F-750

Structure-Activity Relationship of a Series of Echinocandins and the Discovery of CD101, a Highly Stable and Soluble, Once-Weekly Novel Echinocandin

Ken James, Ph.D.
Cidara Therapeutics, Inc.
6310 Nancy Ridge Drive, Suite 101
San Diego, CA 92121
kjames@cidara.com

K. James,[1] C. Laudeman,[2] N. Malkar,[2] R. Krishnan,[1] and K. Polowy[2]

[1]Cidara Therapeutics, Inc., San Diego, CA, USA; [2]Seachaid Pharmaceuticals, Durham, NC, USA

ABSTRACT

Background: Because currently marketed echinocandins are administered by daily intravenous (IV) infusion, their usage is often limited to inpatient settings. A safe and effective echinocandin with physicochemical and pharmacokinetic (PK) properties enabling less frequent and alternate routes of administration is desired.

Methods: Structural modifications of different echinocandin scaffolds were made by rational design and synthesis. Test articles were purified by reversed-phase chromatography. Efficacy was evaluated in a candidiasis mouse model. The most promising candidates were further evaluated based on PK after IV administration in dogs. Test article concentrations were determined by quantitative LC/MS/MS from extracted plasma and comparison to a standard curve. PK parameters were calculated using noncompartmental analyses.

Results: At the pharmacophore sites modified, scaffolds were intolerant of the large substituents, and in vitro activity diminished with increased bulk. Smaller hemiaminal ether and substituted aminal derivatives at C5-ornithine resulted in some compounds displaying enhanced efficacy. Permanently charged, pH-dependent, and charge-neutral analogues produced up to 4-log reductions of fungal burden in mice. Half-lives of the most efficacious compounds varied up to 4-fold (12 to 53 h) in dogs. The compound with the most desirable combination of efficacy and PK (CD101) was selected for nonclinical development.

Conclusions: CD101 is a novel echinocandin with a unique modification of the cyclic peptide core. This modification resulted in an echinocandin with high solubility, physical and chemical stability, enhanced safety, good potency and spectrum of activity, and a long plasma half-life compared to structurally similar compounds. These properties may enable infrequent IV, intramuscular, subcutaneous, and topical applications. In addition, the high drug exposures (C_{max} and AUC) enabled by the PK and high safety margins inherent to CD101 may be utilized to overcome some drug-resistant fungal infections.

BACKGROUND

Since their introduction in 2001, echinocandins have become increasingly important in the treatment of fungal infections and are now first-line therapy against candidemia and some invasive *Candida* infections.[1] However, the currently approved echinocandins are administered once daily by IV infusion, limiting their overall use and application. We sought to discover a next-generation echinocandin with properties enabling alternate routes of administration and a more flexible dosing schedule. Such features would eliminate the need for step-down therapy with a different class of agents (e.g., to an azole) and could expand utilization to include prophylaxis and treatment of recurrent or azole-resistant vulvovaginal candidiasis.[2,3]

METHODS

The compounds for the study were made by an iterative process of rational design and synthesis followed by reversed-phase HPLC and lyophilization.

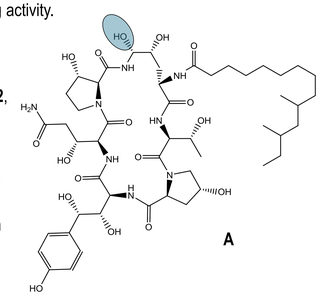
Female CD-1 mice were rendered neutropenic with cyclophosphamide and were inoculated with *C. albicans* R303. Test articles were administered intraperitoneally 2 h after infection. After 24 h, kidneys were harvested, homogenized, and assayed for fungal burden.

The single-dose pharmacokinetics of test agents were compared in beagle dogs. Levels of test article in the plasma samples were measured by quantitative LC/MS/MS analysis compared to a calibration curve and an internal standard.

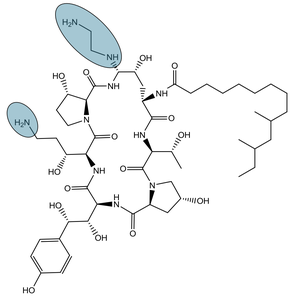
RESULTS

Novel echinocandins were synthesized by modification of pneumocandin B_0 (**A**), caspofungin (**B**), and anidulafungin (**C**). The shaded ovals indicate the regions of derivatization or substitution. Many modifications at these sites, such as with PEG_4 and higher, resulted in diminishing activity.

However, the choline ether derivative at the C-5 ornithine position of **C** (CD101; **Figure 2**, compound **3**) resulted in an echinocandin with high solubility, physical and chemical stability, enhanced potency and spectrum of activity, high safety margins, and a long plasma half-life.

