Medical Oncology (2025) 42:480
https://doi.org/10.1007/s12032-025-03037-0

REVIEW ARTICLE

Apratoxin S10 as a dual-action modulator of receptor tyrosine kinases and tumor microenvironment: emerging anticancer insights from marine-derived analogs

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Received: 25 May 2025 / Accepted: 7 September 2025

Abstract

Marine cyanobacteria are prolific producers of structurally diverse and pharmacologically potent secondary metabolites. Among these, apratoxins, a class of cyclodepsipeptides originally isolated from Lyngbya species have demonstrated broad-spectrum cytotoxic and antiangiogenic activity. However, the clinical development of natural apratoxins has been limited due to systemic toxicity and narrow therapeutic indices. Recent efforts have focused on optimizing these molecules, leading to the development of semi-synthetic analogs such as Apratoxin S10 (Apra S10), which exhibits improved stability, selectivity, and potency. This review synthesizes current evidence on the anticancer mechanisms of Apra S10 and related apratoxins, including their effects on receptor tyrosine kinases (RTKs), growth factor signaling, and tumor microenvironment modulation. Emphasis is placed on Apra S10's preclinical pharmacokinetics, tumor-specific accumulation, and multi-target activity across highly vascularized tumors, including hepatocellular carcinoma, renal cell carcinoma, neuroendocrine tumors, and pancreatic ductal adenocarcinoma. Studies show that Apra S10 downregulates RTKs, suppresses secretion of VEGF-A and IL-6, and disrupts tumor-stroma crosstalk, mechanisms that collectively result in potent growth inhibition and antiangiogenic effects without overt toxicity. These findings highlight Apra S10 and its analogs as promising candidates for adjuvant cancer therapy, meriting further translational research to assess clinical safety, pharmacodynamics, and synergistic potential with existing chemotherapeutics.

Keywords Apratoxin S10 · Apratoxin analogs · Anticancer mechanisms · Marine natural products · Receptor tyrosine kinases · Tumor microenvironment

Abbreviations

RiP	Receptor Interacting Protein
SAR	Structure-activity relationships
HCT116	Human colon cancer cells
PyAOP	7-Azabenzotriazol-1-yloxy) tripyrrolidinophosphonium hexafluorophosphate
PHB	Prohibitin; Troc: 2,2,2-Trichloroethoxycarbonyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

Introduction

Cancer is a medical condition characterized by uncontrolled cell proliferation and infiltration into tissues and a variety of organs, including the heart, lungs, nervous system, colon, and others. According to the International Agency for Research on Cancer, World Health Organization (https://gco.iarc.who.int), in 2022, there were approximately 19.9 million new cancer cases and 9.7 million cancer deaths. Among the most prevalent cases, lung cancer and breast cancer emerged as the most prevalent, with approximately 2.3 million cases, trailed by colorectum, prostate, and stomach cancer. Approximately 1.8 million deaths were attributed to lung cancer, which remained the leading cause of cancer-related mortality, followed by colorectal, liver, stomach, and female breast cancers. Cancer incidence rates have been significantly higher in transitioning countries compared to transitioned ones, with mortality rates also exhibiting notable

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Published online: 20 September 2025