ACS Medicinal Chemistry Letters

In This Issue

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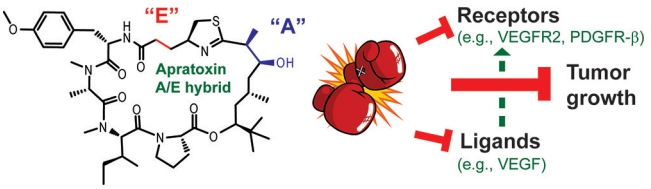
IMPROVING THE POTENCY OF NATURAL TOXINS

Marine cyanobacteria are an important source of secondary metabolites with bioactivity ranging from neurotoxicity to anti-inflammatory, anti-infective, and antiproliferative activities. Some highly cytotoxic compounds might serve as potential anticancer agents. Apratoxin A is a potent cytotoxin from marine cyanobacteria that is highly active in vitro.

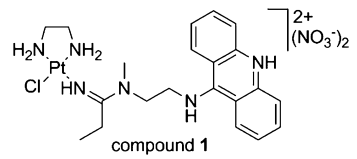
Here, Chen et al. (DOI: 10.1021/ml200176m) prepared synthetic analogues of apratoxin A. One analogue showed significant tumor selectivity and improved potency in vivo. Importantly, the authors also showed that the secretory pathway could be targeted for anticancer therapy, specifically by fine-tuning these apratoxin analogues by structural modification to prevent export of receptors and secretion of ligands. This study highlights a new direction in pursuing cancer therapeutics, which effectively separates anticancer activity from toxicity.



A NEW PROMISING PLATINUM THERAPY

Lung cancer is the leading cause of cancer-related deaths worldwide, with nonsmall cell lung cancer comprising approximately 80% of cases. While cisplatin is the benchmark cancer therapy to date, its treatment outcome has reached a plateau, and the cure rate for the disease remains low.

In this issue, Smyre et al. (DOI: 10.1021/ml2001888) describe the potency of a novel platinum–acridine compound against nonsmall cell lung cancer. They compared the cellular effect of this pharmacophore to cisplatin and observed a pronounced cytotoxicity enhancement. They showed that these two treatments act via distinct mechanisms, with the platinum–acridine compound forming DNA adducts more rapidly than cisplatin. This makes the platinum–acridine a good candidate in tackling chemoresistant DNA repair proficient types of cancer.

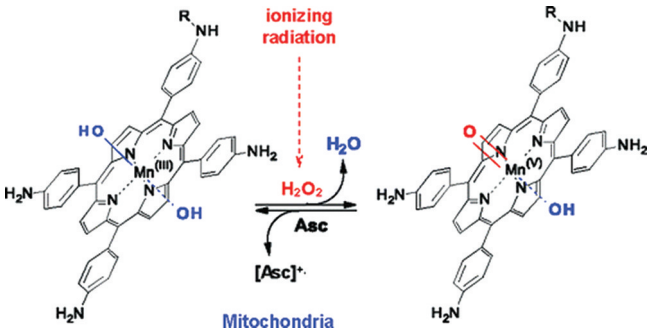


inhibition of DNA replication
S-phase cell-cycle arrest
efficient cell kill at nanomolar concentrations

RADIOMITIGATIVE PROPERTIES OF MANGANESE–PORPHYRIN COMPLEX

While radiation is routinely used in treating a broad range of malignancies, it can result to deleterious effects in normal tissues. Ionizing radiation produces reactive oxygen species that lead to cell death. Hydrogen peroxide is the major intracellular reactive oxygen species intermediate that results from superoxide, which leaks from the mitochondria. Antioxidants and similar compounds that reduce the damage to tissues during radiation are called radioprotectors, while radiomitigators minimize toxicity even after radiation exposure. Although countermeasure agents have long been studied, only one approved radioprotector is available, and none has been approved for mitigating radiation injury.

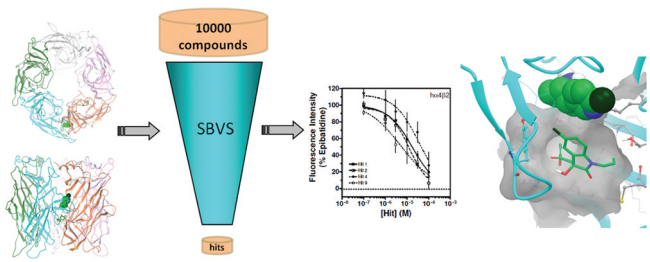
Now, Stoyanovsky et al. (DOI: 10.1021/ml200142x) describe a manganese–porphyrin complex that acts as a radiomitigator in removing mitochondrial hydrogen peroxide in cells exposed to ionizing radiation. This complex increased survival rate for mice exposed to γ-rays. Derivatives of the complex could present higher effectivity and radiomitigative properties.



VIRTUAL SCREENING FOR NEURONAL NICOTINIC RECEPTOR MODULATORS

Neuronal nicotinic acetylcholine receptors are a family of ion channels that are expressed in the central and peripheral nervous system. These receptors contribute to an extensive range of brain and physiological activities that could lead to various diseases such as schizophrenia, Alzheimer's disease, Tourette's syndrome, Parkinson's disease, autism, and nicotine abuse when their function is perturbed. While much time and effort have been devoted to drug discovery for these receptors over the years, most studies are directed to targeting the receptors' orthosteric sites with only a few drugs being identified.

In this issue, Mahasenan et al. (DOI: 10.1021/ml2001714) report the use of a computational approach to identify novel allosteric sites on neuronal nicotinic acetylcholine receptors where selective antagonists could be designed. They successfully employed in silico library docking screening of 10000 compounds, which led to the discovery of four novel allosteric lead antagonists that might be optimized and pursued for the treatment of neurological diseases.



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