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# $^{18}$F-Labelled catecholamine type radiopharmaceuticals in the diagnosis of neurodegenerative diseases and neuroendocrine tumours: approaches to synthesis and development prospects

**Sergey Z. Vatsadze, Olga E. Eremina, Irina A. Veselova, Stepan N. Kalmykov, Valentin G. Nenajdenko**

*Department of Chemistry, Lomonosov Moscow State University*
*Leninskie Gory 1, stroenie 3, 119991 Moscow, Russian Federation*

The pathogenesis of many socially significant diseases such as neurodegenerative dementias and neuroendocrine tumours involves imbalance of neurotransmitters. Among the known neuroimaging methods, positron emission tomography (PET) is the most perfect and informative technique for diagnosing these diseases. The potential of PET is largely determined by the inventory of available radiopharmaceuticals, that is, biologically active molecules containing short-lived nuclides with positron decay. This review gives a systematic account of the application of fluorine-18-labelled catecholamine type radiopharmaceuticals in clinical investigations of the sympathetic and central nervous systems. The methods for the synthesis of these agents and existing problems are considered. The material is arranged according to the mechanisms of reactions that underlie the synthetic approaches: electrophilic, nucleophilic and metal-catalyzed reactions.
The bibliography includes 198 references.

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## 1. Introduction

A significant problem of modern neurosciences is diagnosis and treatment of socially significant diseases such as neurodegenerative diseases (NDDs)[1–3] and neuroendocrine tumours (NETs),[4–6] the pathogenesis of which is related to neurotransmitter imbalance in the human body.[7]

It is noteworthy that the methods of diagnosis of NDDs and NETs are rather well developed and are actively employed in clinical practice.[8,9] As a rule, these methods are used to establish and verify the diagnosis; however, changes in the brain that cannot be visualized by conventional anatomical and morphological methods [computed X-ray tomography (CT) and magnetic resonance imaging (MRI)] appear long before the first symptoms. The progress in the development of modern instrumental methods and the strategies of fine organic synthesis open up increasing opportunities for diagnosing both NDDs and NETs in early stages before the clinical signs appear. The key low-molecular-weight markers of neurotransmitter balance are ca-

**S.Z.Vatsadze**. Doctor of Chemical Sciences, Professor at the Department of Chemistry, MSU.
Telephone: +7(495)939–1234, e-mail: szv@org.chem.msu.ru
**Current research interests**: supramolecular chemistry, coordination polymers, exo- and endo-receptors, polyfunctional heterocycles, bioimaging, synthesis of radiopharmaceuticals based on fluorine and copper, mechanisms of organic reactions.
**O.E.Eremina**. Junior Researcher at the same Department.
Telephone: +7(495)939–3346,
e-mail: olga.eremina@analyt.chem.msu.ru
**Current research interests**: spectroscopic methods of analysis, nuclear and radiation medicine, analytical chemistry, methods for determining diagnostic markers of neurotransmitter exchange disorders, determination of catecholamines and their metabolites in biological fluids.
**I.A.Veselova**. Candidate of Chemical Sciences, Assistant Professor at the same Department.
Telephone: +7(495)939–3346, e-mail: irina.veselova@mail.ru
**Current research interests**: analytical chemistry, nuclear and radiation medicine, diagnosis of neuroendocrine tumours and neurodegenerative diseases, chemical analysis of biological fluids.
**S.N.Kalmykov**. Corresponding Member of the RAS, Doctor of Chemical Sciences, Head of the Division of Radiochemistry and Deputy Dean for Science at the same Department.
Telephone: +7(495)939–4319, e-mail: stepan_5@hotmail.com
**Current research interests**: nuclear and radiation medicine, radiopharmaceuticals and radionuclides; pharmaceutical, preclinical and clinical studies.
**V.G.Nenajdenko**. Doctor of Chemical Sciences, Professor, Head of the Division of Organic Chemistry at the same Department.
Telephone: +7(495)939–2276, e-mail: nenajdenko@gmail.com
**Current research interests**: fluoroorganic chemistry, chirality, peptide synthesis, cyclic imines, click chemistry, multicomponent reactions, olefination, heterocyclic compounds.

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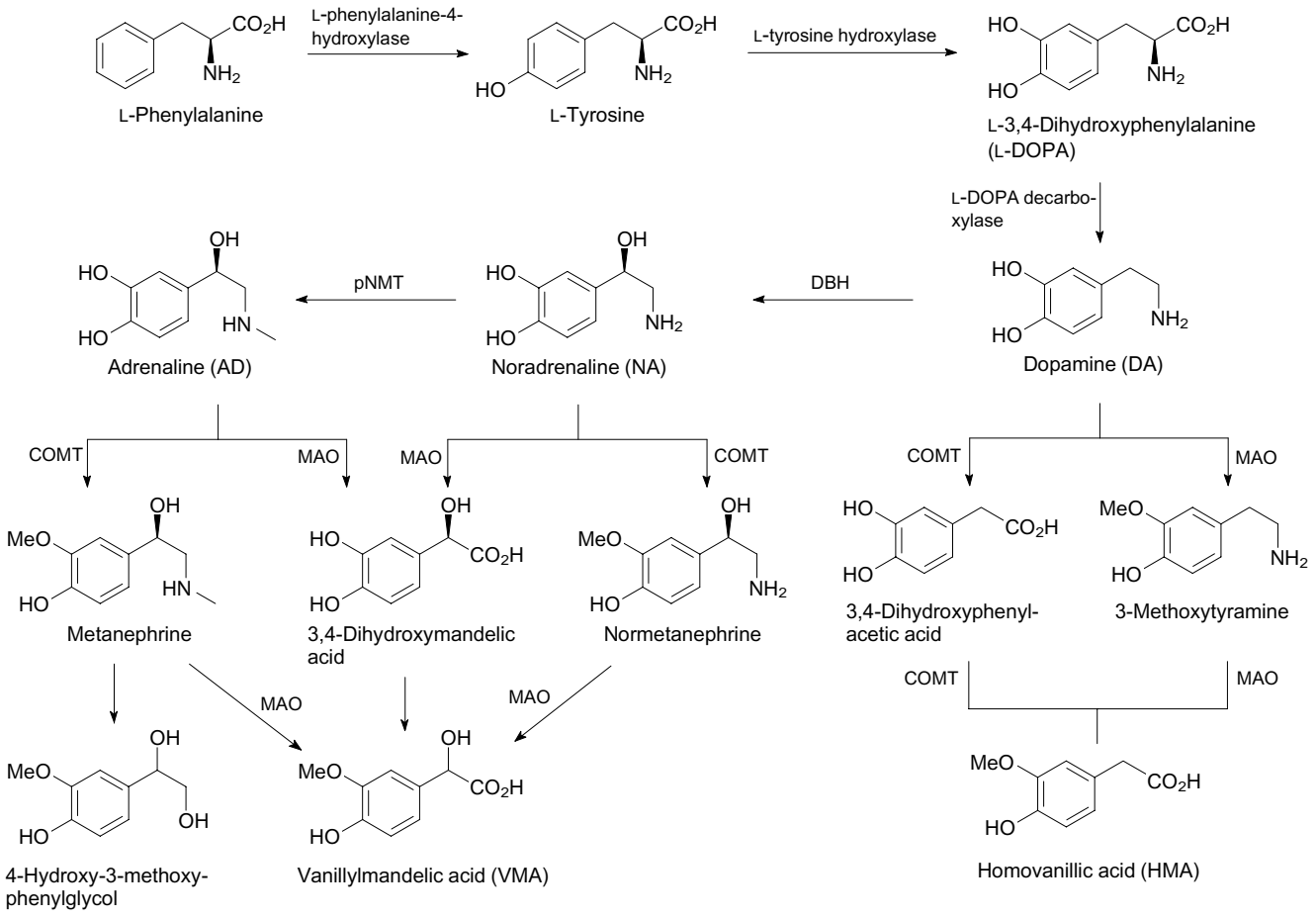
techolamines (CAs) — dopamine [4-(2-aminoethyl)phenyl-1,2-diol], adrenaline {or epinephrine, 4-[(1*R*)-1-hydroxy-2-(methylamino)ethyl]phenyl-1,2-diol}, noradrenaline {or norepinephrine, 4-[(1*R*)-2-amino-1-hydroxyethyl]phenyl-1,2-diol} — and their metabolites such as vanillylmandelic [2-hydroxy-2-(4-hydroxy-3-methoxyphenyl)acetic] and homovanillic (4-hydroxy-3-methoxyphenylacetic) acids, metanephrine [L-(4-hydroxy-3-methoxyphenyl)(methylaminomethyl)methanol] and normetanephrine [L-aminomethyl(4-hydroxy-3-methoxyphenyl)methanol], which are formed in O-methylation reactions catalyzed by the catechol-*O*-methyltransferase (COMT) enzyme and oxidative deamination reaction performed by monoamine oxidase (MAO).[10] Thus, the possibility to monitor the changes in the biosynthesis and metabolism processes (Scheme 1) and in the perception of CA by the body provides a promising solution for preclinical diagnosis of both neurodegenerative diseases and neuroendocrine tumours soon after the onset of the pathological process.

Details of PET/CT and PET/MRI diagnosis (PET is positron emission tomography) of the mentioned diseases are the subjects of numerous publications;[6, 11 – 18] therefore, in this review, we will briefly consider the most important aspects of the diseases related to neurotransmitter imbalance, which attest to the relevance of using PET with $^{18}$F-labelled catecholamine type radiopharmaceuticals ($^{18}$F-RPs). In our opinion based on the thorough investigation of the published sources, $^{18}$F-labelled 6-fluorodopamine is the most promising out of these agents for diagnosing and predicting the development of neurodegenerative diseases and neuroendocrine tumours. Therefore, of substantial interest is to consider approaches to the synthesis of catecholamine type $^{18}$F-RPs, in particular, 6-[$^{18}$F]fluorodopamine, because the short half-life of this radionuclide ($t_{1/2}$ = 110 min) dictates special requirements to the rapidity and efficiency of synthetic procedures. The issues of $^{18}$F introduction into phenols as models of catecholamines are also considered. The publications of the last 5 – 10 years are analyzed in detail and arranged systematically.

### 1.1. Neurodegenerative diseases

The development of NDDs, *i.e.*, degenerative diseases of the central nervous system, is accompanied by progressive death of nerve cells; this reduces the content of CAs and their metabolites in the body. The disorders lead to characteristic changes in the CA biosynthesis and metabolism processes.[19] The key neurodegenerative disorders include Alzheimer's (AD) and Parkinson's (PD) diseases, which are most frequently encountered and well-known NDDs, as well as the Huntington chorea, diffuse Lewy body disease, Pick disease, hyperprolactinemia and some other.[1, 2] Neurodegenerative diseases arise mainly in the senior age; the increase in the life span of people in developed countries is

**Scheme 1**




DBH is dopamine-β-hydroxylase, pNMT is phenylethanolamine *N*-methyltransferase

accompanied by permanent growth of the number of NDD patients. Unfortunately, the development of NDDs always has serious consequences: patient disability, the necessity of expensive rehabilitation, and lethal outcome, which is a grave problem of the modern society.[1] The pre-symptom diagnosis of NDDs, early detection of cognitive deficiency and non-progressive cognitive decline, timely preventive therapy and extension of the comfort life of a potential patient are highly important issues of the fight for national health.

### 1.2. Neuroendocrine tumours

The diagnosis of neuroendocrine tumours is also a considerable problem, because most of biochemical and pathological anatomical laboratories do not have at disposal the appropriate diagnostic capabilities.[20] Often, malignant neoplasms are diagnosed only in retrospective, that is, during the development of metastatic or recurrent stage of the disease. In 2013, more than 500 thousand cases of cancer were newly diagnosed in Russia alone; this is 15% more than in 2003. By the end of 2013, more than 3 million patients were registered in the regional cancer care facilities of Russia.[19]

The diseases of neuroendocrine system are characterized by enhanced synthesis of CAs due to organic lesion or genetic defectiveness of hypothalamus.[19] Phaeochromocytoma and paraganglioma, which are benign and malignant catecholamine-producing tumours, are the most serious diseases of this type, the development of which is accompanied by increasing level of catecholamines in the body. They are formed from chromaffin cells of the sympathoadrenal system, which are localized in adrenal medulla in 90% of cases.[21] Carcinoid tumours account for $<1\%$ of all malignant tumours and, in most cases, they appear in the gastrointestinal tract. They are formed from the cells of the diffuse neuroendocrine system, which arises from the neural crest cells during embryogenesis, and migrate to different organs.[22] One more malignant tumour is neuroblastoma, a sympathetic nervous system tumour, giving rise to numerous metastases. Most of such tumours occur in the retroperitoneal space, most often, in adrenal glands, and more rarely they are found in the mediastinum and in the neck. Neuroblastoma is most frequent in children below 10 years of age.[23] The NETs include also small-cell cancer,[24] tumours of the adenohypophysis,[25] adrenocortical cancer,[26] pancreatic endocrine tumours (insulinoma, somatostatinoma, glucagonoma and gastrinoma)[27,28] and medullary cancer.[29]

## 2. Radiopharmaceuticals based on $^{18}$F for positron emission tomography

Neuroiomaging methods are now efficiently used for the diagnosis of both NDDs and NETs. Unlike the widely employed MRI and CT, which provide an anatomical image of the organs, planar scintigraphy (PS), single-photon emission computed tomography (SPECT) and PET are functional diagnosis methods, which give characteristics of important biochemical processes (metabolism, perfusion, and receptor and neurotransmitter interactions). The amount of information provided by these methods has substantially increased with the advent of hybrid technologies (PET/CT, PET/MRI, *etc.*),[1,30,31] in which areas of biochemical changes can be superimposed onto anatomical structures. A perfect method for preclinical diagnosis should be not only highly sensitive, but also sufficiently specific with respect to various kinds of NDDs and NETs, and should directly reflect the changes caused by the therapy, which may be achieved by imaging of the neurotransmitter imbalance and CA metabolism disorders.

The CT and MRI methods are included in the standard set of diagnostic examination of dementia patients. The diagnosis of AD and PD is based on evaluation of the pattern of metabolic impairment and deformation of tissue structure.[32] In recent years, these methods for NDD and NET diagnosis have been often supplemented by PET, which is based on the use of radiopharmaceuticals (RPs, radiotracers) containing radionuclides with a positron type of decay. The positron decay is accompanied by the formation of two annihilation $\gamma$-quanta with an energy of 0.511 MeV emitted at an angle of 180°, which are detected by the external ring detector system of the PET chamber.[33–35]

The capabilities of the PET/CT method are largely determined by the range of available radiopharmaceuticals, which are injected in advance into the human body.[19] As a rule, biologically significant short-lived ($^{18}$F) (Ref. 36) and ultra-short-lived ($^{11}$C, $^{13}$N, $^{15}$O) positron-emitting radionuclides are used as radiotracers in PET.[37,38] In addition, 'alternative' positron emitters, including those with longer half-lives, have started to be used in recent years; this makes it possible to diagnose processes with slow pharmacokinetics. Among such radionuclides, $^{68}$Ga and $^{64}$Cu are already applied, and $^{89}$Zr and $^{86}$Y have prospects for the use in the future.[39–41]

In the clinical and preclinical PET/CT examination, RPs with the $^{18}$F radionuclide are employed most widely, which is caused by favourable nuclear physical properties, including

— high probability of $\beta^+$-decay (97%);

— low positron energy (0.64 MeV) and short range in tissue (at most 2.4 mm), which gives rise to high-resolution PET images;

— half-life (110 min) that allows for transportation of $^{18}$F-RPs from the production site to the near-by PET centres;

and also owing to

— simple preparation of large amounts of $^{18}$F ($>20$ Ci per single irradiation) in dedicated PET cyclotrons upon irradiation with $^{18}$O-enriched water protons;

— possibility to obtain RPs with high specific activity;

— relatively high radiochemical yields (20%–70%) of $^{18}$F-RP syntheses, which enables the manufacture of tens of clinical doses in one synthesis.[42,43]

### 2.1. $^{18}$F -Based radiopharmaceuticals used in PET/CT diagnosis of neurodegenerative diseases

The most popular and accessible RP that is used in 90% of clinical PET/CT examinations is [$^{18}$F]2-fluoro-2-deoxy-D-glucose ([$^{18}$F]FDG). In the case of NDDs, this RP is used for PET examination of AD patients, because they tend to have reduced glucose consumption in brain hemispheres, which is reflected as asymmetric accumulation of the radioactive glucose analogue.[44] However, as a rule, due to the lack of specificity of this radiotracer and high background level of the physiological glucose accumulation by grey matter, PET with [$^{18}$F]FDG gives little information, estab-

lishing the correct diagnosis in early stages of NDD being a challenge even for experienced doctors.

It is possible to employ specific RPs — receptor radioligands — to diagnose various kinds of NDDs by PET/CT. For example, AD is accompanied by the formation of neurofibrillary tangles in neurons and senile plaques, which is associated with deposition of abnormal proteins: the tau-protein and the β-amyloid protein, respectively. A wide range of $^{18}$F derivatives are applicable as radiotracers for imaging of these two pathological processes; in particular, imaging of the β-amyloid proteins is performed most often using [$^{18}$F]FDDNP ([$^{18}$F](2-(1-{6-[(2-fluoroethyl)(methyl)amino]-2-napthyl}ethylidene)malononitrile),[45] [$^{18}$F]flutemetamol (3′-F-PiB; $^{18}$F-labelled 'Pittsburgh compound B'),[46] [$^{18}$ F]florbetaben ($^{18}$F-AV-1)[47] and [$^{18}$F]florbetapir ($^{18}$F-AV-45).[48] The imaging of tau-proteins[11] is accomplished most often using 2-aryl-6-fluoroalkyloxyquinolines [$^{18}$F]THK-523,[49] [$^{18}$F]THK-5351,[50] [$^{18}$F]THK-5105,[51] [$^{18}$F]THK-5117,[52] pyrimido[1,2-*a*]benzimidazole [$^{18}$F]T808,[53] 5*H*-pyrido[4,3-*b*]indole [$^{18}$F]T807[54] and [$^{18}$F]FDDNP (Fig. 1). The structures of radioligands that bind to β-amyloid are similar to the structures of histological stains such as Congo red, thioflavin-T and chrysamine G. However, the key drawback of the $^{18}$F-RPs of this type is high level of non-specific binding to the white matter. Furthermore, receptor radioligands are suitable, first of all, for detecting the fibrillar deposits of β-amyloid and, hence, for observing cerebral β-amyloidosis. The first RP for imaging of senile plaques — [$^{18}$F]FDDNP — has quite a few shortcomings: high degree of non-specific binding, low brain uptake and the absence of validated procedures for quantitative calculation of the kinetics. The [$^{18}$F]THK-523 agent developed in Japan is the first radioligand to selectively bind to the tau-protein (~20 times higher selectivity to the tau-protein than to the β-amyloid protein). More recent studies of the pharmacokinetics of some analogues of this RP — [$^{18}$F]THK-5351, [$^{18}$F]THK-5105 and [$^{18}$ F]THK-5117 — showed even lower affinity to white matter and a higher affinity to the tau-protein.[50–52] More recently, [$^{18}$F]T808 and [$^{18}$F]T807 have been reported, having a 25-fold higher binding affinity to the tau-protein than to the β-amyloid protein and no binding to white matter.[55]

The understanding of the pathophysiological mechanism of various disorders can be improved and, hence, the diagnostic accuracy for NDDs can be enhanced by using PET radiotracers for neurotransmitter systems (cholinergic, serotoninergic, dopaminergic, glutaminergic and noradrenergic), because various NDDs cause different disorders of neurotransmitter balance. The $^{18}$F-labelled L-3,4-dihydroxyphenylalanine analogue — L-[$^{18}$F]-3,4-dihydroxy-6-fluorophenylalanine {L-[$^{18}$F]6-FDOPA, below designated by [$^{18}$ F]FDOPA} was one of the first agents to be used as a $^{18}$F-RP in the PET examination of the dopami-

