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Closed loop drug monitoring and delivery in intensive care

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Aim and objectives

The aim of this 6 months project is to produce a closed loop control system in which key pharmacological and physiological parameters are monitored in real time and the drug dose altered automatically to optimise patient treatment.

The main objectives are:

1. Synthesis of nanoMIPs for relevant targets (fentanyl, propofol and midazolam);
2. Integration of MIPs with optical fibres (long period grating - OFS);
3. Testing of sensor performance in model samples.

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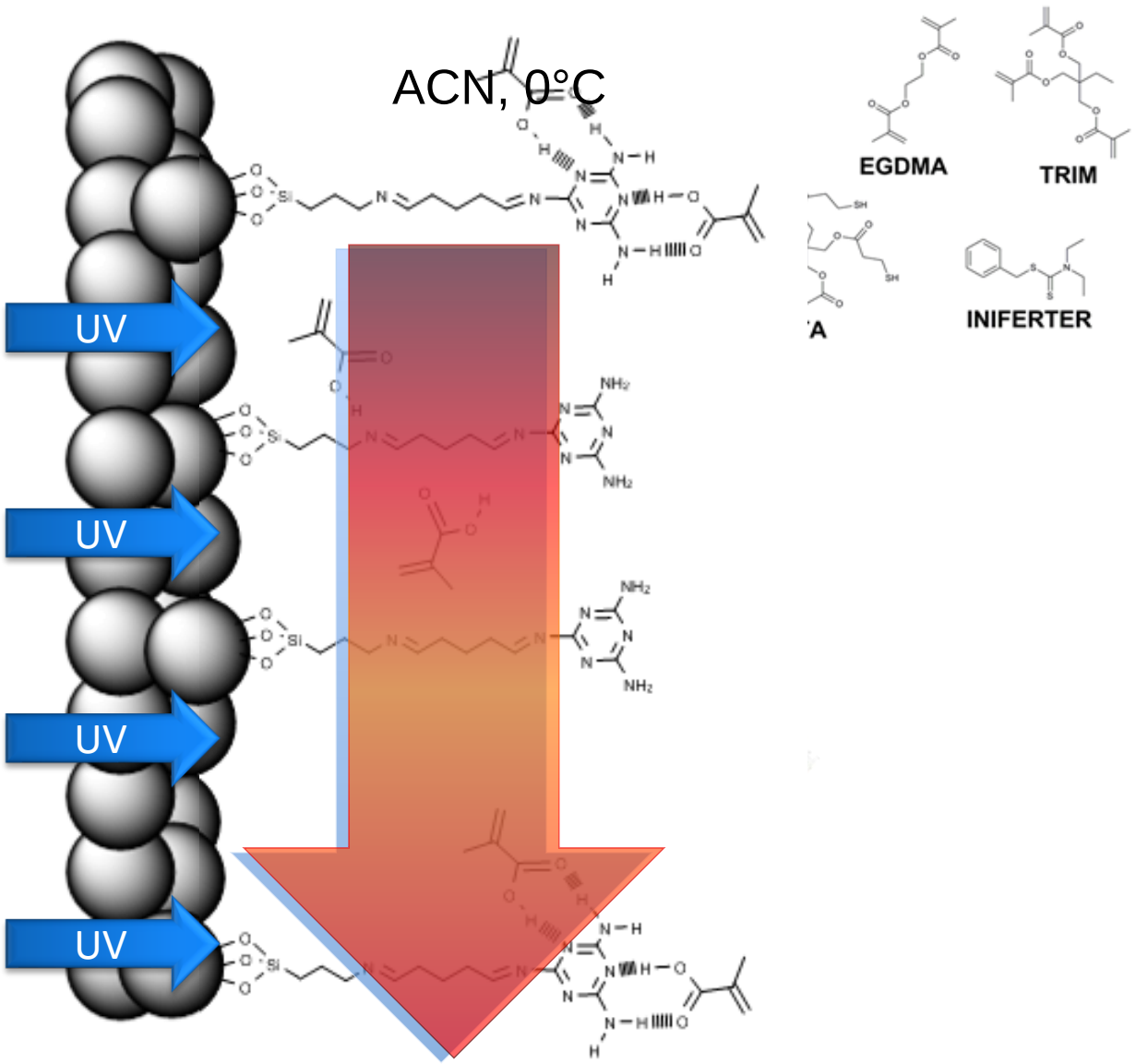
Solid-phase synthesis of nano-MIPs



