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(54) **SELECTIVE PROTON COUPLED FOLATE TRANSPORTER AND FOLATE RECEPTOR, AND GRAFTASE INHIBITOR COMPOUNDS AND METHODS OF USING THE SAME**

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(52) **U.S. Cl.**

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(58) **Field of Classification Search**

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See application file for complete search history.

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(57) **ABSTRACT**

Fused cyclic pyrimidine compounds, including tautomers thereof, and pharmaceutically acceptable salts, prodrugs, solvates and hydrates thereof, are disclosed having the general Formula 1:

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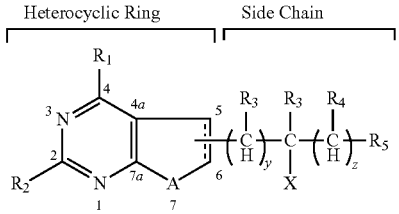

These compounds are useful in methods for treating cancer, selectively targeting cancerous cells via the proton coupled folate transporter, folate receptor alpha, and/or folate receptor beta pathways, inhibiting GARFTase in cancerous cells, and selectively targeting activated macrophages in a patient having an autoimmune disease, such as rheumatoid arthritis.

17 Claims, 6 Drawing Sheets