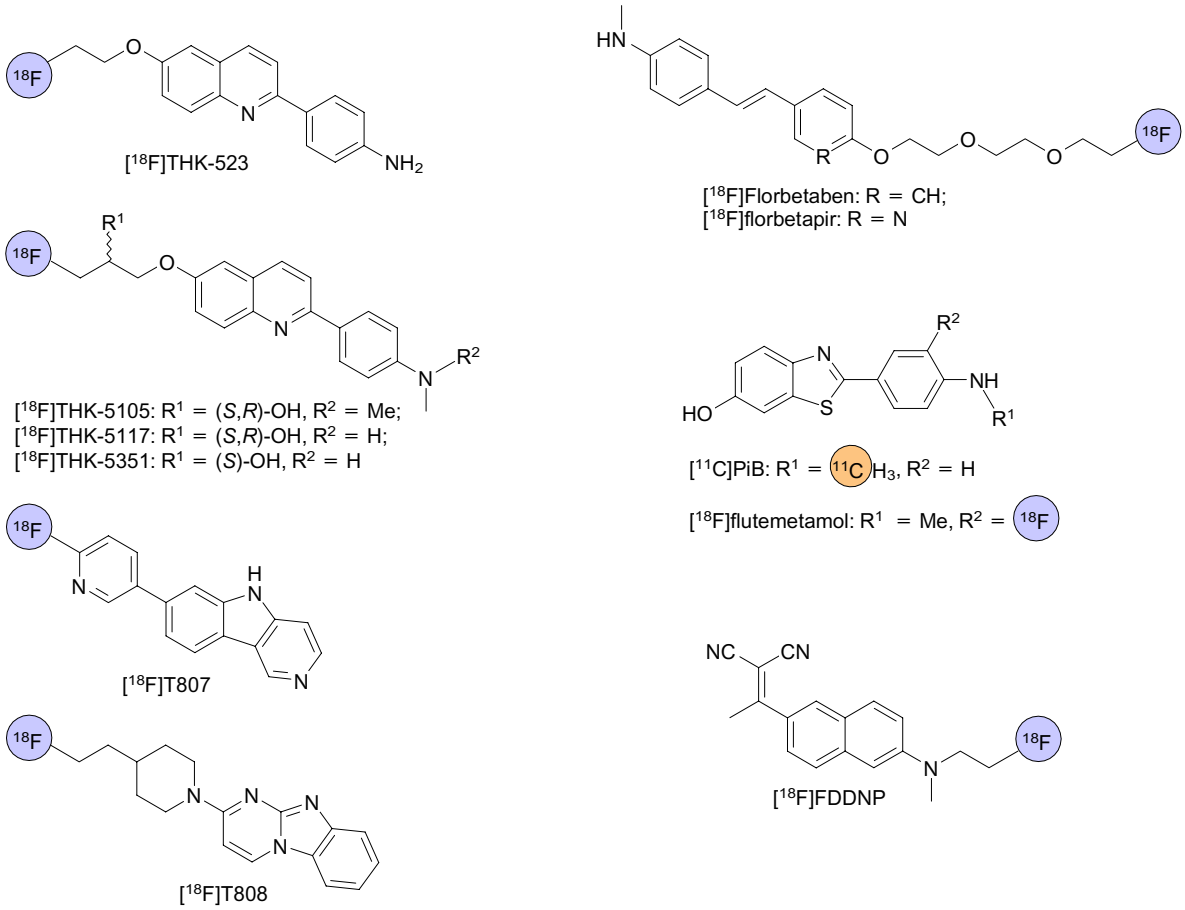



**Figure 1.** Structures of $^{18}$F-labelled radiopharmaceuticals for PET/CT examination of the tau-protein and β-amyloid protein deposition for diagnosis of neurodegenerative disorders.

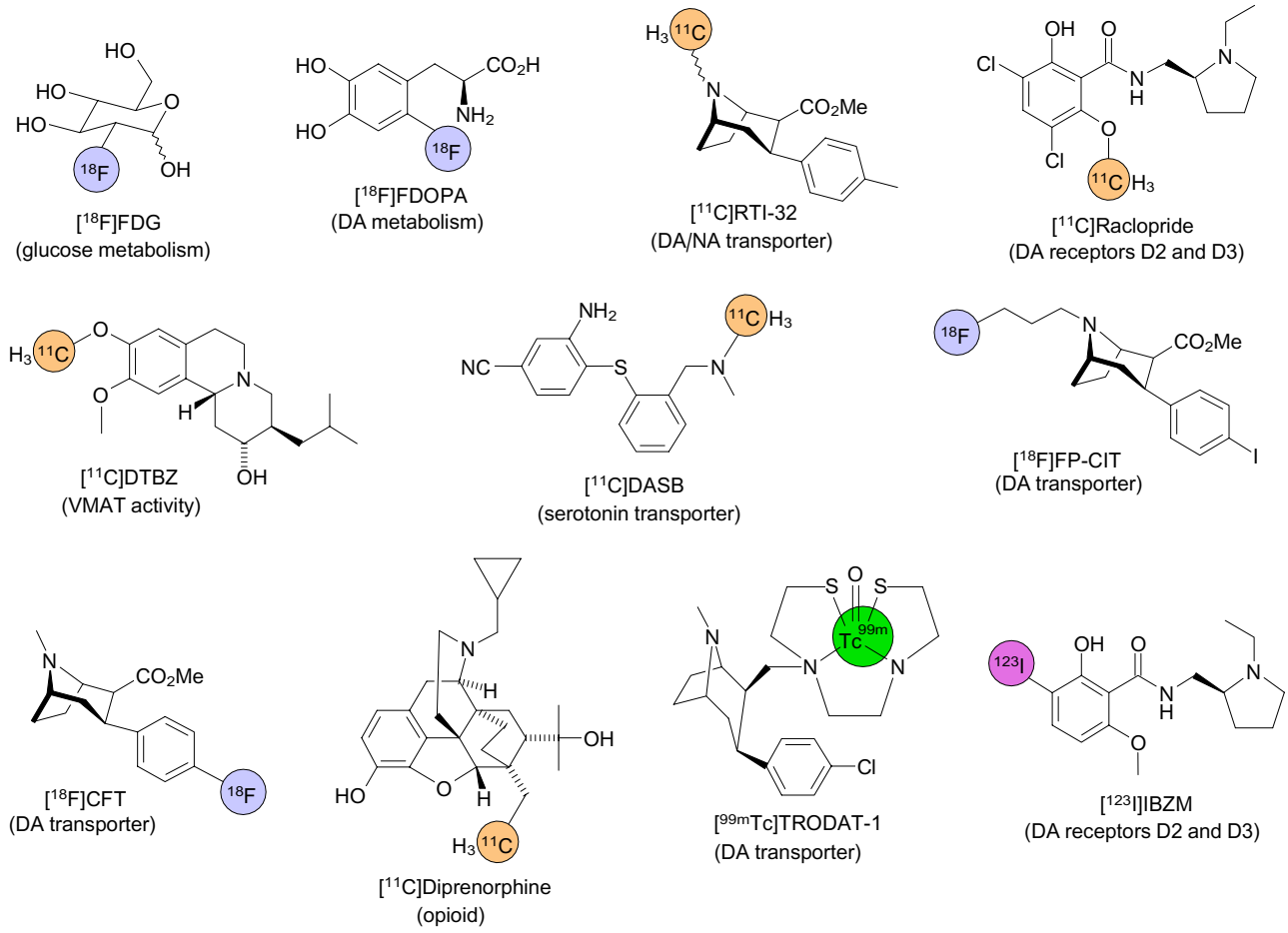



**Figure 2.** Structures of radiopharmaceuticals for PET and SPECT molecular imaging in Parkinson's disease patients.

nergic system and pathogenesis of NDDs (Fig. 2).[15,56–58] The most pronounced disorder in the functioning of the dopaminergic system is inherent in the patients with PD and other analogous NDDs. Figure 2 shows the structures of RPs for the PET and SPECT molecular imaging in Parkinson's disease patients based on estimation of L-DOPA decarboxylase activity, accessibility of dopomine (DA) and noradrenaline (NA) transporters, binding affinity of the D2 and D3 receptors, activity of VMAT-2 (vesicular monoamine transporter), serotonin transporter activity, acetylcholinesterase activity, the accessibility of μ-, κ- and δ-binding sites of the opioid receptor and glucose metabolism. A benefit of using [$^{18}$F]FDOPA is that, unlike [$^{18}$F]6-fluorodopamine ([$^{18}$F]FDA), this radiotracer penetrates the blood–brain barrier (BBB) and can be decarboxylated in the presence of L-DOPA decarboxylase to give labelled DA, which is accumulated in the dopaminergic neurons of various brain regions; this provides quantitative information about the density of dopaminergic neurons.

A problem of PET/CT diagnosis and treatment of NDDs is associated with low permeability of the BBB for most RPs and drugs. However, to date, new clinically acceptable, versatile and safe transport methods are known, so that catecholamines, such as dopamine and 3,4-dihydroxyphenylacetic acid formed as a dopamine metabolite, can penetrate the BBB.[59]

It is worth noting that new prospects in AD and PD diagnosis may be opened by imaging of the CA metabolism (see Scheme 1), in particular, for investigation of cognitive processes and effect of radiation therapy on the nerve and psychological status of patients. However, $^{18}$F-containing CA derivatives are rather difficult to synthesize, because the time of synthesis is commensurable with the $^{18}$F half-life and the chemical yields are moderate.[33] Thus, a very important requirement to the preparation methods of fluorine-18-labelled CA derivatives is rapidity, which is determined by not only the rate of chemical reactions, but also simplicity of operations (addition of reactants, stirring, separation, isolation and so on) and their adaptability to the modern automated modules for the synthesis of PET RPs.

### 2.2. $^{18}$F-Based radiopharmaceuticals used in the PET/CT diagnosis of neuroendocrine tumours

Currently, out of RPs used in the PET/CT detection of cancer, [$^{18}$F]FDG is most widely applied for clinical purposes.[60] The use of this RP in cancer diagnosis is based on the fact that malignant cells are characterized by increased activity of glycolysis caused by increased levels of glucose transport proteins and, to a higher extent, by increased neoplastic activity of hexokinase. However, [$^{18}$F]FDG is not a specific agent for any tumour. Moreover, there is a high probability of false positive results due to [$^{18}$F]FDG uti-

lization in macrophages produced in abscesses, inflammation sites or in the case of infiltrative tumour growth.[61] Characteristics of various RPs applied for functional imaging of NETs are summarized in Table 1 and their molecular structures are shown in Fig. 3.

In recent years, the applicability of new RPs that would be able to compete with [$^{18}$F]FDG in the diagnosis of NETs has been actively investigated. The new agents mainly refer to two biochemical types: amino acids labelled with positron-emitting radionuclides and nucleotide analogues that provide information about cell proliferation activity. However, because of the short half-life of the $^{11}$C nucleus (20.4 min), which can be used only in PET/CT centres equipped with their own cyclotron, fluorinated radiotracers of the aromatic amino acid class are more relevant.[12] The most promising amino acid RP is [$^{18}$F]FDOPA, an endogeneous precursor of dopamine.

The compound [$^{18}$F]FDOPA is a synthetic analogue of phenylalanine, which is a noradrenaline precursor. Like the biological analogue, [$^{18}$F]FDOPA is transported into tumour cells by L-type amino acid transmembrane transporters. Under the action of L-amino acid decarboxylase, [$^{18}$F]FDOPA is successively metabolized to [$^{18}$F]fluorodopamine and then to [$^{18}$F]fluoronoradrenaline (see Scheme 1).[35]

The [$^{18}$F]FDOPA agent was first used to locate NETs such as gastrointestinal carcinoid tumours;[63, 64] then [$^{18}$F]FDOPA was proposed as an alternative agent for imaging and diagnosis of paragangliomas.[65] It was shown that in some cases, PET examination with [$^{18}$F]FDOPA detects head and neck paragangliomas with 100% sensitivity.[63, 66, 67] Currently, [$^{18}$F]FDOPA is efficiently used in the PET/CT examination of NETs (pheochromocytomas, neuroblastomas), thyroid malignant tumours, insulinomas and brain tumours.[68] Thus, [$^{18}$F]FDOPA is employed as a radiopharmaceutical, first of all, for detection of pheochromocytomas and paragangliomas, because the diagnostic accuracy of the method is 90% in detection of the primary site and 100% in tumour staging.[68, 69] It was shown that a wider range of tumour sites can be detected by PET with [$^{18}$F]FDOPA than by PS with [$^{123}$I]MIBG (Ref. 70) or [$^{111}$In]DOTA.[71] Furthermore, PET with [$^{18}$F]FDOPA is highly efficient in detection and staging of the medullary thyroid cancer recurrence. The diagnostic accuracy of the procedure markedly increases when the PET/CT combination is used;[71, 72] PET/CT is recommended for disease

**Table 1**. Characteristics of various radiopharmaceuticals used for functional imaging of neuroendocrine tumours.[62]

| Radiopharmaceutical | Image formation principle | Method | $t_{1/2}$/h |
|---|---|---|---|
| [$^{124}$I]MIBG | Noradrenaline analogues: actively transported into neurosecretory granules through cell membrane with noradrenaline transporter | PS and SPECT | 100.2 |
| [$^{123}$I]MIBG | | PS and SPECT | 13.3 |
| [$^{18}$F]MFBG | | PS and SPECT | 1.83 |
| [$^{11}$C]Adrenaline | Catecholamine: actively transported into neurosecretory granules through cell membrane with noradrenaline transporter | PET | 0.34 |
| [$^{18}$F]FDA | | PET | 1.83 |
| [$^{11}$C]Hydroxyephedrine | Catecholamine analogue: actively transported into neurosecretory granules through cell membrane with noradrenaline transporter | PET | 0.34 |
| [$^{11}$C]FDOPA | Catecholamine biosynthesis intermediate: actively transported into neurosecretory granules through cell membrane with noradrenaline transporter | PET | 0.34 |
| [$^{18}$F]FDOPA | | PET | 1.83 |
| [$^{18}$F]FDG | Glucose analogue: uptake and early intracellular metabolism relative to glucose | PET | 1.83 |
| [$^{68}$Ga]DOTATATE | Somatostatin analogue: expression of somatostatin receptors | PET | 1.14 |
| [$^{68}$Ga]DOTATOC | | PET | 1.14 |
| [$^{68}$Ga]DOTANOC | | PET | 1.14 |
| L-[$^{11}$C]Methionine | Active amino acid transport and protein synthesis. Amino acids are transported to the cells by transport proteins. The uptake and absorption by cells includes protein synthesis or transmethylation | PET | 0.34 |
| [$^{18}$F]FAMT | | PET | 1.83 |
| [$^{18}$F]FCCA | | PET | 1.83 |
| [$^{123}$I]Tyr$^3$-Octreotide | Somatostatin analogue acting on the somatostatin cell membrane receptors. Undergoes receptor-mediated endocytosis, but does not cross lysosomal and cell membranes | PS | 13.3 |
| [$^{111}$In]DTPA-Octreotide | | PS | 67.4 |

**Note**. MIBG is *m*-iodophenylguanidine, MFBG is *m*-fluorophenylguanidine, DOTA is 1,4,7,10-teraazadodecane-1,4,7,10-tetraacetic acid, TATE is D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl, TOC is D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-threonyl-*N*-[(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)propyl], NOC is D-phenylalanyl-L-cysteinyl-3-(1-napthyl)-L-alanyl-D-triptophyl-L-lysyl-L-threonyl-*N*-[(1*R*,2*R*)-2-hydroxy-1-(hydroxymethyl)propyl], FAMT is 3-fluoro-α-methyltyrosine, FCCA is 3-fluorocyclobutane-1-carboxylic acid, DTPA is diethylenetriaminepentaacetic acid.

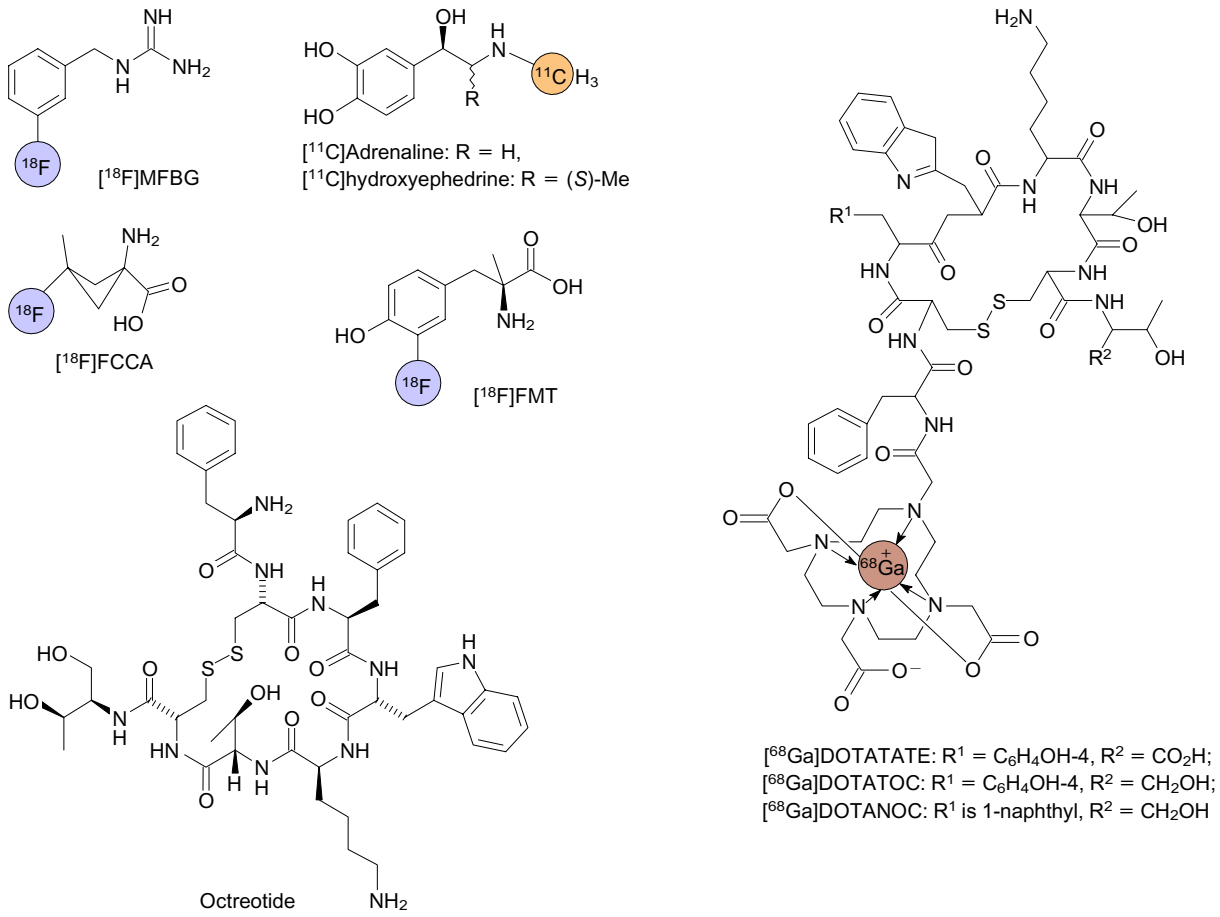



**Figure 3.** Structures of radiopharmaceuticals used in PET/CT diagnosis of neuroendocrine tumours.

staging, first of all, for patients with planned surgery. However, the application of [$^{18}$F]FDG for cancer diagnosis is still significant in those cases where the diagnostic efficiency of PET with [$^{18}$F]FDOPA is limited, for example, in low-grade and recurrent medullary thyroid cancer.[73, 74] An unquestionable benefit of [$^{18}$F]FDOPA is topical diagnosis at various genetic matching indications. Indeed, this procedure has 90% sensitivity and 100% specificity in the detection of lesions in pancreas with focal congenital hyperinsulinism; this is why this technique is widely used in foreign clinics for planning surgical treatment of such diseases.[74]

A study of the transformation of 6-fluorodopamine into 6-fluoronoradrenaline *in vivo* and their metabolism[75, 76] demonstrated that [$^{18}$F]FDA can be used as an RP in the PET method.[77, 78] The application of particularly 6-fluorodopamine rather than isomeric 2- or 5-fluorodopamines is related to different activities and selectivities to receptors of non-monofluorinated dopamine analogues and to considerable influence of the $^{18}$F position in the fluoronoradrenaline molecule on its adrenergic activity.[79–81]

[$^{18}$F]6-Fluorodopamine was initially used for functional imaging of the sympathetic nervous system, and later it has been actively tested for imaging of paragangliomas.[77, 78] It has been found that [$^{18}$F]FDA is more sensitive and efficient for location of pheochromocytomas and paragangliomas than [$^{131}$I]MIBG or [$^{123}$I]MIBG, which is used in clinical practice.[77, 78, 82–84] The PET/CT diagnosis with [$^{18}$F]FDA is highly sensitive to both primary neoplasms (77%–100%) and metastases (77%–90%),[70, 85] and the specificity of the method exceeds 90%.[70] In the diagnostic sensitivity, [$^{18}$F]FDOPA and [$^{18}$F]FDA may be inferior to [$^{18}$F]FDG, but they are favourably distinguished by high specificity. However, [$^{18}$F]FDA is still accessible only as an experimental imaging radiopharmaceutical at the US National Institutes of Health.[86] Table 2 summarizes data on the sensitivity of PET functional imaging with various RPs in relation to the detection of paraganglioma, namely, the percentages of cases where the tumour was detected with a particular RP relative to the total number of patients who were subsequently confirmed to have the NET.

