Radioimaging agents for medical body scans

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Introduction

The diagnosis of disease, such as cancers, neurological diseases and cardiovascular diseases, as early as possible is important to enable treatment to be started at an early stage of disease, thereby maximising the chance of recovery. Being able to map the progress of disease and follow the effectiveness of drugs is also important so that patients are prescribed the correct drugs to allow a faster recovery.

SPECT (single-photon emission computerised tomography) is a non-invasive imaging tool that allows doctors to see through a patient's internal organs (see Figure 1). While other imaging tools only show what the structures inside the body looks like, this 3D imaging technique can show how the organs work and can be used for the diagnosis and prognosis of disease. SPECT scans can be used to screen and monitor heart problems, brain disorders and bone diseases. For example, in the case of heart disease it can give detailed information showing which arteries are clogged and which part of the heart may be pumping poorly. It can be used to diagnose dementia and other injuries in the brain, as well as determining which parts of the brain are affected by the disease. It may be used to diagnose cancers, such as bone cancer, and keep track of their progression. SPECT is also used in drug development and can aid in understanding drug action, establishing dosage regimens and treatment strategies for a number of diseases.

Figure 1 A SPECT Scanner used for imaging of human patients

What are we interested in?

SPECT requires imaging agents in the form of a radioactive element such as iodine-123, which is attached to an ion or molecule (known as a ligand) to form a complex. The resulting radioligand is administered to a patient and must bind with high affinity and selectivity to a target molecule in the body. The radioligand emits gamma rays, which are detected by surrounding gamma cameras to give a 3D image (see Figure 2).

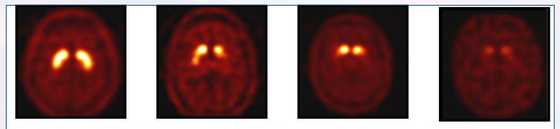

Figure 2 shows SPECT images of the brain. The first image on the left is of a healthy patient, followed by images of a patient with progressively worse Parkinson's Disease. A reduction of binding of the radioligand with the progression of Parkinson's Disease can clearly be seen. Credit for image: Chemical Society Reviews, 2011, Vol 40, p149-162.

The widespread application of SPECT is limited, in part, due to current methods of generating the radioligands, which can involve unstable, highly toxic precursors. The aim of my PhD project was to develop a method to incorporate radioactive iodine into biological compounds, to be used as imaging agents, that is more efficient and less toxic than current methods, with more stable intermediates, fast reaction times and simple purification methods. All these are necessary requirements for radiolabeling.

What did we do?

A common method used for iodination of aromatic ring compounds (based on benzene) is via a diazonium salt (shown as the intermediate in Figure 4). These intermediates are highly reactive as it is very simple for them to lose nitrogen gas. However, diazonium salts are not generally considered for radioiodination of SPECT imaging agents as the reaction is often accompanied by unwanted side reactions due to this highly reactive intermediate. More stable diazonium salts have recently been prepared. I investigated the use of these more stable intermediates in radioiodination reactions (see Figures 3 and 4). The salts used in the reaction were found to be highly stable and this resulted in a much cleaner reaction.

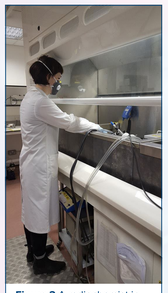

Figure 3 A radiochemist in full lab gear

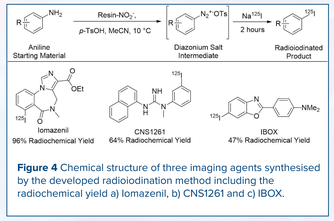

Figure 4 Chemical structure of three imaging agents synthesised by the developed radioiodination method including the radiochemical yield a) Iomazenil, b) CNS1261 and c) IBOX.

What did we find?

We found that the method we developed for labelling with radioactive iodine gives high yields for a variety of structures, with a fast, simple reaction. The reaction was used to synthesise a number of imaging agents which are currently used in SPECT scans of the brain, for example, Iomazenil, CNS1261 and IBOX (see Figure 4). Iomazenil is an imaging agent that can be used to image epileptic seizure. CNS1261 can be used for imaging of patients with neurodegenerative diseases, such as epilepsy, stroke, Parkinson's or Alzheimer's disease and IBOX is also used for imaging patients with Alzheimer's disease.

What does it mean?

This simple method of labelling with radioactive iodine can be used to synthesise imaging agents in high yields. The method developed is attractive for use in radioiodination reactions due to the readily available starting materials, more mild and less toxic reaction conditions than current methods, with simple work-up and purification.

The imaging agents can be used in SPECT scans to detect and follow the progression of cancers, Alzheimer's Disease, Parkinson's Disease, as well as many others.

Who am I?

I am a PhD student at the University of Glasgow. My project is investigating new syntheses of molecular imaging agents to be used for the scanning of disease. I was attracted to the PhD project due to the link with industry, as well as being able to easily see where the chemistry can be applied. I gratefully acknowledge the funding support from Medical Research Scotland and GE Healthcare. Additional thanks to my supervisors Dr Andy Sutherland and Dr Sally Pimlott.

Nikki started her PhD project entitled *"New Methods for the Efficient, Non-toxic Generation of PET and SPECT Tracers: Molecular Imaging of Neurological Disease."* in 2013 and while principally based at the University of Glasgow, supervised by Dr Andrew Sutherland, she is also working closely with GE Healthcare.