Small Molecule HIF-1 Pathway Inhibitors as Anticancer Drugs and Tracers for PET Imaging

Published date: June 10, 2015

Technology description

Market Summary

HIF-1's overexpression is detected in and positively associated with mortality in various human cancers, including bladder, brain, breast, cervix, colon, endometrium, esophagus, head and neck, liver, lung, oropharynx, ovary, pancreas, skin and stomach cancers. In 2012, the number of new cancer patients with tumors overexpressing HIF-1 is expected to be 1.47 million. There are over 18 cancer therapeutics that were found to have a HIF-1 pathway inhibitory action in addition to their primary targets in tumor cells. Some of these compounds are effective HIF-1 pathway inhibitors at nM concentrations. These compounds are at different stages of development, ranging from pipeline drugs to approved therapeutics.

Technical Summary

Tumor cells are fast growing and outgrow their own blood and oxygen supply. To adapt to the hypoxic environment, tumor cells induce transcription of genes that regulate angiogenesis, cell survival and proliferation, glucose metabolism, pH regulation, and cell migration. Many of these genes are regulated by HIF-1 transcription factor, a heterodimer comprised of an oxygen-sensitive HIF-1 subunit and a constitutively expressed HIF-1 subunit. Inhibitors of HIF-1 pathway have diverse modes of action and affect the HIF-1 protein levels, HIF-1 dimerization, HIF-1 DNA binding, and HIF-1 transcriptional activity. The inventors at Emory University developed small molecule HIF-1 pathway inhibitors that reduce HIF-1 transcriptional activity. Theirin vitroassays showed that these HIF-1 pathway inhibitors are effective at or below 5 μM concentration. The inventors also added 11C or 18F tracers to these small molecules so that the pharmacokinetic and pharmacodynamic properties of these inhibitors can be determinedin vivousing positron emission tomography (PET).

Application area

Small molecules that inhibit hypoxia-inducible factor (HIF)-1 pathway for use as cancer therapeutic and imaging agents.

None of the currently available compounds that can be used as HIF-1 pathway inhibitors have the PET tracers forin vivoimaging.

Advantages

Inhibition of HIF-1 activity can prevent tumor vascularization and metastases.
Small molecule HIF-1 pathway inhibitors have good lipid solubility.
Water solubilizing subgroups added to our HIF-1 pathway inhibitors to address poor water solubility.

Institution

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