Speeding up drug discovery

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What is the problem?

Isotopes are different forms of an element that have the same chemical properties but different masses, as they have different numbers of neutrons in their nuclei. Heavy isotopes of hydrogen (deuterium (D) and tritium (T)) are needed in the pharmaceutical industry to 'label' possible new drug molecules so that we can learn about them. For example, D labels are used to find out how our bodies break down a drug, and radioactive T labels are used in studies to track a drug's path through the body. Combined, this approach is described as ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity).

To create these labelled drug molecules, we need a reliable process which gives a high yield of the isotopically labelled molecule, as deuterium and tritium are expensive.
We also need the D/T to replace a specific hydrogen (H) in a molecule, so that we know which fragment of the molecule we are tracking. One of the most common methods of doing this selective labelling is through directed Hydrogen Isotope Exchange (HIE) using a metal catalyst.

The Kerr group at the University of Strathclyde has been researching HIE catalysts for several years, and have developed very successful iridium catalysts which insert D or T in place of H next to a particular group in a molecule, called a directing functional group, which, in partnership with the catalyst, promotes exchange from H to D/T. However, it remains a challenge to insert a D/T label in a controlled manner without a directing group. This is a problem because not all drug candidates contain directing groups and we want to be able to label them all for ADMET.

This project worked on a potential solution to this problem where the directing group is only in place for the labelling, then a chemical reaction converts it into another, non-directing group. We used a 'further reaction' to convert the directing group on a molecule we had labelled with D, producing a new, drug-like molecule which still had the D label (see Figure 1).

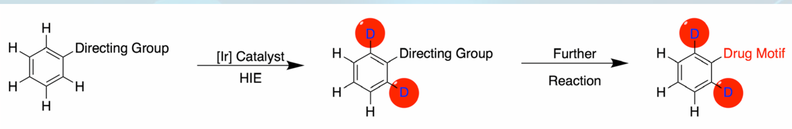


Figure 1 Further reaction of isotopically labelled molecules can be used to create drug molecules that are labelled depsite not having a directing group.

What are we interested in?

It is important that the further reaction is successful with a high yield as the starting material for this is the precious, D labelled molecule. Therefore, we worked on optimising this reaction, using 3 model systems and unlabelled starting material, which is cheap and easy to obtain.

It is also important to monitor the retention of the D label throughout the further reaction. Therefore, we went on to perform our further reaction using D labelled starting material, and used the technique called 2D NMR (nuclear magnetic resonance) spectroscopy to check that the D was still present in the correct position after the reaction.

To show that this method is useful to drug discovery, we used our further reaction to make a type of molecule which is commonly found in drug molecules and candidates, called a biphenyl system (see Figure 2).

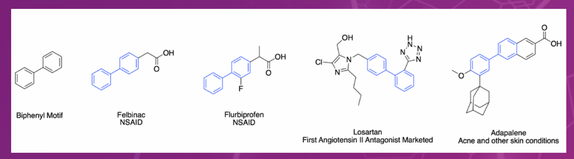


Figure 2 In drug molecules, such as these 4 marketed drugs, the biphenyl system can have many different chemical groups replacing one or more of the H atoms in the biphenyl system. NSAIDs are non-steroidal anti-inflammatory drugs. Losartan is used to treat high blood pressure.

What did we do?

Most of this project involved optimising the 'further reaction' to get the highest possible yield of our final labelled product. The reaction we carried out used a palladium catalyst, and we used cheap, unlabelled material in our optimisation experiments. We worked on 3 model systems and varied the catalyst material, catalyst loading, method of reaction, ratio of reactants, temperature, solvent, reaction time and additives, to find the best reaction conditions.

We then used our optimised conditions to synthesis a biphenyl pro-drug molecule using D labelled material (see Figure 3).

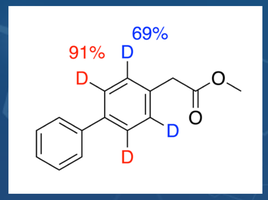


Figure 3 The methyl ester of the NSAID (non-steroidal anti-inflammatory drug) Felbinac, with D labels installed in a biphenyl system, which we synthesised during this project.

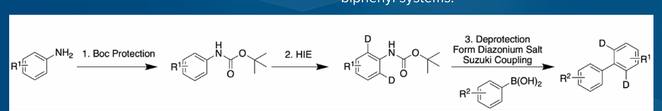
The percentages show the proportion of the molecules synthesised which had D instead of H in the coloured positions.

This synthesis involved 3 steps:

1. Install directing group
2. HIE using previously developed Kerr group conditions and catalyst
3. Further reaction using our optimised conditions to give a biphenyl molecule (see Figures 4 and 5)

Figure 4 A Hydrogen Isotope Exchange (HIE) reaction set up in the lab.

Figure 5 The general method investigated and optimised for production of isotopically labelled biphenyl systems.



What did we find?

We found our 'further reaction' successfully produced D labelled biphenyl systems.

We increased the yield of our 'further reaction' from 21 % to 53 % through our optimisation process.

We showed that D labelling was completely retained in its selective position through the 'further reaction'.

During the synthesis of a labelled pro-drug molecule, a D labelling happened next to a group which had not previously been known to be a directing group. Therefore, a new directing group was found, a methyl ester. Knowing about this directing group provides further isotope labelling opportunities for future research.

What does this mean?

The method we developed in this project allows the production of isotopically labelled drug candidates without a directing group. This opens the possibility for more drug candidates to be labelled in more different places (see Figure 6), for use in ADMET studies where more can be learnt about these drug candidates and how they travel through our bodies.
With isotopic labelling, ADMET studies can take place earlier in the drug discovery process, and those with unsuitable ADMET profiles can be ruled out, saving time and money.

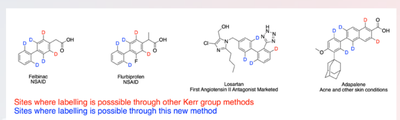


Figure 6 Our new method provides many new labelling possibilities. Real life examples are shown in 4 examples of marketed drugs.

Who am I?

I am a 3rd year Pure and Applied Chemistry student at the University of Strathclyde. I worked with the Kerr group between my 2nd and 3rd years of University. For me this was a fantastic opportunity to experience working as a researcher in organic chemistry, which I really enjoyed and which boosted both my practical and theoretical knowledge, making me hugely more confident going into my 3rd year. I am going to try working in industry in a different field next year on an industrial placement, return for my Masters year then decide what to do next!

Heather was supervised during her Vacation Scholarship project, *"New Iridium-catalysed Methods for the Direct Preparation of Isotopically-labelled Compounds for Metabolism Studies"* by Professor William J Kerr.