Fluorescence Sensing for Non-Invasive and Continuous Glucose Detection

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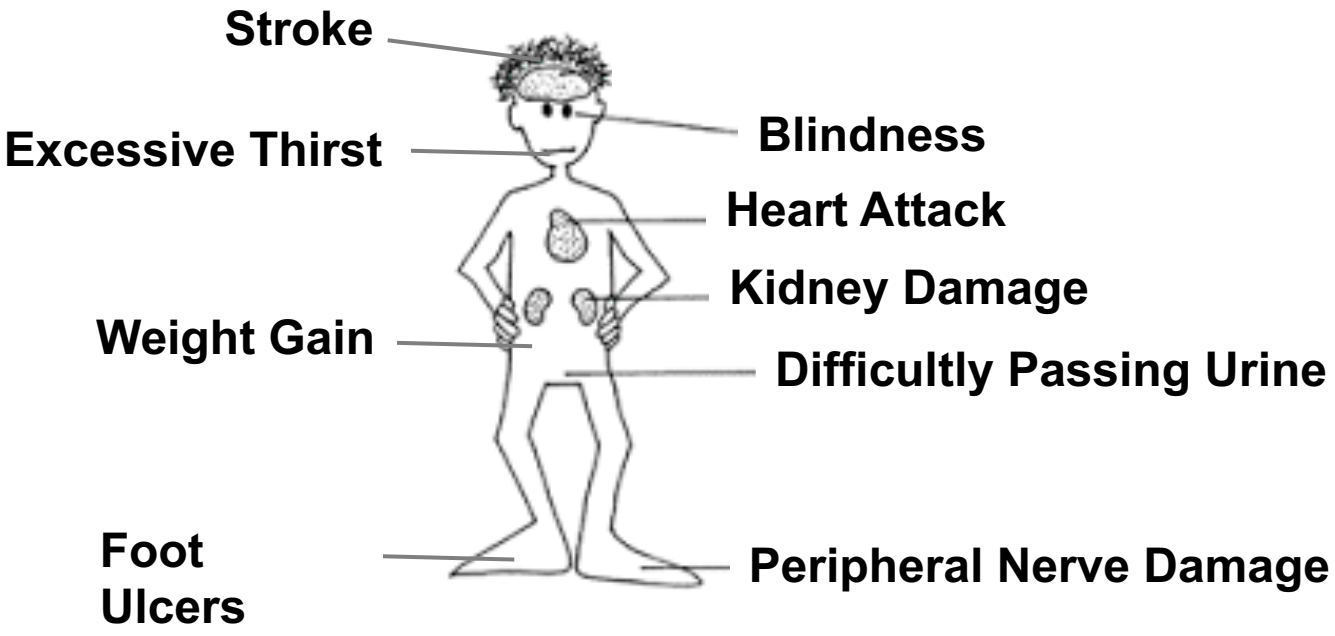
Overview

- Background
  - Diabetes – Side Effects
  - Monitoring Devices
- Project Goal
- Boronic Acids (BAs) for Sugar Recognition
- Direct Sensing in Solution
- Indirect Sensing
  - In Solution
  - In Ionogels
- Conclusions
- Future Work

Importance of Saccharide Sensing

- Disease: Diabetes and the consequential side effects



- Monitoring glucose levels to prolong life expectancy
- Currently no noninvasive, continuous monitoring systems available
- Demonstrates a need for real-time, non-invasive monitoring

Current Monitoring Methods

Implanted Wearable Devices

Roche

ACCU-CHEK®

Advantages:

- Real-time monitoring
- Continuous
- Coupled to insulin pump
- Elimates injections *via* syringe

Disadvantages:

- Invasive

Finger Pricking Method

Advantages:

- Minimally Invasive

Disadvantages

- Not continuous
- Insulin injections required
- Miss episodes of hyper- and hypoglycaemia

https://www.accu-chek.co.uk/gb/products/

Contact Lenses – The Answer!

Electrochemical sensor in a wearable platform

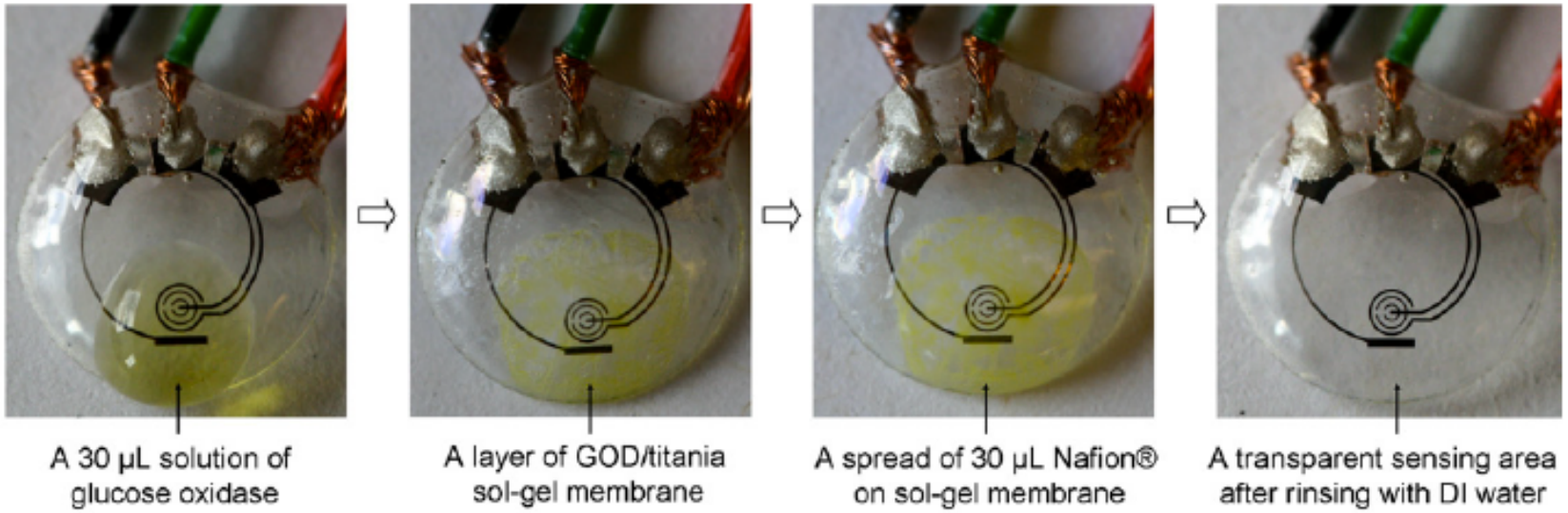
- **Battery Powered** ✗
- **Interference from Electroactive Species in Ocular fluid** ✗
- **Use of Enzymes** ✗

Google

NOVARTIS

H. Yao, et al, *Biosensors and Bioelectronics*, **2011**, *26*, 3290-3296
B.E. Watt, et al, *Toxicol. Rev.*, **2004**, *23(1)*, 51-57

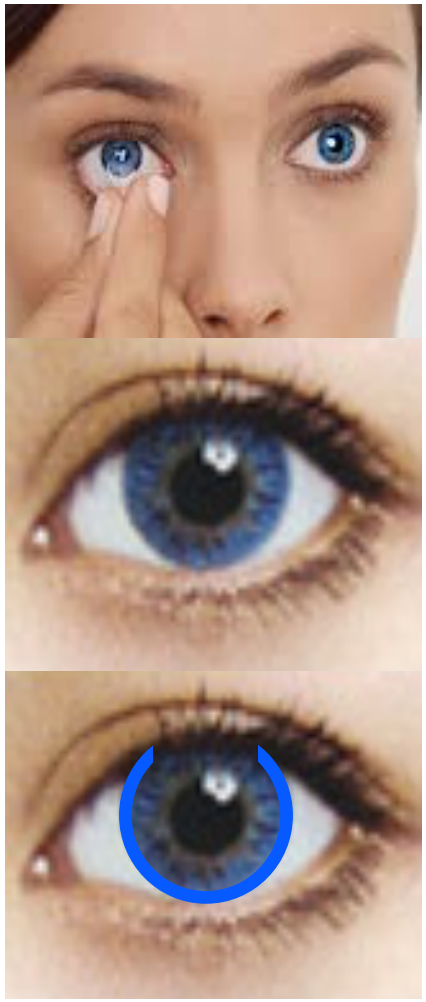
Realistically....Not a Real Working Device

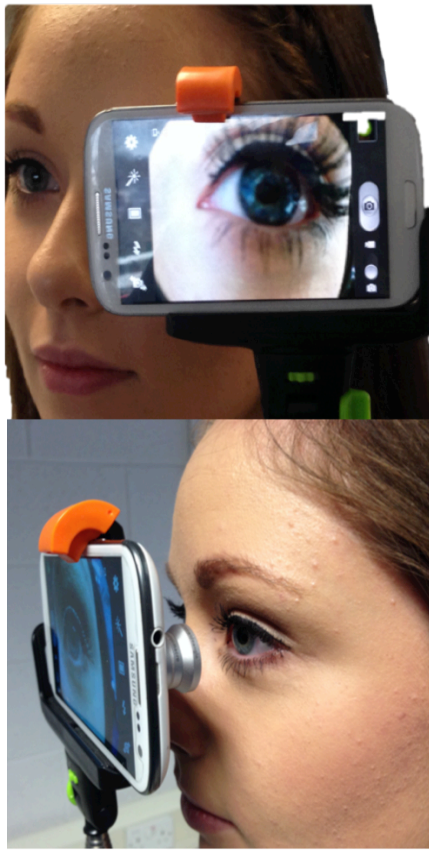


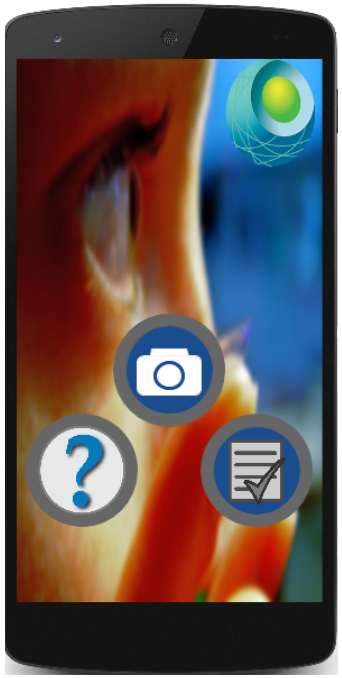
- Attached to a BASi Epsilon- EC Potentiostat +400 mV
- Sensing platform proposes glucose monitoring between 0.5-50 mM
- Ocular glucose range is 0.05-0.5 mM and up to 5 mM in diabetics
- Major shortcomings to meet immediate expectations

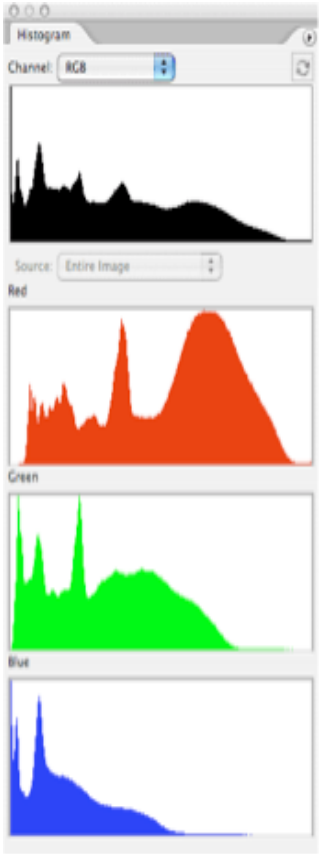
H. Yao, et al, *Biosensors and Bioelectronics*, **2011**, *26*, 3290-3296

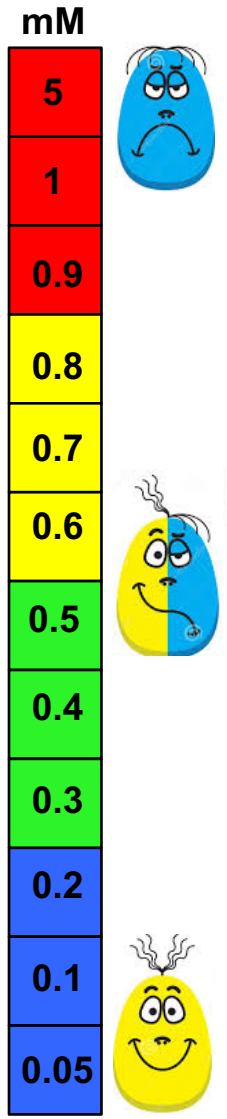
The Solution!



