Project Details	
Project Code	MRCIIAR26Ca Pertusati
Title	Identification of novel antifungals: Synthesis, structure-activity correlation, and antifungal activity of novel molecular scaffolds from repurposable drugs.
Research Theme	IIAR
Project Type	Wet lab
Summary	Fungal infections are a major threat to public health as they are becoming increasingly resistant to treatment. Only four classes of antifungals are available, with few candidates in the clinical pipeline. Fungal diseases can also damage plants and crops, causing major losses in agricultural activities and food production. The discovery of new antifungals is therefore an urgent need. From a small library of molecules, we have identified two classes of compounds (including an approved drug) with antifungal effect, and we aim to improve their activity via structure-activity-relationships. Identification of drug's biological target is also a goal for this project.
Description	**Background:** Antimicrobial (antibiotics, antifungals, and antiparasitic drugs) resistance (AMR) is one of the top global public health and development threats. AMR was directly responsible for 1.27 million global deaths in 2019 and contributed to 4.95 million deaths. The emergence and spread of drug-resistant pathogens threaten our ability to treat common infections and to perform life-saving procedures including cancer chemotherapy, organ transplantation and other surgeries. Drug-resistant infections impact the health of animals and plants, reduce productivity in farms, and threaten food security. Invasive fungal infections (IFIs) are a significant cause of morbidity and mortality worldwide, leading to an estimated 1.5 million deaths per year. WHO published a report highlighting the first-ever list of fungal "priority pathogens" – a catalogue of the 19 fungi that represent the greatest threat to public health. 20 fungal species are responsible for more than 99% of human fungal infections. IFIs are often life-threatening and associate with high mortality in immunocompromised hosts and patients undergoing organ transplants. Clinically available antifungals are limited, far from effective and resistance to the three classes of currently available antifungals is rising rapidly. Development of antifungal has been slow compared to that of other types of drugs: while 18 first-in-class drugs were approved against solid tumor, only a single novel class of antifungal drugs, the echinocandins, was introduced between 2000 and 2015 with caspofungin approved for invasive aspergillosis in 2001. High mortality rates of IFIs, toxicity of available antifungal, and intrinsic and emergent drug resistance highlight the urgent need for new antifungal drugs. Lack of interest from industry about basic research in antimicrobial research, create a research gap that must be filled by now academic researchers that will have a pivotal role for the discovery on novel antifungals. The present proposal is an academic drug discovery project act to identify novel antifungal scaffolds. Also relevant to this application is the concept of drug repurposing that is the use of existing drugs to treat other diseases for which the molecule was not indicated for.

	Key research question. Could drug repurposing be a quick method to identify compounds with an established safety profile and known therapeutic advantages that may prove efficacious as antifungal activity? Approved drugs have already established safety in humans and developed for efficacy in a particular disease and these data allow skipping some of the drug discovery costs and all the risks associated with the process. We have investigated a library of small molecules generated over the years at Cardiff laboratory, which includes chromones derived scaffolds (1), sphingosine analogues (fingolimod) and nucleoside analogues. We have evaluated a library of these compounds against various fungal strains and already identified structures that showed antifungal activity. One of them, fingolimod is the first orally available drug approved for multiple sclerosis. The objectives of the present proposal are: Objective 1. To conduct a structure activity relationship (SAR) to modify the active compounds to improve their antifungal effect. Objective 2. Identification of the mode action/biological target of these molecules. For example, fingolimod has a very close resemblance with N-myristoyltransferase (NMT) inhibitors a crucial enzyme for the fungal life cycle. Since the crystal structure of this protein is available the design of NMT inhibitors will be accelerated. As NMT, is a new biological target, fungal resistance to drugs will be extremely low. Objective 3. Refine the SAR study informed by the biological results to further improve the activity and the drug-like properties of the hit compounds. The student engaged with the project will have the opportunity to design and synthesise analogues of the most promising compounds in a state-of-the-art laboratory at Cardiff in a group that have expertise in the synthesis of a wide range of molecules. Student will then evaluate these new molecules at the Exeter MRC Centre for Medical Mycology a lead institute in mycology research the compounds synthesised. After the first cycle of synthesis/evaluation of the compounds student will be able to take the project lead and suggests potential modifications to the hit compounds to improve the drug like properties of the molecules.
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