(*Attachement no. 4 - Summary of professional accomplishments)*

Design, synthesis and characterization of Ga-68 and Tc-99m labelled conjugates for the diagnosis of Alzheimer's disease, diabetic foot and rheumatoid arthritis by PET and SPECT

Przemysław Koźmiński, PhD

Institute of Nuclear Chemistry and Technology, Centre of Radiochemistry and Nuclear Chemistry
Warsaw, June 2023

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1. **Name and surname:** Przemysław Andrzej Koźmiński
2. **Academic diplomas and degrees:**

- PhD in chemistry (27.09.2012)

  Title of doctoral dissertation „Synthesis and physicochemical properties of conjugates technetium-99m complexes with *n*-octanoyl-[Ser^3]-ghrelin(1-6) peptide as potential diagnostic radiopharmaceuticals"

  Supervisor: prof. dr hab. Jerzy Ostyk-Narbutt, Centre of Radiochemistry and Nuclear Chemistry, Institute of Nuclear Chemistry and Technology, Warsaw
- Msc in chemistry chemii (27.09.2004)

  Title of master thesis „Preconcentration of trace analytes by Batch Injection Analysis (BIA)"

  Supervisor: prof. dr hab. Marek Trojanowicz

  Laboratory for Flow Anaysis and Chromatography, Faculty of Chemistry, University of Warsaw

3. **Information on employment in research institutes:**

- 02/2005 - 09/2006 Instituto Pedro Nunes / University of Coimbra, Portugal, project: Novel Technology for Controlling Wine Production and Quality „NovTech", HPRN-CT-2002-00186)
- 01/2007 - 01/2008 chemist, Institute of Nuclear Chemistry and Technology,
- 02/2008 - 03-2013 assistant, Institute of Nuclear Chemistry and Technology, Warsaw
- 04/2013 - to present adjunct, Institute of Nuclear Chemistry and Technology, Warsaw

4. **Description of the achievements, set out in art. 219 para 1 point 2 of the Act of 20 July 2018 Law on Higher Education and Science (Journal of Laws of 2020, item 85, as amended)**

4.1 Title of scientific achievement

Design, synthesis and characterization of Ga-68 and Tc-99m labelled conjugates for the diagnosis of Alzheimer's disease, diabetic foot and rheumatoid arthritis by PET and SPECT

4.2 List of scientific publications constituting the basis for scientific achievement

The scientific achievement, which is the basis for applying for the degree of habilitated doctor, is the series of publications listed below, consisting (as of June 6th, 2023) of 9 papers with a total IF of **32.292** (MNiSW = **730** points) according to the year of publication. The cycle consists of 8 original papers and 1 review paper. In all publications I am the corresponding author (marked *), including 7 of them also the first author. The number of citations is based on the Web of Science database (dated June 6th, 2023), after the 'slash' the number of citations without self-citations is given.

[H1] E. Gniazdowska, **P. Koźmiński*,** M. Wasek, M. Bajda, J. Sikora, E. Mikiciuk-Olasik, P. Szymański; *Synthesis, physicochemical and biological studies of technetium-99m labeled tacrine derivative as a diagnostic tool for evaluation of cholinesterase level*, Bioorg. Med. Chem., 25 (**2017**) 912-920.

$IF_{2016=}$ **2.454** MNiSW $_{2016}$=**30** points

citations = **7/5**

My contribution to the work: conception of the work, execution of experimental work, analysis, interpretation and elaboration of the obtained results, participation in writing part of the manuscript, final editing of the manuscript and preparation of subsequent responses to the reviewers' comments.

[H2] E. Gniazdowska, **P. Koźmiński***, P. Halik, M. Bajda, K. Czarnecka, E. Mikiciuk-Olasik, K. Masłowska, Z. Rogulski, Ł. Cheda, K. Kilian, P. Szymański; *Synthesis, physicochemical and biological evaluation of tacrine derivative labeled with technetium-99m and gallium-68 as a prospective diagnostic tool for early diagnosis of Alzheimer's disease.* Bioorg. Chem. 91 (**2019**) 103136.

IF_{2018} =**3.926** MNiSW $_{2018}$=**100** points

citations = **6/5**

My contribution to the work: concept of the work, execution of the 'chemical' part of the experimental work (synthesis of radioconjugates, characterization of physico-chemical properties, in vitro stability studies), participation in the preparation and editing of the text of the publication. I also prepared responses for reviewers.

[H3] P. Koźmiński*, D.Niedziałek, G. Wieczorek, P.K. Halik, K. Czarnecka, A. Rogut, Ł. Cheda, Z. Rogulski, P. Szymański, E. Gniazdowska; *New imaging modality of COVID-19 pneumonia developed on the basis of Alzheimer's disease research.* Int. J. Mol. Sci. **2022**, 23, 8405.

IF_{2021}**= 6.208** MNiSW $_{2021}$=**140** points

citations = **none**

My contribution to the work: defining the scientific goal, planning and performing the 'chemical' part of the research, as well as analysis and interpretation of the results, participating in the preparation of the manuscript and I also prepared responses for reviewers.

[H4] P. Koźmiński[*], W. Gawęda, M. Rzewuska, A. Kopatys, S. Kujda, M. K. Dudek, P. K. Halik, L. Królicki, E.Gniazdowska; *Physicochemical and Biological Study of ^{99m}Tc and ^{68}Ga Radiolabelled Ciprofloxacin and Evaluation of [^{99m}Tc]Tc-CIP as Potential Diagnostic Radiopharmaceutical for Diabetic Foot Syndrome Imaging.* Tomography **2021**, 7, 829-842.

IF_{2020} =**3.358** MNiSW $_{2020}$=**40** points

citations = **4/3**

My contribution to the work: proposing the research concept, carrying out research under my supervision as part of the master's thesis of a student of the Faculty of Physics at the University of Warsaw (Weronika Maliszewska (Gawęda)), analysis and interpretation of the results, preparation of the manuscript and subsequent responses to the reviewers' comments.

[H5] P. Koźmiński[*]**,** M. Rzewuska, A. Piądłowska, P. K. Halik, L., E.Gniazdowska; *Synthesis, physicochemical and in vitro biological evaluation of ^{99m}Tc-cefepime radioconjugates, and*

development of DTPA-cefepime single vial kit formulation for labelling with technetium-99m. J. Radioanal. Nucl. Chem. **2022**, 331, 2883–2894.

IF**2021** =**1.754** MNiSW 2021=**40** points

citations = **1/0**

My contribution to the work: proposing the concept of research, conducting research as part of the master's thesis of a student of the Faculty of Physics at the University of Warsaw (Agata Piądłowska) under my supervision, analysis and interpretation of the results obtained, and preparation of the manuscript and subsequent responses to the reviewers' comments.

[H6] P. Koźmiński*, K. Żelechowska-Matysiak, E. Gniazdowska; *Synthesis and physicochemical properties of cefepime derivatives suitable for labelling with gallium-68.* Appl. Sci. **2023**, 13, 5019.

IF2020 = **2.838** MNiSW 2021 = **100** points

citations = **none**

My contribution to the work: proposing the research concept, carrying out research as part of the master's thesis of a student of the Faculty of Physics of the University of Warsaw (Kinga Żelechowska-Matysiak) under my supervision, analysis, and interpretation of the results obtained, and preparation of the manuscript and as well as responses to the reviewers' comments.

[H7] P. Koźmiński*, P. Halik, R. Chesori, E. Gniazdowska; *Overview of Dual-Acting Drug Methotrexate in Different Neurological Diseases, Autoimmune Pathologies and Cancers.* Int. J. Mol. Sci. **2020***, 21,* 3483.

IF**2020** =**5.923** MNiSW 2020=**140** points

citations = **95/93**

My contribution to the work: preparation of the publication outline, literature review, preparation and submission of the manuscript. I also prepared responses for reviewers.

[H8] P. Koźmiński*, P. K. Halik, R. Chesori, E. Gniazdowska; *Common Shortcomings in Study on Radiopharmaceutical Design Research: A Case Study of ^{99m}Tc-Labelled Metxotrexate.* Molecules **2021**, 26, 5862.

IF**$_{2020}$** =**4.412** MNiSW $_{2020}$=**100** points

citations = **1/1**

My contribution to the work: defining the purpose and concept of the research, planning the experimental work, analysis and interpretation of the results, preparation and submission of the manuscript as well as responses to the reviewers' comments.

[H9] P. Koźmiński*, M. Gumiela, R. Walczak, K. Wawrowicz, A. Bilewicz; *A semi-automated module for the separation and purification of ^{99m}Tc from simulated molybdenum target.* J. Radioanal. Nucl. Chem. **2021**, 328, 1217–1224.

IF$_{2020}$ = **1.371** MNiSW $_{2020}$ = **40** points

citations = **2/2**

My contribution to the work: defining the purpose and concept of the research, participation in the experimental work, analysis and interpretation of the results, preparation and editing of the text of the publication, submitting the manuscript and subsequent responses to the reviewers' comments.