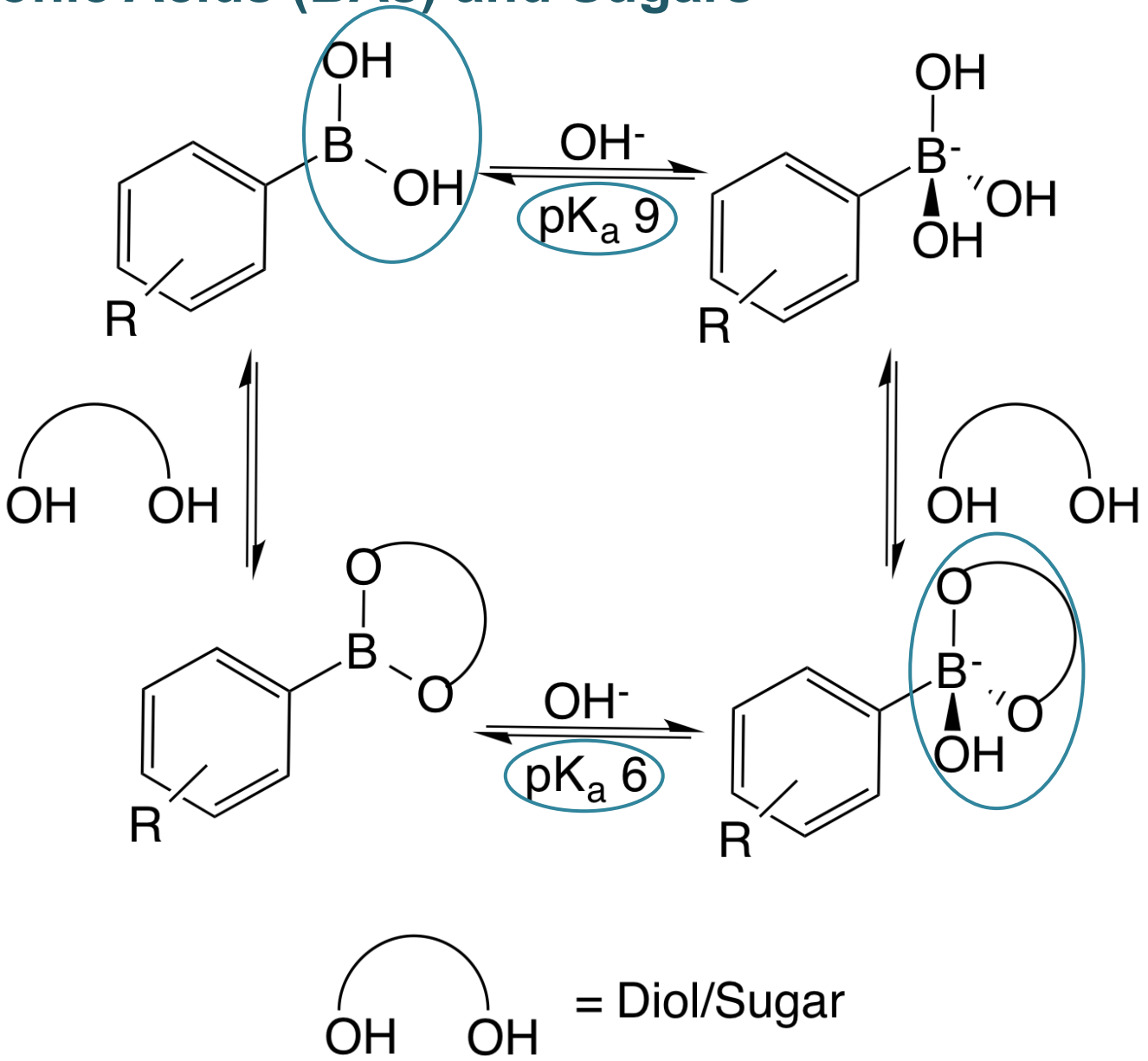






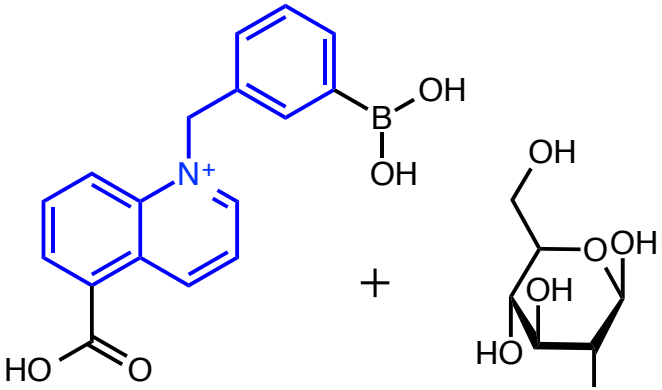


Boronic Acids (BAs) and Sugars



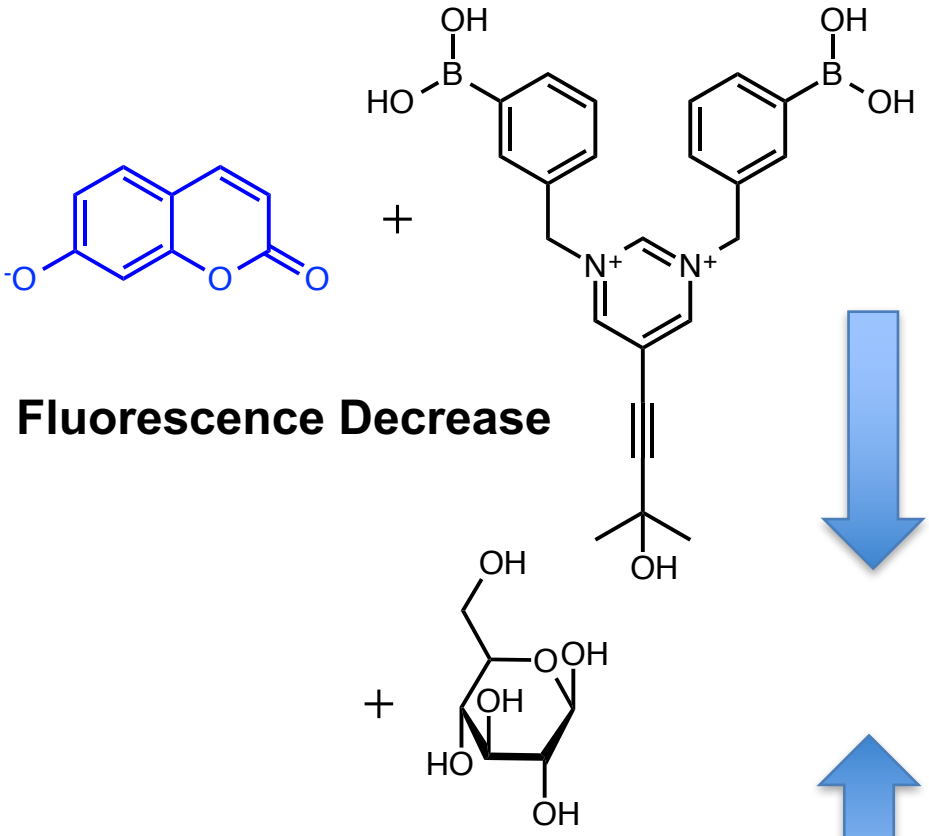
Direct vs. Indirect Sensing

Direct Sensing



Fluorescence Decrease

Indirect Sensing



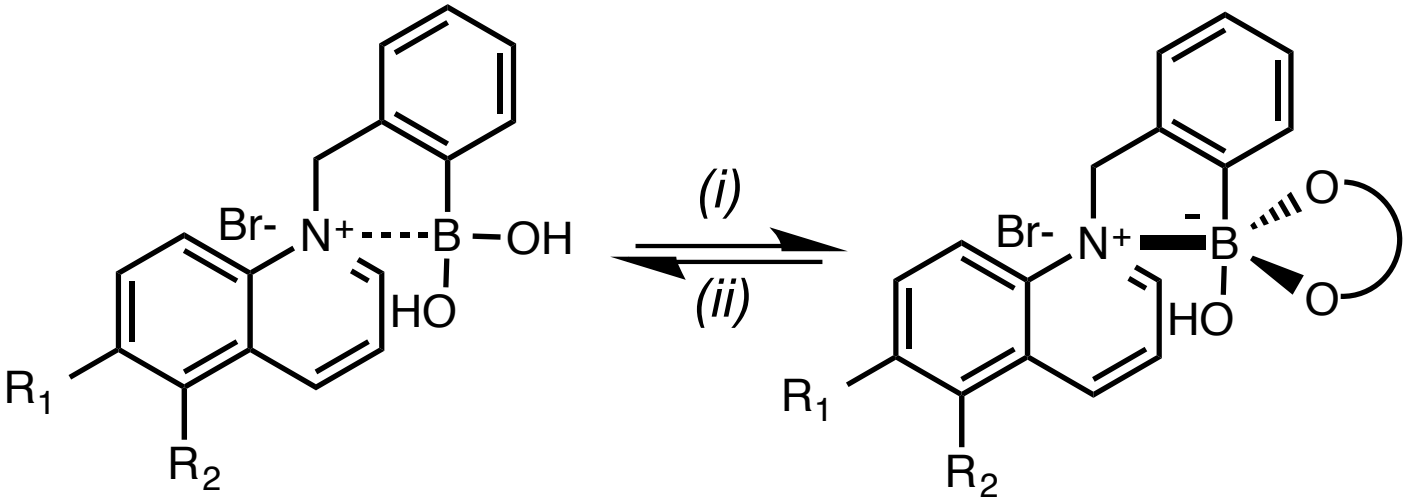
Fluorescence Decrease

Fluorescence Increase

Fluorophore

Direct Sensing

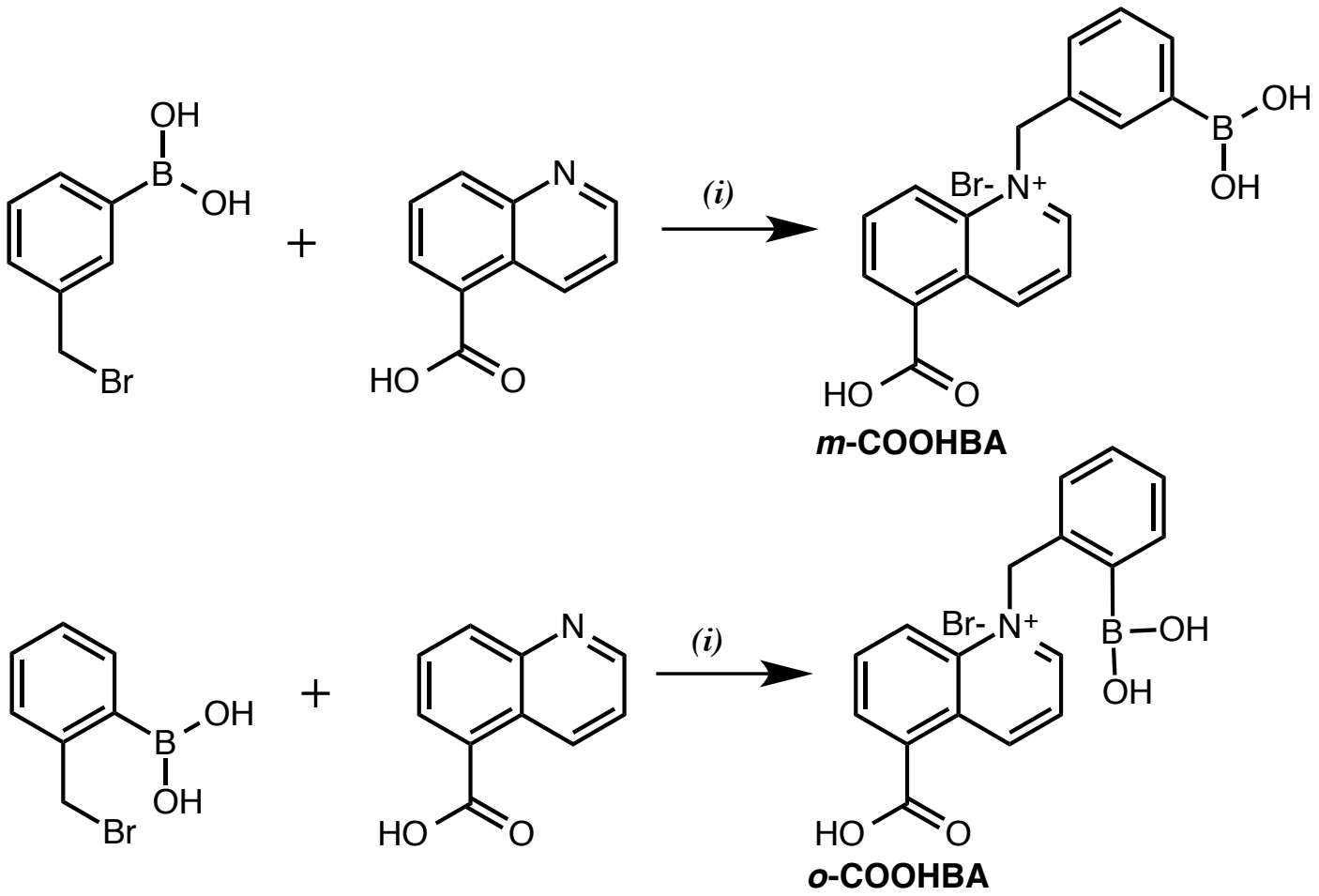
Direct Sensing



Fluorescent **Non-Fluorescent**

(i) Addition of OH^- ions/glucose