It is noteworthy that fluorinated catecholamines still cannot compete with [$^{18}$F]FDG and [$^{18}$F]FDOPA in the level of exploration and the practical use for PET/CT

**Table 2**. Diagnostic sensitivity (%) of PET exemplified by diagnosis of paraganglioma.[87]

| Paraganglioma | Radiopharmaceutical | | | |
|---|---|---|---|---|
| | [$^{18}$F]FDOPA | [$^{18}$F]FDA | [$^{123}$I]MIBG | [$^{18}$F]FDG |
| Non-metastatic | 81 | 77 | 77 | 88 |
| Metastatic | 45 | 76 | 57 | 74 |

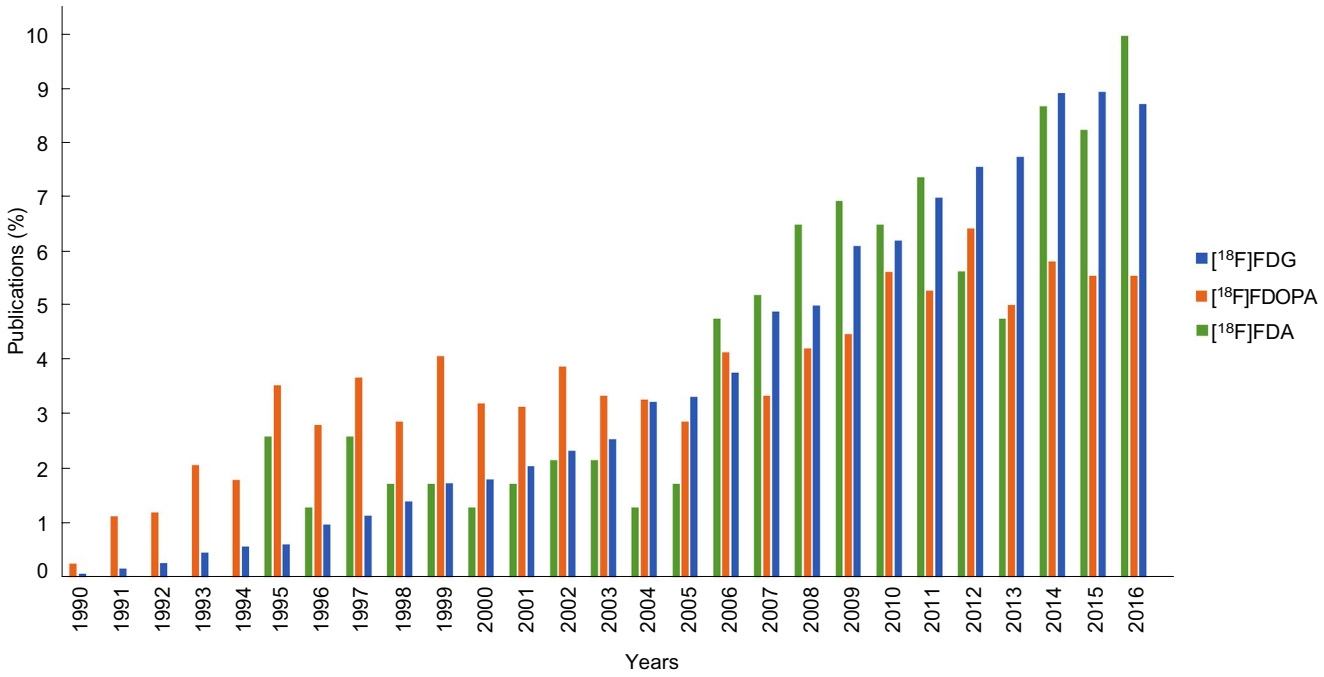



**Figure 4.** Percentage of publications devoted to the diagnosis of neurodegenerative diseases and neuroendocrine tumours using $^{18}$F-based radiopharmaceuticals for PET (Web of Science database).

examination (the more so, because almost all papers devoted to [$^{18}$F]FDA are based on comparison with [$^{18}$F]FDOPA, which thus increases the number of publications on [$^{18}$F]FDOPA). Therefore, Fig. 4 presents the percentages relative to the total number of publications on each particular RP, *i.e.*, the normalized number of papers characterizing the progress of the use of particular RPs in the PET/CT examinations.

Thus, PET/CT examination using various radiotracers is exceptionally important for the early clinical diagnosis of neuroendocrine tumours and neurodegenerative diseases. However, currently, there are still unsolved problems the solution of which is a challenging interdisciplinary task of modern biology, chemistry, physics and medicine. The key problem is that the applicability of PET/CT is determined to a high extent by the set of available biologically active labelled compounds — radiopharmaceuticals. In view of the specificity of catecholamine metabolism and advantages of $^{18}$F over other radionuclides, [$^{18}$F]FDA and [$^{18}$F]FDOPA are undoubtedly promising RPs for the imaging of neuroendocrine tumours and micrometastases.[88] A study of catecholamine type $^{18}$F-RPs and improvement of the synthetic routes to them with the goal of predicting and diagnosing the above-mentioned diseases is a necessary stage in the solution of this key problem. Therefore, below we present data on the application of L-[$^{18}$F]3,4-dihydroxy-6-fluorophenylalanine and [$^{18}$F]6-fluorodopamine and on the synthetic approaches to these RPs.

## 3. Synthetic approaches to $^{18}$F-labelled catecholamine type radiopharmaceuticals

The key methods for the introduction of fluorine into organic molecules can be classified into electrophilic, nucleophilic, radical and metal-catalyzed ones.[88–97] The most well-known commercially available fluorinating reagents are shown in Fig. 5.[33]

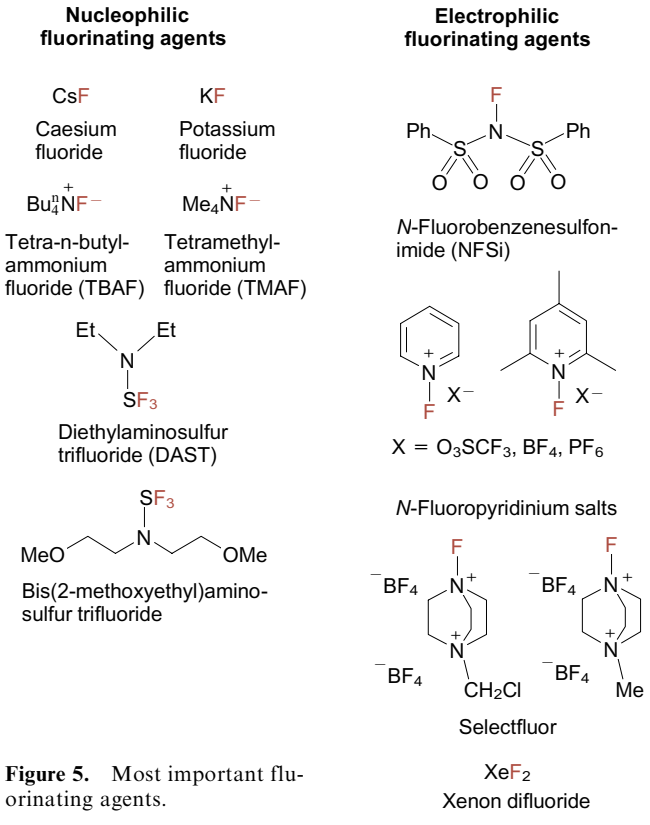



**Figure 5.** Most important fluorinating agents.

Despite the great progress in the synthesis of fluorinated organic compounds based on the natural $^{19}$F isotope, the

introduction of the $^{18}F$ radionuclide into organic molecules is a separate issue,[98] related to the specific features of generation, half-life and used concentrations of this isotope.

Fluorine-18 can be generated in various nuclear reactions,[99] including $^{18}O(p,n)^{18}F$, $^{20}Ne(d,\alpha)^{18}F$, $^{16}O(\alpha,d)^{18}F$, *etc.*, and *via* the formation and radioactive decay of $^{18}Ne$. Only the first of the mentioned reactions is widely used in practice, with $^{18}O$-enriched water targets being employed for this purpose (Scheme 2).

**Scheme 2**

$$^{18}_{8}O + {}^{1}_{1}H \longrightarrow {}^{18}_{9}F + n$$

$$^{20}_{10}Ne + {}^{2}_{1}H \longrightarrow {}^{18}_{9}F + {}^{4}_{2}He$$

$$^{16}_{8}O + {}^{4}_{2}He \longrightarrow {}^{18}_{9}F + {}^{2}_{1}H$$

The benefits of the first method for $^{18}F$ generation is that it requires proton accelerators, which are often available at nuclear and medical centres (accelerators of other nuclear particles are much less frequently encountered) and that the radionuclide is firmed in high yields. This nuclear reaction can be implemented with both aqueous and gaseous targets. Generally, the total amount of $^{18}F$ that can be produced depends on the energy of protons, beam current, irradiation time, degree of $^{18}O$ isotope enrichment and design of the target. According to estimates,[100] it is possible to accumulate about 111 GBq (3 Ci) of $[^{18}F]F^-$ in 1 h of irradiation with a beam with a proton energy of 10–13 MeV and a beam current of 50 μA.

Methods based on nucleophilic fluorination have now been recognized as most efficient, while other methods possess a considerable number of drawbacks (see below).[36] In the nucleophilic substitution methods, $^{18}F$ is formed as the fluoride ion, with no carrier added, upon irradiation of a water target on a cyclotron, with water being enriched in oxygen-18 ($[^{18}O]H_2O$). The volume of the target is 1–3 ml; water irradiated with a flow of helium is delivered to an automated synthesis module. Correspondingly, $^{18}F$ occurs in the irradiated water as a $[^{18}F]F^-$ solution. The fluoride ion is recovered most often *via* anion exchange, while $[^{18}O]H_2O$ can be regenerated and reused. The elution of the $[^{18}F]$fluoride from the anion exchanger is accomplished by a solution of potassium carbonate and kryptofix (see below) in an acetonitrile–water mixture (96 : 4).[101, 102] Then the solvents are eliminated in a vacuum or in a nitrogen flow with heating, and the resulting $K_{222}$ complex with potassium $[^{18}F]$fluoride is directly introduced in the nucleophilic substitution reaction without azeotropic drying, which substantially reduces the time of synthesis. The use of Kryptofix® (Fig. 6) {1,10-diaza-4,7,13,16,21,24-hexaoxabicyclo[8.8.8]hexacosane, kryptand[2.2.2], $K_{222}$), a specific $K^+$-chelating ligand[103] is associated with the fact that the hydrated fluoride ion has low reactivity as a nucleophile, while the kryptofix complex is readily soluble in organic solvents and has a high reactivity.

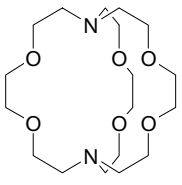


**Figure 6.** Structure of kryptofix (1,10-diaza-4,7,13,16,21,24-hexaoxabicyclo[8.8.8]hexacosane), a $K^+$-chelating ligand.

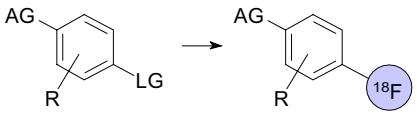
The above procedure for the preparation of $[^{18}F]F^-$ has certain drawbacks. The first one is the necessity of thorough drying of the reactants, because the nucleophilicity of the fluoride anion in water is very low. To eliminate this problem, it is necessary to remove water, to use, as indicated above, special ligands to enclose counter-ions (*e.g.*, kryptofix for $K^+$) and to increase the solubility of the whole system in organic solvents. The second characteristic feature of these processes is low concentration of $[^{18}F]F^-$, which also imposes certain limitations on the choice of reagents and conditions for substitution.

While considering fluorination of catecholamines, we should note that a key feature of classical nucleophilic reactions to introduce a fluorine atom into an aromatic ring is the necessity for both activation of the ring, *e.g.*, the presence of strong electron-withdrawing substituents, and the presence of a highly nucleofugal group, which is usually located in the *ortho*- or *para*-position to the activating function. The fluoride anion attack is directed at this position bearing the leaving group. The difficulty of application of the classical approach is that it is synthetically fairly difficult to introduce an activating and directing, highly electron-withdrawing group and a leaving group into L-3,4-dihydroxyphenylalanine and dopamine molecules and to effectively remove the activating and directing group after the nucleophilic substitution, even in the presence of electron-withdrawing protecting groups (*e.g.*, ester and amide groups).

The main nucleophilic substitution reactions employed for the introduction of $^{18}F$ into aromatic compounds have been described in detail in a number of reviews (see, for example,[98, 104–109]). In the first part of this Section, we will consider the most important issues that are directly associated with the introduction of $^{18}F$ into catecholamines and phenols or can serve for this purpose.

Scheme 3 depicts the nucleophilic introduction of the fluoride anion into an aromatic molecule activated towards nucleophilic substitution. This process is efficient in the presence of an activating group (AG in Scheme 3), usually in the *para*-position to the leaving group; electron-withdrawing substituents traditional for $S_NAr$ reactions such as nitro, carbonyl, cyano and trifluoromethyl substituents are employed for this purpose. The second structural moiety that must be present in the starting compound is the leaving group (LG in Scheme 3). The applicable leaving groups are both the halogen atoms and nitro group traditional for organic synthesis and less frequently encountered positively charged potential nucleofuges: trialkylammonium,[110] aryl-

**Scheme 3**

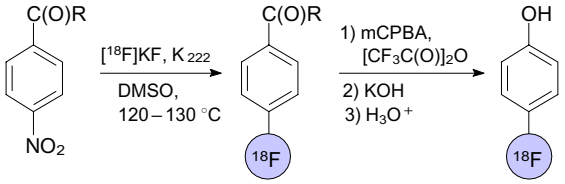



AG = $NO_2$, RC(O), CHO, CN, $CF_3$; LG = I, Br, F, $NO_2$, $^+NR_3$, $^+IAr$, $^+SMe_2$, $N_2^+$, $SnR_3$

iodonium,[111] dimethylsulfonium[112] and diazonium[113,114] (Balz–Shiemann reaction).

Before describing the methods for introduction of $^{18}F$ into catecholamines known from the literature, we will briefly consider the preparation of $^{18}F$-phenols. We do not discuss the introduction of $^{18}F$ by nucleophilic substitution reactions of fluoroalkyl derivatives with good leaving groups on treatment with phenoxide anions (see, *e.g.*, papers[115–120] and reviews[121]). We also do not consider in detail the displacement of good nucleofuges by fluoride ions in carbonyl-activated aromatic substrates followed by the Baeyer–Villiger reaction [Scheme 4; the radiochemical yield (RCY) reaches 65%][122–124] or by Pd-catalyzed decarbonylation in the case of aldehydes.[125]

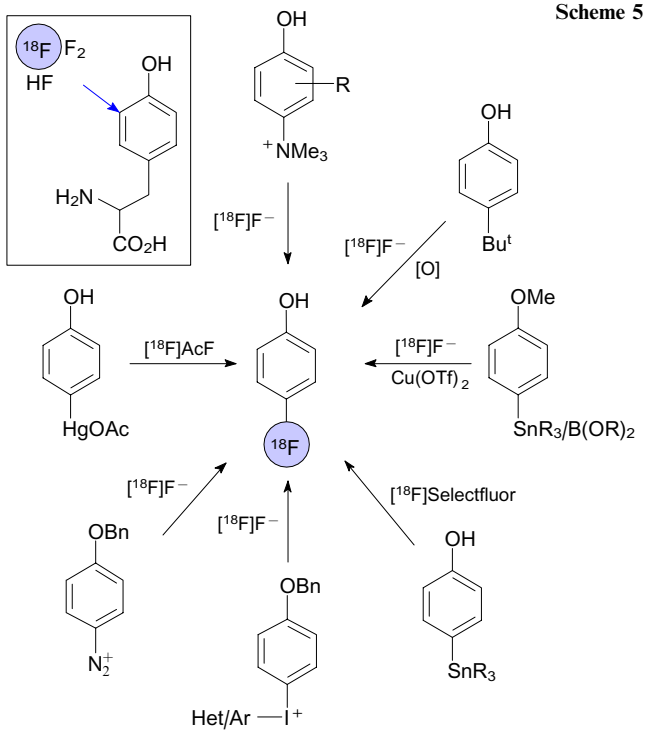
**Scheme 4**




R = H, Me, Ph; mCPBA is *meta*-chloroperoxybenzoic acid

Scheme 5 summarizes the known methods for the introduction of $^{18}F$ into phenol molecules. They include early studies on demercurofluorination,[126,127] Balz–Shiemann reaction[128] (RCY does not exceed 33%; complicated isolation processes),[129] fluoride ion substitution in the iodonium salts of protected phenols[130–132] (by comparison of RCY, it was found that the yields are 5–6 times higher with diaryliodonium salts than in the case of diazonium salts[133]),

**Scheme 5**

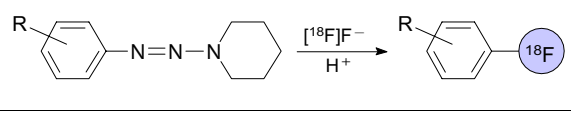



Tf = $CF_3SO_2$

substitution in ammonium salts,[134] electrophilic[97,135] or copper-catalyzed[136] destannofluorination, and one of the most advanced approaches: oxidative fluorination of *p-tert*-butylphenols (see below).[137] Special mention should be made of the electrophilic *ortho*-fluorination of tyrosine in acid medium with molecular fluorine (see the frame in Scheme 5).[138]

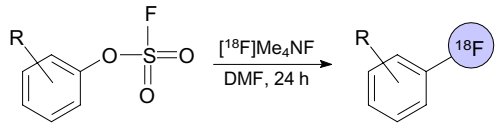
Another way of using diazonium salts is the Wallach reaction[139] in which they are formed as intermediates on treatment of 3,3-dialkyl-1-aryltriazenes with a strong acid.[98] The thermal decomposition of the diazonium salt (formed *in situ* from triazene) in the presence of $[^{18}F]F^-$ gives the corresponding radioactively labelled arenes (Scheme 6).[140] It is noteworthy that despite the short duration of the process (15–20 min), the yields of fluoroarenes do not exceed 50%; therefore, this method cannot be considered as promising for the preparation of fluorinated CAs.

