

High Throughput Screening for Antifungal Drug Discovery

Nosocomial (hospital acquired) infections have profound social, economic, and personal costs to patients. A large number of these infections are fungal infections, which are associated with high mortality rates. One of the reasons for this high mortality is the limited armamentarium of antifungal drugs. The antifungal drug discovery process is faced with difficult challenges, including the eukaryotic nature of the infecting organisms, the changing epidemiology of fungal infections, difficulties in clinical trials design, the toxicity displayed by some of the current antifungal agents, the emergence of resistance to most classes of antifungal agents, and the narrow spectrum of some of the newer agents. A major reason for ineffective antifungal treatments is because most fungal organisms grow as 'biofilms', microbial communities attached to host tissues and/or implanted biomaterials. Biofilm infections are notoriously difficult to treat because of their intrinsic resistance to antimicrobials and host defenses. *Candida albicans* is the main causative agent of candidiasis, the most frequent fungal infection in US hospitals, and most forms of candidiasis are associated with biofilm formation. The nature of our work has been to screen libraries of small molecules for potential inhibitory effects against *C. albicans* biofilm formation. These libraries contain thousands of compounds that are prescreened to have drug-like properties and range from 250 to 550 Daltons in size. To screen these libraries, an in-house developed 96-well microtiter plate-based method was used to form *C. albicans* SC5314 biofilms in the presence and absence of the compounds. To date 20,000 compounds have been screened. Of these, 49 compounds have shown inhibition against SC5314 biofilm formation (hit rate of 0.25%). These small molecules represent "hits" and current experiments in the laboratory are designed to identify the most promising "leads" that represent the best candidates for the development of new antifungal agents

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