(ii) Addition of water/removal of glucose

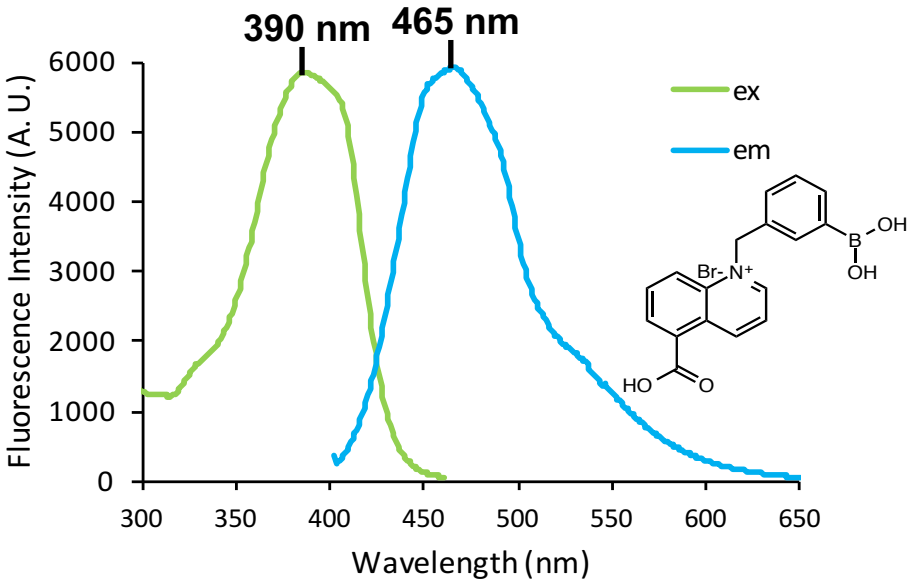
Synthesis of COOHBA Sensors



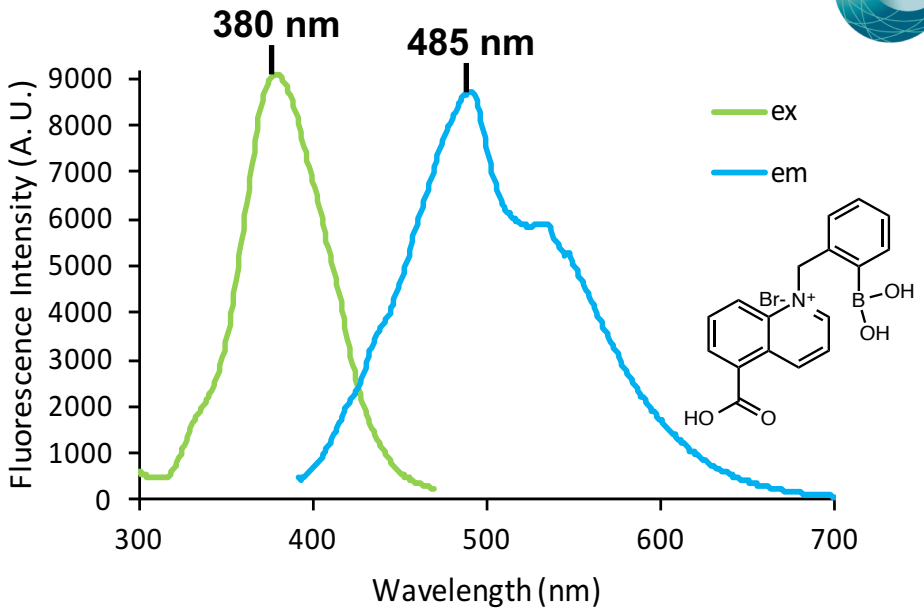
(i) Anhydrous dimethylformamide, N_2, 80 ^{0}C for 48h.

Successful synthesis of novel BA sensors were confirmed by NMR.

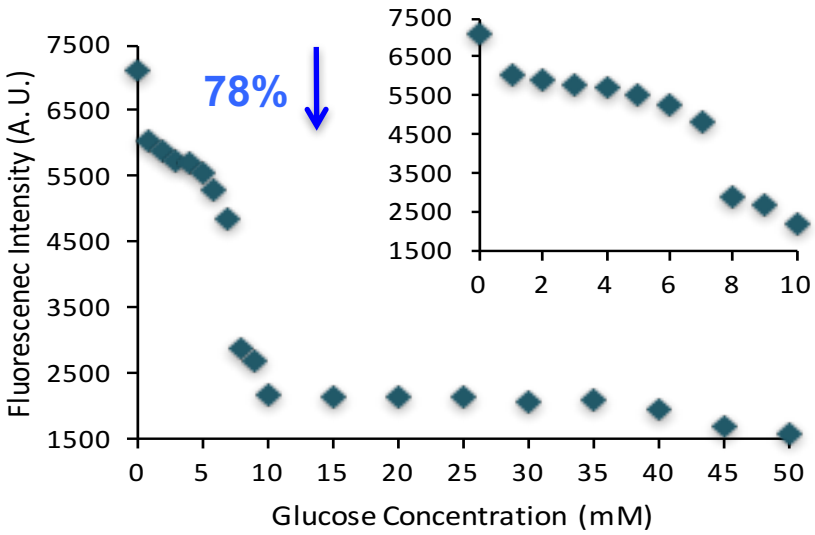
Fluorescence Results

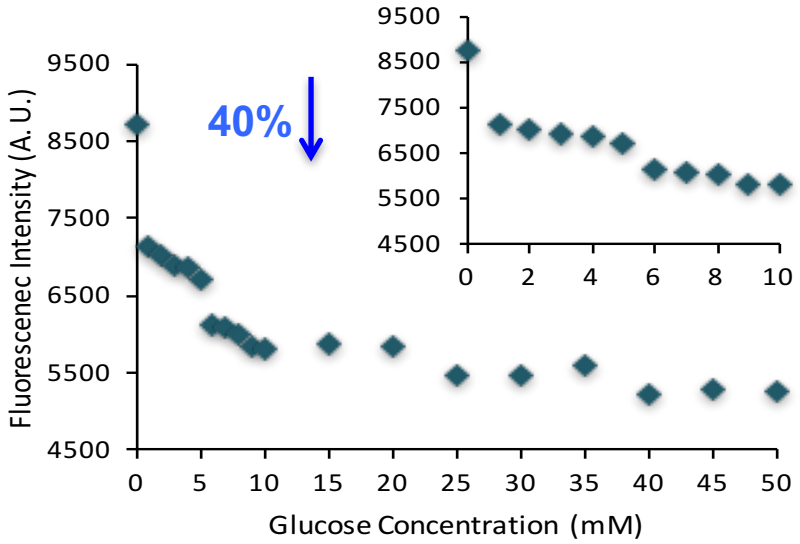


Excitation and emission spectrum of m-COOHBA 0.5 mM in pH 7.4 phosphate buffer.

