ACS Medicinal Chemistry Letters

In This Issue

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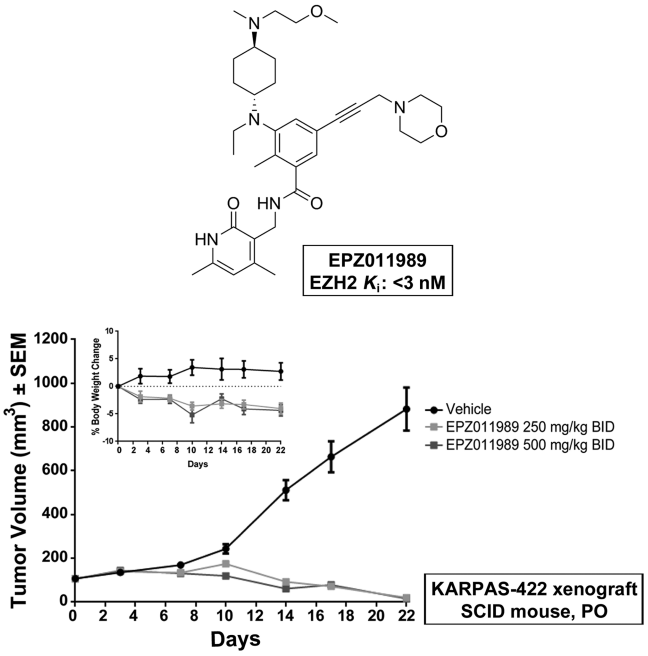
ORALLY AVAILABLE EZH2 INHIBITOR

There is a growing body of evidence suggesting that dysregulated histone methyltransferase enzyme activity contributes to the uncontrolled cell proliferation. Enhancer of Zeste Homologue 2 (EZH2) is one of a family of histone methyltransferase enzymes responsible for regulation of gene expression through modification of the chromatin complex. EZH2 inhibitors have demonstrated significant therapeutic potential for lymphoma treatment, but the full potential of EZH2 inhibitors as treatment for expanded cancer indications and other human disease have not been fully explored. In vivo chemical probes will help deduce the role of EZH2 in pathobiology.

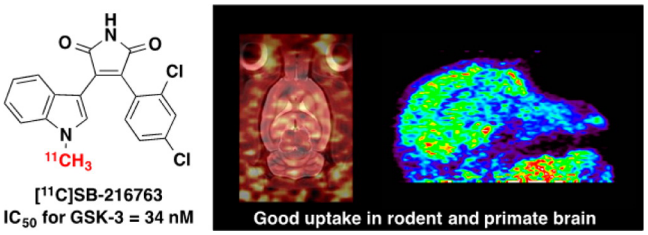
Our Featured Letter by Campbell et al. (DOI: 10.1021/acsmedchemlett.5b00037) reports the discovery of such a probe. The compound probe is a potent, selective, and orally active inhibitor of EZH2. The group describes the discovery and characterization of the probe, and how this tool compound demonstrates significant tumor growth regression in a mouse xenograft model. The PK/PD and in vivo activity data were highlighted to encourage collaborative research in the field.



THE FIRST BRAIN PENETRATIVE RADIOTRACER FOR GSK-3

Glycogen synthase kinase-3β (GSK-3β) has been identified as an enzyme involved in glycogen metabolism, with the highest abundance in the brain, and a key component of many cellular and physiological events. Importantly, its dysregulation plays a role in multiple diseases such as diabetes, neurodegenerative conditions such as Alzheimer's disease, Parkinson disease, neurological disorders, pain, and cancer. A number of GSK-3 inhibitors showing variable potencies and isoform selectivity have been reported in recent literature, but previous reports of PET radiotracers for GSK-3β are limited, and none has been shown to cross the blood−brain barrier.

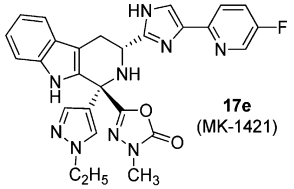
In this issue, Li et al. (DOI: 10.1021/acsmedchemlett.5b00044) describe the development of a novel one-pot two-step radiosynthesis and biological evaluation of a brain penetrative PET radiotracer for probing GSK-3 in vivo. It is the first radiotracer for GSK-3 able to cross the blood−brain barrier and enter the central nervous system in both rodents and nonhuman primates, representing a major step toward the longstanding goal of probing this important target in the living brain.



NEW TYPE 2 DIABETES MELLITUS INHIBITOR

Diabetes has become a worldwide epidemic, affecting 6% of the adult population in the developed world, and causes significant morbidity and mortality. Type 2 diabetes mellitus, a carbohydrate metabolism disorder characterized by high blood glucose levels, accounts for more than 90% of diabetes cases. Despite the availability of a range of agents for the treatment of Type 2 diabetes mellitus, a high proportion of the diabetic patients fail to achieve or maintain glycemic targets, and many therapies suffer from significant limitations.

Somatostatin inhibits the release of growth hormone from the anterior pituitary gland and also suppresses the production of the pancreatic hormones (e.g., insulin and glucagon). Its functions are facilitated through five G-protein coupled receptors, including somatostatin subtype-3 receptor (SSTR3). The Editors Choice Letter, featured on the cover, by Shah et al. (DOI: 10.1021/ml500514w) describes the identification and optimization of a potent, selective SSTR3 antagonist, which showed acceptable preclinical pharmacokinetic profile and could serve as potential treatment for type 2 diabetes.



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