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In the pursuit of ideal hits for antifungal research

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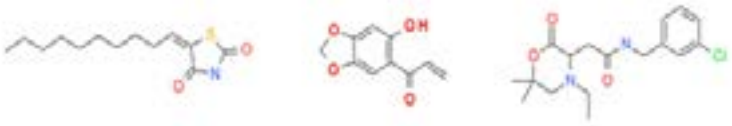
Worldwide, fungal infections take more than 1.3 million lives each year. In addition, over 300 million people are affected by a serious fungal infection. Three classes of antifungals are mainly used to manage these types of invasive fungal infection. The over-reliance on the same medicines acting on a limited number of modes of action has induced a selection pressure amongst the originally susceptible pathogens. As a consequence, drug resistance has become increasingly common and has diminished the arsenal of effective antifungal drugs. Furthermore, some drugs have additional significant limitations. For example, echinocandins need to be administrated intravenously due to their poor oral bioavailability, and amphotericin B has been known to induce adverse nephrotoxicity. This clearly shows the strong need for new molecules which are able to control pathogens showing resistance to our current antifungal products. To bring new antifungals into development, researchers first need to identify new lead molecules. In order to achieve this, they often rely on screening techniques, with phenotypic screening of new compounds being the most preferred. In this presentation, learning's from several years of research and surveys of the antifungal literature will be shared: unwanted compounds not only adversely affect enzyme assays (figure 1) but also phenotypic screens and hits, as a consequence needs to be selected very carefully. In addition, we would like to share examples of what we believe are good hits for antifungal research but that we were not able to pursue further due to resource limitations. We hope that this will encourage scientists to take some of them forward and help to tackle the global challenge of antifungal research.



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Structure-based design of subtype selective antagonists for the ionotropic glutamate receptors: Successes and failures

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Ionotropic glutamate receptor antagonists are highly valuable tool compounds for studies of neurological pathways in the central nervous system. On the basis of rational ligand design, a new class of selective antagonists, represented by (2S,4R)-4-(2-carboxyphenoxy)pyrrolidine-2-carboxylic acid (1b), for cloned homomeric kainic acid receptors subtype 1 (GluK1) was attained (Ki=4 μM). In a functional assay 1b displayed full antagonist activity with IC50=6±2 μM. A crystal structure was obtained of 1b when bound in the ligand binding domain of GluK1. A domain opening of 13-14°C was seen compared to the structure with glutamate, consistent with 1b being an antagonist. A structure-activity-relationship study showed that the chemical nature of the tethering atom (C, O or S) linking the pyrrolidine ring and the phenyl ring plays a key role in the receptor selectivity profile and that substituents on the phenyl ring are well accommodated by the GluK1 receptor. The talk will also cover results from other design studies which have led to successes as well as failures in this field.

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