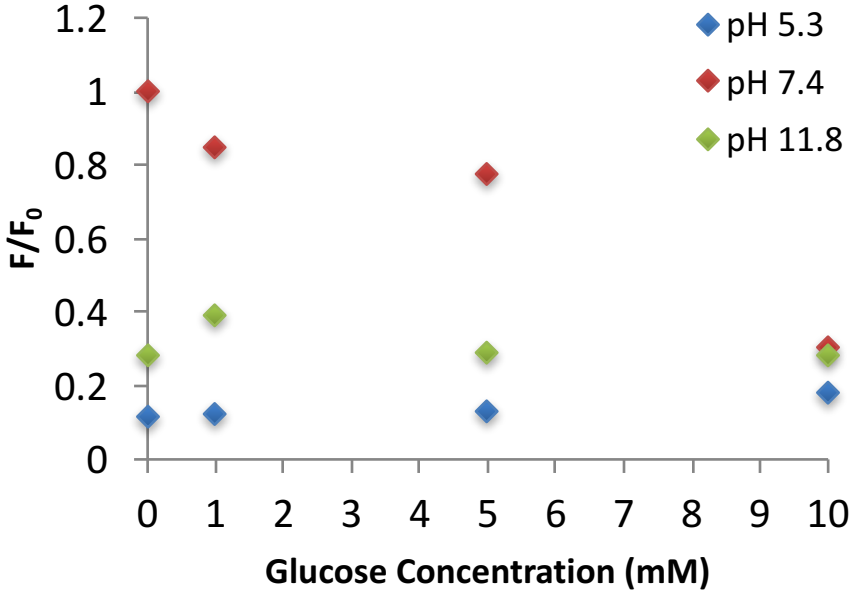


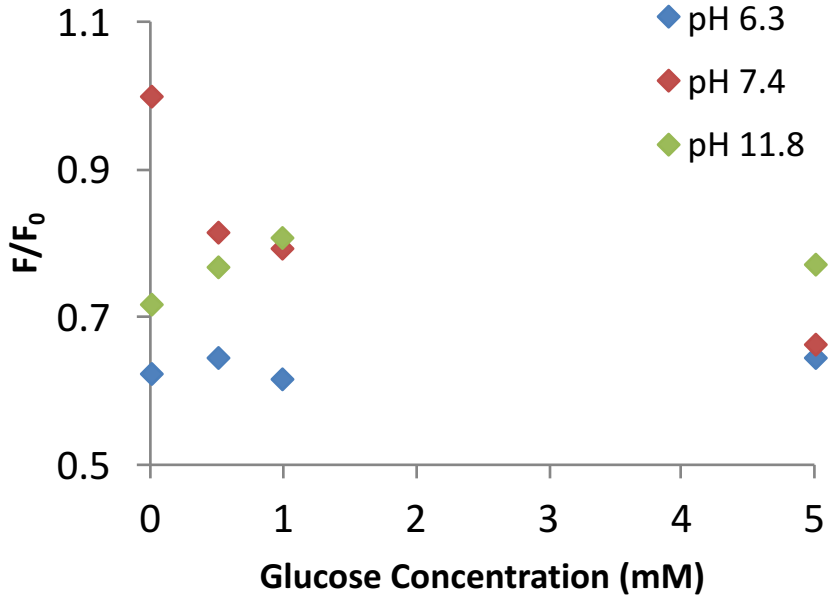
Excitation and emission spectrum of o-COOHBA 0.5 mM in pH 7.4 phosphate buffer.



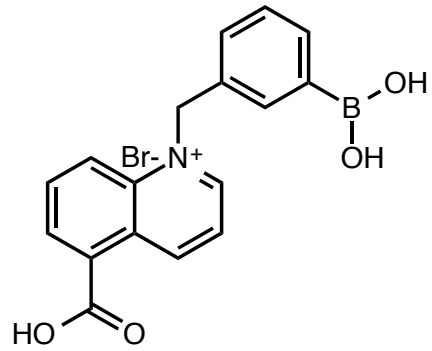


pK_a Investigation – Glucose Sensing pH Range

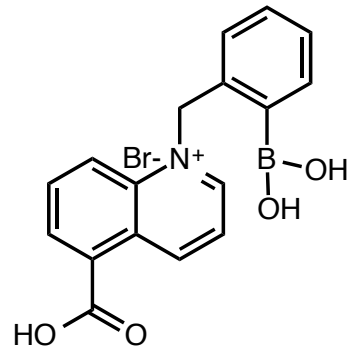




Glucose response for m-COOHBA and o-COOHBA (0.5 mM) in different pH buffer solutions ranging from pH 5-11.



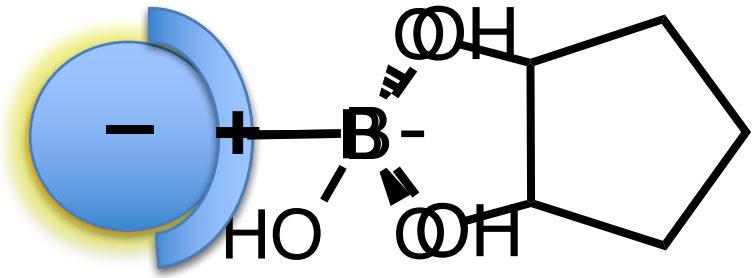
***m*-COOHBA**



***o*-COOHBA**

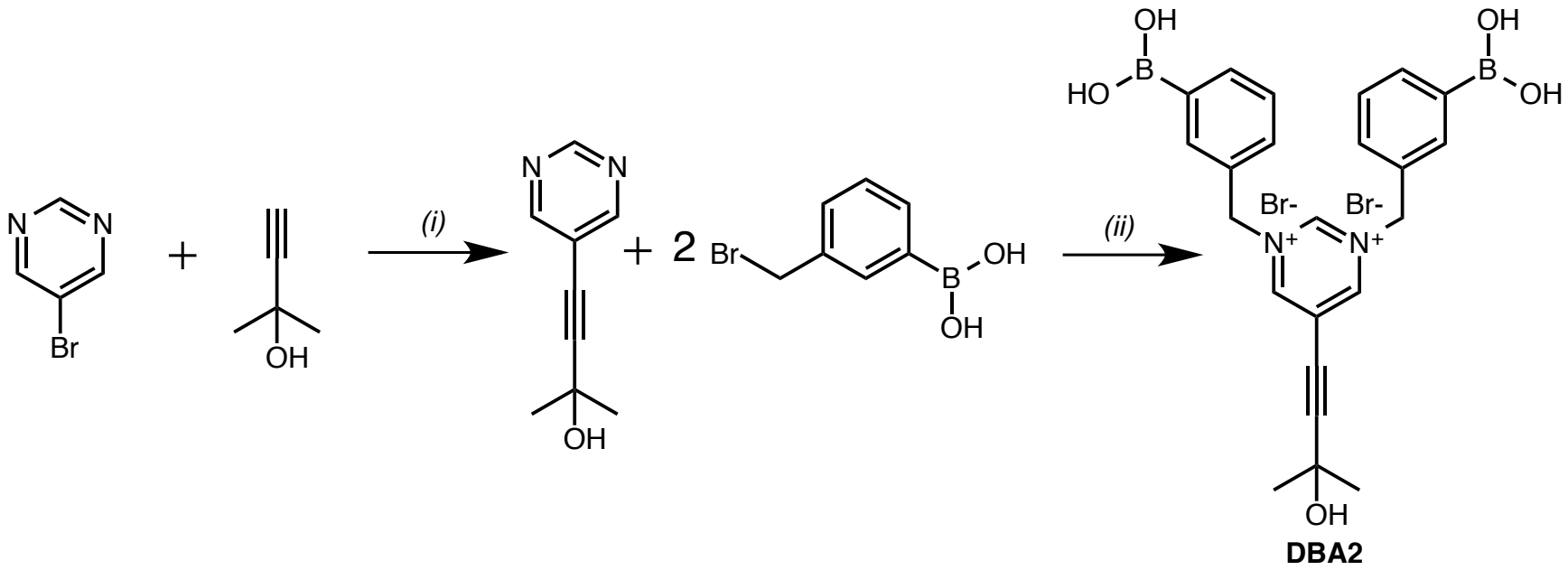
Indirect Sensing

Two-Component Sensing



Indirect Sensing in Solution

Indirect Sensing in Solution – Sensor Synthesis



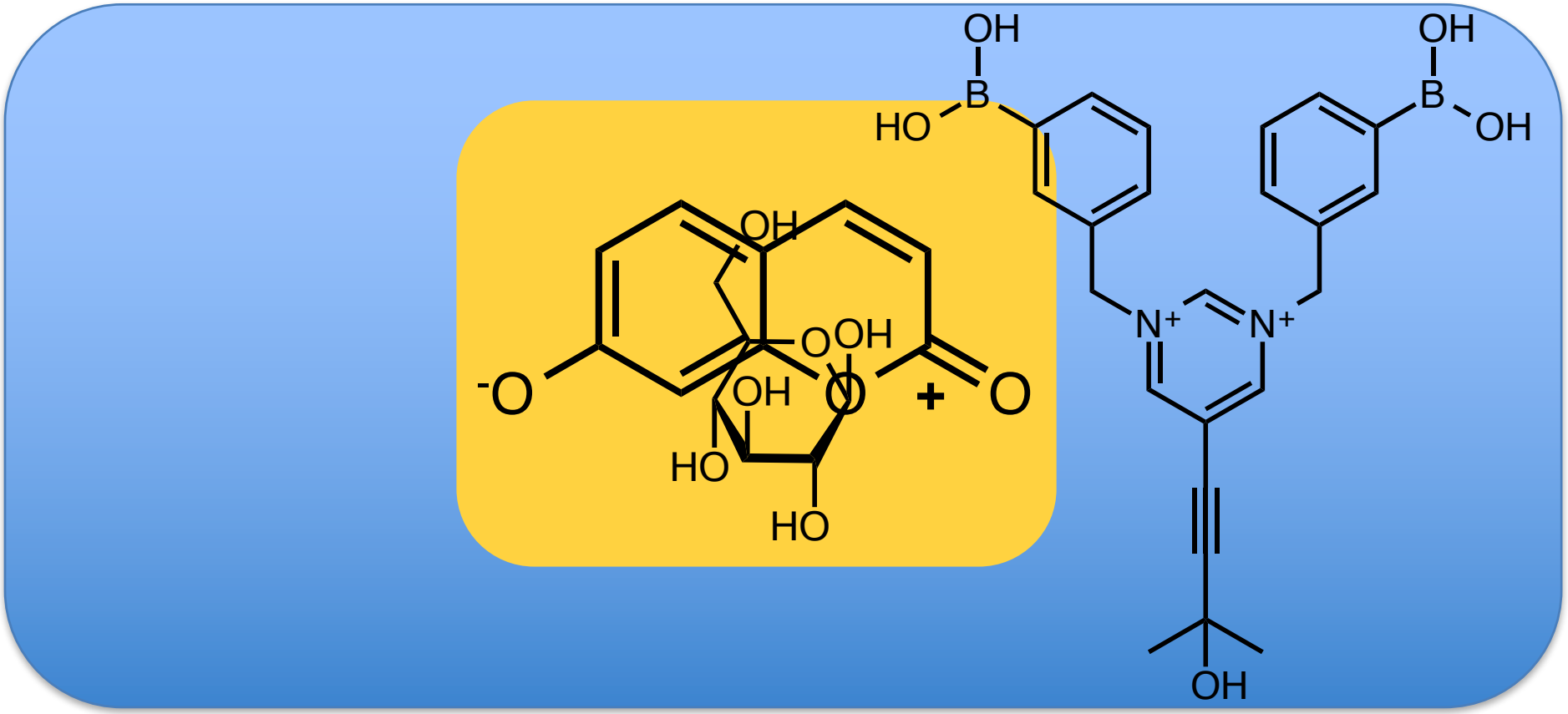
DBA2

(i) $PdCl_2(PPh_3)_2$, CuI, diethylamine, Ar, stirred at RT for 24h (66%).

(ii) anhydrous tetrahydrofuran, N_2, reflux at 80 ^{0}C for 48h (21%).