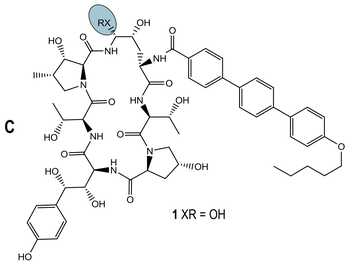


A



B

RESULTS (cont'd)



C

1 XR = OH

Compounds were discovered with activity and/or other properties similar or superior to those of known comparators using the iterative process summarized in **Figure 1**.

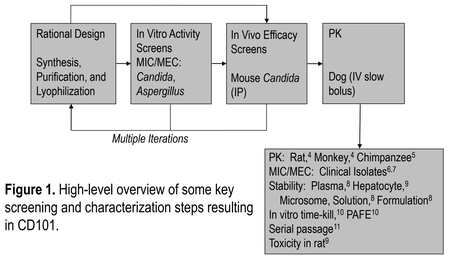
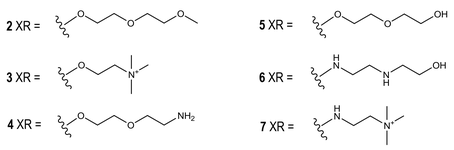


Figure 1. High-level overview of some key screening and characterization steps resulting in CD101.

Select compounds that progressed farthest through screening include the anidulafungin (**C**) derivatives and analogues shown in **Figure 2**. They are notably similar in size and molecular weight; however, they vary widely in the number of hydrogen bond acceptors and donors. Of note, in this select group two compounds have a permanent charge, two are chargeable at physiologic pH, and two are charge neutral.

Figure 2. Structures of select analogues and derivatives of the anidulafungin core (**C**) described in these studies



RESULTS (cont'd)

Figure 3. Fungal burdens in the kidneys of mice 24 h after infection with *C. albicans*. All test articles displayed a good dose response. Results below the limit of detection are reported at the LOD, indicated by the red line. NA = not available.

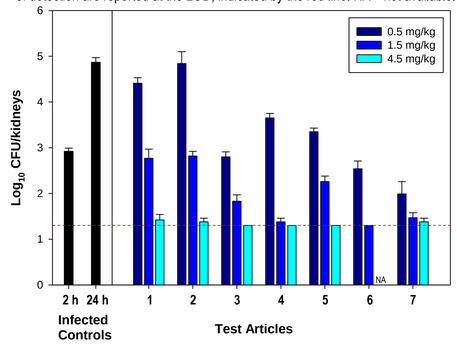
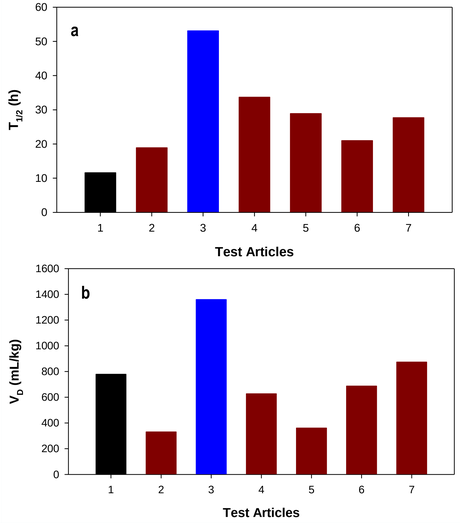


Figure 4. PK parameters of anidulafungin (black) and select test articles after IV administration (10 min slow bolus) in beagle dogs. CD101 (blue) stands apart from the other compounds (red) in both half-life (**a**) and volume of distribution (**b**).



CONCLUSIONS

- CD101 and some other novel echinocandins displayed activity comparable or superior to that of anidulafungin in a mouse model of disseminated candidiasis.
- Promising candidates included charged, chargeable, and charge neutral moieties.
- CD101 has an unusually long half-life in the dog, an observation that has also been observed in the mouse, rat,[4] cynomolgus monkey,[4] and chimpanzee.[5]
- CD101 has desirable tissue penetration, which could be beneficial for invasive infections.
- Both the hemiaminal ether and ammonium moieties of the choline group contribute to the stability and PK advantages of CD101. Structurally similar compounds featuring only one of these moieties did not exhibit the same beneficial PK properties.
- The properties of CD101 may enable more flexible dosing schedules and alternate routes of administration, thereby enabling utilization for indications not amenable to daily infusion therapies.
- The strong antifungal activity of CD101 coupled with high exposures and safety margin afforded by its unique PK profile may prove helpful in overcoming antifungal-resistant organisms.

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