Thiophene Carboxamide Analogs with Long Alkyl Chains Comprising Ethylene Glycol Units Inhibit Glioblastoma Cell Proliferation by Activating AMPK

Abstract

Glioblastoma is a refractory malignant tumor that requires novel therapeutic strategies for effective treatment. We have previously reported that JCI-20679 (1), an analog of annonaceous acetogenins, shows potent antitumor activity against glioblastomas. However, the synthesis of 1 requires 23 steps, including 16 steps for the preparation of a tetrahydrofuran (THF) moiety. This study reports the design and synthesis of 11 analogs with a triethylene glycol moiety in place of the THF moiety in 1. Among these, the analog 2k with an *n*-decyl chain exhibited potent inhibitory activity against the growth of glioblastoma stem cells by inhibiting mitochondrial function and synergistically enhancing the effect of temozolomide (TMZ). Furthermore, 2k significantly suppressed tumor growth without critical toxicity *in vivo*. Hence, this study presents novel potential anticancer agents and a strategy for the development of these agents that can be produced easily.