Synthesis and Structure-Activity Relationship of Antileukemic Arylimidamide-Aazole Hybrid Compounds

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Leukemias are cancers of blood-forming tissues and are the tenth most common form of cancer in the U.S., contributing to 3.9% of cancer deaths in this country. Acute myeloid leukemia (AML) starts in the bone marrow and can quickly spread through the blood to other parts of the body; AML is the most lethal form of leukemia. 1 Hit compound AA3-96 was identified from a series of antiparasitic arylimidamide-azole hybrid compounds 2 for its sub-micromolar activity against J774 macrophages and displays low micromolar activity against AML cell lines. The general synthesis for these compounds involves two SN2 reactions to attach an alkoxy linker and an azole heterocycle to the starting material, 4-nitrophenol. The imidamide moiety is installed via a reduction of the nitro group followed by a nucleophilic acyl substitution by the resulting amine on an aryl thioimidate salt to afford the arylimidamide-azole hybrid product. The antileukemic mechanism of action of these compounds is currently unknown, but clear trends in the structure-activity relationship (SAR) are emerging as derivatives of AA3-96 have been synthesized and evaluated for antileukemic activity. Over 40 analogs have been prepared with specific modifications designed to evaluate the effects on antileukemic activity of various terminal azoles, linker length and composition, essentiality of the imidamide group, and substitution patterns on the central and terminal aryl rings. The most potent compounds identified in this series display sub-micromolar activity against the OCI-AML3, MV411 and U937 AML cell lines. The synthesis and in vitro antileukemic SAR of these compounds will be described in the poster.