

5-Amino-4-Imidazolecarboxamide Riboside and Its Nucleobase as Potentiators of Antifolate Transport and Metabolism

Internal Case/Ref #: 809098-01 (Maintain on Website)

Patent(s): Issued
U.S. Patent

Number: 7,687,473
Issue Date: March 30, 2010

Summary:

The invention provides a method for increasing the efficacy of antifolates which act via inhibition of dihydrofolate reductase (DHFR). The method comprises the steps of administration of 5-amino-4-imidazolecarboxamide riboside (Z) or its base with the antifolate such that the targeted cells are exposed to both the antifolate and Z simultaneously. This results in increased influx of the antifolate. For MTX, accumulation of the more biologically active polyglutamate forms is also potentiated. This potentiation appears to be mediated by an effect on the RFC.

Detail:

The invention provides a method for enhancing the uptake and efficacy of antifolates which act via inhibition of DHFR such as the 2,4 diaminopteridine antifolates methotrexate and aminopterin. The method is based on the unexpected observation that exogenous 5-amino-4-imidazolecarboxamide riboside (Z), a nucleoside precursor of (among others) the triphosphate ZTP, potentiates uptake of MTX and synthesis of MTX polyglutamate in cancer cells. Based on the data presented herein, it is considered that Z potentiates transport of antifolates via the RFC and the increased transport leads to increased synthesis of antifolate polyglutamates and consequently increased drug accumulation. Z was observed to enhance the growth inhibitory potency of MTX against cancer cells. Thus in one embodiment, this invention provides a method comprising the administration of Z or its base (i.e., 5-amino-4-imidazolecarboxamide) with an antifolate which acts via inhibition of the DHFR at concentrations at which the antifolate inhibits DHFR. The administration of Z or its base can be accomplished by any standard method, although systemic administration is preferred. Z has already been tested in clinical trials as a treatment for cardiac ischemia and is known to be nontoxic. In another embodiment, Z or its base and an antifolate which acts via inhibition of DHFR can be administered with a second antifolate(s) which primarily act via another mechanism such as inhibition of thymidylate synthase, inhibition of purine synthesis or other multi-targeted inhibition pathways. Administration of Z or its base with folate(s) which inhibit DHFR (with or without other folates) to enhance the efficacy of the folate(s) can be carried out for inhibiting the growth of cells as in various cancers as well as in other pathological conditions such as rheumatoid arthritis and psoriasis.