Investigating the use of a fluorescent dye for the detection and diagnosis of disease

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An investigation into the use of a fluorescent dye (BODIPY) as the backbone of fluorescent phosphonium salts which can be used to detect mitochondrial dysfunction and thus provide an early diagnosis into diseases such as Alzheimer’s and Parkinson’s.

Fluorescent phosphonium salts

If mitochondrial function is abnormal, due to cell apoptosis for instance, the charge balance between the phosphonium salt and the mitochondrial membrane would be disrupted. Thus, the probe would no longer accumulate within the mitochondrion, leading to a decrease in fluorescence intensity being observed by medical imaging tools. The use of fluorescent probes could allow for early detection of diseases which are caused by or involve mitochondrial dysfunction. Alzheimer’s and Parkinson’s are both examples of diseases that impair or destroy nerve cells within the brain, which would lead to mitochondrial dysfunction. Sufferers of these diseases would benefit from the use of fluorescent probes as it would allow early detection of both diseases without the use of invasive surgery. Early detection could also lead to more successful treatment. Further experimental research could also lead to developments within cancer research, as the use of fluorescent probes could allow doctors to accurately locate tumours, and so provide more precise and effective treatment.

Benefits of the incorporation of BODIPY into a primary phoshine

BODIPY (shorthand for 4,4-difluoro-4-bora-3a,4a-diazisindacene) is a fluorescent dye which comprises the backbone of both the primary phoshine and the phosphonium salt. Incorporation of this dye into the probe confers fluorescence properties and allows it to be used as an imaging agent. BODIPY-based compounds are known as fluorophores which are simply a type of fluorescent chemical compound which can reemit light upon light excitation.

Development of a primary phoshine

The main focus of this summer project was the synthesis of an air-stable primary phoshine starting with the synthesis of fluorescent dye BODIPY.

Figure 5: The reaction scheme used to synthesise the primary phoshine. Step 1 indicates the synthesis of the fluorescent starting material F-BODIPY using bromobenzaldehyde, 2 equivalents of 3-ethyl-2,4-dimethylpyrrole, trifluoroacetic acid (TFA), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), boron trifluoride diethyl etherate and N,N-disopropylethylamine (PrNEt). The resulting product was methylated using methyl magnesium bromide at room temperature in step 2 to produce C-BODIPY. This step was necessary as without it, the boron-fluorine bond would be attacked by the reducing agent. In step 3, Step 3 introduces phoshine onto the BODIPY structure using 1,4-bis(diphenylphosphinophenyl)butane (DPPB), N,N-disopropylethylamine (PrNEt), diethyl phosphite and palladium acetate which acted as a catalyst. The mixture was stirred for 26 hours at 90 °C, and the resulting phoshophone was reduced to the primary phoshine in step 4 using lithium aluminium hydride and chlorotrimethylsilane ((CH3)3SiBr).

Figure 4: 1H NMR (Nuclear magnetic resonance) spectrum taken of the phoshophone (product of step 3) synthesised during the 8 week project. This particular spectrum indicates that this product contains very little impurity as it only displays the peaks assigned to the phosphone. Extra peaks on the spectrum are a sign of an impure product.

References:


Munsey, Ryan. “5 way to boost your mitochondria”. “Natural stacks”. May 2017. September 2017