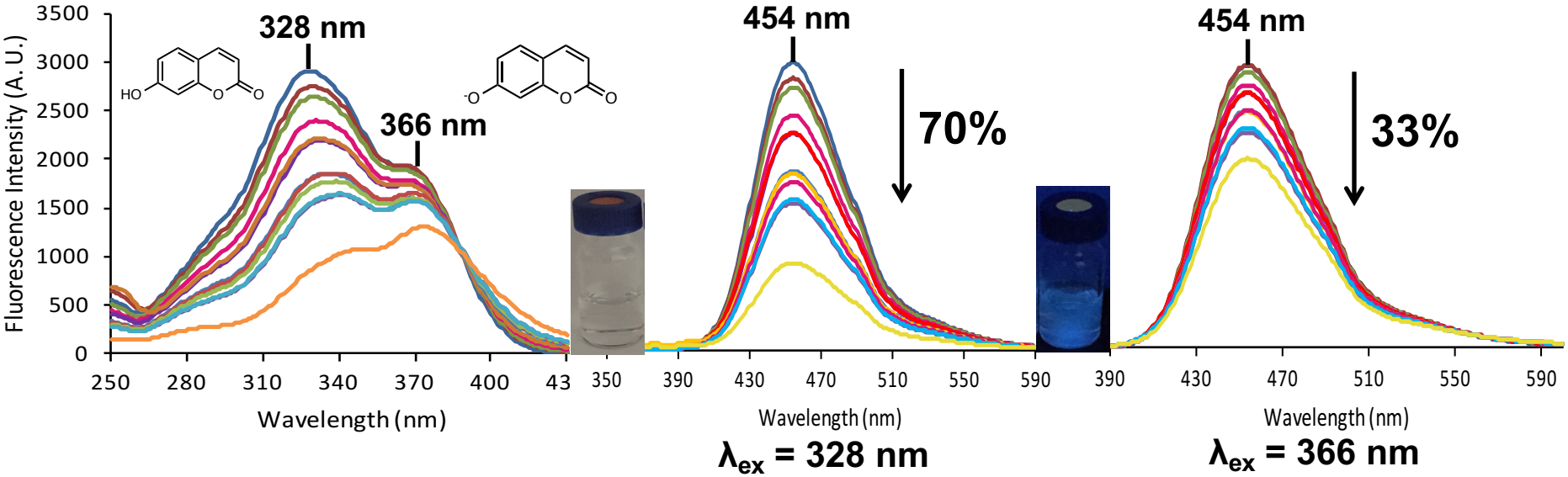
Successful product formation confirmed by NMR.

Two-Component Sensing



Non-Fluorescent

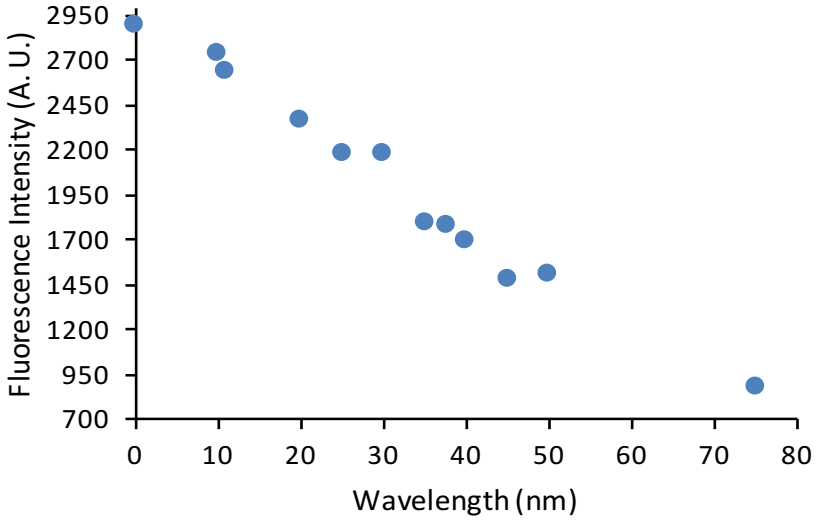
Two-Component Sensing in Solution – Fluorescence Quenching

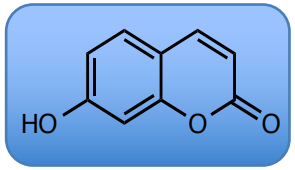


λ_{ex} = 328 nm

λ_{ex} = 366 nm

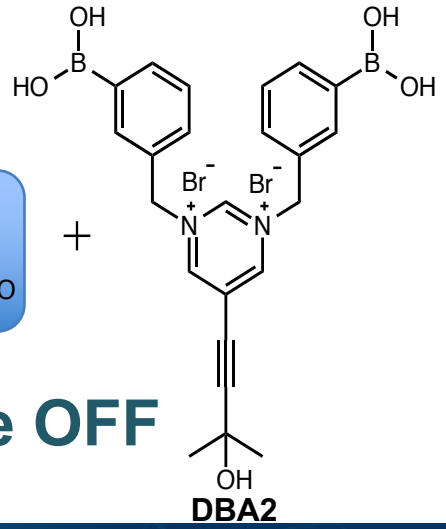
Excitation and emission spectra of 4 µM 7HC in pH 7.4 with minimal MeOH (40 µL) with increasing DBA2 concentrations up to 0.3 mM (75 eq.); Medium sensitivity; 2.5 nm bandwidth





7HC

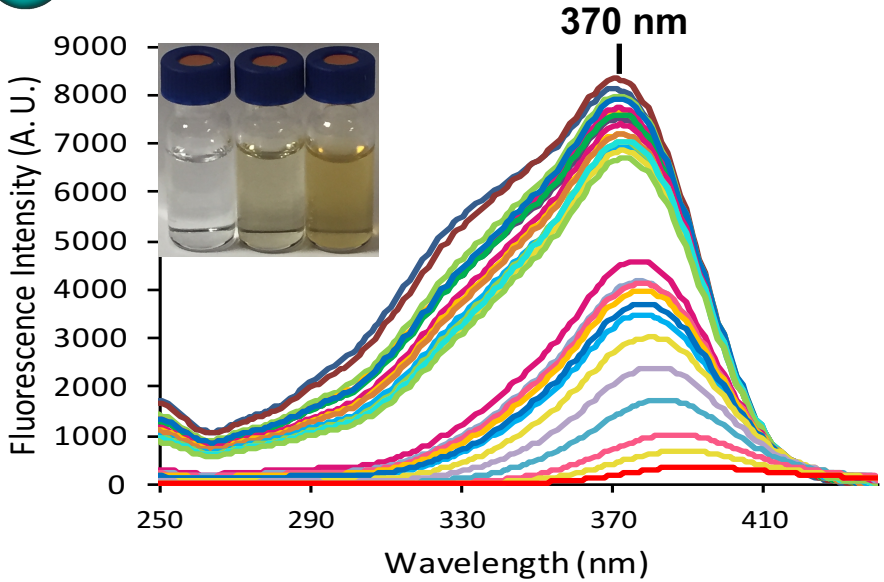
+

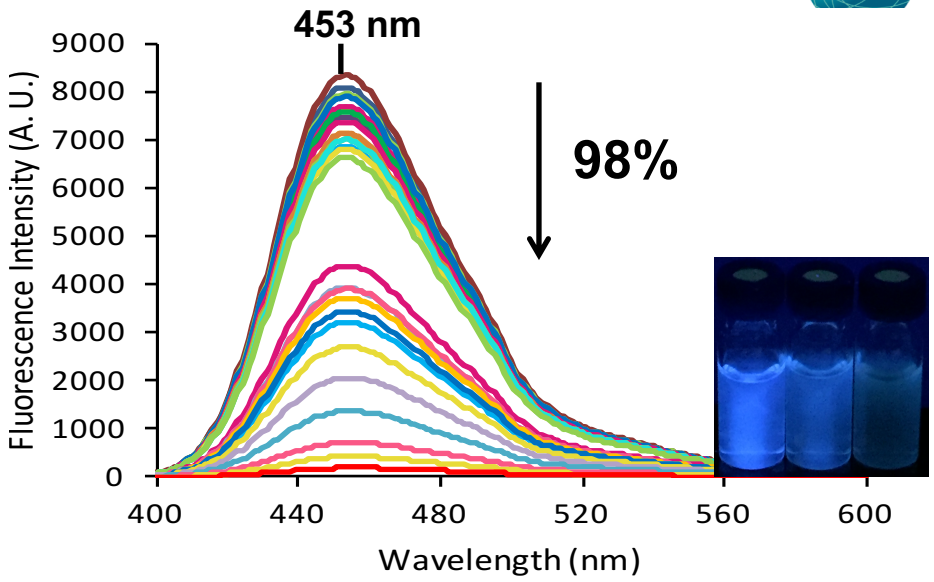


DBA2

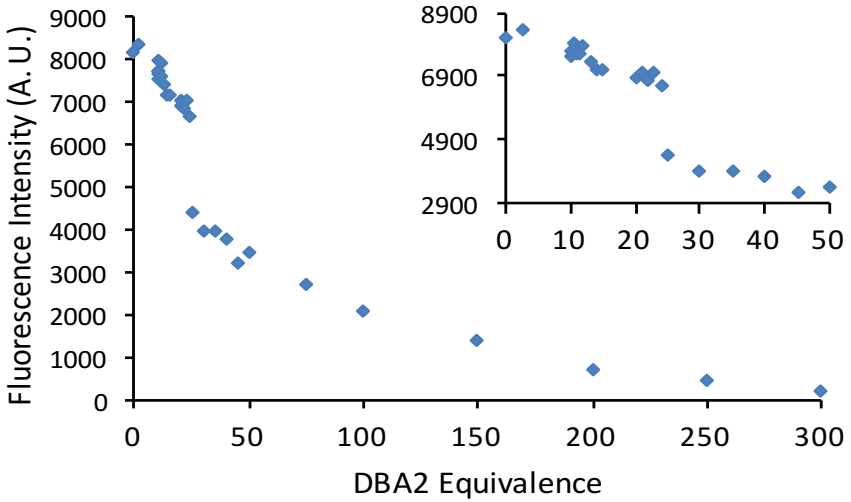
Fluorescence OFF

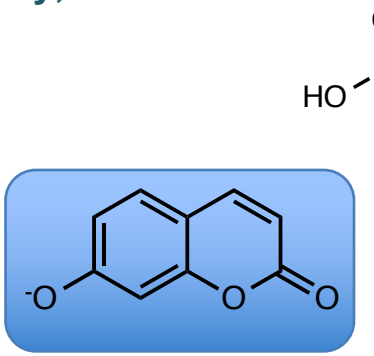
Two-Component Sensing in Solution – Fluorescence Quenching





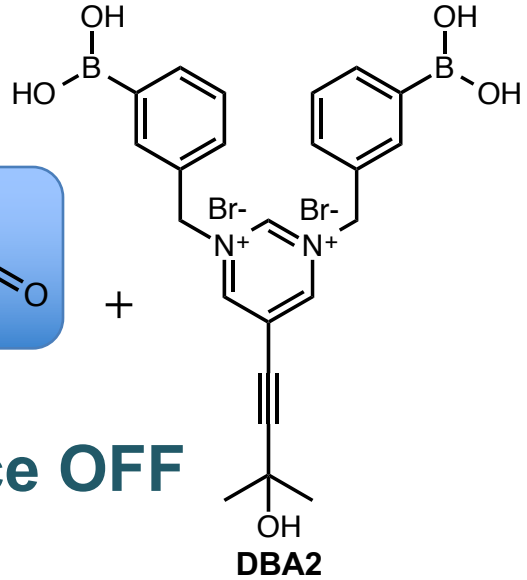
Excitation and emission spectra of 4 µM 7HC in pH 7.4:MeOH (1:1) (pH 8.6) with increasing DBA2 concentrations up to 1.2 mM (300 eq.); Medium sensitivity; 2.5 nm bandwidth





