ± 0.6	28.2 ± 3.8	30.5 ± 3.4	27.5 ± 2.1	28.1 ± 1.8
Temperatur [c] **(°C)**	**80**	2.8 ± 0.6	5.0 ± 1.0	9.3 ± 1.6	11.5 ± 1.9	12.9 ± 2.7
	100	7.3 ± 1.4	16.9 ± 3.1	16.3 ± 2.7	15.4 ± 1.9	13.9 ± 3.3
	120	8.0 ± 0.8	11.1 ± 0.6	14.1 ± 2.5	15.0 ± 2.6	14.8 ± 0.6
	130	16.3 ± 4.6	20.2 ± 4.7	21.4 ± 4.4	21.5 ± 4.9	22.5 ± 4.3
	140	21.6 ± 0.6	28.2 ± 3.8	30.5 ± 3.4	27.5 ± 2.1	28.1 ± 1.8
	150	20.3 ± 2.7	28.5 ± 1.8	29.8 ± 4.9	29.1 ± 3.8	30.4 ± 3.9

Tab. 54. Calculations of activation energy and rate constants for 2,3-dimethoxy-6-nitrobenzaldehyde.

Time (min)	ln (1-RCY)					
	80 °C	100 °C	120 °C	130 °C	140 °C	150 °C
5	-0.0284	-0.0834	-0.0758	-0.1779	-0.2433	-0.2269
10	-0.0513	-0.1177	-0.1851	-0.2256	-0.3313	-0.3355
20	-0.0976	-0.1520	-0.1779	-0.2408	-0.3638	-0.3538
30	-0.1222	-0.1625	-0.1912	-0.2421	-0.3216	-0.3439
60	-0.1347	-0.1497	-0.1803	-0.2549	-0.3300	-0.3624

Temp. (°C)	Best linear graph for ln (1-RCY) vs time	Correlation coefficient	k' (min^{-1})	ln k'
80	Y= - 9.1667E^{-4} – 0.0051 X	-1.00	0.0051	-5.2785
100	Y= 0.0082 – 0.0118 X	-0.97	0.0118	-4.4396
120	Y= - 0.0056 – 0.0185 X	-0.995	0.0185	-4.000
130	Y= - 0.0217 – 0.0226 X	-0.95	0.0226	-3.7898
140	Y= - 0.0259 – 0.0331X	-0.97	0.0331	-3.4082

Tab. 55. Crystal data, data collection and structure refinement for
2,3-dimethoxy-6-nitrobenzaldehyde

Empirical formula	$C_9H_9NO_5$
Formula weight	211.17
Temperature	213 (2) K
Wavelength/radiation	1.54184 A / CuK/a
Crystal system/space group	Monoclinic / P21 /c
Unit cell dimensions	a= 4.0807 (4) Å b= 14.6077 (17) Å c= 15.7792 (15) Å alpha = 90 deg. beta = 97.230 deg. gamma = 90 deg.
Volume	933.11 (16) Å^3
Z	4
Density	1.503 mg/m^3
F(000)	440
Crystal size	0.50 x 0.20 x 0.50 mm
Reflections collected	2473
Reflections (lattice)	13.194 to 26.3045 deg.
Independent reflections	1578 [R(int)= 0.0424]
Reflections observed	1225
Criterion for observation	> 2 sigma (I)
Absorption correction	DIFABS
Max. and min transmission	0.682 and 0.216
Measurement method	Omega
Standard reflections	3
Structure solution	SHELXS-97 (Sheldrick, 1990)
Structure refinement	SHELXS-97 (Sheldrick, 1997)
Molecular graphics	PLATON
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1578 / 0 / 172
Final R indices [i>2sigma[I]]	R1= 0.0526 wR2= 0.1380
Goodness of fit on F2	1.027
Final R indices (all) R1/Wr2	0.0715 / 0.1527

Lebenslauf

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