wellcome centre anti-infectives research

Capacity Building in Drug Discovery

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Introduction

The Wellcome Centre for Anti-Infectives Research (*W*-CAIR) was established in 2017 at the University of Dundee. We combine the Drug Discovery Unit (DDU), Parasitology, and Mode of Action teams. We bridge the gap between research and drug development. Our staff work to industry standards in early stage, small molecule drug discovery. They translate world-class biology into novel drug targets and candidate drugs.

Our staff are highly experienced scientists from industry or academia. They have supported the delivery of 66 clinical candidates and 10 marketed drugs.

Strategic Vision

Our vision is to turn research into candidate medicines. We exploit innovative and unexplored therapeutic targets with new scientific techniques. We aim to train scientists in all aspects of Drug Discovery. This will incorporate Medicinal Chemistry, Biology and Drug Metabolism and Pharmacokinetics (DMPK).

DDU Portfolio and Achievements

More than half the world's population is at risk from infectious diseases. Anti-infective treatments are often unsafe, lengthy, expensive and difficult to administer due to side-effects. These drugs are becoming increasingly ineffective as many organisms develop resistance.

Malaria

A Medicines for Malaria Venture (MMV) funded project identified promising antimalarial compounds. After optimisation, one series delivered a potent anti-malarial candidate compound in rodent disease models. This candidate has the potential to prevent, cure and block the transmission of the parasite in a single dose. MMV included this candidate in their clinical development portfolio. Partnering with Merck-Serono, it has recently commenced phase I clinical trials (September 2017).

W-CAIR is part of the Structure-guided Drug Discovery Coalition (SDDC). This is funded by the Structural Genomics Consortium, with support from the Bill & Melinda Gates Foundation. This coalition uses validated molecular targets to work on structure-based drug discovery.

Tuberculosis (TB)

Our TB work is funded by the Bill & Melinda Gates Foundation and The Wellcome Trust. Our team is part of the international TB Drug Accelerator which collaborates with TB experts and pharmaceutical companies e.g. GlaxoSmithKline (GSK), Eli Lilly, Bayer, and AbbVie. This collaboration works to identify pre-clinical drug candidates.

Kinetoplastid Diseases

Funded by The Wellcome Trust, our Kinetoplastid programme runs in collaboration with GSK. In particular their Kinetoplastids Discovery Performance Unit in Tres Cantos, Spain. Together our research aims to develop new medicines for the following diseases:

Visceral leishmaniasis: We have developed high throughput screening assays to identify compounds that kill leishmania parasites. Compounds have been identified which are active n visceral leishmaniasis in rodent disease models. These compounds are at least as good as current treatments. One of these compounds was selected as a pre-clinical candidate .

Another compound from the collaboration, fexinidazole, has been selected for Phase II clinical trials.. The Drugs for Neglected Tropical Diseases initiative (DNDi) are supporting this clinical trial in Africa.

Chagas' disease: We have developed a chemical series of compounds whose oral activity in a mouse model is comparable to that of the existing, but toxic, drugs. Follow on work has ensured that our compounds use effective modes of action.

Human African Trypanosomiasis (HAT): N-myristoyltransferase (NMT) has been validated as a novel drug target for HAT. We have also developed potential pre-clinical candidates for Stage 1 disease. Further compounds from a phenotypically active series are being developed for animal African trypanosomiasis (AAT). These compounds have cured cattle of AAT and trials are ongoing in South Africa in collaboration with GALVmed.

Discovery Portfolio

The pharmaceutical industry is facing serious pressures. There is the potential loss of $64-100 billion of revenue as key drugs lose patent protection and new drug approvals are decreasing. These mean that conventional approaches to drug discovery must change.

The pharmaceutical industry has responded by increasing partnering and in-licensing activity. They haveintroduced innovations in the drug development process such as computational and informatics technology. Rationalisation of early stage research and development is also helping. They realise that development opportunities may arise from smaller biotech companies and academia. It is often less expensive to work with these projects than to start a new internal drug discovery programme. The W-CAIR Drug Discovery Unit works to the high standards expected of the pharmaceutical industry.

Papers of interest

Baragaña, B. et al., (2015) A novel multiple-stage antimalarial agent that inhibits protein synthesis. Nature 522: 315 – 320.

Wyllie, S., et al. (2012) The anti-trypanosome drug fexinidazole shows potential for treating visceral leishmaniasis. Science Translational Medicine, 4, 119

Frearson et al., (2010) N-myristoyltransferase inhibitors as new leads to treat sleeping sickness. Nature, 464 (7289), 728-732.

Brand et al., (2012) Discovery of a Novel Class of Orally Active Trypanocidal N-Myristoyltransferase Inhibitors. J Med Chem, 55(1), 140–152.

