

A NOVEL SMALL MOLECULE ANTIFUNGAL COMPOUND WITH IN VIVO ACTIVITY AGAINST *ASPERGILLUS FUMIGATUS*

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As part of our effort to discover novel drugs for the treatment of invasive fungal infections, a new family of heterocyclic compounds has been synthesized. The lead compound from these studies, GL48656, has in vitro activity against a variety of fungi, including *Aspergillus* spp., *Coccidioides immitis*, *Cryptococcus* serotypes A-D, and the emerging pathogens *Fusarium* and *Scedosporium*. The anti-*Aspergillus* activity of GL48656 is comparable to amphotericin B (AmB), with MIC values of 1-8 and 1-4 µg/ml, respectively. GL48656 is cidal against *A. fumigatus*, *A. flavus* and *A. niger* with MFC values of 2-8 µg/ml, similar to AmB (MFC of 2-4 µg/ml). GL48656 has fungicidal activity comparable to AmB against *Fusarium* and dermatophytes, and was highly active against *S. prolificans* with an MIC of 0.5 µg/ml.

To evaluate acute toxicity, CD-1 mice were injected IV with increasing concentrations of GL48656 and monitored for 48 h for survival. The minimum lethal dose (MLD), i.e., the lowest dose at which death occurred in at least one animal, was determined for GL48656 and compared to caspofungin and AmB. The MLD values were 20 mg/kg for GL48656, 40 mg/kg for caspofungin and 3 mg/kg for AmB. The pharmacokinetics (PK) of GL48656 was studied in mice and rats after IV or IP administration. Plasma concentrations of GL48656 were determined using an LC/MS/MS method. After IV dosing, the t_{1/2} of GL48656 for mouse and rat was 3.7 and 6.0 hours, respectively. The PK after IP dosing were similar to IV dosing - t_{1/2} for mouse and rat of 3.6 and 5.3 hours, respectively, and characterized by low clearance rates and high volumes of distribution. The in vivo activity of GL48656 was studied in a model of systemic aspergillosis by infecting CD-1 mice IV with 8.4 x 10⁶ conidia of *A. fumigatus*. Ten days of therapy began 1 day later, with GL48656 given IP BID and AmB given IP QD, or IV QOD. Residual CFU was quantitated at day 14 postinfection. All untreated controls died, whereas treatment with 1 or 3.3 mg/kg of GL48656 prolonged survival (p ≤ .0008). These doses of GL48656 were equivalent to 0.8 mg/kg AmB IV or 3.3 mg/kg AmB IP in prolonging survival. Fungal burden in the brain and kidney were reduced by all regimens (p ≤ .0054, in both organs) which were equivalent, except that 3.3 mg/kg GL48656 was superior to AmB (p = .0453) in brain. In summary, GL48656 is active in vitro and in vivo vs. *Aspergillus* with efficacy equivalent to the gold standard AmB. GL48656 has favorable pharmacokinetic properties and less acute toxicity than AmB, comparable to caspofungin. Additional studies to characterize the antifungal efficacy of GL48656 are underway.