**Scheme 6**




An absolutely new approach to fluorination of non-activated aromatic rings is substitution in phenol fluorosulfates (Scheme 7). Despite the impressive results for most substrates, in the case of *p*-methoxyfluorobenzene, the yield is only 6% and the reaction time is 24 h; therefore, this approach can be considered unacceptable for the preparation of labelled phenols.[141]

**Scheme 7**

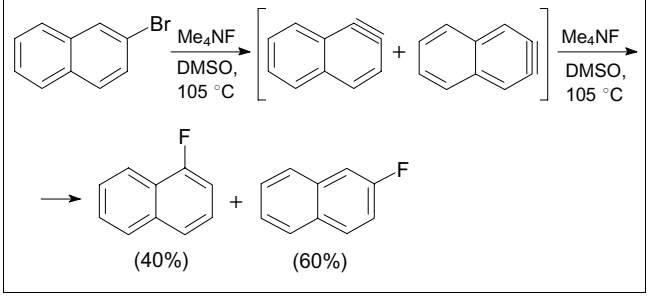



R = H, 4-Ph, 4-CN, 4-Bz, 4-$NO_2$, 4-Cl, 2-CN, 3-CN, *etc.*

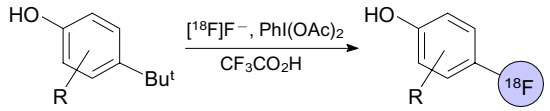
A similar result, that is, long reaction time with the same nucleophile, was detected upon fluorination of non-activated aromatic halides.[142] Presumably, the reaction proceeds *via* an aryne intermediate, which apparently accounts for the long reaction time (Scheme 8). The exchange of bromine in *o*-, *m*- and *p*-bromoanisoles requires 12 h of heating in DMSO at 110 °C.

Recently, Gouverneur's research group[137] discovered the oxidative fluorination of *p-tert*-butylphenols (Scheme 9).

**Scheme 8**



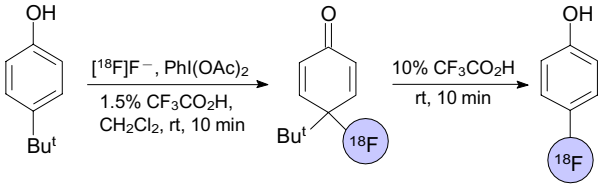
**Scheme 9**




R = H, 2-Me, 2-Bu$^t$, 2-Ph, 2-Bz, 2-Br, 3-Me

For this method, it is crucial that a hydroxyl substituent be present in the *para*-position to the *tert*-butyl leaving group. According to the assumed mechanism, the reaction passes through a quinoid intermediate (Scheme 10). The authors called the new approach the 'substrate umpolung strategy', as the oxidized phenol form has highly electrophilic properties, unlike pristine phenol.

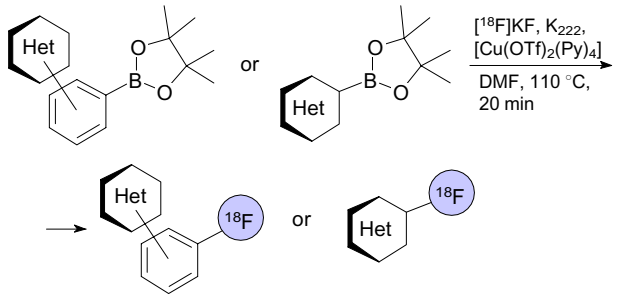
**Scheme 10**




(RCY: 8%–26%)

In the past five years, copper-catalyzed introduction of fluorine into boronic esters has been widely used (Scheme 11).[143] Suitable substrates are phenol ethers,[144] which are subsequently easily dealkylated. This process obviously deserves close attention, as it is one of the most probable future methods for the synthesis of commercially available fluorinated catecholamines (see below).

**Scheme 11**



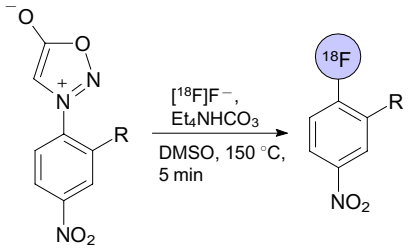

Py is pyridine

A recent publication[145] describes a new approach to the introduction of $^{18}$F into aromatic rings *via* nucleophilic substitution: the authors were able to use a highly nucleofugal sydnone substituent as the leaving group (Scheme 12, RCC is the radiochemical conversion).

The yields of radioactively labelled compounds are high; however, this approach is applicable only to electron-deficient aromatic substrates; indeed, for the *para*-methoxy-substituted arylsydnone, a potential precursor of *p*-fluorophenol, the RCY was 0%.

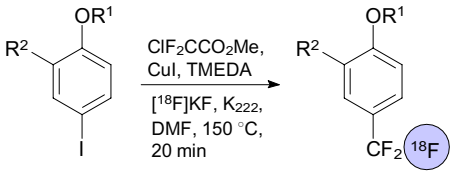
Special mention should be made of two publications that are not formally devoted to the introduction of $^{18}$F into the phenol aromatic ring, but are of interest as regards the potential application. The results of deiodotrifluoromethylation of iodoarenes, including phenol and its ethers and esters, have been reported[146] (Scheme 13).

**Scheme 12**




| R | RCC (%) | R | RCC (%) |
|---|---|---|---|
| H | 78 ± 3 | CN | 92 ± 1 |
| $CF_3$ | 96 ± 2 | Me | 93 ± 2 |

**Scheme 13**



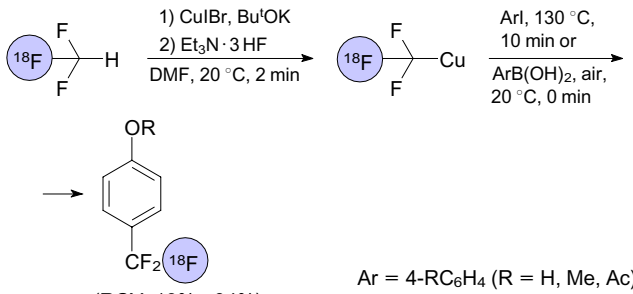

(RCY: 5%–55%)

$R^1$ = H, Me, Ac, Piv, Bn; $R^2$ = H, OMe; Piv is pivaloyl, TMEDA is tetramethylethylenediamine

The reported[146] RCY indicate that this reaction is of low utility for pristine phenol, while it can be quite applicable for ethers, which are readily converted to unsubstituted phenol.

The authors of the second study describing the introduction of the [$^{18}$F]$F_3C$ group into aromatic substrates[147] employed, apart from deiodotrifluoromethylation, the introduction of the trifluoromethyl group into the boronic acids; in this case, the yields were much higher (Scheme 14).

**Scheme 14**

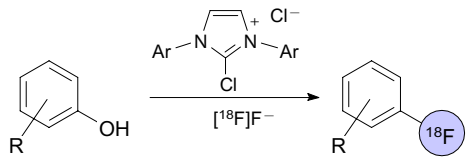



(RCY: 13%–94%)

Ar = 4-$RC_6H_4$ (R = H, Me, Ac)

Recently, a unique study devoted to the direct conversion of phenols to aromatic fluorides has been published (Scheme 15).[148]

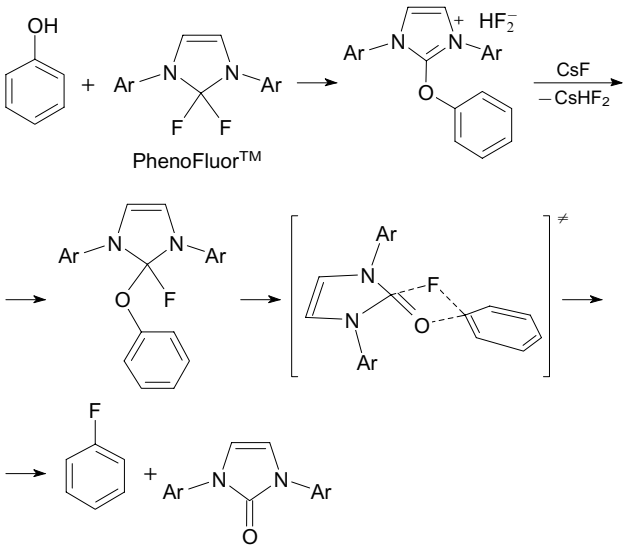
**Scheme 15**




R = 4-CN, 4-$CF_3$, 4-CHO, 4-C(O)$NH_2$, , *etc.*

This unusual transformation may be carried out for phenols containing either electron-withdrawing or electron-donating substituents R and for unsubstituted phenol. A key feature of this substitution, which distinguishes it from the classical addition – elimination, elimination – addition and elimination processes, is that the C – O bond cleavage and C – F bond formation occur synchronously (Scheme 16, the structure of the salt-like intermediate was proved by X-ray diffraction). The reaction can involve a broad range of substrates, including heterocycles. However, the application of this reaction to the synthesis of fluorinated catecholamines has not been described as yet.

**Scheme 16**




Thus, the above brief analysis reveals considerable difference between the protocols for introduction of $^{18}F$ into phenols and the classical nucleophilic fluorination of activated aromatic substrates.

Scheme 17 depicts general approaches to the preparation of $^{18}F$-labelled 6-fluorine-substituted L-3,4-dihydroxyphenylalanine and dopamine. The possible precursors used in the syntheses of these RPs are mercury derivatives [149] (now barely used), diaryliodonium salts [150] (see Sections 3.2.1 and 3.3.1), organotin compounds [151, 152] (see Section 3.1.2), organoboron compounds [153] (see Section 3.3.2), nitro derivatives [154] (see Section 3.2.2), arenetrialkylammonium salts [110] (now barely used), nickel [155] and palladium [156] organometallic compounds (see Section 3.3.3) and proper dopamine [157] and L-DOPA [158] (see Section 3.1.1).

This part of the review addresses the key approaches to the synthesis of $^{18}F$-labelled 6-fluorodopamine and L-FDOPA. The latter does nor formally belong to the class of catecholamines, but can be a precursor or intermediate in their synthesis. In view of the fact that practical application of [$^{18}F$]FDOPA has received much more attention and, hence, there are special reviews dedicated only to the synthesis of [$^{18}F$]FDOPA,[159, 160] we arranged the material as a comparison of approaches to the synthesis of [$^{18}F$]FDOPA and [$^{18}F$]FDA with indication of benefits and drawback of each method. The subsections are arranged in terms of the fluorination mechanism: electrophilic (Section 3.1), nucleophilic (Section 3.2) and metal-catalyzed (Section 3.3) reactions.

## 3.1. Electrophilic methods for introduction of fluorine atom into catecholamines

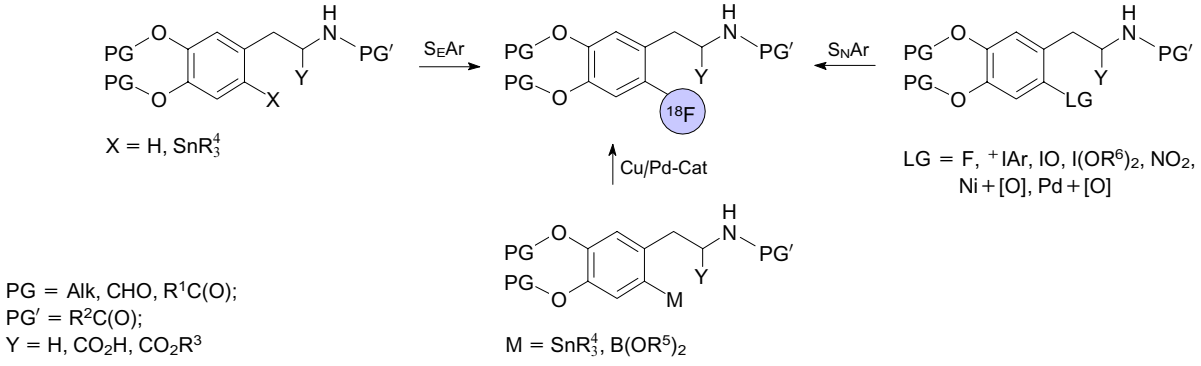
### 3.1.1. Direct fluorination of dopamine and L-3,4-dihydroxyphenylalanine

Chirakal *et al.*[157] presented a method for direct fluorination of commercially available dopamine hydrochloride at reduced temperature (– 65 °C) with gaseous [$^{18}F$]$F_2$ generated immediately before being fed to the reaction medium, which contains dopamine hydrochloride, boron trifluoride and hydrofluoric acid (Scheme 18). This affords a mixture of isomers (25% of 2- and 5-isomers and 46% of 6-isomer; other radioactive components of the reaction mixture have not been identified); the 6-fluoro derivative is isolated by column chromatography in 10% ± 2% RCY.

L-DOPA can be fluorinated under similar conditions [158] (Scheme 19). Fluorine gas [$^{18}F$]$F_2$ (0.5% in neon) is passed through the reaction vessel at – 65 °C. This gave a mixture of 2-, 5- and 6-fluoro derivatives in chemical yields of 12.0%, 1.7% and 21.0%, respectively.

The use of [$^{18}F$]$F_2$ as a fluorinating agent is a rapid method for the introduction of fluorine; however, it is rather expensive and not sufficiently selective. Indeed, these reactions give a mixture of 2-, 5- and 6-isomers,

**Scheme 17**



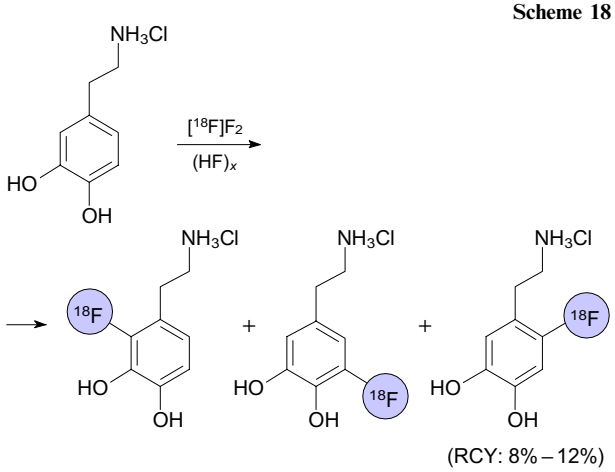

X = H, $SnR^4_3$

LG = F, $^+$IAr, IO, $I(OR^6)_2$, $NO_2$, Ni + [O], Pd + [O]

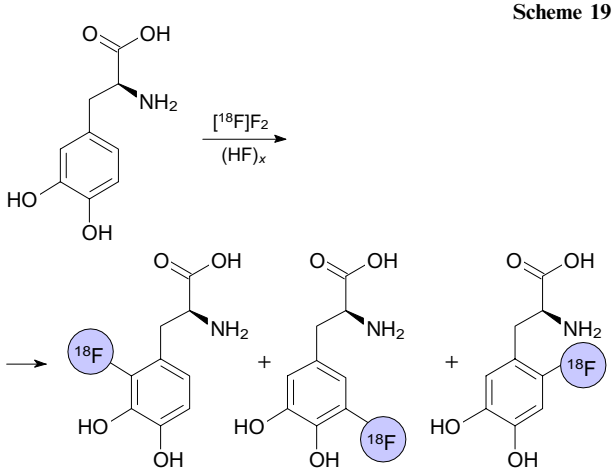
PG = Alk, CHO, $R^1C(O)$;
PG′ = $R^2C(O)$;
Y = H, $CO_2H$, $CO_2R^3$

M = $SnR^4_3$, $B(OR^5)_2$

**Scheme 18**

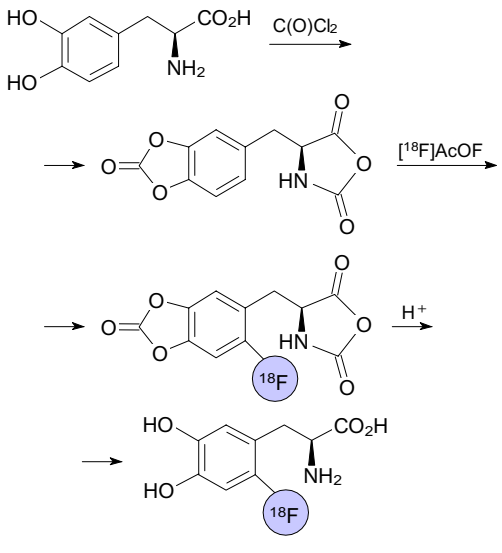



**Scheme 19**




which have to be separated by chromatography; this considerably reduces the preparative value of the method both for dopamine and DOPA.

**Scheme 20**




One more method for electrophilic introduction of a fluorine atom into the aromatic ring of DOPA is the use of acetyl hypofluorite in the case of carbonyl-protected hydroxyl groups and α-amino acid moiety (Scheme 20).[161]

The protecting group is introduced in the first step on treatment with phosgene, and fluorination proceeds regioselectively at position 6. The deprotection occurs on treatment with acid.

The yields and regioselectivity of fluorination of various protected L-DOPA derivatives with acetyl hypofluorite proved to be unsuitable for practical application.[149] Indeed, the RCY does not exceed 8% and the reaction regioselectivity is very low: the ratio of 2-, 5- and 6-fluoro isomers varies from 45 : 0 : 55 to 11 : 3 : 86.

### 3.1.2. Tin-containing precursors in the electrophilic fluorination

For selective introduction of a fluorine atom in catecholamine position 6, most remote from two hydroxyl groups, which are important for biochemical properties of catecholamines (the biological action of 2-, 5- and 6-fluorodopamines[79] and 2- or 6-fluoro-DOPA[149,162] is known to differ), it is necessary to direct the fluorination, in some way, exactly in this position. This is usually attained by preliminary introduction of some group in position 6, which is then displaced by a fluorine atom.

A classical directing and leaving group is the trialkylstannyl group.[163,164] Namavari *et al.*[165] described a method for the preparation of 6-fluorodopamine *via* the formation of a 6-iodo derivative and replacement of iodine by the trimethylstannyl group on treatment with hexamethylditin in dioxane (Scheme 21). Next the $SnMe_3$ substituent is replaced *via* electrophilic substitution by a fluorine atom on treatment with oxygen fluoride, $F_2$ gas in helium or acetyl hypofluorite.

A key drawback of using fluorine is the experimental difficulty of $[^{18}F]F_2$ generation and low specific activity of the $^{18}F$ generated using a gas target, which should contain stable fluorine gas. Nevertheless, this approach is used most widely for the commercial synthesis of [$^{18}$F]FDOPA.

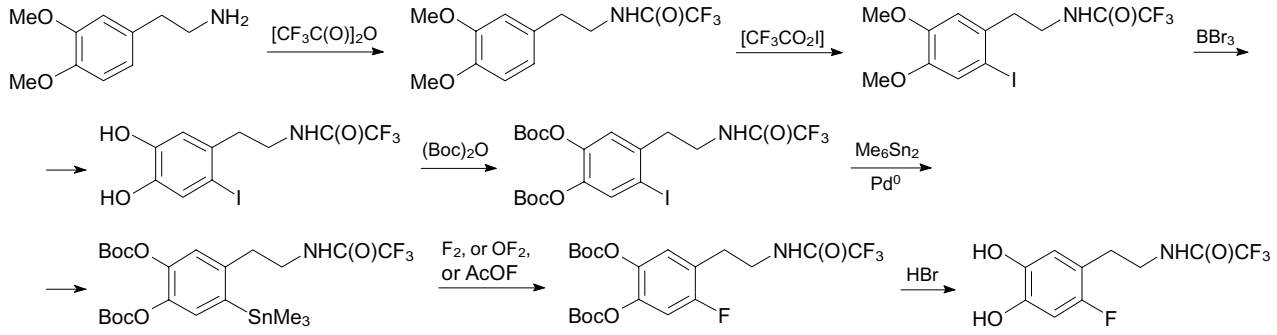
Employees of the PET/CT centre in Turku (Finland) proposed a method for introducing $^{18}F$ into the DOPA molecule, providing relatively high ($>1$ GBq μmol$^{-1}$) specific activity of the specimen, which can be used to diagnose several patients. The approach is based on the generation of $[^{18}F]F_2$ from nucleophilic [$^{18}$F]fluoride produced in the water target on a cyclotrone. In the first step, [$^{18}$F]fluoride is converted to [$^{18}$F]fluoromethane *via* nucleophilic radiofluorination of methyl iodide in the presence of $K_{222}$ in acetonitrile. The [$^{18}$F]fluoromethane thus formed is mixed under electric discharge with a minor (1 μmol) amount of the carrier gas (Ne/0.5% $F_2$), and $[^{18}F]F_2$ is formed *via* the $^{18}F/^{19}F$ isotope exchange reaction (Scheme 22).[166]

A modified procedure for the synthesis of [$^{18}$F]FDOPA (20% ± 3% RCY) has been recently reported by Russian researchers.[167] The distinction from the above protocol is that $CDCl_3$ is used as the solvent in the fluorination step at −20 °C.