4.3 Description of scientific achievement

Introduction

The 21st Century brings many achievements of humanity aimed at improving the quality of life, but at the same time, with the progress of modern civilization, diseases called civilization (social) diseases appeared. These diseases affect not only highly developed countries, but also developing ones, and are currently a huge problem for medicine. Among the most important

civilization diseases, we can distinguish cardiovascular diseases, diabetes with its complications, neurodegenerative diseases such as Alzheimer's disease (AD), cancer, or systemic diseases such as rheumatoid arthritis (RA). Civilization diseases can lead not only to disability, but are also the cause of over 80% of premature deaths [1]. For this reason, it is so important to develop new diagnostic methods that allow for early detection of a civilization disease, allowing for early and thus more effective therapy.

The increasing incidence of neurodegenerative disorders, such as Alzheimer's disease, has become a major challenge around the world. The devastation of the cognitive functions of the brain affected by AD begins with the loss of short-term memory, and through the slow depletion of communication skills, causes problems with orientation, apathy, complete immobility, and consequently loss of body function and death. How serious the problem is is shown by the data of the Alzheimer's Disease International (ADI) organization, which estimates that today, around 55 million people in the world suffer from Alzheimer's disease alone, and the forecasts reach nearly 80 million by 2030 [2]. This disease affects not only the patient himself, but also the environment in which he lives, especially his relatives. The need for constant care of a patient suffering from AD requires both physical and mental effort from the relatives. As of today, despite very intensive research, there is no effective treatment that would prevent the development and stop the disease process, however, early diagnosis of the disease may allow the patient to gain access to support for himself and others, as well as maximally improve the quality of life and enable planning of further management.

Diabetes is a social disease, as evidenced by its prevalence in more than 1 percent of the entire population. According to the International Diabetes Federation, over 530 million people worldwide suffer from diabetes, and by 2030 this number may increase to nearly 650 million. The number of patients affected by diabetes increases by an average of 2.5% each year, and the number of deaths due to diabetes in 2021 amounted to 6.7 million [3]. In Poland, nearly 3 million people struggle with diabetes, and at the current rate of growth at the end of 2030, this number may be 10% of the population. Bacterial infections in diabetic foot syndrome are one of the most serious complications in people with diabetes. This syndrome occurs as a result of poor blood circulation in the foot, which becomes hypoxic and more susceptible to microbial

infection. In addition, the accompanying neuropathy reduces the feeling in the feet, so that damage or a small wound may go unnoticed. Typical symptoms of diabetic foot include loss of feeling in the feet, flaking of the skin, difficult to heal wounds. All these processes lead to the destruction of both soft tissues and bones, and relate to one disease, the so-called Charcot's joint (Charcot's neuroathropathy). The problem of diabetic foot syndrome affects about 15% of diabetics, is complex and requires multi-specialist care, and above all, good diagnostics to avoid amputations, which are performed in Poland several thousand a year (in 2019, this number was 8,000) [4].

Rheumatoid arthritis (RA) is an autoimmune disease that currently affects around 14 million people, according to the World Health Organization (WHO). According to studies of the prevalence of the disease in the population of Europe and the USA, 0.5-2% of the population over 15 years of age suffers from it, while the annual incidence ranges from 31 to 50 people per 100,000. Most analyzes show that the incidence of RA is 2-4 times higher in women than in men [5]. RA causes symptoms of pain and inflammation, primarily involving: hands, wrists, knees, toes or entire feet. All these changes most often lead to joint destruction and severe disability, disability, and even premature death. Although there is currently no cure for rheumatoid arthritis, there are many effective ways to reduce pain and inflammation and slow down the disease process. Therefore, an early diagnosis is very important, allowing for the use of therapy that slows down the progression of the disease (reduces pain and swelling of the joints and improves their function), prevents its complications and enables normal functioning. Currently, the diagnostic methods of nuclear medicine use single photon emission tomography, commonly referred to as SPECT (Single Photon Emission Computed Tomography), and positron emission tomography - PET (Positron Emission Tomography). These techniques allow to visualize the functions of the examined organs, thanks to which they are used in the study of their physiological states, which gives information about their correct or pathologically changed functioning. These methods perfectly complement X-ray examinations and magnetic resonance imaging (MRI).

The SPECT technique uses radionuclides emitting γ radiation with the energy of 100-250 keV, therefore Tc-99m, I-123, In-111 are ideal in this respect. The SPECT test consists in measuring

the gamma radiation emitted by the radiopharmaceutical previously administered to the patient. The measurement is carried out using a camera called a gamma camera, which rotates around the patient and records gamma rays (photons) emitted in different directions. The information obtained in this way is processed using an appropriate computer program into an image showing the places of increased accumulation of the radiotracer in the body. The most common in SPECT are Tc-99m compounds due to the very good nuclear characteristics of this radionuclide (half-life 6 hours, energy 140 keV and very rich coordination chemistry of technetium, resulting from the presence of this element in chemical compounds at many oxidation states [6, 7].

Technetium-99m is the most common radioisotope used in nuclear medicine and accounts for about 85% of these procedures [8]. Technetium-99m is the decay product of molybdenum-99, which can be obtained in a nuclear reactor by irradiating natural or already enriched molybdenum-98 with thermal neutrons. However, due to the very small reaction cross-section of $^{98}Mo(n,\gamma)^{99}Mo$ (0.13 barn), the amount of Mo-99 formed in this transformation is small, therefore the main source of Mo-99 is the fission reaction of ^{235}U. In 2009-2010, there was a severe shortage of ^{99}Mo, caused by the shutdown or refurbishment of aging nuclear reactors producing this isotope. Therefore, in order to become independent of possible interruptions in the production of ^{99}Mo, an intensive search for alternative methods of molybdenum-99 production was initiated. It turned out that using the processes taking place in the cyclotron, it is possible to obtain molybdenum-99 in the reaction of $^{100}Mo(p,pn)^{99}Mo$, and in the reaction of $^{100}Mo(p,2n)^{99m}Tc$ - also Tc-99m directly [9, 10]. Another alternative for the production of technetium-99m is the $^{100}Mo(\gamma,n)^{99}Mo$ photonuclear reaction, in which high-energy photons obtained from an electron accelerator are used [11]. This technology is in the research stage and offers a viable alternative in the form of the RadioGenix system introduced in 2021 by NorthStar Medical Radioisotopes, LLC, which is used to produce Tc-99m from uranium-free molybdenum-99. An important advantage of using technetium-99m in nuclear medicine, regardless of its nuclear properties, is the possibility of obtaining it from a 99Mo/99mTc (molybdenum-technetium) generator directly in a hospital laboratory. Elution takes a few

minutes, and the resulting sterile and non-pyrogenic solution is ready for the synthesis of technetium preparations.

The second intensively developing diagnostic technique of nuclear medicine is positron emission tomography (PET), which uses radionuclides emitting β+ particles - positrons (e.g. C-11, F-18, Ga-68, Zr-89). Positrons emitted during the decay of a radioactive isotope practically immediately collide with the surrounding electrons, resulting in two photons with an energy of 511 keV, propagating along a straight line (at an angle close to 180^{o}), in opposite directions. The gamma camera detectors placed around the patient record the directions of photon propagation, and the intersection of these directions indicates the places where the radionuclide accumulates in the body.

From the perspective of applications in nuclear medicine, the advantage of the ^{68}Ga radionuclide is its nuclear properties where the average energy of positrons emitted by this radionuclide is 836.0 keV, and $T_{1/2}$ is 68 minutes. An additional advantage is the possibility of obtaining it, because, like Tc-99m, this radionuclide is also obtained from the generator, which is a pair of ^{68}Ge/^{68}Ga (germanium-68/gallium-68). The generator allows several elutions per day of the gallium-68 radionuclide directly in the nuclear medicine department, and thanks to the long half-life of germanium-68 ($T_{1/2}$ = 271 days), the gallium generator can be used for a long period of time up to a year.

Concluding the introduction to the subject of my scientific achievement, I would like to add that my work on the design of new radiopharmaceuticals requires an interdisciplinary approach covering knowledge of organic chemistry, analytical chemistry, radiochemistry, but also biochemistry or biology, as well as often contacts with the medical community.

Objective of the work

My scientific and research interests concern the design and synthesis of new potential radiopharmaceuticals (Fig. 1), including i.a. for the diagnosis of civilization diseases, such as Alzheimer's disease (AD), diabetic foot syndrome (DFS) or rheumatoid arthritis (RA). My scientific achievement presented below shows the preparation of radioconjugates based on

tacrine derivatives (diagnostics of AD), antibiotics (diagnostics of DFS) and methotrexate (diagnostics of RA). The works concern the design of new potential diagnostic radiopharmaceuticals dedicated to the early detection of the above-mentioned diseases, i.e. the selection of a chelator and a biologically active molecule (biomolecule, vector), development of a procedure for the synthesis of conjugates containing a chelator and a biomolecule, optimization of radiolabelling conditions for the obtained conjugates, and examination of physicochemical and biological properties of the obtained radioconjugates from the point of view of their use in clinical conditions.