7HC

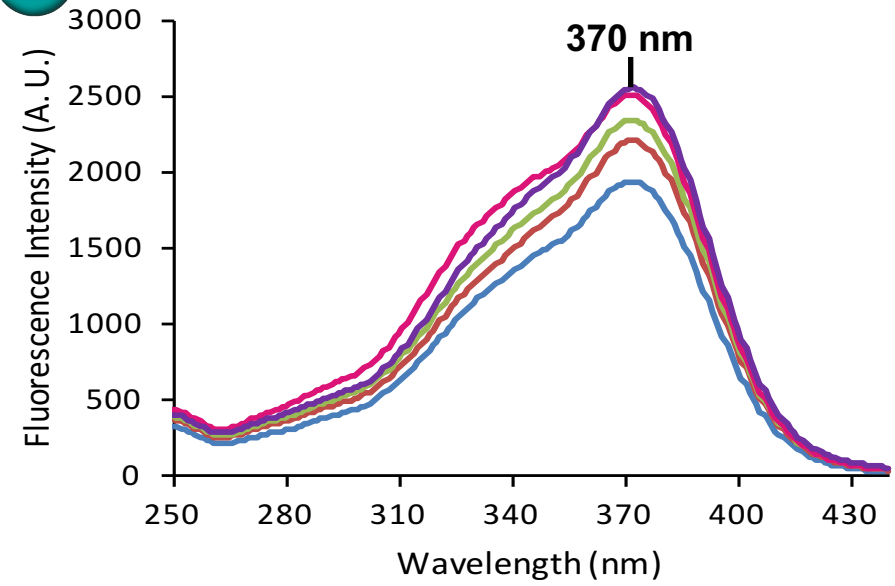
+

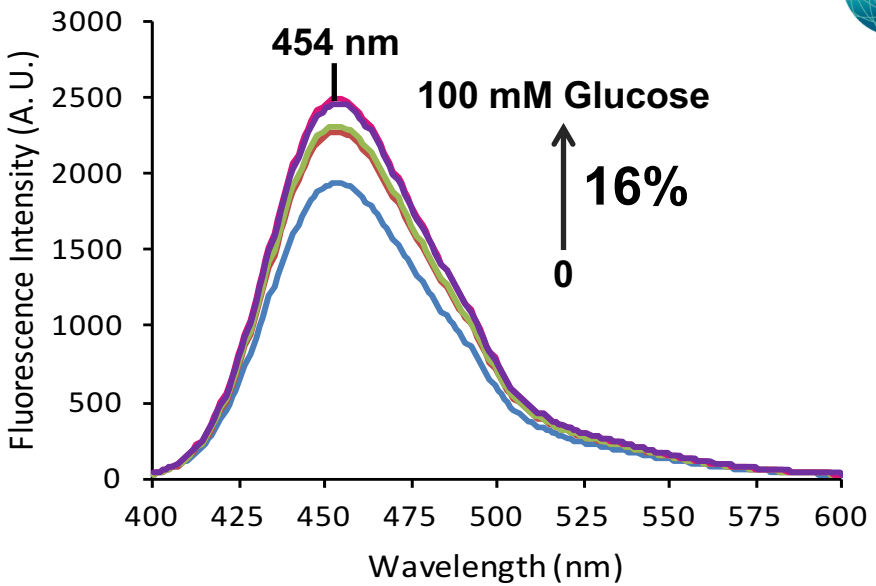


DBA2

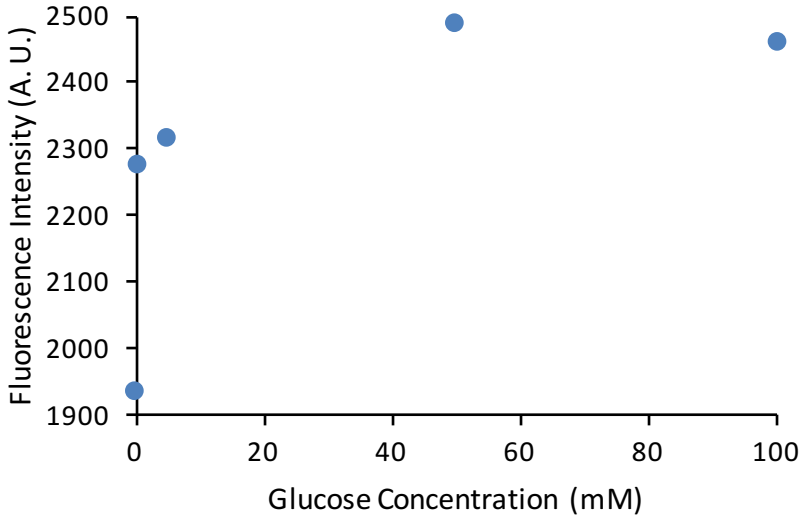
Fluorescence OFF

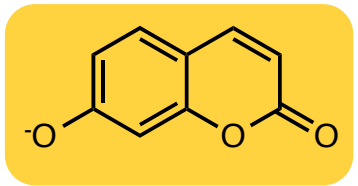
Two-Component Sensing in Solution – Fluorescence Recovery





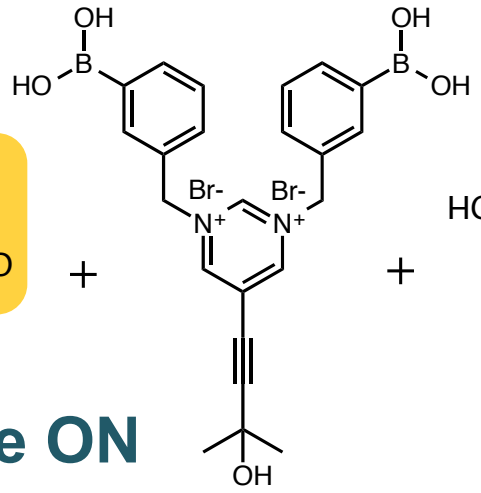
Excitation and emission spectra of 7HC (4 μM) and DBA2 (80 μM) (1:20 eq.) in pH 7.4:MeOH (1:1) (pH 8.6) with increasing concentrations of glucose up to 100 mM; Medium sensitivity; 2.5 nm bandwidth