One more possible leaving group is a silver atom, which is replaced by a fluorine atom on treatment with [$^{18}$F]Selectfluor bis-triflate (Scheme 23).[168]

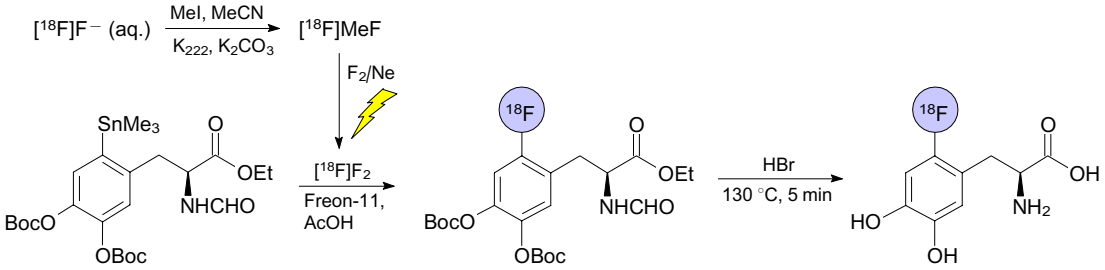
A unique $^{18}F$-labelled reagent, Selectfluor bis-triflate, has been recently developed by Finnish and French researchers;[168] the method for its synthesis is presented in

**Scheme 21**

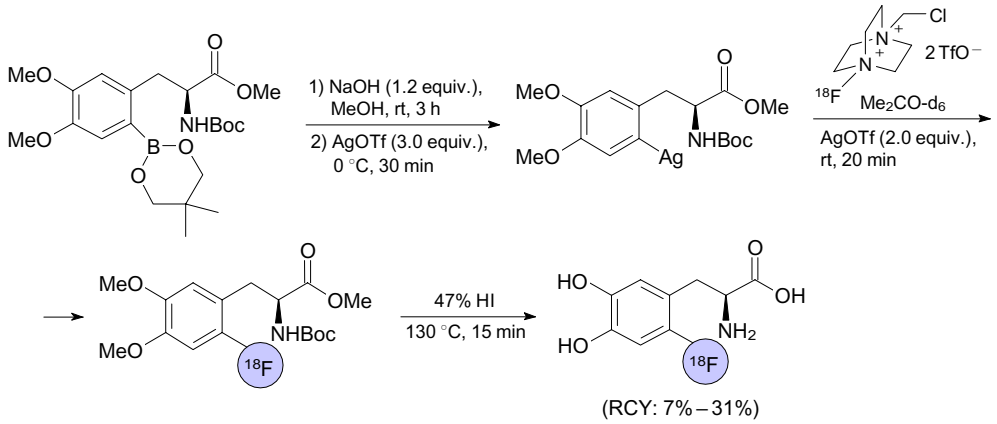



Boc = Bu$^t$OC(O)

**Scheme 22**

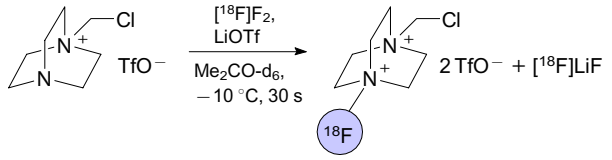



**Scheme 23**




(RCY: 7% – 31%)

**Scheme 24**

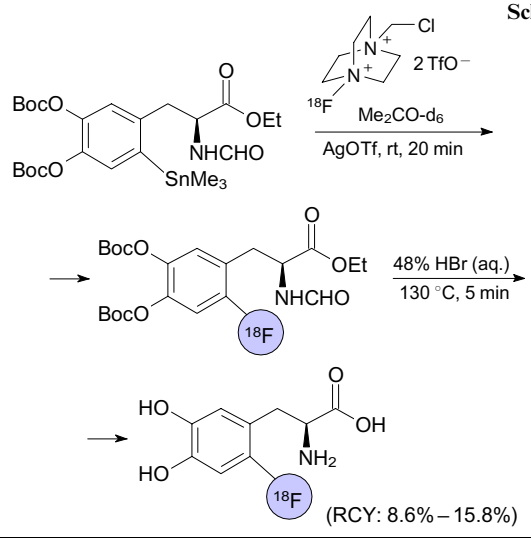



Scheme 24; the $[^{18}F]F_2$ gas required for the synthesis is generated by the method described in Scheme 22.

Stenhagen *et al.*[168] compared the efficiency of using boron- (see Scheme 23) and tin-containing precursors (Scheme 25) transmetallated on treatment with silver triflate prior to fluorination; both approaches were found to give equivalent results.

The approaches to the synthesis of [$^{18}$F]FDOPA presented in Schemes 23 and 25 refer to the newest synthetic routes to radiopharmaceuticals based on electrophilic fluorination and deserve keen attention in the future.

**Scheme 25**




(RCY: 8.6% – 15.8%)

### 3.2. Nucleophilic methods

As noted above, the preparation of a $[^{18}F]F^-$ solution is the most feasible and technically convenient. Hence, an important area of research comprises $S_NAr$ type reactions with appropriately selected leaving groups, which are displaced by the fluorine atom. Since one deals with electron-excessive aromatic systems, the leaving group should be a very good nucleofuge. This condition is met for many charged groups, which are listed in Scheme 3; however, not all of them have been used in the synthesis of $^{18}F$-labelled fluorocatecholamines. Below we consider methods for displacement of the leaving groups by $[^{18}F]F$ as applied to the synthesis of $[^{18}F]$FDOPA and $[^{18}F]$FDA.

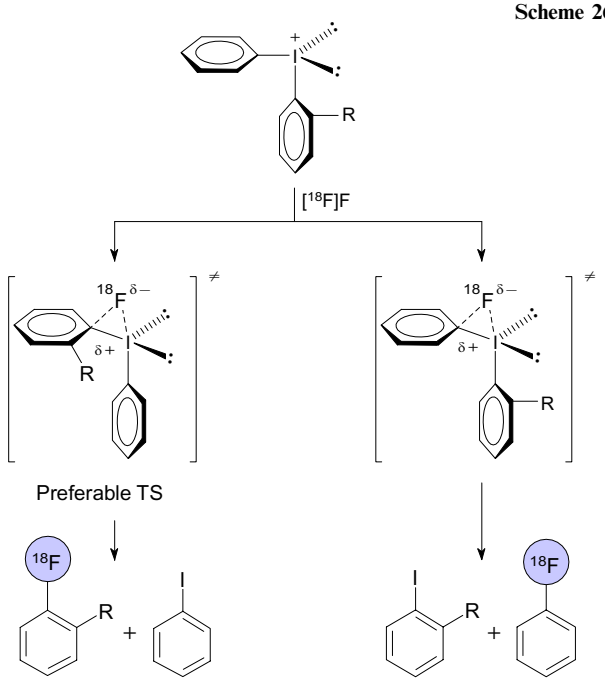
#### 3.2.1. The use of iodonium salts and iodonium ylides

An obvious problem associated with the use of diaryliodonium salts ($Ar-I^+-Ar'$) in the preparation of fluoro derivatives (ArF) is to direct the substitution to one of the aromatic rings. A possible solution to this problem is the targeted use of electronic and/or steric properties of aromatic or heteroaromatic substituents Ar and Ar′.

The assumed mechanism of fluoride ion nucleophilic substitution into diaryliodonium salts is shown in Scheme 26.[169]

The reaction can be directed into a particular aromatic ring by using steric (sterically hindered derivatives[170]) and electronic factors (thiophene type donor heterocycles[171]).

**Scheme 26**

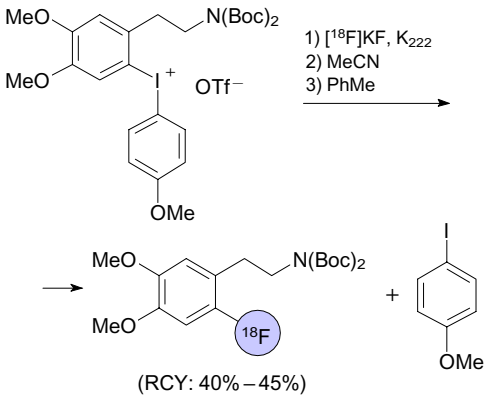



TS is transition state

Methods for the synthesis of $[^{18}F]$FDOPA using diaryliodonium salts are known (see reviews[150,172]). For example diaryliodonium triflate undergoes the ion exchange reaction with fluoride to give the corresponding $^{18}F$-labelled fluoride, which decomposes on heating in non-polar solvents to $[^{18}F]$FDOPA (Scheme 27).[173] However, RCY does not exceed 14%.[174]

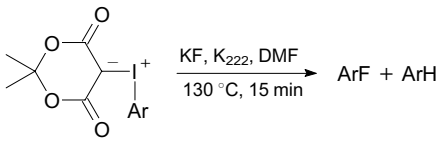
A similar approach is utilized to prepare $[^{18}F]$6-fluorodopamine (Scheme 28).[87]

**Scheme 28**




Fluorination of neutral iodonium ylides deserves special attention, as the electronic structures of these compounds allow for regioselective reactions.[150,175] Fluorination involves only the aromatic ring and does not affect the diketone moiety; arene (ArH) formed in a competing radical process is the major side product (Scheme 29).

**Scheme 29**

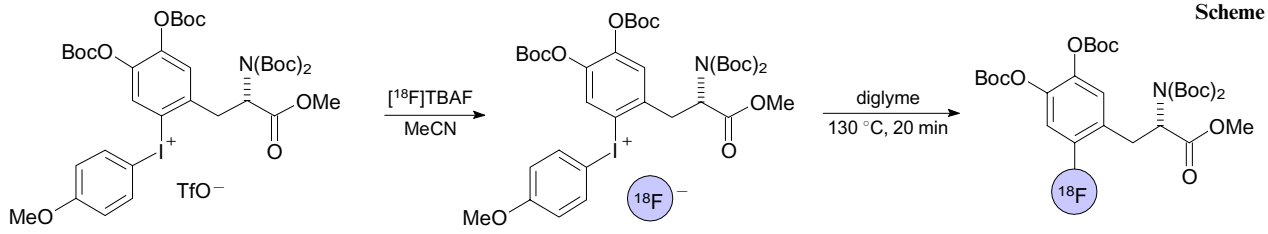



Ar = Ph, 4-$MeC_6H_4$, 2,4,6-$Me_3C_6H_2$, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-$BrC_6H_4$

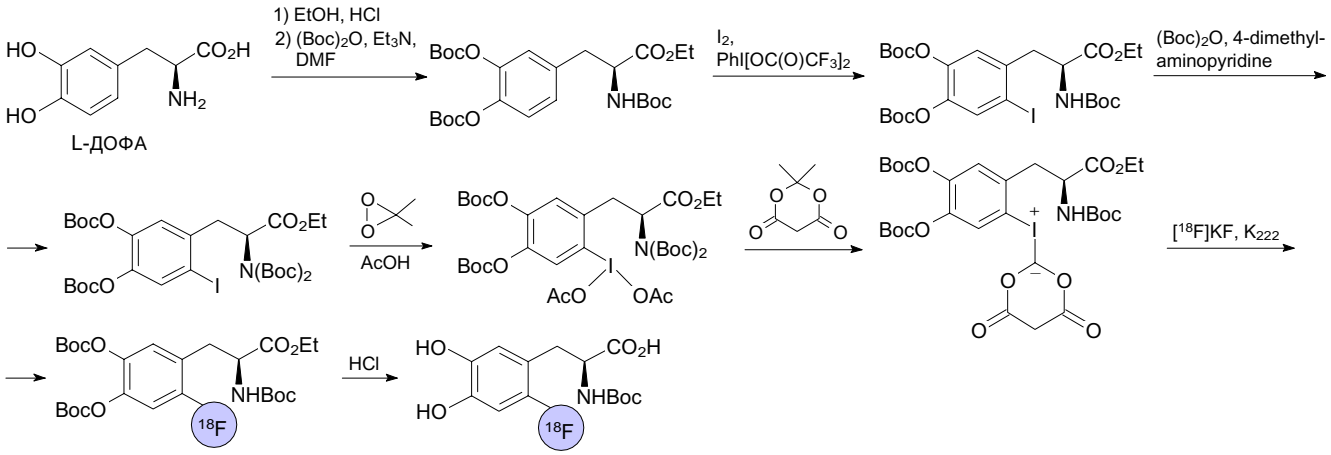
This approach was used for the synthesis of $[^{18}F]$FDOPA (Scheme 30).[176]

The results obtained in recent years, in particular, advances in the use of iodonium precursors and iodonium ylides, convincingly demonstrate good prospects of the development of this approach to the synthesis of $[^{18}F]$FDOPA and $[^{18}F]$FDA.

**Scheme 27**



**Scheme 30**



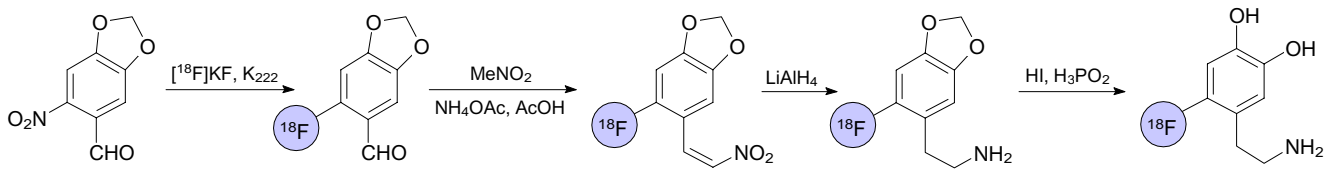

**3.2.2. Introduction of the fluorine atom at different synthetic stages**

Fluoride anion $S_NAr$ substitution for the nitro group is one of the most widely used and accessible methods for the introduction of fluorine into aromatic substrates;[177, 178] in particular, the reactions can be carried out for $[^{18}F]F^-$ (Ref. 179 and 180). Two strategic approaches should be distinguished: the first one is based on the initial nucleophilic introduction of a fluorine atom into a readily accessible precursor, which is then converted to the final fluorinated catecholamine; the second is based on the displacement of nitro group from the already synthesized catecholamine (see Section 3.2.3).

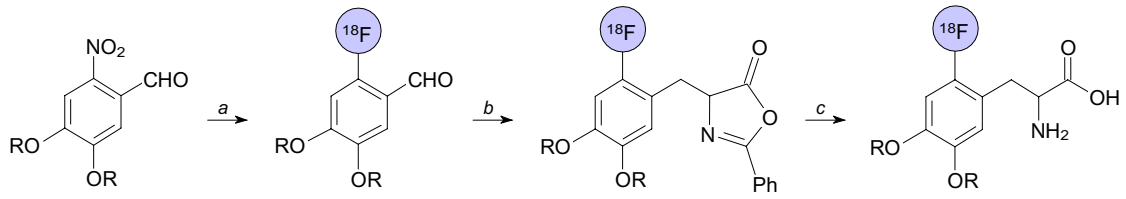
The first approach is exemplified by the syntheses of [$^{18}$F]FDA (Ref. 181) and racemic [$^{18}$F]FDOPA (Ref. 182) (Schemes 31 and 32, respectively).

Krasikova, Belokon and co-workers[180, 183] developed a general method for the synthesis of [$^{18}$F]FDOPA (Scheme 33). The key step is asymmetric alkylation of a Ni complex.[184]

**Scheme 31**

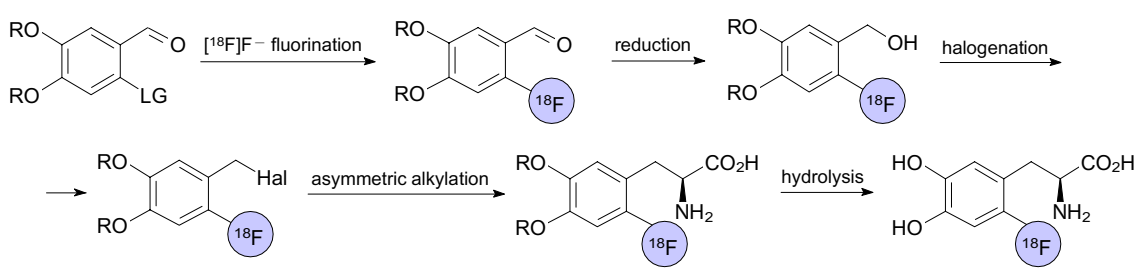



**Scheme 32**

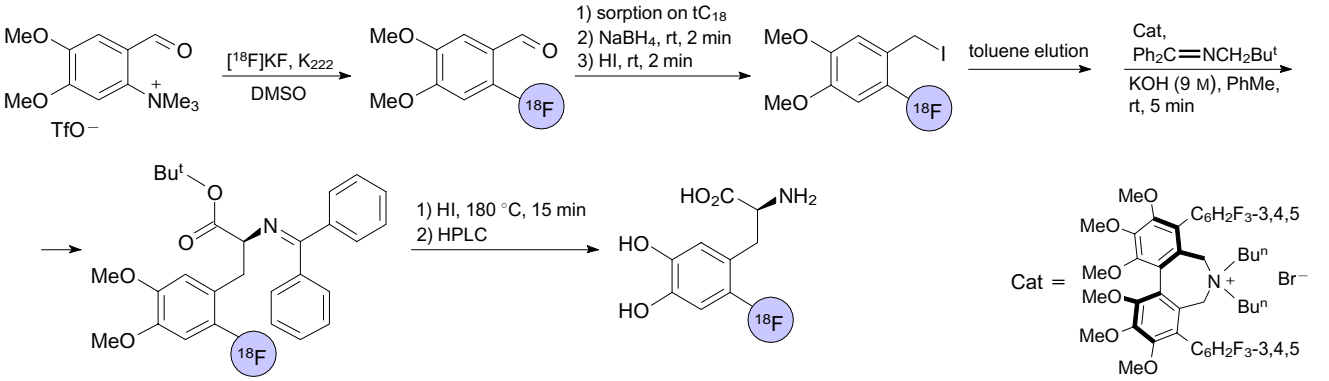


(*a*) [$^{18}$F]KF, $K_{222}$, DMSO, 130 – 135 °C, 20 min; (*b*) 2-phenyloxazol-5-one, DABCO, EtOH, 140 – 145 °C, 10 min; (*c*) HI, red phosphorus, 220 – 235 °C, 15 min; R = Me; R – R = $CH_2$; DABCO is 1,4-diazabicyclo[2.2.2]octane

**Scheme 33**

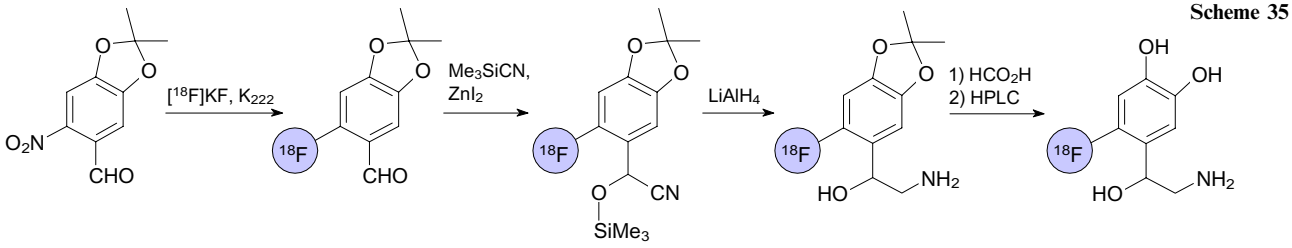


**Scheme 34**

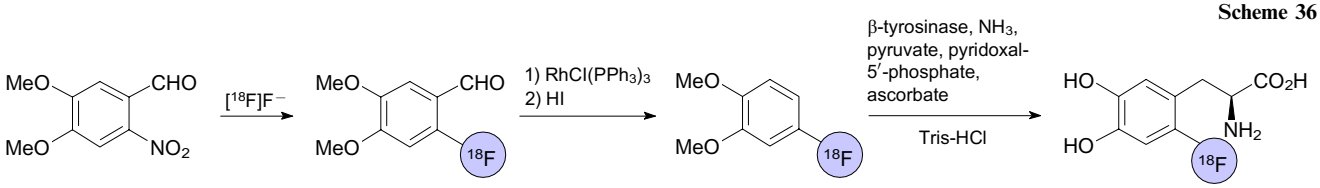



tC18 is a silica gel-based hydrophobic phase with enhanced hydrolytic stability

**Scheme 35**




**Scheme 36**




One more possible leaving group in the first step of the [$^{18}$F]FDOPA synthesis is trimethylammonium (Scheme 34). According to the method developed by Lemaire and co-workers,[185] the displacement of the trimethylammonium group by fluorine is followed by reduction of the activating aldehyde group, and the benzyl alcohol thus formed is converted to benzyl iodide; the asymmetric alkylation of prochiral Schiff base ($Ph_2C{=}NCH_2Bu^t$) with this benzyl iodide catalyzed by the chiral ammonium salt (chiral phase transfer catalysis, CPTC) results in the protected [$^{18}$F]FDOPA.