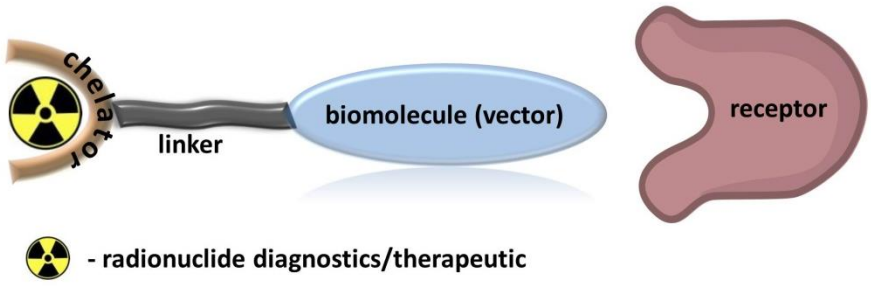

Figure 1. General structure of a receptor radiopharmaceutical.

During the synthesis of conjugates, it was necessary to select appropriate methods or develop completely new synthesis paths that would ensure such linkers and chelators (allowing labeling with gallium-68 or technetium-99m radionuclides) so that the biomolecules included in the obtained radiopreparations did not lose their biological properties. Another important chemical aspect was to obtain the final product with high radiochemical purity and a sufficiently long stability in body fluids, such as human serum or cerebrospinal fluid.

Results and the possibility of their use

Radiopharmaceuticals dedicated to the **diagnosis of Alzheimer's disease (publications H1, H2, H3)**

In the papers presented, studies on new radioconjugates based on a tacrine derivative as potential candidates for the diagnosis of Alzheimer's disease are described. Tacrine (tetrahydroacridine, 9-amino-1,2,3,4-tetrahydroacridine, Tac) belongs to acetylcholinesterase (AChE) inhibitors and, like other drugs in this group, e.g. rivastigmine or donepezil, inhibits the activity of this enzyme, thus preventing decomposition of acetylcholine (ACh) - a neurotransmitter responsible for transmission in the cholinergic system of the central nervous system (CNS). Radiopharmaceuticals based on tacrine derivatives can be used as diagnostic probes to determine the level of AChE in the human body, which in the case of AD will make it possible to locate areas of the brain lacking in ACh, and thus to diagnose the developing disease long before the appearance of visible morphological symptoms. In addition, due to the presence of AChE also in the liver and intestines, and, according to recent reports, in elevated concentrations also in inflammation of the lungs in the course of coronavirus disease (COVID-19) [12], these radiopreparations can also act as markers determining the physiological state of these organs .

In the initial research, I focused on the synthesis and determination of the physicochemical properties of new tacrine analogues labeled with the radionuclide technetium-99m [**H1**], [**H2**], dedicated to imaging with the SPECT method. In the first stage of the work, tacrine derivatives, $NH_2(CH_2)$nTac, were synthesized, differing in the number of -CH_2- groups in the aliphatic hydrocarbon chain, where n was the number of -CH_2 groups in the range of 2-9. Subsequently, these derivatives were labeled with technetium-99m in two different ways: using the '4+1' type technetium complex [**H1**] and using the Hynic chelator [**H2**].

In the first case [**H1**], a bifunctional linker, CN-BFCA (imidosuccinate ester of isocyanobutyric acid), was attached to the tacrine derivatives, in which the ester group was used to connect it to the tacrine skeleton, while the isonitrile group (-N≡C) served as a monodentate ligand , CN-NH(CH2)nTac, complexing the cation of the radionuclide $^{99m}Tc^{III}$. The second – tetradent ligand – was tris(2-mercaptoethyl)amine, NS3. Here, I synthesized radioconjugates of the general

formula [^{99m}Tc]Tc(NS_3)(CN-NH(CH_2)n-Tac)* (Figure 2) containing a technetium complex of the '4+1' type in the shape of a trigonal bipyramid.

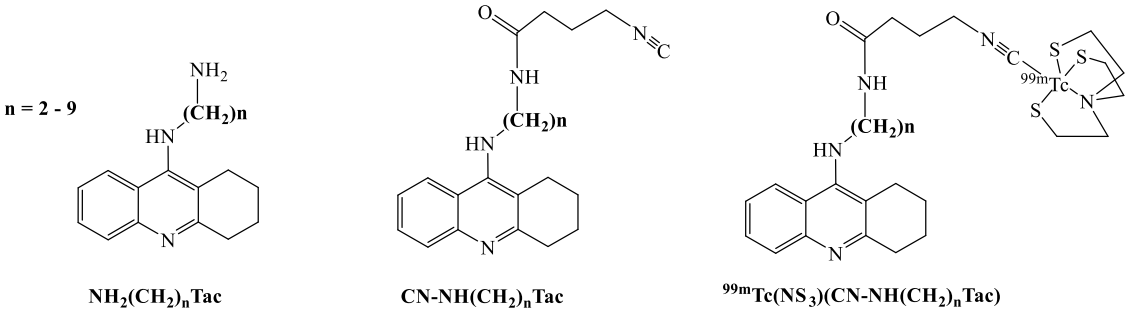

Figure 2. Structures of tacrine derivatives, linker-linked tacrine derivatives and radioconjugates described in [**H1**].

All the radioconjugates obtained herein showed high stability in the presence of an excess of the standard cysteine or histidine amino acids as well as in human serum. The determined lipophilicity parameters (logD values) of all radioconjugates, significant from the point of view of the ability to cross the blood-brain barrier (BBB), ranged from 0.92 to 1.56. The logD value was the key parameter for the selection of the radioconjugate for further studies: biological activity (inhibition of acetylcholinesterase) and multi-organ biodistribution. The IC_{50} parameter determined by the Ellman method of the radioconjugate [^{99m}Tc]Tc(NS_3)(CN-NH(CH_2)$_7$-Tac) selected for further studies (with the highest lipophilicity, logD = 1.56 ± 0.06 - the identity of this radioconjugate was confirmed by synthesizing and chemical characterization of the cold reference compound (NS_3)Re(CN-NH(CH_2)$_7$-Tac) was 45.0 nM, and biodistribution studies of this radiotracer showed its uptake in the brain at the level of 0.07%ID/g, which indicates its ability to cross the blood-brain barrier Molecular modeling performed for this radioconjugate showed that the main structural fragment responsible for most of the interactions within the catalytic and peripheral active sites of AChE is the tacrine moiety, which is arranged between the two amino acids Trp86 and Tyr337 creating π-π interactions However, the aliphatic chain itself is

* formulas of radioconjugates may slightly differ from those in publications because they are given in accordance with the new currently applicable nomenclature

located in the middle of the enzyme's throat and forms hydrophobic bonds with the aromatic rings of Tyr124 and Tyr341. This allows us to conclude that the biological activity of the tacrine contained in the radioconjugate molecule towards AChE has been preserved.

In the second case [**H2**] tacrine derivatives were labeled with technetium-99m using Hynic chelator (and of course appropriate colligands), resulting in high radiochemical yield radioconjugates with the general formula [^{99m}Tc]Tc-Hynic-(NH(CH_2)nTac) (Fig. 3A).

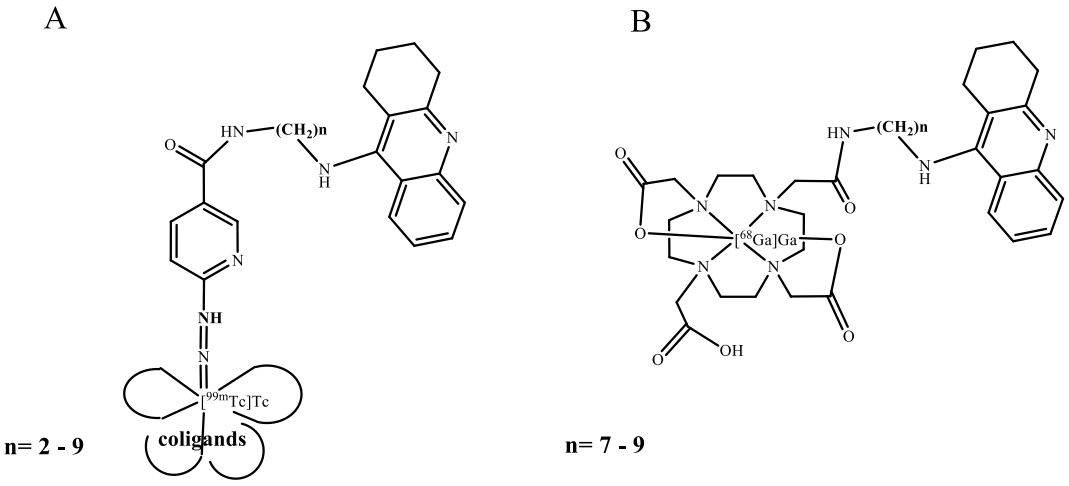

Figure 3. Structures of radioconjugates described in [**H2**].

The logD values determined for these radioconjugates ranged from -2.95 to -1.38, so these radioconjugates were much less lipophilic. -(NH(CH_2)$_9$Tac (logD= -1.38 ± 0.01) As mentioned above, molecular modeling showed that the aliphatic chain is located in the middle of the enzyme throat, which allows us to safely assume that its extension by two CH_2 groups (n=9) should not significantly affect the biological activity of tacrine contained in the radioconjugate molecule. Studies of the physicochemical properties of the [^{99m}Tc]Tc-Hynic-(NH(CH_2)$_9$Tac) radioconjugate have shown its high stability in the presence of excess amounts of competitive amino acids (i.e. cysteine or histidine) and in human serum and cerebrospinal fluid. Biodistribution studies in an animal model showed uptake of this radiotracer in the brain at the level of 0.98 %ID/g, which is much higher than in the case of the much more lipophilic radiotracer [^{99m}Tc]Tc(NS_3)(CN-NH(CH_2)$_7$-Tac).