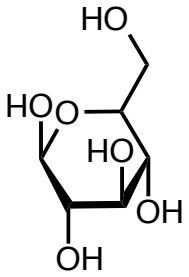
7HC

+



DBA2

+

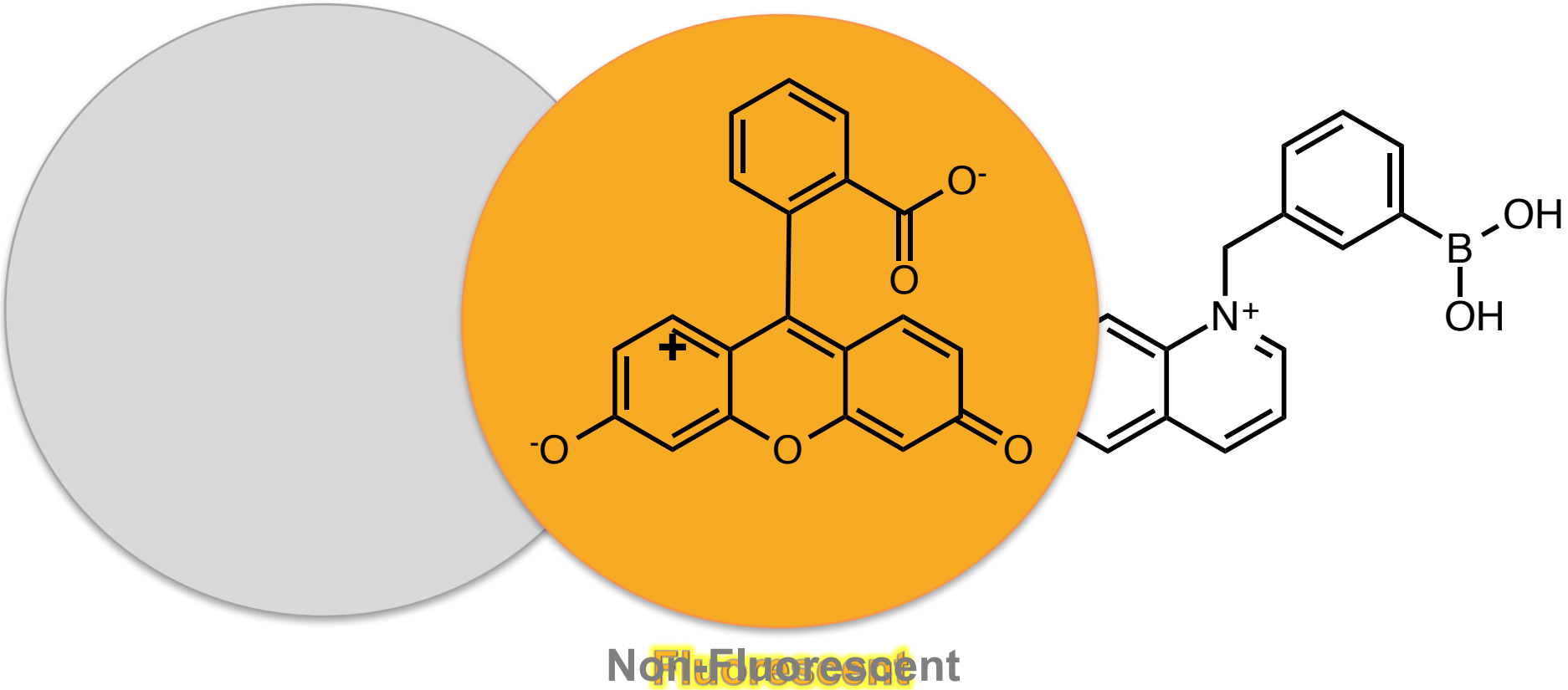


Glucose

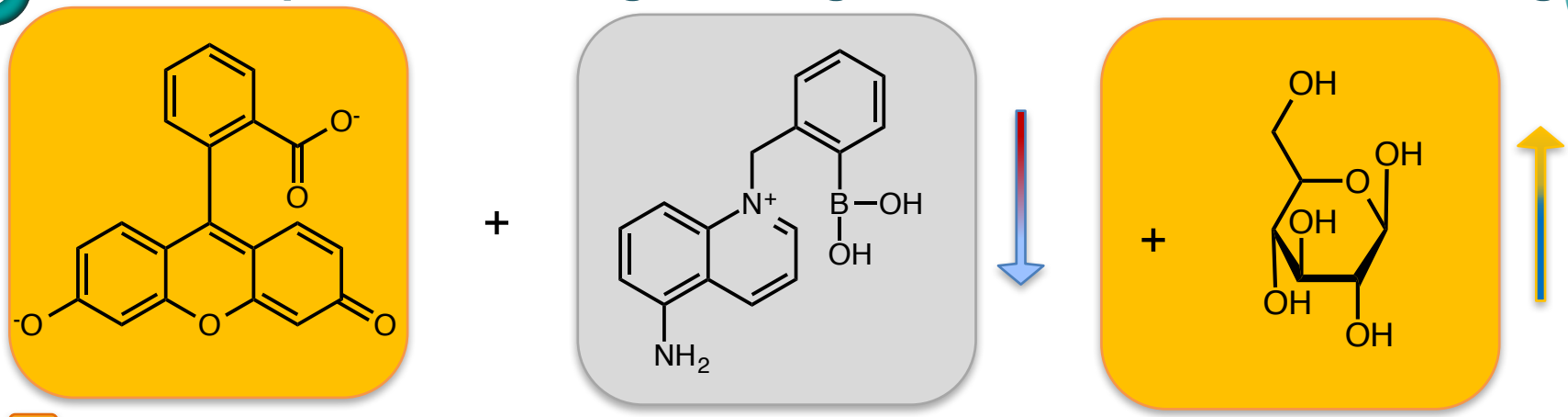
Fluorescence ON

Indirect Sensing in Ionogels

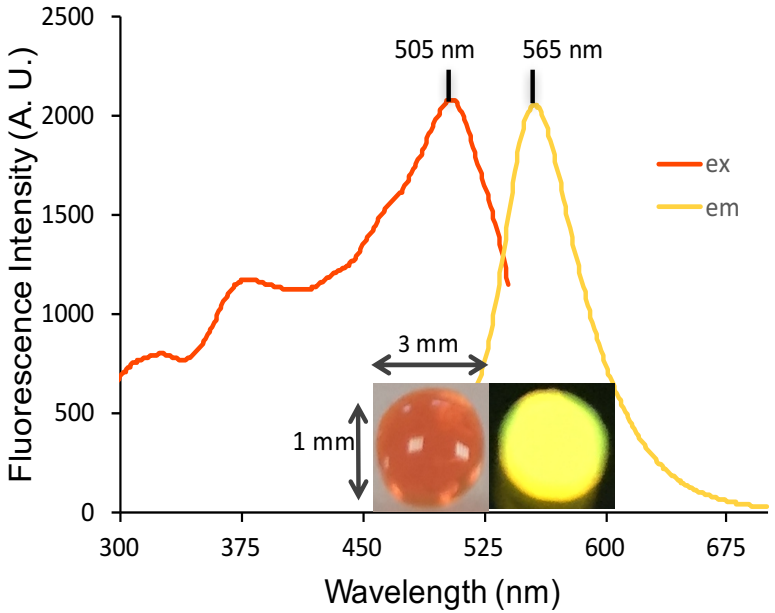
Two-Component Sensing in Ionogels

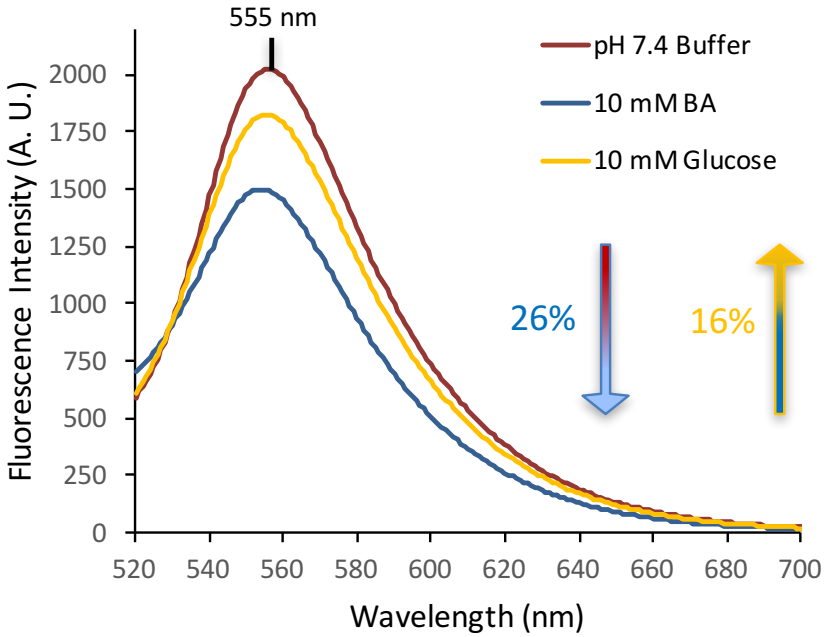


Two-Component Sensing in Ionogels – Fluorescence Quenching



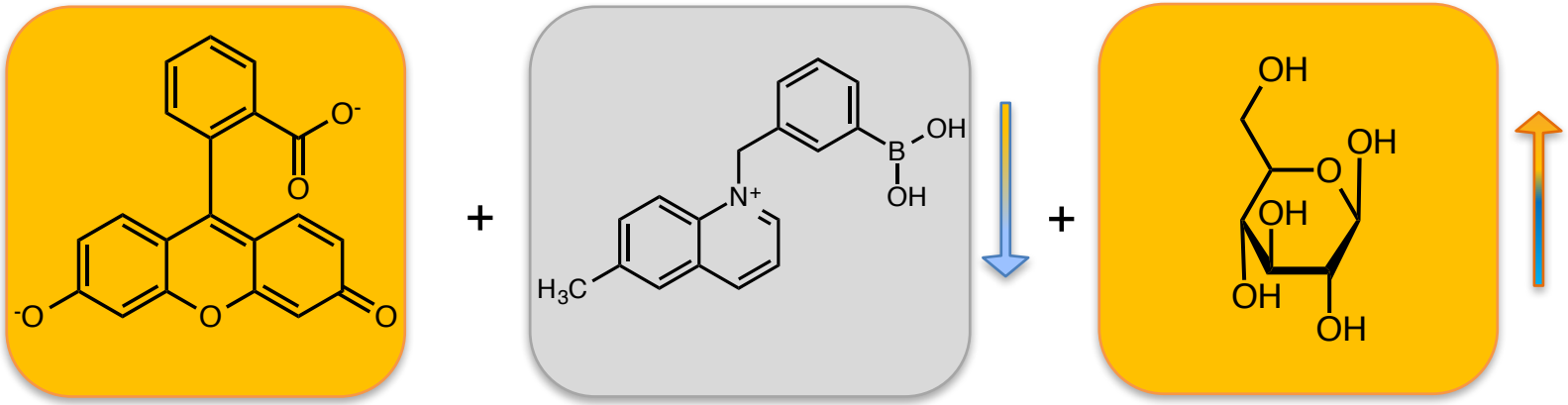
Components for Fluorescence
Components for Fluorescence Quenching



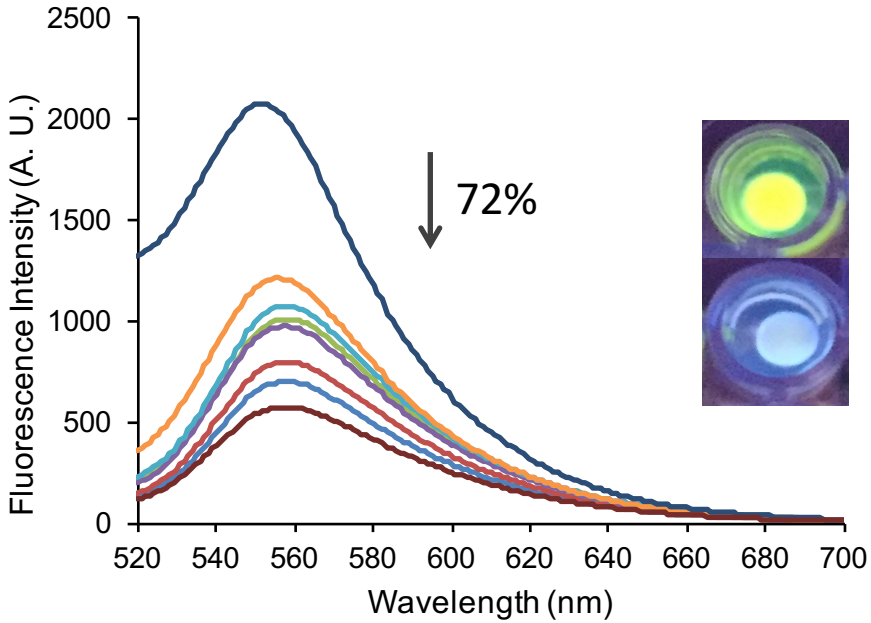


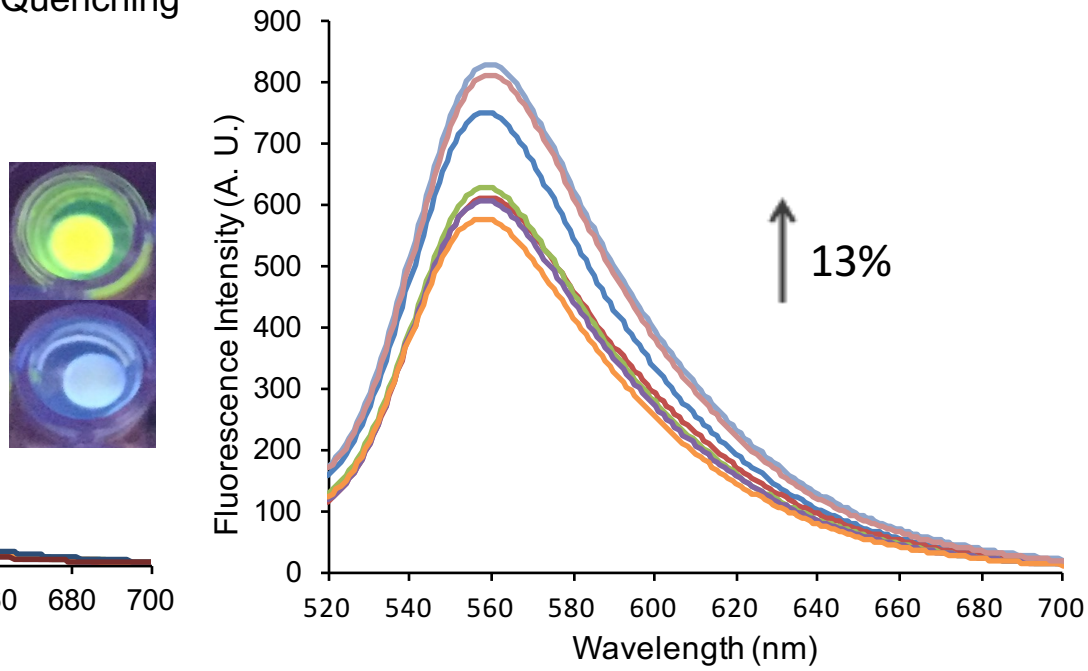
Emission spectrum of the fluorescein ionogel, when immersed in a BA (10 mM) solution and then in a glucose solution (10 mM) demonstrating an increase in fluorescence by 16%.

Two-Component Sensing in Ionogels



Components for Fluorescence
Components for Fluorescence Quenching





Emission spectrum of the fluorescein ionogel, when immersed in a BA (10 mM) solution and then in a glucose solution (44 mM) demonstrating an increase in fluorescence to 40%.

Conclusions

Direct Sensing

- Increased glucose concentrations causes fluorescence quenching in BA.
- -COOH substituent is desired for future anchoring possibilities.

Indirect Sensing

In Solution

- Cationic BA derivative quenches fluorescence of anionic fluorophore and on glucose addition fluorescence can be restored.
- Two-Component Sensing depends on the pK_a of the fluorophore and hence, the pH of the buffer solution.

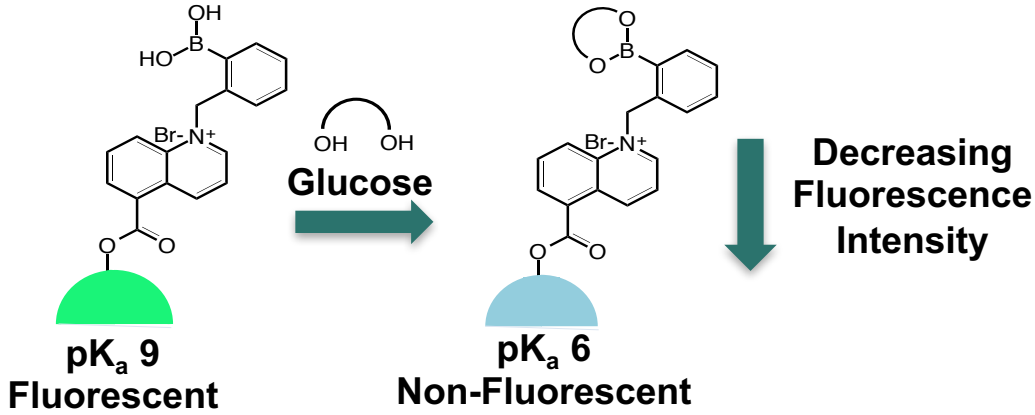
In Ionogels

- When Fluorescein is immobilised: fluorescence decreases in BA addition and is restored on glucose addition.
- Substituents attached to BA play a role in the quenching efficiency.
- Positioning of BA group in *ortho* or *meta* orientation play a role in fluorescence recovery.