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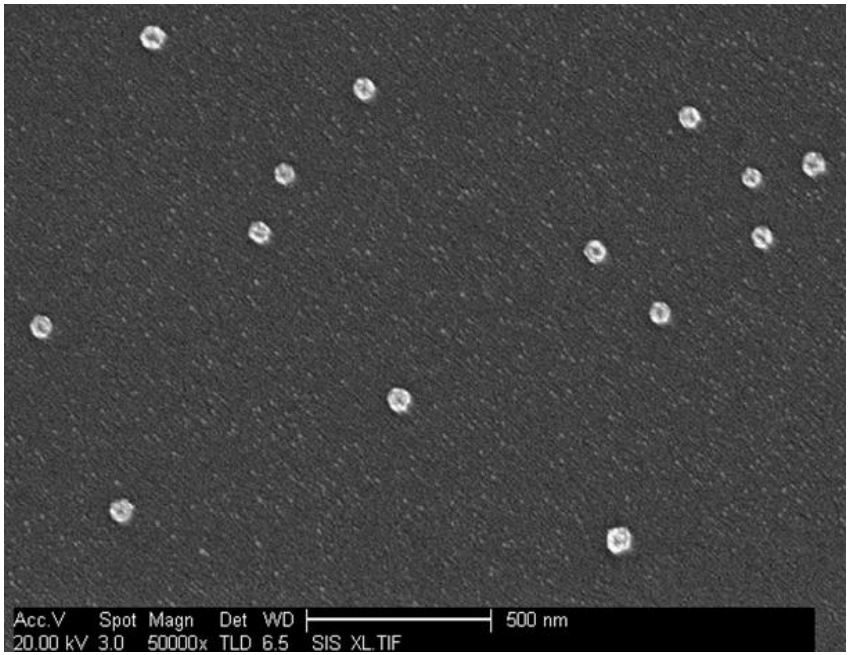
Synthesiser for MIP nanoparticles

Automatic reactor for MIP nanoparticles



- Manufacturing cycle – 3.5 hours
- Yield – 50 mg (can be scaled up)

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Comparison of MIPs and antibodies in ELISA

Template	MIP size, nm	Detecion limit for assay with MIP, nM	Detection limit in assay with antibodies, nM
Biotin	104±6	1.20×10^{-3}	2.54×10^{-3}
L-Thyroxine	164±11	8.07×10^{-3}	17.5
Glucosamine	138±16	4.01×10^{-4}	3.38×10^{-4}
Fumonisin B2	94±4	6.12×10^{-3}	2.5×10^{-2}
Haemoglobin	149±15	8.7×10^{-2}	1.54×10^{-4}
Glycated haemoglobin (“polyclonal”)	103±14	2.46×10^{-3}	-
Glycated haemoglobin (“monoclonal”)*	103±14	9.49×10^{-3}	2.38×10^{-4}

***In contrast to antibodies, ”monoclonal” MIPs had no cross-reactivity for non-glycated haemoglobin**

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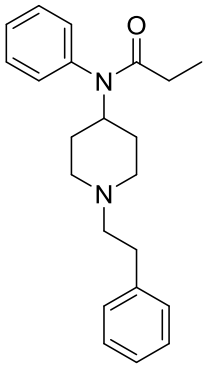
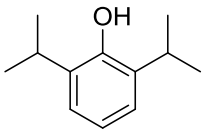
Targets and derivatives

fentanyl



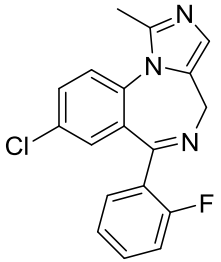
(**1**)

propofol



(**2**)

Midazolam



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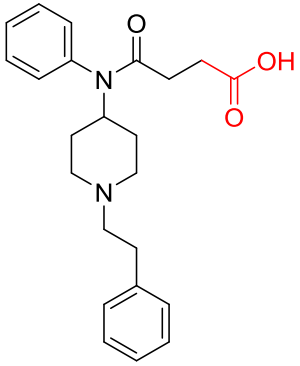
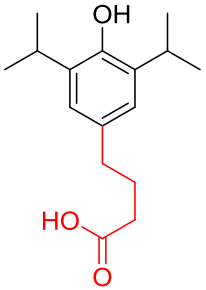
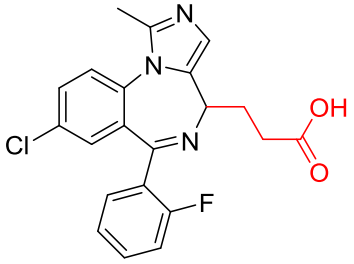