In subsequent studies, tacrine derivatives $NH_2(CH_2)$nTac were labeled with gallium-68 radionuclide using various chelators forming stable complexes with gallium(III) cation [**H2**],[**H3**]. Such radiopreparations can be used in PET imaging, and the fact of obtaining them has been confirmed by synthesizing non-radioactive 'rhenium' reference compounds and characterizing them by mass spectrometry. As the first chelator I used 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) in the form of active ester -N-hydroxysuccinimide (DOTA-NHS) [**H2**]. Due to the fact that the addition of the DOTA chelator reduces the lipophilicity of the obtained product, for the synthesis of radioconjugates I used tacrine derivatives $NH_2(CH_2)$nTac, in which n was 7-9. Three radioconjugates of the general formula [^{68}Ga]Ga-DOTA-NH(CH2)nTac (Fig. 3B) were obtained here with high efficiency, for which the determined logD parameter ranged from -2.52 to -1.52. All three radioconjugates turned out to be stable in solutions of competing amino acids (i.e. cysteine or histidine) as well as in human serum and cerebrospinal fluid, and the [^{68}Ga]Ga-DOTA-NH$(CH_2)_9$Tac radioconjugate was selected for further biodistribution studies, characterized by this series of radiopreparations with the highest lipophilicity (logD= -1.52 ± 0.01). The determined brain uptake of this radiotracer was 0.21 %ID/g. In further works [**H3**], for labeling the tacrine derivative $NH_2(CH_2)_9$Tac with gallium-68, I also used chelators: 1,4,7-triazacyclononane-1-glutaric-4,7-acetic acid in the form of an active NHS ester (NODAGA-NHS), 1,4,7-triazacyclononane-1-glutaric-4,7-acetic acid in the form of active phenyl isothiocyanate (NODAGA-Bn-SCN), 1,4,7,10-tetraazacyclododecane-1-glutaric acid 4,7,10-triacetic acid in the form of active phenyl isothiocyanate (DOTAGA-Bn-SCN), cyclohexane-1,2-diaminpentaacetic acid in the form of active phenyl isothiocyanate (DTPA-CHX-SCN) and tris(hydroxypyridinone) in the form of active phenyl isothiocyanate (THP-SCN). I received five radioconjugates here ([^{68}Ga]Ga-NODAGA-NH$(CH_2)_9$Tac, [^{68}Ga]Ga-NODAGA-Bn-NH$(CH_2)_9$Tac, [^{68}Ga]Ga-DOTAGA-Bn-NH$(CH_2)_9$Tac, [^{68}Ga]Ga-DTPA-CHX-NH$(CH_2)_9$Tac and [^{68}Ga]Ga-THP-NH$(CH_2)_9$Tac, Fig. 4), for which the determined values of the logD parameter ranged from -1.36 to 0.73. As a result of comparing the physicochemical properties (lipophilicity, stability in human serum) of the radiopreparations tested here, the two most promising radioconjugates were selected for the study of biological activity and biodistribution: [^{68}Ga]Ga-NODAGA-Bn-NH$(CH_2)_9$Tac and [^{68}Ga]Ga-THP-NH$(CH_2)_9$Tac. Biological activity studies have shown that both

selected radiotracers are effective inhibitors of cholinesterases, and the brain uptake of these radiotracers determined in biodistribution studies was 0.02 and 0.12%ID/g, respectively.

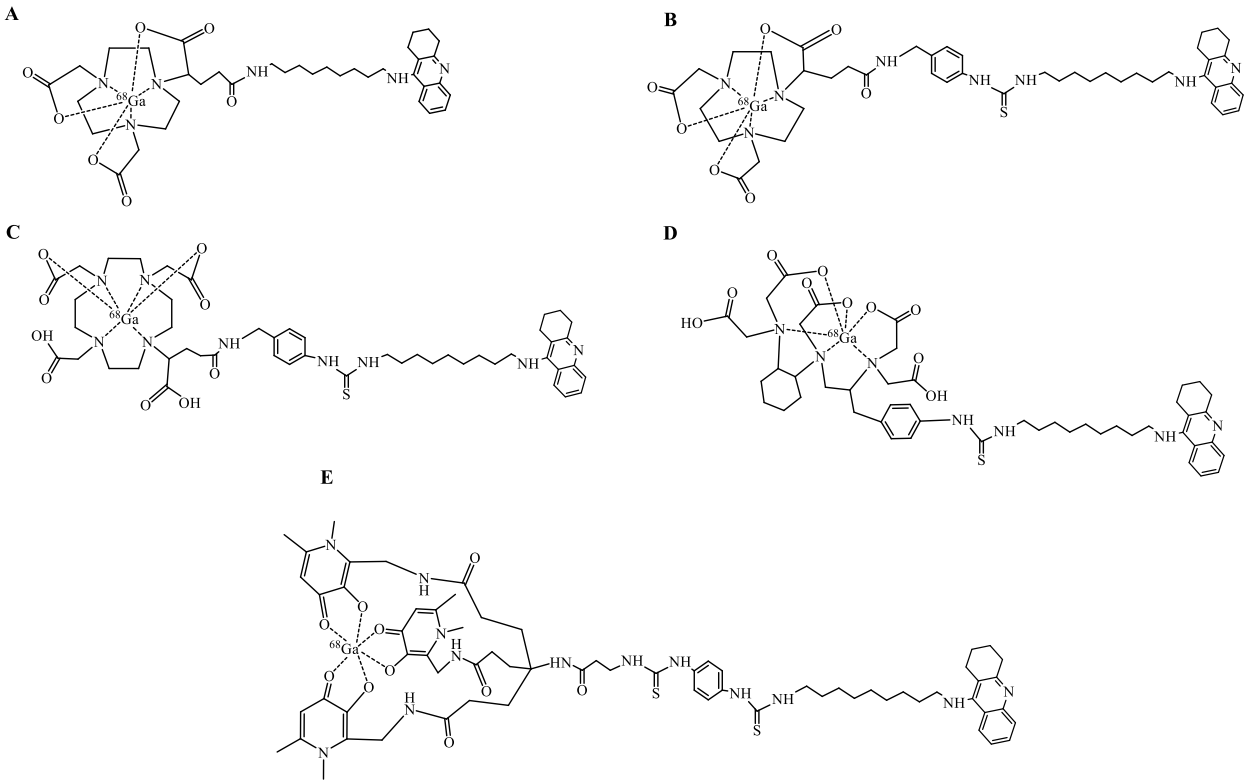

Figure 4. Structures of radioconjugates described in [**H3**].

The physicochemical and biological properties of selected radioconjugates (important from the point of view of their use as diagnostic radiopharmaceuticals in Alzheimer's disease) containing tacrine as a biologically active molecule are listed below in Table 1.

radiocojugate	logD	uptake: [%ID/g]	
		brain	lungs
[^{99m}Tc]Tc(NS_3)(CN-NH(CH_2)$_7$Tac)	1.56 ± 0.06	0.07	3.49
[^{99m}Tc]Tc-Hynic-(NH(CH_2)$_9$Tac	-1.38 ± 0.01	0.98	9.60
[^{68}Ga]Ga-DOTA-NH(CH_2)$_9$Tac	-1.52 ± 0.01	0.21	2.60
[^{68}Ga]Ga-NODAGA-Bn-NH(CH_2)$_9$Tac	-0.03 ± 0.02	0.02	0.61
[^{68}Ga]Ga-THP-NH(CH_2)$_9$Tac	0.73 ± 0.07	0.12	1.11

As can be seen from the presented data, basically all of the mentioned radioconjugates, to a greater or lesser extent, are able to cross the blood-brain barrier. However, only the radioconjugate [^{99m}Tc]Tc-Hynic-(NH(CH$_2$)$_9$Tac) has a brain uptake similar to that of ^{99m}Tc-HMPAO (this is the registered radiopharmaceutical ^{99m}Tc-exametazime, sold under the trade name Ceretec, used for brain perfusion scintigraphy specific to the CNS in only 1%). Particularly noteworthy is the significant uptake in the lungs of all the radiopreparations listed in the table. Considering that the most common cause of death among patients with Alzheimer's disease are infections, especially those causing pneumonia [13], the possibility of the physiological state of the lungs using radiopharmaceuticals (SPECT or PET method) will enable early diagnosis of the disease and early treatment.

Radiopharmaceuticals dedicated to the **diagnosis of diabetic foot syndrome (publications H4, H5, H6)**

My scientific achievement also includes designing, obtaining and testing new potential radiopharmaceuticals for the diagnosis of diabetic foot syndrome. These radiopharmaceuticals contain the diagnostic radionuclide technetium-99m or gallium-68 and are based on antibiotics (ciprofloxacin [**H4**] and cefepime [**H5, H6**]) used in the treatment of this disease entity. The synthesis of these radiopreparations requires special attention to preserve the biological activity of antibiotics due to their instability to various chemical reagents used during syntheses and to elevated temperatures.

