

EVALUATION OF NOVEL ANTILEISHMANIAL ANTIMITOTIC AGENTS

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Leishmaniasis is the cause of significant morbidity and mortality in the developing world. Current therapies include the use of parenteral agents such as pentavalent antimonial compounds, amphotericin B, and pentamidine and the oral agent miltefosine. However, these treatment strategies all have drawbacks including toxicity, route of administration, and/or expense. Tubulin, a heterodimeric protein that comprises microtubules, plays a critical role in cell division and is an established anticancer and anthelmintic drug target. Our lab has prepared *N*1-aryl-3,5-dinitro-*N*4,*N*4-di-*n*-alkylsulfanilamides that possess selective antimicrotubule activity against kinetoplastid parasites in vitro.¹ However, our lead compounds in this series are extensively metabolized in vitro and in vivo, with the major products resulting from *N*1 ring oxidation and *N*4 alkane oxidation. Analogs of our initial lead compounds are being synthesized in an effort to achieve greater metabolic stability while maintaining selective antiparasitic activity. The efficacy of these compounds is currently being assessed against *Leishmania* and trypanosomes (related disease-causing parasites) in vitro as well as against purified leishmanial tubulin. Previously, tubulin has been purified from *L. amazonensis*. However, since *L. amazonensis* causes disease in humans and requires expensive medium for large-scale growth, our initial protocol has been optimized and applied to *L. tarentolae*, a strain which is non-infectious to humans and can be grown to high cell densities in inexpensive medium. Further details of our drug candidate selection process, including the evaluation of the antiparasitic and antitubulin activity of new compounds, will also be presented.

1. Bhattacharya, G. et al. (2004) J. Med. Chem. 47, 1823-1832.

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