(**4**)



(**5**)



(**6**)

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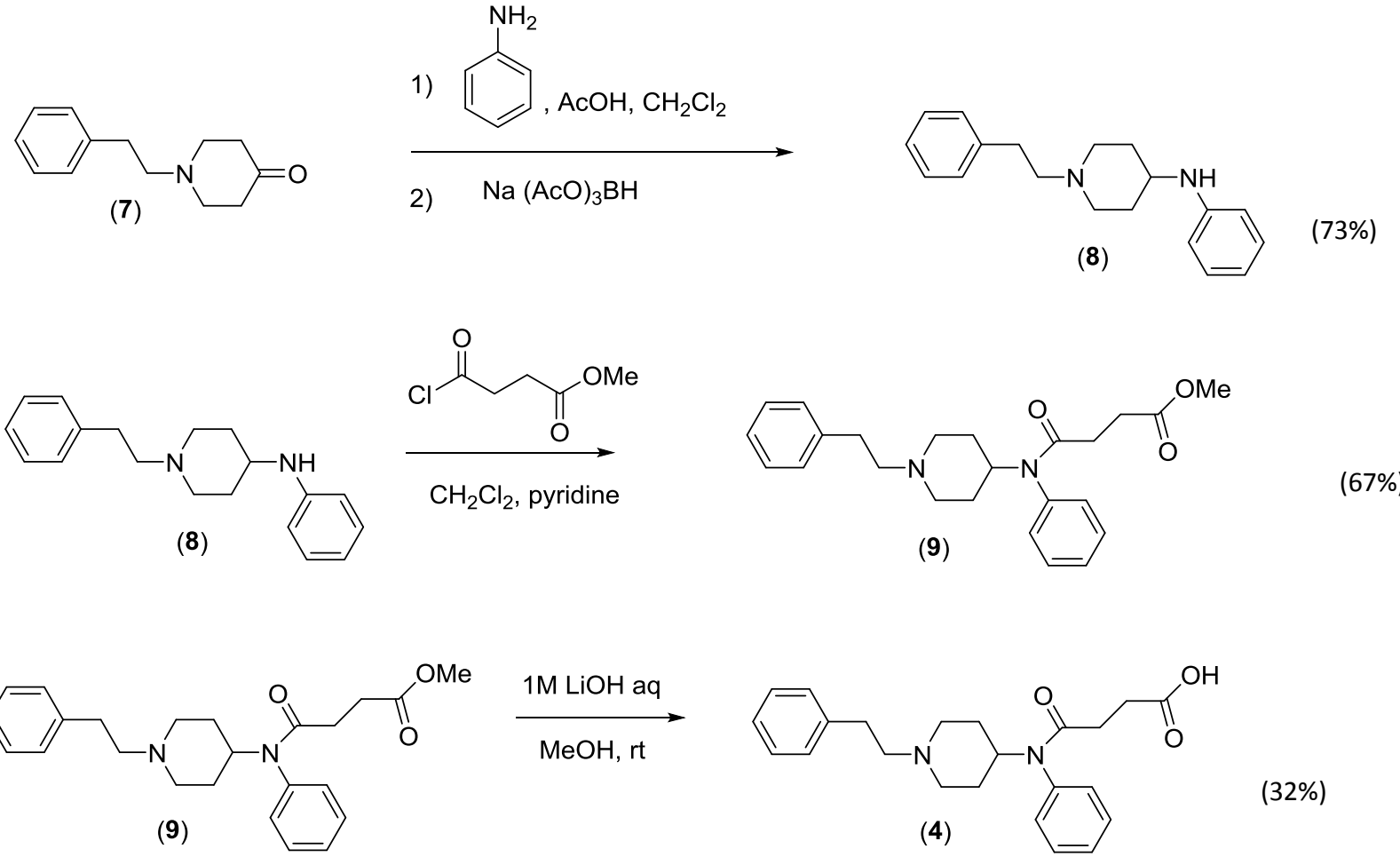
Synthesis of fentanyl derivative



Reaction1: Valdez, C.A.; Leif, R.N.; Mayer, B.P. *PLOS ONE*, 2014, **9**, e108250
Reactions 2 & 3: Bremer, P.T. *et al., Angew. Chem. Int. Ed.* 2016, **55**, 3772-3775 (supporting information).