Building Capacity through Training

W-CAIR trainers are from the disciplines of Medicinal Chemistry, Biological Sciences and Drug Metabolism and Pharmacokinetics (DMPK). They will provide bespoke theoretical and practical training to visiting scientists. This may include learning new skills or a refresher of existing skills in a new lab. We hope our visitors will take this knowledge back to their home institutions and share it with their colleagues.

To help us provide the best training possible, we will need to assess your understanding of key areas. This will allow us to tailor your experience in Biology, Chemistry and/or DMPK at W-CAIR. Upon arrival you will be assigned a trainer to guide you through your placement.

On the following pages are a series of questions in Medicinal Chemistry, Biological Sciences and DMPK. Please answer the questions without the use of reference material. It is not important that you attain the correct answer, these questions are designed to assess your understanding and allow us to personalise your training. If you do not understand a question or cannot answer, please say so.

Synopsis of the Training

Medicinal Chemistry/ Computational Medicinal Chemistry: how to synthesise new chemical entities (NCEs) which are used to explore novel druggable targets.

Biological Sciences: how to set up validated assays to probe novel druggable targets with the new chemical entities (NCEs).

Drug Metabolism and Pharmacokinetic Sciences (DMPK): how to set up assays to find out the fate of the NCEs in the body and time course of the NCEs through the body.

All of the resources listed below will be employed to give the trainee a rounded approach to Drug Discovery:

- Experience of working across a wide range of disease areas, including: cancer; inflammation; CNS diseases; anti-infectives; metabolic diseases; respiratory diseases
- Selection of targets
- Assessment of druggability using a wide range of hit discovery technologies
- Multiple hit discovery strategies and development of suitable assay formats
- Computational methodology for rapid analysis, definition of hit progression strategies and selection of compounds for purchase or synthesis of compounds
- Systems for parallel synthesis and purification of designed compounds
- Characterisation of compounds in a broad range of primary and secondary biological assays
- High throughput screening techniques
- Orthogonal biological assays utilising biophysical methods and cell culture techniques
- Compound optimisation based on pharmacokinetics (PK), pharmacodynamics (PD) and physicochemical parameters, including safety pharmacology data

DMPK Laboratory Skills assessment Test

Question 1

You are required to make a 50µM phosphate buffer pH 7.4 ; How will you make this buffer and how will you ensure that your pH is correct? Show your calculations for preparation of your buffer.

M.Wt of the acid is 141.96 and formula is NaH_2PO_4

M.Wt of the base is 137.99 and formula is $Na_2HPO_4.H_2O$

Question 2

You are required to perform an incubation that has a final volume of 500µL. You have been given the following information: The microsomal protein concentration must be 0.5mg/mL, the concentration of the substrate must be 0.5µM and the cofactor (NADPH) must be 1.0mM. The stocks of protein is 20mg/mL, the substrate comes as 10mM in DMSO solution and NADPH was given as 10mM. You are to use the buffer from Question 1 for your media. Show how you will prepare the incubation media

Question 3

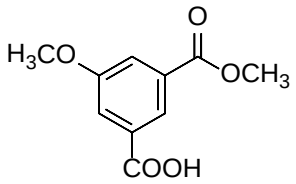
You have been given your microsomal CYP 450 enzyme activity as 2mL/min/g of liver weight and you were also supplied with the information that each g of liver contains 52.5 mg of microsomal protein. Could you please express your enzyme activity as µL/min/mg microsomal protein?

Question 4

You are requested to dose a mouse at 10mg/kg orally and that the dose volume is to 10mL/kg. What will your dose concentration be in mg/mL? How will you correct for the free base if the compound was made as the mono HCl salt: M.Wt is 36.5g? The M.Wt of the salt is 365g.

Question 5

You were supplied with the compound shown below, could you predict, explain and draw the structures of any possible predicted metabolite(s)?



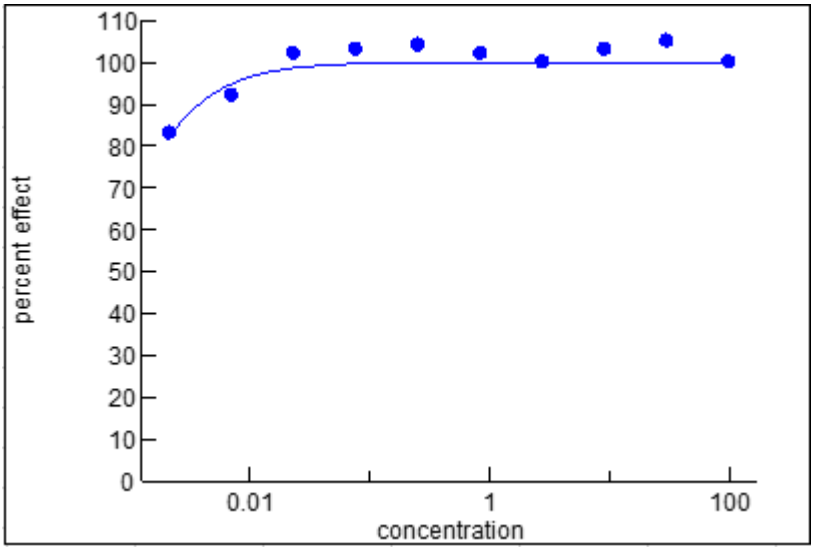
Biology Laboratory Skills assessment Test