Future Work

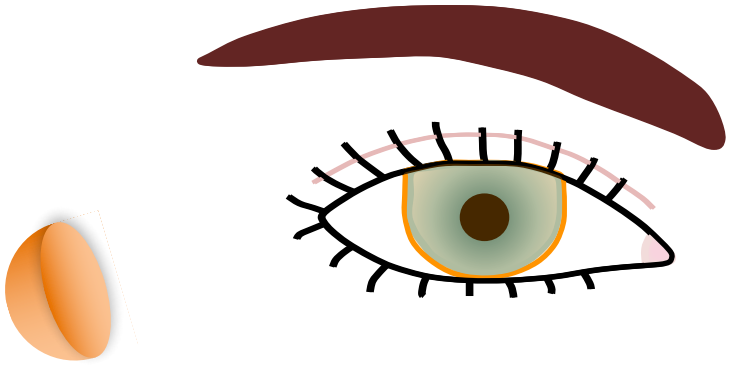
Direct Sensing

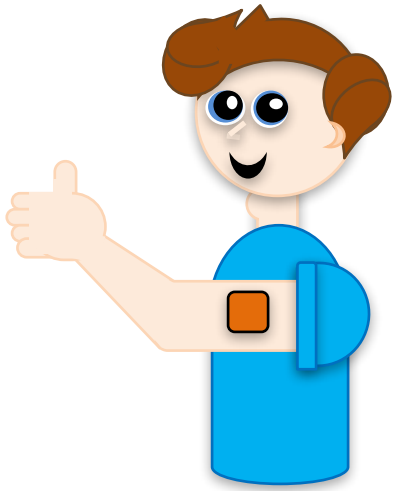
- Immobilisation of the COOHBA sensors on to a lens-like platform.



Indirect Sensing

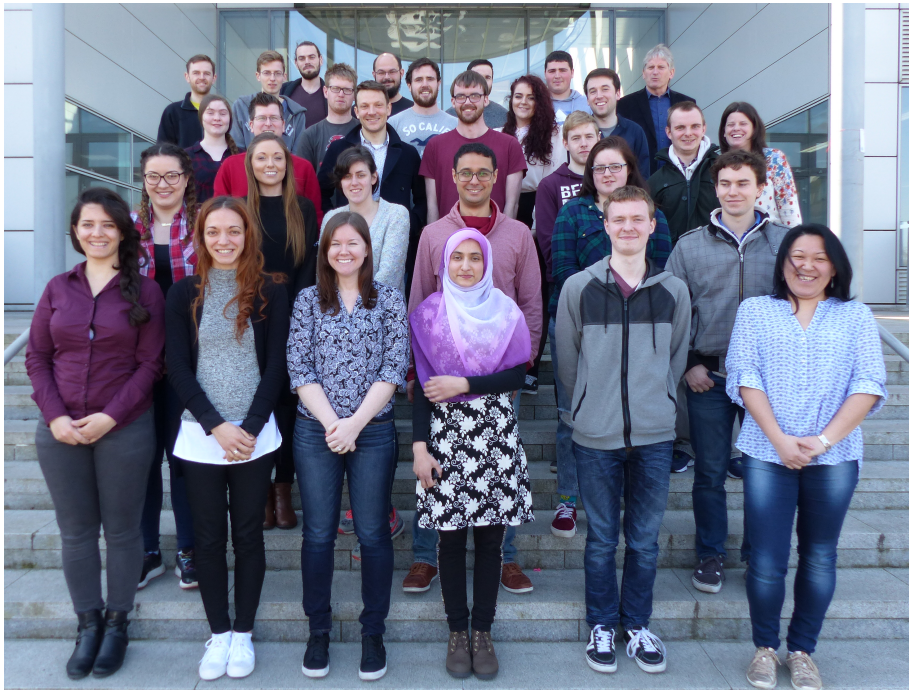
- The incorporation of the two component sensing ionogels in to a sensing platform, such as a hydrogel patch or contact lens, to allow for non-invasive and continuous monitoring of glucose levels in diabetic patients.





Thanks to…..

- In particular Adam McColgan, Dr. Colm Delaney, Dr. Larisa Florea and Prof. Dermot Diamond.
- Alexandru Tudor, Jennifer Deignan, Wayne Francis, Aishling Dunne and Cristiane Daikuzono.
- Science Foundation Ireland & INSIGHT Centre (SFI/12/RC/2289).

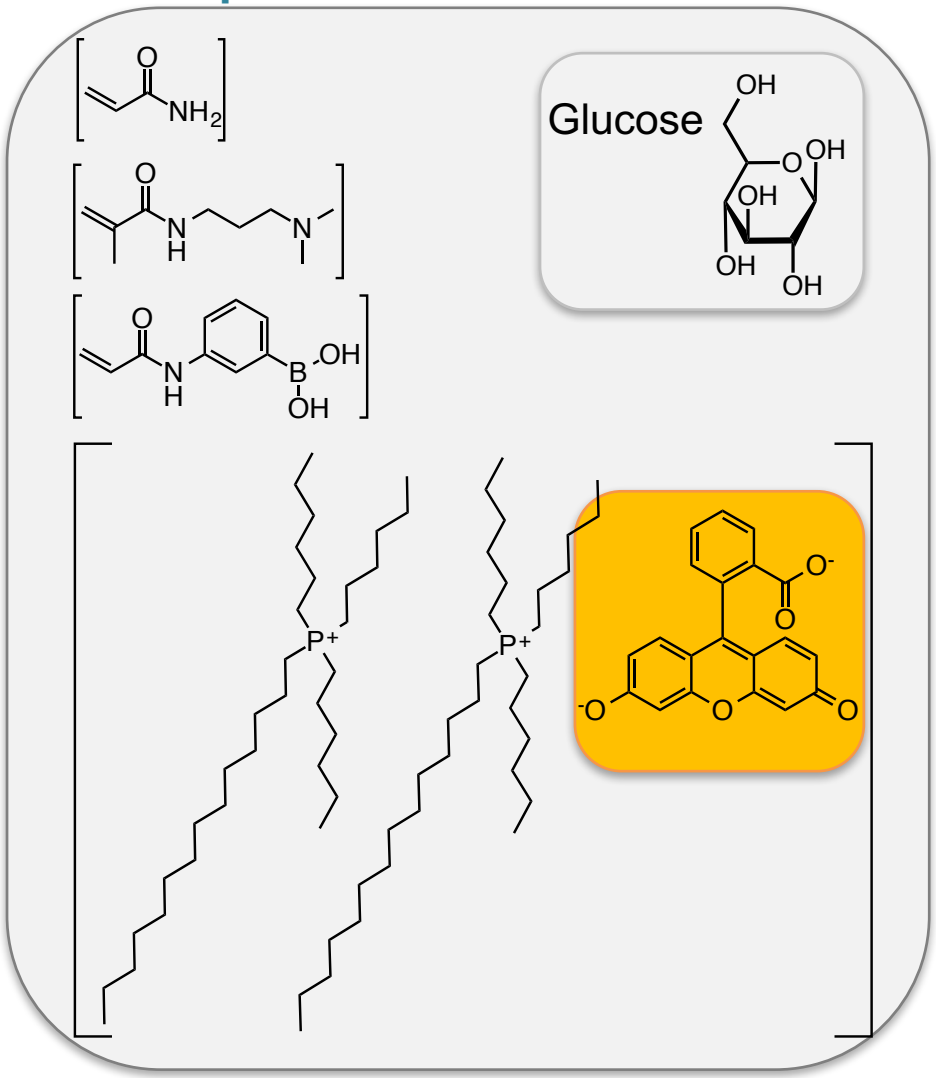


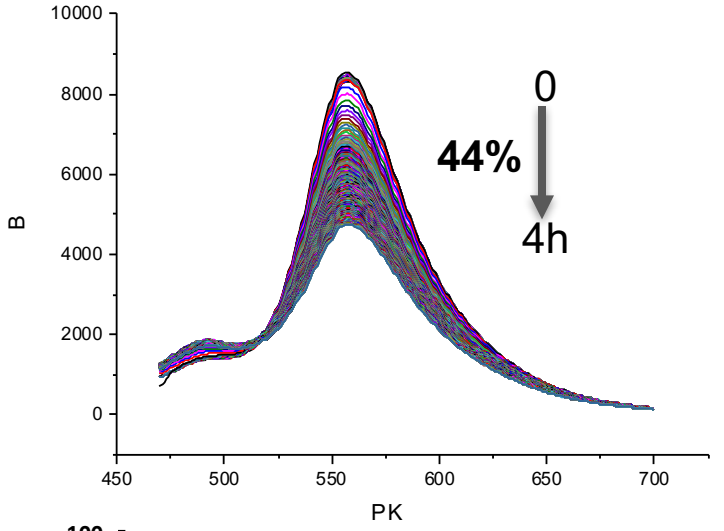
Thank You for Your Attention!

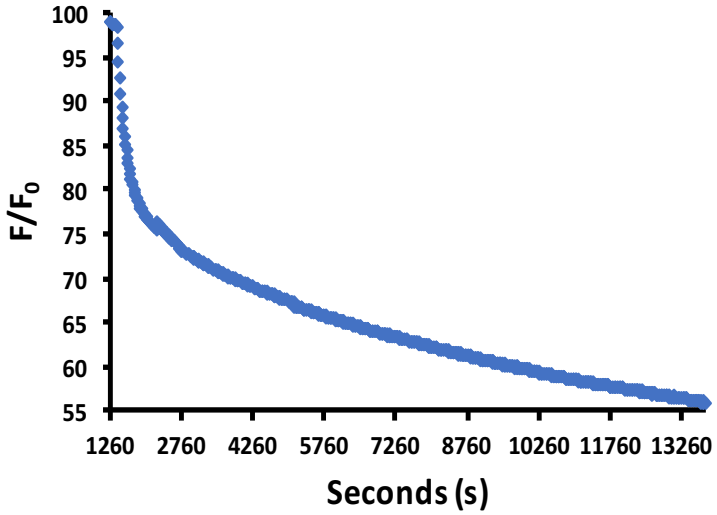
SEVENTH FRAMEWORK PROGRAMME
MARIE CURIE ACTIONS
MASK
Project no: 269302
Materials and Advanced Sensor Knowledge Exchange
OrgBIO
ORGANIC BIOELECTRONICS
NAPES
NEXT GENERATION ANALYTICAL PLATFORMS FOR ENVIRONMENTAL SENSING
COMMON SENSE
MARINE SENSORS - MARINE MONITORING
aquawarn
sfi
DCU
UCC
OÉ Gaillimh
NUI Galway
UCD DUBLIN

Two-Component Sensing in Ionogels

Fluorophore and BA immobilised inside non-fluorescent ionogel matrix







Components for Fluorescence
Components for Fluorescence Quenching