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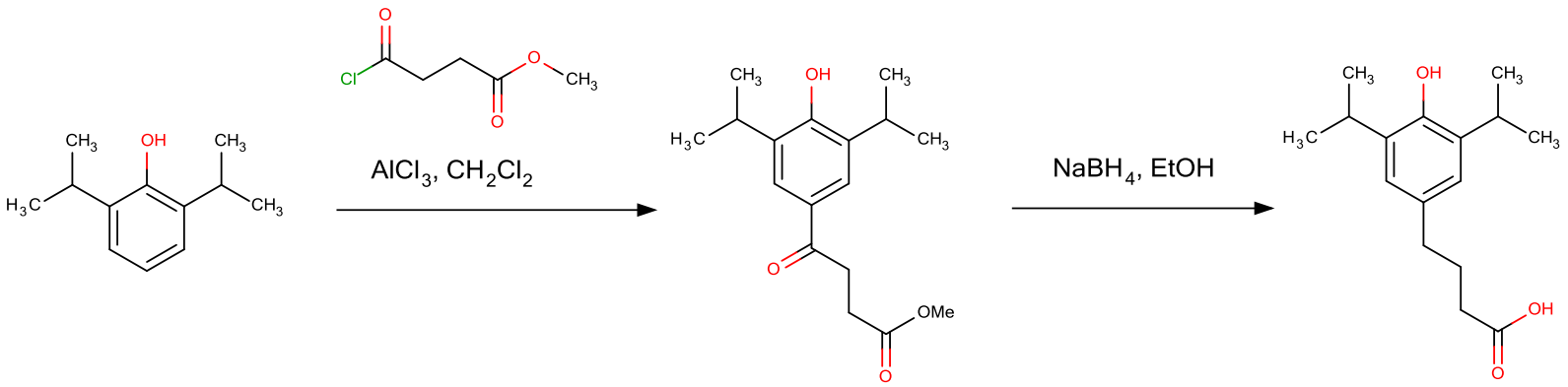
Synthesis of propofol derivative



(~24%)

(70%)

Reaction 1: Adapted from: Pepperberg, D.R. *et al.,* US20130237899A1, Sept 12 2013, p40
Reaction 2: Stewart, D.S . *et al., J. Med. Chem.* 2011, **54**, 8124-8135.

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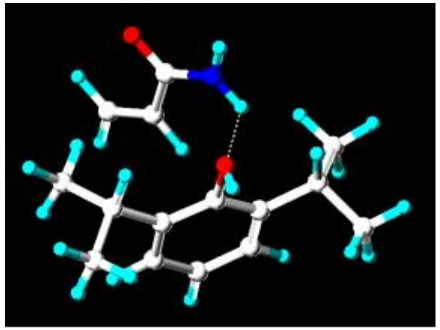
Molecular design of nanoMIPs for propofol

Tripos

SYBYL 7.3™



Selection of monomers based on LEAPFROG

Functional monomer	Binding energy, kcal/mol
Acrylamide	-26.38
TFMAA	-16.29
Itaconic acid	-14.96
Methacrylic acid	-13.63
Vinylimidazole	-6.32

Allows rapid 'dialling' and optimisation of nanoMIPs.
Leads to the selection of monomers displaying strong affinity for the template for polymer preparation.

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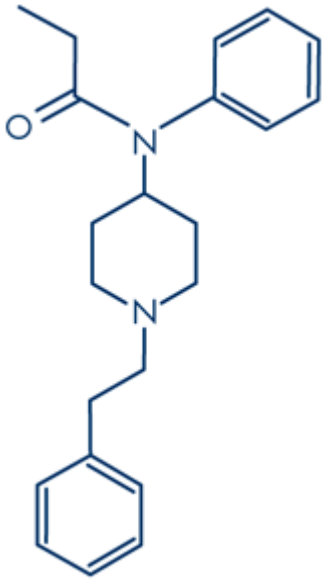
Molecular design of nanoMIPs for fentanyl

Functional monomers	Binding energy, kcal/mol
MBAA	-29.77
Acrylamide	-25.66
Methacrylic acid	-17.19
Itaconic acid	-16.38
EGMP	-16.29
HEM	-14.23