Ciprofloxacin (CIP) is a second-generation fluoroquinolone that is used in the treatment of many bacterial infections, including urinary tract infections, infections of the skin and certain organs, including infections caused by Pseudomonas aeruginosa, *Staphylococcus aureus* or *Escherichia coli*.

Radioconjugates obtained by me (Fig. 5) based on ciprofloxacin ([**H4**]) and containing technetium-99m ([^{99m}Tc]Tc-CIP) or gallium-68 ([^{68}Ga]Ga-DOTA-CIP) radionuclides have been tested for physicochemical (stability, lipophilicity) and biological (*Staphylococcus aureus* and *Pseudomonas aeruginosa* binding study).

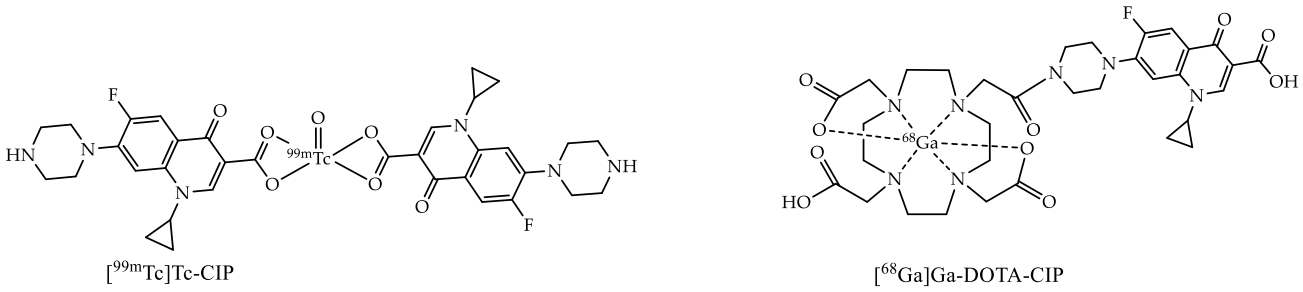

Figure 5. Structures of [^{99m}Tc]Tc[CIP and [^{68}Ga]Ga-DOTA-CIP radioconjugates.

The radioconjugate [^{99m}Tc]Tc-CIP was obtained by direct labeling of the antibiotic with technetium-99m, and its structure shown in Figure 5 is a putative structure. [^{99m}Tc]Tc-CIP is an electrically neutral, slightly hydrophilic compound (logD = −1.8 ± 0.1) with a relatively low molecular weight, which probably favors its binding to bacterial cells. The disadvantage of this radiopreparation turned out to be its incomplete stability in serum, nevertheless, SPECT imaging performed on a healthy person and a patient with DFS gave very good results. In the obtained SPECT/CT imaging of a healthy person, the radioconjugate was visible in the liver, spleen, kidneys and bladder, and slightly visible in the salivary glands and intestines. The lack of visible radiotracer accumulation in the thyroid gland indicated the absence of unbound and unreduced forms of Tc-99m. However, in the case of a person with DFS, the scintigraphy image showed not only the physiological uptake of the radiotracer [^{99m}Tc]Tc-CIP, but also a large accumulation in the infected part of the foot.

The second radioconjugate, [^{68}Ga]Ga-DOTA-CIP, was prepared using the DOTA chelator, has a comparable molecular weight and, unlike the previous radiopreparation, has a well-defined structure (MS and NMR analyses). This radioconjugate was found to be completely stable in human serum. However, it is negatively charged and has a lipophilicity parameter almost two times lower (logD = −3.1 ± 0.1), which may be the reason for its weaker ability to bind to bacterial cells. The binding uptake of the [^{99m}Tc]Tc-CIP and [^{68}Ga]Ga-DOTA-CIP radioconjugates by bacterial cells was approximately 8% and 1%, respectively. , and that both radioconjugates have potential applications in diabetic foot syndrome imaging by SPECT or PET, respectively.

The second antibiotic that I used as a vector in the design of radiopharmaceuticals dedicated to the diagnosis of DFS was cefepime (**CFM**). It is a β-lactam antibiotic belonging to the fourth generation cephalosporins (Fig. 6), with a broad spectrum of activity against Gram-positive and Gram-negative bacteria.

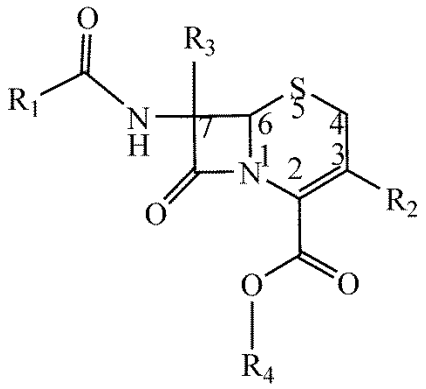

Figure 6. Cephalosporin core structure

In the presented general structure of cephalosporins, the location of the substituents R_1, R_2, R_3 and R_4 is marked, which may be different in different antibiotics belonging to this group. The exchange of these substituents does not significantly affect the biological stability of the antibiotic, so these are the places allowed to be used during the modification of the molecule. The remaining structural fragments essentially belong to the pharmacophore fragment of the antibiotic or are necessary for the stabilization of this fragment.

I undertook research on the labeling of CFM with technetium-99m ([**H5**]) for two reasons. Firstly, in the design of potential radiopharmaceuticals for the diagnosis of DFS, I decided to use CFM as a vector. CFM is a zwitterionic compound (Fig. 7A) having a positively charged substituent at the 3-position and a negatively-charged carboxyl group at the 2-position, which dramatically increases its ability to penetrate the outer membrane of Gram-negative bacteria.

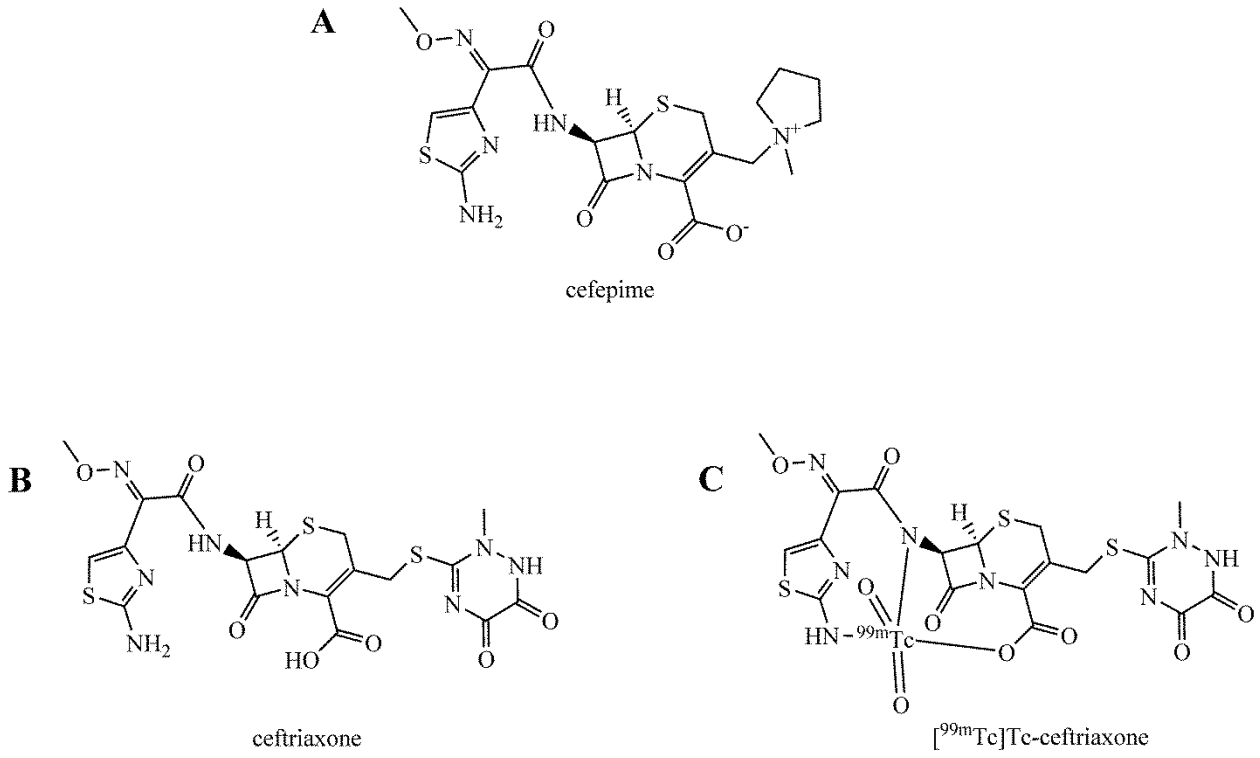

Figure 7. Structures of the antibiotics cefepime (A) and ceftriaxone (B) and the proposed structure of the radiopreparation [^{99m}Tc]Tc-ceftriaxone [14].