The authors report high activity for the obtained specimen: >45 GBq, with the starting [$^{18}$F]fluoride activity being 185 GBq. Thus, this method, which was fully automated using a synthetic module, can be assigned to the most highly productive ones.

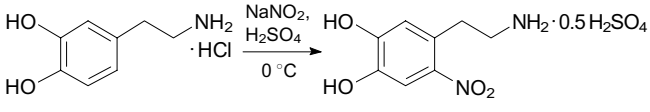
This strategy was applied to obtain racemic [$^{18}$F]6-fluoroadrenaline (Scheme 35).[186]

An original approach developing this strategy is the use of enzymes for functionalization of the $^{18}$F-labelled fluorinated precursor (Scheme 36).[187] The preparation of [$^{18}$F]FDOPA by this method includes nucleophilic displacement of the nitro group by radioactive fluoride followed by Rh-catalyzed decarbonylation of the aldehyde function and removal of the methoxy protecting groups by treatment with hydroiodic acid. The resulting [$^{18}$F]4-fluorocatechol is reacted with pyruvate and ammonia with the β-tyrosinase enzyme as a catalyst.

### 3.2.3. Displacement of the nitro group at late synthetic steps

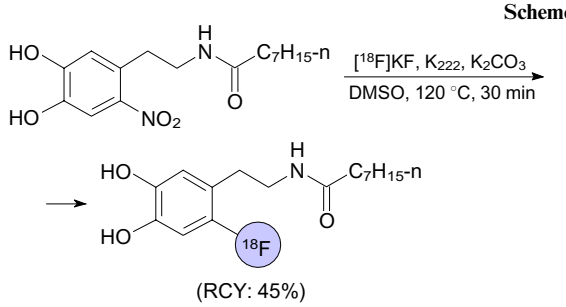
The second approach is described in a single publication of 2016 devoted to the synthesis of labelled *N*-octanoyldopamine.[154] 6-Nitrodopamine was prepared from dopamine hydrochloride and sodium nitrite in acidic aqueous medium on cooling [154, 159] (Scheme 37).

**Scheme 37**




After that, the authors [154] introduced the octanoyl group to the nitrogen atom; however, this was done in an unusual way: first both hydroxyl groups and the amine group were acylated with excess caprylic acid chloride, and then both esters were hydrolyzed by alkali. The 6-nitro-*N*-octanoyldopamine thus formed was reacted with radioactive fluoride, which substituted the nitro group (Scheme 38).

**Scheme 38**




The researchers [154] do not propose a mechanism for this unusual reaction; however, chemical and biological data they obtained leave no doubt that the fluorine isotope is actually present in position 6 of *N*-octanoyldopamine.

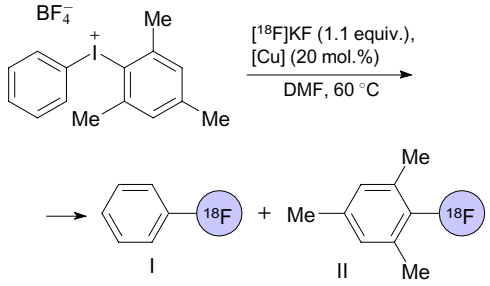
### 3.3. Metal-catalyzed and metal-promoted fluorination methods

Metal-catalyzed fluorination is applied to substrates that do not undergo classical $S_NAr$ reactions.

#### 3.3.1. Diaryliodonium salts

A fundamental difference between the reactions of diaryliodonium salts with the mesityl group (Mes = 2,4,6-$Me_3C_6H_2$) as a component and the reactions considered above in Section 3.2.1 is the course of fluorination in the presence of copper salts. Without copper salts, the fluorine atom mainly enters the mesityl ring, while in the presence of copper salts, the reaction gives fluorobenzene in almost quantitative yield (Scheme 39).[188]

**Scheme 39**

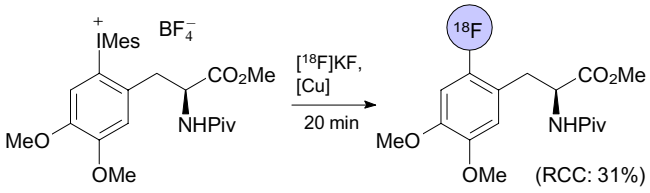



| [Cu] | Time /h | Additive | Yield (%) | I : II |
|---|---|---|---|---|
| $(Bu^tCN)_2CuOTf$ | 18 | – | 71 | 96 : 4 |
| $Cu(OTf)_2 \cdot C_6H_6$ | 18 | – | 57 | 96 : 4 |
| $Cu(OTf)_2$ | 18 | – | 85 | 98 : 2 |
| $Cu(OTf)_2$ | 3 | 18-crown-6 | 81 | 97 : 3 |
| – | 3 | 18-crown-6 | 30 | 20 : 80 |

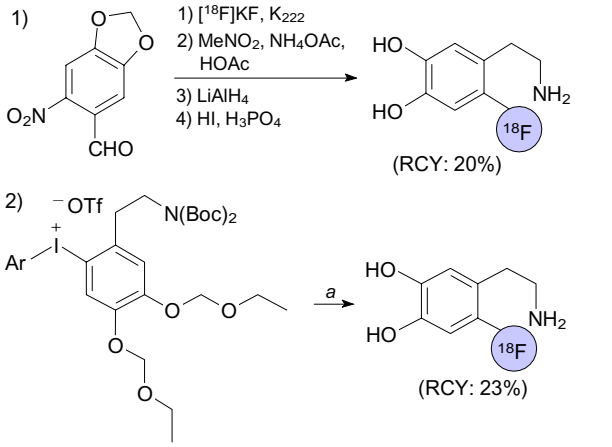
Using this method, protected [$^{18}$F]FDOPA was rapidly synthesized in good chemical and radiochemical yields (Scheme 40).[111]

In the case of dopamine, this approach is fairly promising. Indeed, a comparison of three methods for [$^{18}$F]FDA synthesis, namely (1) nitro group displacement followed by growing of the aminoethyl substituent,[189] (2) thermal substitution in diaryliodonium precursors [181] and (3) copper-catalyzed fluorination of mesityliodonium substrates,[190]

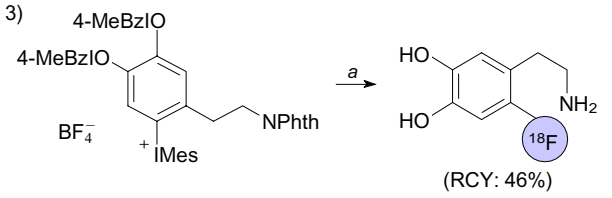
**Scheme 40**




**Scheme 41**




(*a*) 1) [$^{18}$F]KF, $K_{222}$, MeCN, 90 °C; 2) PhMe, 130 °C, 20 min; 3) HI, 140 °C, 8 min




(*a*) 1) [$^{18}$F]F$^-$ elution; 2) MeOH evaporation; 3) [$(MeCN)_4CuOTf$], DMF, 85 °C, 20 min; 4) $N_2H_4 \cdot H_2O$, EtOH, 100 °C, 50 min; 5) 54% HI, 130 °C, 10 min; NPhth is phthalimido, 4-MeBzl = 4-$MeC_6H_4CH_2$

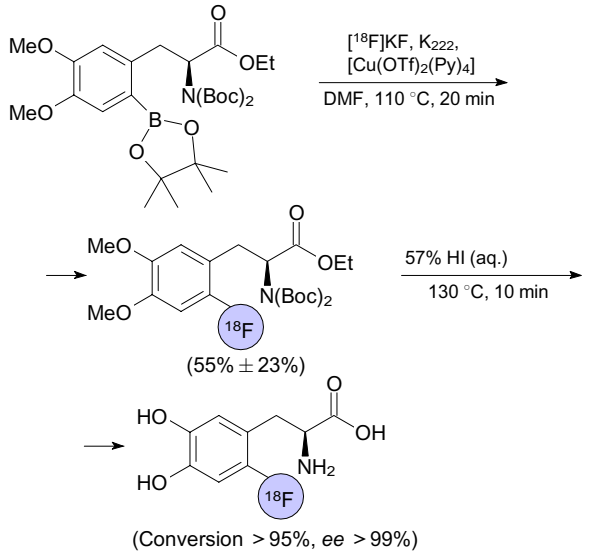
indicates good prospects for copper-catalyzed conversion of mesityliodonium precursors (Scheme 41).

#### 3.3.2. Use of boron-containing precursors

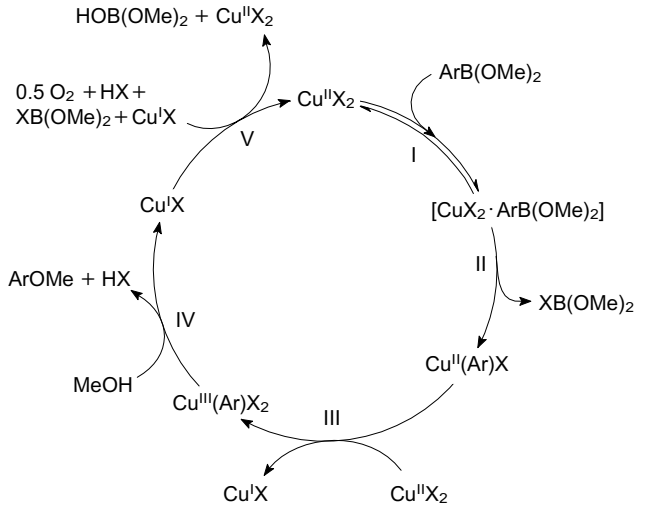
An up-to-date approach to the introduction of a fluorine atom into the aromatic ring is copper-catalyzed fluorine substitution for a boron group.[143] This method was successfully used to prepare [$^{18}$F]FDOPA (Scheme 42).[190] The deprotection was accomplished at the final step by treatment with hydrogen iodide.

The mechanism of copper-catalyzed cross-coupling of arylboronic esters to give the carbon – heteroatom bond, known as the Chan – Lam reaction,[191] includes reductive elimination, disproportionation and oxidation (Scheme 43); the two last-mentioned processes are characteristic of the redox chemistry of copper.

**Scheme 42**




**Scheme 43**




I,II is transmetallation, III is disproportionation,
IV is reductive elimination, V is aerobic oxidation

### 3.3.3. Nickel and palladium complexes as nucleophilic fluorination substrates

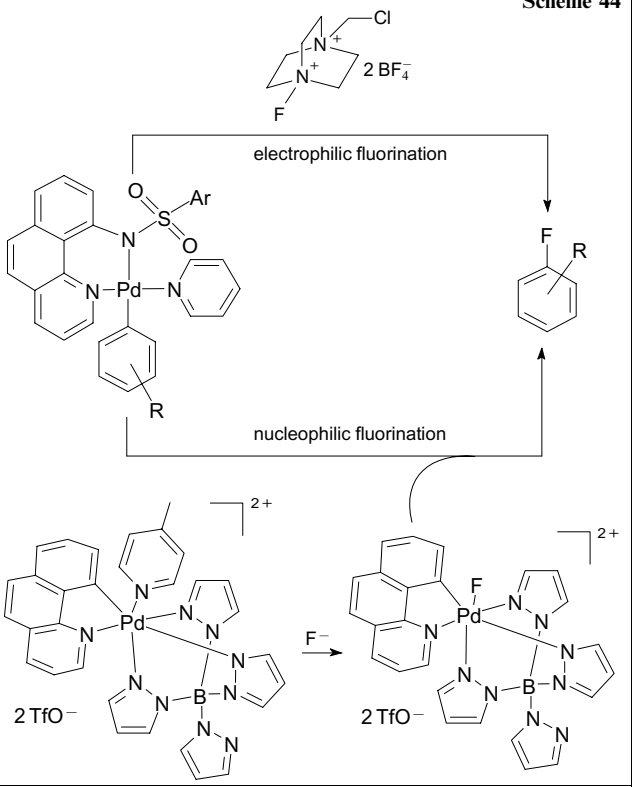
A separate trend in the preparation of radiolabelled DOPA and FDA is the application of pre-synthesized metal complexes with the Ar–M bond.[155]

It has been shown [157] that conversion of the Pd complex to fluoroarene can be accomplished by both electrophilic and nucleophilic fluorinating agents (Scheme 44). The mechanism of the latter reaction implies the involvement of Pd–F-bonded intermediates

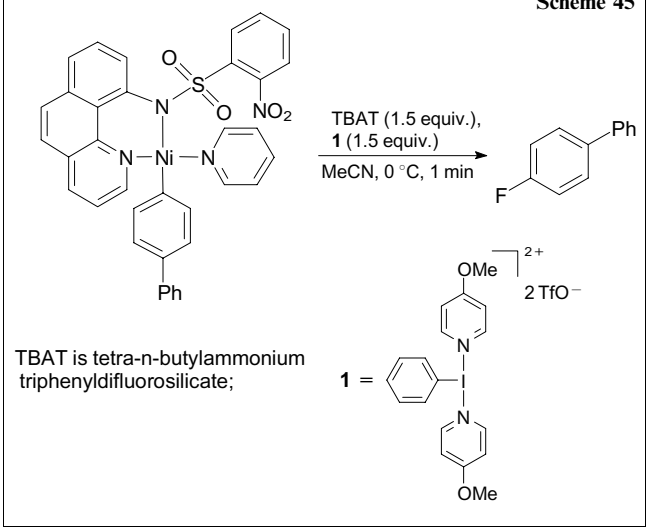
A similar approach was used to convert the Ni complex to the target fluoroarene under the action of iodonium salt **1** as an oxidant (Scheme 45).[155]

An important feature of using nickel complexes is the possibility to conduct fluorination in aqueous medium. The protected [$^{18}$F]FDOPA derivative **2** can be prepared in RCY of 15% ± 7% (Scheme 46).[155]

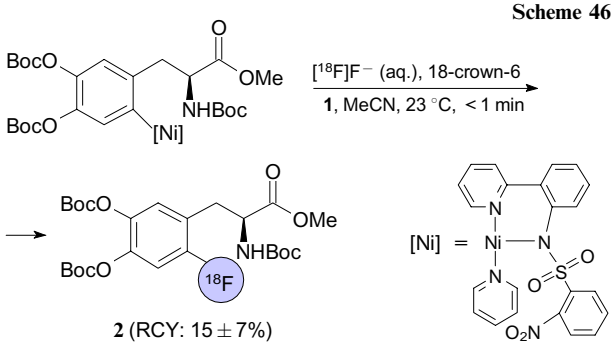
**Scheme 44**




**Scheme 45**

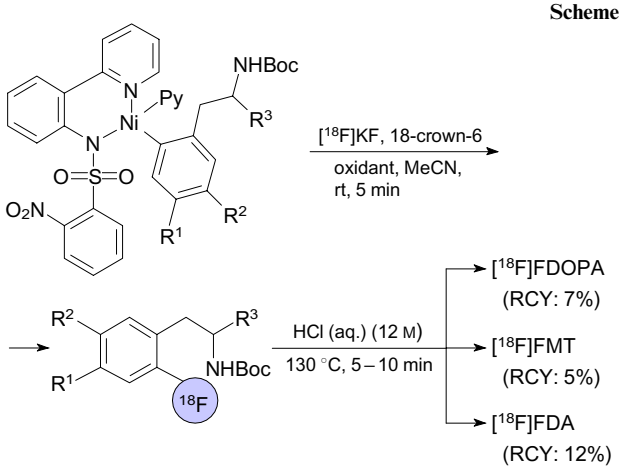



**Scheme 46**



The proposed approach was successfully used to synthesize both [$^{18}$F]FDA and [$^{18}$F]FDOPA (Scheme 47).[192] After deprotection, the radiolabelled products were formed in relatively high RCY.

**Scheme 47**




For [$^{18}$F]FDOPA: $R^1 = R^2 = OBoc$, $R^3 = CO_2Me$;
for [$^{18}$F]FMT: $R^1 = H$, $R^2 = OBoc$, $R^3 = CO_2Me$;
for [$^{18}$F]FDA = $R^1 = R^2 = OBoc$, $R^3 = H$;
FMT is 6-fluoro-*m*-tyrosine

## 4. Conclusion

A key problem of the synthetic and medicinal chemistry of fluorine compounds is the preparation of derivatives containing a fluorine atom or a fluorine-containing group in a strictly specified position of the molecule (with atomic precision [193]). Owing to the considerable progress in the selective fluorination, trifluoromethylation and introduction of small fluorinated groups into the target structure, solution of many practical tasks has substantially moved ahead.

Despite the vigorous development of selective fluorination with the natural fluorine isotope, the preparation of RPs based on dopamine and L-DOPA, which are most promising for the preclinical PET/CT diagnosis of neuroendocrine tumours and neurodegenerative disorders, requires new approaches. Indeed, the key clinically used method for the preparation of [$^{18}$F]DOPA is fluorination of the trimethylstannyl precursor with molecular fluorine.[194] It is known that [$^{18}$F]FDA is often more sensitive and efficient for detection of various types of NETs compared with the RPs used in clinical practice. The PET/CT diagnosis with [$^{18}$F]FDA has high sensitivity to both primary tumours and metastases and high specificity. However, [$^{18}$F]FDA is still available only as an experimental imaging radiopharmaceutical at the US National Institutes of Health.[194]

The above analysis of the synthetic approaches leads to the conclusion that reactions that utilize the nucleophilic properties of the fluoride anion are most promising for the introduction of a fluorine atom into dopamine and L-DOPA molecules; from the standpoint of convenience of laboratory synthesis, most attractive substrates are diaryliodonium salts, iodonium ylides and boronic acids. However, for commercial application, it is necessary to take into account the radiochemical yield; the possibility to obtain several clinical doses in one synthesis; and commercial availability and stability of precursors, both activated aromatic substrates and fluorinating reagents. At the present stage of development of methods and protocols for catecholamine radiofluorination, the asymmetric alkylation using chiral phase transfer catalysts [185] and copper-catalyzed fluorination of boronic esters [143, 195] should be considered as most promising.

One more modern trend of development of fluorinated pharmaceuticals is the targeted use of the specific behaviour of the fluorine atom in organic molecules; fluorine behaves as a chameleon atom capable of changing its electronic properties depending on its position in the molecule.[196] The knowledge of these features is needed for considering the interaction of a fluorinated agent with a biological object; here it is pertinent to quote a publication of Müller *et al.*,[197] which reads: 'exploration of the specific influence of carbon – fluorine single bonds in docking interactions, whether through direct contact with the protein or through stereoelectronic effects on molecular conformation of the drug, has only recently begun'. This is very important for the understanding of details of supramolecular interactions of fluorine-containing molecules with biological objects, with fluorinated catecholamines being no exception.