Composition of the nanoMIPs for fentanyl made in organics:
Functional monomers: MAA, HEM, styrene, TFMAA
Cross-linkers: EGDMA, TRIM
PETMP, iniferter, fluorescein
Solvent: acetonitrile

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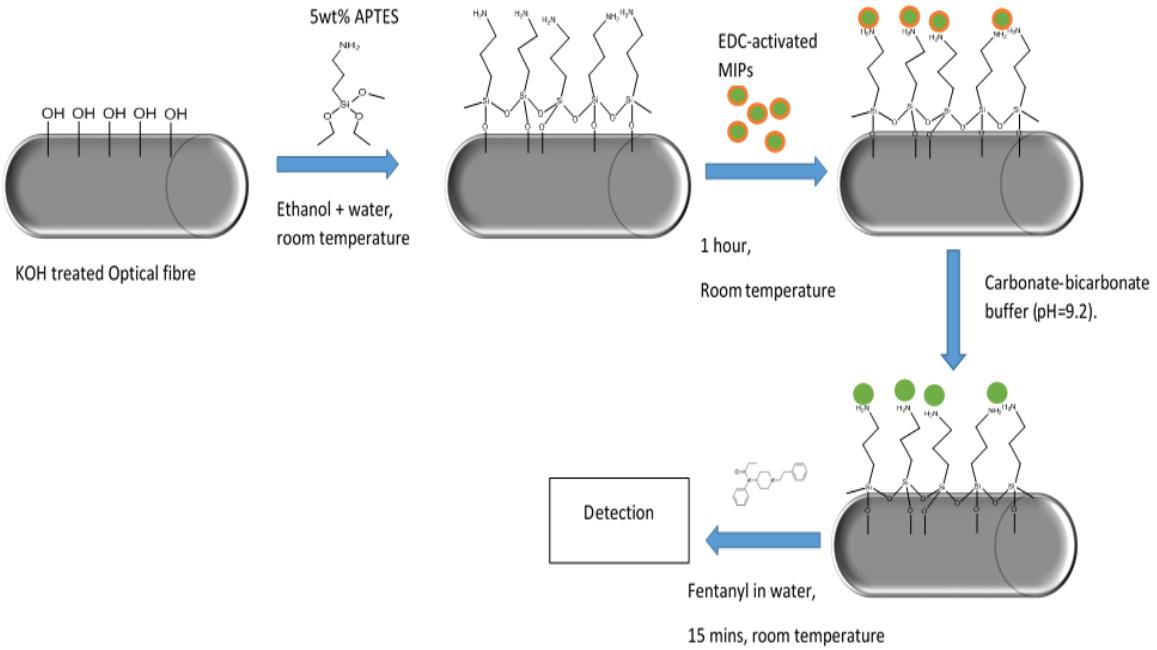
Solid phase synthesis of nanoMIPs

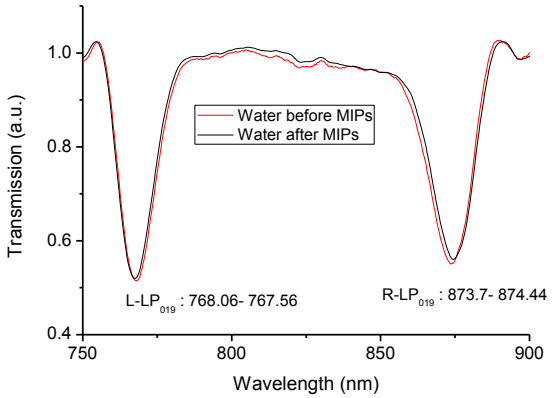
- Immobilisation of propofol derivative onto solid phase (glass beads)
- Preparation of propofol-specific nanoMIPs in water using 30 g of glass beads with immobilised propofol

Monomeric mixture:
19.5 mg of *N*-isopropylacrylamide (NIPAm)
3 mg of *N,N'*-methylene-bisacrylamide (MBAA)
15 mg of *N*-tert-butylacrylamide (TBAm) dissolved in ethanol
50 µL of the solution of 22 mg/mL of acrylic acid in water
3 mg of 3-aminopropyl methacrylate
3 mg of polymerisable rhodamine
50 mL of phosphate buffered saline (PBS)
Initiator: 12 mg of potassium persulfate and 6 µL of TEMED in 400 µL of water

- Deoxygenation by purging with N_2 for 20 min
- Chemical polymerisation for 1 h
- Washing of unreacted monomers and low affinity nanoparticles
- Elution of high affinity nanoparticles using hot water
- Dialysis of high affinity nanoparticles and their characterisation using DLS

OFS functionalisation





The attachment of MIPs on Optical fibre can be confirmed by the shift of wavelength (1.24 nm in total).