Secondly, there is already one paper in the literature concerning the labeling of cefepime with technetium-99m [15], but the labeling process leading to the [^{99m}Tc]Tc-CFM radioconjugate was carried out in a direct reaction of the antibiotic with pertechnetate, and of course in the presence of a reducing agent. Similar to the [^{99m}Tc]Tc-CIP radioconjugate obtained by direct labeling of ciprofloxacin with the radionuclide technetium-99m [**H4**], the structure of [^{99m}Tc]Tc-CFM is also not described. In addition, the authors report in their work that due to the presence of various chemically reactive groups in the molecule, containing different donor atoms (S, N, O), the radionuclide cation can be complexed in various ways. Moreover, I was very surprised by the structure of the radioconjugate based on the antibiotic ceftriaxone (CRO) [14] reported in the literature, which also belongs to the group of cephalospores, and its structure (Fig. 7B) in relation to the structure of cefepime (Fig. 7A) differs only R_2 substituent. Due to the practically identical structure of these two antibiotics (CRO and CFM), it could be assumed that the

technetium-99m complexes in the radioconjugates [^{99m}Tc]Tc-CRO and [^{99m}Tc]Tc-CFM will be the same - the ^{99m}Tc radionuclide cation will be same oxidation state and will be complexed with the same donor atoms. In the case of the radioconjugate [^{99m}Tc]Tc-CRO, the authors of the paper present the proposed structure of this radioconjugate (Fig. 7C), which I consider to be completely incorrect. Due to the inability to synthesize a reference compound containing stable rhenium (in conditions analogous to the reaction of direct labeling of antibiotics with technetium-99m, analogous rhenium compounds are not formed), and then to test it using standard chemical methods (elemental analysis, mass spectroscopy, structural studies) in order to determine its structure, I attempted to develop a different method of CFM labeling with the technetium-99m radionuclide, consisting in modifying only the final fragment of the R_1 substituent and allowing to define the structure of the obtained radioconjugate [**H5**]. To complex the cation of the ^{99m}Tc radionuclide, I used the DTPA chelator (diethylenetriaminepentaacetic acid), which forms stable complexes with the technetium cation already at room temperature, and I developed two different ways of synthesizing the DTPA-CFM conjugate. All syntheses were monitored by HPLC, and the final conjugate was characterized by mass spectrometry and magnetic spectroscopy nuclear resonance. The obtained [^{99m}Tc]Tc-DTPA-CFM radioconjugate turned out to be highly hydrophilic (logD= -4.00 ± 0.14) and positively charged. This radioconjugate was completely stable in the presence of excess cysteine or histidine, and showed significantly better stability in human serum than the radioconjugate obtained by direct labeling (ie without the use of a chelator). The biological tests carried out using the *Staphylococcus aureus* strain showed satisfactory binding of the radiopreparation to the bacterial cell wall, which proves that the modification of the CFM molecule did not reduce its biological activity. Based on the obtained results, the [^{99m}Tc]Tc-DTPA-CFM radioconjugate may be considered to be a potential diagnostic radiopharmaceutical for detection of staphylococcal infections. In paper [**H6**], I presented studies on the labeling of CFM with gallium-68, which makes it possible to diagnose DFS by PET with the use of a radiopreparation based on this antibiotic. The studies presented in the paper are the first literature report on the CFM antibiotic labeled with gallium-68. As a chelator, I used the macrocyclic ligand 1,4,7 triazacyclononane-1-glutaric acid-4,7-acetic acid in the form of the active NHS ester (NODAGA-

NHS). However, due to the low chemical reactivity of the amino group directly bound to the thiazole ring [**H6**], resulting in a very low efficiency of the chelator attachment reaction to the CFM molecule, this reaction required prior modification of the antibiotic molecule, consisting in attaching a selected linker. As a linker, I used two amino acids (containing two carboxyl groups each), aspartic acid (Asp) and glutamic acid (Glu), in which the amino groups were blocked with Fmoc (9-fluorenylmethoxycarbonyl) or Boc (*tert*-butyloxycarbonyl) protecting groups, while carboxylates were present in the anhydride form. After attaching the linker to the CFM molecule, the deprotected amino groups were used for the chelator attachment reaction. Due to the preparation, Glu turned out to be a better linker and finally I obtained and tested the CFM-labeled antibiotic in the form of the [^{68}Ga]Ga-NODAGA-Glu-CFM radioconjugate (Fig. 8), which fully meets the requirements for radiopharmaceuticals.

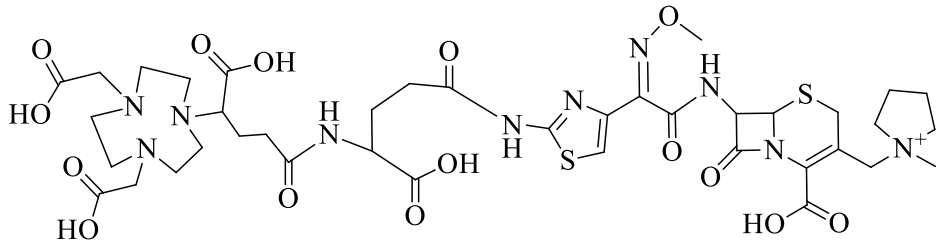

Figure 8. Structure of [^{68}Ga]Ga-NODAGA-Glu-CFM radioconjugate

Radiopharmaceuticals dedicated to the diagnosis of **rheumatoid arthritis (publications H7, H8)**

The third element of my scientific achievement is research on the preparation and characterization of the technetium-99m-labelled drug methotrexate (MTX). MTX (Fig. 8) is a structural analogue of folic acid (FA) and has been used for over 60 years in the treatment of various autoimmune disorders worldwide, and was introduced in the mid-1980s for the treatment of rheumatoid arthritis (RA). Used in low doses, it has become the gold standard in the treatment of this disease ('first-line' drug). In combination therapies with other cytostatics, it is also used in the treatment of many types of cancer. MTX is more effective and safer than other synthetic disease-modifying anti-rheumatoid drugs (DMARDs), although the mechanism

of its therapeutic action is still not fully understood. An extensive review of the current knowledge on the use of this drug and possible modes of action are presented in publication [**H7**]. The widespread interest in the drug MTX may be evidenced by the number of citations of this work.

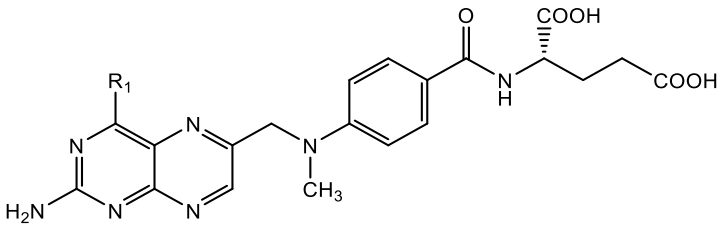

Figure 8. Structure of methotrexate (MTX)

In the literature, there are also works reporting on the labeling of MTX with various diagnostic radionuclides (e.g. ^{99m}Tc, ^{68}Ga, ^{18}F) for the needs of basic science and applications in nuclear medicine [16].

I focused my attention on the method of obtaining the radiotracer [^{99m}Tc]Tc-MTX, which enables early detection of inflammation in small articular rheumatoid nodules, while the already used [^{99m}Tc]Tc-MDP (^{99m}Tc-methyl diphosphonate) differentiates only severely inflamed joints from healthy joints [17]. In the literature, I found nine reports giving the procedure for obtaining the radiopreparation [^{99m}Tc]Tc-MTX, but in my opinion, none of these works gave a full, reliable characterization of the obtained radiocompound (Table 1 in my work **H8**), and despite this, very often also research on living organisms (animals, humans). As I mentioned above, it is not possible to confirm the structure of some 'technetium' radiopreparations by synthesizing their reference compounds under analogous conditions, and then testing them with standard chemical methods, because under given conditions (e.g. direct labeling) 'rhenium' radiopreparations are not formed, and so the 'rhenium' reference compound (containing a stable isotope of rhenium; a stable isotope of technetium does not exist) will also not be formed. Most of the syntheses of the [^{99m}Tc]Tc-MTX radiopreparation in the analyzed reports were performed under the conditions of allegedly direct labeling of the MTX molecule with

technetium-99m using the eluate from the ^{99m}Mo/^{99m}Tc generator and, of course, the reducing agent (e.g. $SnCl_2$). The characterization of the obtained radiopreparation was carried out only by TLC (iTLC) and only one report provided information about the performed HPLC analysis, however, the radiochromatogram was not included in the paper. I use the term 'supposedly' direct labeling because in most of the labeling reactions, auxiliary ligands (acetates, tartrates, ascorbates, citrates, gluconates, Table 1 in **H8**) were present in the reaction mixture, which also form complexes ([^{99m}Tc]Tc-intermediate) with the radionuclide cation ^{99m}Tc (Table 2 in **H8**), and the final radiopreparation [^{99m}Tc]Tc-MTX is formed by the exchange of these accessory ligands for the MTX molecule. Publication [**H8**] presents an analysis of allegedly direct syntheses of the [^{99m}Tc]Tc-MTX radiopreparation, on the basis of which I conclude that the authors did not have a pure radiopreparation at their disposal. In paper [**H8**], I showed that TLC analyzes cannot distinguish between these two chemical species ([^{99m}Tc]Tc-intermediate and [^{99m}Tc]Tc-MTX), and that only HPLC analysis shows the composition of the mixture during the labeling reaction (Fig. 9).