Thus, upgrading of the existing methods [198] and development of new approaches to the preparation of $^{18}$F-RPs based on dopamine and L-DOPA are very important tasks the solution of which would open unique opportunities for the diagnosis of neuroendocrine tumours and their micrometastases as well as neurodegenerative diseases. This is important, in particular, for the fundamental research into the molecular mechanisms of development of cognitive processes caused by changes in the neurotransmitter balance in the human body, which are among the main factors determining not only quality of life, but also the survival of patients with neurodegenerative and neuroendocrine system diseases.

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## References

1. *Neirodegenerativnye Zabolevaniya: ot Genoma do Tselostnogo Organizma*. (Neurodegenerative Diseases: from the Genome to the Whole Organism Vol. 1). (Ed. M.V.Ugryumov). (Moscow: Nauchnyi Mir, 2014)
2. G.G.Kovacs. *Int. J. Mol. Sci.*, **17**, 189 (2016)
3. V.K.Ramanan, A.J.Saykin. *Am. J. Neurodegener. Dis.*, **2**, 145 (2013)
4. D.S.Klimstra, I.R.Modlin, D.Coppola, R.V.Lloyd, S.Suster. *Pancreas*, **39**, 707 (2010)
5. M.T.Barakat, K.Meeran, S.R.Bloom. *Endocr. Relat. Cancer*, **11**, 1 (2004)
6. G.A.Kaltsas, G.M.Besser, A.B.Grossman. *Endocr. Rev.*, **25**, 458 (2004)
7. H.M.Schuller, in *Neuronal Activity in Tumor Tissue. (Progress in Experimental Tumor Research.* Vol. 39). (Eds K.S.Zänker, F.Entschladen). (Basel: Karger, 2007) p. 45
8. G.Eisenhofer, I.J.Kopin, D.S.Goldstein. *Pharmacol. Rev.*, **56**, 331 (2004)
9. J.Brettschneider, K.Del Tredici, V.M.-Y.Lee, J.Q.Trojanowski. *Nat. Rev. Neurosci.*, **16**, 109 (2015)
10. A.Frilling, G.Åkerström, M.Falconi, M.Pavel, J.Ramos, M.Kidd, I.M.Modlin. *Endocr. Relat. Cancer*, **19**, R163 (2012)

11. R.Harada, N.Okamura, S.Furumoto, T.Tago, K.Yanai, H.Arai, Y.Kudo. *Biomolecules*, **6**, 7 (2016)
12. L.Zhu, K.Ploessl, H.F.Kung. *Chem. Soc. Rev.*, **43**, 6683 (2014)
13. A.Nordberg, J.O.Rinne, A.Kadir, B.Långström. *Nat. Rev. Neurol.*, **6**, 78 (2010)
14. L.Zimmer, A.Luxen. *NeuroImage*, **61**, 363 (2012)
15. C.Loane, M.Politis. *Am. J. Transl. Res.*, **3**, 323 (2011)
16. C.B.Johnbeck, U.Knigge, A.Kjær. *Future Oncol.*, **10**, 2259 (2014)
17. A.Sundin, B.Eriksson, M.Bergström, B.Långström, K.Öberg, H.Örlefors. *Ann. N. Y. Acad. Sci.*, **1014**, 246 (2004)
18. K.A.Wood, P.J.Hoskin, M.I.Saunders. *Clin. Oncol.*, **19**, 237 (2007)
19. I.A.Veselova, E.A.Sergeeva, M.I.Makedonskaya, O.E.Eremina, S.N.Kalmykov, T.N.Shekhovtsova. *J. Anal. Chem.*, **71**, 1155 (2016)
20. L.S.Skryabina, E.I.Rossokha, A.M.Avdalyan, A.V.Fedoskina. *Russ. J. Oncol.,* **20** (4), 42 (2015)
21. *Zlokachestvennye Obrazovaniya v Rossii v 2015 godu (Zabolevaemost' i Smertnost')*. [Malignant Diseases in Russia in 2015 (Morbidity and Mortality)]. (Eds A.D.Kaprin, V.V.Starinskii, D.V.Petrova). (Moscow: P.A.Gertsen MNIOI, 2017) p. 250
22. O.V.Krivonos, I.G.Smolentseva, N.A.Amosova. *Saratov. Nauchno-Med. Zh.*, **9**, 863 (2013)
23. D.Yu.Belousov, S.K.Zyryanov, Yu.B.Belousov, A.S.Beketov. *Kachestv. Klin. Praktika*, (S1), 3 (2009)
24. C.G.Moertel, L.K.Kvols, M.J.O'Connell, J.Rubin. *Cancer*, **68**, 227 (1991)
25. P.U.Heitz, in *Morphological Tumor Markers*. (Ed. G.Seifer). (Berlin, Heidelberg: Springer-Verlag, 1987) p. 279
26. P.S.H.Soon, L.J.Tacon, A.J.Gill, C.P.Bambach, M.S.Sywak, P.R.Campbell, M.W.Yeh, S.G.Wong, R.J.Clifton-Bligh, B.G.Robinson, S.B.Sidhu. *Clin. Cancer Res.*, **15**, 7684 (2009)
27. M.Schindl, K.Kaczirek, K.Kaserer, B.Niederle. *World J. Surg.*, **24**, 1312 (2000)
28. W.R.Burns, B.H.Edil. *Curr. Treat. Options Oncol.*, **13**, 24 (2012)
29. H.Chen, R.S.Sippel, M.S.O'Dorisio, A.I.Vinik, R.V.Lloyd, K.Pacak. *Pancreas*, **39**, 775 (2010)
30. S.G.Mueller, M.W.Weiner, L.J.Thal, R.C.Petersen, C.R.Jack, W.Jagust, J.Q.Trojanowski, A.W.Toga, L.Beckett. *Alzheimer's Dement.*, **1**, 55 (2005)
31. M.Ghaemi, R.Hilker, J.Rudolf, J.Sobesky, W.-D.Heiss. *J. Neurol., Neurosurg. Psychiatry*, **73**, 517 (2002)
32. J.T.O'Brien. *Br. J. Radiol.*, **80**, S71 (2007)
33. O.Jacobson, D.O.Kiesewetter, X.Chen. *Bioconjug. Chem.*, **26**, 1 (2015)
34. C.A.Mathis, Y.Wang, D.P.Holt, G.-F.Huang, M.L.Debnath, W.E.Klunk. *J. Med. Chem.*, **46**, 2740 (2003)
35. D.V.Ryzhkova, D.N.Tikhonova, E.N.Grineva. *Sib. Onkol. Zh.* (6), 56 (2013)
36. R.Bejot, V.Gouverneur, in *Fluorine in Pharmaceutical and Medicinal Chemistry: from Biophysical Aspects to Clinical Applications*. (Eds V.Gouverneur, K.Müller). (London: Imperial College Press, 2012) p. 335
37. F.-M.Lu, Z.Yuan. *Quant. Imaging Med. Surg.*, **5**, 433 (2015)
38. K.Oukoloff, M.Cieslikiewicz-Bouet, S.Chao, E.Da Costa Branquinho, C.Bouteiller, L.Jean, P.-Y.Renard. *Curr. Med. Chem.*, **22**, 3278 (2015)
39. B.M.Zeglis, J.S.Lewis. *Dalton Trans.*, **40**, 6168 (2011)
40. A.T.Soderlund, J.Chaal, G.Tjio, J.J.Totman, M.Conti, D.W.Townsend. *J. Nucl. Med.*, **56**, 1285 (2015)
41. R.N.Krasikova, R.A.Aliev, S.N.Kalmykov. *Mendeleev Commun.*, **26**, 85 (2016)
42. M.Reivich, D.Kuhl, A.Wolf, J.Greenberg, M.Phelps, T.Ido, V.Casella, J.Fowler, E.Hoffman, A.Alavi, P.Som, L.Sokoloff. *Circ. Res.*, **44**, 127 (1979)
43. P.A.Culbert, M.J.Adam, E.T.Hurtado, J.M.A.Huser, S.Jivan, J.Lu, T.J.Ruth, S.K.Zeisler. *Appl. Radiat. Isot.*, **46**, 887 (1995)
44. N.I.Bohnen, D.S.W.Djang, K.Herholz, Y.Anzai, S.Minoshima. *J. Nucl. Med.*, **53**, 59 (2012)
45. N.Tolboom, W.M.van der Flier, M.Yaqub, R.Boellaard, N.A.Verwey, M.A.Blankenstein, A.D.Windhorst, P.Scheltens, A.A.Lammertsma, B.N.M.van Berckel. *J. Nucl. Med.*, **50**, 1464 (2009)
46. R.Vandenberghe, K.Van Laere, A.Ivanoiu, E.Salmon, C.Bastin, E.Triau, S.Hasselbalch, I.Law, A.Andersen, A.Korner, L.Minthon, G.Garraux, N.Nelissen, G.Bormans, C.Buckley, R.Owenius, L.Thurfjell, G.Farrar, D.J.Brooks. *Ann. Neurol.*, **68**, 319 (2010)
47. V.L.Villemagne, K.Ong, R.S.Mulligan, G.Holl, S.Pejoska, G.Jones, G.O'Keefe, U.Ackerman, H.Tochon-Danguy, J.G.Chan, C.B.Reininger, L.Fels, B.Putz, B.Rohde, C.L.Masters, C.C.Rowe. *J. Nucl. Med.*, **52**, 1210 (2011)
48. P.M.Doraiswamy, R.A.Sperling, R.E.Coleman, K.A.Johnson, E.M.Reiman, M.D.Davis, M.Grundman, M.N.Sabbagh, C.H.Sadowsky, A.S.Fleisher, A.Carpenter, C.M.Clark, A.D.Joshi, M.A.Mintun, D.M.Skovronsky, M.J.Pontecorvo. *Neurology*, **79**, 1636 (2012)
49. R.Harada, N.Okamura, S.Furumoto, T.Tago, M.Maruyama, M.Higuchi, T.Yoshikawa, H.Arai, R.Iwata, Y.Kudo, K.Yanai. *Eur. J. Nucl. Med. Mol. Imaging*, **40**, 125 (2013)
50. R.Harada, N.Okamura, S.Furumoto, K.Furukawa, A.Ishiki, N.Tomita, T.Tago, K.Hiraoka, S.Watanuki, M.Shidahara, M.Miyake, Y.Ishikawa, R.Matsuda, A.Inami, T.Yoshikawa, Y.Funaki, R.Iwata, M.Tashiro, K.Yanai, H.Arai, Y.Kudo. *J. Nucl. Med.*, **57**, 208 (2016)
51. T.Tago, S.Furumoto, N.Okamura, R.Harada, H.Adachi, Y.Ishikawa, K.Yanai, R.Iwata, Y.Kudo. *Mol. Imaging Biol.*, **18**, 258 (2016)
52. A.Ishiki, N.Okamura, K.Furukawa, S.Furumoto, R.Harada, N.Tomita, K.Hiraoka, S.Watanuki, Y.Ishikawa, T.Tago, Y.Funaki, R.Iwata, M.Tashiro, K.Yanai, Y.Kudo, H.Arai. *PLoS One*, **10**, e0140311 (2015)
53. L.Declercq, S.Celen, J.Lecina, M.Ahamed, T.Tousseyn, D.Moechars, J.Alcazar, M.Ariza, K.Fierens, A.Bottelbergs, J.Mariën, R.Vandenberghe, I.J.Andres, K.Van Laere, A.Verbruggen, G.Bormans. *Mol. Imaging*, **15**, 153601211562492 (2016)
54. D.T.Chien, S.Bahri, A.K.Szardenings, J.C.Walsh, F.Mu, M.-Y.Su, W.R.Shankle, A.Elizarov, H.C.Kolb. *J. Alzheimer's Dis.*, **34**, 457 (2013)
55. S.Ng, V.L.Villemagne, S.Berlangieri, S.-T.Lee, M.Cherk, S.J.Gong, U.Ackermann, T.Saunder, H.Tochon-Danguy, G.Jones, C.Smith, G.O'Keefe, C.L.Masters, C.C.Rowe. *J. Nucl. Med.*, **48**, 547 (2007)
56. E.S.Garnett, G.Firnau, C.Nahmias. *Nature (London)*, **305**, 137 (1983)
57. N.Ibrahim, J.Kusmirek, A.F.Struck, J.M.Floberg, S.B.Perlman, C.Gallagher, L.T.Hall. *Am. J. Nucl. Med. Mol. Imaging*, **6**, 102 (2016)
58. J.P.Seibyl, W.Chen, D.H.S.Silverman. *Semin. Nucl. Med.*, **37**, 440 (2007)
59. N.Goldstein, R.Goldstein, D.Terterov, A.A.Kamensky, G.I.Kovalev, Yu.A.Zolotarev, G.N.Avakyan, S.Terterov. *Biochemistry (Moscow)*, **77**, 419 (2012)
60. K.Chansaenpak, B.Vabre, F.P.Gabbaï. *Chem. Soc. Rev.*, **45**, 954 (2016)
61. O.S.Fedorova, M.V.Kireev, O.F.Kuznetsova, S.V.Shatik, R.N.Krasikova. *Luch. Diagnost. Terap.*, (4), 22 (2015)
62. I.Ilias, B.Shulkin, K.Pacak. *Trends Endocrinol. Metab.*, **16**, 66 (2005)
63. S.Hoegerle, C.Altehoefer, N.Ghanem, G.Koehler, C.F.Waller, H.Scheruebl, E.Moser, E.Nitzsche. *Radiology*, **220**, 373 (2001)

64. A.Becherer, M.Szabó, G.Karanikas, P.Wunderbaldinger, P.Angelberger, M.Raderer, A.Kurtaran, R.Dudczak, K.Kletter. *J. Nucl. Med.*, **45**, 1161 (2004)
65. C.Nanni, S.Fanti, D.Rubello. *J. Nucl. Med.*, **48**, 1577 (2007)
66. N.Charrier, A.Deveze, N.Fakhry, F.Sebag, I.Morange, B.Gaborit, A.Barlier, E.Carmona, C.De Micco, S.Garcia, J.Mancini, F.F.Palazzo, J.P.Lavieille, M.Zanaret, J.F.Henry, O.Mundler, D.Taïeb. *Clin. Endocrinol. (Oxford)*, **74**, 21 (2011)
67. K.S.King, C.C.Chen, D.K.Alexopoulos, M.A.Whatley, J.C.Reynolds, N.Patronas, A.Ling, K.T.Adams, P.Xekouki, H.Lando, C.A.Stratakis, K.Pacak. *J. Clin. Endocrinol. Metab.*, **96**, 2779 (2011)
68. H.Minn, S.Kauhanen, M.Seppänen, P.Nuutila. *J. Nucl. Med.*, **50**, 1915 (2009)
69. F.Imani, V.G.Agopian, M.S.Auerbach, M.A.Walter, F.Imani, M.R.Benz, R.A.Dumont, C.K.Lai, J.G.Czernin, M.W.Yeh. *J. Nucl. Med.*, **50**, 513 (2009)
70. H.J.L.M.Timmers, C.C.Chen, J.A.Carrasquillo, M.Whatley, A.Ling, B.Havekes, G.Eisenhofer, L.Martiniova, K.T.Adams, K.Pacak. *J. Clin. Endocrinol. Metab.*, **94**, 4757 (2009)
71. P.L.Jager, R.Chirakal, C.J.Marriott, A.H.Brouwers, K.P.Koopmans, K.Y.Gulenchyn. *J. Nucl. Med.*, **49**, 573 (2008)
72. A.F.Jacobson, H.Deng, J.Lombard, H.J.Lessig, R.R.Black. *J. Clin. Endocrinol. Metab.*, **95**, 2596 (2010)
73. T.Jindal, A.Kumar, B.Venkitaraman, R.Dutta, R.Kumar. *Korean J. Intern. Med.*, **25**, 386 (2010)
74. G.Kaltsas, M.Korbonits, E.Heintz, J.J.Mukherjee, P.J.Jenkins, S.L.Chew, R.Reznek, J.P.Monson, G.M.Besser, R.Foley, K.E.Britton, A.B.Grossman. *J. Clin. Endocrinol. Metab.*, **86**, 895 (2001)
75. L.I.Goldberg, J.D.Kohli, D.Cantacuzene, K.L.Kirk, C.R.Creveling. *J. Pharmacol. Exp. Ther.*, **213**, 509 (1980)
76. G.Firnau, S.Garnett, A.M.Marshall, P.Seeman, J.Tedesco, K.L.Kirk. *Biochem. Pharmacol.*, **30**, 2927 (1981)
77. K.Pacak, G.Eisenhofer, D.S.Goldstein. *Endocr. Rev.*, **25**, 568 (2004)
78. G.Eisenhofer. *Pharmacol. Ther.*, **91**, 35 (2001)
79. J.-Y.Nie, D.Shi, J.W.Daly, K.L.Kirk. *Med. Chem. Res.*, **6**, 318 (1996)
80. Y.Nimit, D.Cantacuzene, K.L.Kirk, C.R.Creveling, J.W.Daly. *Life Sci.*, **27**, 1577 (1980)
81. S.-f.Lu, B.Herbert, G.Haufe, K.W.Laue, W.L.Padgett, O.Oshunleti, J.W.Daly, K.L.Kirk. *J. Med. Chem.*, **43**, 1611 (2000)
82. K.Pacak, G.Eisenhofer, J.A.Carrasquillo, C.C.Chen, S.-T.Li, D.S.Goldstein. *Hypertension*, **38**, 6 (2001)
83. K.Pacak, D.S.Goldstein, J.L.Doppman, B.L.Shulkin, R.Udelsman, G.Eisenhofer. *J. Clin. Endocrinol. Metab.*, **86**, 3641 (2001)
84. K.Pacak, G.Eisenhofer, J.A.Carrasquillo, C.C.Chen, M.Whatley, D.S.Goldstein. *Ann. N.Y. Acad. Sci.*, **970**, 170 (2002)
85. K.Pacák, M.Palkovits. *Endocr. Rev.*, **22**, 502 (2001)
86. H.J.L.M.Timmers, D.Taieb, K.Pacak. *Horm. Metab. Res.*, **44**, 367 (2012)
87. K.D.Neumann, L.Qin, A.L.Vāvere, B.Shen, Z.Miao, F.T.Chin, B.L.Shulkin, S.E.Snyder, S.G.DiMagno. *J. Labelled Compd. Radiopharm.*, **59**, 30 (2016)
88. D.J.Adams, J.H.Clark. *Chem. Soc. Rev.*, **28**, 225 (1999)
89. A.J.Beaumont, J.H.Clark, N.A.Boechat. *J. Fluorine Chem.*, **63**, 25 (1993)
90. M.G.Campbell, T.Ritter. *Chem. Rev.*, **115**, 612 (2015)
91. E.P.Gillis, K.J.Eastman, M.D.Hill, D.J.Donnelly, N.A.Meanwell. *J. Med. Chem.*, **58**, 8315 (2015)
92. V.G.Nenajdenko, E.S.Balenkova. *Tetrahedron*, **50**, 12407 (1994)
93. *Fluorine in Heterocyclic Chemistry. 6-Membered Heterocycles*. Vol. 2. (Ed. V.G.Nenajdenko). (Cham, Heidelberg, New York, Dordrecht, London: Springer, 2014) p. 760
94. V.G.Nenajdenko, G.N.Varseev, V.N.Korotchenko, A.V.Shastin, E.S.Balenkova. *J. Fluorine Chem.*, **125**, 1339 (2004)
95. V.G.Nenajdenko, G.N.Varseev, A.V.Shastin, E.S.Balenkova. *J. Fluorine Chem.*, **126**, 907 (2005)
96. F.Buckingham, V.Gouverneur. *Chem. Sci.*, **7**, 1645 (2016)
97. H.Teare, E.G.Robins, A.Kirjavainen, S.Forsback, G.Sandford, O.Solin, S.K.Luthra, V.Gouverneur. *Angew. Chem., Int. Ed.*, **49**, 6821 (2010)
98. S.Preshlock, M.Tredwell, V.Gouverneur. *Chem. Rev.*, **116**, 719 (2016)
99. M.Guillaume, A.Luxen, B.Nebeling, M.Argentini, J.C.Clark, V.W.Pike. *Int. J. Radiat. Appl. Instrum., Part A: Appl. Radiat. Isot.*, **42**, 749 (1991)
100. *Cyclotron Produced Radionuclides: Guidance on Facility Design, Production of [$^{18}$F]fluorodeoxyglucose (FDG). (IAEA Radioisotopes, Radiopharmaceuticals Series*. No. 3). (Vienna: International Atomic Energy Agency, 2012) p. 172
101. N.A.Gomzina, V.V.Zaitsev, R.N.Krasikova. *J. Labelled Compd. Radiopharm.*, **44**, S895 (2001)
102. N.A.Gomzina, D.A.Vasil'ev, R.N.Krasikova. *Radiochemistry*, **44**, 403 (2002)
103. J.M.Lehn, J.P.Sauvage. *J. Chem. Soc. D*, 440 (1971)
104. J.Ermert, H.H.Coenen. *J. Labelled Compd. Radiopharm.*, **56**, 225 (2013)
105. J.Ermert. *BioMed. Res. Int.*, **2014**, ID 812973 (2014)
106. L.Cai, S.Lu, V.W.Pike. *Eur. J. Org. Chem.*, **2008**, 2853 (2008)
107. S.H.Liang, N.Vasdev. *Aust. J. Chem.*, **68**, 1319 (2015)
108. R.Krasikova. *Curr. Org. Chem.*, **17**, 2097 (2013)
109. V.V.Orlovskaya, O.S.Fedorova, R.N.Krasikova. *Russ. Chem. Bull., Int. Ed.*, **64**, 1518 (2015)
110. G.-C.Li, R.Zhang, J.-y.Xia. *Radiochim. Acta*, **104**, 897 (2016)
111. N.Ichiishi, A.F.Brooks, J.J.Topczewski, M.E.Rodnick, M.S.Sanford, P.J.H.Scott. *Org. Lett.*, **16**, 3224 (2014)
112. M.Maeda, T.Fukumura, M.Kojima. *Int. J. Radiat. Appl. Instrum., Part A: Appl. Radiat. Isot.*, **38**, 307 (1987)
113. A.Knöchel, O.Zwernemann. *Int. J. Radiat. Appl. Instrum., Part A: Appl. Radiat. Isot.*, **42**, 1077 (1991)
114. M.Argentini, C.Wiese, R.Weinreicht. *J. Fluorine Chem.*, **68**, 141 (1994)
115. N.A.Gomzina, D.A.Vasil'ev, R.N.Krasikova. *Radiochemistry*, **49**, 299 (2007)
116. D.Block, H.H.Coenen, G.Stöcklin. *J. Labelled Compd. Radiopharm.*, **25**, 201 (1988)
117. M.-R.Zhang, M.Ogawa, K.Furutsuka, Y.Yoshida, K.Suzuki. *J. Fluorine Chem.*, **125**, 1879 (2004)
118. S.-Y.Lu, F.T.Chin, J.A.McCarron, V.W.Pike. *J. Labelled Compd. Radiopharm.*, **47**, 289 (2004)
119. N.Jarkas, R.J.Voll, M.M.Goodman. *J. Labelled Compd. Radiopharm.*, **56**, 539 (2013)
120. M.M.Herth, M.Barz, D.Moderegger, M.Allmeroth, M.Jahn, O.Thews, R.Zentel, F.Rösch. *Biomacromolecules*, **10**, 1697 (2009)
121. M.-R.Zhang, K.Suzuki. *Curr. Top. Med. Chem.*, **7**, 1817 (2007)
122. I.Ekaeva, L.Barre, M.-C.Lasne, F.Gourand. *Appl. Radiat. Isot.*, **46**, 777 (1995)
123. T.Ludwig, J.Ermert, H.H.Coenen. *Nucl. Med. Biol.*, **29**, 255 (2002)
124. P.K.Chakraborty, M.R.Kilbourn. *Int. J. Radiat. Appl. Instrum., Part A: Appl. Radiat. Isot.*, **42**, 673 (1991)
125. P.K.Chakraborty, M.R.Kilbourn. *Int. J. Radiat. Appl. Instrum., Part A: Appl. Radiat. Isot.*, **42**, 1209 (1991)
126. S.G.Mislankar, D.L.Gildersleeve, D.M.Wieland, C.C.Massin, G.K.Mulholland, S.A.Toorongian. *J. Med. Chem.*, **31**, 362 (1988)