However, the dynamic binding of MIPs cannot be observed

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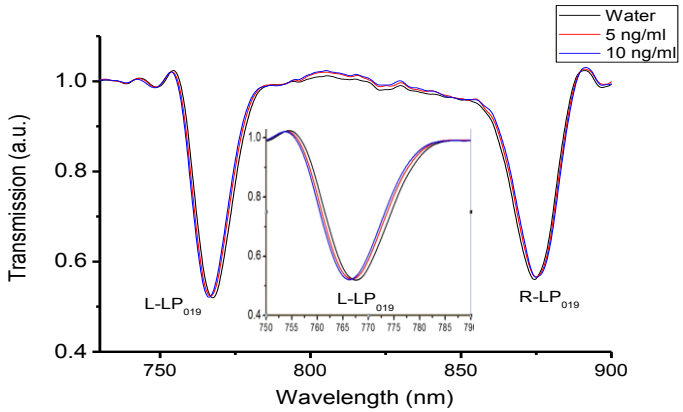
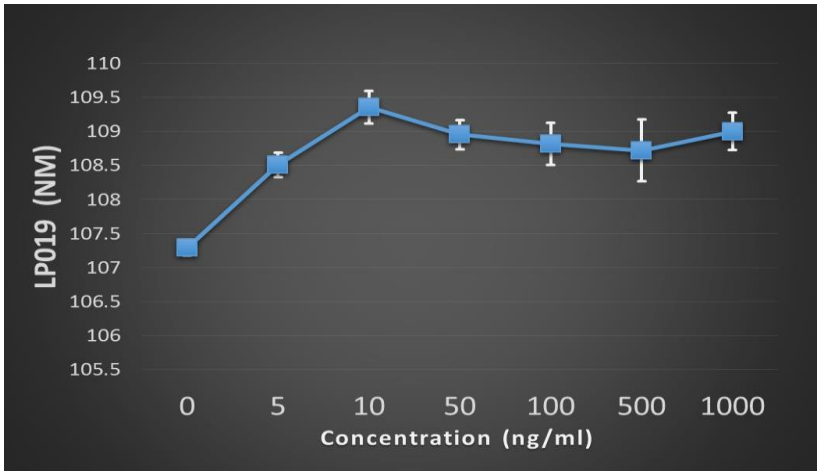
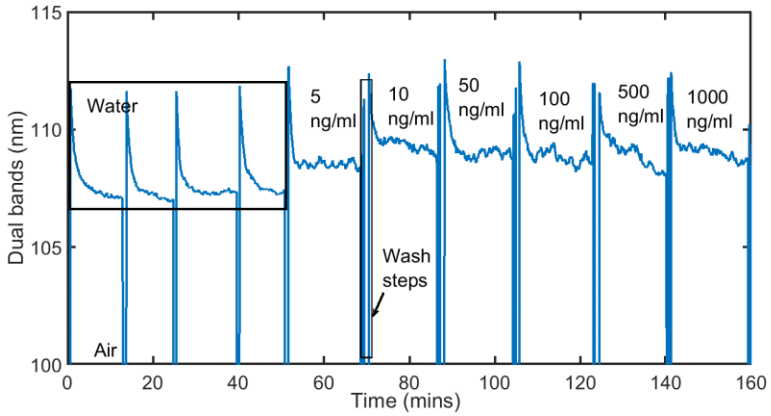
Fentanyl detection







Fentanyl power was dissolved into distilled water with concentration range from 5 ng/ml to 1 mg/ml.
LPG sensor was initially tested with blank sample (distilled water for 4 times in order to evaluate the sample infusion error and turns out the infusion error can be neglected) then subsequently immerse the sensor into different concentration of fentanyl solution from a low to high order with three times washing with distilled water between each concentration.

Room temperature during test : 26.98 ± 0.14 ℃

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Future work

- Optimisation of sensor performance for fentanyl and propofol detection in spiked samples;
- Analysis of detection limit and specificity of sensor response;
- Analysis of sensor regeneration conditions;
- Testing of sensor performance over 3 months period.