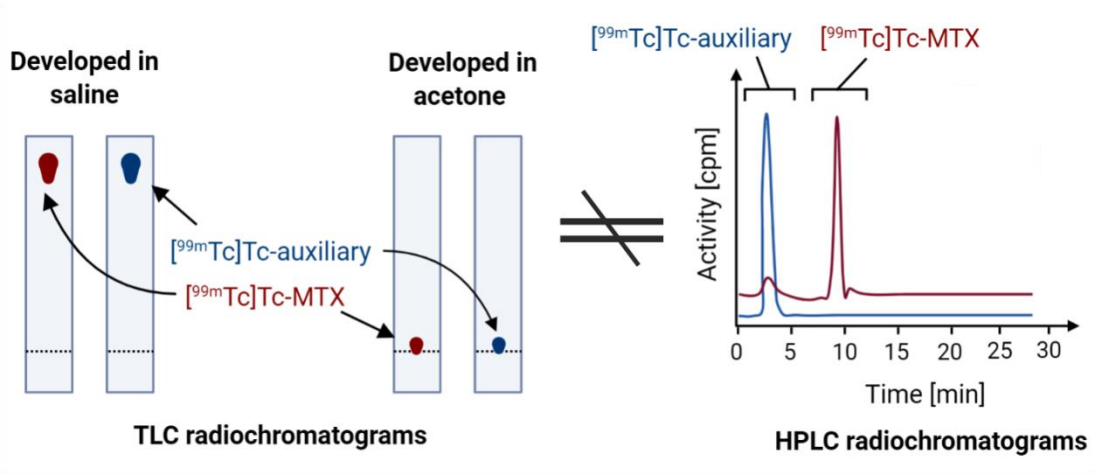

Figure 9. Scheme of TLC and HPLC analysis of [^{99m}Tc]Tc-MTX radioconjugate and intermediate complex.

In most of the syntheses described in the literature, the reaction mixture contained a complex of technetium-99m with an auxiliary ligand and, to a greater or lesser extent, the target

product - the radiopreparation [^{99m}Tc]Tc-MTX. and purity of the desired product, so the given synthesis procedure and the determined parameters characterizing the radiopreparation (e.g. logD expressing lipophilicity) are not reliable.

The results of my research published in [**H8**] are, in my opinion, extremely important due to the fact that radiopharmaceuticals synthesized in hospital nuclear medicine wards directly from kits for use in patients are usually tested only with TLC or ITLC methods in accordance with a procedure validated by kit manufacturer. These methods are the most commonly used and recommended for the determination of potential radiochemical impurities, and in the case of ^{99m}Tc-radiopreparations, to check the possible presence of [^{99m}Tc]TcO_4^- and colloidal [^{99m}Tc]Tc-oxides. These methods can be safely used only in well-known systems, which is why it is so important at the stage of designing and testing a new radiopharmaceutical to characterize it by all possible methods. Paper [**H8**] discusses the most common misakes, e.g. testing the stability of a radiopreparation not isolated from the reaction mixture, i.e. still in the presence of an excess of some reagents, which may stabilize the reaction product), or lipophilicity without checking whether the radionuclide exists only in the form of the tested radiopreparation . There are also indications, the non-observance of which may, in my opinion, lead to misinterpretation of experimental results, and their publication in practice violates the accepted standards of scientific credibility.

Work on an alternative method of **obtaining the technetium-99m radionuclide** (publication [**H9**])

As I mentioned in the introduction, technetium-99m is normally obtained from a ^{99}Mo/^{99m}Tc generator, for the production of which the parent radionuclide molybdenum-99 (^{99}Mo) is routinely produced in nuclear reactors, in the ^{235}U fission reaction, using high or low enriched targets uranium. Due to a serious shortage of ^{99}Mo in 2009–2010 resulting from the need to overhaul aging reactors, it was necessary to look for alternative methods of obtaining both ^{99}Mo and ^{99m}Tc. An additional problem affecting the availability of ^{99}Mo is the issue of non-

proliferation of fissile materials imposing the transition from highly enriched ^{235}U (90%) to uranium with an enrichment not exceeding 20%.

One of such alternative methods of obtaining molybdenum-99 is the photonuclear reaction of $^{100}Mo(\gamma,n)^{99}Mo$, which can be carried out in electron accelerators (irradiation of ^{100}Mo with a high-energy gamma beam), which allows to obtain from 1 to 10 TBq of ^{99}Mo per day. In paper [**H9**] I presented a semi-automated module prototype sep up for the separation and use of ^{99m}Tc radionuclide in 0.9% NaCl solution, ready for use in radiopharmaceutical labeling reactions (Fig. 11). The module consists of three columns (a sequence of columns with AnaLig®Tc-02, DOWEX-50 WX2 bed and Al_2O_3 alumina) in which a solution of ^{99}Mo (in the form of $[^{99}Mo]MoO_4^{2-}$) obtained in the reaction of $^{100}Mo(\gamma, n)^{99}Mo$ is in a cyclic cycle. The $[^{99m}Tc]TcO_4^-$ separation process is fast, yields the desired ^{99m}Tc activity in a final volume of 7 mL, can be used in the eluate purification generator, and can be repeated every 24 hours (time needed to reach maximum ^{99m}Tc activity in the eluate).

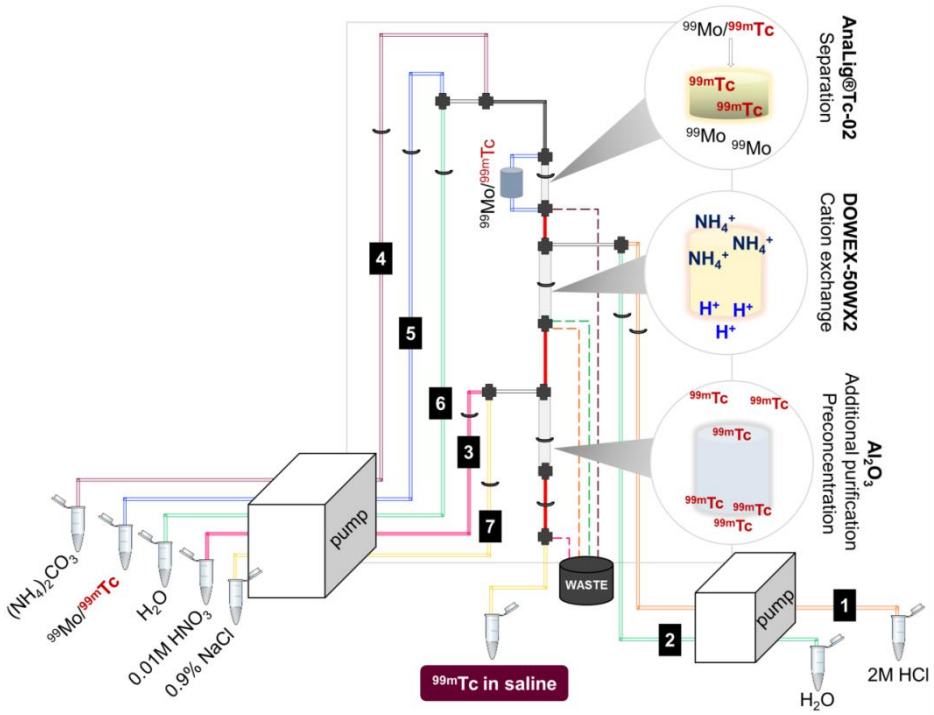

Figure 11. Diagram of ^{99m}Tc separation using three-column process.

The purity of the separated ^{99m}Tc was checked by TLC and HPLC methods, and the suitability for the synthesis of potential radiopharmaceuticals - by the synthesis of the complex with DTPA (diethylene triamine pentaacetic acid). In nuclear medicine, the radiopreparation [^{99m}Tc]Tc-DTPA is routinely used to assess renal function in various conditions and to measure glomerular filtration rate. The quality control of the [^{99m}Tc]Tc-DTPA complex obtained by me using the TLC technique showed a high labeling efficiency of over 95%.

Particularly noteworthy is the fact that the method of ^{99m}Tc production presented in paper [**H9**] is a real alternative to the current method of obtaining this radionuclide (by obtaining ^{99}Mo in a reactor and using it for the production of ^{99}Mo/^{99m}Tc generators). Through the efforts of NorthStar Medical Radioisotopes, LLC, its RadioGenix system (a non-uranium process for the production of Mo-99 to prepare Tc-99m) was approved by the US FDA (United States Food and Drug Administration) in 2018 for use as the first a unique system for the production of technetium-99m.

The most important achievements of my research include:

In general, in the series of publications presented above, I presented the results of research on the radioconjugates designed and obtained by me, which can become potential radiopharmaceuticals for diagnosing Alzheimer's disease, diabetic foot or rheumatoid arthritis using the PET and SPECT technique.

- ✓ design, synthesis, psysicochemical, *in-vitro* and *in-vivo* characterization of new radioconjugates capable of crossing the blood-brain barrier, as well as allowing imaging of the physiological state of the lungs;
- ✓ design and obtaining potential diagnostic radiopharmaceuticals for diabetic foot imaging;
- ✓ developing a comprehensive review of the current knowledge on the use of MTX and its possible mechanism of action, as well as an indication of the most common mistakes made at the stage of designing and testing a new radiopharmaceutical that may lead to misinterpretation of experimental results;

- ✓ development of an efficient method for the cyclic separation of ^{99m}Tc from a target irradiated with gamma radiation using the designed semi-automatic 3-column module.