Question 1

If your stock solution is 500mM, how would you prepare a 2mM dilution in 10ml?

Question 2

If you observed the following result in a dose-dependent test, what would your next experiment be?



Question 3

How many nanolitres of a 10mM stock compound would be required to give a final concentration of 30uM in a 15µl assay?

Question 4

Your screen uses forty 384 well plates per run; the liquid dispenser tubing you use has a 'dead volume' of 10ml; how much reagent would be required to add 7.5µl to each well on this run?

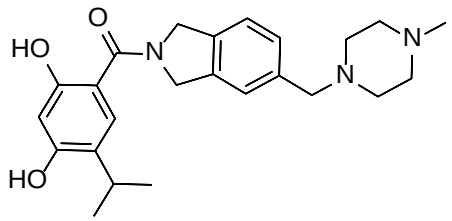
Question 5

You have developed a fluorescence-based assay and have found some interesting compounds. How would you confirm that these compounds are active against your target?

Medicinal Chemistry Laboratory Skills assessment Test

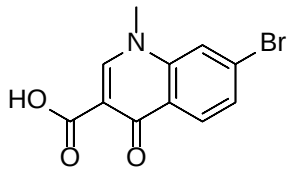
Question 1

A. Provide a retro and forward synthesis for the compound below
B. Can you identify any potential liabilities with the compound below?



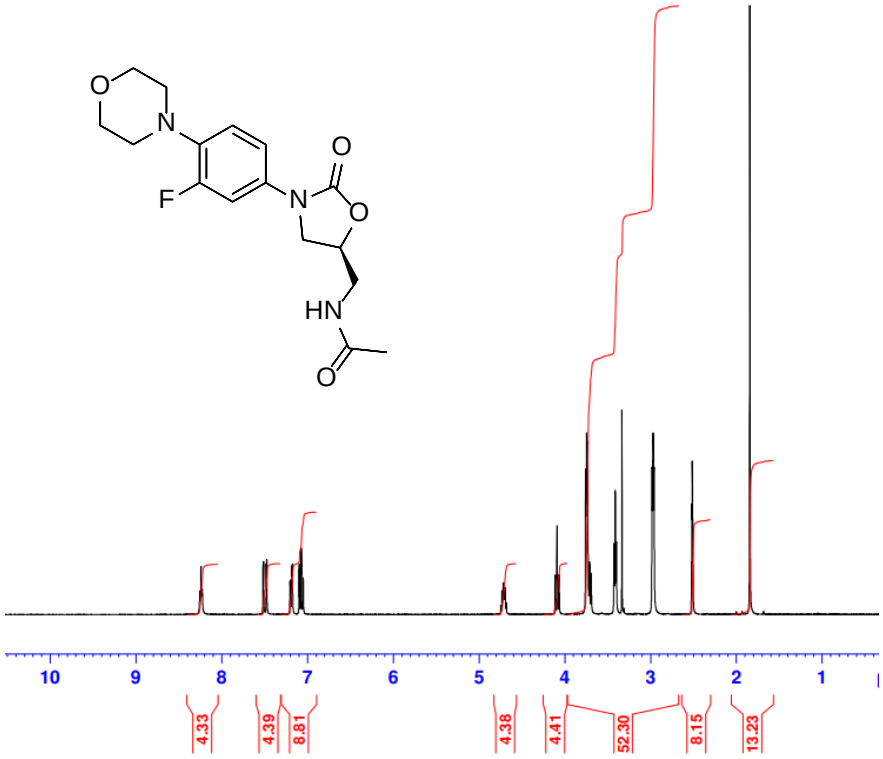
Question 2

List the reactions that could be carried out using the building block below



Question 3

Assign the protons in this 1H NMR of Linezolid run in d6-DMSO?



Question 4

To screen your compound you have been asked to make up 500 μL of a 10 mM solution in DMSO. The molecular weight of your compound is 325 how much would you need to weigh out to make up your stock solution?