ANTITUMOR AND ANTI-PNEUMOCYSTIS CARINII ACTIVITIES
OF NOVEL BISBENZAMIDINES

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Abstract: Among a library of 17 bisbenzamidines connected with various linkers, compounds with a flexible pentanediamide (10) or hexanediamide (12) linker were the most potent derivatives against rat \textit{Pneumocystis carinii} (IC\textsubscript{50} values of 3 and 2 nM, respectively) and had the highest selectivity index ratios (GI\textsubscript{50} of human tumor cells/IC\textsubscript{50} of \textit{P. carinii} cells) of >10\textsuperscript{4}. Seven compounds caused 50\% growth inhibition (GI\textsubscript{50}) of tumor cells at concentrations of <100 \textmu M while the remaining ten were not cytotoxic. DNA binding affinity (ΔT\textsubscript{m}) of the tested compounds did not correlate with either their anti-\textit{P. carinii} activity or cytotoxicity.

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Aromatic dicarboxylic molecules, and more specifically bisbenzamidines, remain exciting potential drug candidates since the discovery of their antimicrobial properties in the late 1930s.\textsuperscript{1,2} They exert their activities against numerous microbial pathogens including Cryptococcus neoformans,\textsuperscript{3} Candida albicans,\textsuperscript{4} Cryptosporidium parvum,\textsuperscript{5} Aspergillus sp.,\textsuperscript{6} Giardia lamblia,\textsuperscript{6} Plasmodium sp.,\textsuperscript{2,7,9} Leishmania sp.,\textsuperscript{10,12} Trypanosoma sp.,\textsuperscript{13,14} Pneumocystis carinii,\textsuperscript{15,21} Toxoplasma gondii,\textsuperscript{22} and Mycobacterium tuberculosis.\textsuperscript{23} These compounds have also been reported to display antiviral\textsuperscript{24} and antitumor properties.\textsuperscript{25-28}

Despite the broad range of activities displayed by the bisbenzamidines, pentamidine (6) is the only drug in this class that is clinically used for the treatment of Pneumocystis jirovecii pneumonia, leishmaniasis and trypanosomiasis. Other representatives of this group of compounds include terephthalamidine (1), diminazene (berenil, 2), stilbamidine (3), hydroxystilbamidine (4), and imidocarb (5). Although the detailed mechanism of action of this class of drugs is not well understood, it has long been hypothesized that their biological activity is related to their ability to bind to the minor groove of DNA at AT-rich sites. Such interactions could lead to the inhibition of one or more of several DNA dependent enzymes.

![Figure 1. Structure of selected bisbenzamidines.](image)

(e.g. topoisomerases\textsuperscript{29} and nuclease\textsuperscript{30}) or possibly by direct inhibition of the transcription process.\textsuperscript{31} Another plausible mode of action is the ability of bisbenzamidines to form complexes with ferrirprotoporphyrin IX as reported recently.\textsuperscript{7,9} Although the structures of the complexes have not been