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5. Presentation of significant scientific activity carried out at more than one university, scientific institution, especially at foreign institutions:

- Helmholtz-Zentrum Dresden-Rossendorf, Germany – dr Hans-Jürgen Pietzsch, dr Jens-Uwe Künstler
- Department of Pharmaceutical Chemistry, Drug Analysis and Radiopharmacy, Medical University of Lodz, Poland - prof. dr hab. Elżbieta Mikiciuk-Olasik
- Department of Pharmaceutical Chemistry, Drug Analysis and Radiopharmacy, Medical University of Lodz, Poland - prof. dr hab. n. farm. Paweł Szymański

- University Clinical Center of the Medical University of Warsaw - prof. dr hab. n. med. Leszek Królicki
- Department of Preclinical Sciences, Warsaw University of Life Sciences- SGGW, Warsaw, Poland - dr hab. Magdalena Rzewuska
- National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, Poland - prof. dr hab. n. med. Brygida Kwiatkowska
- Institute of Biochemistry and Biophysics Polish Academy od Sciences, Warsaw, Poland - dr Dorota Niedziałek, dr Grzegorz Wieczorek
- Faculty of Chemistry, University of Warsaw - dr hab. Zbigniew Rogulski
- Institute of Nuclear and Radiological Sciences, Technology, Energy and Safety N.C.S.R. „Demokritos" Athens, Greece - dr Penelope Bouziotis
- University Hospital Essen, Nuclear Medicine Clinic, Medical Research Center (MFZ), Essen, Germany - dr Janette Iking
- Institute of Experimental Physics, Slovak Academy of Sciences (SAS), Košice, Slovak Republic - doc. dr Zuzana Gažová
- Biological Research Centre, Hungarian Academy of Sciences, Szeged, Hungary- dr István Krizbai
- National Center for Biotechnology Spanish National Research Council (CSIC) – prof. José M. Valpuesta

6. Presentation of teaching and organizational achievements as well as achievements in popularization of science:

before obtaining the doctoral degree:

- participation in the Science Picnic, Science Festival or Night of Museums
- I conducted classes for students of the Faculty of Physics, Warsaw University of Technology

after obtaining the doctoral degree

- Supervisor of 8 master's theses:

  - „Labelling of biologically active molecules for SPECT diagnostic", Agata Piądłowska, Uniwersytet Warszawski, Wydział Fizyki, June 2016

  - „Synthesis and Study of Antibiotics Derivatives for PET-Imaging of Bacterial Infections", Weronika Maliszewska, Faculty of Physics, University of Warsaw, July 2016

- „Labelling Sc–DOTA bioconjugate with 18-F by a metallic bridge", Maciej Wójcik, Faculty of Physics, University of Warsaw, September 2016

- „Synthesis and physicochemical properties of the ^{68}Ga-NODA-GA-Tocilizumab, a potential radiopharmaceutical for the diagnosis of rheumatoid arthrisis", Faculty of Chemistry, University of Warsaw Emilia Balcer, July 2017

- „Cyclic ^{99m}Tc isolation from the gamma irradiated ^{100}Mo target", Kamil Wawrowicz, Faculty of Chemistry, Warsaw University of Technology, January 2019

- „Synthesis and physicochemical properties investigation of ^{68}Ga-cefepim radioconjugate as a potential radiopharmaceutical for PET imaging of bacterial infections", Kinga Żelechowska, Faculty of Physics, University of Warsaw, July 2019 – the thesis was awarded by Polish Nucleonic Society in 2021 for the best master thesis in the field of atomic science

- „Study of the efect of ligand on the physicochemical properties of radiobioconjugate ^{68}Ga-Tac as a potential radiopharmaceutical for the diagnosis of Alzheimer's disease", Monika Rykała, Faculty of Physics, University of Warsaw, July 2020.

- „Synthesis and study gallium-68 lapatinib as a potential radioconjugate for PET imaging of breast cancer", Julia Babraj, Faculty of Chemistry, University of Warsaw, planned defence -July 2023

- Since 2013, I conduct laboratory classes for students of the Faculty of Physics, Warsaw University of Technology (Medical Physics Laboratory/Nuclear Physics and Technology Laboratory)
- in the academic year 2014/2015 and 2015/2016 I conducted laboratory classes for students of Master's studies in the field of Energy and Nuclear Chemistry (University of Warsaw)
- in the academic year 2018/2019, I conducted laboratory classes in the subject of nuclear chemistry for students of civil and military studies (Military University of Technology)
- in the academic year 2018/2019 and 2019/2020, I conducted a monographic lecture "Radiochemistry and radiopharmaceutical chemistry in medicine" (University of Warsaw)
- in 2018-2020, I conducted laboratory classes for PhD students within the framework of the National Centre for Research and Development Project No. POWR.03.02.00-00I009/17(Radiopharmaceuticals for molecularly targeted diagnosis and therapy, RadFarm, Operational Project Knowledge Education Development 2014–2020, co-financed by the European Social Fund)

- in 2022, scientific supervisor of a PhD student from the National Center for Scientific Research N.C.S.R. "Demokritos" (Athens, Greece) within a 3-week stay in the frame of European Cooperation Program in the field of Scientific and Technical Research (COST)

7. Description of other scientific and research achievements:

7.1 Received awards and distinctions

- "SRS Travel Bursary Award" awarded by the Organizing Committee of the 19th International Symposium on Radiopharmaceutical Sciences (ISRS 2011)

- "SRS Travel Bursary Award" awarded by the Organizing Committee of the 7th International Symposium on Technetium and other Radiometals in Chemistry and Medicine (TERACHEM 2010)

- Scholarship financed from the project "Scientific potential as support for the economy of Mazovia - scholarships for doctoral students" by the Marshal's Office of the Mazowieckie Voivodeship in 2011

- Scholarship financed from the project "Mazowieckie doctoral scholarship" by the Marshal's Office of the Mazowieckie Voivodship in 2009

- receiving the IChTJ Director's award for the progress achieved in the implementation of the doctoral thesis and professional activity (2009 and 2011)

- travel grant for the International Symposium on Trends in Radiopharmaceuticals (ISTR-2023) awarded by the International Atomic Energy Agency

- travel grant for the Molybdenum-99 International Symposium 2022 awarded by the International Atomic Energy Agency

- team award at the International Trade Fair "Ideas - Inventions - New Products - iENA 2021, „The modified drug substance molecule, method of its production, diagnostic or therapeutic receptor radiopharmaceutical based on this molecule, method of its production and its application"; P. K. Halik, E. Gniazdowska, **P. Koźmiński** - silver medal

- team award at EUROINVENT 2021 in Romania, „The modified drug substance molecule, method of its production, diagnostic or therapeutic receptor radiopharmaceutical based on this molecule, method of its production and its application" P. K. Halik, E. Gniazdowska, **P. Koźmiński** - gold medal

- team award at the International Warsaw Invention Exhibition IWIS 2020, „The modified drug substance molecule, method of its production, diagnostic or therapeutic receptor

radiopharmaceutical based on this molecule, method of its production and its application"; P.K. Halik, E. Gniazdowska, **P. Koźmiński** - gold medal

- team award at the International Warsaw Exhibition of Inventions IWIS 2019, „Diagnostic radiopharmaceutical for imaging of cholinesterase levels, method for producing it and applications"; E. Gniazdowska, **P. Koźmiński**, E. Mikiciuk-Olasik, P. Szymański – platinum medal

- team award at the International Warsaw Invention Exhibition IWIS 2019, „Diagnostic or therapeutic Her-2 high-affinity radiopharmaceutical, the method for its production" and its application"; E. Gniazdowska, **P. Koźmiński** – gold medal

- team award at the XXII Moscow International Salon of Inventions and Innovative Technologies Archimedes 2019, „Diagnostic radiopharmaceutical for imaging infections, method of its production and its application" **P. Koźmiński**, E. Gniazdowska, M. Chojnowski, A. Kopatys, L. Królicki gold medal

- team award at SEUL INTERNATIONAL INVENTION FAIR 2018, „Diagnostic radiopharmaceutical for imaging of infections, method for producing it and application" **P. Koźmiński**, E. Gniazdowska, M. Chojnowski, A. Kopatys, L. Królicki – gold medal

- team award at SEUL INTERNATIONAL INVENTION FAIR 2018, „Diagnostic radiopharmaceutical for imaging of infections, method for producing it and application" **P. Koźmiński**, E. Gniazdowska, M. Chojnowski, A. Kopatys, L. Królicki – SPECIAL AWARD Indonesian Invention and Innovation Promotion Association No. INNOPA/KOR/SA/627/XII/2018

- team award at the International Warsaw Exhibition of Inventions IWIS 2018, „Diagnostic radiopharmaceutical for imaging infections, method of its production and its application" **P. Koźmiński**, E. Gniazdowska, M. Chojnowski, A. Kopatys, L. Królicki – platinum medal

- team awards of the Director of INCT for the series of publications (2012, 2015, 2017, 2018, 2019, 2021, 2022)

PODPIS ZAUFANY
PRZEMYSŁAW ANDRZEJ
KOŹMIŃSKI
07.06.2023 13:07:27 [GMT+2]
Dokument podpisany elektronicznie
podpisem zaufanym

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(Applicant's signature)