127. M.Perlmutter, N.Satyamurthy, A.Luxen, M.E.Phelps, J.R.Barrio. *Int. J. Radiat. Appl. Instrum., Part A: Appl. Radiat. Isot.*, **41**, 801 (1990)
128. G.Balz, G.Schiemann. *Ber. Dtsch. Chem. Ges.*, **60**, 1186 (1927)
129. L.Barré, L.Barbier, M.-C.Lasne. *J. Labelled Compd. Radiopharm.*, **35**, 167 (1994)
130. T.L.Ross, J.Ermert, H.H.Coenen. *Molecules*, **16**, 7621 (2011)
131. A.Helfer, J.Castillo Meleán, J.Ermert, A.Infantino, H.H.Coenen. *Appl. Radiat. Isot.*, **82**, 264 (2013)
132. B.H.Rotstein, N.A.Stephenson, N.Vasdev, S.H.Liang. *Nat. Commun.*, **5**, Art. No. 4365 (2014)
133. J.Ermert, C.Hocke, T.Ludwig, R.Gail, H.H.Coenen. *J. Labelled Compd. Radiopharm.*, **47**, 429 (2004)
134. E.D.Hostetler, S.D.Jonson, M.J.Welch, J.A.Katzenellenbogen. *J. Org. Chem.*, **64**, 178 (1999)
135. M.Namavari, N.Satyamurthy, M.E.Phelps, J.R.Barrio. *Appl. Radiat. Isot.*, **44**, 527 (1993)
136. K.J.Makaravage, A.F.Brooks, A.V.Mossine, M.S.Sanford, P.J.H.Scott. *Org. Lett.*, **18**, 5440 (2016)
137. Z.Gao, Y.H.Lim, M.Tredwell, L.Li, S.Verhoog, M.Hopkinson, W.Kaluza, T.L.Collier, J.Passchier, M.Huiban, V.Gouverneur. *Angew. Chem., Int. Ed.*, **51**, 6733 (2012)
138. N.Vasdev, R.Chirakal, G.J.Schrobilgen, C.Nahmias. *J. Fluorine Chem.*, **111**, 17 (2001)
139. O.Wallach. *Justus Liebigs Ann. Chem.*, **235**, 233 (1886)
140. T.Pages, B.R.Langlois, D.Le Bars, P.Landais. *J. Fluorine Chem.*, **107**, 329 (2001)
141. S.D.Schimler, M.A.Cismesia, P.S.Hanley, R.D.J.Froese, M.J.Jansma, D.C.Bland, M.S.Sanford. *J. Am. Chem. Soc.*, **139**, 1452 (2017)
142. V.V.Grushin, W.J.Marshall. *Organometallics*, **27**, 4825 (2008)
143. N.J.Taylor, E.Emer, S.Preshlock, M.Schedler, M.Tredwell, S.Verhoog, J.Mercier, C.Genicot, V.Gouverneur. *J. Am. Chem. Soc.*, **139**, 8267 (2017)
144. M.Tredwell, S.M.Preshlock, N.J.Taylor, S.Gruber, M.Huiban, J.Passchier, J.Mercier, C.Génicot, V.Gouverneur. *Angew. Chem., Int. Ed.*, **53**, 7751 (2014)
145. M.K.Narayanam, G.Ma, P.A.Champagne, K.N.Houk, J.M.Murphy. *Angew. Chem., Int. Ed.*, **56**, 13006 (2017)
146. M.Huiban, M.Tredwell, S.Mizuta, Z.Wan, X.Zhang, T.L.Collier, V.Gouverneur, J.Passchier. *Nat. Chem.*, **5**, 941 (2013)
147. D.van der Born, C.Sewing, J.(Koos)D.M.Herscheid, A.D.Windhorst, R.V.A.Orru, D.J.Vugts. *Angew. Chem., Int. Ed.*, **53**, 11046 (2014)
148. C.N.Neumann, J.M.Hooker, T.Ritter. *Nature (London)*, **534**, 369 (2016)
149. M.J.Adam, J.R.Grierson, T.J.Ruth, S.Jivan. *Int. J. Radiat. Appl. Instrum., Part A: Appl. Radiat. Isot.*, **37**, 877 (1986)
150. M.S.Yusubov, A.Yoshimura, V.V.Zhdankin. *ARKIVOC*, **2016** (i), 342 (2016)
151. S.Forsback, O.Solin. *Radiochim. Acta*, **103**, 219 (2015)
152. O.Eskola, T.J.Grönroos, A.Naum, P.Marjamäki, S.Forsback, J.Bergman, S.Länkimäki, J.Kiss, T.Savunen, J.Knuuti, M.Haaparanta, O.Solin. *Eur. J. Nucl. Med. Mol. Imaging*, **39**, 800 (2012)
153. S.Preshlock, S.Calderwood, S.Verhoog, M.Tredwell, M.Huiban, A.Hienzsch, S.Gruber, T.C.Wilson, N.J.Taylor, T.Cailly, M.Schedler, T.L.Collier, J.Passchier, R.Smits, J.Mollitor, A.Hoepping, M.Mueller, C.Genicot, J.Mercier, V.Gouverneur. *Chem. Commun.*, **52**, 8361 (2016)
154. M.Pretze, P.Pallavi, M.Roscher, S.Klotz, J.Caballero, U.Binzen, W.Greffrath, R.-D.Treede, M.C.Harmsen, M.Hafner, B.Yard, C.Wängler, B.Wängler. *J. Med. Chem.*, **59**, 9855 (2016)
155. E.Lee, J.M.Hooker, T.Ritter. *J. Am. Chem. Soc.*, **134**, 17456 (2012)
156. E.Lee, A.S.Kamlet, D.C.Powers, C.N.Neumann, G.B.Boursalian, T.Furuya, D.C.Choi, J.M.Hooker, T.Ritter. *Science*, **334**, 639 (2011)
157. R.Chirakal, G.Coates, G.Firnau, G.J.Schrobilgen, C.Nahmias. *Nucl. Med. Biol.*, **23**, 41 (1996)
158. G.Firnau, R.Chirakal, E.S.Garnett. *J. Nucl. Med.*, **25**, 1228 (1984)
159. M.Pretze, C.Wängler, B.Wängler. *BioMed Res. Int.*, **2014**, ID 674063 (2014)
160. R.Edwards, T.Wirth. *J. Labelled Compd. Radiopharm.*, **58**, 183 (2015)
161. T.Chaly, M.Diksic. *J. Nucl. Med.*, **27**, 1896 (1986)
162. P.Cumming, M.Häusser, W.R.W.Martin, J.Grierson, M.J.Adam, T.J.Ruth, E.G.McGeer. *Biochem. Pharmacol.*, **37**, 247 (1988)
163. M.Namavari, A.Bishop, N.Satyamurthy, G.Bida, J.R.Barrio. *Int. J. Radiat. Appl. Instrum., Part A: Appl. Radiat. Isot.*, **43**, 989 (1992)
164. E.F.J.de Vries, G.Luurtsema, M.Brüssermann, P.H.Elsinga, W.Vaalburg. *Appl. Radiat. Isot.*, **51**, 389 (1999)
165. M.Namavari, N.Satyamurthy, J.R.Barrio. *J. Fluorine Chem.*, **74**, 113 (1995)
166. S.Forsback, O.Eskola, M.Haaparanta, J.Bergman, O.Solin. *Radiochim. Acta*, **96**, 845 (2008)
167. D.O.Antuganov, M.P.Zykov, D.V.Ryzhkova, T.A.Zykova, A.A.Vinal'ev, Yu.O.Antuganova, O.P.Samburov. *Radiochemistry*, **58**, 649 (2016)
168. I.S.R.Stenhagen, A.K.Kirjavainen, S.J.Forsback, C.G.Jørgensen, E.G.Robins, S.K.Luthra, O.Solin, V.Gouverneur. *Chem. Commun.*, **49**, 1386 (2013)
169. M.Tredwell, V.Gouverneur. *Angew. Chem., Int. Ed.*, **51**, 11426 (2012)
170. A.Shah, V.W.Pike, D.A.Widdowson. *J. Chem. Soc., Perkin Trans 1*, 2043 (1998)
171. T.L.Ross, J.Ermert, C.Hocke, H.H.Coenen. *J. Am. Chem. Soc.*, **129**, 8018 (2007)
172. M.S.Yusubov, D.Yu.Svitich, M.S.Larkina, V.V.Zhdankin. *ARKIVOC*, **2013** (i), 364 (2013)
173. R.Edwards, A.D.Westwell, S.Daniels, T.Wirth. *Eur. J. Org. Chem.*, **2015**, 625 (2015)
174. W.-J.Kuik, I.P.Kema, A.H.Brouwers, R.Zijlma, K.D.Neumann, R.A.J.O.Dierckx, S.G.DiMagno, P.H.Elsinga. *J. Nucl. Med.*, **56**, 106 (2015)
175. Patent WO 2015134923A1 (2015)
176. Patent WO 2010117435 (2010)
177. T.Giroldo, L.A.Xavier, J.M.Riveros. *Angew. Chem., Int. Ed.*, **43**, 3588 (2004)
178. M.Maggini, M.Passudetti, G.Gonzales-Trueba, M.Prato, U.Quintily, G.Scorrano. *J. Org. Chem.*, **56**, 6406 (1991)
179. M.Attiná, F.Cacace, A.P.Wolf. *J. Chem. Soc., Chem. Commun.*, 108 (1983)
180. V.V.Orlovskaja, O.S.Fedorova, E.P.Studentsov, A.A.Golovina, R.N.Krasikova, N.P.Bechtereva. *Russ. Chem. Bull., Int. Ed.*, **65**, 507 (2016)
181. Y.S.Ding, J.S.Fowler, S.J.Gatley, S.L.Dewey, A.P.Wolf, D.J.Schlyer. *J. Med. Chem.*, **34**, 861 (1991)
182. G.N.Reddy, M.Haeberli, H.-F.Beer, A.P.Schubiger. *Appl. Radiat. Isot.*, **44**, 645 (1993)
183. R.N.Krasikova, V.V.Zaitsev, S.M.Ametamey, O.F.Kuznetsova, O.S.Fedorova, I.K.Mosevich, Y.N.Belokon, Š.Vyskočil, S.V.Shatik, M.Nader, P.A.Schubiger. *Nucl. Med. Biol.*, **31**, 597 (2004)
184. R.N.Krasikova, O.F.Kuznetsova, O.S.Fedorova, V.I.Maleev, T.F.Saveleva, Yu.N.Belokon. *Bioorg. Med. Chem.*, **16**, 4994 (2008)
185. L.C.Libert, X.Franci, A.R.Plenevaux, T.Ooi, K.Maruoka, A.J.Luxen, C.F.Lemaire. *J. Nucl. Med.*, **54**, 1154 (2013)
186. Y.S.Ding, J.S.Fowler, S.J.Gatley, S.L.Dewey, A.P.Wolf. *J. Med. Chem.*, **34**, 767 (1991)

187. S.Kaneko, K.Ishiwata, K.Hatano, H.Omura, K.Ito, M.Senda. *Appl. Radiat. Isot.*, **50**, 1025 (1999)
188. N.Ichiishi, A.J.Canty, B.F.Yates, M.S.Sanford. *Org. Lett.*, **15**, 5134 (2013)
189. A.Vavere, E.Butch, B.Shulkin, S.Snyder. *J. Nucl. Med.*, **55** (Suppl. 1), 1410 (2014)
190. B.D.Zlatopolskiy, J.Zischler, P.Krapf, F.Zarrad, E.A.Urusova, E.Kordys, H.Endepols, B.Neumaier. *Chem. – Eur. J.*, **21**, 5972 (2015)
191. J.X.Qiao, P.Y.S.Lam. *Synthesis*, 829 (2011)
192. B.D.Zlatopolskiy, J.Zischler, E.A.Urusova, H.Endepols, E.Kordys, H.Frauendorf, F.M.Mottaghy, B.Neumaier. *ChemistryOpen*, **4**, 457 (2015)
193. V.P.Ananikov, L.L.Khemchyan, Yu.V.Ivanova, V.I.Bukhtiyarov, A.M.Sorokin, I.P.Prosvirin, S.Z.Vatsadze, A.V.Medved'ko, V.N.Nuriev, A.D.Dilman, V.V.Levin, I.V.Koptyug, K.V.Kovtunov, V.V.Zhivonitko, V.A.Likholobov, A.V.Romanenko, P.A.Simonov, V.G.Nenajdenko, O.I.Shmatova, V.M.Muzalevskiy, M.S.Nechaev, A.F.Asachenko, O.S.Morozov, P.B.Dzhevakov, S.N.Osipov, D.V.Vorobyeva, M.A.Topchiy, M.A.Zotova, S.A.Ponomarenko, O.V.Borshchev, Yu.N.Luponosov, A.A.Rempel, A.A.Valeeva, A.Y.Stakheev, O.V.Turova, I.S.Mashkovsky, S.V.Sysolyatin, V.V.Malykhin, G.A.Bukhtiyarova, A.O.Terent'ev, I.B.Krylov. *Russ. Chem. Rev.*, **83**, 885 (2014)
194. Y.-M.Chevalme, F.Montravers, J.-P.Vuillez, M.Zanca, C.Fallais, J.Oustrin, J.-N.Talbot. *Braz. Arch. Biol. Technol.*, **50** (Special Issue), 77 (2007)
195. J.Zischler, N.Kolks, D.Modemann, B.Neumaier, B.D.Zlatopolskiy. *Chem. – Eur. J.*, **23**, 3251 (2017)
196. S.Z.Vatsadze, Yu.D.Loginova, G.dos Passos Gomes, I.V.Alabugin. *Chem. – Eur. J.*, **23**, 3225 (2017)
197. K.Müller, C.Faeh, F.Diederich. *Science*, **317**, 1881 (2007)
198. I.S.Antipin, M.A.Kazymova, M.A.Kuznetsov, A.V.Vasilyev, M.A.Ishchenko, A.A.Kiryushkin, L.M.Kuznetsova, S.V.Makarenko, V.A.Ostrovskii, M.L.Petrov, O.V.Solod, Yu.G.Trishin, I.P.Yakovlev, V.G.Nenaidenko, E.K.Beloglazkina, I.P.Beletskaya, Yu.A.Ustynyuk, P.A.Solov'ev, I.V.Ivanov, E.V.Malina, N.V.Sivova, V.V.Negrebetskii, Yu.I.Baukov, N.A.Pozharskaya, V.F.Traven', A.E.Shchekotikhin, A.V.Varlamov, T.N.Borisova, Yu.A.Lesina, E.A.Krasnokutskaya, S.I.Rogozhnikov, S.N.Shurov, T.P.Kustova, M.V.Klyuev, O.G.Khelevina, P.A.Stuzhin, A.Yu.Fedorov, A.V.Gushchin, V.A.Dodonov, A.V.Kolobov, V.V.Plakhtinskii, V.Yu.Orlov, A.P.Kriven'ko, O.V.Fedotova, N.V.Pchelintseva, V.N.Charushin, O.N.Chupakhin, Yu.N.Klimochkin, A.Yu.Klimochkina, V.N.Kuryatnikov, Yu.A.Malinovskaya, A.S.Levina, O.E.Zhuravlev, L.I.Voronchikhina, A.S.Fisyuk, A.V.Aksenov, N.A.Aksenov, I.V.Aksenova. *Russ. J. Org. Chem.*, **53**, 1275 (2017)