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Full-Length Research Paper

Development of a novel conjugatable sunitinib analogue validated through in vitro and in vivo preclinical settings

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Abstract

Sunitinib is an oral FDA/EMEA approved multi-targeted tyrosine kinase inhibitor. It possesses anti-angiogenic and antitumor activity against a variety of advanced solid tumors. However, its chemical core does not allow a potential linkage to tumor-homing elements that could eventually enhance its potency. Therefore, a novel linkable sunitinib derivative, designated SB1, was rationally designed and synthesized. The pharmaceutical profile of SB1 was explored both *in vitro* and *in vivo*. Mass spectrometry and NMR spectroscopy were utilized for characterization, while MTT assays and LC-MS/MS validated protocols were used to explore its antiproliferative effect and stability, respectively. Cytotoxicity evaluation in three glioma cells showed that SB1 preserved the antiproliferative effect of sunitinib. SB1 was stable *in vitro* after 24 h incubation in mouse plasma, while both agents exhibited bioequivalent pharmacokinetic characteristics after i.v. administration in Balb/c mice. To evaluate the levels of SB1 in mouse plasma, a novel analytical method was developed and validated in accordance to the US FDA and the EU EMA guidelines. We formulated a novel linkable sunitinib analog exhibiting similar antiproliferative and apoptotic properties with native sunitinib in glioma cell lines. Both SB1 and native sunitinib showed identical *in vitro* stability in mouse plasma and pharmacokinetics after i.v. administration in Balb/c mice.